Infections in Late Pregnancy and Puerperium

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Raghad A. Hussein, Jonathan D. Perez, Joseph L. Smith, and Mary Jane Reed

Key Points

- Compared to the general population, pregnant women are at higher risk of acquiring infections.
- The definition of maternal sepsis has evolved over the years to focus on organ dysfunction, as this facilitates prompt recognition and treatment of potentially deadly infections.
- Chorioamnionitis is inversely related to gestational age and can lead to premature delivery. Non-specific signs and symptoms can make the diagnosis difficult. Timely recognition and administration of appropriately broad antimicrobials decrease maternal and fetal morbidity and mortality.
- Although rare, surgical wound and soft tissue infections from *Staphylococcus pyogenes* and group A streptococci can lead to toxic shock syndrome with subsequent multiorgan failure.
- Maternal obesity and cesarean section are the two most common risk factors for developing surgical site infection. Prophylactic administration of antibiotics significantly reduces the frequency of these complications.
- Necrotizing fasciitis is a fulminant infection which commonly presents as an ambiguous clinical picture that often leads to delayed diagnosis and a relatively high mortality rate. It is a surgical emergency that requires serial debridement and broad-spectrum antibiotics.
- Pregnant women are at increased risk of urinary tract infections. Preventive screening could lead to early recognition and prevention of potentially life-threatening pyelonephritis.
- Listeriosis is a food-borne illness that, if acquired during pregnancy, could be detrimental to maternal and fetal outcomes. Pregnant women are at increased risk of infections and often present with non-specific complaints.
- Malaria is more likely to be severe in primigravida and pregnant women without immunity to *Plasmodium* sp.

R. A. Hussein
Department of Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA
e-mail: rahussein@geisinger.edu

J. D. Perez
Department of Critical Care Medicine, Medical Center Navicent Health, Macon, GA, USA
e-mail: jdplopez@gmail.com

J. L. Smith
Department of Critical Care Medicine and Infectious Disease, Geisinger Medical Center, Danville, PA, USA
e-mail: jol.smith@gmail.com

M. J. Reed (✉)
Department of Critical Care Medicine and Surgery, Geisnger Medical Center, Danville, PA, USA
e-mail: mreed@geisinger.edu

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19.1 Introduction

Sepsis is a potentially preventable condition which consistently remains the third most common cause of direct maternal deaths in low-, middle-, and high-income countries. In the last 25 years, the annual global number of maternal deaths has declined from an estimated 532,000 in 1990 to an estimated 303,000 in 2015 [1]. Nevertheless, approximately 75,000 women and one million neonates, primarily in resource-limited countries, still die every year from maternal sepsis complications. Postpartum bacterial infections alone account for approximately 10–15% of this global burden of maternal deaths [2, 3]. In the United States, the incidence of antepartum and puerperal sepsis has been estimated to be 0.4–0.6 per 1000 deliveries, accounting for 13% of maternal deaths and 5% of intensive care unit (ICU) admissions [4–6]. In addition to the risk of death and short-term complications, puerperal sepsis is associated with long-term morbidities and unique obstetric complications, such as chronic pelvic pain and secondary infertility due to salpingitis and fallopian tube adhesions [6].

Infections in late pregnancy and puerperal sepsis have received less attention than other causes of maternal death such as peripartum hemorrhage and hypertensive diseases of pregnancy. A fundamental strategy to reduce maternal mortality should include prevention, diagnosis, and treatment of peri-partum infections and sepsis.

19.2 The Complexity of Defining Maternal Sepsis

Determining the global incidence of infections occurring in late pregnancy and the peripartum period is difficult. Most of these infections occur in developing countries. Data from these countries are either missing or extrapolated from retrospective studies. Accordingly, the available information reflects the overall burden of infectious disease rather than the actual incidence of infection. Furthermore, in resource-limited countries, most infections remain undiagnosed and unreported due to inadequate access to health care and lack of postnatal follow-up [2, 3]. Another significant factor limiting the accuracy of epidemiological data is inconsistent definitions. Maternal sepsis, genital tract sepsis, puerperal fever, puerperal sepsis, and puerperal infection have all been used interchangeably in the literature, leading to confusion.

Since 1991, sepsis in the non-pregnant population has been defined by the physiological response to infection, i.e., the systemic inflammatory response syndrome (SIRS). However, SIRS criteria overlap with the normal physiologic response to pregnancy and childbirth. This overlap contributes to the difficulty in promptly identifying maternal sepsis, with consequent inadequate or delayed management [7]. An increasing number of clinicians are therefore using early warning scores that have been modified for pregnancy to facilitate identification of maternal deterioration (Chap. 2). Laboratory testing provides little additional information, as pregnancy is accompanied by a physiological increase in white cell counts and a dynamic inflammatory response [8]. The diagnostic accuracy of lactate in maternal infection remains unclear [9, 10].

The World Health Organization (WHO) defines puerperal sepsis as "infection of the genital tract occurring at any time between the onset of the rupture of membranes or labor and the 42nd day postpartum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, abnormal odor of discharge, or delay in the involution of the uterus." [11, 12] In 2016, in conjunction with the Sepsis-3 consensus, maternal sepsis was redefined as "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period." [7, 13]

19.3 Maternal Sepsis

19.3.1 Risk Factors

Pregnancy-induced immunological adaptation is discussed elsewhere in this book (Chap. 15). Pregnant women are particularly susceptible to

certain infections. Typical examples include parasitic diseases such as malaria, bacterial diseases such as listeriosis, and viral infections such as influenza, hepatitis E, and herpes simplex [12].

Known risk factors for puerperal sepsis include cesarean section (CS), which increases the risk fivefold [14, 15]. Other risk factors include obesity, diabetes, prolonged rupture of membranes, repeat vaginal examinations, bacterial vaginosis, carriage of group A streptococcus (GAS), and urinary tract anomalies, including bladder trauma [16, 17].

19.3.1.1 Categories of Infection Occurring during Pregnancy and the Peripartum Period

Infections in pregnant and postpartum women can be categorized as pregnancy-specific, exacerbated during pregnancy or incidental to pregnancy. Pregnancy-specific infections include acute chorioamnionitis, endometritis (with or without retained products of conception), toxic shock syndrome (TSS), wound infections, necrotizing soft tissue infections of the perineum and lactational mastitis. Lactational mastitis rarely causes severe maternal disease that requires ICU admission and will not be discussed in this chapter. Infections exacerbated during pregnancy include urinary tract infections, pneumonia, listeriosis, toxoplasmosis, and viruses (i.e., rubella, influenza, varicella, herpes, parvovirus, cytomegalovirus). Severe maternal viral infections are addressed in detail in Chap. 17. Infections incidental to pregnancy often include human immunodeficiency virus (HIV), sexually transmitted diseases (STDs), tuberculosis, and endocarditis. However, many common infections can cause serious maternal illness, given the right clinical opportunity. These are not discussed in this chapter.

19.3.2 Pregnancy-Specific Infections

19.3.2.1 Chorioamnionitis (CA)

Chorioamnionitis is a primary infection of the chorion and amniotic membranes accompanied by an inflammatory response. It is also termed intrauterine infection (IAI); recently, an expert panel recommended using the term intrauterine infection and inflammation (triple I) [18]. Chorioamnionitis usually results from the compromise of the amniotic sac integrity (spontaneously or iatrogenically), thus exposing the normally sterile intrauterine cavity to the vaginal flora. It may also occur with intact placental membranes due to specific genital tract mycoplasmas or hematogenous spread of bacteria (e.g., listeriosis) [19, 20]. Chorioamnionitis usually occurs from prolonged rupture of the amniotic membranes [21]. Bacterial vaginosis and invasive procedures (e.g., internal fetal monitoring, amniocentesis, chorionic villous sampling) are also associated with risk factors [18]. The infection is often polymicrobial, with *Ureaplasma urealyticum* and *Gardnerella vaginalis* being the two most frequent isolates [22]. Other typical organisms include *Bacteroides* sp., *Mycoplasma hominis*, group B Streptococcus, *Neisseria gonorrhea*, and *Trichomonas vaginalis*. Viruses such as enterovirus, respiratory syncytial virus, Epstein–Barr virus, cytomegalovirus, and adenovirus may also play a role [22].

Chorioamnionitis should be considered in the differential diagnosis when a gravid patient presents with a temperature exceeding 38.0 °C (100.4 °F), maternal tachycardia, fetal tachycardia, chills, and lower abdominal pain, accompanied by purulent vaginal discharge. Symptoms are often nonspecific and may only appear at a late stage of the illness; hence a high index of suspicion is warranted [18, 21].

Broad-spectrum antibiotic coverage should be started immediately, but to date, there is limited evidence regarding the most appropriate antimicrobial regimen and treatment duration [23]. The combination of ampicillin (2gm q6hrs) with gentamycin (1.5 mg/Kg q8 hours or 5 mg/kg/q24 hours) is most commonly used. Less studied but probably equally efficacious alternatives to beta-lactamase penicillins include second- or third-generation cephalosporins or clindamycin (900 mg q8 hours) [24, 25]. Given that streptococcal and staphylococcal species (particularly group B strep and *S. aureus*) have an increasing

rate of resistance to clindamycin, vancomycin is also an alternative. If cesarean delivery is performed in a patient with chorioamnionitis, antibiotics should also include coverage for anaerobes (e.g., clindamycin, metronidazole) [18, 21]. Duration of therapy is through delivery; however, postpartum clinical end points vary in the literature depending on the patient's response and/or complications [18, 22–25].

Amnioinfusion has been proposed as a therapeutic measure for chorioamnionitis. There is no evidence regarding either the effectiveness or the safety of transcervical amnioinfusion for chorioamnionitis. There are no trials studying transabdominal amnioinfusion [26].

A multidisciplinary team including a senior obstetrician, anesthesiologist, intensivist, infectious disease expert, and neonatologist should decide the timing and mode of delivery. This individualized decision depends upon maternal medical and obstetrical history, the clinical response to antibiotic and supportive therapy, current maternal condition, and fetal viability. Cases which may require induction of delivery are those with precipitous maternal deterioration (to save the mother) and those which do not respond clinically to intravenous antibiotic therapy (to save the fetus). After delivery, both maternal and fetal surfaces of the placenta should be cultured [27–29].

The major maternal complications of chorioamnionitis are maternal septic shock, postpartum hemorrhage, premature delivery, and an increase in postpartum hysterectomies [27–29]. Hysterectomy may be performed in an effort to save the mother. The incidence of chorioamnionitis is inversely related to gestational age, occurring in up to 40–70% of preterm deliveries versus 2–4% of term pregnancies [30].

19.3.2.2 Toxic Shock Syndrome

TSS is a rare, life-threatening illness caused by the massive release of inflammatory mediators. This "cytokine storm" is typically triggered by toxins released by *Staphylococcus pyogenes* (TSS toxin-1, enterotoxin B or C) or by the virulent M-protein produced by group A streptococci [31]. Some authors refer to the latter as Streptococcal toxic shock-like syndrome (STSS) [32].

In developed countries, the incidence of TSS is 0.3–0.5:100,000 in women of menstrual age, and that of STSS is 2–4:100,000 cases per the general population [33, 34] Women may acquire these infections during pregnancy and the postpartum period from infected wounds, mastitis, or any deep-seated subcutaneous and soft tissue infections [32, 35].

TSS, best known for its association with the use of high-absorbency tampons, typically manifests in otherwise healthy women. Conversely, STSS is typically associated with a pre-existing painful skin infection. The early manifestations of both TSS and STSS are non-specific, including fever, myalgias, mild confusion, and hypotension. A diffuse rash, which often resembles sunburn, is more typical of TSS. Clinical deterioration to coma and multiorgan failure ensues rapidly (within hours). A list of six criteria for STSS from the CDC can be used to classify either confirmed (fulfill all six criteria) or probable (fulfill five criteria) cases (Fig. 19.1) [36].

The primary infection location must be identified for TSS treatment (e.g., soft tissue, wound) and the source/cause of infection controlled (e.g., surgical debridement, removal of foreign body). Antibiotics should be provided as soon as possible (see Table 19.1). There is limited data on the utility of intravenous immunoglobulin as adjunctive therapy in TSS [36]. All cases with clinical suspicion of TSS or STSS should be admitted immediately to an intensive care unit where supportive care may rapidly be provided for failing organs. The mortality associated with this condition remains high [37].

A less well known but potentially lethal pathogen is *Clostridia sordellii*, which may cause postpartum endometritis with subsequent TSS. This infection is characterized by a robust leukemoid reaction and hemoconcentration. The usual presentation is afebrile and painless. In one case series of TSS caused by *C. sordellii*, the maternal mortality rate was 100% if occurring after childbirth or abortion [38].

Clinical Criteria TSS-other than Streptococcal [37]

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)
- Rash: diffuse macular erythroderma
- Desquamation: 1-2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection
  - Hepatic: total bilirubin, alanine aminotransferase enzyme, or asparate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
  - Hematologic: platelets less than 100,000/mm^3
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures blood culture may be positive for *Staphylococcus aureus*
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification

Probable

A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present

Confirmed

A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

Fig. 19.1 Clinical criteria for TSS

Table 19.1 Antibiotic coverage for TSS and streptococcal toxic shock-like syndrome

Organism	Antibiotic regimen
Streptococcus species	Clindamycin plus carbapenem or penicillin with a beta-lactamase
Staphylococcus species	Clindamycin plus antistaphylococcal antibiotic; vancomycin for MRSA and nafcillin or oxacillin for MSSA

MRSA methicillin-resistant *Staphylococcus aureus, MSAA* methicillin-sensitive *Staphylococcus aureus*

19.3.2.3 Surgical Site Infection and Necrotizing Soft Tissue Infections

Surgical site infection (SSI) is defined as an infection of the skin and subcutaneous tissue surrounding an incision occurring within 30 days of surgery. Diagnosis requires the presence of at least one of the following signs or symptoms: local pain or tenderness, swelling, redness or heat, purulent drainage from the incision (regard-

less of laboratory confirmation of infection), organisms isolated from an aseptically obtained culture from the incision (fluid or tissue), or clinical diagnosis made by a surgeon or attending physician [39].

Administration of prophylactic antibiotic therapy has been shown to significantly decrease maternal SSIs after cesarean delivery [40]. Administration of antibiotics before skin incision rather than after umbilical cord clamping is associated with a 50% reduction in the rate of maternal SSI without affecting neonatal outcomes [41–43]. Despite this, SSI remains one of the more common complications of lower segment cesarean delivery and subsequent maternal sepsis. The CDC US national surveillance study found that 3.2% of the women undergoing cesarean delivery had SSI [44]. In a UK multicenter study of 14 hospitals, 9.6% of women undergoing cesarean delivery developed SSI [45]. The high rate of SSI is of particular concern given the global increase in cesarean delivery rates and maternal obesity, which are associated with almost double the rate of cesarean delivery [46]. Of note, studies of maternal SSI after cesarean delivery are usually not comparable because of their lack of standardization in the definition of SSI, quality of surveillance, heterogeneity of the studied populations, prophylactic antibiotics coverage, aseptic practices, surgical techniques, and routine lengths of maternal hospital stays.

Necrotizing soft tissue infections (NSTIs) are fulminant and often life-threatening infections of the subcutaneous tissues. Some predisposing factors are diabetes mellitus, obesity, hypertension, immunosuppressive conditions including alcoholism and intravenous drug abuse, renal failure, malignancy, trauma, childbirth, and surgery [47, 48]. Post-cesarean delivery or episiotomy incisions and perineal tears are the most commonly affected sites for necrotizing infections in the peripartum patient [49–51]. Importantly, necrotizing soft tissue infections can also occur postpartum in women who are otherwise healthy [48].

The discrepancy between symptoms of NSTI and clinical findings are almost pathognomonic and should raise suspicion when it occurs. NSTI patients typically present with severe local pain without overlying skin changes. This feature commonly leads to delayed disease recognition. When the diagnosis is delayed, loss of sensation may be noted in the infected area, typically followed by the appearance of erythema and edema. At very late stages, purple- grayish bullae appear with subsequent tissue necrosis and sloughing.

Historically, NSTIs have been categorized into four microbiological types (Table 19.2) [52]. Type I is a mixed polymicrobial infection. Streptococcal and staphylococcal species cause type II. Types I and II are more commonly encountered after childbirth [53]. Types III and IV are generally caused by *Vibrio vulnificus*, *Aeromonas* sp., *Candida* sp., and *Zygomycetes* sp. and are generally seen in immunosuppressed patients or, in the case of *Vibrio* and *Aeromonas* infections, in patients with exposure to salt or brackish water, respectively. When seen during pregnancy and the peripartum period, this should raise suspicion of immune suppression [53].

NSTIs are a surgical emergency. Early aggressive therapy is the key to survival and reduced morbidity [49, 50]. Wide and serial surgical debridement along with antibiotics is crucial. Unlike other infections, the resulting tissue loss leads both to disfiguring deformity, which requires reconstruction, and to disability, which requires rehabilitation. The Infectious Diseases Society of America (IDSA) recommends early broad-spectrum empiric coverage to cover the possibility of polymicrobial infection [53]. Regimens include vancomycin (30 mg/kg/day) or linezolid (600 mg IV/PO every 12 h) plus piperacillin-tazobactam (3.37 g IV every 6–8 h) or a carbapenem (1 g IV every 6–8 h) or ceftriaxone (2 g IV every 6 h) and

Table 19.2 Microbiology in necrotizing fasciitis

Type of necrotising fasciitis	Organism(s)
Type I (polymicrobial or mixed)	Aerobic and anaerobic bacteria
Type II	Group A beta-hemolytic streptococcus (GAS) with or without Staphylococcus species
Type III	Gram negative organisms; Klebsiella, Aeromonas, and Vibrio species

metronidazole (500 mg IV/PO every 6 h). In cases with proven group A streptococcal infection, penicillin (2–4 MU every 6–8 h IV) and clindamycin (600–900 mg/kg every 8 h) are recommended. Patients with NSTIs commonly exhibit signs and symptoms of systemic toxicity, and, regardless of care, mortality rates have been reported from 6% to 76% and more recently 25% [47]. Early intensive care unit admission is indicated for monitoring and supportive care [49, 50].

19.3.3 Infections Exacerbated during Pregnancy

19.3.3.1 Urinary Tract Infections

Pregnant women have an increased risk for urinary tract infections between 6 and 24 weeks' gestation [54]. Urinary tract infections are classified as asymptomatic bacteriuria (ASB), acute cystitis, and pyelonephritis. The American College of Obstetrics and Gynecology recommends screening women for ASB during their first pre-natal visit and repeating a urine culture during the last trimester [55]. ASB is defined as $>10^5$ colony-forming units per mL of urine. If it remains undiagnosed, ASB can lead to the development of acute cystitis and pyelonephritis in 30 and 50% of pregnant women, respectively [56, 57]. Pregnant women have a 20–30-fold increase of developing pyelonephritis when diagnosed with ASB in early pregnancy [58]. Acute cystitis is differentiated from asymptomatic cystitis by the presence of dysuria, frequency, and urgency. Pyelonephritis is diagnosed when genitourinary symptoms are accompanied by systemic manifestations such as fever, chills, nausea, vomiting, and flank pain. If left untreated, maternal pyelonephritis can lead to severe maternal sepsis [57, 58].

The organisms commonly causing urinary tract infections in pregnant women are generally similar to those observed in non-pregnant women. *Escherichia coli* is the most common, causing 70–90% of cases [59]. *Proteus mirabilis* and *Klebsiella pneumonia* are also common causes. Gram-positive infections are less common, but group B streptococcus has been isolated in 7–10% of the cases of ASB in pregnancy [60, 61].

In symptomatic women, following urine sampling, antibiotics should be started empirically to cover the more common organisms. Coverage can be narrowed once urine culture results become available. Treatment options include cephalosporins (cephalexin 250 mg PO 2–4 times a day), nitrofurantoin (50–100 mg four times daily), and fosfomycin (one 3 g sachet) [54]. Fluoroquinolones and sulfonamides should be avoided if possible due to potential harm to the fetus and potential emergence of resistant organisms. However, if indicated, maternal care is the priority. Furthermore, growing evidence suggests that these antibiotics are safe for the fetus and can be used if necessary based on antibiotic sensitivities of the causative organism [54, 62–64]. The duration of antibiotic treatment for asymptomatic bacteriuria, acute cystitis, or pyelonephritis has not been determined for pregnant women [65]. Given the ongoing risk of recurrence during pregnancy (4–5%), treatment with oral antibiotics is given for a longer duration than in the general population (i.e., 7–10 days) [54, 59].

Women with pyelonephritis should be managed and followed closely; the patient should defervesce within 24–48 h of initiation of antibiotic therapy. Those who deteriorate clinically, remain febrile, and develop signs of worsening systemic infection should be admitted for intravenous antibiotic therapy and hydration. Women who fail to improve or have recurrent infections should undergo renal imaging (ultrasonography or intravenous pyelogram) to assess for pyelonephritis or other structural abnormalities [66, 67].

Pyelonephritis is the leading cause of septic shock in pregnancy, followed by renal calculi. The latter, however, is a rare phenomenon [67, 68]. The incidence of nephrolithiasis in pregnancy ranges from 1:200 to 1:1500 [68–71]. Mortality from maternal urosepsis is rare. Management consists of adequate volume resuscitation, antibiotics, and rarely, surgical interventions to achieve source control. Most renal stones pass on their own, making the need for ureteroscopy or percutaneous nephrostomy drainage infrequent. Invasive treatment is suggested in cases with unremitting pain, persistent fever, worsening renal function, or septic shock [70, 71].

19.3.3.2 *Listeria Monocytogenes*

Listeria monocytogenes is a facultative aerobic Gram-positive rod which may cause food-borne illness weeks to months after ingestion. Pregnant women are particularly prone to *Listeria* infection, accounting for up to 27% of all listeria infections. Typically they experience only mild flu-like symptoms, malaise with or without a headache, gastroenteritis, or diarrhea which often contributes to missed diagnosis during pregnancy [72, 73]. If left untreated, *Listeria* infection during pregnancy may lead to miscarriage, septic abortion, stillbirth, premature delivery, or life-threatening infection of the newborn [72, 74]. Rarely, the maternal condition may deteriorate to full-blown meningoencephalitis, chorioamnionitis, or, potentially, sepsis [75]. Systemic disease may be accompanied by the appearance of multiple abscesses and granulomas. *Listeria* is associated with high mortality; 20–50% in immunocompromised individuals and, to a lesser extent, in pregnant woman [72, 75].

During a listeria outbreak, pregnant women with a fever of unknown origin should have blood cultures drawn to assess for bacteremia. Pregnant women presenting with diarrhea (regardless of additional symptoms) should also submit stool for listeria cultures. The decision to initiate treatment is based upon clinical judgment. However, the threshold for treatment should be low given the difficulties of diagnosing severe maternal illness and the fact that bacteremia can lead to maternal neurological compromise and sepsis and transplacental fetal infection [76].

Ideally, treatment of listeriosis during pregnancy should be guided by an expert in infectious diseases. In milder cases (e.g., febrile gastroenteritis), the recommended treatment is oral amoxicillin (500 mg three times daily). Treatment of women with severe disease involving CNS involvement or endocarditis should also include the addition of gentamycin (goal peak of 3–5 mcg/mL and a trough less than 1 mcg/mL) for synergy [77]. Listeriosis with bacteremia in pregnancy is treated with intravenous ampicillin (2 gm q4 hours) or intravenous trimethoprim-sulfamethoxazole (10–20 mg/kg daily) in cases of severe penicillin allergy. In extreme cases, the pregnant woman may require desensitization therapy. Sulfonamides are generally not teratogenic [63, 64]; however, trimethoprim is a folic acid antagonist and its use during the first trimester of pregnancy has been associated with neural tube and cardiovascular defects [76]. It has also been suggested to cause kernicterus, but this has not been proven [78]. Women who are unable to receive either of the agents mentioned above can be treated with meropenem (2 g IV every 8 h) and vancomycin. This requires close monitoring of treatment efficacy. The duration of treatment during pregnancy remains unstudied and should be based on the clinical response. In most cases, 2 weeks of treatment is sufficient for bacteremia and 3–4 weeks for CNS infection.

19.3.3.3 Toxoplasmosis

Acute toxoplasmosis infection is caused by the intracellular protozoan *Toxoplasma gondii*. Transmission to humans occurs through ingestion of undercooked meat, contact with oocyte-containing cat faeces, and by vertical transmission. Prevalence rates vary worldwide, with higher rates seen in countries with tropical climates or with a culinary interest in undercooked meat [79, 80]. Universal screening is not recommended in areas of low prevalence [81, 82].

Pregnant women may be asymptomatic and have a flu-like illness or regional lymphadenopathy in acute infection [83]. Immunocompromised women may develop severe manifestations including encephalitis, myocarditis, pneumonitis, or hepatitis.

Diagnosis of acute infection in pregnancy is challenging and usually requires two serological tests 2 weeks apart demonstrating a fourfold increase in IgG antibody titer. Hence, a high index of suspicion is required. Treatment may initially be empirical in cases of critical illness if the clinical story and findings are highly suggestive. If acute infection is suspected, spiramycin should be administered as soon as possible. Treatment with pyrimethamine, sulfadiazine, and folinic acid of women should be administered in women who are at high risk of fetal infection. Pyrimethamine is teratogenic and should be avoided during the first trimester [82].

Fetal infection—Primary maternal infection carries the greatest risk to the fetus, although cases of fetal transmission have been described in immunocompromised women with reactivation of chronic infection [84]. Following infection, the placenta becomes a reservoir for toxoplasmosis with the risk of fetal transmission increasing from approximately 6% in the first trimester to 72% by the third [81]. PCR of amniotic fluid is highly sensitive and specific for diagnosis of fetal infection and should be performed after 18 weeks' gestations or 4 weeks after acute maternal infection. Characteristic fetal ultrasound findings include intracranial calcification, microcephaly, hydrocephalus, hepatosplenomegaly, ascites, and severe intrauterine growth retardation [85].

19.3.4 Malaria

Malaria is caused by infection with *Plasmodium* species. *P. falciparum* and *P. vivax* are the most common causative agents, with most global deaths caused by *P. falciparum* [86]. Malaria is an important cause of maternal and infant morbidity and mortality. It is estimated that 10,000 maternal deaths and upwards of 200,000 newborns die annually from pregnancy-associated malaria. Epidemiologic studies estimate that the overall prevalence of *Plasmodium* infection in highly endemic areas is approximately 25% (1 in 4 women); this proportion is likely underestimated based on diagnostic studies and sensitivity. The prevalence of malaria outside sub-Saharan Africa is estimated to be lower, 1.8–17.4%. However, in this population, both maternal and fetal outcomes are worse; lacking prior exposure to the disease there is less opportunity for immunity [87–89].

The signs of infection are non-specific and vary depending on several factors such as maternal age, the degree of immunity, gravidity (pauci vs. multiparous), endemicity, and species. Some women, especially in endemic areas, are asymptomatic. Others present with fever, chills, nausea, vomiting, diarrhea, abdominal pain, headaches, myalgia, jaundice, and cough [87].

Pregnant women, especially in the first trimester, are more susceptible to malaria. Cell-mediated immunity is decreased as cortisol increases [87, 90], which allows the placenta to form. During this period, *P. falciparum*-infected erythrocytes are sequestered and bind to the vascular endothelium of various organs, which can cause more severe disease, especially in the primigravida patient [87–90]. The sequestration of the parasite-infected erythrocytes is especially high in the placental intervillous spaces.

In high endemic areas, few women present with fevers. Rather, the maternal inflammatory response to this sequestration as the pregnancy progresses causes marked injury and scarring to the placental basement membrane. This interferes with blood flow across the placenta and impedes nutrient supply to the fetus. This placental damage is the main mechanism for miscarriages, intrauterine-growth retardation, preterm birth, and low birth weight [90].

Any patient presenting with fevers in endemic regions or returning from an endemic region should be tested for malaria. Parasitemia should be assessed with a peripheral smear, Giemsa-stained, or rapid diagnostics [87]. A negative peripheral smear doesn't rule out malaria infection or parasitemia, as patients could have low parasitic counts or placental parasites without evidence on peripheral smear. Placental infection can be diagnosed after birth by histological examination [87, 89, 90]. The gold standard for detection of malaria is polymerase chain reaction (PCR), but its utility in high endemic areas is questionable, and its clinical importance in submicroscopic infections is yet to be determined. Therefore its use is not routinely recommended. Rapid diagnostic tests are more commonly used for programs of diagnosis, treatment, and prevention of malaria in high endemic areas [86, 88].

Acute malaria with signs of organ dysfuntion is deemed severe malaria. Severe malaria can present with hypoglycemia, pulmonary edema, respiratory distress, cerebral edema, seizures, and severe anemia [91, 92]. The treatment of severe malaria is mainly supportive; however, expedient treatment with parenteral antimalarial therapy in the gravid patient is essential to affect the outcome [92]. Artesunate IV/IM 2.4 mg/kg should be administered at hours 0,

12, 24, and 48. Subsequently, oral therapy of atovaquone-proguanil, doxycycline (if postpartum), clindamycin, or mefloquine should be administered [91, 92]. If artesunate is not available, artemether IM is preferred to quinine in later pregnancy because of the high risk of hypoglycemia with quinine [92].

Care should be taken during administration of fluids. While there is no literature specifically regarding pregnant women, a study of early fluid administration in critically ill septic children due largely to severe malaria showed worse outcomes in those receiving larger amount of fluids, presumably due to worsening of cerebral edema. For more details regarding fluid administration, see Chap. 7.

19.3.5 Fetal Considerations in Maternal Infections

Maternal infections and sepsis have an increased risk of pre-term delivery. Antenatal corticosteroid therapy (ACS) has shown to improve newborn outcomes when given between 24 and 34 weeks' gestation when delivery is within 7 days [93]. When caring for a gravid patient with overwhelming infection, there may be hesitation in giving an additional immunosuppressive drug. Corticosteroid use during overwhelming infection and sepsis has been debated. Studies over the years have shown conflicted finding as to benefit and harm [94, 95].

In high-income countries, there is little debate over the maternal safety of a single dose of either betamethasone or dexamethasone as ACS therapy in the 24–34-week gestation period. It appears that this single dose does not increase infection even in the presence of prolonged rupture of membranes or sepsis [93, 96]. Betamethasone is considered a weak immunosuppressive with short-term use even though it has a longer half life than dexamethasone [93]. Of note, hydrocortisone does not cross the placenta and therefore does not affect fetal lung maturity [96]. In low- and middle-income countries, however, there is some debate of the benefits of ACS in enviroments where the gestational age estimation is not reliable, the perinatal care is not available, and risks of maternal infections may be higher [97, 98]. Recommended WHO pre-requisites for antenatal corticosterid use include accurate gestational age estimation, no evidence of maternal infection, and adequate peripartum care for both the mother and infant. The WHO recommends not giving ACS to patients with documented chorioaminonitis but relates that the recommendation is based on very low quality evidence [99].

An additional consideration for the fetus at risk for pre term delivery is the administration of magnesium sulfate to the mother which acts as a fetal neuroprotective agent in gestations less than 32 weeks. One dosing regimen is 4gram load IV. Care must be taken in renal insufficency, as magnesium is renally excreted [100].

19.4 Conclusions

Maternal sepsis is the third leading cause of maternal death. The gravid patient is more susceptible to infections both because of the physiologic changes of pregnancy and because of the unique pathology that occurs with pregnancy. Diagnosis of infection and sepsis in the pregnant patient is more difficult as the signs and symptoms of infection and sepsis may be obscured by the physiology of pregnancy. The clinician should have a high index of suspicion and know the expected normal physical and laboratory values at each stage of pregnancy. Coordination with a multidiscinplinary team is invaluable.

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