Viral Infections in Obstetric Critical Care

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**Bullet Points**

- Viral infections are common causes of critical illness in pregnancy and may be more severe than in the nonpregnant woman.
- Influenza viruses are the most common infectious cause of acute respiratory failure in pregnancy.
- PCR-based diagnostics are preferred when testing for influenza, and early treatment with neuraminidase inhibitors reduces mortality.
- Bacterial superinfection is common in severe viral respiratory infection. In cases of respiratory failure, empiric antibacterial therapy directed against pneumococci and staphylococci is advisable pending culture results.

- Viral encephalitis may be due to many different pathogens, but empiric intravenous acyclovir should be administered early to all pregnant women with suspected viral encephalitis until HSV and VZV infections have been excluded.
- There are limited effective therapies for viral encephalitis due to non-herpesviruses. IVIG, methylprednisolone, or plasmapheresis may be considered for acute disseminated encephalitis (ADEM).
- Fulminant hepatic failure (FHF) in pregnancy should receive treatment with N-acetylcysteine, in addition to any specific antiviral therapies if available.
- Specific therapies exist for acute viral hepatitis due to hepatitis B and herpesviruses (HSV, VZV, CMV, and possibly EBV).
- Dengue, Zika, and chikungunya virus infections have overlapping regions of endemcity and similar clinical syndromes.
- Severe dengue is managed supportively with fluids, organ support, and rarely blood products. Glucocorticoids are not effective in the treatment of dengue.
17.1 Introduction

Viral infections are common in pregnancy, with consequences for the health of both the fetus and the expectant mother. The exposures of a pregnant woman to viruses may be comparable to that of the larger community and are essentially unchanged from that of her prepregnancy self. However, changes in host immunology increase the pregnant woman’s risk of disease as well as the severity of that disease following exposure to a circulating virus.

The immunologic changes of pregnancy are described in greater detail in Chap. 15. To briefly summarize, cell-mediated immunity typically downregulates in the third trimester and early postpartum period, increasing the woman’s risk of infection by certain pathogens, including bacteria (e.g., listeriosis), fungi (e.g., coccidioidomycosis) and, most commonly, viruses. Physiologic changes inherent to pregnancy, such as decreased functional residual capacity in the respiratory system, may additionally increase the risk of severe disease requiring critical care following such an infection.

Although numerous viruses may infect pregnant women, infections of the respiratory tract, the central nervous system, and the liver are most likely to lead to critical illness. In addition, arboviral infections may produce severe syndromes that are becoming more common in our increasingly globalized world. It is unusual for the attending obstetrician, intensivist, or even infectious diseases specialist to know the specific etiology of a viral infection at the time of presentation. Therefore, the presenting syndrome should guide initial workup and empiric therapy while awaiting a specific diagnosis. In general, viral infections leading to critical illness do not specifically require expedited delivery of the fetus or consideration of pregnancy termination, unlike some other causes of obstetric critical illness (e.g., the HELLP syndrome, massive uterine hemorrhage). In addition, certain viral infections are associated with a high risk of transmission to healthcare staff, and precautions must be implemented to reduce risk to caregivers and other patients.

Viral infections associated with significant fetal abnormalities, such as rubella or cytomegalovirus, rarely produce life-threatening maternal disease and will not be discussed in detail here, except as they relate to maternal illness.

17.2 Influenza and Other Respiratory Viruses

Severe acute respiratory infection (ARI) is among the most common illnesses leading to intensive care unit admission among pregnant women, leading to 25% [1] of cases of respiratory failure and 12% of deaths [2] of pregnant women. A wide diversity of RNA and DNA viruses cause ARI in pregnant women. Influenza viruses, in particular, have a unique virulence: pregnant women represented 5% of cases of acute respiratory distress syndrome and 6–13% of deaths [3, 4] in the 2009–2010 H1N1 influenza epidemic. Overall mortality for pregnant women with severe influenza requiring critical care admission is estimated to be as high as 24% [1, 5], particularly in women requiring mechanical ventilation, despite a less than 10% overall mortality rate of pregnant women with acute respiratory failure in developed countries [1] (see Chap. 23).

Extracorporeal membrane oxygenation (ECMO) has been used successfully in pregnant women with influenza, with a meta-analysis suggesting a maternal survival rate of 75% and a 70% rate of live birth, although this is limited by a small number of included studies [6] (see Chap. 14).

The burden of viral ARI has become easier to estimate in recent years, with the advent of widely available and rapid molecular diagnostic testing in resource-rich settings. Polymerase chain reaction (PCR)-based testing is the diagnostic test of choice for suspected viral ARI in a critically ill patient, regardless of pregnancy. These specimens may be obtained at the bedside via nasopharyngeal, oropharyngeal, or endotracheal aspiration and should be obtained routinely for hospitalized women with compatible clinical syndromes (i.e., fever, cough, airspace opacities, or hypoxemia). Existing commercial tests such as the GeneXpert Xpert Flu assay (Cepheid, Sunnyvale, California, USA) have a sensitivity and specificity for the detection of influenza in excess of 95% [7]; multiplex assays such as the FilmArray RP panel (BioFire Diagnostics, Salt Lake City, Utah, USA) detect a wider variety of respiratory viruses but at a potentially lower sensitivity of approximately 85% [8]. Rapid antigen testing for influenza is an alternative, but the lower sensitivity of these assays (60–65%) reduces their utility, especially with negative test results [9].
Evaluation for suspected viral ARI in the critically ill pregnant women includes PCR testing for relevant viruses where available, in addition to chest radiography and bacterial cultures of sputum. If multiplex PCR is not readily available, either influenza-specific PCR or rapid antigen testing is an alternative. If no such viral diagnostics are available, then empiric antiviral therapy for women with a compatible syndrome should be strongly considered.

Antiviral therapy with the neuraminidase inhibitor oseltamivir is associated with improved outcomes in severe influenza, based on retrospective studies that have included pregnant women; therapy within the first 48 h of symptom onset is preferred [10, 11]. There are no prospective studies of oseltamivir use in critically ill pregnant women. A retrospective series conducted by US Centers for Disease Control and Prevention (CDC) studied pregnant women requiring hospitalization during the 2009 H1N1 pandemic; in this study, women who received early neuraminidase inhibitor treatment (<2 days after the onset of symptoms) had decreased rates of ICU admission (9.4% versus 56.9%) and of death (0.5% versus 27%) compared with women treated more than 4 days after symptom onset, with the greatest risk noted in women in the third trimester [12]. Follow-up data on children born to pregnant women treated with oseltamivir have not shown evidence of drug-specific fetal complications [13, 14]. The standard dose of 75 mg twice daily for 5 days is given either orally or via an enteric tube [15]. Higher doses (150 mg twice daily) or more prolonged courses (up to 10 days) have not been associated with improved survival in either critically ill patients or pregnant women [16, 17].

In patients for whom enteral medications are not possible, peramivir is an intravenous neuraminidase inhibitor that is an acceptable alternative to oseltamivir. Peramivir is normally administered as a single 600 mg dose but may be considered for 5 days of therapy in severely ill patients, based on limited data. Specifically in pregnancy, there is some evidence of increased peramivir clearance which may support the more extended course of treatment [18–21]. Oseltamivir- and peramivir-resistant strains of influenza are well-described but unusual [22–24]. For such cases, intravenous zanamivir may be considered as an investigational agent (available via GlaxoSmithKline at gskclinicalsupportHD@gsk.com) [25, 26]. A small number of pregnant women have received intravenous zanamivir, but outcomes in those women have not been reported [26]. Inhaled zanamivir is not recommended in intubated patients [15].

As of 2020, there is an ongoing pandemic due to the Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), leading to a clinical syndrome known as coronavirus disease 2019 (Covid-19). At the time of this writing, clinical evidence regarding the severity of Covid-19 in pregnant women is limited to case series and retrospective observational data. An early case series from Wuhan, Hubei Province, China, at the onset of the pandemic described the course of 116 pregnant women with Covid-19; 8/116 (6.9%) of affected women had severe pneumonia requiring ICU admission, of whom 2/116 (1.7%) required endotracheal intubation and 1/116 (0.9%) required ECMO [27]. A systematic review of 33 studies more recently reported a total of 385 pregnant women with Covid-19 infection, of whom 17/385 (4.4%) required ICU admission and 6/385 (1.6%) required mechanical ventilation, with one death identified (1/385, 0.26%) [28]. Overall, the mortality risk of Covid-19 in pregnancy seems comparable to that of the general population, unlike the specific increased risk of influenza, although limitations in data quality at this phase of the pandemic require clinicians to be cautious in interpreting this information. Vertical transmission seems rare (and difficult to exclude from the possibility of iatrogenic, rather than maternal origin) [29].

Therapy for Covid-19 in pregnancy is presently limited to supportive care. Empiric therapy for community-acquired pneumonia is recommended for mechanically ventilated patients; it is reasonable to include pregnant women in this practice. Hydrocortisone for vasopressor-resistant shock, low tidal volume ventilation, and consideration of intravenous methylprednisolone for the acute respiratory distress syndrome (ARDS) are also recommended, in accordance with routine critical care practice [30]. A large number of investigational agents are under study for Covid-19, including novel antiviral agents such as remdesivir, inhibitors of the inflammatory cascade such as tocilizumab, and repurposed agents such as hydroxychloroquine. Remdesivir,
a nucleotide inhibitor of viral RNA-dependent RNA polymerase, has been administered to pregnant women with Covid-19 through compassionate use programs, but data on their outcomes are not currently available. Remdesivir has been administered safely to pregnant women with Ebola virus disease in a randomized trial, however, without evidence of increased risk [31].

There are limited specific antiviral therapies available for other respiratory viruses. Data in pregnancy is invariably limited, with much of the available evidence derived from the management of patients with hematologic malignancy. Ribavirin (administered intravenously, orally, or inhaled) has in vitro activity against several non-influenza respiratory viruses including adenoviruses, human metapneumovirus, respiratory syncytial virus (RSV), and parainfluenza; however, clinical evidence for its utility in patients without malignancy is limited [32–34]. Ribavirin has historically been considered to be contraindicated in pregnancy due to concern for teratogenicity as well as hemolysis. More recent data of ribavirin when used for chronic hepatitis C infection shows little direct evidence of teratogenicity, although the doses used are smaller than those used for critically ill patients [35]. As such, the use of ribavirin may be appropriate as a lifesaving intervention for the mother [35].

Cidofovir, a long-acting intravenous nucleotide analogue, may be considered for severe adenovirus infections, although embryotoxicity and fetal harm have been seen in animal studies at doses that are maternally toxic, and it is associated with nephrotoxicity [32, 36, 37]. Enterally administered brincidofovir is a produg of cidofovir that may have an improved safety profile in terms of nephrotoxicity [38]. Data regarding teratogenicity is currently lacking due to exclusion of pregnant women from studies using this drug for treatment of Ebola.

Intravenous immune globulin given in combination with aerosolized ribavirin may be preferred for severe RSV infection [39]. Palivizumab, an anti-RSV monoclonal antibody, is recommended only for prophylaxis and not for therapy; therefore it is not a relevant option once a pregnant woman is critically ill. Adjunctive glucocorticoids appear harmful in severe influenza and are not recommended [40].

Bacterial superinfection is common in severe viral ARI. Pneumococci and staphylococci (including methicillin-resistant Staphylococcus aureus) are frequent coinfections in severe influenza infections, occurring in 25–50% of critically ill patients [41]. The rate of post-influenza bacterial pneumonia in critically ill pregnant women does not appear to be higher than that in nonpregnant women (and may in fact be somewhat lower) [42]. Regardless, empiric therapy for community-acquired bacterial pneumonia is advisable in severe ARI until bacterial superinfection can be excluded, including coverage directed against MRSA in patients with influenza, metapneumovirus, or respiratory failure.

**Staff protection:** Respiratory viruses are contagious to hospital staff and to other patients. Appropriate precautions must be taken in the management of all patients infected with respiratory viruses to reduce the risk of transmission. In general, patients with suspected or confirmed respiratory viruses require the use of dedicated hospital room separated from other patients; if this is not feasible, cohorting of patients with a common infection (i.e., influenza A with other influenza A patients) may be acceptable. Seasonal influenza vaccination should be encouraged for all hospital staff, and clinical staff should wear masks when caring for these patients [43]. Standard surgical masks appear to be acceptable; studies comparing the risk of influenza acquisition showed comparable protective efficacy between surgical masks and N95 respirators, although N95 masks may be preferred in cases of airway procedures known to produce aerosols, i.e., endotracheal intubation and bronchoscopy [44, 45].

Certain highly pathogenic respiratory viruses require higher levels of respiratory protection, including the use of negative pressure isolation rooms, N95 respirators, or powered air-purifying respirators (PAPRs). Such viruses include SARS-CoV-2, related coronaviruses such as the Severe Acute Respiratory Syndrome-associated coronavirus (SARS-CoV), and the Middle East Respiratory Syndrome-associated coronavirus (MERS-CoV), as well as highly pathogenic avian influenza strains (H5N1, H7N9) [46]. The Infectious Diseases Society of America (IDSA) has recently published interim guidance on the appropriate use of personal protective equipment for staff safety in the care of patients with Covid-19; such recommendations are likely to be broadly applicable to other highly pathogenic respiratory viruses [47].
17.3 Neurotropic Viruses

Encephalitis is the typical presenting syndrome among pregnant women with neurologic viral infections requiring ICU admission and must be considered in women with unexplained delirium, fever, or focal neurologic signs including new-onset seizures. A specific pathogen may be elusive for many patients with suspected viral encephalitis. In all cases, infectious disease and neurology specialty consultation should be obtained.

Cerebrospinal fluid (CSF) analysis is required for the diagnosis of encephalitis. A lymphocyte-predominant pleocytosis with relatively normal protein and glucose levels is typical, although neutrophil predominance may be seen in early infections. Elevated CSF erythrocyte counts in the absence of traumatic lumbar puncture may be noted in cases of herpes simplex virus type 1 (HSV-1) encephalitis [48]. Bacterial infections, most notably Listeria monocytogenes, may present similarly with a comparable CSF lymphocytosis. Magnetic resonance imaging (MRI) with gadolinium enhancement may demonstrate pathogen-specific features that can aid in the diagnosis. HSV-1, for example, commonly localizes to the temporal lobes. None of these features are pathognomonic, but they may support an existing suspicion or guide further evaluation. Although gadolinium is recommended for use in pregnancy only if the benefits of imaging outweigh potential risks, there is currently no evidence of adverse neonatal effects of gadolinium in human studies [49].

Nucleic acid amplification testing (NAAT), such as PCR, of CSF is the mainstay of diagnosis. Qualitative PCR for HSV, varicella-zoster virus (VZV), and enteroviruses is widely available and confirms the diagnosis [50, 51]. Less common neurotropic herpesviruses, such as human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), may be detected in the CSF but are most often reactivations of latent infections in the setting of a different severe illness; in these cases, quantitative PCR may be necessary to determine causality [52, 53]. Commercially available NAAT platforms, such as the FilmArray Meningitis/Encephalitis panel (BioFire Diagnostics), can rapidly detect a wide array of bacterial and viral pathogens and can minimize the duration of unnecessary empiric antimicrobial therapy [54].

Empiric therapy for encephalitis in pregnancy should include intravenous acyclovir, 10 mg/kg every 8 h [55]. Early empiric therapy is critical, and treatment must not be delayed while awaiting the results of confirmatory assays. Although acyclovir is generally safe, it may crystalize in the renal tubules in settings of low urine output; volume expansion with isotonic crystalloid may be considered in order to maintain adequate urine output [56]. In situations where intracranial hypertension and cerebral edema are a concern, hypertonic saline may be an alternative to isotonic saline to maintain urine output, although there is no prospective data to guide this practice. Treatment with acyclovir should continue until HSV and VZV have been excluded; repeat testing at 3–7 days may be considered in patients with a compatible syndrome and imaging findings but an initially negative CSF PCR [57]. Empiric antibacterial therapy with vancomycin, ceftriaxone or cefotaxime, and ampicillin (for empiric listeriosis coverage) is recommended until bacterial infection can be excluded, either by negative cultures after 48 h of incubation, a negative CSF NAAT, or with the verification of an alternate diagnosis [55, 58].

For confirmed CMV encephalitis, intravenous ganciclovir (pregnancy Category C) 5 mg/kg IV every 12 h may be given in combination with foscarnet (Category C) 90 mg IV every 12 h, although foscarnet carries a significant risk of nephrotoxicity and the combination of these two agents is best validated in HIV-infected persons [55]. Primary CMV infection in pregnancy has been associated with a very high risk of vertical transmission (30–40%) and is the most common viral cause of neonatal neurosensory hearing loss and mental retardation [53–55]. As such, the risk-benefit ratio to both the mother and the unborn child usually justifies treatment despite the potential teratogenicity of both treatment drugs.

Numerous other viruses may occasionally present as encephalitis, including measles (rubeola), mumps, lymphocytic choriomeningitis virus, the equine encephalitides, and others beyond the scope of this chapter. There are limited specific therapies
for these other viral encephalitides. Intravenous immunoglobulin (IVIG) has been utilized with limited success in West Nile virus and Japanese encephalitis virus infections [59, 60]. Postinfectious acute disseminated encephalomyelitis (ADEM) may benefit from treatment with either IVIG or plasmapheresis, in combination with intravenous methylprednisolone [61]. Plasmapheresis can affect maternal hemodynamics and placental blood flow during pregnancy but may improve maternal outcome in ADEM [59].

17.4 Hepatitis and Herpes Viruses

Fulminant hepatic failure (FHF) is rare in pregnancy. Uniquely obstetric disorders, such as HELLP and acute fatty liver of pregnancy, are described elsewhere (see Chap. 33). Worldwide, viral hepatitis is the most common cause of FHF, although acetaminophen (paracetamol) overdose is more common in some industrialized countries such as the United States and the United Kingdom [62]. Supportive care for severe viral hepatitis is similar to that for other causes of FHF, including intracranial pressure management, control of bleeding and coagulopathy, endotracheal intubation and mechanical ventilation if necessary, and management of hemodynamics and secondary infections [62]. N-acetylcysteine (NAC) is the cornerstone of therapy for acetaminophen-induced FHF, but empiric use of NAC for all-cause FHF may be of benefit, especially when the initial diagnosis is in doubt [62, 63]. NAC has no proven risk in pregnancy and has even been associated with improved pregnancy outcomes in both animal models and humans [63–65]. For all cases of viral FHF, liver transplantation may be indicated, and FHF cases should be referred promptly for transplant evaluation [64, 65]. Successful deliveries of healthy infants have occurred even following maternal liver transplantation, and transplantation referral is not an absolute indication for pregnancy termination [66, 67].

Acute hepatitis A (HAV) has declined in incidence in the general and obstetric populations with the advent of widespread immunization [68], although cases remain common in developing settings as well as in localized outbreaks. Acute hepatitis B (HBV) is more strongly associated with fulminant hepatic failure than HAV [68–70], but it too has seen a decline in incidence due to vaccination [71]. Unlike HAV, specific therapies exist for HBV, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF, similar in efficacy to TDF but with less long-term nephrotoxicity), telbivudine, entecavir, and lamivudine. Among these agents, TDF, TAF, and entecavir are generally considered the preferred agents and may be initiated safely during pregnancy [71, 72]. Tenofovir is one of the cornerstones of HIV therapy and has been safely administered to HIV-infected pregnant women for many years. Given the high risk of HBV transmission following percutaneous exposure, all hospital staff should be immunized against HBV; HAV vaccination is also highly effective and is advisable for all patient care staff.

Hepatitis C therapy has been revolutionized in the past decade, with modern antiviral therapy producing durable cure rates of greater than 95%, although cost may be a limiting factor in some settings. Acute hepatitis C rarely causes symptomatic disease but may be diagnosed during the course of pregnancy [73]. Advanced HCV liver disease is physiologically incompatible with pregnancy. Treatment of chronic hepatitis C is rarely an emergency. Hence in the event of diagnosis of HCV, delay of treatment until delivery is safe. In this situation the goal is prevention of long-term complications rather than saving the mother’s life. Deferment of hepatitis C therapy until after delivery is actually advised, given the lack of safety and efficacy data during pregnancy at present [74].

Hepatitis E (HEV) has a global distribution but is markedly more common in developing countries. HEV is responsible for over 25% of cases of acute non-A/non-B hepatitis in much of northern and eastern Africa as well as western, central, and south Asia, with a lower prevalence in industrialized countries [75]. Like HAV, HEV is transmitted via contaminated food and water and produces a usually self-limited disease in adults, but acute HEV in pregnancy is uniquely severe, with 15–20% progressing to FHF; of those women with HEV-associated FHF, mortality may exceed 60% [75–78]. Obstetric complications (e.g., hemorrhage, preterm delivery, intrauterine fetal death, stillbirth) are also significantly more common [76, 79, 80] during acute HEV infection. Diagnosis of
acute HEV infection is made by detection of anti-HEV IgM from patient serum. Therapy with ribavirin has been utilized in immunocompromised patients in whom HEV infection has become chronic, but there are limited data in the immunocompetent or pregnant patient [5]. Despite this lack of data, the use of ribavirin in the critically ill pregnant woman with acute HEV infection is advocated by some experts, especially in light of the limited fetal toxicity of ribavirin described previously [35, 81].

Herpesviruses, including HSV types 1 and 2, VZV, CMV, and EBV have all been implicated in rare but severe infections during pregnancy. Primary HSV infection rarely leads to severe illness, with the exceptions of encephalitis, as described above, and a rare but severe hepatitis that may be distinguished from other hepatitides by the presence of mucocutaneous lesions, although these lesions may absent or delayed in many cases [82]. Primary VZV infection in pregnant women is similarly associated with both encephalitis and a rare but severe hepatitis. Serologic testing is rarely useful in the diagnosis of HSV or VZV infections, given the high prevalence of antibodies to both in the general population.

HSV and VZV may be distinguished clinically from other viral hepatitides by the presence of a typical vesicular exanthem (typically cutaneous in VZV and mucocutaneous in HSV) although these lesions may absent or delayed in many cases [82]. As with other severe forms of HSV and VZV infection, treatment with IV acyclovir at 10 mg/kg IV every 8 h is recommended. In both cases, definitive diagnosis is based on liver biopsy, although the isolation of either virus by PCR from blood is strongly consistent with acute infection and is sufficient to start therapy [83–85]. The risk of liver biopsy in pregnancy appears to be low; pregnancy outcomes for women undergoing liver biopsy are similar to those of women with comparable degrees of liver disease who do not undergo biopsy, with the exception of an increased risk of earlier delivery (by 6 days) and smaller size for gestational age (RR = 5.2) [86].

Maternal mortality is high in both HSV and VZV hepatitis. In the general population, the mortality is approximately 75% for HSV [87], but published data suggests that mortality in pregnant woman, while still high, may be lower than 40% [88]. In addition, HSV and VZV may lead to significant neonatal morbidity. Maternal and newborn antiviral therapy is also indicated to reduce the risk of neonatal herpes simplex in HSV. The risk of caesarean section to maternal health during critical illness may make caesarean delivery inadvisable, depending on the health status and hemodynamic stability of the mother. VZV is associated with congenital varicella syndrome, with musculoskeletal deformity, liver calcifications, facial scarring, and microcephaly, and perinatal VZV infection with widespread visceral involvement; both syndromes carry a high mortality rate for the infant.

Staff protection: Herpes viruses with cutaneous or respiratory manifestations, including HSV and VZV, may pose risks of transmission to hospital staff. Patients with active mucocutaneous lesions due to HSV should be placed into contact precautions, with hospital staff wearing gowns and gloves during patient care until all lesions are dry and crusted. Patients with active cutaneous or respiratory VZV infections should be placed into contact precautions as above, in addition to the use of a negative pressure isolation room and surgical masks by all staff. Hospital staff without documented VZV immunity (either by prior infection or immunization) should not care for VZV-infected patients or enter the patient’s room. For those nonimmune staff members accidentally exposed to a VZV-infected patient, postexposure prophylaxis with valacyclovir and/or varicella hyper-immune globulin (VariZIG, Cangene Corporation, Winnipeg, Manitoba, Canada) is recommended [89].

17.5 Arboviral Infections

With changes in global climate and increases in international travel, insect-borne viral infections are becoming more common in temperate climates [90, 91]. Dengue, Zika, and chikungunya virus infections are particularly endemic in tropical countries, share a common day-biting vector (Aedes aegypti and occasionally Aedes albopictus mosquitoes) that favors urban and semi-urban areas, and produce similar febrile syndromes that may lead to severe maternal and fetal outcomes.
Dengue infections are produced by four closely related single-stranded RNA viruses of the flavivirus family, designated DENV1-DENV4. Infection with a single dengue subtype most often leads to subclinical disease or to a symptomatic illness consisting of fever, rash, and myalgia. Leukopenia, thrombocytopenia, and elevations in liver transaminases are typical laboratory findings [92]. Dengue is most often diagnosed through serologic testing by enzyme-linked immunoassay, by viral detection through PCR of blood or urine, or (in some countries) by point-of-care testing of whole blood for the viral nonstructural protein 1 (NS1) [93]. Each of these assays is sensitive at different phases of the primary infection, and multiple methods may be advisable if suspicion is high.

Pregnancy complicated by dengue is common in endemic areas. Dengue-associated mortality rates are three times higher in pregnant women than in nonpregnant women of similar age and almost nine times higher in the third trimester. One study demonstrated that the proportion of severe cases among pregnant women with probable dengue almost approximated the fatality rate (1.7% and 1.6%, respectively) [94, 95]. Following primary infection, patients may develop long-term (although not necessarily lifelong) immunity to that given subtype but are at risk for severe disease if infected later with a different subtype. This more severe dengue infection, also known as dengue hemorrhagic fever (DHF), or as dengue shock syndrome in its most severe form, may also affect neonates due to an interaction with heterologous maternal antibodies [96]. Vertical transmission of dengue viruses occurs in fewer than 2% of cases of recent dengue infection [97], although case series of hospitalized women suggest rates closer to 12% in severe disease [98]. There is also a markedly increased risk of miscarriage (odds ratio 3.51), preterm delivery (OR 1.71), and low birth weight (OR 1.41) according to a recent meta-analysis [99].

Severe dengue is noteworthy for marked capillary leakage with pleural effusions and ascites, thrombocytopenia, consumptive coagulopathy, hemoconcentration, and (in its most severe form) hypotension and shock with a narrowed pulse pressure. Pulmonary complications of severe dengue include pneumonitis, hemoptysis, and pulmonary edema, all of which may lead to respiratory failure requiring mechanical ventilation [100]. The typical duration of illness requiring hospitalization is between 3 and 7 days [101]. There are no specific therapies for severe dengue. Blood product replacement is rarely indicated except in marked hemorrhage. Crystalloid and colloid resuscitation are essentially equivalent in efficacy [102] (for a more detailed discussion of fluid therapy, also see Chap. 7). There is no role for glucocorticoids in severe dengue [103]. In general, dengue is a self-limited disease, and survivors usually return to their baseline level of health barring specific complications (e.g., intracranial hemorrhage).

The Zika virus is a closely related flavivirus, presenting with a similar syndrome as dengue. Similar to dengue, Zika is diagnosed through PCR of blood or urine or via detection of anti-Zika IgM [104]. Severe Zika infection is less common than severe dengue [105], although cases have been described of a DHF-like syndrome due to Zika in patients with prior dengue infections, suggesting that Zika may interact with anti-dengue antibodies in a manner similar to that of varying dengue subtypes [79, 80]. Neurologic complications, including encephalitis and Guillain-Barre syndrome, may complicate Zika infection; supportive therapy is currently the only available intervention [106, 107]. The principal unique features of Zika to the obstetrician are its propensity for sexual transmission, which may occur months following exposure, and for its effects on fetal neurologic development and the risk for microcephaly. Surveys of neonatal outcomes in fetuses born to Zika-infected mothers have shown between 5% and 15% of such infants with evidence of birth defects [108, 109].

Chikungunya is an alphavirus, unrelated to the aforementioned flaviviruses but transmitted similarly with a comparable zone of endemicity. Like dengue and Zika, fever and rash are common presenting symptoms, but chikungunya is marked by a severe arthralgia and arthritis that may persist for years, in some cases requiring therapy with glucocorticoids or methotrexate in nonpregnant patients [110]. Severe disease does not appear to be more common in pregnancy, although sepsis-like syndromes have been described [111, 112], and pregnancy outcomes in infected women are generally comparable to those of non-infected women [113].
17.6 Conclusion

Viral infections are common and ubiquitous. With the physiologic and immunologic changes of pregnancy, affected pregnant women are at an increased risk of severe disease. The presenting syndromes of severe viral illnesses have been historically difficult to distinguish from those of bacterial, fungal, or parasitic diseases. Recent advances in molecular diagnostics have now given bedside clinicians the ability to diagnose viral disease with greater precision, with the potential for targeted therapy and, hopefully, improved maternal outcomes.

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