

Editorial

Addressing the Effects of Established and Emerging Infections During Pregnancy

In August 2015, when we first discussed the idea of a special issue on infections and pregnancy with Drs. Vekemans and Chambers (editor-in-chief and deputy editor of *Birth Defects Research Part A*), our goal was to highlight infectious diseases, both established and emerging, and their effects on the pregnant woman and her fetus. At that time, Zika virus had been identified in Brazil and was rapidly spreading throughout the country (Campos et al., 2015; Zanluca et al., 2015), but the sharp increase in births of infants with microcephaly had not yet been observed (Kleber de Oliveira et al., 2016). Since then, evidence has accumulated to confirm Zika virus as a teratogen (Rasmussen et al., 2016a), and much has been learned about Zika virus and its effects during pregnancy (Oussayef et al., 2017). Although Zika virus has fueled an interest in infections during pregnancy and their potential teratogenicity, the effects of infectious diseases on the pregnant woman and her fetus have long been recognized. In fact, the first exposure recognized to be a teratogen (rubella) was an infectious one (Webster, 1998; Wesselhoeft, 1947), and several well-recognized teratogens, including cytomegalovirus, toxoplasmosis, syphilis, and varicella zoster, among others, are infections (Običan and Scialli, 2011).

In recent years, increased emphasis has been placed on the effects of emerging infections on maternal and child health (Jamieson et al., 2004; Jamieson et al., 2005; Rasmussen and Hayes, 2005; Jamieson et al., 2006; Faherty et al., 2017). Emerging infections during pregnancy are of concern for several reasons (Rasmussen and Hayes, 2005): (1) pregnant women might be more susceptible to or more severely affected by emerging infections (Rasmussen et al., 2012); (2) emerging infections during pregnancy might have adverse effects on the fetus (Rasmussen et al., 2007); and (3) prophylaxis or treatment of emerging infections recommended for the general population might not be appropriate for or accepted by pregnant women (Cono et al., 2006). Emerging infections, initially brought to the

forefront in 1992 by an Institute of Medicine report (Institute of Medicine, 1992), are defined as “new, reemerging or drug-resistant infections whose incidence in humans has increased within the past 2 decades or whose incidence threatens to increase in the future.” This broad definition has led to many infectious diseases being characterized as emerging, including several that have recently led the news headlines (i.e., West Nile virus, pandemic H1N1 influenza virus, Middle East Respiratory Syndrome Coronavirus [MERS-CoV], Ebola virus, and, most recently, Zika virus) (Petersen and Hayes, 2008; Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, et al., 2009; Baize et al., 2014; Petersen et al., 2016; Rasmussen et al., 2016b). Understanding the impact of emerging infections on the pregnant woman and her fetus is still in the early stages, and for many pathogens, little is known.

In this special issue, we have included articles on both established as well as emerging infections during pregnancy. Several articles aim to update the reader on established infections with adverse effects on the fetus. As reviewed by Ornoy et al. (in this issue), human parvovirus B19, first described as a DNA virus in 1975 (Cossart et al., 1975) became a recognized cause for fetal effects in the late 1980s (Van Elsacker-Niele et al., 1989). Infection during pregnancy does not seem to have a characteristic pattern of birth defects; however, infection in pregnancy can lead to fetal loss, fetal damage, and, in rare cases, brain abnormalities and neurodevelopmental delays. Parvovirus targets the fetal liver, the main site of hematopoiesis in the fetus, and damages fetal erythrocytes, leading to severe fetal anemia, high output cardiac failure, myocarditis, and nonimmune hydrops. Although women are often immune before their childbearing years, the well-established fetal effects of parvovirus B19 infection generate significant concern among women infected during pregnancy.

Pregnancy-related listeriosis is another infection with recognized harmful fetal and neonatal effects: infection during pregnancy is known to cause fetal loss and an increased risk of neonatal mortality. As Wadhwa Desai and Smith (in this issue) discuss in their article, the incidence of infection with this food-borne bacteria has declined over time because of better food safety practices but has now plateaued. Also, improved detection methods have resulted in an increasing number of food recalls and potential exposures. Unfortunately, the underlying

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Disclaimer: The findings and conclusion in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Published online in Wiley Online Library (wileyonlinelibrary.com).
Doi: 10.1002/bdr2.1018

mechanisms for an increased susceptibility to listeriosis among pregnant women are still not well understood. Furthermore, although early diagnosis and treatment of the infection during pregnancy can improve outcomes, reliable diagnostic methods are lacking.

Also in this issue is an update by Davis et al. (in this issue) on cytomegalovirus, the most common congenital infection and a leading cause of infant morbidity. Fetal cytomegalovirus infection causes neurologic damage leading to cognitive, motor, hearing, and vision problems. The authors highlight a characteristic of the viral infection common to other viruses, including Zika virus: the virus can replicate in and cause damage to fetal tissues without eliciting maternal symptoms. In addition, infants may initially seem unaffected at birth, and later go on to develop late onset hearing loss and cognitive impairment. These often “silent” infections pose challenges to diagnosis and treatment.

Syphilis is an example of an established infection that also meets the definition of “emerging,” given its increasing occurrence in recent years. Tsimis and Sheffield (in this issue) provide a historical review of syphilis, outlining the decreasing trends that occurred over time with advent and widespread use of penicillin. However, syphilis rates have since increased as a result of changes in behavior and public health practice. The reemergence of syphilis in the past was attributed to an increase in men having sex with men, the HIV/AIDS epidemic, and increased drug-sex exchange. Most recently, in 2013 to 2014, an increased number of cases of primary and secondary syphilis was reported among young women across the country, affecting all races and ethnicities, with a concomitant rise in congenital syphilis. This resurgence of syphilis highlights that even when the pathophysiology of infections are well understood and effective prevention and treatment are available, congenital infections can reemerge. Continued vigilance is required to ensure pregnant women are appropriately diagnosed and treated.

Ebola virus disease, an emerging infectious disease that captured the world’s attention from 2014 through 2016, is associated with almost universal fetal loss among infected pregnant women. Unfortunately, other than high rates of pregnancy loss, little is known about the maternal and child effects of Ebola virus. As outlined by Bebell et al. (in this issue), pregnant women with Ebola virus disease seem to experience severe morbidity and mortality, similar to what is seen in the nonpregnant population; however, it seems that the effects on pregnant women might be less severe than initially expected based on historical data. Because the fetal consequences of Ebola virus disease were so grim in the outbreak in West Africa, it is not known if birth defects are a component of the clinical manifestations of fetal Ebola infection.

The article by Rasmussen et al. (in this issue) reviews strategies to study the effects of emerging infections on the fetus, using the experiences with studies of West Nile

and Zika viruses as examples. This article reviews challenges faced in the study of prenatal effects of these infections, including the wide range of potential adverse outcomes, differing effects depending on gestational age of maternal infection, difficulty with detecting mild or asymptomatic maternal infections, and problems with laboratory testing of a newly recognized congenital infection. This review of strategies to study the effects of emerging infections on the fetus might be useful to guide the study of the effects of future emerging infections.

Gilboa et al. (in this issue) describe an important approach being used to understand the effects of congenital Zika infection. Their paradigm of combining pregnancy registry data with data collected on infants with adverse outcomes identified through birth defects surveillance systems holds great promise in enhancing the understanding of Zika, because taken together these two surveillance systems are more likely to capture the complete picture of possible fetal effects. This combined approach could also be used for other emerging infections associated with birth defects, and is particularly useful to study the consequences of infections that have substantial rates of asymptomatic maternal infection. In addition, this approach provides an opportunity to study the value of prenatal diagnostic testing (e.g., ultrasonography) and the correlation between a prenatal diagnosis of birth defects and postnatal findings.

Because vaccines and antimicrobials are often recommended for prophylaxis and treatment of both established and emerging infections, this special issue includes articles that discuss issues related to immunization and treatment during pregnancy. Chu and Englund (in this issue) review the importance of maternal immunization to protect pregnant women and infants from infectious disease, with immune benefits in the infant that might extend up until 6 months of life. Examples of greater emphasis on prevention of infection in infants are the recommendations for routine maternal vaccination with inactivated influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines to protect infants from influenza and pertussis. Better understanding of the maternal humoral immune response, specifically that the maternal response to vaccine was similar to that in nonpregnant adults, greater recognition of the limitations of the neonatal immune response, and more data on transplacental passage of maternal antibodies has led to greater acceptance of maternal vaccination.

Noguchi and Beigi (in this issue) outline the importance of studying antimicrobial medications and novel therapeutics for infectious diseases in pregnancy. The majority of antimicrobial medications do not have robust data on use during pregnancy to inform evidence-based prescribing, largely because of the exclusion of pregnant women from participation in clinical trials of new pharmaceutical agents. Significant regulatory and health systems

barriers exist and pharmacokinetic data during pregnancy are sorely needed to appropriately dose to account for the physiologic changes in pregnancy. Additional clinical trials in pregnancy as well as the establishment of pregnancy registries are encouraged to ensure pregnant women are receiving needed treatment while minimizing risk to the fetus.

As the medical and public health communities prepare for future public health emergencies, increasing attention has been placed on the effects of those emergencies and ways to mitigate the effects on pregnant women and their infants. The article by Watson et al. (in this issue) addresses the issues raised by several biological threat agents, infectious agents that could be used to intentionally cause morbidity and mortality. Little is known about the effects on the pregnant woman or her fetus of most of the infectious agents with potential for use as intentional weapons; however, some of these agents seem to be vertically transmitted to the fetus. Effective prophylaxis and antimicrobial treatment are essential for many of these infectious agents, given their association with a high frequency of illness and death. As plans are made for the response to an intentional release of these biological threat agents, specific plans for prophylaxis and treatment of the pregnant woman need to be considered.

Several high profile outbreaks in recent years have emphasized the importance of established and emerging infections in pregnancy. The 2009 H1N1 influenza pandemic influenza provided solid evidence that pregnant women are more severely affected by certain infections. The recent, rapid spread of Zika virus in the Americas has provided additional evidence that infections in pregnancy can cause birth defects. Furthermore, recent events have highlighted the need for better strategies to safely and effectively prevent and treat infections in pregnancy. For example, an effective vaccine for Zika virus is urgently needed to protect pregnant women and infants from the devastating fetal effects of Zika; longer-lasting influenza vaccines could decrease maternal morbidity and mortality. Although interest and knowledge in infectious diseases during pregnancy has increased markedly in recent years, many challenges remain to be addressed.

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