

## REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

## Pregnancy and Infection

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**B**EFORE THE ADVENT OF ANTIBIOTIC AGENTS, PREGNANCY WAS A RECOGNIZED risk factor for severe complications of pneumococcal pneumonia, including death.<sup>1</sup> The influenza pandemic of 2009 provided a more recent reminder that certain infections may disproportionately affect pregnant women. Are pregnant women at increased risk for acquiring infections? Are pregnant women with infection at increased risk for severe disease? During pregnancy, several mechanical and pathophysiological changes occur (e.g., a decrease in respiratory volumes and urinary stasis due to an enlarging uterus), and immune adaptations are required to accommodate the fetus. In this article, we review and synthesize new knowledge about the severity of and susceptibility to infections in pregnant women. We focus on the infections for which there is evidence of increased severity or susceptibility during pregnancy that is not fully explained by mechanical or anatomical changes, and we discuss these infections in light of new findings on immunologic changes during pregnancy.

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## PREGNANCY AND SEVERITY OF INFECTION

As compared with nonpregnant women, pregnant women are more severely affected by infections with some organisms, including influenza virus, hepatitis E virus (HEV), herpes simplex virus (HSV), and malaria parasites. The evidence is more limited for organisms that cause coccidioidomycosis, measles, smallpox, and varicella (Table 1). The threshold for diagnostic evaluation, as well as hospitalization and treatment, may be lower for pregnant women than for other patients, and this factor may bias some of the reports of increased disease severity.

## INFLUENZA

Pregnant women are at increased risk for severe illness from influenza virus infection. Cardiopulmonary adaptive changes occurring during pregnancy, such as increased heart rate and stroke volume and reduced pulmonary residual capacity, may increase the risk of hypoxemia and contribute to the increased severity. During the pandemic of 1918, maternal mortality was 27% (50% when influenza was complicated by pneumonia), and during the pandemic of 1957, 50% of deaths among reproductive-age women occurred among those who were pregnant.<sup>2</sup> During the 2009 H1N1 influenza A pandemic, pregnant women were generally at increased risk for severe disease, including disease leading to hospitalization, admission to an intensive care unit, or death, as compared with nonpregnant women and the general population.<sup>3</sup> In the United States, 5% of all deaths from pandemic influenza were among pregnant women, although pregnant women represent only about 1% of the U.S. population.<sup>4</sup> Higher rates of hospital admission and medical encounters for pregnant women with confirmed or suspected influenza, as compared with the general population, and a greater severity of disease during late pregnancy were also found in inter-pandemic periods.<sup>5-7</sup> During the 2009 H1N1 pandemic, as well as during in-

terpandemic periods, women in the third trimester of pregnancy were at increased risk for severe disease (e.g., disease requiring admission to an intensive care unit or resulting in death), as compared with women in an earlier stage of pregnancy.<sup>4,6,8</sup>

#### HEV INFECTION

Infection with HEV is also more severe in pregnant women, with high mortality during the third trimester. In areas in which HEV infection is highly endemic (India, Southeast Asia, the Middle East, and Africa), it can be a major cause of maternal death and fetal loss. The pathophysiological basis of this increased mortality is not well understood.

In a review of all consecutive cases of acute liver failure from 1989 to 1996 in a region of India in which HEV infection is endemic, 49 of 83 women of childbearing age with acute liver failure were pregnant (33 in their third trimester). In 47 of these pregnant women, the liver failure was due to HEV infection.<sup>9</sup> In a case series from India, 33 to 43% of pregnant women with HEV infection had severe disease or infection that led to fulminant hepatic failure.<sup>10</sup> A review indicated that the case fatality rate among pregnant women with HEV infection is between 15% and 25%, as compared with a range of 0.5 to 4% in the population overall.<sup>11</sup> Among 220 consecutive pregnant women presenting with jaundice caused by acute viral hepatitis,

**Table 1. Infections Associated with Increased Susceptibility or Severity among Pregnant Women, and Relevant Clinical Guidance, According to the Strength of the Evidence for an Association.**

Infection	Increased Susceptibility	Increased Severity	Prevention Strategies	Management Strategies*
<b>Stronger evidence</b>				
Influenza	No	Yes	Influenza vaccination; antiviral prophylactic medication for selected patients	Early identification; early antiviral therapy; supportive care
Hepatitis E virus infection	No	Yes	Sanitation programs	High index of clinical suspicion; supportive care
Herpes simplex virus infection (dissemination with primary infection)	No	Yes	Protection from sexually transmitted infections during pregnancy	High index of clinical suspicion; antiviral therapy; supportive care; care of the newborn
Malaria (mainly due to <i>Plasmodium falciparum</i> )	Yes	Yes	Intermittent preventive therapy; insecticide-treated bed nets (for areas where malaria is endemic); appropriate prophylaxis (for travelers)	Early identification; appropriate antimalarial therapy; supportive care
Listeriosis	Yes	No	Dietary guidance	Early identification; appropriate antimicrobial therapy; care of the newborn
<b>More limited evidence</b>				
Measles	No	Yes	Vaccination	High index of clinical suspicion; supportive care
Smallpox	No	Yes	Vaccination	Very high index of clinical suspicion; supportive care
Human immunodeficiency virus type 1 infection	Yes	No	Consistent and correct condom use; protection from sexually transmitted diseases during pregnancy	Early identification; antiretroviral therapy
Varicella	No	Yes	Vaccination	Appropriate antiviral therapy; supportive care
Coccidioidomycosis	No	Yes	No proven methods of prevention	Early identification; appropriate antifungal therapy

\* Infections for which there should be a higher or very high index of clinical suspicion are those that must be considered by the clinician despite being rare diagnoses in some areas.

fulminant hepatic failure and death were more common among women with HEV infection than among those without HEV infection (relative risk of fulminant hepatic failure, 2.7; relative risk of death, 6.0).<sup>12</sup>

#### HSV INFECTION

Pregnant women with primary HSV infection have an increased risk of dissemination and hepatitis (an otherwise rare complication in immunocompetent adults), particularly during the third trimester. To date, 27 cases of HSV hepatitis during pregnancy have been reported.<sup>13</sup> After patients with immunosuppression, pregnant women are the largest group of adults with disseminated HSV infection; in one review, the mean gestational age at presentation was 31 weeks, and the case fatality rate was 39% for both mothers and neonates.<sup>14</sup> Other reviews have confirmed a high burden of HSV hepatitis among pregnant women<sup>15,16</sup>; however, data on the incidence of primary HSV infection among pregnant women are limited. Recurrences of genital HSV infection increase in frequency during pregnancy,<sup>17</sup> although the clinical characteristics of recurrent genital HSV infection are similar in pregnant women and nonpregnant women.

#### MALARIA

The severity of (and susceptibility to) *Plasmodium falciparum* malaria is determined by the level of immunity, which depends mainly on the intensity and stability of malaria transmission. In areas of low or unstable transmission, infected women become symptomatic, and, if untreated, the infection can progress rapidly to complications, with a high case fatality rate. In three districts in India, 23% or more of maternal deaths between 2004 and 2006 were attributable to malaria, which was the most common cause of maternal death during pregnancy.<sup>18</sup> Pregnant women have a risk of severe malaria that is three times as high as that among nonpregnant women; a median maternal mortality of 39% has been reported in studies in the Asia-Pacific region. Maternal death also has been reported in association with *P. vivax* infection.<sup>18</sup>

In areas of high transmission, most women harboring parasites do not present with symptoms. It was thought that, in such areas, cases of severe or fatal malaria during pregnancy were rare. However, the numbers of maternal deaths

from malaria in sub-Saharan Africa may have been underestimated, and malaria during pregnancy may be an important direct cause of maternal complications and death.<sup>19,20</sup> Of pregnant women who are symptomatic, the majority are women having their first pregnancy; women who have been pregnant more than once and who live in areas where malaria is highly endemic are less likely to present with clinical signs or symptoms of malaria, even if they have high parasite loads.<sup>20,21</sup> The predominant theory to explain this phenomenon is that *P. falciparum* parasites accumulate selectively in the placenta, and particular antigenic variants interact with syncytiotrophoblastic chondroitin sulfate A.<sup>22</sup> Women have a malaria episode caused by chondroitin sulfate A-binding parasites during their first pregnancy because they lack immunity to antigenic variants presented by these strains (even though they may be immune to other antigenic variants of parasites that bind endothelial receptors from previous infections) and are thus highly susceptible to the new infection.

#### COCCIDIOIDOMYCOSIS

Several reports and case series have suggested that pregnancy is a risk factor for the development of severe and disseminated coccidioidomycosis, particularly during the third trimester and the immediate postpartum period, with an estimated rate of 7.7 to 11 cases per 10,000 pregnancies.<sup>23-25</sup> However, the rate of disease during pregnancy was much lower than expected in a large 1988 survey of records from three delivery centers in Tucson, Arizona, covering more than 47,000 deliveries.<sup>26</sup> During the 1993 epidemic in Kern County, California, only 32 cases were identified among pregnant women, a lower number than expected; disseminated disease occurred in 3 of these cases, with no maternal deaths,<sup>27</sup> which suggested that many pregnant women have asymptomatic or clinically mild disease. Taken together, these data suggest that the incidence of coccidioidomycosis is decreasing and that pregnant women may not be at increased risk for dissemination.

#### VARICELLA

Early studies postulated that pregnancy, particularly in the third trimester, is a risk factor for severe varicella. These studies involved mostly case reports or small case series.<sup>28-30</sup> In a 1990 review of 34 published cases of varicella pneumonia, mortality among pregnant women was 35%,<sup>28</sup>

higher than that among nonpregnant adults, reported as 11.4% in another study.<sup>31</sup> Paryani and Arvin reported a varicella pneumonia rate of 9%, with one death among 43 pregnant women with varicella.<sup>30</sup> A review of reports published from 1965 to 1989 on varicella pneumonia in adults showed that of 99 cases, 46 were in women; 28 of these women were pregnant (21 in the third trimester). This suggested an increased rate of varicella pneumonia during pregnancy; however, mortality among pregnant women (10%) was not higher than that among men and nonpregnant women.<sup>29</sup> Other studies do not support the idea that illness due to varicella is more severe during pregnancy. In a New York City survey for the period from 1957 to 1964, only 1 of 144 women with varicella died.<sup>32</sup> In a study from Britain and Germany, in which 1373 women with varicella were followed during pregnancy, no maternal deaths were reported.<sup>33</sup>

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#### PREGNANCY AND SUSCEPTIBILITY TO INFECTION

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In contrast to the rather strong evidence for increased severity of certain infections among pregnant women, the evidence regarding initial susceptibility is weaker. The evidence for increased susceptibility during pregnancy is most credible for infections with organisms such as *P. falciparum* and *Listeria monocytogenes*, both of which have tropism for the placenta; evidence is more limited for human immunodeficiency virus type 1 infection (Table 1).

#### MALARIA

The harmful effects of malaria (mainly due to *P. falciparum*) during pregnancy — maternal anemia, low birth weight, and preterm birth — have long been recognized.<sup>19</sup> In areas of stable endemic transmission (e.g., sub-Saharan Africa), up to 25% of pregnant women have acute infection, leading to placental malaria<sup>34</sup>; this frequency is higher than that among nonpregnant women.<sup>35,36</sup> In several studies in Africa and Asia, the prevalence of malarial parasitemia was found to be higher among pregnant females than among nonpregnant females 15 to 45 years of age.<sup>18,37,38</sup> *P. falciparum* is the only species associated with placental sequestration, which is believed to be the cause of many of the manifestations of *P. falciparum* disease during

pregnancy. Many studies have shown decreasing susceptibility to malaria with increasing parity,<sup>37-39</sup> probably as a result of acquisition of immunity to parasites expressing pregnancy-specific variant surface antigens.<sup>19</sup> This association is most pronounced in areas where malaria is highly endemic.<sup>20</sup> Young maternal age may be an additional and independent risk factor for malaria during pregnancy. The third trimester of gestation has been associated with the highest risk of clinical malaria in some studies<sup>40</sup> but not others.<sup>39</sup> However, maternal parasitemia, placental parasite burden, and episodes of clinical malaria may be expressions of disease severity rather than of initial susceptibility in areas with a high prevalence of malaria.

Limited data suggest that *P. vivax* infections also are more severe during pregnancy.<sup>18</sup> These data, however, are difficult to interpret because most areas where *P. vivax* is the predominant cause of malaria have low or unstable transmission and therefore increased disease severity in all parity groups.<sup>41</sup> Accumulation of *P. vivax* in the placenta has not been reported.<sup>42</sup>

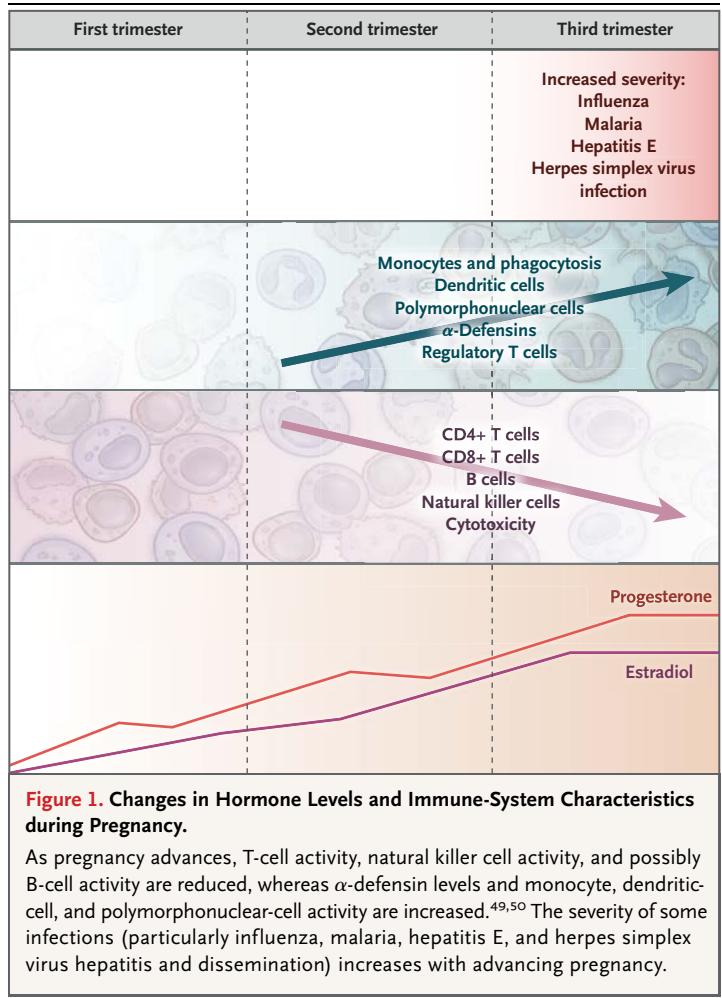
#### LISTERIOSIS

Primarily a foodborne pathogen, listeria can contaminate a variety of raw foods, such as uncooked meats and vegetables, unpasteurized milk, and soft cheeses. Infection may be asymptomatic or may be manifested as an influenza-like illness; severe infection is rare during pregnancy, and no maternal deaths due to listeriosis have been reported among pregnant women who are hospitalized.<sup>43</sup> *L. monocytogenes* infections most commonly occur during the third trimester and seem to be rare earlier in pregnancy.<sup>44</sup> However, listeria has a predilection for the placenta and fetus, and, depending on the stage of pregnancy, listeriosis can lead to pregnancy loss, stillbirth, preterm birth, or serious neonatal disease. Active, population-based surveillance showed that 17% of 762 listeriosis cases reported in 10 U.S. sites between 2004 and 2009 were in pregnant women.<sup>45</sup> Hispanic women seemed to be particularly at risk.<sup>45-47</sup> It has been estimated that invasive listeriosis during pregnancy is 13 times to more than 100 times as frequent as in the general population.<sup>45,46,48</sup> However, in one study, surveillance data indicated that more than 50% of listeriosis cases during pregnancy were associated with a neonatal case,<sup>45</sup> which suggests that neonatal disease leads to

recognition of listeria infections during pregnancy in a substantial proportion of cases and may therefore bias estimates of pregnancy-conferred risk.

**EVOLVING CONCEPTS OF IMMUNOLOGIC ALTERATIONS DURING PREGNANCY**

Immunologic alterations during pregnancy may help explain the altered severity of and susceptibility to infectious diseases during pregnancy. As pregnancy progresses, hormone levels change dramatically and are considerably higher than at any other time.<sup>49</sup> The interplay between sex hormones and the immune system is complex and multifactorial, and it affects many organ systems (Fig. 1). In humans, estradiol can enhance several aspects of innate immunity and both cell-mediated and humoral adaptive immune responses.<sup>51,52</sup> In general, low estradiol concentrations promote CD4+ type 1 helper T-cell (Th1) responses and cell-mediated immunity, and high estradiol concentrations augment CD4+ type 2 helper T-cell (Th2) responses and humoral immunity.<sup>52</sup> Progesterone can suppress the maternal immune response and alter the balance between Th1 and Th2 responses.<sup>49,53,54</sup> Increasing estrogen and progesterone concentrations with advancing pregnancy lead to a reversible thymic involution. The mechanisms of estrogen and progesterone modulation of individual components of the immune system have been extensively studied in vitro but not in humans. There is evidence that aspects of innate immunity (phagocytic activity,  $\alpha$ -defensin expression, and numbers of neutrophils, monocytes, and dendritic cells) are maintained or enhanced during pregnancy, particularly during the second and third trimesters.<sup>50,55</sup> Conversely, the number of CD3+ T lymphocytes (both CD4+ and CD8+) decrease during pregnancy<sup>56,57</sup> as do Th1 and Th2 responses to mitogenic or antigenic lymphocyte stimulation.<sup>55,58</sup> However, there is limited information on the longitudinal trends of such alterations during pregnancy. Levels of several cytokines are altered: levels of interferon- $\gamma$ , monocyte chemoattractant protein 1, and eotaxin are decreased in most pregnant women, whereas tumor necrosis factor  $\alpha$ , interleukin-10, and granulocyte colony-stimulating factor levels rise.<sup>50</sup> In general, levels of inflammatory cytokines are reduced, whereas levels of cytokines that induce phagocytic-cell recruitment or



activity increase; these alterations do not necessarily follow a clear Th1 or Th2 phenotype.<sup>50</sup> Regulatory T cells become more numerous.<sup>59</sup> Several theories have been proposed to explain the immunologic alterations that occur during pregnancy. It was initially thought that pregnancy confers general immunosuppression to ensure tolerance of the semiallogeneic fetus.<sup>60</sup> However, data indicating that fetus-specific cytotoxic T-cell responses can be generated during pregnancy without loss of the fetus,<sup>61</sup> as well as data from studies of pregnant mice showing normal memory T-cell development after lymphocytic choriomeningitis virus infection,<sup>62</sup> contradict the idea of systemic immunosuppression during pregnancy. Adequate immunologic responses to vaccination in pregnant women have been demonstrated in several studies and for several pathogens.<sup>63-66</sup>

The fact that pregnant women do not seem, on the basis of epidemiologic evidence, to be more susceptible to infections in general also contradicts this theory. A more recent theory proposed a shift from Th1 to Th2 immunity during pregnancy.<sup>67</sup> Th2 cells stimulate B lymphocytes, increase antibody production, and suppress the cytotoxic T-lymphocyte response, decreasing the robustness of cell-mediated immunity. A shift to Th2 immunity is postulated to be responsible for altered responses to respiratory viral infections or autoantigens during pregnancy and could explain the increased severity of infections such as influenza or coccidioidomycosis, in which cell-mediated immunity is important.<sup>5,50,68</sup>

Elucidation of the immunologic alterations and adaptations that occur during pregnancy suggests that older concepts of pregnancy as a state of systemic immunosuppression are oversimplified. A more useful model may be the view of pregnancy as a modulated immunologic condition, not a state of immunosuppression.<sup>50</sup> Decreases in adaptive immunity seen in later stages of pregnancy are consistent with the observed increase in the severity of certain infectious diseases during later pregnancy. Decreases in the numbers and function of CD4+, CD8+, and natural killer cells could affect antiviral, antifungal, or anti-parasitic responses and delay clearance of the offending microorganism. However, the increases in innate immunity observed during pregnancy may help to prevent acquisition of infection and thus explain the absence of increased susceptibility to infections.

Furthermore, the placenta is an active immunologic site, capable of interacting with and responding to pathogens. The placental tropism of specific pathogens (e.g., listeria or *P. falciparum*) affects the susceptibility to and severity of certain infectious diseases during pregnancy, as well as pregnancy outcomes.<sup>54</sup> Placental infection that elicits the production of inflammatory cytokines may activate the maternal immune system and lead to placental damage and miscarriage or preterm labor.<sup>69</sup> Although a viral infection of the placenta that triggers a mild inflammatory response may not terminate the pregnancy, it can activate the maternal immune system or that of the fetus, potentially promoting an inflammatory response that may lead to long-term neuro-

developmental or other sequelae,<sup>70</sup> including diseases in adulthood,<sup>54</sup> in the offspring.

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#### FUTURE DIRECTIONS

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The evidence of increased susceptibility of pregnant women to infection is rather weak; to adequately address this question, studies need to include nonpregnant age-matched controls, long prospective follow-up periods, and large samples. Even though pregnant women do not seem to be more susceptible than nonpregnant women to initial infection in general, immunologic alterations with advancing pregnancy may impair pathogen clearance, resulting in an increased severity of disease caused by some pathogens. Increased disease severity may also be due to other physiological changes of pregnancy (e.g., decreased lung capacity, urinary stasis, and changes in blood flow). There are many unanswered questions regarding the immunologic changes that occur as pregnancy progresses and the interplay of infection, pregnancy, and the fetus and placenta. The less detrimental effect of malaria in multiparous than in primiparous women could provide insights into disease pathogenesis during pregnancy that could be expanded to other infections, as well as to concepts of autoimmunity in general.

Given the hormonal shifts during pregnancy and the resultant effects on the immune system, efforts to reduce the pathogenesis of infectious and other diseases by modulating the hormonal environment locally or systemically warrant consideration. Approaches that boost pathogen-specific immunity or particular components of the immune system (e.g., alterations in certain cytokines and in regulatory T-cell subsets) may provide new prophylactic and therapeutic pathways. Interfering with the special interactions between some pathogens and the placenta may also offer a potential strategy for prophylaxis or therapy. Vaccination before and during pregnancy, which has proved safe and effective for a number of infectious agents, could one day be expanded to include vaccines against other relevant pathogens, such as HSV, HEV, and malaria parasites. The beneficial effects of maternal vaccination may not be limited to the mother but, by reducing fetal and placental inflammation, may also provide long-term benefits for the child. The education of

pregnant women about prevention of infections and the early identification and appropriate treatment of infectious diseases during pregnancy remain important strategies for protecting maternal and infant health.

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