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Plague and Pregnancy: Why Special Considerations Are Needed

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Abstract

Pregnant women are an important at-risk population to consider during public health emergencies. These women, like nonpregnant adults, may be faced with the risk of acquiring life-threatening infections during outbreaks or bioterrorism (BT) events and, in some cases, can experience increased severity of infection and higher morbidity compared with nonpregnant adults. *Yersinia pestis*, the bacterium that causes plague, is a highly pathogenic organism. There are 4 million births annually in the United States, and thus the unique needs of pregnant women and their infants should be considered in pre-event planning for a plague outbreak or BT event.

Keywords

Yersinia pestis; plague; pregnancy; maternal; fetal/fetus

Most women's health providers in the Unites States will not have experience with plague [1]. To ensure pregnant women are appropriately cared for during a *Yersinia pestis* outbreak or bioterrorism (BT) event, these providers need clear clinical recommendations on how to manage affected pregnant women [2]. These recommendations should outline the risks of the infection and delineate the most effective treatment and prophylaxis options to reduce maternal morbidity and mortality and improve infant survival [2]. Providers will need information about the rationale for antimicrobial choices (eg, clinical efficacy, availability) and information about any potential adverse maternal and infant outcomes associated with

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prophylaxis and treatment. The Centers for Disease Control and Prevention (CDC) previously developed several clinical guidelines that address considerations for pregnant women exposed to or infected with highly pathogenic infections (eg, anthrax, smallpox) and their infants [3–7]. Several key issues have emerged that are consistent among high-consequence infections [8–11]. Consideration of these issues can guide the overall approach to developing evidence-based recommendations, including for a plague outbreak or BT event.

The first key issue is whether pregnant women are more likely to be disproportionally affected during a plague outbreak or BT event when compared with nonpregnant adults. Answering this question can inform preventive interventions specific to pregnant women (eg, enhanced infection control or other protective measures for pregnant healthcare workers) and prioritization of obstetrical and high-risk care if needed. Ultimately, knowledge about susceptibility may improve planning and reduce the number of pregnant women severely affected.

The second key issue is whether clinical manifestations or severity of illness differ for pregnant women compared with nonpregnant adults. Early, nonspecific symptoms, such as fever, may not alert obstetricians or women's health providers to consider plague, since this is an exceedingly rare diagnosis, in general, and even more rare in this population. During an event, dissemination of information regarding the clinical presentation of plague to women's health providers and the details and geographic area of an outbreak or BT event could promote early diagnosis and prompt treatment. Understanding the severity of illness or expected morbidity among affected pregnant women can also guide planning that will enable better access to higher levels of maternal care, such as routing patients to hospitals with obstetrical intensive care units. In addition, this knowledge can inform clinical management of unique consequences of plague during pregnancy, such as hemorrhage, and enables preparations for possible emergent deliveries in intensive care settings [11].

Third, it is important to determine whether the clinical efficacy and safety of antimicrobials differ during pregnancy when compared with the general population [3, 4, 6, 12, 13]. Pre-event recommendations regarding antimicrobial use for prophylaxis and treatment of plague during pregnancy that maximize maternal and consequently fetal benefit while minimizing potential risks will promote more timely and appropriate care.

Finally, a unique consideration regarding pregnant women with infections due to highly pathogenic organisms, such as *Y. pestis*, is the possibility that the infection can result in maternal–fetal transmission to the developing fetus in utero or to the neonate at the time of delivery [11]. While decisions regarding antimicrobial use are first and foremost driven by clinical efficacy to prevent maternal morbidity and mortality, the choice among highly effective antimicrobials may also be influenced by the potential to prevent or mitigate fetal infection due to maternal–fetal transmission. For example, some antimicrobials cross the placenta and concentrate in the amniotic fluid, thereby theoretically offering greater protection against infection to the fetus [6]. Care plans for neonates at potential risk for congenital or intrapartum-acquired infection would need to consider more intense monitoring and possibly antimicrobial treatment or prophylaxis. Additional information

about the likelihood of maternal–fetal transmission and the effectiveness of antimicrobials to mitigate this risk can inform optimal care of women exposed to or infected with plague during pregnancy or after birth.

In this supplement of *Clinical Infectious Diseases*, 2 articles address different considerations that may influence the care of pregnant women during a plague outbreak or BT event [11, 12]. One article, a systematic review of plague during pregnancy, summarizes all cases of plague among pregnant women identified in the literature, describes the risks of maternal mortality, and evaluates adverse maternal and infant outcomes associated with this illness [11]. The second article, a systematic review of antimicrobial safety during pregnancy, summarizes what is known about the safety during pregnancy of antimicrobials being considered for prophylaxis and treatment of plague [12]. The data in these 2 articles will inform the CDC's forthcoming clinical guidance for prophylaxis and treatment of plague, specifically the recommendations for pregnant women.

Fleck-Derderian et al summarize the worldwide experience with plague during pregnancy, dating back to the 1890s [11]. The authors identified 160 cases of plague during pregnancy and established that plague is associated with high maternal morbidity and mortality, adverse pregnancy outcomes, fetal deaths, and neonatal losses. The authors also identified 21 pregnant women treated with antimicrobials who had improved survival compared with the population of untreated pregnant women. Nevertheless, the mortality among these pregnant women who received treatment for plague was unacceptably high. Antimicrobial treatment appears to have less of a protective effect on fetal and infant survival, although a variety of antimicrobials were used, which may limit interpretation of the utility of antimicrobials to prevent adverse fetal and infant outcomes. Of particular interest in this review is the finding that maternal–fetal transmission of *Y. pestis* appears possible, a finding not previously reported in the literature and one that may influence antimicrobial choice if transplacental passage of antimicrobials is deemed an important consideration in the forthcoming recommendations. Overall, the results of this review make a compelling argument for the need for timely treatment and prompt prophylaxis and treatment with effective antimicrobials for pregnant women during a plague outbreak or BT event and outline some of the obstetrical consequences associated with plague.

Yu et al provide a comprehensive review of the published literature on adverse maternal, fetal, and neonatal effects associated with antimicrobial use during pregnancy [12]. The authors found that most antimicrobials being considered for prophylaxis and treatment of plague appear safe during pregnancy, with several notable exceptions. Consistent with previous literature, trimethoprim-sulfamethoxazole and streptomycin were associated with risks for neonates exposed in utero. Therefore, these antimicrobials would be unlikely to be used as first-line agents for plague if other antimicrobials were readily available. However, in the context of a plague outbreak or BT event where these were the only antimicrobials available, treatment with these antimicrobials to prevent maternal and consequently fetal death outweighs the safety risks for these antimicrobials. Studies included in this review that examined the safety of chloramphenicol and doxycycline demonstrated inconsistent results, making it less likely but not impossible that a substantial safety risk exists for these antimicrobials.

Clinical recommendations for treatment and prophylaxis of pregnant women during a plague outbreak or BT event will be informed by the data presented in these reviews as well as by expert opinion and individual clinical judgment [11, 12]. The over-arching principle for plague, similar to that of other potentially fatal infections, is that the benefit of antimicrobials for plague to both the mother and the infant outcome(s) outweighs any risks related to safety concerns [3, 7, 14]. However, these safety risks do come into consideration when multiple antimicrobials are available and a preferred antimicrobial can be selected [3].

Decisions about antimicrobial prophylaxis can be especially challenging when asymptomatic pregnant women who have been exposed to *Y. pestis* are considered. Inherent uncertainty about the amount of exposure and therefore the true risk of contracting the infection is common. Based on prior guidelines for highly pathogenic infectious biothreat agents, the general principle that guides these decisions is that pregnant women should be given the same intervention as nonpregnant adults, in the absence of a compelling reason to diverge from these recommendations [5, 6]. As noted above, in the situation where more than 1 equally effective antimicrobial option exists, consideration should be given to which antimicrobial will have the least risk to the developing fetus. In addition to defining the specific antimicrobial recommendations, pre-event plans that include the option for the provision of prophylaxis in prenatal care settings can increase the ability to reach asymptomatic pregnant women with *Y. pestis* exposure.

The articles in this supplement demonstrate that the existing evidence on which to base recommendations for plague during pregnancy is limited. Real-time surveillance of women who are pregnant and diagnosed with or exposed to plague is crucial during public health emergencies to assess outcomes. Capturing pregnancy status, gestational age, treatment, and outcomes for both mothers and infants during events will expand the scientific knowledge base and ensure recommendations are based on evolving data [13]. While systematic reviews, such as the ones included in this supplement, can gather and analyze available data, these data are often heterogeneous and old, whereas recommendations during an outbreak or BT event should be based on real-time data collected during the outbreak or BT event. In very large-scale events, prioritization of care for certain populations, such as pregnant women, may be required and crisis standards of care may come into play [15, 16].

While the CDC has experience in developing clinical guidelines for high-consequence pathogens, defining robust, evidence-based antimicrobial prophylaxis and treatment options for these infections during pregnancy has proven challenging [6, 7]. One main reason for this is that the performance of clinical research whereby mothers are intentionally infected with serious pathogens, such as *Y. pestis*, during pregnancy is not ethical. Therefore, our understanding of these infections, such as plague, relies on limited surveillance information and data reported from sporadic and often historical cases. Despite the lack of high-quality data, pre-event recommendations, that is, those defined prior to the confusion associated with a typical large outbreak or BT event, serve as a useful starting point.

Explicit, clear, and simple instructions for prophylaxis and treatment of pregnant women at the start of the outbreak or BT event can be modified as more is learned during the event [3]. Without explicit recommendations, concern about fetal risks related to antimicrobials not

typically used during pregnancy may drive clinicians to avoid or delay life-saving prophylaxis or treatment or promote the use of suboptimal regimens perceived to be "safer" for the developing fetus. Decisions about prophylaxis and treatment regimens made from the main standpoint of minimizing risks to the fetus without consideration of the potential risks of infection on the mother and potential benefits of the treatment to both mother and infant can lead to substantial maternal and infant morbidity and mortality [17]. When a pregnant woman is acutely ill during an outbreak or BT incident with a highly dangerous pathogen, such as *Y. pestis*, she must have unfettered rapid access to the most effective treatment to maximize chances of survival. This is critical for maternal health and well-being, which is indispensable for maintaining the health of the fetus or infant. In the situation where more than 1 equally effective treatment option exists, only then can consideration be given to which treatment will pose the least risk to the developing fetus.

Continued focus on developing recommendations for prophylaxis and treatment of highly pathogenic infectious and potential BT agents is critical to pre-event emergency preparedness and should address the needs of pregnant women and infants [2]. The articles in this supplement along with expert opinion and the framework outlined above will inform forthcoming CDC clinical guidelines for treatment and prophylaxis of plague during pregnancy. These forthcoming plague guidelines will be the fourth in a series of guidelines that include specific recommendations for pregnant women using a consistent approach [3–12].

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