A call for science preparedness for pregnant women during public health emergencies

Laura J. Faherty, MD, MPH, MS; Sonja A. Rasmussen, MD, MS; Nicole Lurie, MD, MSPH

The rapidly expanding Zika virus epidemic and the associated spectrum of birth defects in infants born to mothers with Zika virus infection during pregnancy[1-3] has raised many questions, such as how often does Zika infection during pregnancy result in adverse outcomes and can the risk for these outcomes be reduced once a pregnant woman is infected.

The challenge of involving pregnant women in research during a public health emergency is not new. Two recent examples illustrate missed opportunities to involve pregnant women in research during public health emergencies. Before the 2009 H1N1 pandemic, it was recognized that pregnant women were at an increased risk for influenza-associated complications and that little was known about the effects of antiviral medications on the pregnant woman or her fetus.[4] However, despite extensive use of oseltamivir by pregnant women during the pandemic, only limited data on its pharmacokinetics and the effects of prenatal oseltamivir use on the infant have become available.

Similarly, before the 2014–2015 Ebola epidemic, babies born to mothers infected with Ebola virus during pregnancy were known to be at high risk for mortality,[5] but studies to better understand the outcomes of these babies were not implemented during the epidemic, resulting in a missed opportunity to better understand the reasons for these poor outcomes.

Many challenges exist to conducting research during public health emergencies.[6] Public health professionals, emergency responders, and those directly impacted by the public health emergency are typically focused on the emergency response rather than on conducting research. Furthermore, a variety of complex steps are involved in rapidly developing research protocols, gaining human subjects approval, and identifying funding for these studies. Finally, as in all research, the priorities and experience of the affected communities must be considered.

Similarly, research involving pregnant women presents numerous challenges, including the classification of pregnant women as a vulnerable population with special human subject protection, fear of legal liability, and difficulties enrolling sufficient numbers of participants.[7] As a result, many important questions, such as about the safety of medications in pregnancy,[7,8] remain unanswered. Ethical and logistical considerations for including pregnant women in research, as well as the imperative to reverse their historical underrepresentation in clinical trials, have been well documented.[7,9]

The barriers to conducting research during public health emergencies and involving pregnant women in research are amplified in the special case of pregnant women affected by public health emergencies.[10] The pool of experts with expertise in both the public health emergency at hand (eg, H1N1 influenza, Ebola virus, natural disasters) and pregnancy is limited, and experts in obstetrics, pediatrics, and emergency preparedness, as well as with subject-matter expertise related to the specific public health emergency, are needed to guide these studies. Because the effects of an in utero exposure might not be evident until birth or much later, research on outcomes for pregnant women and their offspring require longer follow-up to fully appreciate the impact of the event.

An additional challenge, particularly for prospective studies, is that often the most profound effects on the developing fetus, whether from infectious agents, toxins, medical countermeasures, or other exposures, occur during the first trimester, when a woman might not know she is pregnant. Creating databases or registries that include linked mother-infant dyads often involves contributions of data from clinicians from different disciplines as well as public health professionals. Ensuring the protection of sensitive information, such as information on pregnancy loss, termination, or birth defects, and determining which data, if any, may be used for research, are critical to the creation of such registries.

Human subject issues are also more complex.[11] Federal regulations require that research involving pregnant women meet certain criteria that balance the prospect of direct benefit to the woman or fetus against the potential risks to both.[7]

From the Robert Wood Johnson Foundation Clinical Scholars Program (Dr Faherty) and Leonard Davis Institute of Health Economics (Dr Faherty), University of Pennsylvania, Philadelphia, PA; Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention, Atlanta, GA (Dr Rasmussen); and Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services, Washington, DC (Dr Lurie).

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Corresponding author: Laura J. Faherty, MD, MPH, MS. Laura122@gmail.com

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Finally, to enroll sufficient numbers of pregnant women in studies following a public health emergency, multisite studies are likely required, increasing the need for coordination and complicating timely human subjects approval.

Science preparedness, or the ability to conduct scientific research early in a public health emergency, is essential to increase the likelihood that during future public health emergencies, important research questions regarding pregnant women (and other special populations such as children)[12] will be addressed while the window of opportunity for data collection is open, the risk-benefit ratio has shifted, and larger numbers of pregnant women might be exposed to certain vaccines or medications.

This type of preparedness should include four interrelated components:

1. Development of generic protocols. Preparedness for public health emergencies in recent years has focused on an all-hazards approach.[13] Protocols for research in pregnant women in a public health emergency could use a similar strategy. Regardless of the public health emergency, be it nearly any emerging infectious disease, a radiological emergency, or natural disaster, certain questions will need to be answered (Table), thus making the development of generic protocols possible. These protocols can be rapidly adapted to the specific event at the time of the public health emergency. One example of an adaptable, all-hazards protocol that could serve as a model for research involving pregnant women is the National Institute of Environmental Health Sciences' Rapid Acquisition of Pre- and Post-Incident Disaster Data (RAPIDD) study, which investigates the health impacts of disasters on response teams (http://dr2.nlm.nih.gov/). If applicable, protocols should provide clear guidance on data and biological specimen access, sharing, and ownership and should consider in advance the unique issues that arise when research is conducted in the international setting.
2. Human subjects approval of generic protocols before a public health emergency, followed by expedited review of

TABLE
Key research questions for pregnant women and their infants in a public health emergency

Underlying susceptibility to the PHE
What physiological changes of pregnancy, as well as underlying medical conditions in the pregnant woman, make her or her fetus more or less susceptible to the negative consequences of the PHE?
Impact of the PHE on the pregnant woman
How does the PHE affect the pregnant woman? • Is she more susceptible to or more severely affected by the PHE than the general population? • Do these effects differ by timing of exposure/infection during pregnancy?
Monitoring the pregnant woman affected by a PHE and mitigation strategies
How should the pregnant woman be monitored to detect adverse effects on the developing fetus? • Are serial assessments, such as ultrasounds or amniocentesis, required and feasible? • Are reference ranges for serial laboratory studies adequately established? What postexposure strategies (eg, medical countermeasures, counseling) can be used to mitigate the adverse effects on the pregnant woman and her fetus? • If medical countermeasures for treatment or prophylaxis are available, are they equally effective during pregnancy or are dosing adjustments needed? • What are the effects of these agents for treatment/prophylaxis on the fetus?
Impact of the PHE on the fetus and infant
When a pregnant woman is affected by a PHE, are there adverse effects on her fetus? • Do these differ by timing of exposure/infection during pregnancy? • What is the underlying mechanism of the effects on the fetus? What are the effects of the PHE on the infant's health and development, both in the immediate neonatal period and throughout his/her life course? What are potential protective factors that make the maternal-infant dyad resilient to the impacts of the PHE?
Other considerations
Is it safe for the mother affected by the PHE to breastfeed her infant if desired? • Does the PHE or its treatment/prophylaxis have an effect on breast milk production or safety for the infant, including as a result of severe stress?

PHE, public health emergency.

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