Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines

The continued global escalation of coronavirus disease 2019 (COVID-19) cases is of particular concern for pregnant and lactating individuals. While many cases of COVID-19 are asymptomatic or relatively mild, recent evidence suggests that pregnant people are at increased risk of hospitalization and have a 3-fold adjusted relative risk of needing intensive care (10.5 vs 3.9/1000 cases) and mechanical ventilation (2.9 vs 1.1/1000 cases) compared with age-matched nonpregnant individuals. Pregnant people with laboratory-confirmed severe or critical COVID-19 disease have higher adjusted relative risks of cesarean delivery (1.57 [95% CI, 1.30-1.90]), postpartum hemorrhage (2.04 [95% CI, 1.19-3.47]), hypertensive disorders of pregnancy (1.64 [95% CI, 1.21-2.23]), and preterm birth (3.53 [95% CI, 2.42-5.15]).

These complications are exacerbated in women who are older, have a higher body mass index, and who have medical comorbidities; evidence is emerging that racial and ethnic disparities also are related to morbidity and mortality among pregnant people. With the development of COVID-19 vaccines, there is the potential for prevention of this illness; however, the evidence for the utility, safety, and effectiveness of the available vaccines in pregnancy is unknown.

Thoughtfully including pregnant and lactating individuals in clinical research will lead to clinical care recommendations based on solid evidence.

The conflicting information being provided to pregnant individuals stems from long-standing obstacles to the inclusion of pregnant and lactating people in clinical research. The data provided by the manufacturers in the Emergency Use Authorizations for both the Pfizer and Moderna vaccines described the specific exclusion of pregnant people, those who became pregnant during the trials (n = 36) provided very limited data to inform evidence of safety and effectiveness in this population. Preclinical rodent data were only included from Moderna and were not conducted early enough to support the inclusion of pregnant people in the subsequent large-scale clinical trial. These rodent data concluded that vaccine mRNA-1273, when given at a dose of 100 μg prior to mating or during pregnancy, was not associated with adverse effects.

Based on more recent risk-benefit calculations, pregnant people are now authorized to receive the vaccine from their physicians or other health care professionals but without the benefit of evidence that has been provided for nonpregnant patients. Efforts by the Centers for Disease Control and Prevention through its V-Safe registry as well as industry and the Food and Drug Administration will yield postmarket vaccine surveillance information from pregnant people, including evidence on the effects of the vaccine on pregnancy and infant outcomes. These data will be useful, but in the meantime, pregnant people and their clinicians must make real-time decisions based on little or no scientific evidence.

As noted in 2016, when the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established as part of the 21st Century Cures Act, there is a continuing need to address gaps in knowledge and research related to the development of safe and effective therapies for pregnant and lactating people. COVID-19 provides a clear and urgent example that these gaps remain and provides compelling reasons why the implementation recommendations of this task force need to be carried out. Pregnant people were excluded from participating in clinical trials of COVID-19 vaccines, but they are now being encouraged to receive the vaccine on a clinical basis.

The recommendations from PRGLAC specified key activities, such as proactive protocol planning for inclusion of pregnant people, that could be implemented to improve this situation, both for the current pandemic and for future efforts to treat or prevent disease in pregnant and lactating persons. First and foremost, a systematic plan should be in place to collect data from pregnant and lactating people early in response to a public health epidemic, including the collection of preclinical, safety, pharmacokinetic, and pharmacodynamic data so that they do not have to wait to be included in ongoing clinical trials. For example, if preclinical data from pregnant rodents and phase 1 data in nonpregnant humans demonstrate safety, a plan should be in place for how and when to incorporate pregnant individuals into clinical trials.

The use of existing registries, usable data sources, and federally funded research networks with specific expertise in this area could accelerate research and allow for common data elements and the use of central institutional review boards for multisite studies. Creating partnerships or expanding existing collaborations among public funders, industry partners, basic scientists, and clinicians involved in this research would encourage the sharing of data, biospecimens, or both and could promote clinical trial recruitment and funding. Additionally, the specific development of
models to estimate the effects of pregnancy on pharmacokinetic and pharmacodynamic testing would assist in advancing this line of research.7

Although revisions to federal regulations for the protection of people who participate in research (ie, the Common Rule) removed pregnant individuals as an example of a “vulnerable population,” ethical concerns and the potential for liability remain barriers to research on therapeutics during pregnancy and lactation. Additional protections that could be provided through rulemaking and the development of regulations would help overcome these barriers, especially for those preventive or therapeutic interventions that are accelerated to address a public health emergency. Other government initiatives, such as the Countermeasures Injury Compensation Program,9 provide benefits to pregnant and nonpregnant people who are injured by products designed to prevent or treat public health threats such as COVID-19, and may reduce the risk of liability for manufacturers.

Pregnant people can provide informed consent to participate in a clinical trial if equivalent safety data from preclinical studies are available. The key principle is that the pregnant person needs the same evidence that all other individuals who receive a medication, therapeutic, or vaccine receive to make an informed decision on whether to receive the treatment. The information that pregnant and lactating people need to make this decision should be tailored to their individual risks based on potential exposures in their home and work environments, their medical comorbidities, and their demographic characteristics, combined with the evidence on the safety and effectiveness of the vaccine and its potential effects on a fetus. Pregnant and lactating persons should not be protected from participating in research, but rather should be protected through research.

Building on the implementation plan provided by the PRGLAC Task Force,6 which included groups that represented multiple federal agencies, industry, academia, and nonprofit organizations, there is an urgent need to provide the resources, protections, and incentives to accomplish the research to generate the evidence that would promote maternal and postpartum health and overcome barriers to the safe and effective treatment for pregnant people. Guesswork must be removed when it comes to vaccination decisions for this important population. Thoughtfully including pregnant and lactating individuals in clinical research will lead to clinical care recommendations based on solid evidence.

ARTICLE INFORMATION
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REFERENCES