Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Pregnant people deserve the protection offered by SARS-CoV-2 vaccines

Melanie M. Maykin [a], Cara Heuser [b], Helen Feltovich [b,*], with the Society for Maternal-Fetal Medicine Health Policy Advocacy Committee [1]

[a] Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Women's Health, John A. Burns School of Medicine of the University of Hawaii, Honolulu, HI, USA
[b] Division of Maternal Fetal Medicine, Department of Obstetrics & Gynecology, Intermountain Healthcare and the University of Utah, Salt Lake City, UT, USA

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1. Introduction

It is imperative that pregnant individuals be included in the design and implementation of vaccine trials for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This population has historically been excluded from clinical trials for several reasons, including ethical concerns about fetal exposure, actual and perceived regulatory barriers, liability concerns, and a failure to invest in the appropriate public and private research infrastructure. However, the historical default of regular exclusion of "vulnerable populations" from early vaccine and drug trials has caused large data gaps in understanding the safety and efficacy of drugs and biologics. In fact, due to insufficient evidence about potential benefits and harms even of commonly used therapeutics, almost all agents used in pregnancy today are based on suboptimally designed studies and/or data extrapolated from non-pregnant populations. An additional complicating factor in SARS-CoV-2 vaccine development is that many companies are using novel platforms and adjuvants with limited or no historical safety data in pregnancy, further propagating a cycle of exclusion. Continued exclusion of pregnant individuals from vaccine trials will lead to a disproportionate burden of Coronavirus Disease 2019 (COVID-19) disease on them, as they may be unable or reticent to obtain vaccination due to lack of safety and efficacy data.

Our search for publicly available proposals from any nation's authority on the governance and oversight of human subjects research related to a SARS-CoV-2 vaccine for pregnant people was fruitless. Correspondingly, a search of 18 global clinical trial registries revealed that pregnancy is an explicit exclusion criterion for all (n = 9) of the phase III clinical trials [1]. Representatives of the United States federal government have repeatedly stated that inclusion of pregnant and lactating individuals in vaccine trials is a top priority. At a July 2020 hearing of the United States Senate Appropriations Subcommittee on Labor, Health and Human Services and Education, the directors of the National Institutes of Health (Dr. Francis Collins) and Centers for Disease Control and Prevention (Dr. Robert Redfield) declared that a top priority for vaccine trials is to include pregnant and lactating people, women of color, and other groups that disproportionately suffer COVID-19 related morbidity and mortality [2]. Yet still pregnant persons are not included in any SARS-CoV-2 vaccine trials. Perhaps this is because of inaccurate perceptions about risk of COVID-19 illness in pregnancy. Indeed, initial epicenter studies suggested a higher propensity for viral acquisition and severe illness in older males with underlying comorbidities, and early studies of pregnant patients described good outcomes [3]. This was unexpected given

* Corresponding author at: Division of Maternal Fetal Medicine, Department of Obstetrics & Gynecology, Intermountain Healthcare, Provo, UT 84604, USA.

[1] The SMFM Health Policy and Advocacy Committee strives to advance rights for pregnant and lactating people by advocating for health policies that improve access to equitable care.

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that immunologic and cardiopulmonary adaptions in pregnancy typically increase the risk of severe illness from respiratory infections and cause disproportionately poor outcomes for pregnant individuals and their offspring, as shown with SARS-CoV-1, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and influenza viruses [4].

Recent reports, however, are more consistent with initial expectations. A systematic multi-national review of 60 studies on SARS-CoV-2 in pregnancy reported that severe illness occurred in up to 18% of pregnant patients and critical disease complicated up to 5% of cases, comparable to rates in the general population [5] {v1.2 [Cited 21 April 2020]. Available from URL: https:// www.who.int/publications-detail/clinical-management-of-sever e-acut e-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected., #436}. Moreover, while initial accounts of outcomes in fetuses and neonates were very favorable, newer data suggest otherwise. Vertical transmission (from mother to fetus) is evidenced by cases such as neonates who tested positive by nasopharyngeal swabs collected immediately after birth (before maternal contact) and neonates with IgM in their serum immediately after birth [5]. In addition, case reports suggest that SARS-CoV-2 infects the placenta and causes histopathologic changes even in the absence of apparent fetal infection [6,7]. One concern related to this is that placental infection can lead to an inflammatory response that increases the risk of preterm birth and its attendant complications [8]. Another concern is that placental injury may increase the risk of long-term adverse neurodevelopmental and other outcomes for affected infants, as it does for many conditions that affect the placenta [9]. In addition, although uncommon, stillbirth has been reported in SARS-CoV-2 infected patients who have no other apparent cause for the fetal demise [7].

Other important facts to consider are that persons of childbearing potential represent a significant proportion of workers in high exposure risk professions such as healthcare [10] and, since pregnancy is often unintended or remains undiagnosed until the second trimester, inadvertent vaccination of pregnant persons will inevitably occur.

In summary, ensuring that SARS-CoV-2 vaccines will be purposefully offered to pregnant individuals without delay is critical to health equity because (a) outcomes in pregnancy are equivalent or worse than in non-pregnant populations, (b) there is potential for harm to not one but two lives, (c) persons of childbearing potential may have increased workplace exposure to SARS-CoV-2, and (d) inadvertent vaccination of pregnant persons is inevitable. This insistence is in line with the mission of the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group, an international team of multidisciplinary experts. In their guide of recommendations for the ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines, they advise establishing a presumption of inclusion of pregnant people in vaccine research, development, and deployment, and suggest that the burden of proof for exclusion be placed upon those who want to argue against that presumption [11].

Immediate action is necessary to ensure equitable access to SARS-CoV-2 vaccines. Vaccine clinical trials should include pregnant people. National health authorities must invest in institutional reforms, such as including maternal health experts on vaccine planning and safety committees, as well as policy reforms, such as removing regulatory barriers to research and reducing liability to study off-patent therapies in pregnancy. Additionally, studies that include individuals of child-bearing potential must employ mechanisms to systematically collect pregnancy-specific safety data from participants who are unknowingly pregnant or conceive during vaccine exposure. Finally, especially amidst an active pandemic, pregnant women should be offered vaccines as part of an outbreak response and should only be excluded if the available evidence demonstrates that risks to pregnant individuals and their offspring from the vaccine are greater than the risks of not being vaccinated.

In conclusion, pregnant persons deserve an equitable distribution of the burdens and the benefits of vaccine research. Professional societies around the world support this position, and we are aware of no formal opposition. We propose that the vaccine and the maternal health communities collaborate to intentionally include pregnant persons in phase III trials of SARS-CoV-2 vaccines now, and ultimately at every stage of vaccine development, to ensure that they have equitable, timely access to both the evidence and the vaccine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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