

Pregnant Women in Trials of Covid-19: *A Critical Time to Consider Ethical Frameworks of Inclusion in Clinical Trials*

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ABSTRACT Ethical issues abound during this unprecedented international public health crisis of Covid-19. While the trade-off between societal and individual interests that occurs at the intersection of public health ethics and clinical ethics affects all populations, this calculus has particular relevance for pregnant women and the question of when they will have access to new Covid-19 therapies and vaccines. Pregnant women are a “scientifically complex” population whose inclusion in clinical research must be done with consideration of the unique state of pregnancy. Yet research on the impact of Covid-19 on pregnant women is lagging. In a rush to prevent and treat SARS-CoV-2 infection, it is crucial that the interests of pregnant women be prioritized to enable them to make autonomous, informed decisions about participating in clinical trials. The global pandemic calls for a revisiting of frameworks for the inclusion of pregnant women in research, as these women have an important stake in the prevention and treatment of Covid-19.

KEYWORDS human subjects research, Covid-19 clinical trials, pregnant research participants, research with pregnant women, maternal-fetal ethics, inclusion of pregnant women in trials

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The global outbreak of Covid-19 is an unprecedented international public health crisis characterized by vast uncertainty about how to prevent and treat the condition against a constantly evolving backdrop of science and policy. Ethical issues abound. This is particularly true regarding the inclusion of pregnant women in clinical trials testing the safety and efficacy of Covid-19 vaccines and treatments.

Pregnant women are recognized as a “scientifically complex” population whose inclusion in clinical research must take into consideration the unique state of pregnancy and the relationships of the maternal-fetal dyad.¹ This is due, in part, to the physiological and anatomical changes accompanying pregnancy. These changes alter pregnant women’s responses to pharmacological agents and can increase the risks of morbidity and mortality from infectious diseases (such as the H1N1 influenza virus) compared to the risks for the general population. In addition, pregnant women’s in-

terests and actions are often the subject of public ethical debate; societal values and beliefs about women’s autonomous choices during pregnancy may be at odds with women’s reported interests and priorities. This becomes apparent in discussions about the nature of risks deemed acceptable for women to expose themselves to during pregnancy and the impact of those decisions on the well-being of their future newborns.² The Covid-19 pandemic is a call to revisit existing frameworks for the inclusion of pregnant women in research, as these individuals have an important stake in accessing new drugs and vaccines. In the rush to prevent and treat SARS-CoV-2 infection, it is crucial that the interests of pregnant women be prioritized in a way that enables them to make autonomous, informed decisions about participating in clinical trials. To neglect their interests could result in grave harm to them, their fetuses and neonates, and their families.

THE IMPACT OF COVID-19 DURING PREGNANCY

Research studies are needed to develop novel approaches to control this pandemic, and that research must address the needs of pregnant women as a population affected by SARS-CoV-2. Significantly, only a few observational case studies and retrospective reviews are available from which to garner information about Covid-19 among pregnant women. Yet from the data that are available, it is evident that much more research is needed to clarify the impact of viral infection on pregnant women and their fetuses. Studies show that some pregnant women have experienced the severe form of Covid-19. In an early study of 43 pregnant women admitted to a hospital labor and delivery unit at or near term, the mean estimated gestational age was 37 0/7 weeks, 86% of the patients had mild disease, 9.3% had severe disease, and 4.7% experienced critical illness requiring intensive care unit admission.³ New evidence has added to this initial picture, raising increased concern for significant maternal morbidity, including multiorgan failure, and mortality for pregnant women infected with the virus.⁴ A study in Iran details the deaths of seven out of nine women with severe illness during pregnancy.⁵ Their illnesses were more severe than those of their family and household members who were also infected.

Studies have also documented serious consequences for the fetus and newborn. One study reported that multiple pregnant Covid patients required early delivery due to maternal decompensation, leading to complicated neonatal courses and multiple neonatal deaths.⁶ Three of the cohort experienced intrauterine fetal demises during the time of clinical decompensation. In addition, there is little data that speaks to the rate and timing of vertical transmission of the virus during pregnancy or delivery.⁷ It is well known that some viruses (such as Zika, HIV, cytomegalovirus, and rubella) cross the placenta and cause serious complications for the fetus and neonate.⁸ Emerging data suggest that SARS-CoV-2 may cross and infect the placenta, increasing concerns about vertical transmission.⁹ Zeng et al. followed six newborns of mothers with mild cases of Covid-19.¹⁰ All were delivered by cesarean in negative-pressure operating rooms and were isolated from their mothers after birth. While none of the neonates tested positive for Covid-19 (using the laboratory technique

reverse transcription polymerase chain reaction), all six had viral antibodies detected serologically, suggesting in utero exposure to the virus, though none of the neonates were symptomatic for Covid-19. These studies demonstrate the need for larger studies and detailed methodologies to unravel questions about the impact of Covid-19 during pregnancy.

Despite the clear interests of pregnant women in accessing new drugs and vaccines for Covid-19, these individuals are not actively being recruited to participate in Covid-19 vaccine and treatment trials. For instance, the drug hydroxychloroquine was one of the first pharmaceutical agents under investigation for the treatment of Covid-19, yet the initial published trial data does not include data from pregnant trial participants,¹¹ even though its use in pregnant women with preexisting autoimmune disease has already been studied. From the available observational studies, the drug is known to cross the placenta and be found in breast milk,¹² but it does not appear to be associated with an increased risk of fetal or maternal complications. Initial studies have not concluded that hydroxychloroquine is an effective treatment for SARS-CoV-2, and, thus, the search for an effective agent must continue. Yet the ways in which these initial studies were conducted raise important questions about attitudes and policies regarding the inclusion of pregnant women in trials during the Covid-19 pandemic.

Other drugs are under investigation. According to the World Health Organization's Coronavirus Roadmap, remdesivir is considered a "first priority" drug due to its broad antiviral spectrum, with the *in vitro* and *in vivo* effectiveness against coronaviruses and the extensive clinical safety already documented.¹³ However, many current trials registered to study remdesivir in participants with moderate to severe infection also exclude pregnant women. A second priority is among antiretrovirals (HIV protease inhibitors). The combination of lopinavir and ritonavir has been widely used in HIV-positive pregnant women. Nevertheless, pregnant women are still excluded from some of the trials involving this antiviral regimen for Covid-19 infection.¹⁴ The emerging picture prompts important questions about the reasons to exclude pregnant women from or delay their involvement in clinical trials during this pandemic.

There are also troubling trends among the efforts to develop a vaccine. At the time of this writing, ten vaccine candidates are undergoing evaluation in human clinical trials, while several others are in preclinical stages of investigation.¹⁵ Estimated projections are that it will take 12 to 18 months to complete the typical three phases of human clinical trials. However, pregnant women are excluded from all ten vaccine trials at this time, and one trial requires participants to be on “effective” contraceptives during its entirety;¹⁶ when pregnant women will be eligible to receive a vaccine is unknown. This situation is not unprecedented. Historically, pregnant women have been excluded from initial vaccine trials, leading to delays in their access to the benefits of immunization against infectious diseases that are available to others.¹⁷

EXISTING FRAMEWORKS AND POLICY REGARDING THE INCLUSION OF PREGNANT WOMEN

Pregnant women’s exclusion from clinical trials testing the safety and efficacy of Covid-19 vaccines and treatments is occurring even though, over the past two decades, several advisory bodies and ethics experts have issued recommendations for including pregnant women in clinical trials. In 1994, a U.S. Institute of Medicine committee unanimously recommended that pregnant women not be excluded from drug trials and that U.S. federal regulations governing research with humans move from a presumption of exclusion of pregnant women to one of inclusion.¹⁸ The latter recommendation came to fruition with guidance the National Institutes of Health (NIH) issued in 2001, but pregnant women were not removed from the list of “vulnerable” groups for research purposes until the revised Common Rule for federally funded research took effect in 2019. Although the NIH has specifically emphasized inclusion in recent guidance, exclusion criteria figure prominently both in the Common Rule and in guidance from the U.S. Food and Drug Administration, contributing to researchers’ ongoing reluctance to include pregnant women in their studies.¹⁹ Moreover, methodologies have been proposed that include a staggered approach, increasing inclusion while allowing for customized safety and research protocols.²⁰ Despite these changes, data from clinical trials reveal that pregnant women are still significantly underrepresented as

trial participants. For example, 73% of drugs approved by the FDA between 2000 and 2010 included no clinical trial data about risk in pregnant women. And a 2012 study found that 95% of industry-sponsored clinical trials that included women of childbearing age specifically excluded pregnant women.²¹ More recently, pregnant women were excluded from all Ebola drug treatment and vaccine trials during the 2013 to 2016 outbreak, despite known high maternal and fetal mortality rates and expert recommendations to include pregnant women.²² Though strong recommendations have also been made for including pregnant women in other infectious disease research, those recommendations have not been robustly implemented.²³

The design and conduct of research including pregnant women may be fraught with logistical and ethical considerations that often require additional time and effort to address. Yet these should not dissuade researchers from conducting the studies needed to advance understanding of Covid-19 in this population.

Recent scholarship has examined the ethics of including pregnant women in clinical research on therapeutics and vaccines. The Second Wave Project was the largest initiative to enumerate the harms of exclusion: limited data on medication pharmacokinetics and safety during pregnancy for both mother and fetus, a reluctance to treat maternal illness during pregnancy, and a lack of access to trials with the prospect of direct benefit to the mother and/or fetus²⁴ (the latter being a violation of the principles of justice and equity). This stance also violates the autonomy of pregnant women, since it implicitly denies them an ability to make reasoned

choices for themselves and their future children about whether to accept or refuse clinical trial participation based on their own judgment—judgment that, after the child’s birth, they would nearly all have the power to exercise.²⁵ The Second Wave Project highlighted pervasive assumptions that exclusion from research is a safer default position than inclusion and pointed out the glaring flaw in this assumption: that, in many contexts, “our evidence base for current treatments is so weak that standard practice is itself more like experiment than treatment.”²⁶ Exclusion carries its own practical risks.

The recommendations of the Second Wave are all grounded in the “presumptive inclusion” of pregnant women in development and deployment of vaccines, emphasizing that “pregnant women should have opportunities to enroll in vaccine studies conducted during outbreaks and epidemics whenever the prospect of benefit outweighs the risks to pregnant women, their offspring, or both.”²⁷ Such opportunities, the group notes, should allow a pregnant woman to join or continue participation in a trial based on her informed consent alone, not requiring the additional consent of her partner or another actor. To support this presumptive inclusion, the guidance also urges vaccine researchers to prioritize preclinical data that will be needed for inclusion of pregnant women in future trials, and research funders to prioritize the development of vaccines that are promising for use during pregnancy over those that are likely contraindicated during pregnancy.

FINDING A PLACE FOR PREGNANT WOMEN IN THE STUDY OF COVID-19

Some may contend that the risks to pregnant women in taking part in experimental trials of drugs or vaccines is unacceptably high when nonpharmacologic alternatives may exist. For instance, a recommendation for prolonged social distancing may initially appear as a more acceptable alternative for the management of pregnant women during a pandemic. There are, however, unique risks to extending the nature or duration of social distancing for pregnant women while other members of the community have access to experimental vaccines and treatments. This approach would disproportionately expose pregnant women to economic and social hardships within their communities, including threats that may be worsened in the context of

pregnancy (such as the risk of domestic abuse). Furthermore, persistent social distancing may limit access to community-based group prenatal care support programs, particularly for women who suffer the brunt of health care disparities and/or do not have access to the Internet.²⁸ Social distancing for postpartum women also requires significant consideration, particularly for those at risk for postpartum depression. Women with an active Covid-19 infection are likely to be temporarily separated from their infants after delivery to reduce transmission to the neonate.²⁹ Yet the risks of mother-and-infant separation as a result of Covid-19 infection have yet to be determined.

In addition, some clinician-researchers (and policy-makers who promote such strategies) may promote nonpharmacologic approaches such as “proning” to support the management of pregnant patients with hypoxia from Covid-19, as the prone posture has demonstrated some benefit for nonpregnant patients.³⁰ The approach entails the patient either turning herself or being turned prone so that she is lying on her stomach. However, because of the size of the gravid uterus and the potential for vascular compression in specific positions, this is not a reasonable approach for women in the second and third trimesters of pregnancy, stages in which the effects of Covid-19 may be most severe for a mother and fetus.³¹ Thus, management approaches that might seem to minimize risks to pregnant women and their fetuses may, in fact, introduce additional harms if researchers and policy-makers do not recognize or address the special complexities of pregnant patients as study participants.

The Covid-19 pandemic highlights the need for giving pregnant women the opportunity to make informed, autonomous decisions about whether to participate in preventive and treatment trials. This should hold true independently of how research risks and benefits are distributed within the maternal-fetal dyad: whether an experimental intervention aims to manage a maternal health condition with some secondary benefit to the fetus (such as treatment of maternal hypertension with the reduction of preeclampsia, intrauterine growth restriction, and preterm delivery) or aims to manage a fetal condition with little or no secondary benefit for the woman (such as in utero repair of meningomyelocele). At the same time, research involving pregnant women

must take into consideration the significant unknowns about Covid-19, its prevention, and treatment. This calls for weighing the unknown risks of SARS-CoV-2 and Covid-19 against the known medical, ethical, and social harms of excluding pregnant women from clinical trials. Finally, research involving pregnant women must be responsive to the evolving understanding of the virus and associated disease for the pregnant woman, fetus, and newborn.

Thus, research involving pregnant women during the Covid-19 pandemic must involve a scientifically and ethically justified methodological design. Meticulous attention is required in defining study outcomes, endpoints, and adverse events, as those variables define risks and benefits to the maternal-fetal dyad. Clinical trial design must also incorporate the newest data, and real-time monitoring must be implemented to efficiently identify if the risk-to-benefit ratio shifts as a result of new understandings or emerging biomedical interventions. Oversight mechanisms must be not only robust enough to address the specific complexities of research involving pregnant women but also responsive enough to react to new data. For instance, if evidence emerges that women with Covid-19 in early pregnancy may be at increased risk of pregnancy loss and preterm labor, then clinical trials involving an experimental vaccine using live virus should be halted and reevaluated.³² Oversight processes should concern both biological outcomes and important psychosocial and ethical issues emerging in conjunction with scientific understanding of the pandemic. Clinical trials involving pregnant women must also entail rigorous human subjects protections to minimize risks to the maternal-fetal dyad. These include a process of ensuring that regulations hold fast to policies for maternal consent and resist motions toward paternal consent.

The design and conduct of research including pregnant women may be fraught with logistical and ethical considerations that often require additional time and effort to address. Yet these should not dissuade researchers from conducting the key studies needed to advance the understanding of Covid-19 in this population, nor should policy-makers refrain from advocating for and supporting such research. Without these efforts, the harms from the Covid-19 pandemic will be increased for pregnant women, their fetuses, and their families—

not just from the virus itself but also from the choices that scientists, policy-makers, and society have made about acceptable levels of risks for women. ♦

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