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VIEWPOINTS

Importance of Inclusion of Pregnant and Breastfeeding Women in COVID-19 Therapeutic Trials

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Investigators are employing unprecedented innovation in the design of clinical trials to rapidly and rigorously assess potentially promising therapies for coronavirus disease 2019 (COVID-19); this is in stark contrast to the continued near-universal regressive practice of exclusion of pregnant and breastfeeding women from these trials. The few trials that allow their inclusion focus on postexposure prophylaxis or outpatient treatment of milder disease, limiting the options available to pregnant women with severe COVID-19 to compassionate use of remdesivir, or off-label drug use of hydroxychloroquine or other therapies. These restrictions were put in place despite experience with these drugs in pregnant women. In this Viewpoint, we call attention to the need and urgency to engage pregnant women in COVID-19 treatment trials now in order to develop data-driven recommendations regarding the risks and benefits of therapies in this unique but not uncommon population.

Keywords. pregnancy; COVID-19; treatment; trial.

The speed at which investigators have designed and initiated trials to evaluate potential coronavirus disease 2019 (COVID-19) therapeutics is truly astonishing. Less impressive is the continued exclusion of pregnant and lactating women from COVID-19 treatment trials. In this Viewpoint, we highlight the discrepancy between the innovative and adaptive ways in which investigators are evaluating COVID-19 therapeutics, in contrast to the continued regressive practice of excluding pregnant and lactating women from treatment trials. While at this time there is no definitive evidence that pregnant women are at increased risk of infection or more severe outcomes, it is clear that pregnancy and the early postpartum periods present unique management challenges that require taking into account maternal, fetal, and neonatal risks and benefits [1–6]. Exclusion of pregnant and breastfeeding women ensures these decisions will continue without the benefit of our highest levels of evidence.

Despite some experience using both remdesivir and hydroxychloroquine in pregnancy, there is near-universal exclusion of pregnant women in COVID-19 clinical trials evaluating these potentially promising therapies. The few trials that allow their inclusion focus on postexposure prophylaxis or outpatient treatment of milder disease. This means the only options currently available to pregnant women with severe COVID-19 disease are limited to compassionate use of remdesivir, or off-label use of hydroxychloroquine or other therapies.

Remdesivir is a nucleotide analogue, initially developed for the treatment of Ebola virus disease (EVD), which shows promise for COVID-19. Notably, pregnant women were included in the Pamoja Tulinde Maisha (PALM ["Together Save Lives" in the Kiswahili language]) randomized controlled trial of EVD therapeutics, which compared ZMapp to MAb114, REGN-EB3, or remdesivir [7]. In the PALM trial, 6.1% (17/277) of women enrolled were pregnant at the time of EVD diagnosis, of whom 35% (6/17) were randomized to remdesivir. There were no maternal-, pregnancy-, or neonatal-related severe adverse events noted in the remdesivir group.

Of the trials evaluating remdesivir for COVID-19 that are currently registered on clinical trials.gov, all exclude pregnant and breastfeeding women, including the National Institutes of Health (NIH)–sponsored multisite Adaptive COVID-19 Treatment Trial (NCT04280705). This trial was specifically designed to incorporate the needed flexibility and complexity for rapid, rigorous assessment of experimental treatments, with efficacious treatments becoming the control for newer investigational agents. Similarly, the World Health Organization-sponsored Solidarity Trial (ISRCTN83971151) strives to remove barriers to implementing a large-scale trial by simplifying procedures and outcomes, including minimizing the burden of data collection to basic baseline characteristics and comorbidities, randomizing patients to locally available drugs or standard of care, with no additional measurements or documentation after enrollment; the final outcome is the day the patient leaves the

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hospital or dies, and whether they required oxygenation or ventilation. Despite acknowledging that pregnant women may have a higher risk of infection in the trial registration, the Solidarity Trial also excludes pregnant women. In stark contrast to these inventive efforts employed by investigators and swift support of regulatory bodies and funders in response to the pandemic, the continued exclusion of pregnant and lactating women represents exnovation, the opposite of innovation.

Although data are limited, there is widespread use of hydroxychloroquine for hospitalized patients with COVID-19 in several settings, and the US Food and Drug Administration (FDA) recently authorized its emergency use while encouraging the conduct and participation in randomized controlled trials to confirm efficacy [8]. There is evidence that hydroxychloroquine confers minimal fetal or maternal risk in case series of pregnant women with systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune disease; a recent meta-analysis of 800 women taking hydroxychloroquine in pregnancy found no increase in pregnancy complications or congenital malformations, but noted a significant increase in spontaneous abortions that may be attributed to underlying autoimmune disease [9]. While multiple trials are evaluating the efficacy of hydroxychloroquine for treatment and postexposure prophylaxis, almost all exclude pregnant or breastfeeding persons. Notable exceptions are the University of Minnesota (NCT04308668) and University of Washington (NCT04328961) hydroxychloroquine postexposure prophylaxis trials and the University of Washington (NCT04354428) and AIDS Clinical Trials Group (ACTG) (NCT043558068) hydroxychloroquine/azithromycin trials for outpatient treatment of milder disease. Recent data suggesting a potential link with macrolides and fetal malformation will require additional counseling regarding the risks and benefits of azithromycin for participants enrolling in early pregnancy [10]. These few studies, which allow the inclusion of pregnant women, are in line with recommendations from multiple institutional review boards (IRBs) that support the policy of providing pregnant women with the same opportunities as nonpregnant women to participate in research, provided that participants are counseled on the known or possible reproductive or lactation risks from the study, and measures that will be taken to minimize them. Per our own institutional IRB guidance, research inclusive of pregnant women increases the likelihood that the knowledge gained can be extended judiciously to this population.

While an initial report of a handful of pregnant women with COVID-19 in the third trimester was somewhat reassuring in that pregnant women did not appear to be more susceptible to enhanced COVID-19 disease than nonpregnant adults [3], other case series provide a more ominous view, with higher rates of preterm labor and stillbirth than would be expected [1], as well as the need for intensive care unit (ICU) admission for pregnant women [2]. In a case series of 7 pregnant women hospitalized with COVID-19 in New York City, 2 women requiring ICU admission were asymptomatic upon initial presentation for indicated labor induction, were diagnosed after delivery, and received off-label use of hydroxychloroquine [2].

There are planned or ongoing observational studies and registries focused on COVID-19 in pregnancy, including in our own state of Washington, home to the first reported COVID-19 cases in the United States. While these studies will provide valuable information on maternal, pregnancy, and infant outcomes, including investigations on potential transmission, it will be difficult to interpret the clinical implications of treatment without a formal study design or comparator group.

There is widening recognition of the need to rapidly identify treatment options for pregnant and lactating women. The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established by the 21st Century Cures Act and charged with providing guidance to the US Secretary of Health and Human Services to address gaps in knowledge and research on safe and effective therapies for pregnant and lactating women [11]. PRGLAC identified a need to alter cultural assumptions that have significantly limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for pregnant and lactating women.

In response to the exclusion of pregnant and lactating women in COVID-19 clinical trials, the Coalition to Advance Maternal Therapeutics (CAMT), composed of more than 20 organizations, has urged NIH and FDA leadership to use their authorities to ensure development of vaccines and therapeutics for pregnant and lactating women, and to proactively remove barriers and work with sponsors and researchers to ensure their inclusion in critical COVID-19 research [12]. Both PRGLAC and CAMT have advocated for a "cultural shift to protect women *through* research rather than protecting them *from* research" [12].

Pregnant women are a unique but not uncommon population and they deserve the opportunity for fair and ethical inclusion and close safety monitoring afforded by carefully designed clinical trials. While it is highly unlikely there will be dedicated clinical trials focused in pregnancy, we should ensure the inclusion of pregnant and lactating women within ongoing large-scale clinical trial efforts. Too often, research includes pregnant women well after the establishment of efficacy in nonpregnant populations, if done at all. The COVID-19 pandemic offers the opportunity, and requires the urgency, to engage pregnant women early in the science in order to develop data-driven recommendations regarding the risks and benefits of therapies for which they may benefit.

Notes

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