Consider pregnancy in COVID-19 therapeutic drug and vaccine trials

131 million women give birth annually. This population is particularly vulnerable to emerging infectious pathogens due to alterations in immune, respiratory, and cardiovascular physiology that occur during pregnancy. Recent outbreaks of severe acute respiratory syndrome, Middle East respiratory syndrome, influenza H1N1, Ebola virus disease, and Zika virus disease exposed high rates of maternal morbidity and mortality, fetal loss, and fetal harm. Early data regarding pregnancy outcomes in COVID-19 are reassuring: maternal outcomes are similar to non-pregnant adults, and vertical transmission and neonatal infection are rare.[1] However, pregnant women remain at risk of severe disease requiring intensive care, and they deserve equity in access to therapeutic options informed by rigorous scientific data.

Pregnant women have systematically been excluded from clinical trials of therapeutics and vaccines. There are currently more than 300 trials exploring therapeutics for COVID-19, yet near universal exclusion of pregnant women, despite many of these trials repurposing drugs already widely, and safely, used in pregnancy.[2] For example, hydroxychloroquine is commonly used in connective tissue disorders, and lopinavir plus ritonavir in combination is a common antiretroviral therapy to prevent vertical transmission of HIV. Intrapartum azithromycin decreases maternal and neonatal infective morbidity. Interferon beta-1a reduces multiple sclerosis relapse. Exposure registry and post-marketing surveillance for these drugs all provide reassuring signals of safety.

These drugs are now the subject of clinical trials to assess efficacy and safety in treatment of COVID-19, yet pregnant women are often missing in these trial populations. The largest of these multicentre trials include the WHO-sponsored SOLIDARITY trial (>90 countries; ISRCTN83971151) and the National Institutes of Health (NIH)-sponsored ORCHID (hydroxychloroquine; NCT04332991) and ACTT (remdesivir; NCT04280705) trials—all of which excluded pregnant women in their original protocol. We welcome the recent development (as of April 21, 2020) whereby the SOLIDARITY trialists have revised the exclusion of pregnant women; this development might provide a useful precedent for other trialists. REMAP-CAP (NCT02735707) will enrol pregnant women admitted to an intensive care unit but exclude them from randomisation to antiviral therapies or immunomodulators. By contrast, RECOVERY (ISRCTN50189673) does include hospitalised pregnant women, randomised to one of four treatment arms.

The COVID-19 pandemic highlights the vulnerability of sick pregnant women if systematically excluded from clinical trials, and potentially limits their access to therapeutics through off-label or compassionate use.[3] Clinical registries might collect data about exposures but will not allow pregnant women access to evidence-based care informed by clinical trials. Moreover, vaccination in pregnancy protects the mother, fetus, and newborn. This tripling of benefit means rapid vaccine development must allow pregnant women safe and timely inclusion in vaccine trials.[4]

Appeals have been made to the NIH and the US Food and Drug Administration for reversal of the exclusion of pregnant women in their trials,[5] but advocacy groups and professional organisations must press for safe inclusion of pregnant women in clinical trials for COVID-19 therapeutics and vaccines. Pregnant women must be afforded the same autonomy offered to other adults to decide about participation in clinical trials.

We declare no competing interests.

*Clare L Whitehead, Susan P Walker
clarew@unimelb.edu.au

Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, VIC 3052, Australia (CLW, SPW); Pregnancy Research Centre, The Royal Women's Hospital, Parkville, VIC, Australia (CLW); and Mercy Perinatal, Mercy Hospital for Women, Heidelberg, VIC, Australia (SPW)

1 Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID 1-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2020; published online March 25. DOI:10.1016%2Fj.ajogmf.2020.100107

2 Mullard A. Flooded by the torrent: the COVID-19 drug pipeline. *Lancet* 2020; **395:** 1245–46.

3 Hinton DM. Request for emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 coronavirus disease. March 28, 2020. https://www.fda.gov/media/136534/download (accessed April 20, 2020).

4 Cohen J. Zika rewrites maternal immunization ethics. *Science* 2017; **357:** 241.

5 Coalition to Advance Maternal Therapeutics. COVID-19 and pregnant women and lactating women. March 18, 2020. https://s3.amazonaws.com/cdn.smfm.org/media/2268/Final_CAMT_COVID_Letter_March_2020.pdf (accessed April 20, 2020).

Published **Online**
May 13, 2020
https://doi.org/10.1016/S0140-6736(20)31029-1