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Current Commentary

Protection by Exclusion

Another Missed Opportunity to Include Pregnant Women in Research During the Coronavirus Disease 2019 (COVID-19) Pandemic

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Coronavirus disease 2019 (COVID-19) is a novel infectious disease that started in Wuhan, China, and has rapidly spread all across the world. With limited ability to contain the virus and relatively high transmissibility and case fatality rates, governmental institutions and pharmaceutical companies are racing to find therapeutics and vaccines that target this novel coronavirus. However, once again, pregnant and breastfeeding women are excluded from participating in clinical trials during this pandemic. This "protection by exclusion" of pregnant women from drug development and clinical therapeutic trials, even during epidemics and pandemics, is not unprecedented. Moreover, it is both misguided and not justifiable and may have excluded them from potentially beneficial interventions. This is another missed opportunity to obtain pregnancy-specific safety and efficacy data, because therapeutics developed for men and nonpregnant women may not be generalizable to pregnant women. Therefore, we recommend and urge the scientific community and professional societies that, without clear justification for exclusion, pregnant women should be given the opportunity to be included in clinical trials for COVID-19 based on the concepts of justice, equity, autonomy, and informed consent.

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Coronavirus disease 2019 (COVID-19) is a novel infectious disease that started in Wuhan, China, in late December 2019, with the first human-to-human transmission reported in mid-January 2020.[1,2] Coronavirus disease 2019 is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) and has rapidly spread all across the world, leading the World Health Organization to declare it a pandemic on March 11, 2020.[1] As of April 22, 2020, more than 2.5 million cases of SARS-CoV-2 have been confirmed worldwide, with more than 175,000 related deaths.[1] Currently there are no approved treatments for COVID-19 or vaccines against SARS-CoV-2. Guidelines have focused on hand hygiene and social distancing and clinical management consisting of supportive and respiratory care, treatment of secondary pulmonary infections and respiratory failure, and management of other complications. Given the limited ability to contain the virus, and the relatively high transmissibility and case fatality rates, governmental institutions and pharmaceutical companies are racing to find therapeutics and vaccines that target this novel coronavirus.[1]

On April 14, 2020, we conducted an online search at www.ClinicalTrials.gov using "COVID" as the search term. This yielded 588 studies, with only four (less than 1%) specifically designed for pregnant women (three registries, two from Italy and one from the United States, designed to determine the clinical characteristics of COVID-19 infection in pregnancy and a survey from Turkey to evaluate physical activity and sleep). Of the 588 studies listed on the ClincalTrials.gov website, 376 (64%) were interventional

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(22% in the United States and 16% in China) and involved agents such as remdesivir, hydroxychloroquine, azithromycin, interleukin-6 inhibitors, lopinavir, ritonavir, hyperimmune or convalescent plasma, and others. Although none of these interventional trials were specifically designed for pregnant women, the majority (more than two thirds) specifically added pregnancy as an exclusion criterion or required a "negative pregnancy test" for participants to be included. Examples of these include ACTT (the Adaptive COVID-19 Treatment Trial), sponsored by the National Institute of Allergy and Infectious Diseases, evaluating the safety and efficacy of remdesivir, and the ORCHID trial (Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease), sponsored by the National Heart, Lung, and Blood Institute, evaluating hydroxychloroquine. Even a trial evaluating high doses of antiinflammatory and antioxidant dietary supplements such as eicosapentaenoic acid and gamma-linolenic acid has excluded pregnant women. A singular bright example of inclusion is the CROWN CORONATION study, aimed to repurpose chloroquine to health workers for coronavirus mitigation. Although this is not a pregnancy-specific trial, the investigators specifically noted that pregnancy and breastfeeding are not exclusions for entry. A similar pattern of exclusion of pregnant women from COVID-19–related trials was noted in other international registries.

This pattern of "protection by exclusion" of pregnant women from research, even during pandemics and epidemics, is not new or limited to emerging infections.[3,4] Even during the Ebola virus epidemic, pregnant women were excluded from all therapeutic and vaccine-development trials. This occurred even with Ebola being a highly lethal virus–the vast majority of cases of Ebola virus infection in pregnancy resulted in the death of the mother and child.[5] This automatic disqualification denies pregnant women the potential for benefit given to other patients. Since the 1950s, and after the discovery of the association between exposure to certain drugs during gestation and birth defects, pregnant and breastfeeding women have been systematically excluded from drug-development and clinical trials. Despite several policy and legislative changes, including the National Institutes of Health Revitalization Act of 1993, the U.S. Food and Drug Administration's guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, the National Institutes of Health's guidance for the inclusion of women in clinical trials, the establishment of the Office on Women's Health, and the establishment of the Task Force for Research Specific to Pregnant and Lactating Women, pregnant women remain therapeutic orphans, with the vast majority of current accepted therapies for medical conditions never having been studied in pregnancy.[4,6]

Results from studies that have excluded pregnant women cannot be automatically extrapolated to a pregnant population. This lack of generalizability is due to the physiologic changes in pregnancy, which affect the pharmacokinetic and pharmacodynamic properties of drugs. The lack of data specific to pregnancy will negatively affect the health of pregnant women and their access to interventions in the current and next outbreak, especially with estimates from public health officials that indicate that this outbreak may last for a significant duration of time until an effective vaccine is identified and a massive vaccination campaign is implemented. Although it is not known how quickly a safe and effective vaccine may be readily available and approved by the U.S. Food and Drug Administration, experts believe it will take at least 12-18 months.[2] Pregnant women with COVID-19 infection may be harmed, because knowledge gained from ongoing research may not be generalizable to them. This will create a knowledge gap concerning the safety and efficacy of any drugs or interventions that may emerge from current COVID-19 research.[4,6,7] Although fetal safety is the most cited reason for the exclusion from research studies of pregnant women and those who could become pregnant, it is unethical to automatically preclude them from carefully designed clinical therapeutic research studies. For example, several trials are investigating the benefit of hydroxychloroquine with or without azithromycin in patients with COVID-19 infection. However, pregnant women are excluded despite the fact that these two medications have been used for decades in pregnancy for women with systemic lupus erythematosus or as malaria treatment and prophylaxis (hydroxychloroquine), and in women with community-acquired pneumonia and those with preterm prelabor rupture of membranes (azithromycin). Moreover, the drugs' safety profiles are well established in pregnancy.

Pregnancy recently was removed as a classification for vulnerable population in the common rule, but the research community has yet to catch up.[6] The perception that pregnant or breastfeeding women are a "vulnerable population" needing protection from exploitation research studies has hindered progression of care. We need to advocate for a cultural shift within the research community to view this population as in

need of more evidence, particularly in pharmaceutical research.[4,7] Pregnant women should be permitted to determine their eligibility and entry into a research study based on the principle of informed consent. Excluding pregnant women from research under the guise of the "vulnerable populations" perception places a restraint on their right to autonomy.[6] Although one must consider the safety of a drug in pregnancy, it is equally important to consider the risks of not treating or inadequately treating pregnant women. Similarly, the risk to the fetus of treatment needs to be weighed against the risk of inadequate treatment, given that many of the conditions that affect the mother will ultimately adversely affect the fetus if not treated. It is crucial that the sequelae of lack of treatment be weighed against the risks of treatment or, at a minimum, inclusion in clinical trials.

The prevalence of pre-existing medical conditions or complications in pregnancy has progressively increased over the past three to four decades. This is secondary to increased maternal age at the time of pregnancy and higher rates of obesity and chronic medical conditions, such as diabetes, hypertension, and asthma, during pregnancy. These comorbidities have been well established as risk factors for mortality for patients with COVID-19 infection.[8] While we face this life-threatening emerging pandemic, it is significant that pregnant women are excluded from potentially beneficial interventions, with researchers failing to consider the concepts of justice, equity, and autonomy. Therefore, we urge the scientific community not to miss this opportunity, and we recommend that, without clear justification for exclusion, pregnant women should be given the opportunity to be included in clinical trials for COVID-19. Rather than automatically excluding them, investigators should consult with experts in obstetrics, teratology, and obstetric pharmacology. This automatic exclusion is both misguided and not justifiable. Pregnant women are fully able to weigh the ethical implications of health decisions they make for themselves and their fetuses, especially when provided with adequate counseling. We also call on the concerned professional organizations, such as the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, to endeavor to provide timely consultation as well as advocate for reversal of the decision to exclude pregnant women from the appropriate trials.

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