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Conducting research during the COVID-19 pandemic

Mirella Mourad*, Sabine Bousleiman, Ronald Wapner, and Cynthia Gyamfi-Bannerman

Department of Obstetrics, Gynecology and Reproductive Science, Division of Maternal Fetal Medicine, Columbia University Irving Medical Center, New York, NY USA

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ABSTRACT

The highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected every aspect of medical practice and has all but ceased clinical, translational and basic science research. Pregnant women appear to be similarly affected by the virus as non-pregnant adults. As obstetricians, not only do we have a duty to care for pregnant women and their fetuses, but to continue to conduct research, inclusive of that which would guide us in delivering care during a pandemic. Conducting such research has its challenges. The objective of this chapter is to review the impact of SARS-CoV-2 on ongoing and new pregnancy research during the pandemic, describe the challenges encountered and summarize the key strategies necessary for a successful research environment.

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Introduction

The first case of severe acute respiratory syndrome coronavirus –2 (SARS-CoV-2) was reported in the United States on January 19th 2020.¹ Since then, the highly contagious SARS-CoV-2 has affected every aspect of how we practice medicine and conduct research. Pregnant women appear to be equally affected by SARS-CoV-2 as compared to the non-pregnant general population,^{2,3} however, there are additional challenges unique to pregnancy. Pregnant women have an ongoing need to present to medical facilities for prenatal care, which introduces challenges, such as the need to adequately time and space the frequency of prenatal visits. With data showing that many of these women are asymptomatic upon presentation for delivery, screening and testing at the time of presentation to labor and delivery and the postpartum period becomes necessary to protect the neonate, other patients and healthcare professionals.^{2,4} As obstetricians, we have a duty to care for pregnant women and their fetuses, but also to conduct research to guide us on how to deliver care.

Impact of the pandemic on ongoing clinical research

Many academic medical centers across the United States have paused clinical research to (i) eliminate non-essential contact to protect study participants and research staff, (ii) to shift focus to SARS-CoV-2 related research, (iii) to adapt to necessary changes in the hospital operations necessary to accommodate safe clinical care.

Research personnel

With the increasing pressure of the pandemic on the health-care system, there have been widespread changes to workflow. Research personnel have been reallocated to other assignments. For example, research nurses functioning as support staff, on labor and delivery and the postpartum units has considerably alleviated pressure on the clinical staff allowing them to respond to the increased demands of sicker patients. COVID-19 infection among staff will also limit the

*Corresponding author.

E-mail address: mjm2246@cumc.columbia.edu (M. Mourad).

research workforce. Our research department has 20 research nurses, staff and coordinators. During the months of March and April, 9 research employees (45%) were redeployed to labor and delivery and the postpartum units, 3 (15%) were already working remotely and continued to do so, 3 (15%) could not be considered for redeployment due to logistical administrative reasons, 2 (10%) could not be redeployed for other reasons and 3 (15%) continued to work on essential research studies.

Research staff will also be concerned about their risk of exposure during in-person visits. Although this risk is hard to quantify it can be reduced by reducing research only visits or scheduling them via video conference. When this is not feasible, it is important to provide the best and most transparent information possible. Appropriate personal protective equipment (PPE) is mandatory to help address some of these concerns.⁵ During times of personal protective equipment shortages, research staff may need to limit activities that require PPE use.

At some institutions, medical students and residents have taken on a more prominent role in screening, consenting and enrolling research participants; tasks generally conducted by research personnel.⁶ For example, for high priority research for public health concerns such as SARS-CoV-2, residents may perform essential in-person research activities in the absence of research personnel. However, consideration should be given to the unique skills provided by experienced research coordinators and the potential impact their replacement with less research-skilled house staff may have on studies.

Research participants

The institutional review boards have posed the fundamental question of whether research visits or their components change the risk-benefit ratio for study subjects, from that initially considered in the informed consent.⁵ This consideration helps principal investigators re-evaluate the balance between the risks of SARS-CoV2 exposure to the risk of delaying or discontinuing study interventions. In an international cross sectional survey, Gobat et al. reported that there was strong public support for pandemic relevant clinical research initiatives. On a patient level basis, trust in the treating physicians and health care system are an important consideration for subjects when making the decision to participate in a research study.⁷ This trust is maximized when research participants in ongoing clinical trials are prospectively informed of changes in protocols due to SARS-CoV2 such as paused, remote, or delayed study visits.

Telehealth visits

As COVID-19 continues to spread travel restrictions, city lockdowns and stay at home orders have been implemented to a varying degree across the United States and internationally. As clinicians decrease the number of in person visits, the number of research visits and study assessments also become limited making remote study visits with telemedicine crucial to maintaining contact with research subjects during the pandemic.⁸ FDA guidance issued in March 2020 allows for

research visits to be conducted by telephone or video contact when feasible and allows researchers to implement the change without prior approval but rather with post implementation notification to the IRB. In some protocols, research study drug can be mailed to participants instead of in-person dispensing.⁹

Clinical trials

The SARS-CoV2 pandemic has had a major impact on clinical trials. The initial response was to defer all start up activities for new trials and to suspend recruitment to existing trials.¹⁰ This response inevitably led to multiple concerns. First, participants who may have potentially benefitted from a particular study arm lost the opportunity to do so. Second, follow up visits on already randomized subjects were interrupted. Third, the halt in research activity undoubtedly led to a loss of investigator revenue. In order to mitigate some of the concerns, a different approach was undertaken. There was a shift in the resources available to focus on continuing care for patients already in trials, especially if there was benefit from the treatment.¹¹ The risk – benefit ratio determination was made initially by the Principle Investigator and approved by Institutional Review Boards.

Basic science research

Basic scientists faced their own unique challenges during the COVID-19 pandemic. Even in the face of institutional shut downs, scientists could not stop attending to their laboratories. Animal models, which are essential to basic science research, need to be fed and cared for, breeding lines must continue and cell cultures need to be maintained. In order to continue to conduct research, multiple strategies have been employed: i. Researchers are now scheduled to work in shifts in order to promote social distancing, ii. Non-essential experiments were stopped, iii. Strategies to conserve research supplies, which could become scarce during a pandemic, were employed.¹²

COVID-19 research in pregnancy

In the early 1990s, significant efforts by the National Institutes of Health (NIH) were made to include a larger proportion of women especially pregnant women in clinical trials.¹³ However, currently, there are over 2100 clinical trials underway to understand and treat COVID-19, of which only 42 trials are being conducted in pregnancy,¹⁴ i.e. less than 2% of current COVID-19 trials include pregnant women.

Planning research in pregnant women requires a thoughtful process. During the 2009 H1N1 pandemic, pregnant women were included in the vaccine trial, after safety and efficacy was confirmed in the general population. Pregnant women in their second and third trimester were included, avoiding the first trimester in an effort to minimize theoretical teratogenic risks.¹⁵ During the 2014 Ebola virus epidemic, pregnant women were excluded from all vaccine and therapeutic trials denying them any potential benefit.¹⁶ Even though pregnancy is a time for caution, it is imperative to

include and advocate for pregnant women in clinical trials in order to allow them to receive potential benefits while being able to safely study the risks, with safety being the unique stoppage criteria for pregnancy.

Data Safety and Monitoring Committees should review and advise any protocol changes to allow the continuation of research in pregnancy during COVID-19 pandemic, while ensuring safety of participants and researchers.

Challenges of conducting research during a pandemic

Numerous considerations arose when conducting research during the COVID-19 pandemic. The first and foremost, was the responsibility of the involved institutions to share their initial experience with the community. To accomplish this, time is of the essence. There needs to be a balance between wanting to be the “first to press” with making sure that sufficient experience has been accrued to avoid transmission of incorrect information. This is best accomplished by developing a plan that progresses from initial alerts to the community and evolves into reports describing in more detail the spectrum of the disorder and its response to treatments. Case reports and results from small case series need to be published rapidly in order to disseminate basic information necessary for initial care.

With COVID-19, initial observations were hindered by lack of adequate screening with only symptomatic pregnant patients being sampled. Observations following patient encounters in which patients that were asymptomatic at presentation to labor and delivery who later became symptomatic exposing health care workers helped appropriately define the subject group and led to the initial publication leading to universal testing of all laboring women.

Universal testing of pregnant women presenting to labor and delivery provided important clinical information,⁴ for the care of the mother and baby, protected the health care workers, but also helped in categorization of patients for future research. Strictly including subjects with varying symptoms or only those with positive or negative nasopharyngeal polymerase chain reaction (PCR) tests and excluding “persons under investigation” would hinder any retrospective precision in defining the clinical groups that may be described in larger cohorts or entered into a trial. Ideally, diagnostic samples should be saved since infectious diseases like SARS-CoV2 may require evolving confirmatory laboratory testing. Since all clinical research must undergo appropriate monitoring, researchers should efficiently collaborate with the institutional review boards in the approval process for performing studies. This requires changes in regular policies allowing for flexibility in the review process. FDA Guidance should be adopted to expedite review of high priority research.⁹ When the research involves collection of patient samples and the risk to the patient is negligible, a deferred consent model may be considered under which collection of samples may take place in time sensitive cases and consent obtained after the collection [18]. Consenting by telephone or video contact should be encouraged. Lastly, consolidating research efforts between investigators working in the same locale avoids

inefficiently duplicating work efforts and forms a collaborative network where results may be achieved faster. This is particularly important in research involving pregnant woman since many disease specialists are not familiar with pregnancy related physiology, terminology, or study procedures.

Conclusion

The COVID-19 pandemic has been by far the greatest challenge of the century that the field of medicine has had to face. Both the clinical and research aspect of medicine have been deeply affected. Multiple strategies have been deployed to address the knowledge gaps on the effects of COVID-19 on pregnancy, however more needs to be done to include pregnant women in clinical trials. Researchers should consult with experts in obstetrics from the American College of Obstetricians and Gynecologists and the Society of Maternal fetal Medicine prior to excluding pregnant women from clinical trials and depriving them of the opportunity to be proven candidates for treatment.

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