American Journal of Epidemiology

Vol. 190, No. 5
DOI: 10.1093/aje/kwab026
Advance Access publication:
February 10, 2021

Data-Driven Commentary

The Impact of Epidemiology on Fertility and Prenatal Care During the COVID-19 Pandemic

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Initially submitted November 12, 2020; accepted for publication February 4, 2021.

The emergence of the novel coronavirus disease 2019 (COVID-19) presented the field of reproductive medicine with many challenges due to an absence of data to guide clinical decision-making and inform patient counseling and management in the early days of the pandemic. Epidemiological studies rapidly filled key gaps in our understanding of the susceptibility of reproductive-aged women to the virus, transmission dynamics during pregnancy and lactation, and the effect of infection during the prenatal, pregnancy, and postpartum periods. This data guided the development of clinical guidelines written by the American Society for Reproductive Medicine as patients and clinicians navigated reproductive decisions during a time of uncertainty. We present a review of epidemiologic studies published between March and December 2020 that have directly informed prenatal and fertility care during the COVID-19 pandemic. Despite a significant increase in our knowledge base over the past year, many questions remain about the impact of COVID-19 on conception, pregnancy, fetal development, and lactation. In the future, a commitment toward inclusion of pregnant persons and those attempting pregnancy in the design of observational and interventional trials is necessary to gain earlier insights about outcomes and assist providers and patients in making data-driven decisions.

conception; COVID-19; inclusion in trials; lactation; pregnancy; vertical transmission

Abbreviation: COVID-19, coronavirus disease 2019.

Editor's Note: *The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the* American Journal of Epidemiology.

The appearance and rapid spread of the novel coronavirus disease 2019 (COVID-19) in 2020 presented the field of reproductive medicine with a number of challenges. At the beginning of the outbreak, our knowledge base to inform clinical care was limited. How infectious is the virus and how is it transmitted? Are pregnant women at higher risk of COVID-19 acquisition or progression to severe disease? Does infection affect in utero fetal development? Is fertility affected? Limited data on these fundamental questions restricted our ability to provide accurate, data-driven counseling to patients who were facing an altered reality caused by the pandemic. Suddenly, providers who care for women of reproductive age were fielding many questions about the ideal timing of conception, risks associated with infection, and the management of women with COVID-19 infection or exposure during preconception, pregnancy, and postpartum periods.

Clinicians routinely counsel individual patients about the risks of untoward events, and we are comfortable managing certain types of uncertainty. Examples from daily practice include the chance of success with fertility treatments and the risk of pregnancy complications after an infection. The goal of shared clinical decision-making relies on a detailed understanding of risk that is usually defined by epidemiologic studies. While clinicians cannot predict the precise probability of an event (such as a spontaneous abortion or a pregnancy-related complication), we can counsel individuals who are pregnant or seeking pregnancy by discussing the range of possible outcomes. The COVID-19 pandemic presented the medical field with the challenge of operating within a context where the risk of adverse outcomes was largely unknown.

Table 1. Susceptibility to Coronavirus Disease 2019 in Women of Reproductive Age

First Author, Year (Reference No.)	Study Finding	Impact on Medical Decision-Making
Stokes, 2020 (3)	In US CDC surveillance, cumulative incidence of COVID-19 infection stratified by gender was similar. Men had higher rates of severe disease and death.	Suggests that women age 18–49 years might be at lower risk of severe COVID-19 compared with men and older adults.
To, 2020 (5)	This early case of COVID-19 reinfection was detected in an asymptomatic adult 6 months after an initial mild infection with a different SARS-CoV2 strain.	Reinforces to patients that prevention measures remain important even after COVID-19 infection.
Szablewski, 2020 (4)	The attack rate at an overnight summer camp in Georgia was 56% among staff members (majority female, median age 17 years; range, 14–59).	Highlights rapid transmissibility of COVID-19 with close and prolonged contact. Supports social distancing.

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

Epidemiologic data illuminated the range of possible reproductive health outcomes of COVID-19. These data provide the framework for our frequently updated clinical recommendations as members of the American Society for Reproductive Medicine COVID-19 Taskforce (1). Once the pandemic was recognized, epidemiologists around the world responded swiftly by mobilizing high-quality data collection and designing large cohort studies and clinical trials. Collaborative research teams with experts in epidemiology and clinical medicine homed in on some of the most important questions in each field. Early studies documented the distribution of infection in various populations, factors associated with viral acquisition or severe disease, and methods to mitigate transmission. After peer review, high-quality published findings were rapidly incorporated into clinical guidance documents that were developed by national and international organizations to improve patient management on the front lines. In the setting of uncertainty, rapid community spread, and an evolving understanding of COVID-19, there has been increased demand to translate new scientific epidemiologic data into clinical guidelines that can equip clinicians with the most up-to-date information for decision-making (2).

In this commentary, we cite specific examples of epidemiologic studies that changed the discussions we had about COVID-19 risk, prevention, and treatment with individuals who were pregnant or seeking pregnancy. We close with a discussion of knowledge gaps and a call to action to support the principle of inclusivity when designing future cohort studies and clinical trials to address and improve reproductive health outcomes of COVID-19.

CALL TO ACTION

Studies cited in Tables 1–4 changed our clinical practice in 2020. These studies sought to understand susceptibility to COVID-19 among women of reproductive age, viral shedding and transmission dynamics, vertical transmission during pregnancy and delivery and from breastfeeding, and outcomes for women and their newborns. In Table 1, we cite 3 studies that highlighted susceptibility to COVID-19 among reproductive-age women. Data from the Centers for Disease Control and Prevention suggested that cumulative incidence was similar among women and men, but reproductive-aged women appeared to be at lower risk of

Table 2. Viral Shedding and Transmission Dynamics of Coronavirus Disease 2019

First Author, Year (Reference No.)	Study Finding	Impact on Medical Decision-Making
He, 2020 (6)	SARS-CoV2 viral load levels peaked soon after symptom onset. Modeled the frequency of presymptomatic spread (44% of secondary cases).	Suggests that COVID-19 transmission to women who are pregnant or seeking pregnancy can occur from asymptomatic carriers with high viral load.
Sutton, 2020 (7)	Most (29/33) women with COVID-19 detected by universal screening at delivery were asymptomatic.	Supports universal COVID-19 screening at the time of delivery.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

Table 3. Vertical Transmission of Coronavirus Disease 2019 During Pregnancy, Postdelivery, and Breastfeeding

First Author, Year (Reference No.)	Study Finding	Impact on Medical Decision-Making
Salvatore, 2020 (10)	No transmission events among 120 neonates born to women with COVID-19 in 3 NYC facilities with rooming-in (for mothers and infants) and breastfeeding.	Reassuring in terms of neonatal transmission risk when masking and hand hygiene protocols are followed.
Chambers, 2020 (11)	Among 64 breastmilk samples from 18 women with COVID-19, 1 sample was PCR-positive, viral culture–negative.	Strengthens breastfeeding recommendations for women with COVID-19.
Edlow, 2020 (8)	Cohort study of pregnant women with COVID-19 ($n = 64$), no evidence of placental infection. 1/77 neonates had IgM+ to nucleocapsid in cord blood in the setting of placental vascular malperfusion and unexplained villitis.	None of the participants had detectable viremia in maternal or cord blood. Additional evidence that transplacental transmission of COVID-19 is not common. Reduced transplacental antibody transfer was noted for COVID-19 compared with influenza.
Kotylar, 2021 (9)	Systematic review of COVID-19 transmission during pregnancy and within 48 hours of delivery from case reports, case series, and cohort studies ($n = 69$ studies, 936 exposed neonates).	Added information that vertical transmission in women with COVID-19 during late pregnancy is uncommon. Many cases had incomplete testing data—this highlighted the need to standardize sample collection procedures at delivery and case definitions.

Abbreviations: COVID-19, coronavirus disease 2019; IgM, Immunoglobulin M; NYC, New York, New York; PCR, polymerase chain reaction.

severe disease compared with men and older adults (3). It also became clear from carefully conducted COVID-19 epidemiologic investigations that reinfection with a different strain was possible and that the virus could spread rapidly with close contact (4, 5). Both studies supported adherence to effective public-health mitigation strategies.

Table 2 shows studies that allowed us to glean information about viral transmission dynamics. An early study of viral load kinetics by He et al. (6) showed that transmission risk was likely highest at the onset of COVID-19 symptoms and 1–2 days prior. Another small but highly impactful study from New York, New York, led to immediate changes in screening policies in many US facilities. Sutton et al. (7) showed that a vast majority of women with COVID-19 detected by polymerase chain reaction (29/33) were asymptomatic at the time of sample collection. This led to recommendations for universal screening at delivery and supported strict infection control guidelines to prevent respiratory transmission of COVID-19.

Studies cited in Table 3 focused on critical questions about vertical transmission of COVID-19 during pregnancy, postpartum, and breastfeeding. Fortunately, data from cohort studies, case series, and case reports documented infrequent occurrence during pregnancy (8–9) and in the immediate postpartum period (10). Postpartum management was also guided by a study by Chambers et al. (11) that showed that severe acute respiratory syndrome coronavirus 2 could not be cultured in the laboratory from 64 breast milk samples collected from 18 women. This suggested that, with proper precautions, breastfeeding could be safely undertaken.

After these results were published, the American College of Obstetricians and Gynecologists recommended that women with COVID-19 at the time of delivery should be supported in rooming-in with their newborn (a hospital practice in which postnatal mothers and infants stay in the same room 24 hours a day) and breastfeeding, while following mitigation strategies such as mask wearing and hand hygiene to minimize the risk of transmission to the infant (12). Initially, hospitals grappled with ways to decrease risks of COVID-19 transmission, and labor support persons were excluded from delivery rooms. This had a profound impact on the laboring woman, who often felt isolated and alone. The support person—often a partner or spouse—also suffered from not experiencing the delivery of their child. With better understanding of transmission-mitigation strategies, viral infection of newborn infants in the hospital could be significantly decreased and perhaps nearly eliminated. Once hospitals and clinicians recognized the effectiveness of personal protective equipment in preventing transmission in the hospital, the evidence-based reintegration of partners and support persons into the process has become nearly ubiquitous.

Studies of COVID-19 outcomes shown in Table 4 suggested that risk factors such as obesity, older age, chronic hypertension, and diabetes predicted worse outcomes of COVID-19 in pregnancy, and that younger women were at lower risk of hospitalization (13, 14). A large prospective national cohort study by Afshar et al. (15) showed that symptom resolution in pregnancy can be prolonged (median 37 days) among people with symptoms. Centers for Disease Control and Prevention data also showed a possible association between infection and preterm delivery, and the disproportionate burden of infection and adverse outcomes on women of color became increasingly clear (16, 17). These

Table 4. Coronavirus Disease 2019 Outcomes in Women and Pregnancy

First Author, Year (Reference No.)	Study Finding	Impact on Medical Decision-Making
Richardson, 2020 (13)	Among 5,700 inpatients in NYC, <40% were female, median age was 63 years (IQR, 52–75).	Suggests that younger women are at lower risk of hospitalization with COVID-19 compared with older adults.
Allotey, 2020 (14)	Living systematic review of risk factors and outcomes of COVID-19 in pregnancy. Studies are heterogeneous, but key risk factors for severe disease included older age, obesity, chronic hypertension, and diabetes.	Useful in counseling patients about individual risk levels and infection-prevention strategies. Reviews are quickly outdated given the pace of publication on COVID-19.
Afshar, 2020 (15)	Prospective cohort study of 736 symptomatic pregnant/postpartum women with known or suspected COVID-19. Among those with symptoms, median 37 days to resolution.	Initial report on maternal outcomes from registry (PRIORITY). Highlights benefit of collaborative efforts to track pregnancy outcomes.
Zambrano, 2020 (16)	CDC data on severe outcomes of COVID-19 in pregnancy ($n = 23,000$). With adjustment, models showed that pregnancy was associated with critical illness requiring intensive care and death compared with nonpregnant women aged 15–44 years.	Useful to counsel pregnant women that they might be at higher risk of severe COVID-19 disease compared with nonpregnant women. Highlights racial disparities in outcomes.
Woodworth, 2020 (17)	CDC report of women with COVID-19 ($n =$ 5,252) and birth outcomes. Preterm delivery 12.9% vs. 10.2% historical control.	Useful to counsel patients about potential adverse pregnancy outcomes if they acquire COVID-19.

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; IQR, interquartile range; NYC, New York, New York.

studies directly inform discussions with patients about COVID-19 testing, physical distancing, and the timing of pregnancy based on individual-level risks.

Taken together, these investigations paved the way for the development of data-driven guidelines and modifications to minimize risk of infection while positively affecting labor, delivery, and the continued support of breastfeeding. However, the limitations of single-center descriptive studies in assessing infrequent outcomes also highlight the need for coordinated and prospective cohort data collected across a number of clinical centers. Additional questions arise with each new study that is published. As the pandemic evolves, we cite areas where research collaborations between clinicians and epidemiologists are needed to shed light on important questions in the management of patients who are pregnant or planning a pregnancy.

To date, too little is known about the effect of COVID-19 infection during the first trimester, when organogenesis and placental development occur. It also remains unknown whether the presence or severity of COVID-19 during this early period of fetal development can lead to adverse outcomes at birth or later in childhood. Assessing the Safety of Pregnancy in the Coronavirus Pandemic (ASPIRE) is an example of a prospective study that seeks to answer these questions via maternal survey and sample collection from women seen in infertility clinics (18). Population-based studies of early exposure are also needed to be more representative of women in the general population. These findings will be invaluable to women as they decide whether to attempt pregnancy, and to providers who need to know whether exposure in the first trimester is associated with an increased risk of spontaneous abortion, preterm delivery, congenital anomalies, or abnormal neurological development, and whether specific subgroups of women are at increased risk.

Another pivotal issue is vaccine uptake among women who are pregnant or planning pregnancy. Similar to COVID-19, women who contract influenza during pregnancy are at increased risk of severe disease and complications (16, 19). A study from 2009 found that a higher percentage of pregnant women received the influenza vaccine compared with nonpregnant women, but uptake was low in both groups (24% vs. 20%) (20). More recent Centers for Disease Control and Prevention data indicated that approximately 1 in 3 women of reproductive age received influenza vaccination, irrespective of pregnancy status (21). Vaccine hesitancy has caused alarm in the US public health community, and messaging has been developed to address common concerns. Unique factors might influence vaccine uptake among women who are pregnant or contemplating pregnancy. In September, the Pew Research Center reported that just over half of Americans (51%) would definitely or probably get a vaccine to prevent COVID-19 if it were available (22). Vaccine acceptance rates vary over time according to the reported safety and efficacy of available vaccines (23). In December 2020, a Gallup poll found that 63% of people in the United States would be willing to receive an FDA-approved COVID-19 vaccine (24).

Further complicating decisions regarding vaccination is the unjustifiable exclusion of pregnant women, lactating women, and those attempting to conceive from vaccine trials published to date. As such, early data regarding safety and efficacy of vaccination is limited to the few women who became pregnant during follow-up ($n = 36$ in 2 phase-3 mRNA vaccine studies by Pfizer (New York, New York)–BioNTech (Mainz, Rhineland-Palatinate, Germany) and Moderna (Cambridge, Massachusetts) that enrolled 75,000 adults) (25–27). The American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, and the American Society for Reproductive Medicine have highlighted this deficit and encourage the safe inclusion of pregnant and lactating patients in vaccine trials and vaccination efforts with an informed discussion of risks and benefits (1, 12). The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group has developed a groundbreaking set of guidelines to inform ethically responsible, socially just, and respectful inclusion of pregnant women and those who could become pregnant in vaccine trials (28). Additionally, the US task force on research specific to pregnant women and lactating women (PRGLAC) has highlighted the need to implement a proactive approach to protocol development and study design both to include pregnant and lactating women in clinical research and to remove regulatory barriers (29).

Many women are open to and interested in participating in vaccine trials during pregnancy, and they often have questions about safety to the fetus and secondarily to themselves (30). Research designs that incorporate the views of pregnant women will help create protocols that include this important group (31, 32). While postmarketing surveillance is one way to understand the risks and benefits of vaccination in these scientifically complex populations, women of reproductive age, pregnant women, and breastfeeding women have unique risks and outcomes that warrant focused study and a commitment to the principle of inclusivity in clinical trials with informed consent (33). Exclusion of children from vaccine trials creates another important knowledge gap. Phase-3 vaccine trials for the Pfizer/BioNTech and Moderna COVID-19 vaccine products have recently been extended to include ages 12–17 years, with plans for additional expansion in the future.

CONCLUSIONS

Clinicians in the field of reproductive medicine and our patients have benefited from early, well-thought out, and rapidly published epidemiologic studies on COVID-19. While much has been elucidated in a matter of months, we are still in the infancy of our understanding of the reproductive health outcomes of COVID-19. Epidemiologists are uniquely positioned to lead investigations to advance our understanding of viral transmission dynamics and the determinants of health outcomes. Collaborative efforts between epidemiologists and clinicians will be invaluable in designing clinical studies that are more inclusive, with the ultimate goal of improving outcomes for women during the preconception, pregnancy, and postpartum periods.

ACKNOWLEDGMENTS

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This work was supported by The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (awards 1K23HD090993 and R01HD101545 to J.D.).

Conflict of interest: none declared.

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