

VIEWPOINT

Clarifying the Sweeping Consequences of COVID-19 in Pregnant Women, Newborns, and Children With Existing Cohorts

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The sweeping consequences of the coronavirus disease 2019 (COVID-19) pandemic for pregnant women, newborns, and children remain uncharted. The greatest outcomes may not be on those with known infections, who have dominated the early avalanche of literature. Interactions between humans and viruses evolve over time, judging from previous pandemic histories, and we will soon lose the opportunity to understand the current one. This Viewpoint suggests that the only way to truly capture the long-term consequences of the COVID-19 pandemic for these groups may be in agile reconfiguration of existing, large birth cohort studies.

While the broad shapes of pandemics are similar, each has its unique detail. The 2003 severe acute respiratory syndrome coronavirus (SARS-CoV) had higher rates of maternal and neonatal complications¹ and death in younger adults, but SARS-CoV-2 is more prevalent and transmissible. Zika virus can be devastating to the fetus, while the relatively few cases of COVID-19 in fetuses, neonates, and young children have tended to be mild. However, recent reports of a serious, Kawasaki-like illness in young children coincident with the COVID-19 pandemic suggests that its full pediatric story may be yet to emerge.² With few pediatric confirmed cases and low rates of severe disease,^{1,3,4} unknown effects on infants and children at heightened vulnerability in low-income countries,⁵ and an unknown extent of subclinical infection, testing children has been deprioritized and their contribution to COVID-19 epidemiology remains something of a mystery.

To prepare for the inevitable next pandemic, we need systems designed to help model profiles of transmission, diagnosis, treatment, and prevention. We need to understand the outcome of COVID-19 on pregnant women, infants, and children, including vulnerable and minority groups. Outcomes must cover those with and without infections, who will both bear the burdens of altered health services, psychosocial stress, and economic downturn. We need evidence to strengthen preventive measures and understand the consequences of infection, chemoprophylaxis, vaccination, and treatment. Risks and benefits need to be clarified, including balancing breastfeeding against transmission, physical distancing, and mental health. Infection prevention and control strategies must be developed to minimize the spread of COVID-19 in antenatal settings, the household, and community. We need to document common, rare, and subtle outcomes over time and the genetic and other contributors to their variations.

Some questions are specific to COVID-19 while others are more generalizable. Examples follow.

1. True incidence: rates of asymptomatic, minimally symptomatic, and presumptive COVID-19 are unknown; we know only the numbers of confirmed cases. To our knowledge, pregnant women and neonates are the only groups that routinely undergo systematic, universal blood testing.⁶ Assuming that the reach of COVID-19 in pregnancy approximates that of the general population, infection rates in this group should mirror the true reach of COVID-19 across all communities and support modeling of population surveillance. Serological testing in pregnancy would also enable study of gestational timing of COVID-19 and modeling the burdens of COVID-19 to pregnant mothers, the fetus, children, families, and society.⁵
2. Mother-to-child transmission: in utero SARS-CoV-2 transmission findings are not convincing, because testing relies on antibody detection,⁷ and the virus is not detected in amniotic fluid, cord blood, breast milk, or neonatal throat swabs.⁸ In several reports of maternal infections, the physicians caring for those patients chose cesarean delivery while others chose vaginal delivery, without evidence to guide either choice. Little is known about maternally derived antibodies, including whether this is protective for newborns and for what duration and how long before delivery a mother with a COVID-19 infection can produce sufficient antibody levels to protect a neonate from postnatal exposure.
3. Breastfeeding recommendations: at present, the US Centers for Disease Control and Prevention recommends considering separation of the mother and infant at delivery, but this recommendation is controversial and must be balanced against the known harms to establishing lactation and bonding, particularly at a time of pandemic-associated isolation and stress. If maternal antibodies can protect a neonate, this may permit breastfeeding without prophylaxis, masking, or separation.
4. Long-term effects on fetal development and child health: thus far, the outcome of COVID-19 on women who are vs are not pregnant appears similar.³ However, perinatal outcomes from a small cohort of women with third-trimester infections are insufficient to identify rare events, long-term complications, or problems that may arise during fetal organogenesis—particularly if the pandemic response restricts access to screening of fetal anomalies. It is vital to capture these outcomes before vaccination and antiviral treatments are established or cases disappear. For example, should an antiviral drug become available with adverse pregnancy effects, risks and benefits cannot be balanced in the absence of

data from an untreated cohort. A very large birth cohort capable of case-cohort analyses could identify rare adverse outcomes over time, including neurodevelopment or immune functioning.

5. Long-term health service outcomes: the international disruption to usual health and other services is extreme. Forced innovations include transitions to telehealth, reduced access to antenatal care and screening, unaccompanied deliveries, changes in cesarean delivery use, and/or early discharge into a socially distanced world. These are seismic, untested, and unprecedented health service delivery changes with unknown but possibly profound outcomes. We must not only document but tease out the causality of these wide-reaching systems changes on the care and outcomes of conditions other than COVID-19 itself and their long-term economic and psychosocial outcomes.

None of this is possible without an appropriate pregnancy and birth cohort. It would need to be very large, longitudinal, population based, and prepared to collect data now. It would need to include appropriate biological samples, requiring innovation in universal-capable home self-collection of room-temperature samples. Advanced and innovative information technology systems would be essential, since physical distancing policies preclude traditional face-to-face clinical or community research. A well-designed, safe, digital platform could replace laborious traditional face-to-face research assessments of wide-ranging psychosocial, phenotypic, and functional outcomes (using images and videos) and also provide research support to participants. Removing the need for in-person vis-

its, transit time, and expense, such a program could be more accessible for participants and recruiters. These are highly desirable features, especially now.

The value of such a megacohort cannot be doubted. For elderly people, the UK Biobank recently took the unprecedented step of releasing primary care, hospitals, and intensive care data for its 500 000 participants to enable research nearly in real time into the mediators and outcomes of COVID-19.⁹ This was authorized by the UK Secretary of State.⁹ Unfortunately, for pregnancy and early life, attempts to mount such cohorts have failed even in happier times. However, some do exist that are at the right stage of planning, have well-established infrastructure and organizational collaboration, and are ready to incorporate a focus on COVID-19 with the right government partnerships and support. This would provide a sustainable infrastructure to minimize adverse outcomes associated with the current pandemic for mothers and infants over coming decades, while maximizing knowledge to help address the inevitable pandemics to come.

The philosopher Georg Hegel said, "We learn from history that we do not learn from history." Certainly, the world was unprepared for the COVID-19 pandemic. By late June 2020, total cases had exceeded 9 million, with nearly 500 000 deaths.¹⁰ We can be less cynical for future pandemics if we rapidly reconfigure our existing large international birth cohorts. A handful of such studies around the world that are already in place could provide real data critical to understanding this pandemic and model mitigation strategies for the next one as its unique footprint emerges.

ARTICLE INFORMATION

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