



The COVID-19 pandemic, preterm birth and the potential role of composition of gestations

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In this Special Issue of *Paediatric and Perinatal Epidemiology*, Gemmill et al.¹ evaluate changes in preterm birth in the United States after the onset of the COVID-19 pandemic. In addition to demonstrative visual plots, the authors used interrupted time series with autoregressive integrated moving average (ARIMA) models to limit the influence of temporal trends, including monthly fluctuations, and ultimately identify changes in monthly rates of preterm, early preterm and late preterm birth, as well as caesarean delivery, from 2015 to 2020 in the United States.

Gemmill et al. described a 5%–6% decrease in preterm birth rates following the onset of the pandemic. They observed the largest relative decreases in rates during March–June and November–December 2020 for preterm birth, March and November (and to a lesser extent June, August and September) 2020 for early preterm birth, and March, April, November and December (and to a lesser extent May and June) 2020 for late preterm birth. We emphasise the value of thoughtfully presented and carefully interpreted descriptive data for understanding the complicated impacts of the COVID-19 pandemic, as exemplified by Gemmill et al. in this report.

Gemmill et al. interpreted their findings as the result of several possible mechanisms, including decreases in harmful environmental exposures via stay-at-home recommendations and changes in clinical management of labour and delivery potentially related to strain on hospital capacity. The authors also noted the role of SARS-CoV-2 infections in affecting pregnancy outcomes, and briefly mentioned a potential role for 'composition of gestations' as a contributor to their findings. In this commentary, we focus on the potential role of composition of gestations after the onset of the COVID-19 pandemic with respect to foetal survival (discussed by the authors) and pregnancy intent (not discussed by the authors).

1 | COMPOSITION OF GESTATIONS: PREGNANCY LOSS

Infection and stress are known to negatively affect maternal and foetal health.^{2,3} The onset of the COVID-19 pandemic introduced a new infection-related risk to pregnant individuals—namely, infection by the SARS-CoV-2 virus. Studies have previously described harmful effects of SARS-CoV-2 infection on pregnancy outcomes like preterm birth and stillbirth.² The onset of the COVID-19 pandemic also likely introduced many stress-related risks to pregnant individuals—specifically the social and economic consequences of the pandemic, isolation due to lockdowns and restrictions, and their associated difficulties/uncertainties. While studies of pandemic-related stress and pregnancy outcomes are not yet as common, stress more broadly is known to increase risk of adverse perinatal outcomes, including preterm birth.³ Given the harmful impacts of infection and stress on pregnancy outcomes, it is plausible that the pandemic may have been harmful to foetal survival, and thus increased risk of pregnancy loss.

What is the impact of the COVID-19 pandemic on pregnancy loss? Pregnancy losses (particularly at early gestational ages) are incompletely captured in routine databases like the one used by Gemmill et al., which makes this outcome especially difficult to study. Yet, the effect of the pandemic on pregnancy loss has relevance for preterm birth. This is because of the hypothesis that pregnancy losses, had they survived to viable gestational ages, may have been more susceptible to adverse antenatal and/or postnatal outcomes (i.e. 'depletion of susceptibles' theory).⁴ If an exposure causes relatively more pregnancy losses, and if these pregnancy losses are discounted in an analysis, the study population appears artificially healthier (and thus the preterm rate lower) than it should. This type of selection bias

is conceptually similar to the 'birthweight paradox' (the apparent protective effect of smoking on mortality among infants with low birthweight), which is another gestational age-dependent outcome of pregnancy.⁵

While we cannot apply the approach by Gemmill et al. to study pregnancy losses, since this outcome is not reliably captured in National Center for Health Statistics data, we can examine whether there was a corresponding precipitous change in live births following the pandemic's onset. We assume that, like preterm birth, there are monthly fluctuations and temporal trends in the number of pregnancies over time; once the influence of these trends is removed, any increase in live births might suggest a decrease in pregnancy losses, and any precipitous decrease in live births might suggest an increase in pregnancy losses.⁶

To further examine this theory, we applied an approach similar to that of Gemmill et al.⁷ to describe changes in the number of live births after the onset of the pandemic. We obtained monthly counts of live births from the National Center for Health Statistics. We did not specifically replicate the model-building strategy employed by Gemmill et al., but instead fit an ARIMA model that is typically used to simultaneously model a linear temporal trend and monthly variation [ARIMA(0,1,1) \times (0,1,1)₁₂]. This notation indicates that the predicted number of live births is a function of both first order seasonal (or year-to-year) and non-seasonal (or month-to-month) differences, and that the model incorporates one-unit lagged seasonal and non-seasonal moving averages. The subscript 12 indicates that there are 12 periods (or months) in a season (or year).⁸ Like Gemmill et al., we fit this model only among live births from January 2015 to February 2020, and then extrapolated the model to predict the number of live births from March 2020 to December 2020. We found that the observed number of live births was lower than predicted throughout time period after pandemic onset, especially during months from August 2020 through December 2020 (Figure 1). Notably,

these pregnancies would have been conceived between November 2019 and March 2020, experiencing the first trimester of pregnancy during the first wave of the COVID-19 pandemic in the United States. Like Gemmill et al., we interpret these observational data with caution, and emphasise that these descriptive data are not enough to definitively suggest that the pandemic caused pregnancy loss. Nonetheless, these data lend credibility to the 'depletion of susceptibles' theory with respect to preterm birth, and highlight the potential role of left-censoring in the apparent decrease in preterm birth rate after pandemic onset.

We suggest that this strategy may only be informative immediately after the COVID-19 pandemic's onset because of another potential pandemic-related change to composition of gestations discussed below.

2 | COMPOSITION OF GESTATIONS: PREGNANCY INTENT

Few studies have discussed whether pregnancy intent has changed—and in what direction for what group(s)—since the onset of the pandemic. However, we hypothesise that the same social and economic changes that may have caused more stress among pregnant individuals may also have influenced decisions with respect to pregnancy intent. Was there an increase in pregnancy intent among certain groups—namely those who experience more economic stability and were/are able to work from home? Was there a decrease in pregnancy intent among certain groups—namely those who experience less economic stability and were/are not able to work from home and thus could potentially be more susceptible to SARS-CoV-2 infection. More importantly, are the characteristics of these groups also correlated with preterm birth? It is plausible that the answer to all of these questions is 'yes', and if so, changes in pregnancy intent

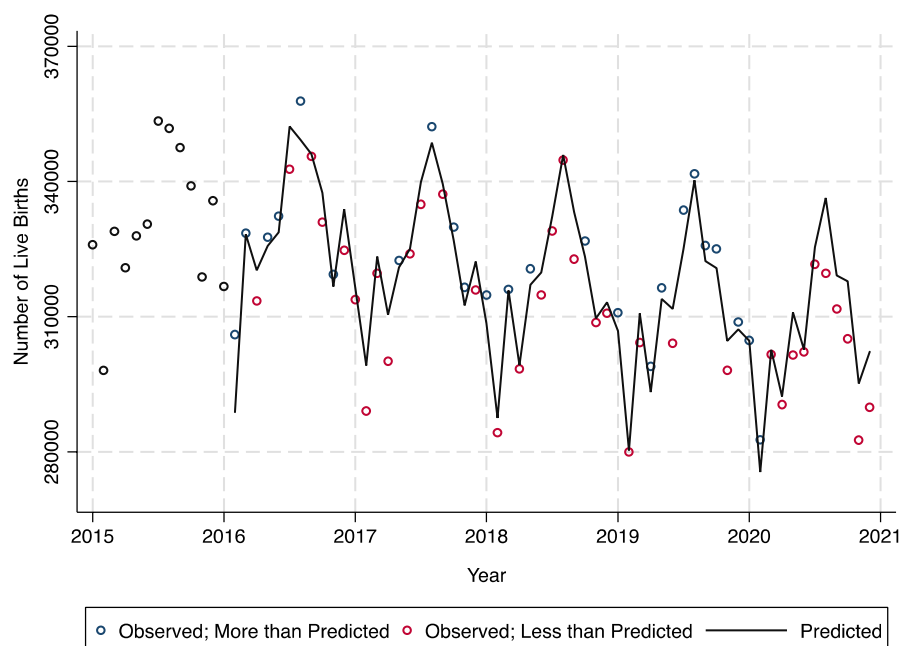


FIGURE 1 Observed and predicted number of live births by calendar month in the United States from 2015 to 2020. Predicted number of live births were estimated by fitting an ARIMA(0,1,1) \times (0,1,1)₁₂ among live births from January 2015 to February 2020 and extrapolating model to the March 2020–December 2020 period

after the onset of the pandemic may have changed the composition of gestations with respect to known socioeconomic determinants of pregnancy outcomes, including preterm birth.

We do not anticipate that differences in the composition of gestations related to pregnancy intent arose immediately after the pandemic's onset; intention for these pregnancies was established before, while pregnancies themselves were gestated during, the pandemic. However, this potential change in the composition of gestations may complicate further interpretation of increases or decreases in rates of preterm birth in future, as suggested by Gemmill et al., as time since the onset of the pandemic increases. We suggest that pregnancy intent-related changes in the composition of gestations warrants further study.

3 | MEASURING PREGNANT INDIVIDUALS' EXPERIENCES OF THE PANDEMIC

We, and others, have previously written about potential difficulties of studying the effects of the COVID-19 pandemic, and particularly cautioned against its use as an instrumental variable.^{9,10} We suggest that Gemmill et al. have effectively navigated these difficulties by presenting descriptive data and thoughtful interpretation within their report. Whether epidemiologists intend to examine the pandemic as an instrumental variable or simply as a determinant of pregnancy outcomes, measuring individual-level experiences of the pandemic will enable us to empirically examine potential mediators or mechanisms. In this Special Issue, Regan et al. demonstrated that merely measuring SARS-CoV-2 infection during pregnancy solely within administrative data proved challenging.¹¹ In addition to SARS-CoV-2 infection, effects of the pandemic are likely experienced differently by different groups, and these groups may already be characterised by higher or lower risk of adverse pregnancy outcomes. The report by Gemmill et al. is but one piece of the complex puzzle of the COVID-19 pandemic's impacts on pregnancy outcomes in the population.

ABOUT THE AUTHORS

Michelle Dimitris is a Research Fellow in the Centre for Global Child Health at the Hospital for Sick Children. She is part of the Centre's Academic Global Child Health Fellowship program and is funded by the Hospital's Lap-Chee Tsui Fellowship. Dr. Dimitris is interested in applying advanced statistical and causal methods to address research questions that are global in scale and impact, particularly in the area of perinatal epidemiology.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available via "Centers for Disease Control and Prevention. About Natality, 2007-2020" at <https://wonder.cdc.gov/natality-current.html>, reference number 7.

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