Title: International Registry of Coronavirus Exposure in Pregnancy (IRCEP) – Cohort

Description and Methodological Considerations

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ABSTRACT

Limited data are available about the potential health effects of infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on pregnant women and their developing offspring. We developed the International Registry of Coronavirus Exposure in Pregnancy (IRCEP) to provide data on the risk of major adverse obstetric and neonatal outcomes among women with varying degrees of severity and timing of COVID-19 exposure during pregnancy. We describe here the cohort and share the lessons learned. The IRCEP enrolls women tested for SARS-CoV-2 or with a clinical diagnosis of COVID-19 during pregnancy and obtains information using an online data collection system. By March 2021, 17,532 participants from 77 countries had enrolled; 54% enrolled during pregnancy and 46% afterwards. Among women with symptomatic COVID-19 with a positive SARS-CoV-2 test (N=4,934), symptoms were mild in 41%, moderate in 52% and severe in 7%; 7.7% were hospitalized for COVID-19 and 1.7%
were admitted to an intensive care unit. The biggest challenges were retention of participants enrolled during pregnancy, and the potential bias introduced when participants enroll after pregnancy outcomes are known. Multiple biases need to be considered and addressed when estimating and interpreting the effects of COVID-19 in pregnancy in these types of cohorts.

**BACKGROUND**

Over one hundred million women have given birth worldwide since the Coronavirus Disease 2019 (COVID-19) pandemic started in China in late 2019. To date there is no consistent evidence that pregnant women are more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; and conflicting findings have been published on whether they have more severe COVID-19, if infected, than non-pregnant women of similar age. In early reports, based on small samples, the risk of both symptomatic infections and death in pregnant women with COVID-19 was similar to that in non-pregnant women. Subsequently, larger studies suggested that hospitalization rates, intensive care unit (ICU) admissions and mortality in pregnant women diagnosed with COVID-19 are higher than in non-pregnant women of similar age. More recent studies concluded that pregnant women are not more likely to get seriously ill from SARS-CoV-2 infection. These discrepancies may be at least partially explained by international and temporal differences in SARS-CoV-2 virulence, population vulnerability to its effects, or COVID-19 treatments.

Regardless, even if infection and severity risks were not above general population levels, consequences of severe COVID-19 are likely exacerbated when the patient is pregnant and has to deliver and take care of a newborn. Moreover, severe COVID-19 may not only cause maternal morbidity and mortality, but also lead to iatrogenic preterm delivery due to concerns about COVID-19 transmission and progression, and potential coagulation disorders that may cause placental-related complications such as miscarriages. Vertical SARS-CoV-2 transmission is rare but can occur.

A dearth of information, especially during the first months of the COVID-19 pandemic, led to increased levels of anxiety among pregnant women, as well as unnecessary cesarean deliveries and elective terminations. Therefore, there was, and still is, an urgent need to gather and
communicate reliable information. The direct-to-participant International Registry of Coronavirus Exposure in Pregnancy (IRCEP) was established to describe COVID-19 in pregnant women worldwide and to assess the relative risk of major adverse obstetric and neonatal outcomes in pregnancies exposed to varying degrees of severity and timing of SARS-CoV-2 infection. We share here the lessons we learned from designing and conducting IRCEP.

METHODS

Study Design

The IRCEP is an ongoing observational cohort that began enrollment in June 2020. Data on baseline characteristics, reproductive history, chronic medical conditions and medication use, exposure to SARS-CoV-2, COVID-19 manifestations, prenatal care, pregnancy outcomes, and neonatal outcomes are collected during pregnancy and postpartum. The IRCEP allows enrollment throughout pregnancy and during the first 180 days after the end of pregnancy.

Study Population

The study population includes women 18 years of age or older from around the world with a current or recent pregnancy and tested for SARS-CoV-2 (regardless of the result) or with a clinical diagnosis of COVID-19 between the first day of the last menstrual period (LMP) and end of pregnancy. Inclusion criteria also require willingness to provide responses to a minimum set of demographic questions. The rationale for including cases without a positive SARS-CoV-2 test is that, in many countries, early in the pandemic, the reverse transcriptase-polymerase chain reaction (RT-PCR) test was inaccessible to a large proportion of the population. Therefore, the presence of clinical symptoms (e.g., typical pulmonary lesions on chest CT, loss of sense of smell or taste), confirmed by a health care professional, was sufficient to be considered a COVID-19 clinical diagnosis.

Enrollment

Information about the IRCEP is available on a dedicated website. Venues for increasing awareness include social media channels frequently visited by pregnant women (e.g., Facebook,
Instagram) and online parenting forums. The advertisements were translated to the most frequently spoken local languages and the awareness campaigns targeted websites frequently visited by pregnant women within each country. Women self-enroll using the IRCEP website without the participation of physicians involved in the testing or treatment of COVID-19, obstetric or neonatal care. The enrollment process validates the contact information by sending a random code to the submitted mobile phone number.

**Follow Up**

Follow-up for analyses begins on the date of the first SARS-CoV-2 test or first COVID-19 symptoms during pregnancy, whichever occurs earlier, and continues until a pregnancy loss, loss to follow-up, or 90 days after delivery. Information on pregnancy outcome (i.e., SAB, termination, stillbirth, live birth) is collected and livebirths are followed until three months after birth. Optional email and short message service (SMS) phone reminders are available throughout the study to facilitate retention. The web and mobile app also generate automated reminders to provide medical records. In addition, contact information is collected for a close friend or family member who will serve as an alternate contact that can provide minimal information (i.e., is participant healthy?) if we lose contact with the participant for unknown reasons before COVID-19 clinical resolution.

**Data Collection and Timing of Assessments**

Data are collected via self-administered online, easy-to-complete modules. Each module usually takes 5 to 15 minutes to complete. Given the international nature of the IRCEP, the questionnaires are available in 10 languages (English, Spanish, French, Italian, Portuguese, Russian, Urdu, German, Marathi, and Hindi). The translations were done with professional software followed by review and correction by interpreters. At enrollment, women complete 2 modules (Web Figure 1). These modules collect data on baseline characteristics (e.g., demographics, illnesses, reproductive history, prenatal screening and its results); and on timing of SARS-CoV-2 testing and COVID-19 clinical signs, their duration, severity, and treatment. For women enrolling during pregnancy, monthly follow-up questionnaires are collected until delivery, when obstetric and neonatal outcomes are collected. The follow-up modules include COVID-19-related questions to assess active COVID-19 cases as well as to detect potential new
positive SARS-CoV-2 tests in women that initially tested negative. In case of an early pregnancy loss (SAB or termination), the participant is directed to an End-of-Pregnancy brief questionnaire and is not asked to complete any more modules. Finally, around 90 days after delivery, a module collects information on postpartum and neonatal outcomes, with questions targeted to the most common specific obstetric and pediatric conditions and events. Women enrolling retrospectively within 90 days post-delivery complete the Baseline, COVID-19, and Delivery modules upon enrollment, and the postpartum outcomes at 90 days after end of pregnancy. Women who enroll between 90 and 180 days after the end of pregnancy can complete all modules, including information on pregnancy and the first 90 days post-partum, at enrollment.

In addition to self-reported information, participants are asked to photograph and upload all available SARS-CoV-2 test results, delivery and neonatal medical records, and any other health care records they consider relevant, after redacting personal identifiers. These records could be used to validate maternally reported diagnoses and to allow for potential adjudication of outcomes by experts blinded to the maternal COVID-19 status for specific studies. Uploaded records are checked for redaction prior to storage and will be translated with professional software followed by human review as they became relevant for analyses (e.g., when evaluating malformations).

The identifying and anonymized data of individual study participants are linked via a unique subject identifier. The file containing the personal identifiers used during the informed consent process is securely stored in a separate server. Files for analysis do not include any personal identifiers. Once the participant completes the study, the key used to link analytic files with identifiers is deleted.

**Exposure definitions**

A registry participant is considered *infected* if she had a positive RT-PCR or serologic test for SARS-CoV-2 between the first day of the LMP and end of pregnancy. In sensitivity analysis, those with clinical diagnoses of COVID-19 are also considered to be infected, regardless of SARS-CoV-2 testing. The primary reference group consists of women with a negative SARS-CoV-2 test and no positive test nor clinical diagnosis of COVID-19 during pregnancy. The goal of the reference group is to provide an estimate of the expected incidence or prevalence of
obstetric and neonatal events in women from the same source population as the exposed, upon adjustment for potential confounders associated with either infection or testing. Women in the reference group that test positive later in pregnancy would be considered exposed at that point.

Sub-cohorts defined by COVID-19 severity are identified. The classification of severity is summarized in Web table 1. To evaluate the effect of disease severity on adverse pregnancy outcomes among women exposed to the virus, severe cases will be compared to those with mild COVID-19 presentations. The IRCEP will also be able to assess the potential effects of specific COVID-19 characteristics or treatments, predictors of COVID-19 severity, and frequency of infections in newborns.

Timing of Pregnancy

The first day of the LMP is used to define the timing of pregnancy and the length of gestation. Gestational age is determined by an algorithm using the best available information, including reported LMP, due date based on LMP, and due date based on ultrasound. Gestational timing is needed to define exposure since the etiologically relevant period for each outcome of interest varies. Web Table 2.

Outcomes

The main outcomes of interest include SAB (spontaneous pregnancy loss prior to 20 weeks gestation), stillbirth (fetal death after 20 weeks gestation), major congenital anomalies (specific types will be explored where sample size permits), preterm delivery, maternal obstetric complications (e.g., preeclampsia, gestational hypertension, cesarean delivery, postpartum hemorrhage, postpartum depression), small for gestational age (≤10th centile on birth weight for the infant’s sex and gestational age), head circumference at birth, admission to the neonatal intensive care unit, vertical transmission of SARS-CoV-2, and neonatal death. Questions on access to care during the COVID-19 pandemic, maternal mental health, and breastfeeding will allow evaluation of other aspects of wellbeing.

Primary analyses will be restricted to participants that enrolled before specific outcomes occur or can be known, to avoid both selection and recall biases. For example, in the case of congenital anomalies, before any informative prenatal test. The exposure windows of interest will also
depend on the outcome; for example, to evaluate whether SARS-CoV-2 infection affects the risk for preterm delivery, those exposed in the month before a preterm delivery may be compared to the unexposed in that risk set defined by gestational age.

Covariates

The IRCEP collects data on a wide range of covariates including maternal demographic characteristics, comorbid medical conditions, habits, reproductive history, obstetric characteristics, use of medications, and measures of healthcare utilization. Women may enroll after the onset of COVID-19 infection but baseline questions collect information on characteristics existing before the infection to allow proper adjusted in future analysis.\(^{27}\)

Study termination and loss to follow-up

Participating women may withdraw from the IRCEP at any time at their own request, at which time all their information will be deleted from the database (except for select de-identified sociodemographic characteristics, which are retained to assess data representativeness in aggregate analyses relative to the initial population and correct for informative censoring if needed). The website inquires about the reason for withdrawal. When a participant does not respond to repeated online prompts requesting further information on the pregnancy, they will be considered lost to follow-up. Participants that do not complete all the modules by 180 days after the end of pregnancy will be censored from the cohort at the time of last contact.

Human Subjects

The IRCEP protocol was approved by the Harvard Longwood Campus Institutional Review Board (IRB20-0622). Eligible participants provide consent electronically with an e-Form on the IRCEP website.

RESULTS

Study Population

As of end of March 2021, 17,532 participants from 77 countries had enrolled in IRCEP. Of those, 54\% enrolled during pregnancy and 46\% after the end of pregnancy, i.e., postpartum or
after a pregnancy loss (Table 1). The frequency of participants by country of residence resembles the distribution of COVID-19 worldwide at that time, consistent with the IRCEP awareness campaigns online. Participants in the IRCEP are racially and socioeconomically diverse (Table 2). The frequency of both negative and positive tests in asymptomatic women reflect screening intensity in those groups (e.g., more in those living in North America or Europe, white race, having asthma, or smoking tobacco). The median number of weeks post-LMP at enrollment was 26 (interquartile range [IQR] 17, 34) for those enrolled during pregnancy and 49 (IQR 44, 54) for those enrolled after the end of pregnancy (Figure 1).

COVID-19 during pregnancy

At enrollment, 5,858 (34%) participants reported a positive test for SARS-CoV-2 (84% were symptomatic), 2.5% had a clinical diagnosis of COVID-19 without a positive test, and 10,215 (58%) had a negative test and no clinical diagnosis of COVID-19 (Table 3). A small number of participants reported neither clinical diagnoses nor a SARS-CoV-2 test (n=20) and were excluded.

The timing of COVID-19 diagnosis was equally distributed throughout pregnancy (Web Figure 2). However, testing tended to cluster around the time of delivery, since it has become standard practice in many countries to screen for SARS-CoV-2 at the time of hospital admission for delivery. Increased screening of asymptomatic women pre-delivery resulted in more negative tests, and positive tests in women without symptoms, towards the end of pregnancy.

Among those with symptomatic COVID-19 confirmed with a positive test, symptoms were mild in 41%, moderate in 52% and severe in 7%. Among 1,235 women with a clinical diagnosis of COVID-19 without a positive test confirmation, 38% had mild, 58% had moderate, and 3% had severe symptoms. Overall, the most common symptoms were upper respiratory manifestations (e.g., cough), fatigue, loss of taste or smell, and gastrointestinal symptoms (e.g., nausea, diarrhea). Moderate and severe presentations frequently included shortness of breath, fever, and muscle aches. Overall, among symptomatic women with a confirmed positive test, 7.7% were hospitalized for COVID-19, 2.2% required oxygen, ventilator assistance or extracorporeal membrane oxygenation (ECMO), and 1.7% were admitted to an intensive care unit (ICU). Other
than analgesics, the most common pharmacotherapies used to treat COVID-19 were azithromycin, oseltamivir, corticosteroids, and hydroxychloroquine/chloroquine.

Outcomes

Of the 9,471 participants enrolled during pregnancy, 5% have completed participation in the study and 6% are still pregnant and completing modules, as of March 31, 2021. Of the 8,061 participants enrolled postpartum or after fetal loss, 74% have completed participation (Figure 2). Among those participants with complete follow-up, the frequencies of the most common obstetric outcomes were similar to what would be expected in the general population (i.e., 0.8% stillbirths, 6% preeclampsia, 1.9% twins or higher-level multiples, and 2.6% major congenital malformations) (Table 4.) The frequency of pregnancy losses is lower than the usual cumulative risk throughout pregnancy in the population since women that enroll late in pregnancy represent a survivor cohort and those that enroll retrospectively had shorter opportunities to have a test or an infection.

DISCUSSION

We have enrolled a large international cohort of pregnant women with and without COVID-19 in the IRCEP. Future studies will be able to assess a variety of specific research questions related to COVID-19 and pregnancy, such as the effect of COVID-19 severity on multiple outcomes. We learned many lessons designing and conducting the IRCEP, including the following:

• Enrollment and retention of participants in multinational pregnancy registries

The increasing number of pregnancies affected by COVID-19 and the wider availability of tests for SARS-CoV-2 facilitated enrollment over the study period. Nonetheless, we learned that social media awareness campaigns are key to enrolling participants in internet-based studies. Enrollment in the IRCEP dropped substantially between campaigns, despite a large amount of pregnancy and COVID-19-related resources available on the Pregistry website. Web Figure 3. While completion of modules among retrospective enrollees has been over 70%, retention of participants registered during pregnancy is below 10%. The IRCEP tries to increase retention and data completeness by fostering an online community where participants not only share data but also receive relevant information. Optional automatic reminders are also sent via SMS to remind
participants to upload information. We did not offer economic incentives to participate in the study to minimize the risk of ineligible subjects enrolling for money. The study appeals to the altruism and solidarity of volunteers by conveying the importance of their loyalty to the study for the generation of evidence that will help other pregnant women. Unfortunately, these approaches were insufficient. Similarly, a small proportion of participants has submitted redacted photos of their medical records despite an easy system to upload documents. Consequently, our intention to validate and adjudicate self-reported outcomes may not be feasible.

Despite the attrition, this remains one of the largest cohorts of pregnant women with COVID-19. However, the substantial losses to follow up might select a biased sample. Characteristics of participants lost to follow-up will be compared to the observed cohort and weights may be applied if censoring is not random. For example, among prospective enrollees, retention was higher among those negative for COVID-19, from North America or Europe, and of White race, higher education, and higher income (Web Table 3). Future studies should strive to attain higher retentions. For example, by allocating sufficient budget to a more personalized and proactive contact with enrollees or demanding stronger commitment to research from the beginning (e.g., making uploading test results an inclusion criteria).

- **Generalizability of results**

While the multinational design is meant to facilitate generalizability of results across the globe, it also represents a challenge a) logistically, because of the need to translate the materials to many languages and to make them culturally appropriate across countries (e.g., race categories, health coverage modalities), and b) methodologically, because country of residence is a strong determinant of both COVID-19 infection and of testing, and of incidence and diagnosis of the outcomes. Therefore, the statistical analyses will need to take country of residence into consideration, for example with stratification or introducing a random effect component. In retrospect, a multinational study in fewer selected countries might have been preferable from a research perspective to guarantee sufficient numbers within strata while still providing a global perspective.

In addition, enrollment of women in pregnancy registries is voluntary and, therefore, participants are a non-random sample of all women with COVID-19. Consequently, the characteristics and experience of women who participate in a registry may differ from those of non-participants, and
these characteristics may modify the observed effects of SARS-CoV-2. Our primary awareness campaigns were designed to appeal to people of a wide variety of backgrounds, but our enrolled sample turned out to be more educated than the general population (65% with at least a college education). Although biological effects of viruses tend to be universal, the health consequences of COVID-19 among those volunteering to participate in the registry, who tend to be more educated and health conscious, is likely to underestimate the absolute impact on more vulnerable populations.

- **Estimation of SARS-CoV-2 prevalence and COVID-19 incidence in pregnancy**

Non-random samples cannot provide an estimate of the distribution of SARS-CoV-2 seroprevalence or COVID-19 severity in the source population. The proportion of participants with SARS-CoV-2, or with COVID-19, should not be interpreted as a “risk” and should not be compared with the risk in non-pregnant populations. Asymptomatic pregnant women are tested more often than asymptomatic non-pregnant young women. This targeted screening results in higher detection of SARS-CoV-2 in pregnant women with asymptomatic infection (Web Figures 4 and 5). During pregnancy, more participants reported asymptomatic infection only detected by a positive test around delivery, when more screening is done. Similarly, because of preferential screening, pregnant women receive more negative test results, particularly around delivery. Consequently, the participants who joined after delivery included more negative tests, because the prospective participants enrolled based on tests conducted before screening at delivery. Therefore, study designs like ours are not appropriate to estimate the incidence of SARS-CoV-2 or COVID-19.

- **Using individuals with negative tests as the reference group**

Non-random samples selected based on testing can provide valid estimates of COVID-19 effects on pregnancy outcomes if risk factors associated not only with the infection but also with testing are controlled. Asymptomatic participants with test results for SARS-CoV-2 (either positive or negative) represent populations with increased access to screening (e.g., more affluent) or high-risk groups (e.g., women with asthma). Therefore, the unbalanced characteristics observed between participants with COVID-19 and the reference group with negative tests may be risk factors for infection, or risk factors for testing. This selection introduced by the inclusion criteria (i.e., requiring a test) can be conceptualized as conditioning on a collider. Although, this
potential selection bias is less likely to affect the assessment of COVID-19 severity within symptomatic cases, if milder cases with risk factors were still preferentially tested, we would underestimate the effect of severity. While we will adjust for factors associated with testing, residual confounding remains a concern. Web Figure 6.

• **Pregnant women as a vulnerable population**

Some studies that evaluated the effect of pregnancy on people with SARS-CoV-2 infection suggested a higher frequency of ICU admissions and hospitalizations among pregnant women with COVID-19, even after accounting for age and healthier overall status of pregnant women. However, results might be explained by preferential hospitalization and ICU admissions of pregnant women given the same disease severity and by inclusion of hospitalizations for pregnancy-related reasons in the outcome (Web figure 5). That is, even without COVID-19, pregnancy increases the likelihood of hospitalizations relative to non-pregnant women of similar age, even if only for obstetric reasons (e.g., delivery, preeclampsia). We did not include non-pregnant women in our study and, therefore, the IRCEP cannot answer the question of whether pregnant women constitute a “vulnerable population” with respect to COVID-19. We designed this study not to answer the question *what would have been the outcome had the person not been pregnant*, but *what would have been the outcome had the pregnant person not become infected, or not had severe COVID-19*.

• **Confounders, mediators, and colliders**

When assessing the effect of SARS-CoV-2 infection on pregnancy outcomes in observational studies, an association could be explained by a direct effect of the virus on the outcomes, an effect mediated through maternal symptoms (e.g., pneumonia or fever), or by confounding (e.g., women more likely to be infected might also be at higher risk of adverse pregnancy outcomes). It is also important to note that a factor may cause severe COVID-19 by increasing exposure to SARS-CoV-2, increasing susceptibility to being infected if exposed, or increasing the likelihood of progression to severe COVID-19 if infected. Studies that condition on the steps in the causal pathway (e.g., studying hospitalized participants) may be conditioning on colliders. For example, when evaluating the effect of COVID-19 on preterm delivery and using a reference group recruited in the same center, within pregnancies hospitalized, those not admitted for COVID-19 would have other reasons for admissions (e.g., preeclampsia) that may be risk factors
for preterm birth. Web Figure 6. Similarly, when testing is required to classify whether the person has COVID-19, if the outcome triggers testing, there would be a higher proportion of confirmed COVID-19 (and negative tests) among those with the outcome.\textsuperscript{28} Future statistical analyses using the IRCEP data will consider these explanations for observed associations and carefully classify confounders, mediators, and colliders depending on the research question.

- **Enrollment post-infection**

  Of concern in cohort studies with primary data collection is the selection of non-lethal COVID-19 since most women will enroll after COVID-19 resolves. Although maternal mortality is expected to be low (<1%), this selection will result in optimistic descriptions of the nature of COVID-19 during pregnancy. Studies with population-based samples enrolled before infection (e.g., healthcare databases) will be able to provide the full picture.

- **Enrollment post-outcome**

  Enrollment after pregnancy outcomes are known (during or after the end of pregnancy) may self-select a group with adverse outcomes and more eager to share their experience in a study, thus overestimating risks; or it might underestimate the risk if the distressing event reduces the likelihood of participation.\textsuperscript{30} Overall, when we compared participants that enrolled after vs before the end of pregnancy, the frequency of pregnancy outcomes was slightly higher for some (e.g., preterm delivery 10% vs 9%) and slightly lower for others (e.g., major malformations 2.6% vs 2.7%). Table 4. If participation after an adverse outcome is diagnosed is more (or less) likely for patients with COVID-19, retrospective participation may lead to spurious associations. Therefore, primary analyses will be restricted to women enrolled before the pregnancy outcome of interest is known. For example, analyses of malformations will be restricted to women that enroll before the results from informative prenatal screening tests are known.

  However, events that occur right after COVID-19 may only enroll retrospectively. For example, although inclusion of known SABs might introduce selection bias if participants were more likely to enroll after suffering an SAB, particularly if they attribute it to COVID-19, enrollment of retrospective SABs is necessary to capture SABs that could potentially occur immediately after an infection (i.e., pregnant women that become eligible at the time of infection might not have time to enroll prospectively before the outcome). Similarly, there are few participants who had severe COVID-19 in the third trimester and enrolled before delivery – likely because they
remained hospitalized through the end of pregnancy or had a natural or induced delivery and could only enroll after delivery. The above two scenarios challenged our plans to focus on prospective participants when evaluating the effects of infections near end of pregnancy. Studies that enroll the population before the infection (e.g., healthcare databases) will avoid the potential bias introduced by retrospective enrollment.

- **Misclassification**

The IRCEP collects information directly from participants. Women often know more about their habits, occupations, and compliance with medication use than their health care providers; however, clinicians might provide more complete and accurate information regarding diagnoses.\(^{31}\) The accuracy of recall in the IRCEP is facilitated by using structured questionnaires, detailed questions that allow only plausible responses, and calendars to help establish gestational timing and enhance recall of dates.\(^{32}\) To reduce misclassification of infection, primary analyses can be restricted to COVID-19 confirmed with laboratory testing, which became more available over time. Web Figure 7. Misclassification of COVID-19 severity (e.g., need for respiratory assistance or ICU) is unlikely. Outcome misclassification could be non-differential or differential between COVID-19 cases and the reference group. Concern that COVID-19 might pose a risk could lead to more prenatal diagnostic measures such as ultrasound and to more careful examination of infants for defects postnatally, potentially leading to differential accuracy in detection and classification of defects among exposed and unexposed. This potential surveillance bias can be minimized by focusing on major outcomes that are less vulnerable to differential misclassification (e.g., prematurity, SABs, malformations).

**CONCLUSIONS**

Many publications on COVID-19 during pregnancy that shared our limitations failed to address important sources of biases. We summarized the lessons we learned so that future studies can do better. Figure 3. In our experience with an online international pregnancy cohort, the biggest challenges were retention of participants during follow-up and the potential bias introduced when participants are enrolled retrospectively. Given the large sample size, restricting our analyses to prospectively enrolled participants and standardizing risk factors associated with censoring may preserve the utility of the current study for at least some of the questions of interest.
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Table 1. Number of women enrolled during pregnancy or within 180 days after end of pregnancy by country of residence by March 2021

| Country            | Pregnant at Enrollment (N = 9471) | Enrollment After End of Pregnancy (N = 8061) | Overall (N = 17,532) | WHO Prevalence ranking<sup>a</sup> |
|--------------------|----------------------------------|---------------------------------------------|----------------------|----------------------------------|
|                    | No  %                            | No  %                                       | No  %                   |                                  |
| United States      | 2,013 (21.0)                     | 2,814 (35.0)                                | 4,827 (28.0)          | 1                                |
| Brazil             | 1,664 (18.0)                     | 467 (5.8)                                   | 2,131 (12.0)          | 3                                |
| United Kingdom     | 484 (5.1)                        | 810 (10.0)                                  | 1,294 (7.4)           | 5                                |
| Russia             | 690 (7.3)                        | 526 (6.5)                                   | 1,216 (6.9)           | 4                                |
| Mexico             | 641 (6.8)                        | 317 (3.9)                                   | 958 (5.5)             | 13                               |
| Spain              | 370 (3.9)                        | 540 (6.7)                                   | 910 (5.2)             | 7                                |
| India              | 435 (4.6)                        | 359 (4.5)                                   | 794 (4.5)             | 2                                |
| France             | 559 (5.9)                        | 182 (2.3)                                   | 741 (4.2)             | 6                                |
| Chile              | 275 (2.9)                        | 452 (5.6)                                   | 727 (4.1)             | 24                               |
| Italy              | 297 (3.1)                        | 412 (5.1)                                   | 709 (4.0)             | 8                                |
| South Africa       | 320 (3.4)                        | 360 (4.5)                                   | 680 (3.9)             | 15                               |
| Peru               | 338 (3.6)                        | 244 (3.0)                                   | 582 (3.3)             | 18                               |
| Colombia           | 427 (4.5)                        | 89 (1.1)                                    | 516 (2.9)             | 11                               |
| Philippines        | 250 (2.6)                        | 169 (2.1)                                   | 419 (2.4)             | 32                               |
| Argentina          | 331 (3.5)                        | 84 (1.0)                                    | 415 (2.4)             | 12                               |
| Germany            | 240 (2.5)                        | 150 (1.9)                                   | 390 (2.2)             | 10                               |
| Others<sup>b</sup> | 137 (1.4)                        | 86 (1.1)                                    | 223 (1.3)             |                                  |

<sup>a</sup> World Health Organization (WHO) ranking of top countries in number of cases reported as a reference.

<sup>b</sup> Other countries: Algeria, Andorra, Angola, Armenia, Australia, Austria, Bahamas, Bahrain, Belgium, British Indian Ocean Territory, British Virgin Islands, Burkina Faso, Cameroon, Canada, China, Comoros, Costa Rica, Democratic Republic of the Congo, Denmark, Dominican Republic, Ecuador, Ethiopia, Georgia, Ghana, Gibraltar, Greece, Guam, Guatemala, Hungary,
Iran, Ireland, Israel, Jordan, Kenya, Libya, Lithuania, Malawi, Mayotte, Montenegro, Namibia, Netherlands, Nigeria, Pakistan, Portugal, Puerto Rico, Qatar, Romania, Saudi Arabia, Senegal, Singapore, Slovakia, South Korea, Sweden, Switzerland, U.S. Virgin Islands, Ukraine, United Arab Emirates, Uruguay, Zambia, Zimbabwe
Table 2. Distribution of baseline characteristics by SARS-CoV-2 test results and presence of COVID-19 symptoms among those with positive test results.

| Characteristics       | SARS-CoV-2 Test | Symptoms among SARS-CoV-2 Positive |
|-----------------------|-----------------|-----------------------------------|
|                       | Positive N = 7,148 | Negative N = 10,139               | Asymptomatic N = 1,437 | Symptomatic N = 5,654 |
|                       | No. | %   | No. | %   | No. | %   | No. | %   |
| **Age** b             | 30.0 (5.0) | 30.5 (5.0) | 29.5 (5.4) | 30.1 (4.9) |
| Continent             |      |      |      |      |      |      |      |      |
| Africa                | 293  | 4.1  | 440  | 4.3  | 86   | 6.0  | 205  | 3.6  |
| Asia                  | 644  | 9.0  | 618  | 6.1  | 271  | 19   | 366  | 6.5  |
| Europe                | 1,656| 23   | 3,547| 35   | 335  | 23   | 1,298| 23   |
| North America         | 1,841| 26   | 3,914| 39   | 246  | 17   | 1,580| 28   |
| Oceania               | 3    | <0.1 | 3    | <0.1 | 0    | 0    | 3    | <0.1 |
| South America         | 2,711| 38   | 1,614| 16   | 499  | 35   | 2,202| 39   |
| Education             |      |      |      |      |      |      |      |      |
| Less than high school | 334  | 6.4  | 356  | 4.3  | 99   | 10.0 | 236  | 5.6  |
| High school           | 1,665| 32   | 2,361| 29   | 311  | 31   | 1,344| 32   |
| College               | 1,754| 33   | 3,039| 37   | 302  | 30   | 1,433| 34   |
| Graduate education    | 1,488| 28   | 2,470| 30   | 282  | 28   | 1,183| 28   |
| Race/ethnicity        |      |      |      |      |      |      |      |      |
| American Indian/Alaska Native | 21 | 0.4 | 27 | 0.3 | 6 | 0.6 | 0.6 | 15 | 0.4 |
| Asian                 | 281  | 5.3  | 339  | 4.1  | 86   | 8.6  | 193  | 4.6  |
| Black                 | 343  | 6.5  | 334  | 4.0  | 71   | 7.1  | 271  | 6.4  |
| Latina                | 1,215| 23   | 1,201| 15   | 242  | 24   | 964  | 23   |
| Middle Eastern        | 32   | 0.6  | 18   | 0.2  | 11   | 1.1  | 21   | 0.5  |
|                          |       |    |    |    |    |    |    |
|--------------------------|-------|----|----|----|----|----|----|
| **Mixed**                | 551   | 10 | 635| 7.7| 102| 10 | 445|
| Native Hawaiian/Pacific Islander | 4     | <0.1 | 6 | <0.1 | 1 | <0.1 | 3 | <0.1 |
| South Asian              | 65    | 1.2 | 110| 1.3 | 20 | 2.0 | 43 | 1.0 |
| White                    | 2,760 | 52 | 5,591| 68 | 463| 46 | 2,263| 54 |
| **Economic status**      |       |    |    |    |    |    |    |
| Poor                     | 605   | 12 | 925| 11 | 143| 15 | 459| 11 |
| Lower-middle class       | 1,477 | 29 | 1,962| 24 | 267| 27 | 1,198| 29 |
| Middle class             | 2,445 | 47 | 3,808| 47 | 460| 47 | 1,955| 47 |
| Wealthy                  | 643   | 12 | 1,371| 17 | 101| 10 | 535| 13 |
| **Health insurance**     | 4,385 | 84 | 7,238| 88 | 776| 78 | 3,561| 85 |
| **Current employment**   |       |    |    |    |    |    |    |
| Not working              | 1,746 | 33 | 2,902| 36 | 390| 39 | 1,343| 32 |
| Working in an office     | 507   | 9.7| 619| 7.6 | 82 | 8.3 | 420 | 10 |
| Working in food services | 114   | 2.2 | 177| 2.2 | 18 | 1.8 | 95 | 2.3 |
| Working in health care   | 922   | 18 | 1,156| 14 | 133| 13 | 784 | 19 |
| Working from home        | 1,447 | 28 | 2,551| 31 | 283| 29 | 1,144| 27 |
| Other work               | 497   | 9.5 | 746| 9.2 | 83 | 8.4 | 407 | 9.7 |
| **Smoking**              |       |    |    |    |    |    |    |
| No                       | 3,558 | 75 | 5,250| 68 | 627| 74 | 2,895| 76 |
| Before pregnancy         | 969   | 21 | 1,812| 23 | 186| 22 | 771 | 20 |
| During                   | 188   | 4.0 | 654| 8.5 | 39 | 4.6 | 146 | 3.8 |
|                                | Before pregnancy | During pregnancy |     |     |     |     |
|--------------------------------|------------------|------------------|-----|-----|-----|-----|
| **Vaping**                     |                  |                  |     |     |     |     |
| No                             | 4,183            | 6,465            | 84  | 755 | 89  | 3,385|
| Before pregnancy               | 462              | 1,047            | 14  | 88  | 10  | 366  |
| During pregnancy               | 62               | 203              | 2.6 | 7   | 0.8 | 55   |
| **Recreational drugs**         |                  |                  |     |     |     |     |
| No                             | 4,072            | 6,249            | 81  | 737 | 87  | 3,295|
| Before pregnancy               | 573              | 1,260            | 16  | 103 | 12  | 460  |
| During pregnancy               | 62               | 203              | 2.6 | 9   | 1.1 | 52   |
| **Alcohol in first trimester** |                  |                  |     |     |     |     |
| Never                          | 3,573            | 6,045            | 78  | 627 | 74  | 2,910|
| Once per month                 | 772              | 1,152            | 15  | 143 | 17  | 618  |
| Weekly or more                 | 358              | 514              | 6.7 | 78  | 9.2 | 276  |
| **Vitamin in first trimester** |                  |                  |     |     |     |     |
| Never                          | 541              | 684              | 8.9 | 124 | 15  | 411  |
| Some days                      | 892              | 1,536            | 20  | 140 | 17  | 742  |
| Every day                      | 3,265            | 5,483            | 71  | 584 | 69  | 2,646|
| **Pre-pregnancy BMI**          |                  |                  |     |     |     |     |
| < 18.5                         | 137              | 236              | 3.3 | 26  | 3.4 | 106  |
| 18.5-24.9                      | 1,938            | 3,075            | 44  | 366 | 47  | 1,549|
| 25.0-29.9                      | 1,177            | 1,848            | 26  | 207 | 27  | 955  |
| ≥30                            | 1,032            | 1,905            | 27  | 172 | 22  | 851  |
| Condition                                      | Count | Proportion | Count | Proportion | Count | Proportion | Count | Proportion | Count | Proportion |
|-----------------------------------------------|-------|------------|-------|------------|-------|------------|-------|------------|-------|------------|
| Primiparous                                   | 2,042 |            | 3,549 |            | 46    |            | 429   |            | 50    |            |
| Multiple gestations                           | 83    | 1.8        | 147   | 1.9        | 16    | 1.9        | 1,590 | 41         |
| Fertility treatment used                      | 199   | 8.0        | 424   | 8.7        | 45    | 10         | 149   | 7.4        |
| Pregnancy planning                            |       |            |       |            |       |            |       |            |
| Trying for 6-12 months                        | 428   | 9.2        | 698   | 9.2        | 64    | 7.5        | 360   | 9.7        |
| Trying for at least 12 months                 | 602   | 13         | 1,067 | 14         | 127   | 15         | 468   | 13         |
| Unplanned                                     | 2,142 | 46         | 2,721 | 36         | 410   | 48         | 1,706 | 46         |
| Trying for < 6 months                         | 1,465 | 32         | 3,106 | 41         | 256   | 30         | 1,193 | 32         |
| Thyroid disease                               | 284   | 6.0        | 529   | 6.8        | 57    | 6.7        | 223   | 5.8        |
| Pre-pregnancy hypertension                    | 179   | 3.8        | 310   | 4.0        | 36    | 4.2        | 141   | 3.7        |
| Diabetes (I or II, pre-pregnancy)             | 77    | 1.6        | 143   | 1.8        | 18    | 2.1        | 57    | 1.5        |
| Any cardiovascular condition                  | 94    | 2.0        | 148   | 1.9        | 10    | 1.2        | 82    | 2.1        |
| Asthma                                        | 345   | 7.3        | 820   | 11         | 58    | 6.8        | 283   | 7.4        |
| Autoimmune disease                            | 92    | 1.9        | 157   | 2.0        | 18    | 2.1        | 73    | 1.9        |

\(^{a}\) The proportions are estimated among those that responded to that specific module or question.

\(^{b}\) Values are expressed as mean (standard deviation)

\(^{c}\) Weight (kg)/height (m)\(^2\).
Table 3. Distribution of participants according to COVID-19 clinical diagnosis and SARS-CoV-2 test results during pregnancy as reported at enrollment.

| COVID-19                  | SARS-CoV-2 Test at Enrollment |
|--------------------------|-------------------------------|
|                          | Positive | Negative | Inconclusive | Test not done | Total |
|                          | No.      | %        | No.          | %            | No.   | %    |
| Clinical diagnosis       | 3,756    | 64       | 704          | 6.4          | 441   | 96   | 4,988 | 28   |
| Self-reported symptoms only | 1,584    | 27       | 1,625        | 15           | 56    | 19   | 3,273 | 19   |
| No                       | 473      | 8.1      | 8,465        | 78           | 80    | 27   | 9,018 | 51   |
| Uncertain                | 45       | 0.8      | 125          | 1.1          | 71    | 24   | 253   | 1.4  |
| Total                    | 5,858    | 33       | 10,919       | 62           | 294   | 2    | 17,532 | 100  |
Table 4. Obstetric and neonatal outcomes among women with completed pregnancies by March 2021.

| Outcomes                                      | Pregnant at Enrollment N = 438 | Enrollment After End of Pregnancy N = 5978 | Overall N = 6416 |
|-----------------------------------------------|---------------------------------|-------------------------------------------|------------------|
|                                               | No.    | %     | No.    | %     | No.    | %     |
| Pregnancy outcomes                            |        |       |        |       |        |       |
| Live birth                                    | 416    | 95    | 5,844  | 98    | 6,260  | 98    |
| Spontaneous abortion                          | 13     | 3.0   | 56     | 0.9   | 69     | 1.1   |
| Stillbirth                                     | 7      | 1.6   | 43     | 0.7   | 50     | 0.8   |
| Termination (fetal problem)                   | 0      | 0     | 20     | 0.3   | 20     | 0.3   |
| Termination (other)                           | 2      | 0.5   | 15     | 0.3   | 17     | 0.3   |
| Gestational diabetes                          | 37     | 8.9   | 613    | 10    | 650    | 10    |
| (Pre-) Eclampsia                              | 25     | 6.0   | 363    | 363   | 388    | 6.2   |
| Caesarean section                             | 168    | 41    | 2,466  | 43    | 2,634  | 43    |
| Postpartum hemorrhage                         | 22     | 5.3   | 239    | 4.1   | 261    | 4.2   |
| Breastfed in hospital                         | 350    | 89    | 4,637  | 85    | 4,987  | 85    |
| Multiples                                     | 7      | 1.6   | 115    | 2.0   | 122    | 1.9   |
| Neonatal outcomes\(^a\)                       |        |       |        |       |        |       |
| Birthweight in grams\(^b\)                    | 3,336 (535) | 3,249 (614) | 3,257 (608) |
| Gestational weeks at delivery\(^b\)           | 38.8 (2)  | 38.8 (2)  | 38.8 (2)  |
| Gestational age at delivery                   |        |       |        |       |        |       |
| Gestational Age   | 
|------------------|
| ≥42.0 weeks      | 10 2.4 95 1.6 105 1.6 |
| 39.0-41.9 weeks  | 275 65 3,504 59 3,779 59 |
| 37.0-38.9 weeks  | 102 24 1,774 30 1,876 29 |
| 32.0-36.9 weeks  | 34 8.0 527 8.8 561 8.8 |
| 28.0-31.9 weeks  | 3 0.7 57 1.0 60 0.9 |
| <28.0 weeks      | 0 0 27 0.5 27 0.4 |
| Small for gestational age | 33 7.8 482 8.1 515 8.0 |
| Large for gestational age | 49 12 726 12 775 12 |
| NICU admission   | 52 13 796 14 848 14 |
| Major congenital malformation | 11 2.7 147 2.6 158 2.6 |
| Roomed-in with mother | 337 84 4,333 77 4,670 78 |
| Every day        | 337 84 4,333 77 4,670 78 |
| Some days        | 19 4.7 326 5.8 345 5.8 |
| No               | 42 10 829 15 871 15 |
| I don't know     | 4 1.0 109 1.9 113 1.9 |
| Tested for COVID-19 | 38 9.5 684 12 722 12 |
| Positive for COVID-19 | 2 0.5 48 0.9 50 0.8 |
| Neonatal death   | 1 0.2 12 0.2 13 0.2 |

\(^a n = 6410\) infants.

\(^b\) Values are expressed as mean (standard deviation)
Figure 1. Distribution of months from the last menstrual period (LMP) at enrollment for participants that enrolled during or after end of pregnancy by March 2021.

Figure 2. Study population flow chart from consent to study completion by March 2021. Eligible for these analyses was everyone who consented to participate, filled out the initial module on COVID-19 tests and clinical diagnosis, and met the inclusion criteria.

Figure 3: Lessons learned from the International Registry of Coronavirus Exposure in Pregnancy.
Completed Any Survey (n = 17,532)

- Joined After Pregnancy (n = 8,061; 46%)
  - COVID Inconclusive (n = 77; 1%)
  - COVID Positive (n = 1,935; 24%)
    - Have Outcome Data (n = 1,319; 68%)
      - Provided Medical Record (n = 68; 5%)
    - Missing Outcomes (n = 616; 32%)
- Joined During Pregnancy (n = 9,471; 54%)
  - COVID Inconclusive (n = 172; 2%)
  - COVID Positive (n = 5,156; 54%)
    - Completed Pregnancy (n = 170; 3%)
      - Provided Medical Record (n = 2; 1%)
    - Missing Outcomes (n = 4,775; 93%)
  - COVID Negative (n = 4,143; 44%)
    - Completed Pregnancy (n = 261; 6%)
      - Provided Medical Record (n = 2; 1%)
    - Missing Outcomes (n = 3,600; 87%)
- COVID Inconclusive (n = 77; 1%)

COVID Positive (n = 1,935; 24%)
- Have Outcome Data (n = 1,319; 68%)
  - Provided Medical Record (n = 68; 5%)
- Missing Outcomes (n = 616; 32%)

COVID Negative (n = 6,049; 75%)
- Have Outcome Data (n = 4,633; 77%)
  - Provided Medical Record (n = 110; 2%)
- Missing Outcomes (n = 1,416; 23%)

COVID Inconclusive (n = 77; 1%)
- Complete Pregnancy (n = 211; 4%)
  - Provided Medical Record (n = 2; 1%)
- Missing Outcomes (n = 4,775; 93%)

Still Pregnant (by Monthly Survey)
- Completed Pregnancy (n = 282; 7%)
  - Provided Medical Record (n = 2; 1%)
- Missing Outcomes (n = 3,600; 87%)

Have Outcome Data (n = 1,319; 68%)
- Completed Pregnancy (n = 170; 3%)
  - Provided Medical Record (n = 2; 1%)
- Missing Outcomes (n = 4,775; 93%)

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- Missing Outcomes (n = 3,600; 87%)
Lessons Learned

- A key implementation challenge for online international pregnancy cohorts is the retention of prospectively enrolled participants during follow-up.
- A key methodological challenge for pregnancy cohorts is the potential bias introduced when participants are enrolled retrospectively.
- Multiple biases need to be considered and addressed when estimating and interpreting the effects of COVID-19 in pregnancy in these types of cohorts.