INTERNATIONAL REGISTRY OF CORONAVIRUS EXPOSURE IN PREGNANCY (IRCEP)

PROTOCOL

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LIST OF ABBREVIATIONS

AE	Adverse event
CDC	Centers for Disease Control and Prevention
CEC	Clinical Events Committee
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
EDD	Estimated date of delivery
FDA	US Food and Drug Administration
IRCEP	International Registry of Coronavirus Exposure in Pregnancy
IRB	Institutional review board
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MERS-CoV	Middle East respiratory syndrome coronavirus
NICU	Neonatal intensive care unit
NOS	Not otherwise specified
PS	Propensity score
RR	Relative risk
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

US	United States
WHO	World Health Organization

1. SYNOPSIS

Rationale and background: There is insufficient information on the potential effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on pregnant women and their developing offspring. However, these populations are classified as vulnerable.

Research aims and objectives: The International Registry of Coronavirus Exposure in Pregnancy (IRCEP) aims to describe the natural history of Coronavirus Disease 2019 (COVID-19) in pregnant women and to estimate the relative risk of major adverse obstetric and neonatal outcomes among women with varying degrees of severity and of timing of COVID-19 exposure and their offspring, respectively.

Study design: The IRCEP will be an observational cohort study with prospective and retrospective components. Registration and participation via website or mobile app especially developed for the IRCEP will be voluntary. Women 18 years of age and older will be encouraged to enroll if, at any time during pregnancy, they had a test performed for the coronavirus (regardless of the result) or if they had clinical confirmation of COVID-19 in the absence of a SARS-CoV-2 test. Women with confirmed COVID-19 via clinical or test methods will be included in the exposed group and women with a negative test will be included in the control group. Eligible women will be able to enroll at any time during gestation. Given the public health emergency due to the COVID-19 pandemic and the urgent need for data, the IRCEP will also enroll eligible women retrospectively during the first 180 days after delivery (if they delivered after December 2019). As numbers accumulate, the natural history of COVID-19 during pregnancy will be reported stratified by days since COVID-19 confirmation at enrollment (i.e., from prospective if immediate to retrospective if enrolled after resolution) and the risk of pregnancy outcomes by COVID-19 exposure group will be reported stratified by trimester at enrollment. For the assessment of miscarriages, only participants enrolled during the first trimester will be included and the analyses will be stratified by gestational week at enrollment. For other outcomes, the primary analysis will include all enrollees. However, sensitivity analyses of 1) teratogenicity will be restricted to participants enrolled before an informative prenatal screening was done; 2) late-pregnancy outcomes (e.g. preeclampsia) will be restricted to participants enrolled before the third trimester; and 3) delivery or neonatal outcomes will be restricted to participants enrolled before delivery.

Information will be obtained directly from the participating women. Given the international nature of the IRCEP, the questionnaires will be available in 7 languages (English, Spanish, French, German, Italian, Mandarin, and Farsi). Participant confidentiality and anonymity will be strictly upheld. The IRCEP will collect data on potential confounding factors (such as maternal sociodemographic characteristics, behaviors, reproductive history, chronic conditions, use of medications, and measures of healthcare utilization), on COVID-19 infection (symptoms, test results, treatment, and resolution), and information related to obstetric and neonatal outcomes. Follow-up will include questions at various time points during the pregnancy and will continue through the infant's first 90 days of life. There are two main data analyses: 1) a real-time descriptive surveillance that will report the COVID-19 characteristics and the frequency of outcomes in the exposed and control groups, and 2) hypothesis-based causal inference analyses that will

investigate the potential effects of specific COVID-19 characteristics or treatments and will adjust through multivariate regression models or using propensity score (PS) matching to account for potential confounders, as appropriate. The goal of the IRCEP is to provide women, clinicians, public health agencies, and investigators with the empirical evidence they need to make informed decisions and recommendations, and to develop a data repository to conduct studies within this cohort that might inform the management and treatment of pregnant women with COVID-19.

2. INTRODUCTION

Millions of women will give birth during the pandemic of Coronavirus Disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Since this virus is not known to have caused infection in humans before the cases identified in 2019 in Wuhan, China, and few exposed pregnancy outcomes have been reported since then,[2] the consequences of COVID-19 for pregnant women and their offspring are unknown. This lack of information leads to misinformation and anxiety among pregnant women, women who are considering getting pregnant, and their families. It is, therefore, an urgent necessity to obtain and communicate reliable information. Concluding that there is absence of increased risk compared to the general pregnant population would be as important as identifying risks, since the current dearth of information is likely resulting in unnecessary cesarean sections[2] and therapeutic terminations.

The aim of the IRCEP is to provide women, clinicians, public health agencies, and investigators with 1) the evidence they need to make informed decisions and recommendations, and 2) a data repository to conduct studies within this cohort that might inform the management and treatment of pregnant women with COVID-19. Specific questions IRCEP will be able to inform include:

- ***If pregnant women become infected, will they be sicker than infected non-pregnant women their age?*** There is no evidence to support that infected pregnant women have more severe COVID-19 illnesses than infected non-pregnant women of similar age. Small case series have suggested clinical characteristics similar to those in the general population.[2] By March 2020, there had been no reports of COVID-19 related maternal deaths. However, based on small studies of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), pregnant women infected with coronavirus might be more vulnerable to severe respiratory problems and death.[3,4] Infection with respiratory viruses, such as influenza subtype H1N1, result in more severe illness and a higher mortality in pregnant women than in the general population.[5]
- ***Can COVID-19 cause problems for a pregnancy or affect the health of the baby?*** There is no evidence that COVID-19 affects the course of pregnancy or the health of the developing fetus or the newborn after birth. There have been a small number of reports suggesting that women infected late in pregnancy may be at higher risk premature rupture of membranes, fetal distress, stillbirth and premature delivery.[6,7] However, these were non-controlled case series and it is not clear if the events were caused by the virus, maternal hypoxia, or underlying risk factors. Moreover, some of the preterm cases reported were iatrogenic (i.e., elective cesarean to control the delivery in the context of the outbreak)[2] and not due to spontaneous preterm labor.[8] Other viral respiratory infections, such as flu, during pregnancy have been associated with a higher risk of preterm birth, whether triggered by the virus or by the severe maternal symptoms. No meaningful association has been demonstrated between influenza infection and other adverse pregnancy outcomes. However, SARS during pregnancy was associated with a high incidence of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction.[9,10] Moreover, what is known is that both

uncomplicated and complicated pregnancies will seek care at saturated hospitals during the pandemic, which might also impact the health of mothers and newborns.

- ***What are the benefits and risks of different COVID-19 treatments in pregnancy?*** There is no evidence to inform the risk-benefit profile of most of the treatments currently considered, or being evaluated, for COVID-19. Their effectiveness reducing COVID-19 severity in pregnancy and the potential effects on obstetric and neonatal outcomes need to be evaluated.
- ***Does COVID-19 infection pass from the mother to the fetus or newborn?*** Vertical transmission is unlikely but cannot be ruled out. SARS-CoV-2 has not been found in samples of newborn, amniotic fluid, placenta or breastmilk,[2,11] and there were no reports of mother-to-baby transmission for other coronaviruses (MERS-CoV and SARS-CoV)[9]. However, elevated IgM antibodies in blood at birth have been reported in infants born to mothers with confirmed infection in the third trimester (IgM are not transmitted in-utero and appear days after infection); yet, the infants tested negative for the virus.[12,13] Whether the virus can be transmitted during vaginal delivery is also not known. However, there are reports of COVID-19 in newborns despite active precautions,[14] demonstrating that they are susceptible and can get infected by the mother, or others, likely through contact after delivery.[15] Although cases in children tend to be mild, children under one year of age have a higher proportion of severe disease[16]; and newborns may have the highest risk since they have not yet developed immunity against other coronaviruses.

Pregnancy registries are designed to collect clinically relevant data and to provide information for treating or counseling pregnant women. They are observational cohort studies of women receiving routine clinical care, who enroll voluntarily during gestation and, ideally, before pregnancy outcomes are known (i.e., prospective ascertainment). Registry participants are followed-up until at least the end of pregnancy to systematically collect information on specific pregnancy and infant outcomes. The frequency of these outcomes can then be assessed in women exposed (e.g., to COVID-19) relative to a scientifically valid reference population.[17] Recent advancements in technology, including blockchain and artificial intelligence, facilitate the execution of large global pregnancy registries.

Other study designs offer complementary advantages and limitations. For example, clinical cohorts with data collection at hospitals provide detailed data on patients, occasionally including biological samples, producing comprehensive information and highly accurate diagnoses. However, the sample size gathered in this context is usually insufficient to assess most outcomes of interest, and the cost in time and resources is larger. Another option is to use administrative databases, such as insurance claim files or electronic medical records. These databases provide prospectively collected information of large populations, are more efficient than pregnancy registries, and include populations often excluded from volunteer-based studies. However, many of these databases will not include the results of the test for COVID-19 and most will take years to have enough analyzable data.

Therefore, the IRCEP was established to describe the natural history of COVID-19 in pregnant women and to assess the relative risk of major adverse obstetric and neonatal

outcomes among women with varying degrees of severity and of timing of COVID-19 exposure and their offspring.

3. OBJECTIVES

The aims of the IRCEP are 1) to describe the natural history of COVID-19 in pregnant women and the natural history of pregnancy in women with COVID-19, in real-time; and 2) to evaluate obstetric and perinatal outcomes in women with COVID-19 during pregnancy and their newborns. The resulting information will ultimately be communicated to the public, health care providers, and public health agencies, facilitating their ability to make informed recommendations.

The IRCEP will collect data on baseline risk factors, COVID-19 course, and the most common obstetric and neonatal outcomes including pregnancy loss (spontaneous abortion or stillbirth, elective terminations), major congenital malformations in the offspring, obstetric complications (e.g., preeclampsia, emergency cesarean section), and perinatal outcomes (e.g., prematurity, fetal growth deficiency, NICU admission).

There will be two levels of analysis:

1. **Real-Time Public Health Surveillance.** The purpose of this analysis is to describe the severity of COVID-19 infection in pregnancy and to quantify the frequency of obstetric and neonatal pregnancy outcomes among women with varying degrees of severity and of timing of COVID-19 exposure. The frequency of these outcomes in women with no clinical confirmation of COVID-19 and negative coronavirus test, enrolled at the same time and followed with the same methods, will provide a reference.
2. **Causal inference, hypothesis driven.** The purpose of this analysis is to determine whether the observed frequency of specific pregnancy outcomes in women with COVID-19 differs from the expected had those women been unaffected. The risk among women with COVID-19 will be compared to a PS-matched reference group of women with a negative test, with similar characteristics and comparable gestational enrollment periods. Other internal reference groups may be women infected outside etiologically relevant periods; women with milder COVID-19 severity, or previous pregnancies by the same woman (sibling design). Based on the data collected, IRCEP investigators will also be able to assess the potential effects of specific COVID-19 characteristics or treatments, characteristics associated with COVID-19 severity, frequency of infections in newborns, impact on breastfeeding, geographic variation in pregnancy course and outcomes for COVID19 infected women, etc.

4. RESEARCH METHODS

The design of the IRCEP is consistent with relevant national and international guidelines and recommendations.[17,18]

4.1 Study Design

The IRCEP is designed as a prospective observational study of adult pregnant women with clinical confirmation of COVID-19 or tested for SARS-CoV-2 at any time during their pregnancy. Participation in the IRCEP is voluntary. To increase the validity of the data, specific efforts will be made to enroll women as soon as possible after they are diagnosed with COVID-19 or they obtain the results of the test for SARS-CoV-2. Women will be followed-up during pregnancy and for three months after delivery (in the case of a livebirth) in order to assess outcomes in the offspring. Given the international nature of the IRCEP, the questionnaires will be available in 7 languages (English, Spanish, French, German, Italian, Mandarin, and Farsi).

Data on baseline characteristics, COVID-19 characteristics, pregnancy outcomes, and neonatal outcomes will be collected during pregnancy and postpartum. Ideally, information on COVID-19 and maternal risk factors will be provided prospectively by the participants (i.e., before the outcome of interest is known). However, given the public health emergency due to the COVID-19 pandemic and the urgent need for data, the IRCEP will also enroll eligible women retrospectively during the first 180 days after delivery. Data will be entered by the participant directly into the IRCEP website or mobile app-based data capture system. All data components for an individual will be linked through a unique subject identifier. A file containing the study list of personal identifiers used during the informed consent process (first and last names) and personal contact information (email addresses) will be securely stored in a separate US-based server only accessible to the Principal Investigator and the Registry Coordinators.

The longitudinal design allows estimation of both absolute and relative risks for a range of obstetrical and neonatal outcomes. Sub-cohorts of pregnant women defined by COVID-19 severity and gestational timing will be identified and compared to four reference groups. The primary reference group will include all pregnancies in the IRCEP with a negative SARS-CoV-2 test and no clinical confirmation of COVID-19, matched on gestational week at enrollment, country, and month at LMP. This group will provide the baseline expected incidence or prevalence of obstetric and perinatal events in women from the same source population as the exposed. A second reference group will be women with clinically mild COVID-19 presentations. This group will allow an evaluation of the effect of disease severity on adverse pregnancy outcomes. A third reference group will include women with COVID-19 outside the etiologically relevant period (e.g., risk of major malformations in women infected around conception versus those infected in the second half of pregnancy). Lastly, the fourth reference group will compare outcomes in the current pregnancy affected by COVID-19 with those in past pregnancies (i.e., sibling design) among multiparous women.[19] To correct for potential trends (e.g. higher risk of preeclampsia in primiparous), the IRCEP will use test-negative controls to estimate and remove the effect of trends from the relative risk estimate.[20]

4.2 Study Population

The target study population consists of pregnant women, 18 years of age or older, tested for SARS-CoV-2 or with clinical confirmation of COVID-19, willing to provide information using the IRCEP website or mobile app. The rationale for including cases without a positive test is that in the worst-hit areas, where nucleic acid tests were scarce, epidemiological considerations and clinical symptoms (i.e., pneumonia, chest CT findings) sufficed to assign a diagnosis.

4.2.1 Inclusion criteria

- Pregnant women or women that delivered or had a pregnancy loss within the last 180 days
- Aged 18 years or older
- Tested for SARS-CoV-2 or had clinical confirmation of COVID-19 between the last menstrual period (LMP) and delivery
- Able and willing to sign the informed consent form agreeing to the conditions and requirements of the IRCEP, and
- Willing to upload the minimum required data of the initial baseline questionnaire

As part of the informed consent process, women understand that they will be asked to provide SARS-CoV-2 test results and medical record information of themselves and of their infant(s), should the pregnancy result in live birth (see Appendix 1). To protect privacy, women will be required to redact all identifying information before uploading test results or medical records. The Registry data management staff will check in the database if all personal information is redacted and redact any identifiers.

It is anticipated that a proportion of participants will not upload their tests or medical records. Women without records will be eligible for analysis. The potential impact of using non-validated information will be addressed through sensitivity analyses restricted to women with validated tests and outcomes.

The study population will consist of volunteers from any country in the world. It is expected that the Registry participants will represent a wide range of maternal age, race/ethnic background, and health status given the ubiquitous presence of smartphones and high-speed Internet connectivity among millennials (18 to 34 years of age) and Gen X (35 to 46 years of age).

4.2.2 Awareness

Information about the IRCEP will be made available on the dedicated IRCEP website (https://corona.pregistry.com/). It is expected that links to the IRCEP website will be added in many relevant websites worldwide (e.g., at CDC, WHO, NICHD, ACOG, SMFM, FDA, EMA, etc.).

Additional venues for increasing awareness of the IRCEP may include:

- Partnering with patient-centric virtual communities, such as PatientsLikeMe

- Actively participating in social media channels frequently visited by pregnant women (e.g., on Facebook and Instagram)
- Publishing short articles and blogs on LinkedIn and other media
- Linking the IRCEP website to other maternal health interest websites
- Posting notices in relevant journals or advocacy publications
- Presenting IRCEP data at obstetrics, maternal-fetal medicine, and teratology scientific and clinical meetings, and
- Publishing results in peer reviewed scientific journals

4.2.3 Enrollment and Follow up

Women will self-enroll using the IRCEP website or mobile app. Women can enroll from LMP to 180 days after delivery. Follow-up for analyses will start at the coronavirus test or COVID-19 confirmation and continue until three months after delivery. Status of pregnancy (miscarriage, termination, stillbirth, live birth) will be collected and livebirths will be followed until three months after birth or date of death during first three months.

Attempts will be made to collect a minimum set of de-identified information (demographics) from all eligible women who are lost-to-follow up in order to assess data representativeness in final analyses relative to the initial population.

The optimal group for analyses will be women enrolled **before both the COVID-19 clinical resolution and the pregnancy outcome** are known. The advantages of early enrollment are to reduce potential selection bias and to collect reliable prospective information on COVID-19 exposure and other characteristics, unaffected by the outcomes. The meaning of “retrospective” may vary for each outcome. Women who enroll after the onset (suspicion or recognition) of an outcome (e.g., spontaneous loss, stillbirth, or termination) will be classified as *retrospective enrollees*. Women who enroll before the event of interest can be known will be considered *prospective enrollees*. Primary analyses of COVID-19 evolution in pregnancy will be restricted to women who enroll soon after a SARS-CoV-2 test or COVID-19 symptoms initiation. Primary analyses of early pregnancy losses will be restricted to women enrolled in the first months of pregnancy. For other outcomes, the IRCEP will consider all enrollees, given the urgent need for data. However, the following sensitivity analyses will also be conducted: the analyses of malformations will be restricted to women that enroll before the results from informative tests (e.g., screening ultrasound after 12 weeks of gestation) are known. The analyses of late pregnancy outcomes (e.g. preterm delivery) will be restricted to women who enroll before the third trimester. Finally, the analyses of perinatal outcomes (e.g. NICU admission) will be restricted to women who enroll before delivery.

Women can withdraw from the IRCEP at any time, in which case all their information will be deleted from the database (except for select de-identified sociodemographic characteristics, to be retained for comparison in the aggregate with remaining participants). As enrolled women are automatically reminded by the web and mobile app systems to upload information, losses to follow-up are anticipated to occur when women ignore or uninstall the app. Losses to follow-up will be censored from the cohort at the

time of last contact. For specific variables, characteristics of those lost to follow-up will be compared to the observed cohort and weights may be applied if censoring is not random.

Infants and mothers will be followed-up until three months of age and their outcomes will be collected. This length of follow-up time is appropriate, as some structural and many functional malformations become clinically apparent months after birth.[21,22] Inclusion of prenatal diagnoses and outcomes identified during infancy will result in higher risks than if the IRCEP were restricted exclusively to hospital delivery discharge diagnoses. Therefore, the IRCEP's estimated risk of major malformations may be higher and not comparable with some external references, such as birth defects surveillance systems.

4.2.4 Retention methods

Retention will be facilitated by dividing the questionnaires into short, easy-to-complete modules. Optional email and mobile phone notifications will be available during the study. General results from the IRCEP will be released to the public on a regular basis to increase awareness of the IRCEP and to emphasize the importance of completing the modules.

4.3 Data Collection and Timing of Assessments

Data will be collected mainly by structured web and app-based modules on multiple occasions during pregnancy, after pregnancy completion, and, in the case of a live birth, 12 weeks after pregnancy completion. Several modules will collect data on timing of SARS-CoV-2 testing and COVID_19 clinical signs, their duration, severity and treatment. Redacted coronavirus test results will be solicited. Other modules will collect data on covariates (e.g., demographics, illnesses, reproductive history) that may be confounders or effect modifiers. Another module will collect data on obstetric complications (e.g., preeclampsia, mode of delivery) and pregnancy losses. In case of a delivery (stillbirth or livebirth), the mother will be asked about delivery and infant complications, infant size, and presence of birth defects. Redacted neonatal medical records will be solicited. Data collection will continue until three months after delivery for livebirths, when data on health conditions will be collected (Figure 1).

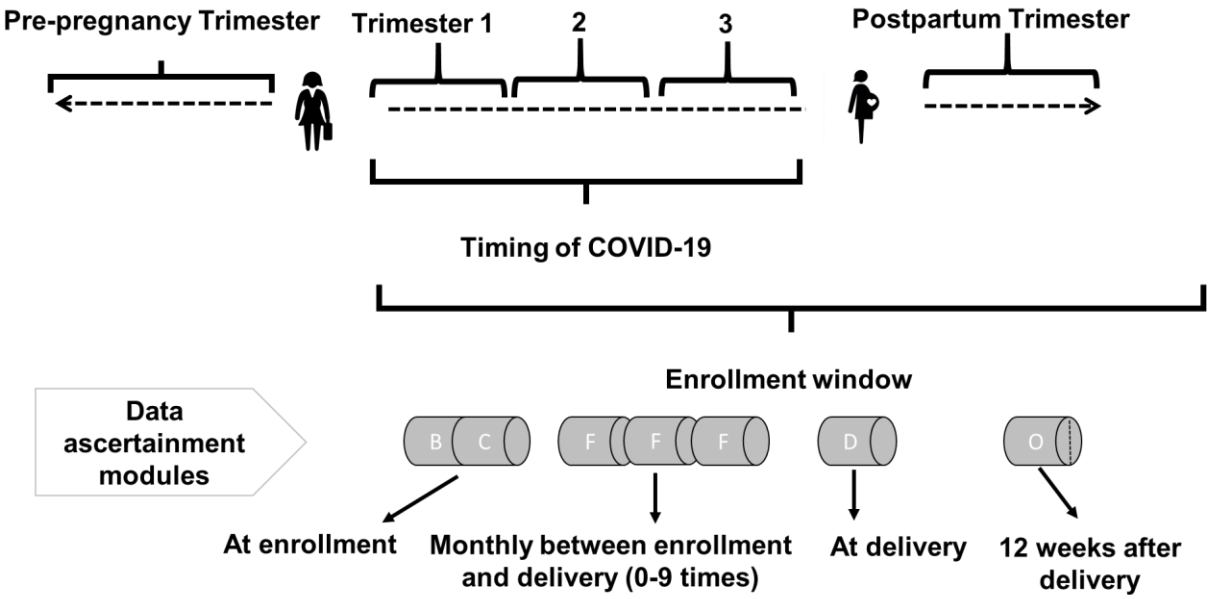

Figure 1. Summary of Study Design: Timing of COVID-19, enrollment and data collection modules for baseline characteristics (B), COVID-19 (C), follow up (F), Delivery (D) and outcomes three months after delivery (O).

Regarding the timing of inquiries, the web and app systems will collect information monthly using brief follow-up modules. It is anticipated that this approach will minimize attrition and maximize engagement. At enrollment, women will fill out modules up until the gestational period in which they currently are. For example, a woman enrolling at gestational week 15 will fill out all the baseline information as well as exposures up to that gestational week, including all information on her COVID-19. Then, she will be prompted to fill out follow-up information monthly until delivery, when she will complete the delivery information questionnaire, followed by the last questionnaire 12 weeks later. The follow up module will include COVID-related questions to follow up active COVID-19 cases as well as to detect potential positive SARS-CoV-2 tests in women that initially tested negative.

In addition to self-reported information, the web and app systems will request medical records. Participants will be asked to redact their personal identifiers, take a photo and upload into the web or app of all available coronavirus test results, medical records from the hospital discharge from the delivery, pediatric reports, in case of a problem in the infant, and any other health care records they consider relevant. These records will be used to validate maternally reported diagnoses and to allow for potential future adjudication of outcomes by experts (e.g., dysmorphologist) blinded to the COVID-19 status for specific studies. Pre-defined criteria for each of the study outcomes will be used for classification. IRCEP staff will review the document and photo uploads for any remaining identifiers and will redact the identifying information prior to uploading it for analysis. For specific studies, confirmation of outcome will be blinded to exposure and confirmation of exposure will be blinded to the outcome.

4.4 Timing of Pregnancy and Denominator

There are two general aspects that deserve special mention since they are key to define the timing of pregnancy and the study population (i.e., number of fetuses/infants per pregnancy).

While conception is the official beginning of pregnancy, the first day of the last menstrual period (LMP) has been traditionally used to define the length of gestation. Gestational age will be determined by an algorithm using the best available information. If the first day of LMP is known, and ultrasound measures of dating are not discrepant, the menstrual period dating will be used to calculate gestational age. However, if results from an ultrasound are given to the mother as “estimated date of delivery (EDD)”, the IRCEP will use this EDD and subtract 279 days to estimate the LMP. The second trimester begins at week 14 and the third trimester begins at week 28.

Pregnancy will be the unit of observation for obstetric and neonatal outcomes. Twins or higher order multiples will be handled as one obstetric outcome in the analyses. For example, if the pregnancy culminates with at least one live born infant, the outcome will be considered a live born outcome. If either or both twins have a major birth defect, the outcome will be considered one major birth defect outcome. This approach defines pregnancy as the unit of observation. However, information in twins or higher order multiples will be recorded. Individual twins will contribute as independent observations to the infant follow-up analyses post-delivery. In both phases (pregnancy and infant cohorts), multiples will be used as covariate in the analyses, when appropriate, and the models will also consider the clustering if the same woman were to contribute information for more than one of her pregnancies.[23] When reporting risks, whether using fetuses or pregnancies as the unit of analysis, both the numerator and denominator will be consistent with the choice.[24]

4.5 Exposure definition

The main exposure of interest for this study is SARS-CoV-2 infection. Specific characteristics of the COVID-19 disease, including symptoms, severity, and treatments are the main considerations of the exposure. Exposure definition will also consider the specific gestational timing, since the etiologically relevant period for each outcome of interest will vary. For example, for many severe major malformations, the period of interest is the first trimester, but a narrower window is appropriate for specific anomalies (e.g., first few weeks after conception for neural tube defects). Exposures earlier or later in pregnancy can adversely affect some malformations and other outcomes.[25-27]

Exposure of embryos to teratogens during the preimplantation stage usually does not cause congenital malformations unless the agent persists in the maternal body beyond this period. However, periconceptional exposures to COVID-19 might increase the risk of miscarriages. The embryonic period, from 18 to 54-60 days after conception, is the period when the basic steps in organ development occur. This is the period of maximum sensitivity to teratogenicity since not only are tissues differentiating rapidly but damage to them is irreversible. Exposure to teratogenic agents during this period has the greatest likelihood of causing a structural anomaly.

The fetal phase, from the end of the embryonic stage to term gestation, is the period when growth and functional maturation of organs and systems already formed occur. Exposures late in pregnancy tend to affect fetal growth (e.g., intrauterine growth retardation), the size of a specific organ, or the function of the organ, rather than cause gross structural anomalies. Infections with other respiratory viruses (e.g., H1N1, SARS) were associated with fetal growth retardation and preterm delivery, as has been COVID-19 in case series. The etiologically relevant window may be unclear if the pathophysiology of the outcome is poorly understood or multifactorial (e.g., preeclampsia) or if the mechanism by which the infection confers excess risk is not defined. In these circumstances, it is important to explore different, potentially relevant windows, while always acknowledging the windows explored.

4.5.1. Exposed group.

We defined as exposed women with a positive nucleic acid or serologic test for SARS-CoV-2 or clinically confirmed COVID-19 between LMP and end of pregnancy. Pregnant women with clinically confirmed COVID-19 but without a confirmatory test for COVID-19 are eligible for enrollment because, in the worst-hit areas, the test might not have been available for all patients and, the combination of epidemiological context and symptoms (e.g., pneumonia, chest CT), is considered sufficient basis for clinical confirmation. In sensitivity analysis, the confirmed and plausible cases will be distinguished depending on the evidence of a positive test.

4.5.2. Reference groups.

The primary reference group will be women with a negative SARS-CoV-2 test and asymptomatic for COVID-19 matched to those in the exposed group on gestational week at enrollment, country of residency, and month at LMP. The reference group will provide an estimate of the expected incidence or prevalence of obstetric and neonatal events in women from the same source population as the exposed (i.e., pregnant under similar outbreak circumstances, including health care conditions). It should be acknowledged that, since the qRT-PCR test has a false-negative rate of at least 30%,[28] a proportion of the controls might have been infected or may develop COVID-19 later in pregnancy. However, false negatives will occur most likely among women with clinical signs of COVID-19. Therefore, symptomatic women with a negative test will not be included in the reference group. Rather, in a secondary analysis, women with a negative test with symptoms will be considered potential COVID-19 cases. In addition, women will be followed-up in the reference group to detect those that may test positive later in pregnancy. If so, those women will be transferred from the reference to the exposed group at that point.

A second reference group will be women with clinically mild or asymptomatic COVID-19 presentations but confirmed infection. This group would serve as reference for more severe cases and will allow an evaluation of the effect of disease severity on adverse pregnancy outcomes within women exposed to the virus. A third reference group will include women with COVID-19 outside the etiologically relevant period. This group will serve as a reference for women exposed during relevant periods (e.g., risk of major malformations in women infected around conception versus those infected in the second half of pregnancy). Lastly, the fourth reference group will compare outcomes in the current

pregnancy affected by COVID-19 with those in past pregnancies (i.e., sibling design) within the same woman, among multiparous.[19] To correct for potential trends (e.g. higher risk of preeclampsia in primiparous), asymptomatic test-negative controls will be used to estimate and remove the effect of trends from the relative risk estimate.[20,29]

The IRCEP investigators will also be able to assess the potential effects of specific COVID-19 characteristics or treatments, predictors of COVID-19 severity, frequency of infections in newborns, impact on breastfeeding, impact on maternal mental health, etc. Reference groups may vary accordingly.

4.6 Outcome definitions

The IRCEP will collect a wide range of outcomes. The most common specific obstetric and pediatric conditions and events will be asked with targeted questions. Outcomes will be reported by the mother and validated with medical records when they are received. The web and app systems will also autogenerate reminders in order to obtain medical records, especially when severe conditions are reported. The outcomes of interest will include:

- **Miscarriage** (or spontaneous abortion): spontaneous pregnancy loss prior to 20 weeks' gestation.
- **Elective Termination**: termination of pregnancy due to a prenatally diagnosed anomaly or for social reasons.
- **Stillbirth**: fetal death that occurs >20 weeks' gestation.
- **Preterm Delivery:** a spontaneous or induced delivery at <37 gestational weeks. Very preterm delivery is defined as delivery at <34 weeks. In addition, gestational age at birth (in completed weeks), will be considered as a continuous variable also.
- **Small for Gestational Age:** ≤10th centile on birth weight for the infant's sex and gestational age using gestational period and sex-specific references.[31] In addition, birthweight will be considered as a continuous variable and low birth weight (defined as weight at birth <2500gr) will be considered as an outcome affected by both length of gestation and fetal growth.
- **Head circumference at birth:** collected in centimeters. Microcephaly will be defined as a head size that is two standard deviations below the mean for infants of the same sex and gestational age at birth.
- **Major structural defects**: abnormalities in structural development that are medically or cosmetically significant, present at birth, and persist in postnatal life unless or until repaired. Positional deformities that are transient (e.g., plagiocephaly) and maturational defects, such as a patent ductus arteriosus or an inguinal hernia that might occur in a preterm infant simply as an artifact of shortened gestational age, do not represent abnormalities in embryonic or fetal development and will be excluded. Small muscular ventricular septal defect that may spontaneously close with no consequence for the infant and retractile testis that may spontaneously descent will be excluded. Minor structural defects that may not be reliably assessed will be excluded (e.g., birth marks). Major malformations will be coded based on standard coding systems for inclusion and exclusion of structural defects, such as the U.S. Centers for Disease Control and Prevention's (CDC) Metropolitan Atlanta Congenital Defects program.30 Major malformations reported by the mother will be confirmed with medical records, if available. Genetic disorders, including chromosomal

abnormalities and Mendelian disorders, will be excluded since they have a genetic etiology.

- **Neonatal death:** death of a live born in the first 0-27 days of life, where day 0 is the first day of life.
- **Admission into the Neonatal Intensive Care Unit:** collected as the number of days the neonate spent admitted at the NICU.
- **Infant percentile in growth charts:** length for age and weight for length percentiles, head circumference for age and sex percentile.
- **Maternal obstetric complications and post-partum health**: The post common complications of pregnancy will be prompted (e.g., preeclampsia, gestational hypertension, Cesarean section, postpartum hemorrhage, postpartum depression).

4.7 Confounders and effect modifiers

In addition to information on COVID-19, the IRCEP will collect data on a wide range of maternal and pregnancy covariates specifically prompted by the web and app systems which include maternal demographic characteristics, comorbid medical conditions, habits, reproductive history, obstetric characteristics, use of medications, and measures of healthcare utilization. Some of the collected covariates will be used for specific analyses when they are potential risk factors for the outcomes or potential proxies for such risk factors.

Ideally, covariates will be measured before the outcome occurs to avoid selection bias and recording bias.[32,33] However, given the urgent nature of this study, retrospective enrollment will be allowed and, thus, baseline covariates might be recorded after some of the outcomes occurred. To assess the impact of retrospective data collection in women that enroll after outcomes are potentially known, the analysis will restrict to prospectively enrolled women. Also, women will be enrolled after the exposure of interest (COVID-19) but baseline covariates will collect information on characteristics existing *before* the infection to avoid adjusting for factors in the causal pathway.[34]

4.8 Data Sources

The primary source of information on exposure, outcomes, and covariates is the registry participant. The data are collected using a website and a mobile app. The IRCEP participants will be prompted to answer short follow-up questionnaire modules monthly. Users will be automatically reminded of un-answered questions up to 3 times.

Participants will be requested to upload redacted (de-identified) photographs of relevant medical records. Adjudication and validation of adverse outcomes could be performed for specific studies using available records. In case of discrepancy between two sources of the report, the participant might be re-contacted through the website/app to determine if the discrepancy can be resolved.

4.9 Sample Size

The IRCEP will be an ongoing surveillance and observational research resource that will enroll as many women as possible. Therefore, estimation of sample size is meaningless. Random error will be quantified by estimating 95% confidence intervals (CIs). Given that by March 2020 the literature had accumulated fewer than 60 case reports of pregnancies affected by COVID-19, even small study sizes will provide valuable information relative to the current absence of evidence. To provide context, the statistical power to detect significant differences (α=0.05, 2-sided) was estimated at various frequencies of exposed women and levels of relative risk for outcomes assuming a prevalence in the unexposed of 10% (e.g., preterm delivery, abortion) to 3% (e.g., preeclampsia, major malformations). A ratio of 2 unexposed to each exposed woman is assumed. For example, a cohort of 45 pregnancies exposed to COVID-19 during a relevant period is enough to detect relative risks larger than 3 of preterm birth, with 80% power and a Type I error rate of 5%. Appendix 2.

4.10 Data Management and Handling

Modules will be self-administered via the website or mobile app and will usually take 5 to 15 minutes to complete. At enrollment, women will complete 2 modules (**B**aseline and **C**OVID-19), which will take around 15 minutes in total. Regardless of the COVID-19 status, monthly **F**ollow up questionnaires that will take around 5 minutes to complete will be collected until **D**elivery, when obstetric and neonatal outcomes will be collected (estimated less than 10 minutes). Finally, around 90 days after delivery a less than 10 minutes questionnaire will collect information on post-partum and neonatal **O**utcomes. In case of an early pregnancy loss (miscarriage or termination), the participant will be directed to an End-of-Pregnancy brief questionnaire and will not complete any more modules. In case of retrospective enrollment within 90 days post-delivery, that participant would complete the Baseline, COVID-19, and Delivery modules upon enrollment, and the post-partum outcomes at 90 days after end of pregnancy. Women who enroll between 90 and 180 days after the end of pregnancy would complete all modules at enrollment.

These questionnaires are semi-structured and follow collection algorithms to ensure the answers are linked, as necessary. Data from each module will be stored in real time both locally in the user's device (if using the mobile app) and in the IRCEP's database. Data will be de-identified and all uploaded medical record data will be checked for redaction prior to storage.

Data quality is of the utmost importance in the IRCEP. Therefore, multiple levels of quality assurance will be used, beginning with the design of the data collection modules. Instructions for self-reporting are clear and succinct. The data collection algorithms in the IRCEP website and mobile app include multiple validity checks. Once captured, the data go through a rigorous cleaning and quality assurance process to reduce errors, missing data, and misclassifications. Whenever possible, user-reported data will be verified by user-uploaded medical records.

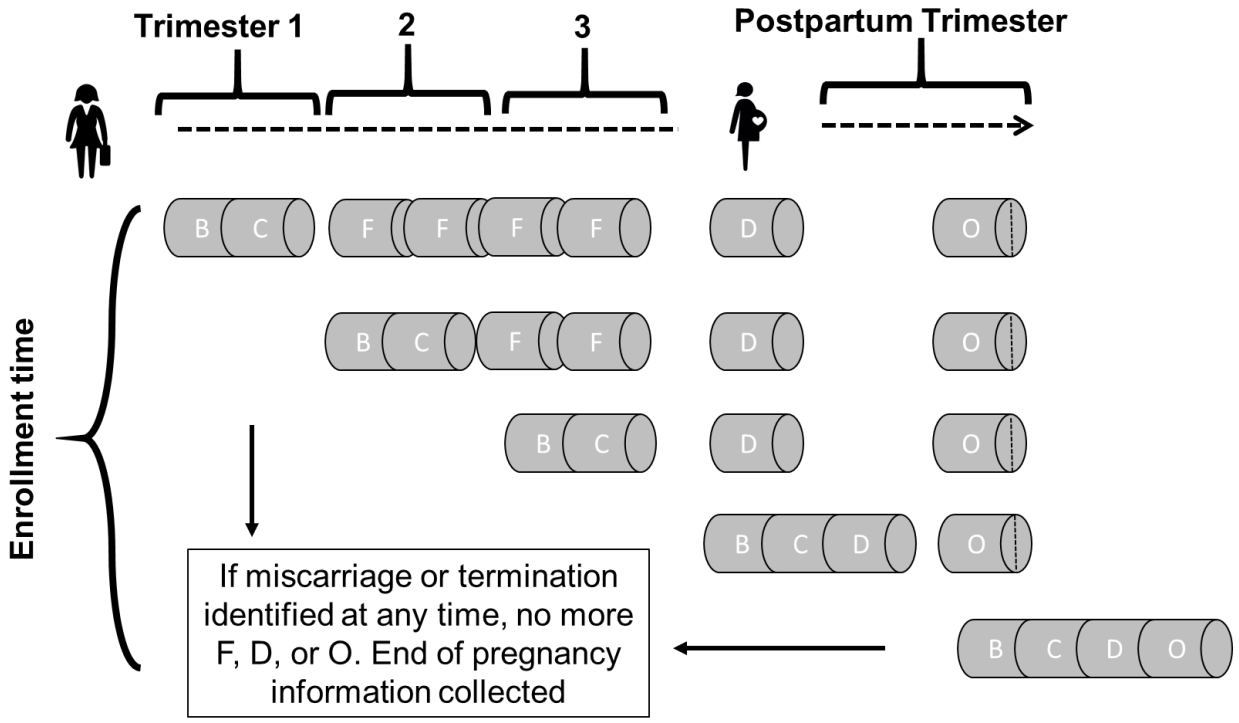

Figure 2. Timing of modules depending on timing of enrollment during pregnancy, or after delivery.

4.11 Data Analyses

The analyses will include a surveillance component with descriptive analyses and a causal inference component.

4.11.1 Descriptive Analyses

This analysis will describe the duration, severity, and treatment of COVID-19 during pregnancy. Then, the distributions of socio-demographic, clinical, and healthcare utilization characteristics in women with COVID-19 will be contrasted to the reference group of women with a negative SARS-CoV-2 test enrolled at the same time and followed with the same methods. Descriptive tables will display, as appropriate, medians, ranges, means, standard deviations, and percentages. The most common or relevant pregnancy outcomes will be tabulated for the exposed and for the reference group. The frequency of obstetric and neonatal pregnancy outcomes will be quantified in women infected at different times during pregnancy and with different COVID-19 severity. It is worth emphasizing that, due to multiple comparisons, it is likely that there will be several numerical imbalances between exposed and the reference groups. On the other hand, the sample size may be limited to rule out real effects when the relative risk is modest and/or the outcome is infrequent. In addition to random error, systematic errors such as confounding (e.g., women with susceptible to infection also at high risk of adverse pregnancy outcomes) may explain differences between the exposed and reference groups.

4.11.2 Hypothesis-Based Analysis

To assess the effect of COVID-19 on pregnancy outcomes, the risk of pregnancy outcomes among women with COVID-19 will be compared to a reference group of asymptomatic women with a negative SARS-CoV-2 test, from the same country and comparable gestational enrollment periods. Other internal reference groups will be women infected outside etiologically relevant periods; women with milder COVID-19, or previous pregnancies within the same woman (sibling design). First, crude comparisons will be made using exact methods to relative risks (RRs) and their corresponding 95% confidence intervals (CIs). Second, adjusted analyses, where numbers permit, will be conducted using propensity score (PS)-matching. If the number of exposed pregnant women is insufficient to employ PS, confounders for each adjusted analysis will be considered separately using the method of change in estimate of the effect of exposure to the drug by 10% or more. If one or various confounders are identified, direct adjustment will be performed. Generalized linear models will be used to estimate RRs and their corresponding 95%CIs to compare the exposed group with the appropriate reference group (SAS PROC GENMOD with a weight statement and Log Link function). Propensity scores will be derived from the predicted probability of COVID-19 (positive test or clinically confirmed infection) estimated in a logistic regression model which will contain all covariates of interest. The analyses will include comparisons of the distributions of socio-demographic, clinical, and healthcare utilization characteristics during the baseline period for the exposed and reference groups. Balance will be assessed using the standardized mean difference. An absolute standardized difference > 0.1 will be considered an indicator for substantial imbalances between the two exposure groups.[35] Absolute risks, risk differences, and RRs with 95% CIs will be calculated and presented graphically, when appropriate. When gestational age is relevant (e.g. spontaneous abortion), survival curves (Kaplan-Meier) will present estimate rates and CIs accounting for gestational timing at enrollment in the study.

4.11.3 Endpoints of interest

The endpoints of interest include multiple maternal, obstetric, neonatal, and infant outcomes. Each requires specific analytic considerations.

Major structural defects. The primary comparison will be between first trimester COVID-19 exposure and major structural malformations. The optimal analysis will be restricted to women who enroll before any informative prenatal test (i.e., nuchal translucency, chorionic villous sampling, amniocentesis, alpha fetoprotein measurements and ultrasound after 15 gestational weeks). Congenital malformations are defined following the guidelines of the Center for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program (MACDP).[36] The following frequency measures will be reported:

- Cumulative risk: The numerator includes the identified malformations and the denominator the number of pregnancies with known outcomes (i.e. excludes pregnancies with no information on malformations, e.g., abortions). This competing event will be reported independently, and later pregnancy outcomes will be conditional on surviving pregnancy.

- Prevalence at birth: this includes stillbirths and livebirths in the denominator and diagnosed malformations among these pregnancies in the numerator. This conditional probability (on surviving until delivery) may have questionable causal interpretation but it is clinically relevant and informative for patients. The report would provide the proportion of losses and terminations and, among livebirths, those with malformations.

Spontaneous Abortions: It is estimated that up to half of all fertilized eggs die and are lost (aborted) spontaneously, usually before the woman recognizes that she is pregnant, and that 10-15% of pregnancies end in recognized spontaneous abortions.[37,38] The risk of spontaneous abortion accounting for left truncation by stratification for gestational age at enrollment will be compared between those in the exposed group and the reference cohort. Rates of abortion per week among eligible women (i.e., enrolled and pregnant) will be graphically represented for exposed and reference groups when the sample size allows and to the degree that the information is available. The optimal analysis would be restricted to women enrolled in the study prior to 10 weeks' gestation.

Stillbirths: The proportion of pregnancies ending in stillbirth will be compared between the exposed group and the reference cohort. The optimal analyses would be restricted to women enrolled in the study prior to 20 weeks' gestation.

Preterm Deliveries: The proportion of pregnancies ending in livebirth <37 weeks' gestation will be compared between the exposed anytime in pregnancy prior to 34 weeks' gestation and the reference cohort. The analyses will stratify by twins or higher order multiples and singletons and by spontaneous versus medically induced preterm (Cesarean section or induction). The proportion of post-term births (>42 completed weeks) and the gestational age at birth distributions will also be reported.

Small for Gestational Age Infants: The proportion of pregnancies ending in a live born infant ≤10th centile on birth weight for gestational age and sex will be compared between the exposed group and the reference cohort. The analyses will stratify by twins or higher order multiples and singletons. The proportion of low birth weight (<2500 grams), very low birthweight (<1500 grams), macrosomic (>4000 grams), and the birthweight distributions will also be reported.

Maternal obstetric and postpartum health: The proportion of women with specific obstetric complications (e.g. preeclampsia, emergency cesarean section) will be compared between the exposed group and the reference cohort. Questions on access to care during the COVID-19 pandemic, maternal mental health, and breastfeeding will allow evaluation of a wide range of aspects.

Unknown outcome will be coded when it is unknown whether one or more serious, pregnancy-related adverse events were experienced by the fetus/infant or the mother at the end of the pregnancy. Subgroups of an unknown pregnancy outcome include:

- *Lost to follow-up*: When participant no longer responds to repeated contacts through the app, requesting further information on the pregnancy.

- *Outcome pending*: no information has yet been received yet following a recent delivery.
- *Pregnancy ongoing:* no information is available because the pregnancy is still ongoing.
- *Outcome NOS:* the information is complete, but the outcome will remain unknown (e.g. spontaneous abortion without pathology when the outcome is major malformations).

4.12 General Considerations for Data Analyses and Interpretation

4.12.1 Dealing with multiples

Pregnancy will be the unit of observation for obstetric and neonatal outcomes. Twins or higher order multiples will be handled as one obstetric outcome in the analyses. For example, if the pregnancy culminates with at least one live born infant, the outcome will be considered a live born outcome. If either or both twins have a major birth defect, the outcome will be considered one major birth defect outcome. This approach defines pregnancy as the unit of observation. However, information in twins or higher order multiples will be recorded. Individual twins will contribute as independent observations to the infant follow-up analyses post-delivery. In both phases (pregnancy and infant cohorts), multiples will be used as covariate in the analyses, when appropriate, and the models will also consider the clustering if the same woman were to contribute information for more than one of her pregnancies.[23] When reporting risks, whether using fetuses or pregnancies as the unit of analysis, both the numerator and denominator will be consistent with the choice.[24]

4.12.2 Confounding

Like in any observational study, several sources of confounding may affect specific comparisons within pregnancy registries. When assessing the risk of COVID-19, the direct effect of the virus on the outcomes will not be distinguishable from the effect mediated through maternal symptoms (e.g., pneumonia or fever). Other covariates of concern would be risk factors for the outcome of interest that may be also associated with a higher risk of exposure or infection with the coronavirus, or with more severe COVID-19 (e.g., diabetes, smoking). To assess the exchangeability of exposed and reference groups, the first step in the analysis is to compare the distributions of socio-demographic, clinical, and healthcare utilization characteristics at baseline for the groups compared. Balance can be assessed using the standardized mean difference. Typically, an absolute standardized difference > 0.1 is considered an indicator for imbalances between the two groups.[35] Unbalanced characteristics will be controlled by model adjustment or PS. Given that adverse pregnancy outcomes tend to be rare and the set of pre-specified potential confounding variables may be large, the use of data reduction techniques such as PS is often be advisable to avoid problems with model over-fitting.[39] Briefly, PS represent the predicted probability of treatment conditional on observed characteristics and, in their simplest form, are estimated in a logistic regression model. Confounding can then be

controlled through matching, stratification, weighting, or covariate adjustment using the PS.[40] In addition, three additional comparisons will be used to triangulate the potential effect of COVID: different severity, different timing, and sibling comparisons of infected pregnancies with non-infected previous pregnancy within same woman.

4.12.3 Selection mechanisms and potential bias

The ideal pregnancy cohort would enroll women at conception, before any outcome, and at or before the infection, and then follow them for years after delivery. However, this is unrealistic for logistical reasons. Therefore, the IRCEP will have truncation on both sides of the ideal follow-up. Left truncation occurs because participants enroll after SARS-CoV-2 exposure initiation and therefore after some outcomes may be known. Right truncation (or censoring) occurs when there are enrolled pregnancies with unknown outcomes due to lost to follow-up, pregnancy miscarriages, or terminations or stillbirths without fetal autopsy. Losses before organogenesis can be considered a **competing event**. That is, a pregnancy loss will compete with the risk of future outcomes. Competing events will be incorporated in the analyses according to different strategies, conditioning on not having the competing event, composite outcomes, cause specific and sub-hazard methods

Left truncation (late enrollment) may underestimate the risk of early pregnancy events (e.g., miscarriages, maternal death). Women who enrolled after COVID-19 may tend to have less severe (non-lethal) outcomes. Enrollment after outcomes (e.g., miscarriage) may self-select a group with adverse outcomes and more eager to share their experience in a Registry. Differences in gestational age at enrollment between exposed and reference groups could lead to biased risk ratio and rate ratio estimates if the risk varies with gestational age. To prevent this bias, the most useful approach is to enroll subjects as soon as possible after infection and before outcomes can be suspected and to begin follow-up of exposed and unexposed pregnancies at comparable gestational ages.[41]

Retrospective enrollment of women after prenatal screening, whether the test is *normal or abnormal*, can introduce bias towards a lower or higher risk of malformations.[17] Underestimation of the risk might occur if enrolment after informative screening tests selects a survivor cohort of women with uneventful pregnancies (e.g., women might be less willing to contact a pregnancy exposure registry after a major malformation diagnosis).[41] Overestimation of the risk might occur if participation is allowed after an abnormal test and there is a preferential enrolment of women with a diagnosis (e.g., the diagnosis prompts the exposed woman to look for information, find the registry, and enrol). These two scenarios can coexist, biasing the effect estimates. Because this bias is difficult to identify and correct in the analytic phase, it needs to be prevented in the design by enrolling subjects prospectively *before* an outcome may be known - that is, before the completion of informative screening tests. However, women after an abnormal pregnancy test may be enrolled and analysed separately as part of the surveillance aim. Malformations can still be evaluated for biological plausibility, and specific patterns of malformations or distinct congenital abnormalities can generate hypotheses.

Another bias might be associated with **right truncation or censoring** of the registry cohort. This occurs when pregnancies end the follow-up before the outcome is known (censoring), or with unknown outcomes (truncation). Since pathology is rarely available

for spontaneous abortions and terminations for social reasons, most cohorts consider the prevalence of malformations in livebirths rather than the cumulative incidence over gestation. Failure to include defects detected among terminations can underestimate the incidence of malformations and decrease power, particularly for defects for which termination is often chosen after prenatal diagnosis (e.g., neural tube defects)[42,43] but, if the missingness is random with respect to exposure, the relative risk for malformations will be unbiased.

By excluding terminations, spontaneous abortions, and losses to follow-up, it is assumed that the exposure had the same effect in these pregnancies as in those that remain under observation. Such assumption is less plausible if the exposed group has a higher frequency of these outcomes than the reference group. Efforts will be made to minimize losses to follow-up and to obtain outcome information for all participants. Whenever possible, the IRCEP will report the number of spontaneous and therapeutic abortions, losses to follow-up, and withdrawals for the exposed and reference groups. Of note, a higher frequency of terminations among COVID-19 exposed women might reflect a higher risk of malformations, as well as heightened fear of malformations with consequent termination if COVID-19 is suspected of being teratogenic, or just the presence of factors associated with both the exposure and the likelihood to terminate a pregnancy or discontinue participation.

Of concern in this registry is the selection of non-lethal COVID-19 if women enroll retrospectively with respect to the infection, i.e., after COVID-19 resolves and they feel healthy enough to enroll in the study. Although maternal mortality, even among COVID-19 women, is expected to be low (<1%), this selection would nevertheless result in optimistic descriptions of the nature of COVID-19 during pregnancy. The robustness of the findings will be assessed by restricting secondary analyses to participants that enroll soon after the first test. Similarly, even if women enroll early in the course of COVID-19, those with the worse courses leading to prolong hospitalization or death may be lost to follow up. To reduce this challenge, information will be collected on a close friend or family member that 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.

Lastly, selection bias during the analysis can be introduced by adjusting for variables that share common causes with the outcome or are affected by it. Thus, analytically adjusting for these variables (e.g., low birth weight) will not reduce confounding and can introduce selection bias.[32,34,44] Knowledge of the causal structure is a prerequisite to accurately labelling a variable as a confounder. In studies of pregnancy, variables that occur after organogenesis cannot cause birth anomalies and, therefore, are not confounders.

4.12.4 Misclassification

The IRCEP will collect information directly from the subjects using a website and mobile app. Women often know more about their habits, occupations, medical and obstetrical history, and compliance with medication use than their health care providers. Other registries rely on reporting by clinicians and have no contact with the patient. These clinicians might provide more complete and accurate information regarding diagnoses

and indications.[45] For key outcomes, the IRCEP will make an effort to validate maternal reports with medical charts to improve the credibility of the findings.[46-48]

As noted above, pregnancy registries are preferentially "prospective" in design. Therefore, the outcome cannot directly affect the accuracy of exposure information, and any misclassification of COVID-19 characteristics would tend to be non-differential with respect to the outcome.[49-51] The accuracy of recall in the IRCEP will be maximized by using structured questionnaires, detailed questions, and calendars to help establish gestational timing and enhance recall of dates.[52]

A peculiarity affecting exposure definition in the IRCEP is that not all pregnancies will be 40 weeks in duration, and many outcomes of interest will be associated with shorter gestational length (e.g., preterm delivery).[53,54] For these outcomes, the time until infection is "immortal" in the exposed group (in the extreme, COVID-19 after week 37 would not have preterm deliveries). To incorporate the different length of pregnancy COVID-19 will be considered a time-varying exposure and will follow time-to-event outcomes accounting for time at infection.

Diagnostic bias, or outcome misclassification, can also occur in pregnancy registries. These biases could be either non-differential or differential between the exposed and the reference group and could skew the estimate of an effect towards or away from the null. Concern that COVID-19 might pose a risk could lead to more access to or uptake of 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. By using internal controls and using comparable reference groups, the IRCEP will minimize diagnostic bias. Also, the IRCEP will mainly focus on hard outcomes less vulnerable to differential misclassification.

As mentioned above, reported major malformations can be validated. Although neither treating physicians nor women are blinded to COVID-19, registries can provide blinded validation and adjudication of outcomes. Although specificity is most important, and thus confirmation of reported cases is a priority to detect malformations not reported by the patients, records for all pregnancies would have to be reviewed. For example, women might be less likely to volunteer information regarding male genital malformations in their infants, which could result in under-ascertainment of these malformations. To detect malformations that can be detected by screening and that often result in a terminated pregnancy (e.g., anencephaly), therapeutic abortions need to be included. To detect an increase in abnormalities incompatible with life, it is important to collect information on autopsy results at stillbirth and, if possible, on examinations of the fetus after spontaneous or induced abortion. The study of spontaneous abortions and pregnancy terminations is challenging due to legal and practical reasons.

4.12.5 Handling missing data

For key covariates with a prevalence of missing data above 10%, sensitivity analyses will be conducted whereby only women with complete information will be included. In the general tabulations, a 'missing' category will be included.

4.12.6 Generalizability of results

Enrollment of women in pregnancy registries is voluntary and self-selected and, therefore, registry participants may represent a small non-random proportion of all women who have COVID-19. Consequently, the characteristics and experience of women who participate in a registry may differ from those of nonparticipants, and those characteristics might modify the observed effects of the coronavirus. However, biological effects of viruses are usually universal.

4.12.7 Statistical power and confidence intervals

While registries are efficient means to assess rare exposures and detect strong effects, they lack the statistical power to evaluate rare outcomes and modest effects. Pregnancy registries are statistically powered to detect common outcomes, such as the total prevalence of all malformations, and can only detect very large increases in rare individual defects or patterns. However, registries can generate hypotheses that form the basis for further investigation using complimentary approaches, study designs, and data sources. The sample size of the IRCEP will be determined by the number of women (i.e. pregnancies) that enroll, and it is not pre-defined. The statistical power of the study to detect an effect at or above a certain level is affected by the sample size and the baseline risk for the outcome in the population.[21]

4.13 Limitations of the research methods

As discussed above, potential random findings in the context of multiple comparisons, missing real effects due to an underpowered sample size, biased self-selection and survivor cohort effects, and confounding are potential threats the IRCEP will make efforts to minimize. A final limitation of pregnancy registries is the length of time typically required to enroll enough numbers of exposed women to generate statistically robust estimates of pregnancy outcomes. Given the scope, methodology, and anticipated sample size of the IRCEP, it is expected that some of these limitations will be minimized.

5. PROTECTION OF HUMAN SUBJECTS

5.1 Informed Consent

The IRCEP will request IRB and ethics committee waivers of written informed consent for this registry study. Instead, eligible women will give consent electronically with an e-Form on the IRCEP website or mobile app. A signed copy of the e-Form will be emailed to the registry participant. Another copy will be available in her registry profile.

A waiver of documentation of informed consent is appropriate for the IRCEP for the reasons outlined below:

- This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the IRCEP will have well-established procedures in place to prevent any such breach of confidentiality. The following safeguards will be in place to ensure that subjects' privacy is protected:
    - An adequate plan will be provided to protect the identifiers from improper use and disclosure.
    - Adequate assurances will be provided that the protected health information will not be reused or disclosed to any other person or entity, except as required by law and for purposes of the IRCEP.
- The IRCEP involves no procedures for which written consent is normally required outside the research context. Enrollment in this observational study is strictly voluntary.

5.2 HIPAA Authorization (for USA)

Based on U.S. FDA regulations (45 CFR 164.512), HIPAA authorization is not required and, therefore, will not be obtained from subjects who enroll in the IRCEP. The IRCEP is exempt from HIPAA authorization requirements because subjects may disclose their protected health information for public health purposes.

5.3 Participant Withdrawal

Participating women may withdraw from the IRCEP at any time at their own request, or they may be withdrawn at any time at the discretion of the IRCEP Principal Investigator for safety, behavioral, or administrative reasons. In any circumstance, every effort will be made to document subject outcome, if possible. The website or mobile app will inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events. If the subject withdraws from the IRCEP and withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The IRCEP may retain and continue to use any data collected before such withdrawal of consent.

5.4 Institutional Review Board (IRB) and Ethics Committee

The IRCEP will comply with ethical principles and regulatory requirements involving human subjects research. Therefore, this protocol and informed consent described in 5.1 must be approved by an Institutional Review Board (IRB) or ethics committee. The chairperson or the recording secretary of the IRB or ethics committee must have signed a form indicating approval.

5.5 Ethical Conduct of the Study

This IRCEP will be conducted in compliance with this Protocol, the International Society for Pharmacoepidemiology's "Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States" [55], US FDA regulatory requirements, and in accordance with the ethical principles of the Declaration of Helsinki.[56]

6. ADMINISTRATIVE CONSIDERATIONS

6.1 Scientific Advisory Committee

An important aspect of the IRCEP is the Scientific Advisory Committee, which will be comprised of representatives from governmental and non-governmental organizations of various countries (Appendix 3). The members will represent specialists in maternal-fetal medicine, teratology, infectious diseases, epidemiology, and biostatistics. The Scientific Advisory Committee will meet regularly and review the aggregate data, assist in resolving issues, and determine strategies for increased awareness, etc. At the meetings, the Advisory Committee will make a full assessment of the individual cases and review the accumulated body of data from the prospective and retrospective reports. That assessment and review will be summarized in the Scientific Advisory Committee Consensus Statement, which will be documented in the meeting minutes and in the Summary section of the formal Registry Reports.

For more detail on the roles, responsibilities, and membership of governance committees, please see Appendix 3.

6.2 Principal Investigator

The Principal Investigator is responsible for the conduct of the registry, which includes the management of the Registry operations and all submissions to the IRB or ethics committee (protocol, amendments) and acts as the single point of contact for registry communication for the Scientific Advisory Committee.

6.3 Disclosure of Data

6.3.1 Confidentiality

The IRCEP will make every effort to assure patient confidentiality. When information on reports is distributed to Advisory Committee members, no participant identifiers will be included.

Only aggregate results will be included in the Registry periodic reports and in all other publications or presentations (except for the clinical description of cases of interest, which will remain de-identified).

6.3.2 Who will have access to the data

IRCEP Staff: IRCEP personnel, under the supervision of the Principal Investigator, will have access to de-identified electronic data. Only the Principal Investigator and the Registry Coordinator will have access to the personal identifiers (name and email address) provided during the inform consent process.

IRCEP Dysmorphologist: The dysmorphologist is a medical birth defects expert who will review the de-identified uploaded medical records, including birth defect reports, submitted to the IRCEP and assess medical charts, and other supporting information (if applicable) detached of provider information or subject identifier. Once the case has been reviewed, the dysmorphologist will return all documents to the IRCEP with an evaluation summary of the case. The IRCEP Dysmorphologist may be a member of the Scientific Advisory Committee.

Patient Identifiers: The participants' names and email addresses will be obtained as part of the informed consent and linked with a code to the pregnancy history, exposure, and outcome data from the maternal interviews and medical records. This information will be maintained securely and will not be shared with any external parties other than what is required by law. Data summaries will be generated only after the data have been stripped of personal identifiers.

Published Data: Care will be taken to assure that a patient is not identifiable in the data tables published in the IRCEP periodic reports or other publications. No protected health information will be included in any published information. *Ad hoc* requests for IRCEP data will be reviewed and approved by the IRCEP Principal Investigator with the advice of the Scientific Advisory Committee.

6.4 Public Release of the Data

The IRCEP will publish data, encourage and initiate presentations, and use several strategies to raise awareness of its existence. However, the IRCEP will never identify individual participants. Requests by external investigators of IRCEP data for their own projects will be discussed by the Principal Investigator and selected IRCEP staff and members of the Scientific Advisory Committee and a prompt decision will be communicated.

6.4.1 Periodic Reports

Periodic reports will be produced according to a fixed schedule to summarize the IRCEP data. If enough new significant information becomes available, the periodic reports may be generated monthly, but no less frequently than semi-annually. Since these reports will contain historical information as well as new data, they will completely replace all previous reports. The latest periodic report will be made publicly available on the IRCEP website / mobile app.

6.4.2 IRCEP Website

The IRCEP website (https://corona.pregistry.com) will include general information about the objectives and methodology of the IRCEP, contact information, and instructions to enroll, as well as the most recent periodic report. The website will also include educational resources on COVID-19 and pregnancy (e.g., Q&A, blogs, videos, interviews, summaries of articles published in the medical literature) as well as a moderated chat room.

6.4.3 Publications/Presentations

The IRCEP data will be considered for presentation at scientific conferences and for publication in scientific journals. These manuscripts will be prepared by the IRCEP staff and the members of the Scientific Advisory Committee will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. Members of the Scientific Advisory Committee may also be eligible to be authors or co-authors of publications with the IRCEP data if they meet authorship criteria based on the journal guidelines.

6.5 Discontinuation of the IRCEP

Discontinuation of the IRCEP will be considered at such time as:

- Other methods of gathering appropriate information become achievable or are deemed preferable, or
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of poor enrollment or lack of funding.

7. REFERENCES

1 Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).
2 Chen, H. *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* **395**, 809-815, doi:10.1016/S0140-6736(20)30360-3 (2020).
3 Lam, C. M. *et al.* A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. *BJOG : an international journal of obstetrics and gynaecology* **111**, 771-774, doi:10.1111/j.1471-0528.2004.00199.x (2004).
4 Alfaraj, S. H., Al-Tawfiq, J. A. & Memish, Z. A. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. *J Microbiol Immunol Infect* **52**, 501-503, doi:10.1016/j.jmii.2018.04.005 (2019).
5 Siston, A. M. *et al.* Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA : the journal of the American Medical Association* **303**, 1517-1525, doi:10.1001/jama.2010.479 (2010).
6 Qiao, J. What are the risks of COVID-19 infection in pregnant women? *Lancet* **395**, 760-762, doi:10.1016/S0140-6736(20)30365-2 (2020).
7 Liu, Y., Chen, H., Tang, K. & Guo, Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect*, doi:10.1016/j.jinf.2020.02.028 (2020).
8 Zhu, H. *et al.* Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* **9**, 51-60, doi:10.21037/tp.2020.02.06 (2020).
9 Wong, S. F. *et al.* Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *American journal of obstetrics and gynecology* **191**, 292-297, doi:10.1016/j.ajog.2003.11.019 (2004).
10 Shek, C. C. *et al.* Infants born to mothers with severe acute respiratory syndrome. *Pediatrics* **112**, e254, doi:10.1542/peds.112.4.e254 (2003).
11 Fan, C. *et al.* Perinatal Transmission of COVID-19 Associated SARS-CoV-2: Should We Worry? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, doi:10.1093/cid/ciaa226 (2020).
12 Dong, L. *et al.* Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. *JAMA : the journal of the American Medical Association*, doi:10.1001/jama.2020.4621 (2020).
13 Zeng, H. *et al.* Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA : the journal of the American Medical Association*, doi:10.1001/jama.2020.4861 (2020).
14 Yu, N. *et al.* Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *Lancet Infect Dis*, doi:10.1016/S1473-3099(20)30176-6 (2020).
15 Zeng, L. *et al.* Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. *JAMA pediatrics*, doi:10.1001/jamapediatrics.2020.0878 (2020).

16 Dong, Y. *et al.* Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics*, doi:10.1542/peds.2020-0702 (2020).
17 Kennedy, D. L., Uhl, K. & Kweder, S. L. Pregnancy Exposure Registries. *Drug Safety* **27**, 215-228 (2004).
18 Hernandez-Diaz, S. in *Registries for Evaluating Patient Outcomes: A User's Guide: 3rd Edition* (ed AHRQ) Ch. 21, 135-168 (2014).
19 Hernandez-Diaz, S., Hernan, M. A., Meyer, K., Werler, M. M. & Mitchell, A. A. Case-crossover and case-time-control designs in birth defects epidemiology. *Am J Epidemiol* **158**, 385-391 (2003).
20 Suissa, S. The Case-Time-Control Design. *Epidemiology* **6**, 248-253 (1995).
21 Honein, M. A., Paulozzi, L. J., Cragan, J. D. & Correa, A. Evaluation of selected characteristics of pregnancy drug registries. *Teratology* **60**, 356-364 (1999).
22 Cragan, J. D. & Gilboa, S. M. Including prenatal diagnoses in birth defects monitoring: Experience of the Metropolitan Atlanta Congenital Defects Program. *Birth defects research. Part A, Clinical and molecular teratology* **85**, 20-29, doi:10.1002/bdra.20508 (2009).
23 Liang, K.-Y. & Zeger, S. Longitudinal data analysis using generalized linear models. *Biometrika* **73**, 13-22 (1986).
24 deMoor, C., Covington, D. & Golembesky, A. Differing Strategies for Analyzing Multiple Gestation Pregnancies in Pregnancy Registries: Impact on Birth Defect Rates. *Pharmacoepidemiol & Drug Safety* **19 (Supplement 1)**, S124 (2010).
25 Tabacova, S., Little, R., Tsong, Y., Vega, A. & Kimmel, C. Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment. *Pharmacoepidemiol & Drug Safety* **12**, 633-646 (2003).
26 Chambers, C. D., Johnson, K. A., Dick, L. M., Felix, R. J. & Jones, K. L. Birth outcomes in pregnant women taking fluoxetine. *New England Journal of Medicine* **335**, 1010-1015 (1996).
27 Chambers, C. *et al.* Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn. *New England Journal of Medicine* **354**, 579-587 (2006).
28 Yang, H., Wang, C. & Poon, L. C. Novel coronavirus infection and pregnancy. *Ultrasound Obstet Gynecol*, doi:10.1002/uog.22006 (2020).
29 Meyer, K. A., Williams, P., Hernandez-Diaz, S. & Cnattingius, S. Smoking and the risk of oral clefts: exploring the impact of study designs. *Epidemiology* **15**, 671-678 (2004).
30 Correa, A. *et al.* Reporting birth defects surveillance data 1968-2003. *Birth defects research. Part A, Clinical and molecular teratology* **79**, 65-186, doi:10.1002/bdra.20350 (2007).
31 Oken, E., Kleinman, K. P., Rich-Edwards, J. & Gillman, M. W. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC pediatrics* **3**, 6, doi:10.1186/1471-2431-3-6 (2003).
32 Hernandez-Diaz, S., Schisterman, E. F. & Hernan, M. A. The birth weight "paradox" uncovered? *Am J Epidemiol* **164**, 1115-1120, doi:10.1093/aje/kwj275 (2006).

33 MacDonald, S. C., Hernan, M. A., McElrath, T. F. & Hernandez-Diaz, S. Assessment of recording bias in pregnancy studies using health care databases: An application to neurologic conditions. *Paediatric and perinatal epidemiology* **32**, 281-286, doi:10.1111/ppe.12459 (2018).

34 Hernan, M. A., Hernandez-Diaz, S., Werler, M. M. & Mitchell, A. A. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol* **155**, 176-184 (2002).

35 Austin, P. C. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Communications in Statistics-Simulation and Computation* **38**, 1228-1234 (2009).

36 MACDP. *Metropolitan Atlanta Congenital Defects Program (MACDP)*, <https://www.cdc.gov/ncbddd/birthdefects/macdp.html> (2019).

37 Wilcox, A. J. *et al.* Incidence of early loss of pregnancy. *The New England journal of medicine* **319**, 189-194, doi:10.1056/NEJM198807283190401 (1988).

38 Wilcox, A. J., Treloar, A. E. & Sandler, D. P. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. *Am J Epidemiol* **114**, 548-553 (1981).

39 Glynn, R. J., Schneeweiss, S. & Sturmer, T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic & clinical pharmacology & toxicology* **98**, 253-259, doi:10.1111/j.1742-7843.2006.pto_293.x (2006).

40 Austin, P. C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research* **46**, 399-424, doi:10.1080/00273171.2011.568786 (2011).

41 Margulis, A. V., Mittleman, M. A., Glynn, R. J., Holmes, L. B. & Hernandez-Diaz, S. Effects of gestational age at enrollment in pregnancy exposure registries. *Pharmacoepidemiology and drug safety* **24**, 343-352, doi:10.1002/pds.3731 (2015).

42 Svensson, E. *et al.* Estimating the proportion of all observed birth defects occurring in pregnancies terminated by a second-trimester abortion. *Epidemiology* **25**, 866-871, doi:10.1097/EDE.0000000000000163 (2014).

43 Friedberg, M. K. *et al.* Prenatal detection of congenital heart disease. *The Journal of pediatrics* **155**, 26-31, 31 e21, doi:10.1016/j.jpeds.2009.01.050 (2009).

44 Hernan, M. A., Hernandez-Diaz, S. & Robins, J. M. A structural approach to selection bias. *Epidemiology* **15**, 615-625 (2004).

45 Reiff_Eldridge, R. *et al.* Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: A pharmaceutical company commitment. *American journal of obstetrics and gynecology* **182**, 159-163 (2000).

46 Cooper, W. *et al.* Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors. *New England Journal of Medicine* **354**, 2443-2451 (2006).

47 Cooper, W., Hernandez-Diaz, S. & Ray, W. Positive Predictive Value of computerized databases for birth defects in a medicaid population. *Pharmacoepidemiol & Drug Safety* **13**, S1-S334 (2004).

48 Schelleman, H. *et al.* Cardiovascular events and death in children exposed and unexposed to ADHD agents. *PEDIATRICS* **127**, 1102-1110 (2011).

49 Werler, M. M., Pober, B. R., Nelson, K. & Holmes, L. B. Reporting accuracy among mothers of malformed and nonmalformed infants. *American journal of epidemiology* **129**, 415-421 (1989).
50 Weiss, N. S. Should we consider a subject's knowledge of the etiologic hypothesis in the analysis of case-control studies? *American journal of epidemiology* **139**, 247-249 (1994).
51 Drews, C. D., Kraus, J. F. & Greenland, S. Recall bias in a case-control study of sudden infant death syndrome. *International journal of epidemiology* **19**, 405-411 (1990).
52 Mitchell, A. A., Cottler, L. B. & Shapiro, S. Effect of questionnaire design on recall of drug exposure in pregnancy. *American journal of epidemiology* **123**, 670-676 (1986).
53 Suissa, S., Dell'aniello, S., Vahey, S. & Renoux, C. Time-window bias in case-control studies: statins and lung cancer. *Epidemiology* **22**, 228-231, doi:10.1097/EDE.0b013e3182093a0f (2011).
54 Hernández-Díaz, S. Name of the Bias and Sex of the Angels. *Epidemiology* **22**, 232-233, doi:10.1097/EDE.0b013e318209d654 (2011).
55 Andrews, E. A. *et al.* Guidelines for Good Epidemiology Practices for drug, device, and vaccine research in the United States. *Pharmacoepidemiology and drug safety* **5**, 333-338, doi:10.1002/(SICI)1099-1557(199609)5:5<333::AID-PDS244>3.0.CO;2-5 (1996).
56 World Medical Association General, A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects (revised October 7, 2000). *HIV Clin Trials* **2**, 92-95, doi:10.1310/GTFR-2DRX-M6YE-ELXR (2001).

APPENDIX 1. INFORM CONSENT DOCUMENT

Thank you for joining the International Registry of Coronavirus Exposure in Pregnancy (IRCEP)! Completing your registration involves just a few more steps. The process should only take a few minutes.

Please keep in mind that you will be allowed to enroll only if you are 1) 18 years of age or older, 2) currently pregnant, or if your pregnancy ended in the last 6 months, and 3) if you either had a COVID-19 test during pregnancy (whether positive or negative) or a health care provider confirmed that you had COVID-19 during pregnancy.

First, we need you to "officially" agree or consent to take part in the IRCEP by reading the information and following the instructions below. Then, we need you to set up your profile – including username and password – and create your unique IRCEP ID. Lastly, we need you to type in a special code that helps protect your information and IRCEP from spammers and other security threats.

Informed Consent for the IRCEP
Please read this electronic consent form carefully. For more information, visit the Frequently Asked Questions (FAQs) at https://corona.pregistry.com. You can also contact the IRCEP Principal Investigator, Dr. Diego Wyszynski, at IRCEP@pregistry.com, or the IRCEP co-Principal Investigator, Dr. Sonia Hernandez-Diaz, at shernan@hsph.harvard.edu, with any other questions related to the IRCEP. You will be able to print the entire IRCEP consent text to keep a written statement regarding the research.

Note: Taking part in IRCEP is your choice. You will be able to discontinue participation at any time. Only the Principal Investigator and the IRCEP Study Coordinator will have access to your personal identifiers.

What is the IRCEP?
The IRCEP is a health research study led by Pregistry, LLC. We are asking pregnant women to tell us about their health, including medical problems caused by COVID-19 and other health-related information. We also will ask about how their babies are doing after birth.
IRCEP has been approved by the XXXX Institutional Review Board.

Why are we doing the study?
We are doing this study to learn what happens to women infected or not with COVID-19 physically and emotionally during pregnancy and after giving birth. We hope to learn the following:

- Effects of COVID-19 on the pregnancy and on the baby
- Challenges some women face, such as issues related to being infected with COVID-19
- Features common to pregnancies with COVID-19

The information we gather in this study may help us find ways to improve health for pregnant women with COVID-19 in the future.

What will I have to do in the study?

You can participate in this important study by giving us information about your pregnancy. You will enter information throughout your pregnancy and during your baby's development into online surveys and trackers via a website and/or mobile application ("app").

What are the benefits of joining the study?
By taking part in IRCEP, you can see how your pregnancy experiences compare to those of other women in the study, since aggregate results of the Registry will be reported to participants.

You and your baby may not benefit directly from joining the IRCEP. But sharing your health information might help us find better ways to care for pregnant women with COVID-19 and their babies in the future.

What are the risks of joining the study?
Physical Risks
Because the IRCEP focuses on gathering information, joining the study does not pose any known physical risks. You can skip any question that you do not want to answer.

Please note that, when comparing your pregnancy experiences to others in the IRCEP, you may learn something that is different from what you expected. Each person is unique, and each pregnancy is unique.

Taking part in the IRCEP is not meant to replace medical advice, diagnosis, or treatment from your healthcare provider. You should always seek the advice of your health care provider with any questions or concerns you may have about your health, your pregnancy, or your baby's health.

Risk of Release of Personal Information
One possible risk of taking part in IRCEP is the loss or release of personal information from a database security "break in" or breach. We will protect your data very well, but if a breach does occur, we will let you know as soon as possible.

We store your data in a secure database with multiple safety features. An independent security expert checks our system regularly. IRCEP also complies with all of the following:

- The Code of Federal Regulations, 45 CFR Part 46 subpart D
- Federal Information Security Management Act of 2002 (FISMA), 44 U.S.C. § 3541

Even though we are using many tools and practices to keep information secure, we cannot guarantee security of:

- Data on your computer or mobile device, or
- Information while it is transmitting to the IRCEP database.

What happens after I join the study?
Once you decide to join, we will ask you some general questions about your health history. Then, as you go through your pregnancy, we will contact you regularly to ask more questions about how you are feeling. We will also contact you three months after your baby is born to ask about your and your baby's health.

What happens to the information I share with IRCEP?
Using computer tools and formulas, researchers will group and organize all the information to look for patterns or issues common to women with COVID-19. For instance, the data could show which women with COVID-19 are more likely to go early into labor. Or, it could show that women with COVID-19 have some "spotting" during their second trimester.

Researchers will not know who you are even when they are organizing and studying the information. We will remove your name, email address, and other personal information to de-identifyor anonymize the data, as a way of keeping your information confidential. Only the IRCEP Principal Investigator and Coordinators will have access to information about who you are.

The IRCEP also may share de-identified data with other studies to help uncover new topics for future studies. But neither the researchers for other databases, nor the IRCEP researchers will know who you are from the shared data.

Will researchers contact me?
No. Researchers and physicians cannot directly contact any IRCEP participants. Only the IRCEP Principal Investigator or the IRCEP Study Coordinator will contact you directly.

If you say we can contact you about joining other studies, we may let you know about other research studies that you might want/be able to take part in. We will give you the study information, and then you can decide if you want to contact the study leaders to learn more. We will not share your contact information with the researchers.

What if I no longer want to take part in IRCEP?
If you no longer want to take part in IRCEP, you can simply stop giving information. You can also change your profile so that the system stops sending you reminders and messages. However, we would appreciate it if you could indicate on the form your intention to discontinue so that the system does not contact you in the future.

If you want to remove your information from the database, you can contact the IRCEP Coordinators to do so. But we cannot get back any de-identified data already shared with scientists, others in IRCEP, or other studies before you made your request and we have time to process it.

Will I be paid to take part in IRCEP?
You will not receive any money for taking part in this study. There also is no cost to join IRCEP.

What if I have other questions?
If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Diego Wyszynski, at IRCEP@pregistry.com, or the IRCEP co-Principal Investigator, Dr. Sonia Hernandez-Diaz, at shernan@hsph.harvard.edu.

A copy of this consent document will be emailed to the address you provided. It will also be available in "My Profile" after you complete the other sections on this page.

For the purposes of the consent form below, "I", "my", "you" and "your" refers to the pregnant woman who is giving consent.

Please type the full name of the person giving consent: _____

By consenting, I agree to the following:

- I have read the informed consent document. I have had a chance to ask questions and get answers, and I have no other questions at this time.
- I understand the purposes, risks, and benefits of taking part in IRCEP.
- I understand that taking part in IRCEP is entirely my choice.
- If I change my mind and no longer want to take part in IRCEP, I am free to do so and do not have to give any reason.
- I agree to allow the IRCEP Principal Investigator and the IRCEP Study Coordinator to contact me.

□ I am the participant (pregnant woman), I am 18 years of age or older, and I am able and willing to complete the questions in this study. I consent to take part in the IRCEP.

APPENDIX 2. POWER TO DETECT ASSOCIATIONS BASED ON THE NUMBER OF EXPOSED PREGNANCIES AND RELATIVE RISKS

	RR					**RR**				
Exposed	1.25	1.5	2	3	5	1.25	1.5	2	3	5
RISK IN UNEXPOSED: 10%						**RISK IN UNEXPOSED: 3%**				
150	0.16	0.44	0.90	1.00	1.00	0.08	0.18	0.46	0.87	1.00
300	0.27	0.70	0.99	1.00	1.00	0.12	0.29	0.70	0.99	1.00
450	0.36	0.85	1.00	1.00	1.00	0.15	0.39	0.84	1.00	1.00
600	0.45	0.93	1.00	1.00	1.00	0.18	0.48	0.92	1.00	1.00
750	0.53	0.97	1.00	1.00	1.00	0.20	0.55	0.96	1.00	1.00
900	0.60	0.99	1.00	1.00	1.00	0.23	0.62	0.98	1.00	1.00
1,050	0.67	0.99	1.00	1.00	1.00	0.26	0.68	0.99	1.00	1.00
1,200	0.72	1.00	1.00	1.00	1.00	0.29	0.74	1.00	1.00	1.00
1,350	0.77	1.00	1.00	1.00	1.00	0.32	0.78	1.00	1.00	1.00
1,500	0.81	1.00	1.00	1.00	1.00	0.34	0.82	1.00	1.00	1.00
RISK IN UNEXPOSED: 1%						**RISK IN UNEXPOSED: 0.1%**				
150	0.06	0.10	0.22	0.50	0.87	0.04	0.06	0.09	0.15	0.26
300	0.07	0.14	0.34	0.73	0.99	0.04	0.06	0.11	0.20	0.38
450	0.08	0.18	0.45	0.86	1.00	0.05	0.07	0.13	0.24	0.48
600	0.09	0.22	0.54	0.93	1.00	0.05	0.08	0.14	0.29	0.57
750	0.11	0.25	0.62	0.97	1.00	0.05	0.08	0.16	0.32	0.64
900	0.12	0.29	0.69	0.99	1.00	0.05	0.09	0.17	0.36	0.71
1,050	0.13	0.32	0.74	0.99	1.00	0.05	0.09	0.18	0.40	0.76
1,200	0.14	0.35	0.79	1.00	1.00	0.06	0.10	0.20	0.43	0.80
1,350	0.15	0.38	0.83	1.00	1.00	0.06	0.10	0.21	0.46	0.84
1,500	0.15	0.41	0.86	1.00	1.00	0.06	0.10	0.22	0.49	0.87

APPENDIX 3. MEMBERSHIP OF THE SCIENTIFIC ADVISORY COMMITTEE

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