

Protocol

Examining the Impact of the 2019 Novel Coronavirus and Pandemic-Related Hardship on Adverse Pregnancy and Infant Outcomes: Design and Launch of the HOPE COVID-19 Study

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Abstract: The 2019 novel coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread and worsen in many parts of the world. As the pandemic grows, it is especially important to understand how the virus and the pandemic are affecting pregnant women and infants. While early data suggested that being infected with the virus did not increase the risk of adverse pregnancy or infant outcomes, as more information has emerged, it has become clear that risks for some adverse pregnancy and infant outcomes are increased (e.g., preterm birth, cesarean section, respiratory distress, and hospitalization). The Healthy Outcomes of Pregnancy for Everyone in the time of novel coronavirus disease-19 (HOPE COVID-19) study is a multi-year, prospective investigation designed to better understand how the SARS-CoV-2 virus and COVID-19 impact adverse pregnancy and infant outcomes. The study also examines how the pandemic exacerbates existing hardships such as social isolation, economic destabilization, job loss, housing instability, and/or family member sickness or death among minoritized and marginalized communities. Specifically, the study examines how pandemic-related hardships impact clinical outcomes and characterizes the experiences of Black, Latinx and low-income groups compared to those in other race/ethnicity and socioeconomic stratum. The study includes two nested cohorts. The survey only cohort will enroll 7500 women over a two-year period. The survey+testing cohort will enroll 2500 women over this same time period. Participants in both cohorts complete short surveys daily using a mobile phone application about COVID-19-related symptoms (e.g., fever and cough) and complete longer surveys once during each trimester and at 6–8 weeks and 6, 12 and 18 months after delivery that focus on the health and well-being of mothers and, after birth, of infants. Participants in the survey+testing cohort also have testing for SARS-CoV-2 and related antibodies during pregnancy and after birth as well as testing that looks at inflammation and for the presence of other infections like Influenza and Rhinovirus. Study results are expected to be reported on a rolling basis and will include quarterly reporting for participants and public health partners as well as more traditional scientific reporting.

Keywords: pregnancy; 2019 novel coronavirus disease (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); preterm birth; intra-uterine-growth-restriction (IUGR); preeclampsia; cesarean section; infancy; newborn; neonatal

1. Introduction

As the 2019 novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads worldwide, it is essential that researchers collaborate in unprecedented ways. This includes partnering on projects and sharing plans and protocols in early stages in order to encourage feedback, transparency, and, where possible, the rapid adoption of common methods for studying infection, disease course, outcomes, and lived experiences. This early stage sharing has the potential to encourage the rapid identification of patterns and mechanisms, and, ultimately, interventions that are able to lessen the impact of SARS-CoV-2 and COVID-19. To that end, here we present our proposed plan and protocol for assessing the impact of the SARS-CoV-2 and COVID-19 pandemic-related loss on adverse pregnancy and infant outcomes (plan and protocol for the Healthy Outcomes of Pregnancy for Everyone in the time of novel coronavirus disease-19 (HOPE COVID-19 study, https://hope.ucsf.edu/covid_19). This protocol is meant to be shared and methods adopted or modified (with appropriate referencing) where deemed helpful to other researchers and investigative groups.

Background and Rationale

COVID-19 caused by SARS-CoV-2 has caused significant death and illness worldwide [1]. Data are emerging about the incidence of SARS-CoV-2 infection, and findings about the risk of adverse

pregnancy outcomes in women who are SARS-CoV-2 positive have been varied [2–4]. The most comprehensive data on the pregnancy outcomes in women with SARS-CoV-2 infection comes from a recent systematic review from Khalil and colleagues that focused on 2567 pregnant women with PCR-confirmed COVID-19 [5]. They found that 85.5% of pregnant women were symptomatic at the time of a positive screen, with the most common symptoms being fever (63.3%), cough (71.4%), and dyspnea (34.4%). Additionally, 21.8% of women with SARS-CoV-2 had a preterm birth and 48.3% had a cesarean section due to SARS-CoV-2 infection [5].

Although infants born to mothers with COVID-19 have been shown to be unlikely to test positive immediately after delivery [6,7], some evidence exists for both vertical and newborn transmission [8]. Existing data on neonates without SARS-CoV-2 born to mothers with SARS-CoV-2 at full term have been shown to have good outcomes compared to newborns born to mothers without SARS-CoV-2 infection based on comparable Apgar scores, rates of fetal distress, meconium-stained amniotic fluid, and neonatal asphyxia [2,9]. Reported symptoms in neonates with SARS-CoV-2 infection have included fever, shortness of breath, lethargy, vomiting, and pneumonia [10]. Early data suggested that infants and children with COVID-19 have mostly mild symptoms [11,12], but more recent data are emerging showing that many infants and children with COVID-19 experience moderate to critical illness. Recently, a study of 130 infants and children with confirmed COVID-19 found that among infants less than 6 months of age, 37.1% experienced moderate to critical illness, and 12.0% of the infants and children in the study required admission to the ICU—6 of whom were less than 6 months of age. Infants less than 6 months of age were also more likely than all other children to experience critical disease severity (6/35 (17.1%) compared to 3/86 (3.5%), respectively) [13]. Combined, these adverse pregnancy and infant outcomes place women and their infants at increased risk for short- and long-term illness and disease as well as developmental delay and death [14,15]. Moreover, there is a critical need to collect data prospectively in order to analyze how timing and severity of SARS-CoV-2 infection throughout pregnancy affects adverse maternal and infant outcomes

The disparate distribution of the rates of and impact of SARS-COV2 also highlight longstanding health inequities along racial/ethnic and socioeconomic lines. One study found that the incidence of SARS-CoV-2 in Black pregnant women was 28.4% compared to 3.5% in White pregnant women [7]. Another recent study in Boston found that 72% of pregnant and postpartum Hispanic women had SARS-CoV-2 while only 27% of non-Hispanic pregnant and postpartum women were positive. Racial disparities in the rates of infection were found to persist in women utilizing public health insurance, as 64.6% of Hispanic women utilizing public insurance had SARS-CoV-2, whereas only 27.8% of non-Hispanic pregnant and postpartum women utilizing public insurance were positive [16]. When combined with already existing disparities in birth outcomes [14,17–19], the SARS-CoV-2 pandemic has the potential to exacerbate adverse maternal and infant outcome inequities for Black and other marginalized and minoritized women.

It is possible that family, social, and clinical care experiences influence the occurrence of adverse pregnancy and infant outcomes in women with SARS-CoV-2 infection and their infants. It is well known that the experience of stress and trauma can increase a woman's likelihood of having adverse pregnancy outcomes and can also influence the health of infants born to women who are highly stressed, depressed, or traumatized [20–22]. It is also known that some factors like social support and nutritional support from programs like the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) can help to buffer against adverse outcomes [23]. It is also critical to note that health care providers (including nurses, physicians, and others) exert an important influence over how comfortable a woman feels when seeking help and health care for pregnancy, birth, and postpartum [24].

Emerging data related to SARS-CoV-2 infection and COVID-19 indicating increased risk for adverse pregnancy and infant outcomes point to an urgent need for comprehensive studies to examine the association between infection, outcomes, and social, structural, and clinical determinants of health—particularly in diverse and inclusive cohorts with respect to race/ethnicity, socioeconomic

status, and lived experiences. There is also a critical need to examine the impact of the pandemic itself on adverse outcomes and experiences including the impact of related stress due to social isolation, job loss, sickness in family and friends, as well as the added trauma of interpersonal, institutional and structural racism on minoritized and marginalized pregnant women, particularly within Black communities [5–13,15,16,25–29]. Despite this critical need, to date, no investigations of COVID-19 pregnancy and infant outcomes that we are aware of have also included an investigation of how pandemic-related stress and racism may be impacting pregnancy and infant outcomes in Black and other marginalized and minoritized women who may or may not be infected with the SARS-CoV-2 virus.

The HOPE COVID-19 study is a multi-year prospective population-based study designed to assess the impact of the SARS-CoV-2 infection on adverse pregnancy and infant outcomes. The study addresses key gaps in existing approaches by comparing rates of outcomes in women with and without SARS-CoV-2 (rather than taking a case-based approach), examining whether timing of infection influences observed results, and assessing how maternal, family, social, and care experiences and pandemic-related hardships are impacting outcomes. The study is also powered to examine pregnancy and infant outcomes in Black, Latinx, and low-income women and their children specifically including measuring how stress, racism, and trauma are impacting observed patterns.

2. Materials and Methods

The HOPE COVID-19 study is a phased population-based study with pregnant women and their infants. There are two study cohorts: a survey only cohort that allows all pregnant women to enroll regardless of where they live and a survey+testing (SARS-CoV-2 RT-PCR testing) cohort that will initially be carried out in the four largest metropolitan areas of California: the San Francisco Bay Area, Los Angeles County, Orange County, and San Diego County. If additional funding is identified, the survey+testing cohort may expand into other areas of California and into Oregon and Washington.

2.1. Aims

The study focuses on four specific aims:

Aim 1: Assess whether there is any association between SARS-CoV-2 infection and adverse pregnancy and infant outcomes. We hypothesize that women with SARS-CoV-2 infection and their infants will have an increased risk of adverse outcomes. Further, we hypothesize that higher rates of infection and adverse pregnancy and infant outcomes among Black, Latinx and low-income women will be observed when compared to non-Black or Hispanic participants and to participants in higher-income groupings (within both the infected and uninfected stratum).

Aim 2: Measure whether timing or severity of SARS-CoV-2 infection influences the likelihood of adverse pregnancy or infant outcomes. We expect that infection earlier in pregnancy and infection with more severe symptoms present will be related to an increased risk for adverse pregnancy and infant outcomes. While we anticipate that this pattern will persist across race/ethnicity and income groupings, we expect to observe earlier rates of infections and worse symptomatology at onset among Black, Latinx and low-income women.

Aim 3: Evaluate whether maternal family, social, or clinical care experiences impact observed relationships between SARS-CoV-2 infection and adverse pregnancy and infant outcomes. We anticipate that women with SARS-CoV-2 infection with and without adverse pregnancy and infant outcomes will differ with respect to family, social and clinical care experiences. We believe there will also be considerable differences in the rates and types of experiences reported by Black and Latinx women compared to women of other races/ethnicities due to differential distribution in clinical, social, and structural determinants of health. We expect the same to be true for low- compared to higher-income participants. Further, we expect to identify patterns that confer greater risk and patterns that confer protection against adverse pregnancy and infant outcomes across and within race/ethnicity and income stratum.

Aim 4: Examine whether there is a relationship between COVID-19 pandemic-specific hardship (measured by job loss, significant loss of income, reported experiences of racism and discrimination, sickness, or death of family member) and pregnancy and infant outcomes. We believe we will find that hardship earlier in pregnancy and more severe hardship will be associated with an increased risk for adverse pregnancy and infant outcomes. We expect a higher risk of pandemic-specific hardship and the highest rates of adverse pregnancy and infant incomes among Black, Latinx and low-income women when compared to non-Black or Hispanic participants and to participants in higher-income groupings (within both the infected and uninfected stratum).

2.2. Study Design

This will be a phased population-based study enrolling a maximum of 10,000 women over a two-year period: 7500 into a survey only cohort and 2500 into a survey+testing cohort. Focused enrollment will be performed in Black, Latinx, and low-income communities to ensure that at least 25% of the sample identifies as being of Black race/ethnicity, 25% of Latinx race/ethnicity, and 50% low-income. Study phasing will occur in the survey+testing study cohort in order to manage resource expenditure and laboratory capacity, which is currently at 100–110 research participants per month in order to not impact routine clinical lab work. As such, for the survey+testing cohort, enrollment is phased to accommodate the enrollment of a maximum of 660 women per six-month period. We expect to enroll 660 participants in study phase 1 (study months 1–7), 660 (total enrolled = 1320) in phase II (study months 8–13), 660 (total enrolled = 1980) in phase III (study months 14–19), and 520 (total enrolled = 2500) in phase IV (study months 20–24). For infants, given it is an opt-in test that involves a heel prick, we expect approximately 50% of mothers to opt in, resulting in an infant enrollment of 1250.

2.3. Selection and Enrollment of Participants

2.3.1. Inclusion Criteria

Both study cohorts

1. 18 years of age or older.
2. Comfortable reading and writing in English (Spanish to be added in early 2021).

Survey+testing cohort

3. Live in target geography for phase (phase I–2: San Francisco, Marin, Sonoma, Napa, Solano, Contra Costa, Alameda, Santa Clara, San Mateo Yolo, Sacramento, Los Angeles, Orange, and San Diego counties in California; phase 3–4: all of these counties plus Seattle and Tacoma, Washington and Portland and Eugene, Oregon, if funding is secured).
4. Willingness to have their hospital records reviewed for study purposes.
5. Willingness to contribute nasal swab and blood specimens at all study time points (enrollment, subsequent trimesters, and 6–8 weeks after birth).

Infants

1. Able to contribute blood spots from an infant heel prick.

2.3.2. Exclusion Criteria

Women

1. Not able or willing to fill out surveys on phone or computer.
2. Not able or willing to download and use mobile phone applications.

Infants

1. Infants will be excluded if in the care of the NICU or of uncertain viability.

2.4. Recruitment

Women will be recruited through the UCSF Citizen Science COVID-19 study [30], the MotherToBaby California service [31], social media (Facebook, Twitter, and Instagram), Google ads based on search terms, community mailing, posters/billboards, and using electronic message boards at college campuses and businesses with specific outreach to Black and Hispanic/Latinx women and in low-income communities. We will also perform targeted enrollment of women with existing SARS-CoV-2-positive testing results to ensure a minimum positive rate of at least 15% and to maximize power by utilizing targeted recruitment materials and efforts through the above listed channels.

Study Enrollment and Consent

Women will be identified through existing partner COVID-19 studies like the UCSF Citizen Science COVID-19 study [30], which tracks daily, weekly and monthly patterns of COVID-19-related symptoms and treatments as well as psychosocial impacts and social distancing behavior. At the onset of enrollment and quarterly, participants in the Citizen Science COVID-19 study who report being pregnant will be sent notifications via text about the launch of the HOPE COVID-19 study with a link to the HOPE COVID-19 website (www.HOPE.UCSF.edu/COVID_19) which will invite them to enroll. We will also utilize the MotherToBaby COVID-19 Breastfeeding study [31], a participant support and research platform, which means that pregnant women who are interested in the HOPE COVID-19 study will be able to call, text, live chat, or email MotherToBaby to learn more about the study and about how to sign up.

Infants receiving care in a neonatal intensive care setting at 6–8 weeks will not be enrolled in the biospecimen collection part of the study. We expect that this will include all infants of questionable viability. Other data collection for infants will not involve any interaction with the infants and as such would have no influence on health or viability.

Informed consent will be obtained from women who meet selection criteria, with separate consents for women in the survey only study cohort and in the survey+testing study cohort. Initial consent will be conducted online via the emailing of consent documents for electronic signature. Consent will also cover the potential future use of biological specimens obtained during the course of the study.

Women in both study cohorts will be required to co-enroll in the UCSF Citizen Science COVID-19 study that will involve downloading of the application for that study onto their cell phones, enrolling, and participating in that study separately. Data from the Citizen Science COVID-19 application will be connected to HOPE COVID-19 data by phone number. Participants in the HOPE COVID-19 study will be asked to consent to this linkage.

In order to capture heart rate as an important covariate, participants in both study cohorts will also be asked to download and use the Instant Heart Rate application that will require the downloading of this application onto their cell phones and by signing up on the application [32]. Data from the Instant Heart Rate application will be connected to HOPE COVID-19 data by username and password that will be entered into the Citizen Science COVID-19 study application. Participants in the HOPE COVID-19 study will be asked to consent to the linkage between platforms.

2.5. Participant Management

Participant Follow-Up

All participants in the study will be followed from the time of enrollment until 18 months after the infant's birth. For all study participants (in both study cohorts), this includes participating in the UCSF Citizen Science study that will include filling out daily surveys about COVID-19-related symptoms and pandemic-related behaviors (e.g., social distancing). This also includes having their heart rate measured using the Instant Heart Rate application [32].

All participants in the study will also complete online surveys (accessed by computer or mobile phone) that include a baseline contact information survey and enrollment survey (combined,

these take approximately 45 min to complete), subsequent trimester surveys (which take approximately 30 min to complete), a 6–8 week postpartum survey (which takes approximately 30 min to complete), and a 6 month, 12 month, and 18 month survey (which take approximately 30 min to complete). An overview of timeline, expected measures, and the study flow for women in the survey only cohort and in the survey+testing cohort of the study are included in Figure 1.

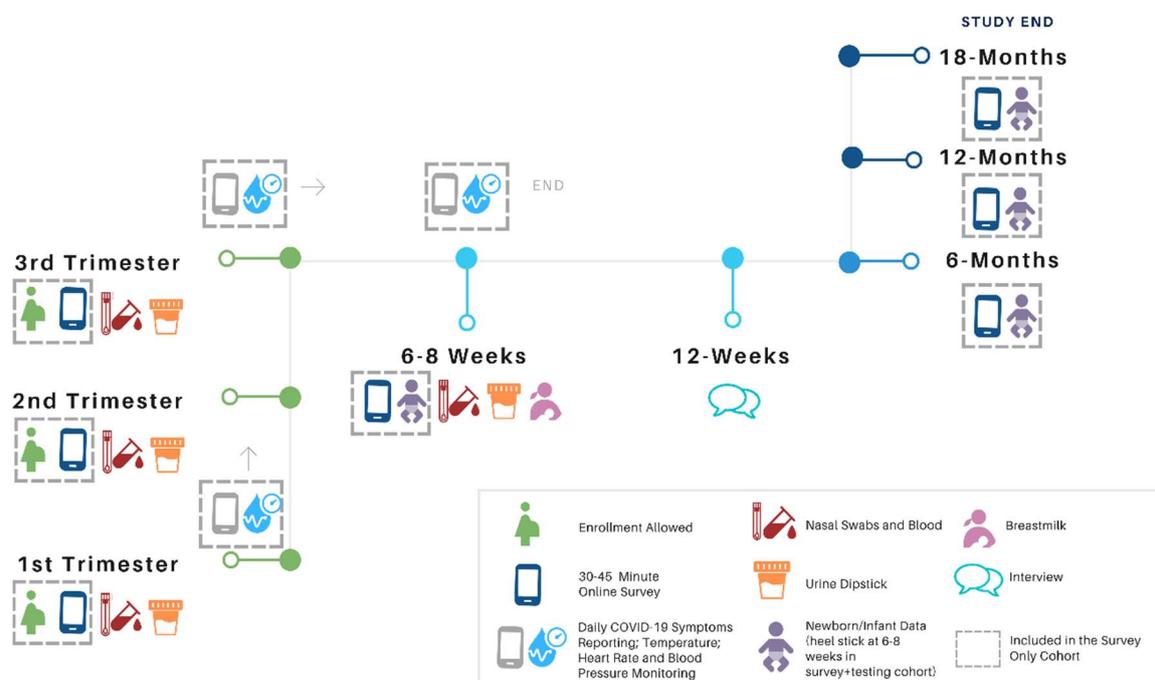


Figure 1. Overview of planned data and specimen collection in the HOPE COVID-19 study.

Participants in the survey+testing cohort also have biospecimens collected at scheduled time points including at enrollment, in each following trimester (depending on time of enrollment), and at 6–8 weeks after delivery. Some participants in this cohort will also be interviewed between 2 and 3 months after delivery.

2.6. Specimen and Data Collection

2.6.1. Detail: Survey Measures

As depicted in Figure 1, study participants will be able to enroll in the study throughout pregnancy and will complete an enrollment survey with additional surveys in subsequent trimesters depending on timing of enrollment as well as surveys after birth, at 6 to 8 weeks, 6 months, 12 months, and 18 months [33–45].

Enrollment surveys are completed at enrollment (any time during pregnancy) and ask about demographics, health care, and physical and psychosocial health before and during pregnancy, and about COVID-19-related physical and emotional health.

Trimester surveys are completed in each trimester following enrollment and ask about health care, physical and psychosocial health, and about COVID-19-related physical and emotional health since enrollment.

Infant Health Surveys are administered at 6 to 8 weeks after the expected date of delivery and at 6 months, 12 months, and 18 months after birth and include questions about infant health and development, about satisfaction with care in the neonatal intensive care unit (NICU, if admitted), about labor and delivery and about breastfeeding [46–49]. Participants are also asked about prenatal

care experiences, psychosocial health, and about COVID-19-related physical and emotional health since their last survey.

Additional SARS-CoV-2/COVID-19 Surveys are administered daily and weekly via the Citizen Science COVID-19 application and ask specific questions about daily symptoms of participants and family members, about health history and medications, about social distancing behaviors, and about the impact of the pandemic on mood and health.

Table 1 provides more detailed information about HOPE COVID-19 survey measures including the use of standardized measures where applicable. Supplemental Tables S1 and S2 include the complete survey battery.

Table 1. Survey item groupings and measures: HOPE COVID-19 study.

Prenatal	6–8 Week Postpartum	Infant Health at 6, 8 and 12, and 18 Months
“E” = Enrollment Survey “S” = Subsequent Trimester Surveys Contact/Demographics 17 Questions/sets (all E, some S) Psychosocial Health before Pregnancy 2 Questions/sets (all E only) Including (in part): <ul style="list-style-type: none"> • ACEs revised questionnaire [33] • Philadelphia expanded ACE survey (partial) [34] Physical Health before Pregnancy 8 Questions/sets (all E only) Health Care 2 Questions (all E, some S) Physical Health Current Pregnancy 19 Questions/sets (all E, S) Psychosocial Health Current Pregnancy 25 Questions/sets (all E, S) Including (in part): <ul style="list-style-type: none"> • Food insecurity [45] • Everyday discrimination scale [35] • Satisfaction with life scale [36] • Generalized anxiety disorder (GAD-7) [37] • Perceived stress scale 4 (PSS-4) [38] • Pregnancy-related anxiety scale [39] • UCLA loneliness scale [40] • Interpersonal support evaluation list [41] • Brief and Conner–Davidson resilience scales [42,44] COVID-19 Physical and Emotional Health 23 Questions/sets (all E, some S) Including (in part) <ul style="list-style-type: none"> • Michigan COVID-19 pregnancy [43] 	New Baby Information 14 Questions/sets <ul style="list-style-type: none"> • 4 from modified neonatal satisfaction survey [46] Infant Development 5 Questions/sets Including: <ul style="list-style-type: none"> • Ages and stages [47] Labor and Delivery 11 Questions/sets Including (in part): <ul style="list-style-type: none"> • CDC PRAMS [48] Breastfeeding 4 Questions/sets Including (in part): <ul style="list-style-type: none"> • CDC PRAMS [48] Prenatal Care, Health and Well-Being 21 Questions/sets Psychosocial Health (since last survey to current) 21 Questions/sets Including (in part): <ul style="list-style-type: none"> • Generalized anxiety disorder (GAD-7) [37] • Perceived stress scale 4 (PSS-4) [38] • Edinburgh postnatal depression scale [49] • Interpersonal support evaluation list [41] COVID-19 Physical and Emotional Health 18 Questions/sets Including (in part): <ul style="list-style-type: none"> • Michigan COVID-19 pregnancy [43] 	Infant Health 7 questions/sets Infant Development 5 questions/sets Including (in part) <ul style="list-style-type: none"> • Ages and Stages [47] Breastfeeding 3 Questions/sets Including (in part): <ul style="list-style-type: none"> • CDC PRAMS [48] Psychosocial Health (since last survey to current) 24 Questions/sets Including (in part): <ul style="list-style-type: none"> • Generalized anxiety disorder (GAD-7) [37] • Perceived stress scale 4 (PSS-4) [38] • Edinburgh postnatal depression scale [49] • Interpersonal support evaluation list [41] COVID-19 Physical and Emotional Health 18 Questions/sets Including (in part): <ul style="list-style-type: none"> • Michigan COVID-19 pregnancy [43]

2.6.2. Molecular Measures

SARS-CoV-2 RT-PCR testing will be performed using NP or OP swabs which will rely on RT-PCR that will be performed in the Providence St. Joseph Health Molecular Genomics Laboratory, a clinical lab certified under Clinical Laboratory Improvement Amendments using a RT-PCR assay certified for clinical use under FDA emergency use authorization (EUA) [50–52]. SARS-CoV-2 viral genome sequencing may also be performed for research purposes. This will be performed using hybrid-capture targeted library preparation with sequencing on an Illumina sequencer.

SARS-CoV-2 antibody testing will be performed using maternal serum samples collected by venous draw and fingerstick microsamples collected during each trimester and at 6 weeks postpartum. Infant microsamples will also be collected and tested with consent. Antibody testing will be performed using enzyme-linked immunosorbent assay (ELISA). The laboratory currently runs the DiaSorin LIAISON SARS-CoV-2 S1/S2 IgG assay, which is run under Emergency Use Authorization granted by the FDA [53]. Testing on microsample finger stick samples in mothers and heel stick samples in babies is being performed for research purposes only and, as such, will not be reported to participants.

Cytokine and cytokine receptors testing will be performed using venous blood from women and infant blood microsamples collected by heel stick (with consent). This testing will rely on a broad

panel of 45 cytokines and chemokines that will be tested in blood samples using Luminex xMAP (multianalyte profiling) technology [54]. This testing is performed for research purposes only.

Other respiratory infection testing (also using NP or OP swab samples drawn in women who are symptomatic) will be performed using the Verigene Respiratory Pathogen Flex Nucleic Acid Test (RP Flex) on the Verigene platform. This test has been cleared by the FDA for clinical use and is the primary broad respiratory panel used in clinical practice at Providence. Specific viral results will be included for *Adenovirus*, *Human Metapneumovirus*, *Influenza A*, *Influenza A subtype H1*, *Influenza A subtype H3*, *Influenza B*, *Parainfluenza Virus 1*, *Parainfluenza Virus 2*, *Parainfluenza Virus 3*, *Parainfluenza Virus 4*, *Rhinovirus*, *Respiratory Syncytial Virus A*, *Respiratory Syncytial Virus B*, *Bordetella pertussis*, *Bordetella parapertussis/bronchiseptica* and *Bordetella holmesii* [55]. This test has been cleared by the FDA for clinical use by labs certified to perform high-complexity tests.

Breast milk testing for SARS-CoV-2 and SARS-CoV-2 antibodies will be performed at the University of California San Diego's Human Milk Biorepository in collaboration with the Department of Medicine where they are currently finalizing their preferred testing protocol for the SARS-CoV-2 virus and SARS-CoV-2 antibodies [56]. This testing is being performed for research purposes only.

Urinary bacterial testing for urinary tract infection will be performed using multi-reagent dipsticks on the same day as in-home trimester visits [57]. Results of this test will be reported by text on the day of laboratory visit.

2.7. Medical Chart Review and Biomonitoring

For those in the survey+testing cohort of the study, maternal demographic data, reported diagnoses and illness during pregnancy, routine laboratory testing results, weight and height measures, gestational age and weight of infant at delivery, type of delivery (induced, cesarean delivery), days from delivery to discharge, infant diagnoses and illnesses and laboratory testing results will be extracted from the mother and infant hospital records. After enrollment, participants will be sent consents to complete online or on paper (depending on hospital requirements) for medical record release from the expected birthing facility or hospital (if planning to birth at a specific facility).

Biomonitoring will include heart rate measurement using the Instant Heart Rate application [32,58] (for participants in both cohorts), and, for participants in the survey+testing cohort, daily temperature checks using a study provided Healthsmart Digital Forehead Thermometer [59] (with daily reporting of any temperature at or above 100.4F), and weekly exact temperature and in-home blood pressure measurement [60] requested and reported to study personnel by secure text messaging.

2.8. Qualitative Interviews

At the conclusion of the survey, some participants will be asked whether they are willing to be contacted to participate in a one-on-one qualitative interview, which will take place over the phone or via teleconference. We will conduct one-on-one qualitative interviews with up to 80 study participants from the survey+testing cohort (or until saturation is reached) who agree to be contacted. There is no established standard for calculating sample size for qualitative studies. Based on our experience conducting qualitative studies, we believe 80 participants should be sufficient to reach saturation. We will use purposeful sampling to ensure variation with respect to age, previous pregnancies, and exposure to COVID-19. We will oversample Black and Latinx participants, as well as low-income participants, to help ensure representation of these populations. In total, 75% of the sample will be comprised of pregnant women, and 25% will be postpartum women. Interviews will take up to 45 min. Trained interviewers will use a semi-structured interview guide to elicit women's experiences with and concerns about pregnancy, childbirth, and caring for an infant during and after the pandemic. Topics will include physical and mental health; experience of prenatal, delivery, and postnatal care; income and work-related issues (employment, leave, job security); and social support. The interviews will be recorded (with permission from the participant) and transcribed. Supplemental Table S3 includes an overview of the qualitative interview.

2.9. Results Reporting

Results of SARS-CoV-2 testing by PCR and antibody testing will be reported to participants within 7 days of specimen draw. This same time schedule will be used to report other respiratory infections in any instance where tested (when collected due to maternal fever at or above 100.4F and the presence of a cough or when any person in the household has tested positive for SARS-CoV-2).

Participants will be asked to contact their health provider to discuss results and will be told that it is especially important to do so after a positive test for the SARS-CoV-2 virus or for any other respiratory infection.

2.10. Duration of Follow-Up and Criteria for Premature Study Withdrawal

Pregnant women and infants will be followed for 18 months after a baby's birth. Study participants will be prematurely withdrawn from the study for: (1) inability to be located for more than 60 consecutive days, (2) withdrawal of informed consent, (3) inability to comply with the study schedule and procedures, (4) at the discretion of the study coordinator if the study is not in the best interest of the participant, (5) subject judged by the site investigator to be at significant risk of failing to comply with the study protocol as to cause them harm or seriously interfere with the validity of study results. If a subject is withdrawn for reasons #1–3, we will be unable to perform any additional study procedures. If a subject is withdrawn for reasons #4–5, plans to obtain appropriate follow-up tests outside of the study will be individualized for each subject depending on the health status of the subject at the time of withdrawal and the willingness of the participant to proceed with additional surveys or testing.

3. Statistical Considerations

3.1. Analyses

3.1.1. Quantitative Analyses

Multivariable logistic regression will be used to address all aims. The primary predictors are SARS-CoV-2 and no infection (for Aim 1 and Aim 3), timing and severity (for Aim 2), and pandemic-related hardship (for Aim 4). These factors will be entered into the model in addition to potential confounders, such as maternal hypertension, diabetes, and previous preterm birth. The Aim 2 analyses will be conducted only among COVID-19-positive participants. In Aim 3, we will focus on moderation due to high versus low maternal stress, resilience, and social support by standardized measures wherein we will analyze the data by adding interaction terms to the model from Aim 1. We will also add interaction terms for race/ethnicity and income into all resulting models to assess impact.

We will utilize machine learning techniques (e.g., structured and unstructured prediction) to find links between SARS-CoV-2 infection/COVID-19/pandemic-related hardship, pregnancy-related complications, and severe infant morbidity using molecular, clinical, social, and biometric data. To explore the full richness of the dataset and possible moderating effects, we will explore dimension reduction using principal component analysis and model fitting using LASSO, neural networks and recursive partitioning. We will consider two-way interactions in logistic models resulting from the LASSO fits. Risk factors will include but not be limited to examination by pre-pregnancy and pregnancy specific medical conditions, timing of infection, medications used, lifestyle factors, immunological profiling, and treatment/hospitalizations directly related to SARS-CoV-2 infection and diagnosed COVID-19. We will also explore causal modeling approaches (e.g., graphical causal models [61]) to derive mechanistic predictive models from the data. These data will be incorporated into the existing HOPE Data Store and Accelerator platform (developed in partnership with Omics Data Automation, Inc. (ODA) [62]) with data visualization and modeling performed using the embedded automation. Models will be informed by both external annotation and expert knowledge obtained from physicians and scientific experts. Figure 2 provides an example of visualization performed through the HOPE

Accelerator platform (<https://hope.ucsf.edu/hope-accelerator>)—specifically, the 3D capability, which allows investigators to look for novel signals across diagnostic and molecular factors.

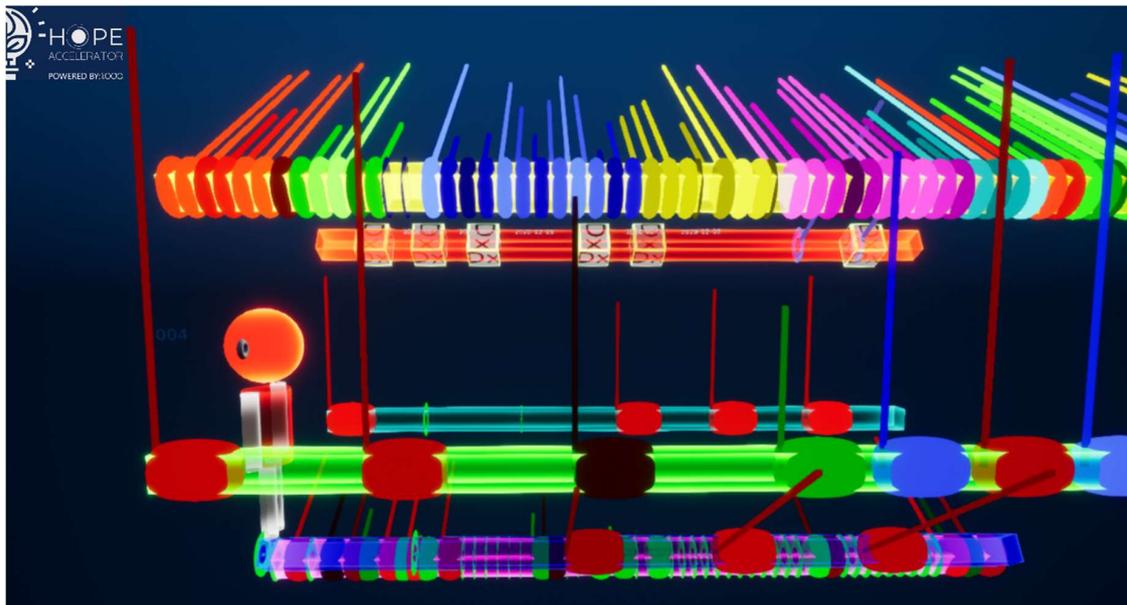


Figure 2. 3D data visualization using the HOPE Accelerator (<https://hope.ucsf.edu/hope-accelerator>).

All analyses will be performed in the combined sample and within Black, Latinx, and in income-specific stratum.

3.1.2. Qualitative Analyses

Qualitative Data will be entered, coded, memoed, and organized using the Dedoose software program [63], which allows for open coding, theoretical memoing, and detailed conceptual matrixing of transcript and memo data within and across participants. Sorting functions allow for cross-group comparison by code or characteristic and for establishing a system of inter-coder reliability.

3.2. Sample Size and Power

Our goal is to enroll 7500 women into the survey only cohort and 2500 into the survey+testing cohort over a two-year period (25% Black, 25% Latinx, 50% low income). We anticipate analyzing survey only and survey+testing cohort data separately, given that we expect the percent of participants reporting SARS-CoV-2 exposure to differ between the two groups, since women in the survey only group will have had to have been tested by their own doctor or in their own community to have a result (for PCR or antibody) and all women in the survey+testing cohort will have been tested multiple times. It should also be noted that it is unclear what the actual positive rate for SARS-CoV-2 will be in either cohort. Table 2 notes the differences in rates and relative risks (RRs) we expect to be able to detect with 80% power (two-tailed at $p < 0.05$) in adverse pregnancy and infant outcomes at 5%, 10%, and 15% infection rates given a minimum prevalence of adverse pregnancy complications in these geographies of 35% and a minimum rate of 17.5% for neonatal illness and death based on existing statewide data [64]. Our estimated SARS-CoV-2-positive infection or positive antibody test rate of between 5% and 15% is based on positive rates of infection at a single time point of 13.0% and 7.2% in San Francisco and in San Diego, respectively [65–67].

Table 2. Detectable differences (DDs) and relative risks (RRs) for adverse pregnancy and infant outcomes in unadjusted and adjusted models by rate of SARS-COV-2 infection and sample size.

	Rate of SARS-COV-2 in Sample		
	5%	10%	15%
	DD, RR	DD, RR	DD, RR
Sample size/unadjusted models/adverse pregnancy outcomes *			
600	0.25, 1.76	0.18, 1.56	0.15, 1.48
1200	0.18, 1.53	0.13, 1.39	0.11, 1.33
2400	0.13, 1.37	0.09, 1.27	0.08, 1.23
4800	0.09, 1.26	0.06, 1.19	0.05, 1.16
9600	0.06, 1.18	0.05, 1.13	0.04, 1.11
Sample size/adjusted models **/adverse pregnancy outcomes *			
600	0.29, 1.88	0.21, 1.64	0.18, 1.55
1200	0.21, 1.61	0.15, 1.45	0.13, 1.38
2400	0.15, 1.42	0.11, 1.31	0.09, 1.26
4800	0.10, 1.30	0.07, 1.22	0.06, 1.18
9600	0.07, 1.21	0.05, 1.15	0.04, 1.13
Sample size/unadjusted models/adverse infant outcomes *			
600	0.20, 2.22	0.15, 1.90	0.12, 1.77
1200	0.14, 1.84	0.11, 1.62	0.09, 1.53
2400	0.10, 1.58	0.07, 1.43	0.06, 1.36
4800	0.07, 1.41	0.05, 1.30	0.04, 1.25
9600	0.05, 1.29	0.04, 1.21	0.03, 1.18
Sample size/adjusted models **/adverse infant outcomes *			
600	0.24, 2.42	0.17, 2.05	0.14, 1.91
1200	0.17, 1.97	0.12, 1.72	0.10, 1.62
2400	0.12, 1.68	0.08, 1.50	0.07, 1.42
4800	0.08, 1.47	0.06, 1.35	0.05, 1.24
9600	0.06, 1.33	0.04, 1.24	0.04, 1.21

* Based on a rate of adverse pregnancy outcomes of 35% and a rate of 17.5% for neonatal illness and death based on existing statewide data [59]. ** Assuming a correlation with other predictors of 0.25.

Not surprisingly, Table 2 shows that our statistical power increases as our sample size increases and the prevalence of infection increases. For example, with 600 women and infants enrolled and retained, at a 5% infection rate (and an adverse pregnancy outcome rate of 35%), we will be able to detect differences in adverse pregnancy outcome rates of 0.25 or higher and RRs of 1.76 and higher in unadjusted models and differences of 0.29 and RRs of 1.88 in adjusted models (assuming a correlation with other factors in the model of 0.25). At a sample size of 9600, this increases to an ability to detect differences of 0.06 or more and RRs of 1.18 or more in unadjusted models and differences of 0.07 or more and RRs of 1.21 or more in adjusted models. This pattern is also observed for infant outcomes where with 600 enrolled and retained infants, a maternal infection rate of 5%, and an adverse infant outcome rate of 17.5%, we will be able to detect differences of 0.20 and greater and RRs of 2.22. With 9600 infants this increases to an ability to detect differences of 0.05 or more and RRs of 1.29 or more.

What Table 2 also demonstrates is that as our sample size grows, so will our ability to look more deeply at patterns within particularly vulnerable groups. For example, at 9600 women and infants enrolled and retained and our intended enrollment percentages of 25% Black, 25% Latinx and 50% low-income, we would have 1200 Black women, 1200 Latinx and 2400 low-income women.

4. Human Subjects

4.1. Subject Selection Criteria

Study subjects will be women 18 years or older with singleton pregnancies and the children born to them who meet our selection criteria and provide informed consent.

4.2. Reimbursement of Subjects

Participants in the survey only cohort of the study do not receive monetary compensation. These participants receive quarterly newsletters updating them about new research on COVID-19, pregnancy, infant and child health and about study progress and publications. Participants in the survey only cohort are notified about other research opportunities that emerge in which they may be qualified (provided they agree to such contact on their consent forms). In some instances, these studies may include monetary compensation for their participation.

Participants in the survey+testing cohort will receive \$100 after completion of their biospecimen collection visits at enrollment, in each subsequent trimester, and at 6–8 weeks after birth. They will also receive \$50 after their phone interview if they are selected to participate in that part of the study. Women also receive \$100 after completion of their 18 month survey (for example, total compensation would be \$550 for a participant enrolled in the first trimester who contributes surveys and biospecimens at all time points and completes an interview). Participants in the survey+testing cohort also receive quarterly newsletters updating them about new research on COVID-19, pregnancy, infant and child health and about study progress and publications. Participants in this study cohort are also notified about other research opportunities that emerge in which they may be qualified (provided they agree to such contact on their consent forms). In some instances, these studies may include additional monetary compensation for their participation.

5. Institutional Review Board (IRB) Review and Informed Consent

This protocol, all procedures and consent forms, and any subsequent modifications must be reviewed and approved by the IRBs of all the participating institutions. For this initial study, this includes the UCSF and UCSD Committees on Human Research (CHR).

6. Study Launch

Enrollment into the survey only cohort of the HOPE COVID-19 study started in July 2020. All pregnant women who qualify anywhere in the world are now able to enroll. Enrollment in the survey+testing cohort will start in California once funding is secured. Initial survey only results are expected to be available in late 2020.

7. Discussion

As SARS-CoV-2 and COVID-19 has spread across the world (including in the United States), researchers have been working as quickly as possible to understand the virus and its impact. This critical need for answers as rapidly as possible has led to many disparate investigations where comparison of findings and results across populations is challenging. While data on the impact of SARS-CoV-2 and COVID-19 on pregnancy and infant outcomes are beginning to emerge, findings are often confusing, with some noting little to no impact of the virus on outcomes and some noting substantial impact. The HOPE COVID-19 study intends to take a broad approach to looking at the impact of the virus on outcomes that includes consideration of key drivers and comorbidities. The study also examines the impact of pandemic-related hardship on outcomes, including in women with and without infection, a key component of the current experience that has received little focus thus far. Crucial in this work is the investigation of how the virus and pandemic are differentially affecting persons most at risk for adverse pregnancy and infant outcomes, as a result of unequal and inequitable risk exposures,

including Black and other marginalized and minoritized women and their children. We believe our study will highlight the ways in which racism structures and social and labor hierarchies in the U.S. and elsewhere (a phenomenon called racial capitalism) [68] cause Black and Latinx people to be disproportionately likely to work in occupations that increase their risk exposure to COVID-19. In examining pandemic-related hardships, we anticipate observing higher rates of COVID-19 infection and other clinical and social sequelae due to elevated occupational risk. We intend for the HOPE COVID-19 plan and protocol to be adopted and adapted where useful in order to align studies, compare findings, and uncover and drive interventions aimed at lessening the impact of SARS-CoV-2 and the COVID-19 pandemic in the United States and worldwide.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2673-3897/1/2/7/s1>.

Author Contributions: All authors participated in the conceptualization of the study and protocol including in the selection of methodologies used. All authors participated in the drafting, review and editing of the initial protocol and have read and agreed to the published version of the manuscript. Other specific contributions include: formal analysis (planning), L.L.J.-P., C.C., S.P.O., C.E.M., M.K., G.S., H.W.; resources, L.L.J.-P., C.C., L.R., X.P.; data curation, L.L.J.-P., S.P.O., R.B.; visualization, L.L.J.-P., G.S., H.W.; supervision, L.L.J.-P., A.O., R.B.; project administration, L.L.J.-P., A.O., R.B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: Ganapati Srinivasa and Hollis Wright work for and have a vested interest in Omics Data Automation, Inc. No other conflicts are reported.

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