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Effect of in utero exposure to SARS-CoV-2 infection on pregnancy outcomes and growth and development of infants: protocol for a multicentre ambispective cohort study in India

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ABSTRACT

Introduction Poor pregnancy and neonatal outcomes in infants born to COVID-19 positive mothers have been reported, but there is insufficient evidence regarding subsequent growth and development of these children. Our study aims to explore the effect of in-utero exposure to SARS-CoV-2 on pregnancy outcomes and growth and development of infants.

Methods and analysis A multicentric ambispective cohort study with comparison group (1:1) will be conducted at six sites. A total of 2400 participants (exposure cohort, n=1200; comparison cohort, n=1200), ie, 400 participants from each site (200 retrospectively; 200 prospectively) will be included. Exposure cohort will be infants born to women with documented COVID-19 infection anytime during pregnancy and comparison cohort will be infants born to women who did not test positive for SARS-CoV-2 anytime during pregnancy. All infants will be followed up till 1 year of age. Anthropometric measurement, age of attainment of developmental milestones and clinical examination findings will be recorded at each follow-up. Data regarding possible cofactors affecting the outcomes will be collected from both groups and adjusted for during analysis. The two groups will be compared for prevalence of every variable considered in the study. Relative risk, attributable and population attributable risks will be calculated. All risk factors with p<0.1 on bivariate analysis will be subjected to multiple logistic regression analysis. A final multivariable model will be developed by including the statistically significant risk factors.

Ethics and dissemination The study has been approved by the Institutional Review Board of IIHMR Delhi (IRB/2021-2022/006) and will be required to be approved at all participating study sites. The study is scheduled from September 2021 to August 2023. Data from retrospective cohort will be reported by August 2022. All participants will provide written informed consent. We plan to publish our results in a peer-reviewed journal and present findings at academic conferences.

Strengths and limitations of this study

- Our multicentric study representing diverse geographical locations and sociodemographic profiles will increase the external validity of our results.
- We will be able to determine the relationship of multiple pregnancy outcomes with the exposure because of our cohort study design.
- The data from our retrospective cohort will be available in a short span of time thus aiding rapid evidence synthesis.
- Only the women who are willing to report for follow-up along with their infants for a period of 1 year will be included in the study which may introduce selection bias.
- Since we will be collecting some of the data for our retrospective study group from available hospital records, some degree of unavoidable observer bias might be introduced in our retrospective data.

INTRODUCTION

The year 2020 saw the advent of the COVID-19 pandemic across the globe. The disease was first reported in the city of Wuhan in China in December 2019 following which it rapidly spread to several countries across the globe within 3 months. The disease was declared a pandemic by the WHO on 11 March 2020.[1] Over 183 million cases of the disease have been reported worldwide as on 7 July 2021 of which more than 30 million are from India. The pandemic has also claimed over 3.9 million lives globally.[2]

COVID-19 is caused by a novel coronavirus called the SARS-CoV-2 and all age groups and genders are susceptible to the disease. The virus has been reported to mainly spread through the respiratory route either through respiratory droplets or aerosols, and also by direct contact with contaminated surfaces or objects and infecting by touching eyes, nose and mouth with contaminated hands. Several other possible modes of spread of COVID-19

has been explored, including feco-oral transmission and transmission through body fluids.[3] Infections have also been reported in pregnant women, hence there is a possibility of transmission to the infant. Several studies have also reported the disease in neonates born to COVID-19 positive mothers thereby strengthening a possibility of vertical transmission.[4 5]

COVID-19 has affected all age groups, but a greater proportion of older people have suffered from severe disease, hospitalisation and death as compared with younger age groups. The disease is being reported from pregnant women across the globe, though pregnancy has not been seen to be a risk factor for severe COVID-19. Severe disease among pregnant women was seen to be associated with older age and underlying comorbidities.[6] Infections during pregnancy raises the concern of transmission of the infection from the mother to the baby, either in utero or during the intrapartum and early postpartum period. Reports have shown the possibility of vertical transmission of SARS-CoV-2 from mothers infected with the virus to their babies.[2]

A review on congenital, intrapartum and postnatal transmission of SARS-CoV-2 infection generated evidence to support the potential maternal–fetal–neonatal transmission of COVID-19.[7] Another review of reported neonatal SARS-CoV-2 infections reported 30% of the infections occurring due to vertical transmission, of which 17% were acquired during the intrapartum period while the remaining were congenital.[5] Several other studies also report findings suggestive of possible congenital and intrapartum infection.[8–10] Though SARS-CoV-2 RNA was detected in breast milk samples as reported by some studies,[7 11 12] there is no evidence of transmission of COVID-19 through breast milk. The infection might, however, spread through airborne transmission from a COVID-19 positive mother to her infant if no precautions are followed during breast feeding.

It is known that maternal infections, especially of viral origin, during pregnancy can have deleterious effects on the developing fetus.[13] The TORCH group of infections viz; Toxoplasma gondii, other agents (syphilis, varicella zoster, parvovirus B19), rubella, cytomegalovirus and herpes simplex virus, though having mild maternal manifestations, have serious fetal consequences including birth defects. Treatment of maternal infections usually do not improve fetal outcomes, thereby suggesting increased focus on prevention of these infections during pregnancy.[14 15]

Several researchers have studied the implications of COVID-19 infection for pregnant women and their infants. Corona virus disease in pregnancy has been shown to be associated with adverse pregnancy and neonatal outcomes. COVID-19 infections as well as severe COVID-19 infections during pregnancy were associated with increased risk of pre-eclampsia, preterm birth and intrapartum fetal distress.[16–23] A greater odds of fetal deaths, birth by emergency caesarean delivery and prolonged hospital stay after delivery were also reported in a study on a large cohort of pregnant women with SARS-CoV-2 infection.[19] Association between maternal COVID-19 and low birthweight of infants has also been reported.[24 25] In terms of adverse neonatal outcomes, babies born to mothers with SARS-CoV-2 infection were seen to be at greater risk of neonatal intensive care unit admissions.[19 21 25]

A systematic review[26] suggests that global maternal and fetal outcomes have worsened during the COVID-19 pandemic, with an increase in maternal deaths, stillbirth, ruptured ectopic pregnancies and maternal depression. The review indicates that the impact seems to be higher in low-income and middle-income communities, though the numbers of studies from LMICs were limited. There is a need to generate more evidence for better understanding especially from countries where the background rates of infant and child mortality are high.

Even though several studies have explored the risk of maternal SARS-CoV-2 infection on adverse pregnancy and neonatal outcomes, there is paucity of information regarding long term sequelae for infants and children born to mothers who were affected with COVID-19 during pregnancy. Maternal infections during pregnancy not only lead to poor neonatal outcomes but also increases risk of autism spectrum disorders and cerebral palsy in the child.[27 28] Viral infections other than the TORCH complex have also shown effect on childhood development.[29] Similarly, the possibility of an association between in-utero exposure to SARS-CoV-2 and growth and developmental delay in the child cannot be ruled out. Studies have recommended further research in this area, especially to explore the effect on growth and development of children born to COVID-19 positive mothers. Therefore, the need arises to observe the infants of COVID-19 infected pregnant mothers for their growth and development.

The aim of our study is to explore the effect of SARS-CoV-2 infection on pregnancy outcomes and growth and development of infants born to COVID-19 positive mothers. Our objectives are:

1. To find out the association between in-utero exposure to SARS-CoV-2 infection and pregnancy outcomes (primary objective),
2. To assess the effect of maternal COVID-19 infection during pregnancy on neonatal outcomes.
3. To explore the effect of maternal COVID-19 infection during pregnancy and growth and development of infants.

METHODS AND ANALYSIS

Study design

The study will be of combined retrospective and prospective (ambispective) cohort design with comparison group (1:1).

Half the total number of women will be recruited retrospectively from available hospital records and the other half will be recruited prospectively from the hospital

wards. The infants of both exposure and comparison cohorts of women will be followed up till they reach 1 year of age.

Study setting

It will be a multicentric study conducted at six Government Medical Colleges, one from each State representing all six regions of India, as listed below: North—Himachal Pradesh, Central—Madhya Pradesh, South—Telangana, West—Rajasthan, East—Odisha, North East—Tripura.

Study duration

The recruitment of study subjects is scheduled to begin after we obtain approval from institutional review boards from the study sites. The total study duration will be 24 months.

Study population

The exposure cohort of our study will be the infants born to pregnant women who tested positive for SARS-CoV-2 infection at any time during pregnancy. The comparison cohort will be the infants born to pregnant women who did not test positive for SARS-CoV-2 infection at any time during pregnancy. Study subjects will comprise pregnant women who have delivered/will deliver at the study sites.

Pregnant women with a documented positive report for SARS-CoV-2 Molecular based test (RT-PCR/ CBNAAT/ TruNAT) or Rapid Antigen Test at any time during pregnancy will be eligible to be recruited in the exposure cohort whereas pregnant women with a documented negative report for SARS-CoV-2 Molecular based test (RT-PCR/ CBNAAT/ TruNAT) or Rapid Antigen Test during pregnancy. The Point of Care Rapid Antigen test kits available for use in India have sensitivity of at least 50% and specificity of at least 95%, as mandated by the Indian Council of Medical Research.[30]

Among other criteria of inclusion would be pregnant women who give consent for follow-up for a 1-year period. For the retrospective cohort group, those women whose date of delivery was on or after 9 months prior to the start of recruitment will be included in the study. This would ensure that the infant is available for follow-up at least once before the age of 1 year.

Pregnant women who do not give informed consent to participate in the study will be excluded. Pregnant women who reported COVID-19 symptoms during pregnancy but were not tested or test results are not available for verification will also be excluded from the study to avoid classification bias.

Sample size

We have used odds of COVID-19 positive pregnant women delivering preterm babies for sample size estimation.

Assuming the relative risk of preterm birth babies among COVID-19 positive mothers as 1.47,[22] rate of preterm birth among pregnant women in India as 13%,[31] confidence level of 95%, power of 80% for a two-sided test, lost to follow-up of 10% and non-response rate of 10%, the sample size is 984 each for exposure and control cohort[32] which we have rounded off to 1000, thus yielding a total sample size of 2000.

The study will be carried out in six study sites. A total of 400 pregnant women will be recruited from each study site. Of these, 200 women will be recruited retrospectively (100 exposure and 100 comparison) and 200 women will be recruited prospectively (100 exposure and 100 comparison) in each study site.

Selection of study participants

The retrospective cohort of pregnant women will be selected from the hospital records of women who delivered at the facilities/study sites and the prospective cohort group will be recruited from the postnatal wards and labour rooms of the facilities/study sites. An equal number of exposed and unexposed pregnant women will be selected for the study in both retrospective and prospective cohorts (figure 1).

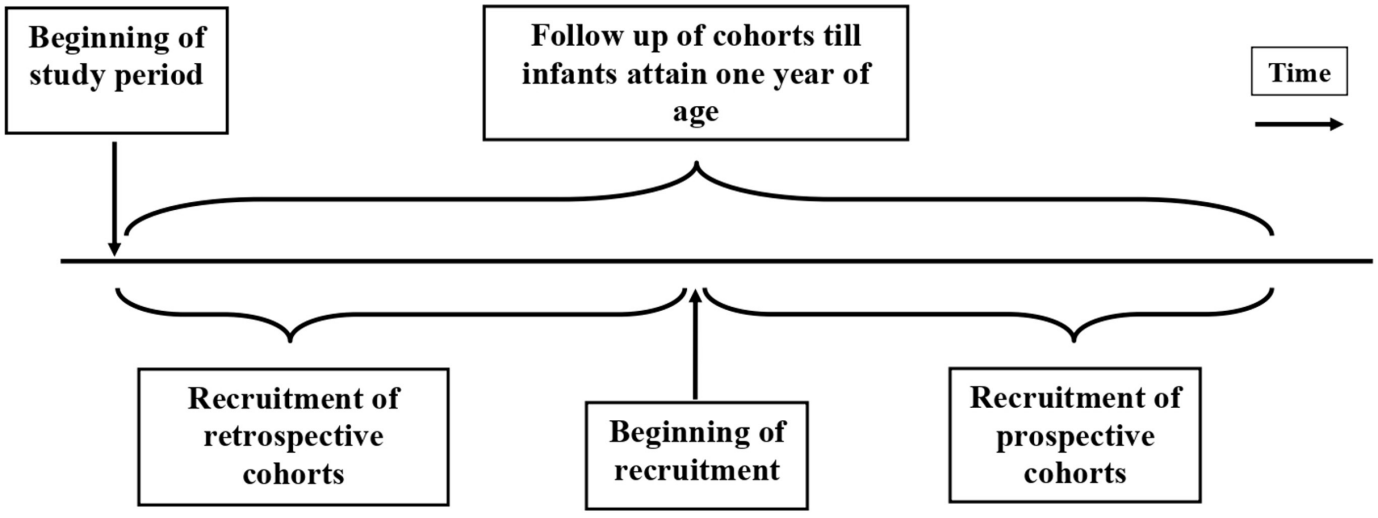

Figure 1 Diagrammatic representation of study design. (created by authors)

Sampling of retrospective cohorts

For recruitment of the retrospective exposure cohort, the following method will be adopted. In study sites where the number of COVID-19 positive pregnant women who have delivered in the facility till the time of recruitment is less than or equal to the required sample size, all of them will be recruited (after fulfilling selection criteria and giving consent). In the event of a study site having more women than the required sample size, consecutive sampling will be done, starting from the women who delivered most recently, till the desired sample size is reached. This approach will be followed to minimise recall bias.

Time-matched selection of retrospective comparison cohort will be done according to the following method. For each COVID-19 positive woman selected for the study, a sampling frame of all the COVID-19 negative pregnant women who delivered on the same date will be made and one will be selected by simple random sampling method. In case more than one COVID-19 positive women who have delivered on a particular date have been included in the study, an equal number of COVID-19 negative women will be selected randomly from the sampling frame for that particular date.

Sampling of prospective cohorts

Consecutive sampling of all COVID-19 positive pregnant women will be done from the beginning of the recruitment period till the desired sample size is reached, to obtain the prospective exposure cohort.

A similar time-matched method will be followed for selection of the prospective comparison cohort. For each COVID-19 positive woman selected for the study, a sampling frame of all the COVID-19 negative pregnant women who delivered on the previous date will be made and one will be selected by simple random sampling method. In case more than one COVID-19 positive women who have delivered on a particular date has been included in the study, an equal number of COVID-19 negative women will be selected randomly from the sampling frame for the previous date.

Study variables

Exposure variable

The exposure variable in our study is maternal COVID-19 infection during pregnancy. This will be recorded from documented SARS-CoV-2 Molecular based test (RT-PCR/ CBNAAT/ TruNAT) or rapid antigen test reports from either the women or the hospital where they delivered. For women who took a COVID-19 test during pregnancy and have a documented test report, COVID-19 positive/ negative status during pregnancy will be recorded as a categorical variable.

Cofactors

We will record details of co-factors (as categorical variables) which may potentially affect the study outcome. These will either be ascertained from interviews of the women and/or from records wherever applicable.

- Socioeconomic status and education of mother.
- COVID-19 exposure during pregnancy: History of household contact and/or high-risk contact[33] with COVID-19 confirmed and/or suspected case anytime during pregnancy, severity of COVID-19 infection.
- Maternal vaccination against COVID-19 before/ during pregnancy.
- Pregnancy-related factors: These would be ascertained either from case records (presence of anaemia during pregnancy, gestational diabetes mellitus, hypertension in pregnancy, preterm labour, prolonged labour) or from history (history of infection/symptoms of bacterial and viral infection during pregnancy, intake of medications for any illness during pregnancy).
- Nutritional factors: breast feeding and infant feeding practices.
- Socioenvironmental factors: Hand washing practices, source of drinking water, waste disposal and sanitation practices, personal hygiene and food hygiene.

Outcome variables

Our primary outcome variables are pregnancy outcome (live birth/ stillbirth; preterm/ term babies), ascertained from case records.

The secondary outcome variables in our study are related to neonatal outcomes (low or normal birth weight; birth injury) and growth and development of the infants up to 1 year of age. Assessment of growth will be done by measuring the infant's weight-for-age, length-for-age, head circumference-for-age and chest circumference at birth and each follow-up visit. These will be recorded as continuous variables. Digital infant weighing scale with an accuracy of 0.01 kg, infantometer with an accuracy of 0.01 cm and non-stretchable measuring tape with an accuracy of 0.01 cm will be used for anthropometric measurements.

Assessment of development will be done by recording the age of attainment of 20 selected milestones covering motor, language, cognitive and social development up to 1 year of age. A pictorial checklist depicting the selected developmental milestones will be given to all the women in the prospective cohort group and they will be asked to note down the date on which each milestone was achieved. For the retrospective cohort group, attainment of age-appropriate milestones at the follow-up visits will be recorded and any delay will be noted.

The infants will be examined for any congenital anomaly at birth by a paediatrician, and any history of illness, hospitalisation and treatment taken will be enquired for at every follow-up. The infant's primary immunisation history will also be noted from the MCP card at the last visit.

Method of data collection

For retrospective cohort

The purpose of the study will be explained to the women telephonically and their verbal consent will be obtained. Details regarding pregnancy and birth outcome will

be obtained from hospital records. Details regarding COVID-19 exposure during pregnancy will be obtained telephonically.

Due to ethical reasons associated with follow-up of infants during the pandemic, mothers will be encouraged to bring their infants to the hospital for routine follow-up such as immunisation.

These visits will be used for examination of the infant (anthropometry and attainment of age-appropriate developmental milestones) as well as collecting history regarding immunisation, feeding practices, illness of the infant and mother, and socioenvironmental details after taking consent.

For any woman who is willing to come for an additional follow-up at 6 months postdelivery, the above-mentioned history and examination will be conducted at that visit as well.

For prospective cohort

The purpose of the study will be explained to the women and written informed consent will be obtained. Details regarding pregnancy and birth outcome will be obtained from hospital records and details regarding COVID-19 exposure during pregnancy will be recorded by interview. The women will be given a checklist (pictorial) containing the developmental milestones at the time of recruitment and asked to record the date/approximate time when the infant achieves each milestone for the first time. In case the woman is illiterate, she will be asked to take the help of any literate family member/relative/neighbour to record the date.

The women will be encouraged to bring their infants to the hospital for follow-up at 14 weeks, 6 months and 9–12 months of age (visits for routine immunisation will be used), when examination of the infant (anthropometry and attainment of age-appropriate developmental milestones) will be done and history regarding immunisation, feeding practices, illness of the infant and mother, and socioenvironmental details will be collected.

For both cohorts

For all study participants, clinical examination of the infants and mothers will also be done at each follow-up by a paediatrician/physician. Any history of illness in the infant will be referred to the medical facility if required. Immunisation details of the infants will be noted from the MCP card. Any infant with high clinical suspicion of COVID-19 where a test is mandated by the treating paediatrician/physician, will undergo a COVID-19 test at the discretion of the physician.

If any woman does not report on the day of follow-up, efforts will be made to establish telephonic contact. In rarest of situations, home visit will be conducted for contacting the study subject. If the woman is not reachable even after three attempts, she will be considered as a drop-out.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data management

Structured questionnaires will be developed keeping the study objectives and variables in mind. The closed ended questions will be coded beforehand. Data from all the sites will be collected on paper forms administered by the interviewer. Those will be collated electronically in preloaded formats with proper checks to minimise errors. Data from all the sites will be compiled at the principal study site and checked for accuracy.

The data will be transferred to SPSS V.21.0 for analysis. Data will be presented in mean (SD) and median (IQR) for continuous variables and percentages (proportions) for categorical variables. The exposure and comparison groups will be compared using χ^2 test/Mann-Whitney U test.

The two groups will be compared for the prevalence of every factor/co factor considered in the study. The relative risk will be calculated to explore the association of any factor with the primary and secondary outcomes separately. All the risk factors with $p<0.1$ on bivariate analysis will be subjected to multiple logistic regression analysis. A final multivariable model will be developed by including the risk factors that are found to be statistically significant between the two groups or those that are judged as clinically important.

A stratified analysis will be done to assess the association of exposure (COVID-19 status) with the outcomes after adjusting for the factors (explanatory variables). Sub group analysis will be done similarly for women who were tested positive in different trimesters.

For the factors that are found to be statistically significant; attributable risk (AR) and population ARs will be calculated.

The results will be reported for pregnancy outcomes, neonatal outcomes and growth and developmental outcomes of infants separately.

ETHICS AND DISSEMINATION

The study has been approved by the Institutional Review Board of International Institute of Health Management Research, New Delhi (IRB/2021-2022/006) and will be required to be approved at all participating study sites. A participant information sheet (in English and local vernacular language) will be developed explaining the purpose of the study. Written informed consent will be obtained from all subjects prior to their inclusion in the study, and video consent will be obtained in place of written consent wherever feasible. The name/signature of participants appearing in the consent form will not be linked to any identifier in the study tool. Only those subjects who meet the inclusion criteria and declare their willingness to participate in the study will be included.

Telephone number of participants obtained during the study will strictly be kept confidential and used for study and follow-up purposes only. Any illness in the infant as a result of maternal COVID-19 or its sequelae which occur during the course of the study will be referred for medical treatment. All data collected will be kept confidential and will be used for study purpose only. The data will be kept under safe custody of the PI and no one will have access to the data. Data will be preserved for a period of 5 years after completion of the study.

The recruitment of study subjects is scheduled to begin from September 2021 and the study is expected to be completed by August 2023. Follow-up of the retrospective cohort group including collection and analysis of data is expected to be completed by August 2022 and an interim report of findings from this study group will be planned to be released at the time. Results of the study will be reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies. We plan to publish our results in a peer-reviewed journal and present findings at academic conferences.

DISCUSSION

The study is expected to generate evidence on the effect of in-utero exposure of SARS-CoV-2 on the growth and development of the infant. Experiences from the past have shown us that maternal infections during pregnancy are associated with poor pregnancy outcomes and can also have deleterious effect on the developing fetus resulting in intrauterine growth retardation and congenital anomalies, and in some cases impaired growth and development in the child. COVID-19 is a novel disease caused by a novel virus of the coronavirus family which has already manifested as a range of symptoms in varying severity among all age groups. Several variants of SARS-CoV-2, the causative agent of the disease, have already emerged and circulated globally. COVID-19 affects pregnant women and has been reported to be associated with preterm births and increased neonatal intensive care unit admissions. This necessitates further investigation to find out whether intrauterine exposure to COVID-19 infection has any effect on postnatal growth and development of neonate and infant.

The study has several strengths—to the best of our knowledge, this is the first Indian study which aims to follow-up a cohort of infants to assess the effect of COVID-19 in the mother during pregnancy on their growth and development. The COVID-19 19 registry by National Neonatology Forum aims to document the perinatal events.[34] Studies report inconsistent results on perinatal transmission and this variation may be caused by difference in viral variant as well as vaccination status of the population. Our study will provide an insight to the clinical outcomes of COVID-19 positive pregnant mothers. However, perinatal viral transmission is beyond the scope of our study and further virological research is recommended to add to our findings. Our study is a multicentric study representing diverse population from six different geographical locations and sociodemographic profiles as well as involves a large sample size, both of which will increase the external validity of our results. We aim to follow up the infants for 1 year initially, and subject to results obtained and feasibility further extension of follow-up period will be considered. Our study is an ambispective cohort study where half the study subjects will be enrolled retrospectively, whose data will be available in a short span of time thus aiding rapid evidence synthesis. These findings will be strengthened by the data obtained from the prospective cohort group. Since we will conduct a cohort study with comparison group, we expect to get good estimates of our outcome variables. Moreover, we will be able to determine the relationship of multiple pregnancy outcomes with the exposure because of our cohort study design. We will collect detailed data from both exposure and comparison cohort of women on possible confounders which will be addressed during data analysis.

Our study may also face some possible limitations with respect to follow up of the study subjects. Only the women who are willing to report for follow-up along with their infants for a period of 1 year will be included in the study which may introduce selection bias. The women recruited for the study will be encouraged to report for follow-up to the study site, so as to facilitate detailed clinical examination of the infants by a paediatrician. Since the COVID-19 pandemic as well as government guidelines to control it might pose ethical issues for calling the infants more frequently for follow-up, we will use the visits for routine immunisation to collect follow-up data from the mothers and conduct examination of the infants. The COVID-19 incidence in India has been steadily declining since October 2021, we may be able to recruit lesser number of cases in our prospective study group. Since we will be collecting some of the data for our retrospective study group from available hospital records, some degree of unavoidable observer bias might be introduced in our retrospective data. Factors which are not limited to social, economic, environmental, nutritional and healthcare factors may confound the study results. The pandemic itself as well as the mental health of the mothers may have a significant impact on growth and development of the infants. Collection of information regarding these variables might not be operationally feasible as it will involve exploring in greater detail and will add considerably to the length of the questionnaire. Not collecting information related to these factors can result in introduction of non-differential misclassification bias in our study, and though this might reduce the effect size it is not likely to change the direction of association.

Our ambispective cohort study to assess the effect of maternal COVID-19 infection during pregnancy on pregnancy outcomes and growth and development of infants is expected to provide valuable data to aid in decision making for prevention and management of COVID-19 in

pregnancy and management of infants born to COVID-19 infected mothers.

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Competing interests None declared.

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