PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Banerjee, Rupsa; Neogi, Sutapa; Grover, Ashoo; GS, Preetha; Agrawal, Usha

VERSION 1 – REVIEW

REVIEWER	Rai, Daljeet Stanford University School of Medicine, Department of Family Medicine
REVIEW RETURNED	21-Jul-2021

GENERAL COMMENTS	Your proposed study is critical to further our understanding of SARS-CoV-2 impact on newborns and young children. Your large sample size is a strength as well. You may want to consider adding vaccination status of the enrolling pregnant patients.

REVIEWER	Song, Dongli Santa Clara Valley Health and Hospital System, Pediatrics, NICU
REVIEW RETURNED	01-Nov-2021

GENERAL COMMENTS	Comments 1. The aim of the study was not stated consistently in different parts of the manuscript. Please clearly define the primary and secondary outcomes of the study. In the abstract: “Our study aims to explore the effect of in-utero exposure to SARS-CoV-2 on growth and development of infants.” In the rationale for the study: “The aim of our study is to explore the effect of SARS-CoV-2 infection on pregnancy outcomes, growth and development of infants born to COVID-19 positive mothers.” In the Outcome variables: “Our primary outcome variables are pregnancy outcome (live birth/ stillbirth; preterm/ term babies), ascertained from case records.” Are these the primary study outcome? “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 one year of age.” Are these the secondary study outcomes?

	2. Perinatal transmission rate: “Given the fact that perinatal transmission is common among COVID positive mothers, it becomes necessary to explore its impact in infancy.” Page 4, line 54. The SARS-CoV-2 perinatal transmission rate is relatively low in the published studies conducted in other countries. Data from India (NATIONAL NEONATOLOGY FORUM (NNF) COVID-19 REGISTRY GROUP, Rsf 33, publication March, 20121) showed a much higher perinatal transmission (8%). These data reflect the transmission rate of the original viral variant in the mostly unvaccinated population. The transmission rate in the proposed perspective period is likely very different given the different viral variants in a vaccinated population. 3. Inclusion criteria: “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.” Please provide the sensitivity and specificity of the Antigen test. 4. Exclusion criteria need to be clearly specified. Other in-utero-exposure that are known to affect infant growth and development, such as congenital infection (TORCH), Drug exposure, and Congenital anomalies – identified by the prenatal US before maternal PCR positivity. 5. Data collection. Consider collecting maternal and infant information regarding: -maternal vaccination information -maternal COVID severity -maternal mental health -newborn PCR test in babies who are born to mothers with active infection <10-14 days, at least in the perspective study period -family social, economic status, and maternal education 6. Limitation: Please address other factors that can confound the study outcomes. These factors include but are not limited to social, economic, maternal mental health, infant health care issues. Thus, the pandemic may have a significant impact on infant growth and development mediated through “in-utero-exposure” to the maternal infection.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Daljeet Rai, Stanford University School of Medicine
Comments to the Author:
1. Your proposed study is critical to further our understanding of SARS-CoV-2 impact on newborns and young children. Your large sample size is a strength as well.
You may want to consider adding vaccination status of the enrolling pregnant patients.

Reply: We thank you for your comments and valuable inputs. We have added vaccination status of the pregnant women to our list of co-factors on which information will be collected.

Reviewer: 2
Dr. Dongli Song, Santa Clara Valley Health and Hospital System
Comments to the Author:
1. The aim of the study was not stated consistently in different parts of the manuscript. Please clearly define the primary and secondary outcomes of the study. In the abstract: “Our study aims to explore the effect of in-utero exposure to SARS-CoV-2 on growth and development of infants.” In the rationale for the study: “The aim of our study is to explore the effect of SARS-CoV-2 infection on pregnancy outcomes, growth and development of infants born to COVID-19 positive mothers.” In the Outcome variables: “Our primary outcome variables are pregnancy outcome (live birth/ stillbirth; preterm/ term babies), ascertained from case records.” Are these the primary study outcome? “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 one year of age.” Are these the secondary study outcomes?

Reply: Thank you for pointing this out. We have made the necessary changes as per your suggestion. The primary study outcome is pregnancy outcomes (we have now added this in the part where we have listed our objectives as well as the section on “Outcomes”) and the secondary study outcomes are neonatal outcomes and growth and development of the infant.

2. Perinatal transmission rate: “Given the fact that perinatal transmission is common among COVID positive mothers, it becomes necessary to explore its impact in infancy.” Page 4, line 54.
The SARS-CoV-2 perinatal transmission rate is relatively low in the published studies conducted in other countries. Data from India (NATIONAL NEONATOLOGY FORUM (NNF) COVID-19 REGISTRY GROUP, Rsf 33, publication March, 20121) showed a much higher perinatal transmission (8%). These data reflect the transmission rate of the original viral variant in the mostly unvaccinated population. The transmission rate in the proposed perspective period is likely very different given the different viral variants in a vaccinated population.

Reply: We thank you for your valuable input. We have reframed this point and included it in the main text in “Discussion”. 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.

3. Inclusion criteria: “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.” Please provide the sensitivity and specificity of the Antigen test.

Reply: We have provided the values for sensitivity and specificity range of Rapid Antigen Test Kits in use in India as recommended by our national level research organization and apex body for COVID-19 research, Indian Council of Medical Research.

4. Exclusion criteria need to be clearly specified. Other in-utero-exposure that are known to affect infant growth and development, such as congenital infection (TORCH), Drug exposure, and Congenital anomalies – identified by the prenatal US before maternal PCR positivity.

Reply: Thank you for your suggestion. In India it is not a routine practice to conduct prenatal ultrasonography for the purpose of ruling out congenital anomalies and therefore it may be difficult to obtain this from all women in the retrospective cohort. However, we will try to collect this information as far as possible from the prospective cohort.

5. Data collection. Consider collecting maternal and infant information regarding:
 maternal vaccination information
 maternal COVID severity
 maternal mental health
 newborn PCR test in babies who are born to mothers with active infection <10-14 days, at least in the perspective study period
 family social, economic status, and maternal education

Reply: We agree that collecting this information is very important. We have included information regarding maternal vaccination, maternal COVID-19 severity and socio-economic and educational status of the mother as suggested in our data collection form. Collecting data on maternal mental health is also very important and we thank you for your suggestion. However, this might not be operationally feasible as it will involve exploring in greater detail and will add considerably to the length of the questionnaire. In the retrospective cohort, in addition, it might lead to recall bias and introduce variability to our study. We have cited this as a limitation to our study. Newborn PCR is not a common practice in India, especially in the government set up, and is not routinely practised in any of our study sites. In case newborn PCR was done for any of the neonates included in our study, we will gather the relevant information from those cases.

6. Limitation: Please address other factors that can confound the study outcomes. These factors include but are not limited to social, economic, maternal mental health, infant health care issues. Thus, the pandemic may have a significant impact on infant growth and development mediated through “in-utero-exposure” to the maternal infection.

Reply: We thank you for this very valuable suggestion. We have addressed this as a limitation at the end of “Discussion” section. 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.