

Letter-to-Editor

Methodological considerations regarding comparison group verification in maternal COVID-19 research

Sir,

I read with great interest article entitled ‘Association between maternal SARS-CoV-2 infection and clinical outcomes in infants: A multicentric retrospective cohort study in India’ published recently in the November 2025 issue of the Indian Journal of Medical Research.¹ Although the authors have thoroughly acknowledged limitations in the discussion section, one critical limitation warrants further elaboration; the identification and verification of the comparison group. This may have significant implications for interpreting the study's results.

While, the study appropriately identified the exposure group as confirmed through RT-PCR or RAT testing, the comparison group was defined as women ‘who did not contract COVID-19 during pregnancy’ based solely on the absence of documented positive tests creating an asymmetry in exposure ascertainment between exposure and comparison groups.¹ Thus the comparison group was classified on the basis of assumed negativity and absence of infection was unverified. In an infectious condition like Covid-19, where asymptomatic disease is a known entity, this asymmetry has the potential of introducing an exposure misclassification. This misclassification typically biases effect estimates toward the null, and therefore might obscure true associations between COVID-19 and adverse outcomes. This assumes significance in view of attempt of the authors to establish an association about a pandemic condition. It is important to mention here that studies from India conducted during the time of participant recruitment for this study have reported that a large proportion of the Indian population were asymptomatic for SARS-CoV-2 infection.²

Another important concern is the paradoxical enrichment of the exposed cases which happens when we exclude symptomatic women without test documentation in the exposure cohort as there is higher likelihood of inclusion of patients with more severe form of disease in the exposure group. This enrichment has the potential to exaggerate the association.

Lastly, while it is known that the challenge of retrospective exposure ascertainment during a pandemic is substantial, and there are practical constraints in recruitment of participants, but since the study contributes valuable data from the Indian context and opens up prospects for similar research, there are a few suggestions for researchers facing such challenges in future. One of the ways is to clearly define cases/comparison through use of operational definitions like ‘documented infection,’ ‘probable infection,’ ‘no documented infection’ or ‘confirmed uninfected’ rather than simply ‘negative’. Since the documentary evidence of infection was available with the included participants, second way of dealing with the challenge could be to analyse outcomes by trimester of infection, disease severity, or vaccination status, with biological plausibility corroborating the association between infection and outcome.

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References

1. Banerjee R, Khan PK, Goswami B, Mahapatra S, Kammilli N, Saini R, *et al.* Association between maternal SARS-CoV-2 infection and clinical outcomes in infants: A multicentric retrospective cohort study in India. *Indian J Med Res.* 2025;162:660–9.
2. Singh PP, Rai SK, Chaubey G, Serosurveillance consortium BHU. Estimation of real COVID-19 cases in India during the first wave. *IJID Reg.* 2023;6:803.

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