INTRODUCTION

Preterm birth (PTB) is a major cause of mortality and morbidity in the neonatal period, especially in developing countries. The etiology of preterm birth is multifactorial. Higher preterm births were reported in women with coronavirus disease 2019 (COVID-19) (14%–25%) mainly from high-income countries. There is limited information on PTB rates in women with COVID-19 in low- and middle-income countries. A recent meta-analysis reported the disproportionate impact of COVID-19 on pregnant women residing in low- and middle-income countries. Earlier, we reported higher rates of intensive care unit admission and maternal mortality among pregnant women with COVID-19 in low- and middle-income countries. A recent meta-analysis reported the disproportionate impact of COVID-19 on pregnant women residing in low- and middle-income countries.
Therefore, we aimed to analyze preterm deliveries and compare the rates of spontaneous preterm births (SPTBs) and iatrogenic preterm births (IPTBs) during the first and second waves of COVID-19. The SPTBs and IPTBs during the pandemic were compared with those in the pre-pandemic period.

2 | MATERIALS AND METHODS

We conducted a hospital-based, retrospective cohort study using data from the PregCovid registry database at BYL Nair Charitable Hospital (NH), Mumbai, India. The data of women with COVID-19 and PTB admitted to NH, Mumbai, India from April 4, 2020 to July 4, 2021.9 Details of the PregCovid registry protocol and data collection methods are described elsewhere.10 Data from 1630 pregnant and postpartum women with COVID-19 were analyzed for this study. PTB was defined as all births before 37 completed weeks of gestation.11 PTBs were further classified as spontaneous (due to spontaneous preterm labor, or preterm prelabor rupture of membranes [PPROM]), or iatrogenic (due to provider-initiated cesarean, or labor induction, for a maternal, or fetal indication).12 Gestational age was calculated based on last menstrual period and obstetric ultrasound. PTBs were subcategorized based on gestational age: extremely preterm (less than 28 weeks); very preterm (28–32 weeks); and moderate to late preterm (32–37 weeks).

The COVID-19 pandemic period was divided into two waves: a first wave from April 1, 2020 to January 31, 2021 and the second wave from February 1, 2021 to July 7, 2021. Diagnosis of COVID-19 was made as per the existing National testing guidelines during both waves. All pregnant women with confirmed COVID-19 who were near-term or postpartum, those who needed obstetric interventions, with high-risk pregnancies, or with moderate or severe COVID-19 were admitted to NH.9 The disease severity of COVID-19 was categorized as per the National Clinical Management Protocol for COVID-19.13

NH is a part of the PregCovid Registry network hospitals in India. Institutional Ethics Committee approval was obtained from the NH (ECARP/2020/63 dated May 27, 2020) and ICMR-NIRRH (D/ICEC/Sci-53/55/2020 dated June 4, 2020). The study is registered with the Clinical Trial Registry of India (CTRI/2020/05/025423). A waiver of consent was granted by the Institutional Ethics Committee because the data were collected from the medical case records of the pregnant women with COVID-19. The statistical analyses were performed using IBM SPSS Statistics Base version 26 (SPSS South Asia Pvt. Ltd., Bangalore, India). The data were presented as frequency (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. The Kolmogorov-Smirnov test was applied to evaluate the distribution of data. The χ² or Fisher Exact test were used to evaluate the differences in categorical outcomes and Student’s t test or Mann-Whitney U test were used for continuous data accepting a P value less than 0.05 as significant.
| TABLE 2 Characteristics of women with spontaneous preterm births with SARS-CoV-2 infection in Indiaa |
|---------------------------------------------------------|
| **Prepandemic period (October 1, 2019 to March 31, 2020)** (n = 197) | **COVID-19 Pandemic period (April 1, 2020 to July 7, 2021)** (n = 108) | **P valueb** | **Pandemic** | **First wave (April 1, 2020 to January 31, 2021)** (n = 67) | **Second wave (February 1, 2021 to July 7, 2021)** (n = 41) | **P valueb** |
| Age, years | 25.0 (22.0–30.0) | 29.0 (25.0–32.0) | <0.001 | 30.0 (25.5–32.0) | 28.0 (24.0–30.0) | 0.04 |
| Sub-categorization of PTBs as per gestational agec | | | | | | |
| <28 weeks | 7 (3.6) | 5 (4.6) | 0.76 | 3 (4.5) | 2 (4.9) | 0.92 |
| 28–32 weeks | 32 (16.2) | 11 (10.2) | 0.14 | 4 (6.0) | 7 (17.1) | 0.06 |
| >32 weeks | 158 (80.2) | 92 (85.2) | 0.27 | 60 (89.6) | 32 (78.1) | 0.10 |
| Mode of delivery | | | | | | |
| Vaginal birth | 136 (69.0) | 69 (63.9) | 0.359 | 40 (59.7) | 29 (70.7) | 0.247 |
| Cesarean section | 61 (31.0) | 39 (36.1) | | 27 (40.3) | 12 (29.3) | |
| Clinical and pregnancy characteristics | | | | | | |
| Primigravida | 68 (34.5) | 35 (32.4) | 0.709 | 19 (28.4) | 16 (39.0) | 0.250 |
| Multigravida | 129 (65.5) | 73 (67.6) | | 48 (71.6) | 25 (61.0) | |
| Previous cesarean section | 33 (16.8) | 26 (24.1) | 0.122 | 20 (29.9) | 6 (14.6) | 0.104 |
| ART | NA | 8 (7.4) | | 6 (9.0) | 2 (4.9) | 0.707 |
| Previous stillbirth | NA | 6 (5.6) | | 2 (3.0) | 4 (9.8) | 0.198 |
| Previous abortion | 41 (20.8) | 34 (31.5) | 0.039 | 25 (37.3) | 9 (22.0) | 0.135 |
| PPROM | 53 (26.9) | 13 (12.0) | 0.003 | 9 (13.4) | 4 (9.8) | 0.762 |
| Multiple pregnancy | 13 (6.6) | 14 (13.0) | 0.061 | 7 (10.4) | 7 (17.1) | 0.381 |
| Blood transfusion | 17 (8.6) | 19 (17.6) | 0.020 | 10 (14.9) | 9 (22.0) | 0.436 |
| Pre-eclampsia | 10 (5.1) | 15 (13.9) | 0.015 | 7 (10.4) | 8 (19.5) | 0.252 |
| GDM | 12 (6.1) | 6 (5.6) | 1.000 | 4 (6.0) | 2 (4.9) | 1.000 |
| Comorbidities | | | | | | |
| Anemia (haemoglobin <11 g%) | 84 (42.6) | 63 (58.3) | 0.009 | 38 (56.7) | 25 (61.0) | 0.663 |
| Chronic hypertension | 2 (1.0) | 3 (2.8) | 0.350 | 2 (3.0) | 1 (2.4) | 1.000 |
| Heart disease | 5 (2.5) | 4 (3.7) | 0.725 | 3 (4.5) | 1 (2.4) | 1.000 |
| Thrombocytopenia (<125K/μL) | 4 (2.0) | 7 (6.5) | 0.057 | 3 (4.5) | 4 (9.8) | 0.423 |
| Deranged liver enzymes | 7 (3.6) | 9 (8.3) | 0.104 | 6 (9.0) | 3 (7.3) | 1.000 |
| Maternal mortality | 2 (1.0)d | 3 (2.8) | 0.350 | 1 (1.5)e | 2 (4.9)f | 0.556 |

Abbreviations: ARDS, acute respiratory distress syndrome; ART, assisted reproductive technologies; COVID-19, coronavirus disease 2019; GDM, gestational diabetes mellitus; NA, not available; PPROM, preterm prelabor rupture of membrane; PTB, preterm birth; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a Data are presented as median (interquartile range) or as number (percentage).

b The χ² or Fisher exact test was applied at the significance level of P < 0.05. The comparison of age between groups was performed using the Student’s t test or Mann-Whitney U test at the significance level of P < 0.05.

c PTBs are sub-categorized based on gestational age: extremely preterm (less than 28 weeks); very preterm (28–32 weeks); moderate to late preterm (32–37 weeks).

d One mortality due to ARDS with acute renal failure and other due to aspiration pneumonitis with subacute intestinal obstruction.

e Respiratory failure in severe ARDS.

f One patient died because of acute fulminant viral hepatitis with hepatic encephalopathy with coagulopathy with ARDS and other died because of lower respiratory tract infection with ARDS with septic encephalopathy with active pulmonary tuberculosis.
3 | RESULTS

A total of 1136 women with COVID-19 delivered during the first (n = 807) and second (n = 329) waves of the COVID-19 pandemic. Significantly more women with COVID-19 were symptomatic during the second wave (166/487; 34.1%) compared with the first wave (162/1143; 14.2%) (P < 0.001). Out of 1136 deliveries, 128 (11.3%) were preterm. Preterm delivery rate was reported to be higher during the second wave (46/329; 14%) compared with the first wave (82/807; 10.2%) of the COVID-19 pandemic (P = 0.065). Very preterm (28–32 weeks of gestation) SPTB rates were reported to be higher during the second wave (17.1% versus 6.0%, P = 0.06). A higher rate of SPTBs was reported during the second wave than the first wave (12.5% versus 8.3%, P = 0.03) as well as the prepandemic period (12.5% versus 10.5%, P = 0.286). IPTBs were significantly lower in the pandemic period than in the prepandemic period (1.8% versus 3.3%, P = 0.012). There was no significant difference in IPTB during the first and second waves of COVID-19 (P = 0.694) (Table 1).

The median age of women with SPTB in the first wave was significantly higher than in the second wave (30 versus 28 years; P = 0.048). Interestingly, the median age of women with SPTB during the COVID-19 pandemic period was significantly higher compared with the prepandemic period (29 versus 25 years; P < 0.001). The majority of women with SPTB were multigravida during both the pandemic and pre-pandemic periods (P = 0.709). The proportion of women with a previous history of abortion was significantly higher in the study cohort during the pandemic period compared with the prepandemic period (31.5% versus 20.8%; P = 0.039). Women with anemia had a significantly higher SPTB rate in the pandemic period compared with the pre-pandemic period (58.3% versus 42.6%, P = 0.009). PPROM rate was significantly lower during the pandemic compared with the pre-pandemic period (12% versus 26.9%; P = 0.003). The proportion of women with pre-eclampsia was significantly higher among women with SPTB in the pandemic period compared with the pre-pandemic period (5.1% versus 13.9%; P = 0.015). (Table 2).

COVID-19 symptoms were present in 23.1% (25/108) of women with SPTB, with no difference in the presentation of COVID-19 symptoms during both waves (P = 0.811). Fever, dry cough, and dyspnea being the predominant symptoms, nine women (9/25, 36%) had moderate to severe disease and needed intensive care unit/high dependency unit admission, and six needed ventilator support. Out of the total three maternal deaths reported in the study cohort, one death was due to COVID-19 respiratory failure (see Table S1).

4 | DISCUSSION

The study demonstrates increased SPTB rates in the second wave compared with the first wave of the COVID-19 pandemic and the prepandemic period. In the present study, the SPTB rate during the first wave of the COVID-19 pandemic was 8.3%, higher than the SPTB rate reported during the first wave in the UK (4.9%) and Spain (6.1%). The majority of the SPTBs in the present study were due to preterm labor, as PPROM was reportedly low (12%) during the COVID-19 pandemic period. The etiology of SPTB during the COVID-19 pandemic is largely unclear and possibly multifactorial, hampering effective prevention.

The possible explanation for the increased SPTB rate during the second wave of COVID-19 could be the highly virulent δ variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; B.1.617.2) infection in pregnant women. It is speculated that proinflammatory cytokines compromise the balance of cytokines at the maternal-fetal interface inducing PTBs in women with COVID-19. Therefore, we can predict that SARS-CoV-2 delta (B.1.617.2) could be associated with more pronounced cytokine storm and inflammatory cascades, which could have triggered preterm labor in our cases. Second wave of COVID-19 pandemic has witnessed significantly more maternal complications, such as maternal mortality in India. However, the direct association of B.1.617.2 leading to SPTB can only be established with genome sequencing data.

In the present study, the SPTB rate during the first wave of the COVID-19 pandemic was 8.3%, higher than the SPTB rates reported during the first wave in the UK (4.9%) and Spain (6.1%). This could be because of the higher number of women who were anemic (58%) contributing to PTB in our cohort.

In contrast to other studies, from the UK2 and Spain,3 we did not find any increase in the occurrence of IPTB. Both studies reported a very high proportion of IPTB: 60% in the UK2 and 32% in Spain3 due to elective premature termination of pregnancy to improve the worsening maternal respiratory distress in severe COVID-19. The IPTB in our study cohort (1.8%) includes termination for obstetric and fetal indications only, and it is significantly less compared with studies from the UK (20.2%) and Spain (7.7%). The multidisciplinary team at our hospital decided on a case-to-case basis for emergency cesarean section or labor induction; either for facilitating maternal resuscitation or because of fetal health concerns. Therefore the PTB rate remained low in the present study throughout the COVID-19 pandemic and consistent with the global prepandemic PTB rate of 11%. A study from Kuwait also described management similar to that in the present study where all IPTB were as a result of term indication only.5 We believe that labor induction or operative delivery in patients who are already medically unfit might increase the risk of maternal mortality and morbidity, as seen in other maternal infections. Premature termination increases cesarean section rates and neonatal morbidity and mortality, which was also observed globally during the pandemic. PTB also increases the financial burden on healthcare systems, especially in low- and middle-income countries. The increased rates of IPTB reported in other populations during the early phase of the COVID-19 pandemic could be a result of the lack of evidence on the impact of SARS-CoV-2 on pregnancy, resulting in the non-availability of evidence-based guidelines for obstetric management of COVID-19. As the pandemic advances, and with the availability of scientific evidence,
elective deliveries for the sole indication of maternal COVID-19 disease are now discouraged. The universal screening that was implemented in the present study for detection of SARS CoV-2 infection in pregnant women, showed that 20% of the infected population was symptomatic. This is similar to a study from Spain (29%), which also incorporated universal testing and much lower in comparison with a study from the UK (81%).

We have observed a significant difference in age distribution of patients with SPTB in the pandemic period compared with the pre-pandemic period. Our results demonstrated that with advancing age, risk of SPTB increased among women with COVID-19. We speculate that older women are more susceptible for SPTB compared with younger women. The higher percentage of pre-eclampsia among the women with COVID-19 in the present study emphasizes the theory that the SARS-CoV-2 infection predisposes pregnant women to a greater risk of developing pre-eclampsia because of its pro-inflammatory state. Anemia in pregnancy is an important risk factor for premature birth. Our observations are consistent with this, showing higher incidence of anemia in the study cohort of SPTB during the pandemic period.

To the best of our knowledge, the present study is the first to describe the effects of both the first and second waves of the COVID-19 pandemic on SPTB and it generated contradictory evidence about the rates of IPTB among women with COVID-19. Limitations of the present study include that it is a single-center study, lacks testing for vaginal cytokines for detection of intra-amniotic inflammation, and lacks genome sequencing data on SARS-CoV-2 strains to definitively establish a direct relationship of SARS-CoV-2 infection with PTB.

Preterm birth not only causes an increased risk of long-term negative consequences such as adverse cognitive and motor development, behavioral and mental health problems, respiratory disorders, adding increased mortality and morbidity in early childhood but also leads to an increased financial burden on public health care. Considering the increased burden of PTBs during the ongoing COVID-19 pandemic, appropriate healthcare policies are to be developed for achieving the Sustainable Development Goals.

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CONFLICTS OF INTEREST
The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS
NM, and RG had full access to all data, and take responsibility for data integrity, and the accuracy of the analysis. RG and NM were responsible for the study concept, and design. RP, CG, PM, MP, SK, and BJ acquired the data. All authors interpreted the data. NM performed the statistical analysis. NM, SM, and RG provided administrative, technical, and material support. RP, NM, CG, and RG drafted the manuscript. NM, SM, and RG revised the manuscript.

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