Indian J Med Res 153, May & June 2021, pp 629-636
DOI: 10.4103/ijmr.ijmr_1938_21

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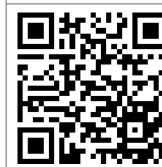

Clinical characteristics, outcomes, & mortality in pregnant women with COVID-19 in Maharashtra, India: Results from PregCovid registry

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***Background & objectives*: The PregCovid registry was established to document the clinical presentations, pregnancy outcomes and mortality of pregnant and post-partum women with COVID-19.**

***Methods*: The PregCovid registry prospectively collects information in near-real time on pregnant and post-partum women with a laboratory-confirmed diagnosis of SARS-CoV-2 from 19 medical colleges across the State of Maharashtra, India. Data of 4203 pregnant women collected during the first wave of the COVID-19 pandemic (March 2020-January 2021) was analyzed.**

***Results*: There were 3213 live births, 77 miscarriages and 834 undelivered pregnancies. The proportion of pregnancy/foetal loss including stillbirths was six per cent. Five hundred and thirty-four women (13%) were symptomatic, of which 382 (72%) had mild, 112 (21%) had moderate, and 40 (7.5%) had severe disease. The most common complication was preterm delivery (528, 16.3%) and hypertensive disorders in pregnancy (328, 10.1%). A total of 158 (3.8%) pregnant and post-partum women required intensive care, of which 152 (96%) were due to COVID-19 related complications. The overall case fatality rate (CFR) in**

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pregnant and post-partum women with COVID-19 was 0.8 per cent (34/4203). Higher CFR was observed in Pune (9/853, 1.1%), Marathwada (4/351, 1.1%) regions as compared to Vidarbha (9/1155, 0.8%), Mumbai Metropolitan (11/1684, 0.7%), and Khandesh (1/160, 0.6%) regions. Comorbidities of anaemia, tuberculosis and diabetes mellitus were associated with maternal deaths.

***Interpretation & conclusions*: The study demonstrates the adverse outcomes including severe COVID-19 disease, pregnancy loss and maternal death in women with COVID-19 in Maharashtra, India.**

Key words COVID-19 - maternal deaths - miscarriage - pregnancy complications - pre-term birth - severe disease

The World Health Organization declared a global pandemic of coronavirus disease (COVID-19) in March 2020[1], and since then, there are continued reports on the effects of SARS-CoV-2 infection among pregnant women. Previous respiratory virus outbreaks, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome, are associated with increased risk of stillbirth, pre-term birth and foetal growth restriction[2]. In the context of SARS-CoV-2, although initial reports had suggested no detrimental effects of the infection on pregnant women[3-5], large-scale studies and systematic reviews have shown that pregnant women with COVID-19 are at a higher risk for severe disease, abortions and maternal deaths[6-8]. A systematic review of available systematic reviews suggests that the risk of maternal death, stillbirth and neonatal death is around one per cent of pregnancies complicated with SARS-CoV-2 infection[9]. In addition, 2-6 per cent of infants born to mothers with COVID-19 are positive for SARS-CoV-2, and a proportion of these could be due to placental infection[10-12].

Our group has recently conducted a meta-analysis and observed that despite the symptomatic presentations being less common in pregnant women with COVID-19 from low- and middle-income countries (LMICs), compared to those from high-income countries (HICs), the overall risk of adverse pregnancy outcomes was is much higher in LMICs compared to HICs[8]. Thus, there is a need for country/region-specific data on the outcomes of SARS-CoV-2 infection in pregnancy.

Most of the reports on obstetric complications due to COVID-19 from India are limited to case report[13]/case series or single-centre data[14]. Considering the emerging threat of COVID-19 and the need for data on the health effects of SARS-CoV-2 infection in pregnant women in India, the Municipal Corporation of Greater Mumbai (MCGM), Medical Education and Drugs Department (MEDD), Government of Maharashtra and Indian Council of Medical Research (ICMR)-National Institute for Research in Reproductive Health (NIRRH) collaborated and established the PregCovid registry.

Material & Methods

PregCovid registry is an ongoing prospective cohort study of pregnant and post-partum women with a laboratory-confirmed diagnosis of SARS-CoV-2 infection as per the ICMR testing guidelines[15]. The study is registered with the Clinical Trials Registry, India (CTRI) (CTRI/2020/05/025423). The PregCovid registry protocol including the selection of study sites, development and validation of data collection instruments and data quality controls was published elsewhere[16]. The Institutional Ethics Committees of all the 19 participating medical colleges in Maharashtra, as well as ICMR-NIRRH was sought before its commencement. Here, we present clinical characteristics and pregnancy outcomes of women with COVID-19 enrolled during the first wave of the COVID-19 pandemic in Maharashtra are presented. Furthermore, additional information on maternal deaths associated with COVID-19 during pregnancy are also reported here.

Statistical analysis: The data are presented as frequencies, proportions and/or odds ratios (OR) with a 95 per cent confidence interval. Statistical comparison between two groups was made using the Pearson's Chi-square or Fisher's exact test and $P<0.05$ was considered statistically significant. For multiple comparisons to predict the risk associated with disease severity, binominal logistic regression was applied using SPSS Base V26 (SPSS South Asia Pvt Ltd., Bengaluru).

Results & Discussion

Between March 1, 2020 to January 31, 2021, data were available for 4276 pregnant and post-partum

women with laboratory-confirmed diagnosis of SARS-CoV-2 infection in the PregCovid registry portal. Among the 4276 women, data on 73 women were incomplete and hence excluded from the analysis, so in all the data of 4203 women with COVID-19 were analysed for the present study. The majority of pregnant and post-partum women with COVID-19 were recruited from the Mumbai metropolitan region (1684, 40%) followed by Vidarbha (1155, 27.5%), Pune (853, 20.3%), Marathwada (351, 8.4%) and Khandesh region (160, 3.8%). The majority of women (3441, 82%) were in the age group of 18-30 yr, 92 per cent of the women were in the third trimester and the median gestational age was 38 wk (interquartile range: 36-39).

Out of 4203 women, 3865 were registered during their ongoing pregnancy and 338 were enrolled during the post-partum period. A total of 4108 women conceived naturally; 95 required assisted reproductive technologies. A total of 3250 women were delivered; 77 women had miscarriages, 15 women had ectopic pregnancies; and 27 underwent medical termination of pregnancy (MTP). Eight hundred and thirty four women were undelivered. Vaginal delivery occurred in 1719 (53%) of women and 1531 (47%) were delivered by caesarean section (Table I). Live birth occurred in 3213 women with 3189 singletons, 60 twins and one set of triplets, resulting in a total of 3312 neonates born to mothers with COVID-19. The twinning rate in the COVID-19 positive mothers was 18.4 per 1000 births.

Majority (3669, 87.3%) of the pregnant and post-partum women with COVID-19 were asymptomatic and only 534 (12.7%) women were symptomatic. The COVID-19 disease severity was classified as per the Clinical Management Protocol for COVID-19 (in adults)[17] as mild (382, 71.5 %), moderate (112, 21%) and severe (40, 7.5%). Pregnant and post-partum women aged ≥30 yr had two times higher severity of COVID-19 disease as compared to women aged <30 yr. Among severe COVID-19 cases, the most common presenting symptoms were shortness of breath (34, 85%), dry cough (23, 57.5%) and fever (22, 55%). Of the 494 mild–moderate cases, fever (317, 64.2%) and dry cough (248, 50.2%) were the most common symptoms. Shortness of breath and diarrhoea were significantly higher in severe cases as compared to mild–moderate cases ($P<0.005$) (Table II).

Amongst the comorbidities, 179 (4.3%) had hypothyroidism, 43 (1%) had haemoglobinopathies [mainly sickle cell disease, 32 (74%)], 38 (0.9%) had chronic hypertension, 17 (0.4%) had asthma, 16 (0.4%) had diabetes mellitus and 16 (0.4%) had pre-existing cardiac disease (rheumatic heart disease, Supplementary Table). About 49 per cent (1928/3885) women had anaemia, of which 74 (3.8%) had severe anaemia. A higher proportion of anaemia was reported in severe COVID-19 cases (28, 70%) compared to mild–moderate cases (255, 51.6%, Table II). Comorbidity of tuberculosis was significantly higher in severe COVID-19 cases (5, 12.5%) compared to mild–moderate cases (Table II). Co-infections were reported in 82 (2%) of pregnant and post-partum women with COVID-19. Thirty nine (1%) women had tuberculosis and 12 (0.3%) women had human immunodeficiency virus (HIV) infection, followed by hepatitis B in 14 (0.3%), malaria 9 (0.2%) and dengue 4 (0.1%).

The pregnancy complications in the study cohort are described in Table I. The most common pregnancy complication was pre-term delivery in 528 (16.3%) with extreme preterm delivery (≤28 wk gestation) in 38 (7.2%). Hypertensive disorders in pregnancy were reported in 328 (10.1%) women [gestational hypertension (97, 3%), pre-eclampsia (191, 6%) and eclampsia (40, 1.2%)]. Hypertensive disorders in pregnancy were significantly higher (48%) in pregnant women with severe COVID-19 as compared to mild–moderate cases (18.3%, P=0.002) (Table II). A total of 158 (3.8%) pregnant and post-partum women with COVID-19 required admission to the high-dependency unit (HDU)/intensive care unit (ICU). Out of these, 152 (96%) HDU/ICU admissions were due to COVID-19 complications and six admissions were due to non-COVID-19 causes.

All the patients in this study received the standard treatment as per the National clinical management protocol for COVID-19[17]. Treatment included antibiotics, hydroxychloroquine, remdesivir, dexamethasone, methylprednisolone, prednisolone, low-molecular-weight heparin, intravenous immunoglobulin, *etc*. Two hundred and eighty-one women (7%) required blood transfusion, 166 (3.9%) required oxygen therapy, 11 (0.3%) needed high-flow nasal oxygen, 20 (0.5%) required non-invasive ventilation and 31 (0.7%) required invasive ventilation support.

There were a total of 34 deaths reported among pregnant and post-partum women with COVID-19. Out of 34 maternal deaths, 10 women died during the

Table I. Pregnancy outcomes, complications and maternal deaths among pregnant and post-partum women with COVID-19 in Maharashtra, India

Parameters	n (%)	95 per cent CI
Pregnancy outcomes (n=3369)		
Total delivered	3250	-
Vaginal deliveries	1719 (52.9)	51.2-54.6
Caesarean section	1531 (47.1)	45.4-48.8
Total birth	3312	-
Preterm birth	567 (17.1)	15.9-18.5
Stillbirth	99 (2.9)	2.4-3.6
Miscarriage	77 (1.8)	1.4-2.2
Ectopic pregnancy	15 (0.4)	0.3-0.8
Medical termination of pregnancy	27 (0.6)	0.4-0.3
Pregnancy complications (n=3250)		
Preterm delivery	528 (16.3)	15.0-17.6
PROM/PPROM	135 (4.2)	3.5-4.9
Hypertensive disorders of pregnancy	328 (10.1)	9.1-11.2
Gestational hypertension	97 (3.0)	2.4-3.6
Preeclampsia	191 (5.9)	5.1-6.7
Eclampsia	40 (1.2)	0.9-1.7
Gestational diabetes mellitus	42 (1.3)	0.9-1.7
Oligohydramnios	166 (5.1)	4.4-5.9
Polyhydramnios	15 (0.5)	0.3-0.8
Foetal growth restriction	41 (1.3)	0.9-1.7
Congenital malformations in foetus	11 (0.3)	0.2-0.6
Placenta praevia	23 (0.7)	0.5-1.1
Placental abruption	14 (0.4)	0.2-0.7
APH	16 (0.5)	0.3-0.8
PPH	27 (0.8)	0.6-1.2
Cholestasis of pregnancy	3 (0.1)	0.0-0.3
Uterine rupture	3 (0.1)	0.0-0.3
Case fatality rate	34/4203 (0.8)	0.6-1.1

PROM, premature rupture of membranes; PPROM, preterm PROM; PPH, postpartum haemorrhage; APH, antepartum haemorrhage; CI, confidence interval

post-partum period. Twenty-five women (73%) were ≤30 yr of age while the others were in the age range of 30-45 yr. Women with comorbidities of anaemia, tuberculosis and diabetes mellitus had a higher risk of death ($P<0.05$) (Supplementary Table). Respiratory failure (22, 64.7%), multi-organ failure (7, 20.6%), acute kidney injury (3, 8.8%) and heart failure (5, 14.7%) were commonly associated with maternal deaths. The overall case fatality rate (CFR) in pregnant women and post-partum women with COVID-19 was 0.8 per cent (34/4203). Higher CFR was observed in Pune (9/853, 1.1%) and Marathwada (4/351, 1.1%) regions as compared to Vidarbha (9/1155, 0.8%), Mumbai metropolitan (11/1684, 0.7%) and Khandesh (1/160, 0.6%).

This is the first large-scale report of systematically collected, multicentre data on the clinical presentation, pregnancy outcomes and maternal deaths amongst women with COVID-19 in Maharashtra, India. The proportion of symptomatic COVID-19 women in our study was 12.7 per cent, a number consistent with that reported earlier from the same cohort[18]. We observed

Table II. Risk factors associated with severity of coronavirus disease-19 in pregnant and post-partum women

Variables	Severe (n=40), n (%)	Mild - moderate (n=494), n (%)	OR (95% CI)
Age (n=528)$			
<30	21 (52.5)	344 (70.5)	Reference
≥30	19 (47.5)	144 (29.5)	2.2 (1.1-4.1)*
Pregnancy complications versus none			
Hypertensive disorders of pregnancy†	11 (47.8)	51 (18.3)	3.3 (1.5-7.0)**
Symptom *vs*. no symptom			Adjusted OR 95 per cent CI
Fever	22 (55)	317 (64.2)	0.95 (0.44-2.0)
Dry cough	23 (57.5)	248 (50.2)	1.4 (0.6-3.2)
Shortness of breath	34 (85.0)	76 (15.4)	49.1 (15.7-154.1)#
Running nose	2 (5.0)	56 (11.3)	0.85 (0.15-4.8)
Throat pain	2 (5.0)	44 (8.9)	1.5 (0.24-9.2)
Cough with sputum	5 (12.5)	34 (6.9)	2.0 (0.6-6.8)
Fatigue	4 (10.0)	27 (5.5)	1.4 (0.3-6.0)
Nausea, vomiting	3 (7.5)	24 (4.9)	1.4 (0.3-6.4)
Myalgia	5 (12.5)	19 (3.8)	4.0 (0.9-16.4)
Diarrhoea	2 (5.0)	12 (2.4)	15.7 (2.5-100)#
Comorbidities versus no comorbidities			
Diabetes mellitus	1 (2.5)	4 (0.8)	2.1 (0.1-36.4)
Chronic hypertension	2 (5.0)	10 (2.0)	3.8 (0.5-29.0)
Tuberculosis	5 (12.5)	7 (1.4)	18.4 (4.3-80.0)##
Hypothyroidism	4 (10.0)	29 (5.9)	3.1 (0.8-12.0)
Sickle cell disease	1 (2.5)	5 (1.0)	4.8 (0.4-54.0)
Anaemia	28 (70.0)	255 (51.6)	2.8 (1.2-6.3)
Multiple comorbidities	8 (20.0)	47 (9.5)	0.43 (0.1-1.7)

$Age was not available for six mild-moderate COVID-19 women. †Includes gestational hypertension, pre-eclampsia and eclampsia. *P* *<0.05, **<0.01. Bonferroni correction was applied for multiple comparisons *P* #<0.005 (0.05/10), ##<0.007 (0.05/7). OR, odds ratio

that nearly 30 per cent of the symptomatic cases had moderate to a severe disease requiring ICU/HDU admission. What could contribute to such high regional differences in ICU/HDU admissions need to be determined. Nonetheless, irrespective of the region, almost 96 per cent of the ICU/HDU admissions were due to COVID-19 and only 4 per cent were due to non-COVID-19 causes. Thus, our analysis suggests that SARS-CoV-2 may infect a higher proportion of pregnant women, and when symptomatic, a large proportion can develop moderate-to-severe diseases. Therefore, pregnant women with COVID-19 need immediate medical attention from the healthcare system in India.

Similar to previous reports[19,20], the presenting symptoms in pregnant women with SARS-CoV-2 were fever and those with upper respiratory tract (dry cough and shortness of breath). The other symptoms were related to the gastrointestinal tract (diarrhoea) which were observed in less than five per cent of cases. Anaemia was observed in nearly 50 per cent of women with SARS-CoV-2 infection which is almost similar to the reports of the National Family Health Survey (NFHS-5) 2019-20 for Maharashtra[21]. Thus, anaemia did not pose an increased risk of COVID-19 among pregnant women in the present study. Similarly, hypothyroidism also emerged as one of the comorbidities which is also prevalent (~7%) amongst pregnant women in Maharashtra[22]. Albeit low in numbers, a proportion of women had co-infections including those of dengue, malaria, hepatitis, HIV and tuberculosis. Our group has earlier shown that women with co-infection are at a higher risk of adverse pregnancy outcomes due to COVID-19[23,24]. Thus, co-infections could be a greater threat to pregnant women with COVID-19 in the Indian context.

A recent systematic review has indicated that comorbidities such as obesity (OR 2.48), diabetes (OR 5.7) and asthma (OR 2.02) are significantly associated with maternal mortality[6]. In the present study, comorbidities such as anaemia, tuberculosis and diabetes mellitus were associated with an increased risk of maternal death in pregnant and post-partum women with COVID-19. The finding of tuberculosis as a risk factor is important as India has one of the highest burden of tuberculosis in the general population[25] as well as in pregnant women[26]. As suggested previously[23], this study further reiterates that the healthcare services for the treatment of tuberculosis and COVID-19 must be integrated and pregnant women with respiratory symptoms should be tested for both COVID-19 and tuberculosis.

The pre-term birth in the present study group (16.3%) is comparable to those reported by other countries[27,28]. However, in the absence of detailed data of pre-term birth from pregnant women without COVID-19, it is difficult to comment if COVID-19 is a risk factor for pre-term birth. Prospective, large-scale, case–control studies are required to further assess the risk of pre-term births and PROM (premature rupture of membranes) in women with COVID-19. Pregnancy loss is a major health concern for obstetricians and whether COVID-19 is a contributing risk factor is an important aspect to be considered. Almost 6 per cent of pregnancy losses (miscarriage, ectopic pregnancy and stillbirths) were reported in our registry cohort. As per the NFHS-4 data, in the age range of 20-30 yr, the rate of stillbirths was >1 per cent in the State of Maharashtra[29]. Thus, case–control studies are required to determine the relative risk of pregnancy loss due to COVID-19. The CFR was found to be 0.8 per cent, which is comparatively higher than PAN-COVID (0.5%)[27] and AAP-SONPM (0.2%)[27] registries, but lower than the UK registry (1.2%)[20].

The presented PregCovid registry is, however, not without some limitations: (*i*) the data are collected from the hospital records until the time of discharge and further follow up data were not collected; (*ii*) data are limited to selected 19 study sites in Maharashtra and may not represent the entire State of Maharashtra, India; (*iii*) data on pregnant women without COVID-19 were not available for comparison; (*iv*) there is a possibility of missing out on some of the cases not reporting to the network hospitals of the PregCovid registry in Maharashtra.

PregCovid registry has allowed us to assimilate the characteristics of more than 4000 pregnant and post-partum women with COVID-19 and also reported rare complications such as neurological[30] and psychiatric complications[31]. To conclude, the present study demonstrates the adverse outcomes including severe COVID-19 disease, pregnancy loss and maternal death in women with COVID-19 in Maharashtra, India. With the availability of the vaccine, pregnant women may be counselled for vaccination to reduce the adverse impact of COVID-19 on maternal health.

***Acknowledgment*:** The authors sincerely acknowledge the support of Drs Balram Bhargava, Secretary, Department of Health Research and Director General, ICMR, New Delhi and Geetanjali Sachdeva, Director, ICMR-NIRRH. Mr Saurabh Vijay, Secretary, Drs Sanjay Mukherjee, former Secretary, T.P. Lahane, Director, and Prashant Howal, MEDD. Drs Padmaja Keskar, former Executive Health Officer, MCGM; Ramesh Bharmal, Dean, TNMC and BYL Nair Hospital, Mumbai; Mohan Joshi former Dean, TNMC and BYL Nair Hospital, Mumbai, are acknowledged for administrative support in implementing the PregCovid registry. Drs Vandana Bansal, Dipti Tandon, Anushree Patil, Sudha Rao, Drs Shakuntala Prabhu and Pooja Bandekar are sincerely acknowledged for their critical inputs in the development of case record form; Drs Garima Arora, Shyam Dalvi, Snehal Tinaikar, Arun Ambadkar, Naina Jawaharmalani, Amita Kakade, Sonali Dongarwar, Shailja Pandey, Tejal Borate, Ritesh K. Sondawale, Rajat Sharma, Chitikala Haritha, Vrushali Nandre, Basavaraj Honna, Pratiksha Padghane, Mayuri Dixit, Vaibhav Bajrang Patil, Sonali Nagargoje and Ms Divya Balgoniwar, Kalyani Jadhav, Samrudhi Kothe, Supriya Jawale, servshri Shrinivas Parpelli and Chetan Jadhav for technical support in data entry.

***Financial support & sponsorship*:** PregCovid registry is supported by an intramural grant of ICMR-NIRRH (ICMR-NIRRH/RA/1086/06/2021). The first and corresponding author RKG is an awardee of the DBT Wellcome India alliance clinical and public health intermediate fellowship (Grant No. IA/CPHI/18/1/503933).

***Conflicts of Interest*:** None.

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Supplementary Table. Comorbidities as a risk factor for maternal mortality in Maharashtra

Comorbidities	Death (n=34), n (%)	Recovered (n=4169), n (%)	OR (95% CI)
Anaemia	24/33 (72.7)	1904/3852 (49.4)	2.7 (1.3-6.0)**
Chronic hypertension	1 (2.9)	37 (0.9)	3.4 (0.5-21.4)
Cardiac disease (RHD)	1 (2.9)	15 (0.4)	8.4 (1.1-65.4)
Diabetes mellitus	2 (5.9)	14 (0.3)	18.6 (4.1-85.0)**
Tuberculosis	4 (11.8)	35 (0.8)	15.8 (5.3-47.1)***
Hypothyroidism	2 (5.9)	177 (4.2)	1.4 (0.3-5.9)
Sickle cell disease	1 (2.9)	31 (0.7)	4.0 (0.5-30.5)
Multiple comorbidities	8 (23.5)	195 (4.7)	6.3 (2.8-14.0)***

P **<0.01, ***<0.001. RHD, rheumatic heart disease