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CLINICAL ARTICLE

Obstetrics

Impact of SARS-CoV-2 on multiple gestation pregnancy

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Abstract

Objective: To assess clinical presentations, pregnancy complications, and maternal and neonatal outcomes among women with multiple gestation pregnancy (MGP) and confirmed SARS-CoV-2 (COVID-19) infection and to compare the data with a pre-pandemic period.

Methods: A retrospective study at a dedicated COVID-19 Hospital in Mumbai, India. Data were obtained from the PregCovid Registry of pregnant and postpartum women with PCR-confirmed SARS-CoV-2 infection from April to September, 2020. Data were also compared with a cohort of women with MGP attending the hospital pre-pandemic (n = 63).

Results: Data from 879 women (singleton pregnancy, n = 859; MGP, n = 20) with COVID-19 were assessed. The twinning rate was 34.2 per 1000 births. As compared with singleton pregnancies, a higher proportion of women with MGP and Covid-19 delivered preterm (P = 0.001). Spontaneous abortions were also higher in the MGP group than in the singleton group (P = 0.055). The incidence of pre-eclampsia/eclampsia was higher in the COVID-19 MGP group than in both the COVID-19 singleton (41.6% vs. 7.9%) and pre-pandemic MGP (50.0% vs. 12.7%) groups.

Conclusion: There was a higher risk of pre-eclampsia among women with MGP and COVID-19. Women with MGP and COVID-19 infection should receive special attention with a multidisciplinary approach to both maternal and neonatal care during the pandemic.

KEYWORDS
Acute respiratory distress syndrome, COVID-19, Multiple gestation pregnancy, SARS-CoV-2 infection

1 | INTRODUCTION

The incidence of multiple pregnancies varies in different populations and countries. Twinning rates in India are reported to be below 9 per 1000 births.[1] As of October 20, 2020 SARS-CoV-2 (COVID-19) had affected approximately 40 million individuals globally and caused more than 1 million deaths,[2] including many pregnant women with twin gestation.

Multiple gestational pregnancies (MGP) are associated with a high risk of both fetal and maternal complications and require

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special care. COVID-19 infection independently has adverse effects on pregnant women.[3,4] However, there is limited information on the impact of infection on MGP.

The primary aim of the present was therefore to assess clinical presentations, and maternal and neonatal outcomes among women with COVID-19 infection and assess the impact of COVID-19 on MGP as compared with singleton pregnancy. A secondary aim was to compare pregnancy complications, and maternal and neonatal outcomes of women with MGP in the pre-pandemic and pandemic period.

2 | MATERIALS AND METHODS

The present retrospective study analyzed data from pregnant women who were treated in a dedicated COVID-19 hospital,[5] BYL Nair Charitable Hospital, Mumbai, India, one of the participating centers of the PregCovid registry network,[6] from April 4 to September 10, 2020. The study was approved by the Ethics Committees of TNMC (no. ECARP/2020/63; May 27, 2020) and ICMR-NIRRH (IEC no. D/ICEC/Sci-53/55/2020; June 4, 2020). A waiver of consent was granted because the study data were obtained from medical case records.

Information was retrieved on clinical presentations, and maternal and neonatal outcomes for all women with MGP or singleton pregnancies and COVID-19 infection confirmed by RT-PCR. Delivery outcomes were also obtained for a pre-pandemic cohort of pregnant women attending the hospital between April 1, 2019, and March 31, 2020.

Statistical analyses were performed by using Prism (GraphPad). Categoric variables were recorded as number (percentage) and continuous variables were expressed as median (interquartile range). Pearson χ^2, Fisher exact, odds ratio and Mann–Whitney *U* tests were used to compare differences between the groups. A *P* value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Outcomes of singleton pregnancy and MGP among women with COVID-19

In total, data from 879 women (singleton pregnancy, n = 859; MGP, n = 20) with confirmed COVID-19 infection were included in the study. Fifteen (75.0%) women with COVID-19 and MGP were in their third trimester, and 5 (25.0%) had a gestation of less than 28 weeks. At the time of manuscript preparation, 12 women with MGP had delivered, and 8 had ongoing pregnancies. Of the 12 women, 11 women delivered twins and 1 delivered triplets. All neonates tested negative for COVID-19 in the nasopharyngeal swabs taken at birth.

The clinical presentations and laboratory parameters did not differ significantly between singleton pregnancy and MGP among women with COVID-19 infection. The proportion of symptomatic and asymptomatic pregnant women was similar in the two groups (*P* = 0.505) (Table 1). The women with MGP were significantly older than those with singleton pregnancies (*P* = 0.023) and reported to the hospital at an earlier gestation. A significantly higher proportion of MGP women with COVID-19 delivered preterm (66.7%) as compared with their singleton counterparts (8.6%) (*P* = 0.001). Anemia was found in high proportion of cases in both the singleton (40.5%) and MGP (45.0%) groups. The incidence of spontaneous abortion was higher in MGP than in singleton pregnancy (10.0% vs. 1.7%, *P* = 0.055) (Table 1). The two cases of spontaneous abortion in the MGP group occurred in the second trimester: one woman was referred for retained placenta and the other woman had undergone cervical encerclage at 16 weeks, but developed preterm premature rupture of membranes (PPROM) at 22 gestational weeks. Pre-eclampsia and eclampsia were higher in MGP as compared to singleton (41.6% vs. 7.9%).

3.2 | Comparison of MGP outcomes between the pandemic and pre-pandemic period

At the study hospital, the twinning rate was (34.2 per 1000 births) during the COVID-19 pandemic study period and 37.6 per 1000 deliveries in pre-pandemic period (Table 2). The women with MGP and COVID-19 were also older as compared with those without COVID-19 (*P* = 0.009). The proportion of preterm deliveries among women with MGP was similar in the pandemic and pre-pandemic groups (60.0% vs. 73.0%, *P* = 0.459). The incidence of pre-eclampsia and eclampsia was also higher in the COVID-19 group than in the pre-pandemic group (50.0% vs. 12.7%) (Table 2). Admission to the neonatal intensive care unit (NICU) occurred significantly more frequently in the pre-pandemic period than in pandemic period (67.5% vs. 38.1%, *P* = 0.014; OR, 3.4; 95% confidence interval [CI], 1.3–8.8).

3.3 | Management of the women with MGP and COVID-19

One woman with triplets had pre-eclampsia and another had moderate anemia with deranged liver enzymes (she received a transfusion of 3 units of packed red blood cells). Postpartum hemorrhage and eclampsia were observed in one woman with MGP. The hemorrhage was controlled by medical management and a transfusion of 2 units of packed red blood cells. None of these cases of pre-eclampsia needed specific management regarding COVID-19.

Two women with MGP (<28 gestational weeks) had type-1 respiratory failure with acute respiratory distress syndrome. Both women recovered after receiving 15 L of oxygen therapy via a non-rebreather mask. Glucocorticoids and anticoagulants were administered in both of these severe cases of COVID-19 in MGP. Antivirals were not used and mechanical ventilation was not needed in either case.

TABLE 1 Comparison of clinical presentations and outcomes among women with confirmed COVID-19 infection by type of gestation[a]

Characteristics	Singleton pregnancy (n = 859)[b]	MGP (n = 20)	*P* value
Maternal age, years	27 (24–30)	30 (26–34)	0.0224
GA at admission or delivery, weeks	38 (37–39)	34.5 (26–37)	<0.001
Comorbidity	360 (41.9)	10 (50.0)	0.498
Thyroid	58	0	NA
Anemia	348 (40.5)	9 (45.0)	0.819
Gravida	2 (1–3)	2 (1–2)	0.511
Parity	1 (0–1)	0 (0–1)	0.223
ART conception	17 (2.0)	11 (55.0)	<0.001
Total deliveries[c]	618	12	
Mode of delivery			
Vaginal	378 (61.2)[d]	5 (41.7)[e]	
Cesarean[f]	240 (38.8)	8 (66.7)[e]	
Delivery outcome			
Livebirth	608	25[g]	NA
Stillbirth[h]	10 (1.6)	0 (0)	NA
Spontaneous abortion	15 (1.7)	2 (10.0)	0.055
Preterm delivery[h]	53 (8.6)	8 (66.7)	<0.001
PROM/PPROM[h]	26 (4.2)	3 (25.0)	0.015
Preterm labor[h]	28 (4.5)	4 (33.3)	0.002
PPH[h]	7 (1.1)	1 (8.3)	0.143
Pregnancy complications			
GDM	18 (2.1)	0 (0)	
Gestational HT	25 (2.9)	0 (0)	
Pre-eclampsia[h]	46 (7.4)	4 (33.3)	
Eclampsia[h]	3 (0.5)	1 (8.3)	
Oligohydramnios	41 (4.7)	1 (5.0)	
IUGR	26 (3)	0 (0)	
Clinical presentation			
Symptomatic	117 (13.6)	4 (20.0)	0.505
Asymptomatic	742 (86.4)	16 (80.0)	
COVID-19 symptoms			
Fever	64 (7.5)	2 (10.0)	0.657
Cough	62 (7.2)	3 (15.0)	0.179
Dyspnea	36 (4.2)	2 (10.0)	0.213
Lab tests[i]			
WBC	9700 (8000–11 600)	9230 (8100–11 430)	0.864
Platelet	225 500 (185 300–286 000)	187 500 (153 800–232 300)	0.018
Treatment			
Antiviral	6 (0.7)	0 (0)	NA
Steroids	26 (3)	4 (20.0)	0.004
HCQ	12 (1.4)	0 (0)	NA
ICU admission	16 (1.9)	2 (10.0)	0.060
Maternal death	7 (0.8)	0 (0)	NA

Abbreviations: ART, assisted reproductive technology; GA, gestational age; GDM, gestational diabetes; HCQ, hydroxychloroquine; HT, hypertension; ICU, intensive care unit; IUGR, intrauterine growth restriction; MGP, multiple gestation pregnancy; NA, not applicable; PPH, postpartum hemorrhage; PPROM, preterm PROM; PROM, premature rupture of membrane; WBC, white blood cell.

[a]Values are given as median (interquartile range) or number (percentage).

[b]One woman had vanished twin at 12 weeks and delivered a singleton.

[c]Includes 27 postnatal admissions (25 singleton and 2 MGP).

[d]Nine women had instrumental delivery.

[e]One woman with MGP had vaginal delivery for first twin and cesarean delivery for second twin.

[f]Includes one triplet delivery.

[g]Includes 11 twin pregnancies (n = 22) and 1 triplet (n = 3) pregnancy.

[h]Sample size: n = 618 for singleton pregnancy and 12 for MGP.

[i]Data were available for 756 women (WBC) and 758 women (platelet count).

TABLE 2 Comparison of maternal and pregnancy characteristics and outcomes in MGP between women with confirmed COVID-19 and a pre-pandemic cohort[a]

Characteristics	Pre-pandemic period	Pandemic period	*P* value
Total deliveries	3289	603	
Total cesarean deliveries	1402 (43)	233 (38.6)	
Prenatal admission	6401	852[b]	
Twinning rate per 1000 births	37.6	34.2	
MGP cohort	63	10[c]	
Maternal age, years	27 (25–31.5)	31.5 (29.5–34.5)	0.009
Primigravida	14 (22.2)	5 (50.0)	0.114
IVF conception	Data not available	7 (70.0)	NA
Gestational hypertension	2 (3.2)	0	NA
Pre-eclampsia	7 (11.1)	4 (40.0)	0.091
Eclampsia	1 (1.6)	1 (10.0)	0.257
Gestational diabetes mellitus	1 (1.6)	0 (0)	NA
High-risk pregnancy	3 (4.6)	0 (0)	NA
Heart disease	1 (1.6)	0 (0)	
Hepatitis E	1 (1.6)	0 (0)	
Blood transfusion	8 (12.7)	2 (20.0)	0.619
Preterm birth	46 (73.0)	6 (60.0)	0.459
PPROM/PROM	6 (9.5)	3 (30.0)	0.101
Delivery			
Vaginal	28 (44.4)	4 (40.0)[d]	
Cesarean	35 (55.6)	7 (70.0)[d]	0.723
Delivery outcome			
Live birth[e]	117 (92.8)	21 (100)	
Stillbirth[e]	9 (7.2)	0 (0)	0.358
Postpartum complications			
Postpartum hemorrhage	2 (3.2)	1 (10.0)	0.362
PRES	1 (1.6)	0 (0)	NA
NICU admission[f]	79 (67.5)	8 (38.1)	0.014
Neonatal death	1 (1.6)	0 (0)	NA

Abbreviations: IVF, in vitro fertilization; MGP, multiple gestation pregnancy; NA, not applicable; NICU, neonate intensive care unit; PPROM, preterm PROM; PRES, posterior reversible encephalopathy syndrome; PROM, premature rupture of membrane.

[a]The pandemic period was April 4 to September 10, 2020; the pre-pandemic period was April 1, 2019, to March 31, 2020. Values are given as median (interquartile range) or number (percentage).

[b]Includes 27 postnatal admissions.

[c]Two postnatal admissions were not included in the analysis.

[d]First twin delivered vaginally and second delivered by cesarean.

[e]Sample size: *n* = 126 for pre-pandemic period and n = 21 for pandemic period.

[f]Among total live births. Sample size: n = 117 for pre-pandemic period and n = 21 for pandemic period.

4 | DISCUSSION

The present study reported a higher incidence of twinning (34%) as compared with other studies from north and south India.[7,8] This is due to the fact that the study hospital was the only dedicated COVID-19 hospital providing maternity care for pregnant women with COVID-19 in Mumbai, and thus received all referral cases from Mumbai city and the nearby regions. In addition, the majority of women with MGP in the present study conceived through assisted reproductive technology, resulting in a higher twinning rate.

Women with COVID-19 infection are at a higher risk of delivering preterm.[9] In the present study, the rate of preterm delivery was almost 8-fold higher for MGP than for singleton pregnancies. However, the incidence of preterm delivery among women with MGP and COVID-19 during the 5-month study period was marginally lower than that among uninfected women with MGP

during the 12 months preceding the pandemic (60% vs. 73%). The proportion of pre-eclampsia and PROM among women with MGP during the 5-month study period was significantly higher than that among women with MGP in the pre-pandemic period (P = 0.023 and P = 0.015, respectively). Although the risk of pre-eclampsia is known to be higher in twin pregnancies than in singleton pregnancies,[10] SARS-CoV-2 infection might also be a risk factor for pre-eclampsia.[11] Based on the present results, we propose that healthcare providers should be aware of the increased risk of pre-eclampsia and other complications due to COVID-19 infection. Women with MGP and COVID-19 infection should be monitored for signs and symptoms of these complications.

Although a risk of postpartum psychosis has been reported among women with COVID-19,[12] no such events were detected among the 20 women with MGP in the present study, suggesting that women with MGP may not be at an increased risk of postpartum psychosis. However, the sample size was too limited to draw any firm conclusions. Coinfection with malaria and dengue has been reported among pregnant women with COVID-19[13]; however, no coinfections were observed in the present cohort of women with MGP and COVID-19.

Neonatal outcomes, including good Apgar scores, were promising for all live births. All neonatal nasopharyngeal swab tests were negative for COVID-19 at birth. Of the 21 neonates born to 10 women with MGP, 8 (38%) were admitted to the neonatal intensive care unit for observation and none had any complications of prematurity. Notably, admission to this unit was significantly higher (68%) during the pre-pandemic period.

The study also observed that women with MGP and COVID-19 did not require any additional COVID-19-related management protocols as compared with women with singleton pregnancies. We believe that early case detection with the help of universal testing[14] is the key to good outcomes when treating COVID-19 infection in MGP. The preparedness of the administration to manage the pandemic helped to efficiently establish a dedicated COVID-19 hospital.[5] Thus, based on this experience, we recommend that a multidisciplinary team should be assembled to manage such cases of COVID-19 in MGP and management options should be selected on a case-by-case basis.

In conclusion, COVID-19 infection was found to be associated with increased risk of pre-eclampsia and PROM among women with MGP. Among the MGP cohort, two women with severe COVID-19 were infected in the second trimester and showed good outcomes. However, the study is limited by the sample size from a single center. Further studies are required to confirm the present observations. We recommend that women with MGP and COVID-19 infection should receive special attention and require a multidisciplinary team approach to both maternal and neonatal care during the COVID-19 pandemic.

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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 study concept and design. PJ, CG, DT, MP, and AB acquired the data. All authors interpreted the data. AB, CG, and NM performed statistical analysis. NM, SM, and RG provided administrative, technical and material support. NM, MA, CG, AB, and DM drafted the manuscript. NM, SM, RG, and DM revised the manuscript.

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