https://jrhm.org/

Journal of
Reproductive Healthcare
and Medicine

Indian Society for the Study of Reproduction & Fertility

Review Article

Impact of COVID-19 pandemic on maternal and neonatal outcomes: A narrative review and evidence from the PregCovid registry

Sarika Zala[1#], Hrishikesh Munshi[1#], Niraj N. Mahajan[2], Suchitra Surve[3], Rahul Gajbhiye[1]

[1]Clinical Research Laboratory, Indian Council of Medical Research-National Institute for Research in Reproductive and Child Health, [2]Department of Obstetrics and Gynecology, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital, [3]Department of Child Health Research, Indian Council of Medical Research-National Institute for Research in Reproductive and Child Health, Mumbai, Maharashtra, India.

[#]Equal contribution as first author.

***Corresponding author:**
Dr. Rahul K. Gajbhiye, MBBS, PhD, Scientist D and Head, DBT Wellcome India Alliance Clinical and Public Health Intermediate Fellow, Clinical Research Laboratory, ICMR-National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH), Mumbai, Maharashtra, India.

gajbhiyer@nirrch.res.in

Received : 21 July 2022
Accepted : 24 December 2022
Published : 23 January 2023

DOI
10.25259/JRHM_11_2022

Quick Response Code:

ABSTRACT

More than 533 million Coronavirus Disease 2019 (COVID-19) cases and associated 6 million fatalities were reported globally whereas 43 million cases and 0.5 million deaths in India were reported till June 2022. Maharashtra state alone reported about one-third of the total cases of COVID-19 in India in the early period of COVID-19 pandemic. The lack of epidemiological, demographic, and impact data of COVID-19 on pregnant women and newborns, advocated the need for recording and documenting population specific data for clinical management and policy decisions in India. The PregCovid registry was launched in April 2020 by the Indian Council of Medical Research-National Institute for Research in Reproductive and Child Health, Mumbai, in collaboration with the Medical Education and Drugs Department, Government of Maharashtra, and Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital to gain insights into clinical and socio-epidemiological characteristics of pregnant women with lab confirmed COVID-19 and assess its impact on maternal and neonatal outcomes. The registry has collected data of 8428 pregnant and postpartum women with COVID-19 from 19 participating centers across Maharashtra in a near real-time manner. The registry first reported that the delta variant (B.1.617.2) dominant second wave was more lethal (case fatality rate 5.7%) to pregnant and postpartum women than the alpha (0.7%) dominant wave of COVID-19 in India. There was also a higher incidence of moderate to severe cases, intensive care admissions and maternal complications including pre-eclampsia, low birth weight and preterm deliveries during the delta wave. The omicron dominant third wave of the COVID-19 pandemic exhibited a higher transmission rate compared to the previous two waves, causing a surge in cases but minimally impacting adverse outcomes. The registry further analyzed and reported the impact of COVID-19 on pregnant and postpartum women with comorbidities, coinfections, twin pregnancies, and neonatal outcomes, while providing crucial policy inputs to improve maternal and newborn health during the pandemic. The registry model can be replicated at tertiary care hospitals across India to understand various maternal-neonatal outcomes. The evidence generated from PregCovid registry was useful for improved clinical management and also contributed to a policy decision on COVID-19 vaccination in pregnant women in India. The registry envisions a collaboration with similar regional, national and international registries to form an international consortium for data sharing and reporting to promote global policy level interventions and advocates a sustainable and collective response to improve the COVID-19 global vaccination coverage.

Keywords: COVID-19, PregCovid registry, Pregnancy, SARS-CoV-2, India

INTRODUCTION

The world has witnessed many pandemics through the middle ages. The bubonic plague (14th century) known as Black Death wiped out a quarter or more of the affected populations.[1] Smallpox resulted in the untimely collapse of the native American civilizations, killing about 90% of the inhabitants.[2] The Spanish flu in the early 20th century infected half a billion people and killed about 50 million people globally with about 10–15 million fatalities in India alone.[3] Pregnant women, with their lower immune status, have always been vulnerable to sudden outbreaks of epidemics.[4] The 2009 H_1N_1 Influenza pandemic which infected about 700 million to 1.4 billion global population,[5] was associated with an increase in maternal mortality by 25–75%, greater disease severity and adverse fetal outcomes in affected pregnant women.[6] Maternal Zika Virus infection has been associated with microcephaly and Guillain-Barre Syndrome (GBS).[7] Miscarriage, preterm deliveries, and intrauterine growth restrictions were reported in pregnant women with Severe Acute Respiratory Syndrome (SARS).[8]

Wuhan in the Hubei Province of China reported the first Coronavirus Disease 2019 (COVID-19) case in December 2019. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a zoonotic virus with bats as the possible reservoir and mammals like pangolins, mink, and cats as possible intermediary.[9] Human to human transmission of the virus was confirmed in December 2019.[10] Emigration of Wuhan inhabitants and the New Year travel peak led to the rapid spread of the disease within as well as outside China. About three-fourths of the initial COVID-19 cases in China reported contact with a Wuhan resident and one-third reported a visit to the city.[11] On January 30, 2020, COVID-19 was declared a public health emergency of international concern and on March 11, 2020, it was declared a pandemic.[12] India reported its first COVID-19 case on January 30, 2020, from Thrissur, Kerala. Soon, two more people tested positive. All three were Indian medical students returning from Wuhan.[13] Since then, more than 533 million cases of COVID-19 and associated 6 million fatalities have been reported from the world whereas 43 million cases and 0.5 million deaths have been reported in India till June 2022.[14]

Pregnant women with comorbidities, malnutrition, and anemia are vulnerable to severe infection due to SARS-CoV-2.[15] A rural cohort of pregnant women recruited from 2009 to 2016 in India reported anemia in >90% of participants, malnourishment in about one-third of the participant and both the conditions in 35% participants.[16] Malnourishment can result in pregnancy induced hypertension, postpartum hemorrhage and can even prove fatal.[17] However, in the earlier days of COVID-19 spread, the impact of the SARS-CoV-2 on pregnancy in India was unknown. A Chinese case series evaluating maternal outcomes and complications in pregnant women diagnosed with SARS-CoV-2 infection reported a 20% incidence of preterm births.[18] A systematic review covering the data of pregnant women with confirmed COVID-19 reported adverse maternal and neonatal outcomes.[19] Comparative studies on perinatal outcomes in women with COVID-19 showed that comorbidities such as diabetes mellitus, hypertension, and asthma were frequently reported from High-Income Countries (HICs); whereas hypothyroidism, anemia, and co-infections were mainly reported in Low- and Middle-Income Countries (LMICs).[20] In addition, risk of adverse pregnancy outcomes was found to be higher in LMICs.[20] The newer and emerging data from HICs did not adequately represent the impact of COVID-19 on pregnant women in India.[20] The progressive pandemic situation in India and lack of knowledge on novel coronavirus and its effect on pregnant women advocated the need for recording, documenting and analyzing population specific data. Maharashtra state was one of the worst affected states in India due to COVID-19. However, there was no data on epidemiological, demographic, maternal and neonatal outcomes. In addition, mother to child transmission of SARS-CoV-2 virus was not documented in the Indian population. To address these knowledge gaps, PregCovid registry (https://pregcovid.com/) was initiated. In this review, we summarize effects of SARS-CoV-2 infection on maternal, neonatal outcomes, and mother to child transmission based on the evidence generated through the PregCovid registry.

GENESIS OF PREGCOVID REGISTRY

The PregCovid registry was launched in April 2020 by the Indian Council of Medical Research-National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH), Mumbai in collaboration with the Medical Education and Drugs Department (MEDD), Government of Maharashtra, and Topiwala National Medical College and Bai Yamunabai Laxman (BYL) Nair Charitable Hospital (NH). The aim of the PregCovid registry was to gain insights into socio-epidemiological and clinical characteristics of pregnant and post-partum women with laboratory confirmed COVID-19 and its impact on maternal and neonatal outcomes. The PregCovid registry was implemented through NH and 18 Government Medical Colleges under MEDD, in Maharashtra State [Figure 1]. The details of the data collection tools and quality controls are published elsewhere.[21] Worldwide registries on COVID-19 and pregnancy have contributed significantly to generating evidence on the impact of COVID-19 on maternal and neonatal outcomes [Table 1].

TIMES OF COVID-19 PANDEMIC IN INDIA

The COVID-19 cases started rising from March 2020 mainly in Maharashtra with Mumbai becoming the pandemic epicenter. Nearly 1/3rd of the total cases of COVID-19 in India were reported from Maharashtra alone. The details of the first, second, and third waves of COVID-19 in

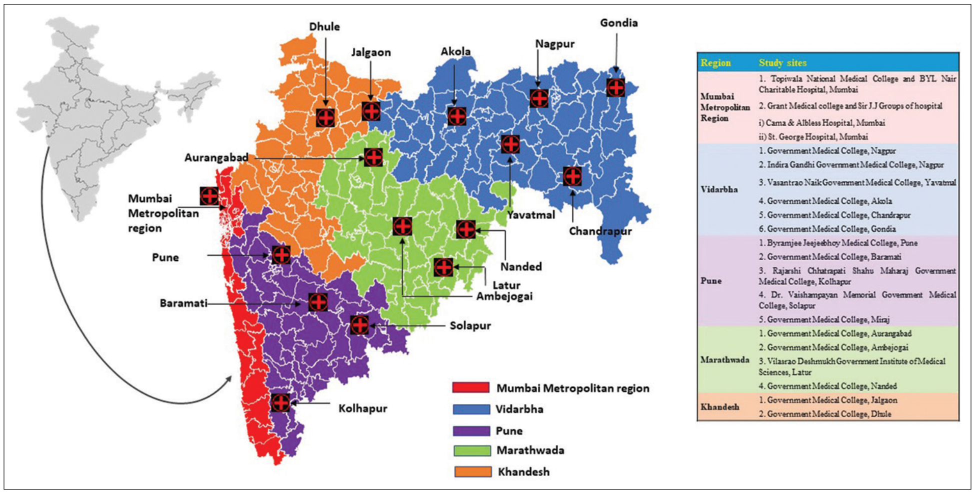

Figure 1: PregCovid registry study sites in Maharashtra, India.

Table 1: Global registries on COVID-19 and pregnancy.

Country	Registry Name
USA	PRIORITY: Pregnancy Coronavirus Outcomes Registry (University of California San Francisco)
	US CDC - United States, Centers for Disease Control (CDC)
	IRCEP - International Registry of Coronavirus Exposure in Pregnancy (IRCEP)
	SONPM - Society of Neonatal and Perinatal Medicine (SONPM)
	National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection.
India	PregCovid - National Registry of Pregnant women with COVID-19 in India (CTRI registration - CTRI/2020/05/025423)
	FOGSI's National Registry on COVID-19 infection in Pregnancy
UK	UKOSS - The United Kingdom Obstetric Surveillance System (UKOSS)
	PANCOVID - Pregnancy And Neonatal outcomes for women with COVID-19.
	Run by Imperial College London and University of Wales.
	ICNARC - The UK Intensive Care National Audit and Research Centre (ICNARC)
	ObsCovid - For maternity healthcare workers to record and follow-up encounters with mothers with suspected or confirmed COVID-19
	The International Registry on Pregnancy and COVID-19 Associated Coagulopathy and Thrombosis (COV-PREG-COAG)
	PeriCovid - Understanding COVID-19 infection in pregnant women and their babies.
	Run by St George's, London.
	COVID-19 New Mum Study - A UCL research project studying the impact of the COVID-19 pandemic on the experiences of new mothers with infant feeding
Switzerland	COVI-PREG (Lausanne University Hospital)
The Republic of Ireland	ROI COVID-19 - The Republic of Ireland Covid-19 registry
Netherlands	NethOSS - The Netherlands Covid-19 registry
Australia	CHOPAN (Coronavirus Health Outcomes in Pregnancy and Newborns) - The Australian Registry
Italy	ItOSS -The Italian registry
Spain	Obs Covid Spain - Spanish Registry of Pregnant Women with COVID-19
	GESNEO-COVID - National prospective Multicenter study
Colombia	RECOGEST - The National Registry for the study of COVID-19 in pregnancy in Colombia
Canada	CanCovid-preg - Canadian registry of Covid-19 in pregnancy
	BORN Ontario - Better Outcomes Registry and Network is co-ordinating Covid-19 data collection in pregnancy in Ontario
Sweden	COVID-19 in Pregnancy and Early Childhood (COPE) - A national Swedish multicenter study
Multinational cohort study	INTERCOVID - A prospective case control study using the centers who participated in the INTERGROWTH-21st Project

Maharashtra are presented in [Figure 2]. During the initial part of the first wave (January–June 2020), circulating B.1 lineage caused a surge in cases.[22] Delta variant (B.1.617.2) dominated the second wave (May and June 2021).[23] The Omicron variant was responsible for COVID-19 cases during the third wave (January–March 2022) in India.[24] The sub-variants of the Omicron (BA.4 and BA.5) are in circulation globally. Interestingly, BA.4 and BA.5 variants of omicron were not associated with an increased risk of COVID-19 disease severity or increased hospitalizations.[25]

UNIVERSAL SCREENING POLICY

Clinical presentation of COVID-19 disease ranges from asymptomatic, mild, and moderate to severe disease. Universal screening policy for SARS-CoV-2 infection in pregnant women was implemented in India as per the ICMR guidelines.[26] To understand the impact of the universal testing policy, we collected data from 15 collaborating hospitals during the early phase of the first wave. A total of 1140 pregnant women presenting either in labor or most likely to have a delivery in the coming 5 days were screened for COVID-19 by RT-PCR. The prevalence of COVID-19 in pregnancy during this period was 12.3% (*n* = 141) varying from zero to 40% across hospitals in Maharashtra. The study demonstrated presence of nearly 90% of the asymptomatic pregnant women when screened for COVID-19 indicating one symptomatic for every 9 asymptomatic women in the community.[27] Sutton *et al*. reported similar findings with a 13.5% prevalence of infection and 87.9% asymptomatic pregnant women with SARS-CoV-2 at admission in New York, U.S.A.[28] Multiple studies during the pandemic first wave reported the rates of asymptomatic pregnant women ranging from 43% to 89%.[29,30] PregCovid strongly recommended compliance with the universal testing policy for COVID-19 for pregnant women in India. Subsequent findings from the PregCovid study on the clinical profiles of pregnant and postpartum women with COVID-19 (*n* = 4203) reported that the majority of the participants (87.3%, *n* = 3669) were asymptomatic.[31]

It was suggested that the universal screening policy was useful for the protection of newborns and other patients, the protection of healthcare workers, and also useful to curb spread of the infection in the community.[27] A systematic review evaluating the universal testing policy in pregnancy reported a 5.3% prevalence of SARS-CoV-2 infection and among these, 75% were asymptomatic for COVID-19 at the time of testing.[32] The findings of PregCovid and other registries suggest that universal testing policy among pregnant women presenting either in labor or likely to deliver within a week was useful to identify pregnant women with infection, to prevent maternal complications and to reduce transmission to the fetus and HCWs, especially in areas with a high prevalence of COVID-19.

PSYCHOLOGICAL IMPACT OF COVID-19 ON PREGNANT AND POST-PARTUM WOMEN

Maternal mental health is a public health issue in India and globally with 10–35% of pregnant and postpartum women suffering from depression.[33] Pregnant and post-partum women are more likely to develop anxiety, stress, and depression during the COVID-19 pandemic due to various reasons. The increased vulnerability for mental illness in pregnancy is associated with biological changes occurring due to hormonal changes, psychological changes due to apprehensions concerning the course, outcome of pregnancy, transmission to the baby and social factors due to need of family support and care during pregnancy and the post-partum period.[34] Implementation of measures to contain the transmission of COVID-19 including lockdown, restriction of movement and social isolation/ quarantine strategies led to additional health problems including

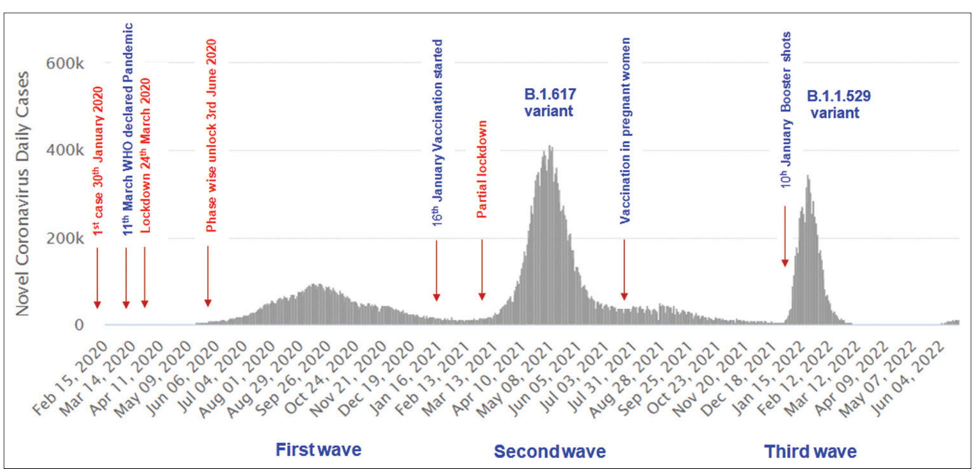

Figure 2: Timelines of COVID-19 in India.

mental health disorders.[35] However, the COVID-19 crisis situation in India made it difficult to seek care and treatment from health facilities and providers.[33] In mid-2020, during the rising cases of COVID-19, we reported postpartum psychosis[36] and delirium[37] in pregnant women managed at NH. Three women with asymptomatic COVID-19 were diagnosed with postpartum psychosis within 7 days of delivery based on the presence of symptoms such as delusion of persecution, the delusion of reference, self-harm behavior, auditory hallucinations, ideas of reference and ideas of persecution. Two women required separation from their newborns while one required supervision. All women recovered within 7 days of treatment with antipsychotic medications.[36] SARS-CoV-2 infected pregnant woman reported symptoms including aggression, altered sensorium, sleep disturbances, headache, and violent behavior. Diagnosis of delirium was confirmed by neurological and psychiatric evaluation.[37] A systematic review on postpartum psychosis in the pre-pandemic period in HICs (United States, Sweden, Denmark) and LMICs (Nigeria and India) reported postpartum psychosis incidence range between 0.89 and 2.6/1000 births and a prevalence of 5 in 1000 births (United States).[38] A recent systematic review reported a cumulative incidence of postpartum psychosis ranging from 1.1 to 16.7/1000 births in LMICs (Nigeria, Tanzania, India).[39] A study from the United States exploring the correlation between COVID-19 and postpartum psychosis reported that the pandemic should be considered as a risk factor for postpartum psychosis.[40] The risk of having adverse infant health outcomes, namely, malnutrition and febrile illness was found to be 1.61 (95% CI: 1.34–1.95) times higher among mothers who had perinatal depression in African women.[41] Another study from India[42] on women with postpartum psychosis highlighted issues faced by women while accessing psychiatry services and getting inpatient admission at a Mother-Baby Unit. Difficulty to follow COVID-19 appropriate behavior, guilt for having contracted COVID-19 and fear of transmission of infection to the infant and family members were expressed as major concerns by the participating women.[42] An online, cross-sectional survey of 6894 pregnant and postpartum women hosted on the Pregistry platform reported elevated posttraumatic stress (43%), anxiety/depression (31%), and loneliness (53%). It is widely studied that mental disorders in pregnancy influence adverse pregnancy and neonatal outcomes.[43,44] Hence, identifying and addressing mental health issues must be a high priority for healthcare providers. Capacity building for the early detection of psychiatric illnesses and their appropriate management is strongly recommended for obstetricians and the healthcare workforce.[37]

SARS-COV-2 AND CO-INFECTIONS IN PREGNANCY

The burden of infectious diseases in India is enormous. SARS-CoV-2 in pregnancy was an added burden on the existing health hazards. The proportion of pregnant women with COVID-19 presenting with co-infections is 6 times more common in LMICs than HICs (0.5% vs. 0.1%).[20] In the WHO Africa region, it is estimated that 34% of women were exposed to malaria infection in pregnancy[45] whereas the Indian burden of malaria in pregnancy awaits assessment.[46] Malaria, dengue, and COVID-19 have similar presentations as they share common symptoms such as fever, tiredness, and headache.[47,48] leading to a higher probability of misdiagnosis. In our initial case report, out of the three women co-infected with malaria and SARS-COV-2, one had an intrauterine fetal death while premature rupture of membranes (PROMs) was reported in another. Women co-infected with dengue and SARS-CoV-2 also had PROM and signs of intrauterine fetal growth restriction.[49]

Moreover, India has the highest burden of tuberculosis (TB) in the world.[50] Pregnant women are at increased risk for TB in high burden countries when compared with non-pregnant women[51] and untreated TB in pregnancy can have a mortality of up to 40%.[52] The Indian National TB Elimination Program has been unfavorably affected by the COVID-19 pandemic.[53] Both TB and COVID-19 infections affect the lungs. It was reported from the PregCovid study ($n = 879$) that women with active pulmonary TB (0.7%, $n = 6$) and SARS-CoV-2 infection had low oxygen saturation at admission. Active TB also led to a higher proportion of symptomatic COVID-19 cases ($n = 4$) than women with a history of TB ($n = 12$). Two women with active TB developed ARDS and required intensive care while maternal death occurred in a woman with extensively drug resistant TB.[54] Based on the data of the PregCovid registry, TB was significantly associated with the severity of symptoms in COVID-19 (OR 18.4 [4.3–80.0]).[31] Coinfections in the PregCovid registry cohort ($n = 4203$) reported were TB (1%), HIV (0.3%), hepatitis B (0.3%), malaria (0.2%), and dengue (0.1%).[31] A multicounty registry-based cohort study involving 172 centers from 34 countries reported 0.9% ($n = 767$) of TB-COVID-19 co-infected pregnant women.[55] To minimize the deleterious impact of overlapping endemics with the COVID-19 pandemic in vulnerable population - differential diagnosis, strengthening of healthcare facilities and intervention strategies must be implemented. In countries with a heavy TB case load, pregnant women must undergo testing for TB and COVID-19 if respiratory symptoms appear.

CO-MORBIDITIES AND COVID-19 IN PREGNANT WOMEN

The presence of cardiovascular disease, chronic respiratory disease, diabetes mellitus, asthma, and hypertension with COVID-19 has been associated with increased in-hospital complications and mortality. Several earlier studies in 2020 from China reported hypertension as the most common comorbidity while mortality was higher in patients with diabetes or coronary heart disease.[56] People infected with COVID-19 and having at least one comorbidity showed poor clinical outcomes compared to those without any comorbidity.[57] Jering *et al*. reported that rates of venous thromboembolism and myocardial infarction were higher in COVID-19 infected pregnant women relative to the non-infected.[58]

Pregnant women with Rheumatic Heart Disease (RHD) are at risk of adverse outcomes due to physiological changes involving increased stroke volume putting more pressure on the heart valves.[59] Three women with RHD and two with Peripartum Cardiomyopathy in pregnant women with COVID-19 (n = 879) were reported in our study. Pregnancy outcomes were compared with uninfected pregnant women in the pre-pandemic period (n = 43).[60] Low birth weight, preterm PPROMs, preterm delivery, and neonatal death were observed in COVID-19 infected pregnant women with heart disease.[60]

GBS is rare in pregnancy (1.2–1.9 cases/per 100,000 people annually) and a delay in diagnosis due to non-specific symptoms mimicking physiological pregnancy changes. Any pregnant woman presenting with malaise, finger tingling, muscle weakness, and respiratory difficulty must be screened for GBS.[61] The disease is usually preceded by nonspecific respiratory or gastrointestinal symptoms.[62] In the PregCovid study, a symptomatic pregnant woman on neurological examination was diagnosed with GBS which was possibly triggered by the SARS-CoV-2 infection. Her gestation age was 12 weeks and she was previously diagnosed with Systemic Lupus Erythematosus and Antiphospholipid Syndrome. Her obstetric ultrasonography appeared normal, however, within 10 days of developing weakness, she aborted spontaneously. She received IVIG therapy, antibiotics, heparin, steroid and hydroxychloroquine and recovered fully.[63] A case report from turkey by Tekin *et al*. in a woman with 37 week gestation and SARS-CoV-2 infection acute motor-sensory axonal neuropathy variant of GBS were reported. Cesarean section delivery was performed due to fetal distress and due to the presence of transient tachypnea, the newborn was admitted for intensive care.[64] In another case report, a woman with 37 week gestation, diagnosed with COVID-19 6 weeks before admission, reported bifacial weakness and paresthesia associated with vestibulocochlear neuritis.[65] CSF analysis in our study showed elevated cell count with normal protein and glucose levels[63] whereas the increased level of protein and no white blood cells were found in two studies.[64,66]

MATERNAL OUTCOMES

COVID-19 in pregnant women has been associated with an increased risk of pre-eclampsia, stillbirths, preterm births, PPROM, caesarean birth, and maternal mortality.[67,68] In women infected during 1st and 2nd trimesters of pregnancy increased risk of preterm delivery and stillbirth were reported.[69] The incidence rates for caesarean delivery were found to be higher in COVID-19 positive pregnant women[67,70,71] Some studies have described obstetric indications for caesarean birth as intrauterine fetal distress, history of stillbirth, elevated liver functions, and previous cesarean birth.[72,73] The salient findings of the registries on COVID-19 and pregnancy from India[31,74] and abroad[75-83] are described in Table 2.

Pregnancy complications

In pregnant women with SARS-CoV-2 infection, several studies including PregCovid have reported preterm birth and preeclampsia as the most prevailing pregnancy complications.[31,69,73,76] Findings from the prospective longitudinal INTERCOVID study demonstrated preeclampsia in COVID-19 infected group was higher as compared to the non-infected group (8.1% vs. 4.4%).[84] It was found that COVID-19 was diagnosed in women with preeclampsia mostly during 33–37 weeks of gestation and the risk ratio was 4.05 for preterm birth in women with COVID-19 and preeclampsia. The study suggested a strong association between COVID-19 during pregnancy and preeclampsia with each other.[84] A recent study by Palomo *et al*. demonstrated that in culture, serum from pregnant women with both preeclampsia and severe COVID-19 showed overexpression of intercellular adhesion molecule 1, soluble biomarkers of coagulopathy, Von Willebrand factor, and p38 MAPK phosphorylation activation in endothelial cells, suggesting that both severe COVID-19 and preeclampsia can cause inflammatory signaling pathways' activation.[85] A systematic review and meta-analysis analyzed 28 studies involving 790,954 pregnant women in total, among which 15,524 had COVID-19 infection. The odds of developing preeclampsia were found to be significantly higher among pregnant women with COVID-19 than those without. In addition, a significant increase was reported in the odds of severe preeclampsia, eclampsia, and HELLP syndrome in pregnant women with COVID-19 infection compared to pregnant women without.[86]

We reported outcomes in COVID-19 and Multiple Gestation Pregnancy (MGP) through the registry data. The incidence of pre-eclampsia/eclampsia was found to be higher in COVID-19 and MGP groups than in pre-pandemic MGP (50.0% vs. 12.7%) group and the COVID-19 singleton (41.6% vs. 7.9%) group. A higher risk of preterm birth, spontaneous abortion, and PROM was also observed in MGP compared to a singleton pregnancy.[87]

A retrospective cohort study from seven hospitals in New York City, USA following universal testing protocol observed that preterm births were twice as common

Table 2: Salient findings in pregnant women with COVID-19 from global registries during first wave of COVID-19.

Name of the Registry and reference	PregCovid	FOGSI's National Registry on COVID-19 infection in Pregnancy	Priority	PAN-COVID	AAP-SONPM	INTERCOVID	GESNEO-COVID	COVI-PREG	CANCOVID -Preg	UKOSS	NethOSS	ItOSS
Country	India	India	USA	Multi-national	Multi-national	Multi-national	Spain	Switzerland	Canada	UK	Netherland	Italy
Duration of data collection	March 1, 2020–January 31, 2021	April 28–August 28, 2020	March 22–July 10, 2020	January 1–July 25, 2020	April 4–August 8, 2020	March–October 2020	March 15, 2020–July 31, 2021	March 24–July 26, 2020	March 1, 2020–October 31, 2021	March 1–April 14, 2020	March 1–August 31, 2020	February 25, 2020–June 31, 2021
Number of cases	4203	989	594	1606	2399	706	105	926	6012	427	376	3306
Most common symptoms (%)	Fever (63.5%), dry cough (50.7%), dyspnea (20.6%)	Fever (48%), Mild SARI (19.3), Generalized symptoms (6.6), Multiple presenting symptoms (20.6%)	Cough (20%), sore throat (16%), body aches (12%), fever (12%)	Cough (56.5%), Fever (48.4%), Fatigue (31.3%)	Fever (8.1%), Myalgia and Fatigue (4.9%)	Cough (34.1%), Fever (28.2%), loss of smell (17%), tiredness (15.6%)	Fever (36.2%), cough (35.2%), dyspnea (19.0%)	Cough (40.4%), fever (32.4%), ansomnia/ageusia (17.8%)	Cough (48.6%), fever (24.7%)	Fever, Cough, Breathlessness	Cough (47%), breathlessness (24%), fever (39%), flu-like symptoms (25%)	-
Comorbidities	Hypothyroidism (4.3%), Hemoglobinopathies (1.0%), Tuberculosis (0.9%), Chronic hypertension (0.9%)	*n*=68 Hypertension (26.5%), Thyroid disorders (26.5%), Diabetes mellitus (13.2%), >1 comorbidity (10.3%)	-	Asthma or chronic obstructive pulmonary disease (4.9%), chronic hypertension (2.3%)	-	Overweight (48.6%), Thyroid and other endocrine (10.6%), Diabetes (4.7%), hypertension (3.7%), chronic respiratory disease (3.5%)	Obesity (6.7%), hypertension (1.9%), asthma (1.9%)	Pulmonary comorbidities (3.8%), Thyroid dysfunction (3.7%), Hypertension (2.1%), Cardiac comorbidities (1.5%)	Hypertension (3.4%), Type 1 or 2 diabetes (2.6%), Asthma (3.6%)	pulmonary conditions (25%), pre-existing cardiac disease (17%)	Pulmonary disease (7%), cardiac disease (2%), diabetes (2%)	Autoimmune disease (2.0%), Chronic hypertension (1.4%)
Neonatal outcomes	High risk of neonatal sepsis and death were observed in infected neonates of SARS-CoV-2 mothers *n*=524 (Malik *et al*., 2021)	42 (6%, *n*=728) of neonates had birth weight<2 kg. 195 (28.3%, *n*=688) infants required NICU admission. Total 13 (3%, *n*=435) infants infected with COVID-19 (vertical transmission)	NICU admission and Preterm birth was more common for infants born to mothers testing positive for SARS-CoV-2 at 0–14 days before delivery than for those testing positive at other times *n*=263 (Flaherman *et al*., 2020)			New-borns of women with COVID-19 diagnosis had significantly higher severe neonatal morbidity index and severe perinatal morbidity and mortality index compared with newborns of women without COVID-19 diagnosis.	Only one newborn was positive at 15 days of life and none of the newborns presented any symptom of SARS-CoV-2 infection. Sixteen percent newborns required admission to a neonatal intensive care.	Newborns born to mothers with severe adverse pregnancy outcomes were more frequently admitted to NICU compared to mild outcomes.		Five percent infants of infected mothers tested positive for SARS-CoV-2 RNA, six of them within the first 12 h after birth		

in women presenting with symptomatic COVID-19 compared with women with asymptomatic infection or without infection.[88] Pregnant and postpartum women with COVID-19 registered in the PregCovid registry (n = 1630) reported higher spontaneous preterm births during the second wave than the first wave and pre-pandemic period.[89] No evidence of a decline in preterm births pre- and post- implementation of COVID-19 containment measures was reported by Scandinavian countries using national population-based data.[90] Whereas, a decline in preterm births with an increase in stillbirths during the lockdown in the pandemic is reported by few studies.[91,92] This may be due to failure to identify antepartum stillbirth, lockdown compromised antenatal care or psychological changes in pregnant women due to COVID-19 restrictions.

Pregnancy loss

SARS-CoV-2 placental lesions can be involved in pregnancy loss particularly in the third trimester.[93] Occurrence of intrauterine fetal death (10% of cases) in 1–3 weeks after maternal infection in the second and third trimesters of pregnancies is also reported.[94] In spite of mild or asymptomatic maternal COVID-19 symptoms, severe placental lesions are reported to have occurred.[93,94] PregCovid study found during the delta dominant wave that the stillbirth rate among COVID-19 pregnant women was higher compared to the alpha dominant wave (P = 0.027). Preeclampsia was found to be higher during the second wave among pregnant women having stillbirths (P = 0.590). One in every four stillbirths in the second wave could be due to moderate to severe COVID-19 disease as the pregnant women had dyspnea on admission.[95]

The risk of miscarriage may be elevated if the woman is infected with COVID-19 during the preconception period or first half of pregnancy due to effect on Angiotensin Converting Enzyme 2 (ACE2) activity and excessive pro-inflammatory maternal immune response.[96] In the PregCovid study, spontaneous abortion rate was found to be significantly higher during the second wave than the first wave (82.6 vs. 26.7) and pre-pandemic period (OR 1.7). The proportion of women with symptomatic COVID-19 disease and spontaneous abortion was higher in the first wave (31.8%) than in the second wave (17.9%).[97] In a population based study of the UK (CAP-COVID – Online survey) rates of early miscarriage (<13 weeks' gestation) were found to be 14% compared to 8% in uninfected women.[84]

Clinical presentations during different waves of COVID-19

During the first wave of the COVID-19 pandemic, findings from 19 participating study sites in the PregCovid registry observed hypertensive disorders of pregnancy, breathlessness, diarrhea, TB, and anemia as the risk factors associated with the severity of COVID-19.[31] Further analyses of 1530 pregnant and postpartum women admitted at NH during the first wave (April–January 2021) and the second wave (February–May 2021) of the pandemic, revealed that symptomatic cases were significantly higher in the second wave than the first wave (28.7% vs. 14.2%). During the second wave, significantly higher cases of severe COVID-19 (8.5%), intensive care units (ICU)/high dependency units (HDU) admissions (11.6%) were also observed as compared to the first wave. COVID-19 pneumonia and respiratory failure resulted in a majority of maternal deaths (93%, 28/30). The findings of these studies suggested the need for vaccination of pregnant and lactating women and ensuring multispecialty care during the ongoing COVID-19 pandemic.[98] Increased frequency of ectopic pregnancies during the second wave of the pandemic was reported possibly due to the B.1.617. 2 (Delta) VoC.[99]

According to the WHO, Omicron had a rapid spread in the community causing higher case incidence than previous variants.[100] PregCovid study observed that the hospitalization rates of COVID-19 infected pregnant women during the first 4 weeks of the third wave were higher than in previous waves. However, moderate to severe COVID-19 was low in the third wave (0.3%) of COVID-19 and highest in the Second wave (14.4%).[101] Vaccination of pregnant women for COVID-19 in India was implemented in July 2021 post-Delta-Variant surge and 3.8% of pregnant women were vaccinated among COVID-19 infected during the third wave.[101] This observation is in line with Parkland Health Texas USA study, increased severity was observed during the delta variant surge (Local SSARS-CoV-2 delta variant sequencing was performed) and vaccination was inadequate (21.4% received at least 1 dose).[102] An association study for disease severity in delta and omicron variant predominance observed higher severe or critical infection during delta variant surge (11.8%) compared to pre-delta (4.1%) and omicron variant (0.20%) after adjusting for vaccination.[103] According to the United Kingdom Obstetrics Surveillance System study women are more likely to have pneumonia, require respiratory support, and admitted to intensive care during the delta dominance period.[104] Further study during the Omicron dominance period revealed a proportional rate of moderate to severe infection in unvaccinated pregnant women and the wild type dominance period was similar. Moderate to severe infections were low in women who had received two doses of vaccine compared to those who received a single or no dose.[105] Table 3 depicts a summary of selected studies on COVID-19 in pregnancy.

Considering the literature majorly on unfavorable maternal outcomes in pregnant women with COVID-19 and differences in the observations during the rise of different

Table 3: Case fatality rate reported during different waves of COVID-19 in India and worldwide.

Country	Study period	Circulating dominant variant	Case fatality rate (%)
India	March 2020–January 2021	Alpha (B.1.1.7)	0.8
India	February–May 2021	Delta (B.1.617.2)	5.7
India	December 2021–February 2022	Omicron (B.1.1.529)	0.3
UK	May–October 2021	Delta (B.1.617.2)	0.4
Brazil	February 2020–September 2021	September–December 2020: Zeta (P. 2)	12
		January–July 2021: Gamma (P. 1)	
		July 2021 onwards: Delta (B.1.617.2)	
Turkey	March 2020–January 2022	November 2020–July 2021: Alpha (B.1.1.7)	1.3
		August 2021–December 2022: Delta (B.1.617.2)	7.0
		December 2022 onwards: Omicron (B.1.1.529)	2.6
South Africa	May 2020–December 2021	May 2020–November 2021: Alpha (B.1.1.7), Delta (B.1.617.2)	21.3
		November–December 2021: Omicron (B.1.1.529)	4.5
Mexico	February 2020–March 2022	February–May 2020: Pre-Delta	1.2
		May–December 2021: Delta (B.1.617.2)	1.5
		December 2021–March 2022: Omicron (B.1.1.529)	0.05
Malawi*	January 2021–March 2022	January–April 2021: Beta (B.1.351)	25
		June–October 2021: Delta (B.1.617.2)	17.9
		December 2021–March 2022: Omicron (B.1.1.529)	5.3

*Only symptomatic cases included for calculation of case fatality rate in Malawi

viral strains suggests a need for a long term follow-up study to reduce the risk of post COVID effect in this group.

MOTHER TO CHILD TRANSMISSION OF SARS-COV-2

ACE-2 receptor, a hallmark of vulnerability to SARS-CoV-2 is expressed on the ovaries, uterine lining, vagina and placenta indicating that vertical transmission of SARS-CoV-2 from mother to child is possible. The initial report from China[106] on six pregnant women infected with COVID-19 stated that no virus was found in their amniotic fluid and cord blood; also the neonatal throat swab and breast milk samples were negative for SARS-CoV-2. We reported hydrops fetalis in a woman with 8 weeks of gestation who had asymptomatic COVID-19. SARS-CoV-2 was detected in the amniotic fluid and fetal membranes while localized spike proteins (S1 and S2) were found in placental villi.[107] Dumont *et al*. reported that pathological examination of the placenta in women with SARS-CoV-2 and oligohydramnios revealed histiocytic intervillositis, ischemic necrosis of villi and intervillous deposition of fibrin, depicting an acute onset of placental insufficiency, and fetal distress. However, neonatal nasopharyngeal samples were negative for SARS-CoV-2 in this study.[108] Our study reported generally avascular villi with peri-villus deposition of fibrin and lysis of the syncytiotrophoblast layer at some places. The decidua was also inflamed suggested by the presence of fibrin deposition and leukocyte infiltration.[107] Argueta *et al*. analyzed placenta of 55 SARS-CoV-2 infected women in late pregnancy of which 42% tested positive for viral RNA. Highly infected placental tissues showed trophoblast necrosis, peri-villus fibrin deposition, and infiltration of maternal immune cells with signs of inflammatory damage which likely contributed to adverse birth outcomes such as stillbirth and preterm birth that required extended intensive care.[109] Ferraiolo *et al*. have reported placental swabs positive for SARS-CoV-2 RNA[110] while Hsu *et al*. in their study demonstrated the presence of SARS-CoV-2 antigens throughout the placenta under the umbilical cord.[111] Ours was the first study providing evidence associating hydrops fetalis and intrauterine fetal demise with placental SARS-CoV-2 infection and its congenital transmission.[107]

MATERNAL MORTALITY

The case fatality rate (CFR) in pregnant and postpartum women with SARS-CoV-2 infection during different waves of the pandemic is presented in [Table 3]. During the early phase of the pandemic, there was inconsistent information on maternal mortality associated with COVID-19 as some of the studies reported very low CFR whereas others reported a high CFR.[20] A systematic review involving data from more than 10,500 pregnant and postpartum women with SARS-CoV-2 during the early phase of the pandemic from 35 countries worldwide reported a 2% maternal death rate related to COVID-19.[20]

In India, the PregCovid registry study reported 0.8% CFR during the COVID-19 first wave (March 2020–January 2021).[31] There were regional differences in CFR in Maharashtra state in India, with Marathwada (1.1%) and Pune (1.1%) reporting higher CFR than Vidarbha (0.8%), Mumbai

Metropolitan (0.7%), and Khandesh (0.6%) regions. Majority of the maternal deaths due to COVID-19 (71%) occurred during the antepartum period while 29% of maternal deaths occurred in the postpartum period. A higher risk of maternal death was observed in pregnant women with comorbidities including anemia, TB, and diabetes mellitus.[31] The CFR reported during the first wave in Maharashtra, India was comparable with UK populations (0.7–1%)[81,104] and the US population (1.3%)[112] but was higher than the multinational PAN-COVID (0.5%) and AAP-SONPM registries (0.4%).[76]

Some of the countries such as Brazil,[113] Iran,[114,115] South Africa,[116] Malawi[117] and Mexico[118-121] reported higher maternal mortality during early phase of the COVID-19 pandemic. In Brazil, maternal mortality was reported as 12.3% between February and September 2021.[113] Early reports from a single center study in Iran between March 2020 and June 2020 showed 15 maternal deaths (46.8%) among 32 pregnant women with laboratory diagnosed COVID-19.[114] However, a cross-sectional multicenter study conducted during the same period reported seven maternal deaths (0.04%) out of 182 pregnant women infected with COVID-19.[115] An increase in maternal mortality ratio (MMR) by 56.8% was observed in Mexico during the 1st year of the pandemic (February 2020–February 2021), in which MMR due to COVID-19 was 13.6.[118] A single center study in Mexico reported higher CFR (2.3%) from the start of the pandemic till May 2020[119,120] while the Mexican National Registry of Coronavirus reported 1.4% maternal deaths between April 2020 and July 2021.[121]

Ethnic and racial variations in maternal mortality were reported as black women and Hispanic women faced higher risk of death due to COVID-19 in Brazil.[113] Similar observations were also reported from UK wherein Black, Asian, Minority Ethnic (BAME) pregnant women were disproportionately affected by COVID-19.[81] A study in USA, relative to the pre-pandemic period, reported an increase of 8.9 maternal deaths per 100000 live births in Hispanic women during the pandemic period, 16.8 maternal deaths in black women and 2.9 maternal deaths in white women.[122] The numbers indicating racial variations in COVID-19 related mortality are however, an underestimation of the actual magnitude of the existing disparities between the mortality in the black women and white women the USA.[123]

The delta variant (B.1.617.2) dominant second wave was more lethal to pregnant and postpartum women than alpha and omicron dominant waves of COVID-19 in India. The PregCovid registry data of NH showed an eight-fold increase in maternal mortality in the second wave (CFR 5.7%) as compared to the first wave (CFR 0.7%). COVID-19 pneumonia and respiratory failure were associated with more than 90% of maternal deaths (93%, 28/30).[98] A similar impact of the delta wave was found in other parts of India and outside India. Khoiwal *et al*., reported a higher maternal death rate (16.2%) during the COVID-19 delta wave compared to the alpha wave (1.7%) in the north Indian population.[124] Similar to the PregCovid study, a study from Jamshedpur in Eastern India also reported a steep increase in maternal deaths due to COVID-19 in the second wave (3.6% vs. 0.0%) than in the first wave.[125]

The seven-fold rise in the proportion of maternal deaths was reported in the delta dominant phase of the pandemic (2.9% vs. 0.4%,) in Turkey.[126] Another study in Turkey reported a higher maternal mortality rate in the delta period compared to the pre-delta period (7% vs. 1.3%).[127] An upward trend in maternal mortality was also reported from Brazil that showed a two-fold increase in maternal deaths by COVID-19 during the second wave of the pandemic (7.7% in the first wave vs. 15.4% in the second wave).[128] Another retrospective cohort study recruited pregnant women from two tertiary care hospitals, one in Turkey and one in the UK, and reported 3.6 times higher maternal death rate during the delta dominant period relative to the pre-delta period of the pandemic (5.3% vs. 1.5%).[129] A study from 194 obstetric units in the UK reported that there was no considerable difference in maternal death rates in the alpha and the delta periods (0.4% vs. 0.4%). Maternal deaths reported from the wild-type variant dominant period were 0.7%, similar to PregCovid study estimates during the COVID-19 first wave.[104]

Although the omicron dominant third wave of the COVID-19 pandemic exhibited a higher transmission rate compared to the previous two waves in India, the impact on pregnant women was minimal. The PregCovid registry data from NH during the 1st month of the third wave of the pandemic (December 2021–January 2022) showed about a 3.5-fold rise in symptomatic COVID-19 cases in pregnant and post-partum women during the omicron dominant period (45.5%) as compared to the alpha variant period (14.2%). The proportion of moderate to severe COVID-19 disease in pregnant and post-partum women was significantly lower during the third wave (0.6%) compared to the first wave (2.4%) and second wave (14.4%).[101] These findings of the PregCovid registry from NH suggested a reduction in severe COVID-19 cases and lower maternal mortality in the omicron dominated period of the pandemic in the Mumbai Metropolitan Region, India compared to the alpha and delta periods.

A retrospective cohort study between December 2021 and February 2022 at three tertiary care hospitals, two in Turkey and one in the UK, was consistent with the PregCovid study findings of no maternal deaths during the study period, both in the vaccinated and non-vaccinated pregnant women.[130] Another study from Turkey and UK reported that the maternal mortality rate in the third wave was similar to the pre-delta period (1.3% vs. 1.3%).[129]

Wide variations in COVID-19 related maternal mortality are observed across the globe. Variations in mortality could be attributed to many factors, namely: (1) Differences in the pandemic preparedness between HICs and LMICs, (2) differences in the case reporting systems between countries along with a lack of a standardized set of rules for medical certification of death, (3) differences in the circulating strains during study periods. Delta dominant period of the COVID-19 pandemic was associated with higher maternal mortality rates than the alpha, gamma, and omicron periods [Table 3], (4) differences in race and ethnicity, socioeconomic conditions, and demographic disparities in the study population, (5) availability of affordable and competent healthcare systems and (6) accessibility to COVID-19 vaccines. Fast track development and roll-out of COVID-19 vaccines have saved more than 19 million lives globally.[131] Transparent vaccine approval procedures, campaigns for vaccine awareness and to stop misinformation, equitable distribution, and promotion for vaccination in conflicted areas can further save thousands of lives. A sustainable and collective global response to improve vaccination coverage will aid to mitigate the mortality associated with COVID-19.

NEONATAL OUTCOMES OF MOTHERS WITH COVID-19

There is growing evidence of the impact of SARS-CoV-2 on newborns. The incidence of SARS-CoV-2 is reported in nearly 3–7% of neonates born to COVID-19 infected mothers.[132,133] CRONOS study (Germany) revealed 4.5% SARS-CoV-2 infection in neonates born to mothers infected ≤2 weeks before delivery.[134] However, neonatal outcomes were not affected by the time of maternal SARS-CoV-2 infection. Majority of studies did not report major adverse neonatal outcomes.[135-137] US-based PRIORITY also did not observe significant differences in neonatal outcomes among the infected and non-infected groups.[75] However, severe course and adverse outcomes are reported in neonates.[138] INTERCOVID study found 13% positivity in newborns of COVID-19 infected women and reported that the severe perinatal morbidity and mortality index and the severe neonatal morbidity index were significantly higher compared with newborns of non-infected women.[77] The USA population and UK registries reported an increased risk of preterm delivery and NICU admission in neonates of COVID-19 infected mothers.[73,139] A prospective observational study from the Spanish GESNEO-COVID cohort reported increased risk of preterm birth and adverse prognosis of SARS-CoV-2 infected newborns.[78] In the UAE, women with moderate to severe COVID-19 were found to have an increased risk of preterm deliveries, lower birth weight, neonatal infection, and neonatal intensive care admissions.[140] The National Neonatology Forum, India's cohort study including 1713 suspected and confirmed SARS-CoV-2 infected newborns revealed a 1.5% horizontal transmission and a 8% perinatal transmission. It showed increased morbidity in infected infants related to prematurity and perinatal events.[141]

Some studies have been reported clinical profile and outcomes of neonates born to SARS-CoV-2 infected mothers during the delta period of the COVID-19 pandemic. A higher incidence of SARS-CoV-2 in newborns during the second wave has been reported in Spanish population[142] whereas a higher incidence of neonatal complications and NICU admissions among SARS-CoV-2 infected neonates was also reported during the omicron wave in the UK.[129]

A retrospective analysis of 2524 neonates (from 5 centers in Maharashtra, India) from PregCovid registry born to mothers with SARS-CoV-2 infection during the first wave (n = 1782) and second wave (n = 742) of the COVID-19 pandemic showed that the prevalence of neonatal SARS-CoV-2 infection was almost similar (4.2% vs. 4.6%). However, the second wave showed a higher incidence of preterm birth (15.0%, 111/742), birth asphyxia (3.8 times higher) and prematurity (2.1 times higher). The second wave also had a significantly higher proportion of neonates required NICU care (19.0%, 141/742) than the first wave (14.8%, 264/1782). Higher neonatal complications were reported in Mumbai metropolitan region than other parts of Maharashtra. The neonates mainly presented with hyperbilirubinemia (4.04%), respiratory distress (3.2%), and feeding difficulties (1.8%).[143] Higher proportion and severity of adverse neonatal outcomes in the second wave highlights the need to devise appropriate strategies for management of neonates.

The evidence generated from the PregCovid registry was submitted to Director General, ICMR on June 14, 2021. Subsequently, evidences of impact of Second wave of COVID-19 on pregnant women in India were also submitted to ICMR, New Delhi for review of the evidence by Chairman, National Technical Advisory Group in Immunization (NTAGI) on June 18, 2021. Based on the recommendations from NTAGI, the Union Ministry of Health and family Welfare (MoHFW) on July 2, 2021, pregnant women became eligible for COVID-19 vaccination in India. Thus, the evidence generated from the PregCovid registry was not only useful for improved clinical management but also useful for facilitating the policy decision on COVID-19 vaccination of pregnant women in India.

COVID-19 VACCINATION IN PREGNANT WOMEN

Despite clear pre-pandemic guidance, all the randomized clinical trials of COVID-19 vaccines excluded pregnant and lactating women.[144] Therefore, there was a delay in policy decision on vaccination on COVID-19 for pregnant and lactating women in India and globally. A population-based study in Canada, compared three groups - COVID-19 vaccination during pregnancy, vaccination after pregnancy and no COVID-19 vaccination, and reported that COVID-19 vaccination during pregnancy showed no significant increase in the risk of adverse outcomes.[145] Recent systematic review and meta-analysis reported the significantly lower risk of stillbirth in the COVID-19 mRNA vaccinated cohort compared to unvaccinated women. No evidence of an increased risk of adverse outcomes were reported in COVID-19 mRNA vaccinated pregnant women compared to unvaccinated cohort thereby suggesting safety of COVID-19 mRNA vaccines.[146] Despite this, there exists vaccine hesitancy for COVID-19 vaccination amongst pregnant women.[147] The probable reasons for COVID-19 vaccination could be: (a) Data paucity on safety and effectiveness of COVID-19 vaccine in pregnant women globally, (b) inadequate counseling leading to lack of trust on healthcare workers, and (c) misleading information circulating through social media. Addressing vaccine hesitancy is very challenging and requires a multisectoral involvement.

LESSONS LEARNT FROM THE PREGCOVID REGISTRY AND WAY FORWARD

- PregCovid Registry serves as a replicable and generalizable model that can be implemented through a network of tertiary care hospitals. A robust surveillance system, quality control mechanisms, and committed frontline healthcare workers with scientific vigor can prove crucial in mitigating the emerging and reemerging infections.
- The PregCovid registry covered population with a range of SARS-CoV-2 infection severity from asymptomatic, mildly symptomatic, moderately symptomatic to severely symptomatic disease, making it generalizable to entire obstetric populations.
- The PregCovid registry captured the data from the beginning of the pandemic covering first, second and third wave data from all over the Maharashtra State and therefore the dataset has very vital information for comparison with global populations.
- The PregCovid registry experience is not just applicable to rapid response to COVID-19 pandemic but useful for other infections in pregnancy.
- The registry demonstrated the strength in collaboration right from the medical graduates to the head of the department across 19 government medical colleges in Maharashtra and these networks should be strengthened further for addressing the larger goals of maternal and child health.
- Based on the experience of setting up and managing the PregCovid registry, we recommend setting up a network in medical colleges in different geographical zones all over India for addressing the future pandemics.
- Universal screening of pregnant women for COVID-19 can aid in identifying all the cases and limit the spread of infection in the community.
- Maternal mental health is a vital public health issue in India and COVID-19 increases the vulnerability to postpartum depression and psychosis. Early detection and appropriate management of psychiatric illnesses is a priority.
- Co-infections and comorbidities in pregnant women with COVID-19 could be detrimental to the recovery efforts.
- While the delta dominant second wave severely affected the maternal mortality, still births, preterm births, preeclampsia and increased hospitalizations, the omicron dominant third wave caused a surge in number of cases but minimally affected hospitalization rate, pregnancy complications and maternal mortality.
- COVID-19 is associated with lower birth weight, neonatal infections and an increase in neonatal ICU admission rates.
- Addressing vaccine hesitancy is a challenging task and a multi-sectorial participatory approach could prove useful in improving the coverage.

CONCLUSION

PregCovid registry, implemented since April 2020, has documented and reported crucial aspects of pregnancy and SARS-CoV-2 infection in a near real-time manner. Further, it has provided evidence-based inputs to form and revise policies to improve healthcare during the COVID-19 pandemic. The registry serves as a model that can be implemented at tertiary care hospitals across India to understand various maternal-neonate outcomes and support the decision-making process in daily clinical practice. The registry plans to determine long term impact of COVID-19 in these women and their infants in the future. The registry also envisions a collaboration with similar regional, national and international registries to form an international consortium for data sharing, reporting, and combine analysis to advocate feasible global policy level interventions to mitigate COVID-19 and similar emerging and re-emerging diseases in the future.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this review article.

Acknowledgment

The authors sincerely acknowledge the support of Director General, Indian Council of Medical Research. Secretary, Medical Education and Drugs Department; Director, Medical Education and Drugs Department, Maharashtra; Dean, BYL Nair Charitable Hospital, Mumbai. Dr. Smita Mahale, Dr. Geetanjali Sachdeva, Dr Rakesh Waghmare, Dr Deepak Modi, are sincerely acknowledged. The authors acknowledge the Site Investigators, Faculties, Resident doctors and Interns of the network of National Registry of Pregnant women with COVID-19 in India (PregCovid Registry, CTRI/2020/05/025423). We acknowledge Ms. Divya Balgoniwar, Ms. Kalyani Jadhav, Ms. Samrudhi Kothe, Ms. Supriya Jawale, Mr. Shrinivas Parpelli, Mr. Chetan Jadhav for data entry and Dr Itta Krishna Chaaithanya for assisting in graph preparation. PregCovid registry is supported by an intramural grant of ICMR-NIRRCH (ICMR-NIRRCH/RA/1289/07/2022). RG is an awardee of the DBT Welcome India alliance clinical and public health intermediate fellowship (Grant no. IA/CPHI/18/1/503933).

Author contributions

Concept and design: RG. Data collection: SZ, HM, SS, NNM, and RG. Analysis and interpretation of results: SZ, HM, NNM, SS, and RG. Manuscript preparation and revision: All authors.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflict of interest.

REFERENCES

1. Dennis DT. Plague as an emerging disease. In: Emerging Infectious Diseases 2. Washington, DC: ASM Press; 2014. p. 169-83.
2. Weiss RA, Esparza J. The prevention and eradication of smallpox: A commentary on Sloane (1755) An account of inoculation. Philos Trans R Soc B Biol Sci 2015;370:20140378.
3. Taubenberger JK, Morens DM. 1918 Influenza: The mother of all pandemics. Emerg Infect Dis 2006;12:15-22.
4. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. Am J Obstet Gynecol 2011;205:10-8.
5. Kelly H, Peck HA, Laurie KL, Wu P, Nishiura H, Cowling BJ. The age-specific cumulative incidence of infection with pandemic influenza H1N1 2009 was similar in various countries prior to vaccination. PLoS One 2011;6:e21828.
6. Bhalerao-Gandhi A, Chhabra P, Arya S, Simmerman JM. Influenza and pregnancy: A review of the literature from India. Infect Dis Obstet Gynecol 2015;2015:867587.
7. Kuadkitkan A, Wikan N, Sornjai W, Smith DR. Zika virus and microcephaly in Southeast Asia: A cause for concern? J Infect Public Health 2020;13:11-5.
8. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, *et al*. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004;191:292-7.
9. Aylward B, Liang W. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). WHO-China Jt Mission Coronavirus Dis 2019; 2020. p. 16-24. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf [Last accessed on 2022 Jun 08].
10. You M, Wu Z, Yang Y, Liu J, Liu D. Spread of coronavirus 2019 from Wuhan to Rural villages in the Hubei province. Open Forum Infect Dis 2020;7:ofaa228.
11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
12. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020;91:157-60.
13. Andrews MA, Areekal B, Rajesh K, Krishnan J, Suryakala R, Krishnan B, *et al*. First confirmed case of COVID-19 infection in India: A case report. Indian J Med Res 2020;151:490-2.
14. COVID-19 Map-Johns Hopkins Coronavirus Resource Center. Available from: https://www.coronavirus.jhu.edu/map.html [Last accessed on 2022 Jun 08].
15. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, *et al*. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. BMJ 2020;370:m3320.
16. Patel A, Prakash AA, Das PK, Gupta S, Pusdekar YV, Hibberd PL. Maternal anemia and underweight as determinants of pregnancy outcomes: Cohort study in eastern rural Maharashtra, India. BMJ Open 2018;8:e021623.
17. United Nations Children's Fund. UNICEF Programming Guidance. Prevention of Malnutrition in Women Before and during Pregnancy and While Breastfeeding. Published online. New York: United Nations Children's Fund; 2021.
18. Guo Y, Yuan J, Wang M, Yu Y, Bian J, Fan C. Case series of 20 pregnant women with 2019 novel coronavirus disease in Wuhan, China. J Obstet Gynaecol Res 2021;47:1344-52.
19. Gajbhiye RK, Modi DN, Mahale SD, Gajbhiye R. Pregnancy outcomes, newborn complications and maternal-fetal transmission of SARS-CoV-2 in women with COVID-19: A systematic review of 441 cases. medRxiv 2020:2020:20062356.
20. Gajbhiye RK, Sawant MS, Kuppusamy P, Surve S, Pasi A, Prusty RK, *et al*. Differential impact of COVID-19 in pregnant women from high-income countries and low-to middle-income countries: A systematic review and meta-analysis. Int J Gynecol Obstet 2021;155:48-56.
21. Gajbhiye RK, Mahajan NN, Waghmare R, Surve SV, Howal P,

Bhurke A, *et al*. Protocol for a prospective, hospital-based registry of pregnant women with SARS-CoV-2 infection in India: PregCovid Registry study. BMJ Open 2022;12:e050039.
22. INSACOG. Insacog Bulletin Weekly Bulletin 18 June 2021. Jorhat: INSACOG; 2021. p. 2. Available from: https://dbtindia.gov.in/sites/default/files/INSACOG BULLETIN - 18-06-21 for public release.pdf [Last accessed on 2022 Jul 03].
23. INSACOG. INSACOG Weekly Bulletin 09 August 2021. INSACOG; 2021. Available from: https://www.dbtindia.gov.in/sites/default/files/INSACOG bulletin july 19.pdf [Last accessed on 2022 Jun 23].
24. INSACOG. INSACOG Weekly Bulletin 03 January 2022. INSACOG; 2021. Available from: https://www.dbtindia.gov.in/sites/default/files/INSACOG bulletin july 19.pdf [Last accessed on 2022 Jun 23].
25. INSACOG. INSACOG Press Release 21 May 2022; 2022. Available from: https://dbtindia.gov.in/sites/default/files/INSACOG PRESS RELEASE_21 May 2022.docx [Last accessed on 2022 Jun 23].
26. Indian Council of Medical Research. Strategy for COVID-19 Testing in India. Natl Task Force COVID-19. Version 5; 2020. p. 1-4. Available from: https://www.mohfw.gov.in/pdf/AdvisoryonstrategyforCOVID19testinginIndia.pdf [Last accessed on 2022 Jun 08].
27. Waghmare R, Gajbhiye R, Mahajan NN, Modi D, Mukherjee S, Mahale SD. Universal screening identifies asymptomatic carriers of SARS-CoV-2 among pregnant women in India. Eur J Obstet Gynecol Reprod Biol 2021;256:503-5.
28. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. N Engl J Med 2020;382:2163-4.
29. Khalil A, Hill R, Ladhani S, Pattisson K, O'Brien P. Severe acute respiratory syndrome coronavirus 2 in pregnancy: Symptomatic pregnant women are only the tip of the iceberg. Am J Obstet Gynecol 2020;223:296-7.
30. Miller ES, Grobman WA, Sakowicz A, Rosati J, Peaceman AM. Clinical implications of universal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing in pregnancy. Obstet Gynecol 2020;136:232-4.
31. Gajbhiye R, Mahajan N, Waghmare R, Zala S, Chaaithanya I, Kuppusamy P, *et al*. Clinical characteristics, outcomes, & mortality in pregnant women with COVID-19 in Maharashtra, India: Results from pregcovid registry. Indian J Med Res 2021;153:629-36.
32. Hashim NA, Mahdy ZA, Rahman RA, Kalok AH, Sutan R. Universal testing policy for COVID-19 in pregnancy: A systematic review. Front Public Health 2022;10:38.
33. Jungari S. Maternal mental health in India during COVID-19. Public Health 2020;185:97-8.
34. Priya A, Chaturvedi S, Bhasin S, Bhatia M, Radhakrishnan G. Depression, anxiety and stress among pregnant women: A community-based study. Indian J Psychiatry 2018;60:151-2.
35. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. J Affect Disord 2020;277:5-13.
36. Subramanyam AA, Nachane HB, Mahajan NN, Shinde S, D Mahale S, Gajbhiye RK. Postpartum psychosis in mothers with SARS-CoV-2 infection: A case series from India. Asian J Psychiatr 2020;54:102406.
37. Mahajan NN, Gajbhiye RK, Pednekar RR, Pophalkar MP, Kesarwani SN, Bhurke AV, *et al*. Delirium in a pregnant woman with SARS-CoV-2 infection in India. Asian J Psychiatr 2021;55:102513.
38. VanderKruik R, Barreix M, Chou D, Allen T, Say L, Cohen LS, *et al*. The global prevalence of postpartum psychosis: A systematic review. BMC Psychiatry 2017;17:1-9.
39. Kalra H, Tran T, Romero L, Chandra P, Fisher J. Burden of severe maternal peripartum mental disorders in low-and middle-income countries: A systematic review. Arch Womens Ment Health 2022;25:267-75.
40. Bider EN, Coker JL. Postpartum psychosis and SARS-CoV-2 infection: Is there a correlation? Arch Womens Ment Health 2021;24:1051-4.
41. Dadi AF, Akalu TY, Wolde HF, Baraki AG. Effect of perinatal depression on birth and infant health outcomes: A systematic review and meta-analysis of observational studies from Africa. Arch Public Health 2022;80:1-11.
42. Nagendrappa S, Vinod P, Pai NM, Ganjekar S, Desai G, Kishore MT, *et al*. Perinatal mental health care for women with severe mental illness during the COVID-19 pandemic in India-challenges and potential solutions based on two case reports. Front Glob Womens Health 2021;2:648429.
43. Hoirisch-Clapauch S, Brenner B, Nardi AE. Adverse obstetric and neonatal outcomes in women with mental disorders. Thromb Res 2015;135:S60-3.
44. Mongan D, Lynch J, Hanna D, Shannon C, Hamilton S, Potter C, *et al*. Prevalence of self-reported mental disorders in pregnancy and associations with adverse neonatal outcomes: A population-based cross-sectional study. BMC Pregnancy Childbirth 2019;19:412.
45. World Health Organization. Word Malaria Report 2021. Geneva: World Health Organization; 2021.
46. Pandey M, Rahi M, Sharma A. The Indian burden of malaria in pregnancy needs assessment. Med (N Y) 2021;2:464-9.
47. Hussein MI, Albashir AA, Elawad OA, Homeida A. Malaria and COVID-19: Unmasking their ties. Malar J 2020;19:457.
48. Is it Dengue or is it COVID-19? Dengue CDC. Available from: https://www.cdc.gov/dengue/healthcare-providers/dengue-or-covid.html [Last accessed on 2022 Jun 08].
49. Mahajan NN, Kesarwani SN, Shinde SS, Nayak A, Modi DN, Mahale SD, *et al*. Co-infection of malaria and dengue in pregnant women with SARS-CoV-2. Int J Gynecol Obstet 2020;151:459-62.
50. Tuberculosis. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis [Last accessed on 2022 Jun 08].
51. Jonsson J, Kühlmann-Berenzon S, Berggren I, Bruchfeld J. Increased risk of active tuberculosis during pregnancy and postpartum: A register-based cohort study in Sweden. Eur Respir J 2020;55:1901886.
52. Zumla A, Bates M, Mwaba P. The neglected global burden of tuberculosis in pregnancy. Lancet Glob Health 2014;2:e675-6.
53. Global Tuberculosis Report. Geneva: World Health Organization; 2020. Available from: https://www.apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

[Last accessed on 2022 Jul 03].
54. Gajbhiye RK, Mahajan NN, Kamath N, Bahirat S, Patokar G, Bhurke AV, *et al*. Clinical presentations, pregnancy complications, and maternal outcomes in pregnant women with COVID-19 and tuberculosis: A retrospective cohort study. Int J Gynecol Obstet 2021;153:176-9.
55. TB/COVID-19 Global Study Group. Tuberculosis and COVID-19 co-infection: Description of the global cohort. Eur Respir J 2022;59:2102538.
56. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
57. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, *et al*. Comorbidity and its impact on 1,590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J 2020;55:2000547.
58. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, *et al*. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. JAMA Intern Med 2021;181:714-7.
59. Rheumatic Heart Disease. Available from: https://www.who.int/news-room/fact-sheets/detail/rheumatic-heart-disease [Last accessed on 2022 Jun 08].
60. Tilve A, Mahajan NN, Pandey A, Jnanananda B, Gadekar S, Mahale SD, *et al*. Impact of COVID-19 on pregnant women with Rheumatic heart disease or Peripartum cardiomyopathy. Eur J Obstet Gynecol Reprod Biol 2021;258:459-61.
61. Zafar MS, Naqash MM, Bhat TA, Malik GM. Guillain-Barré syndrome in pregnancy: An unusual case. J Fam Med Prim Care 2013;2:90.
62. Pacheco LD, Saad AF, Hankins GDV, Chiosi G, Saade G. Guillain-Barré syndrome in pregnancy. Obstet Gynecol 2016;128:1105-10.
63. Mahajan NN, Srivastava S, Chakor R, More P, Mahale SD, Gajbhiye RK. Neurological complications of COVID-19 and spontaneous abortion in a pregnant woman-A case report. Eur J Obstet Gynecol Reprod Biol 2021;263:278-9.
64. Tekin AB, Zanapalioglu U, Gulmez S, Akarsu I, Yassa M, Tug N. Guillain Barre syndrome following delivery in a pregnant woman infected with SARS-CoV-2. J Clin Neurosci 2021;86:190-2.
65. Aasfara J, Hajjij A, Bensouda H, Ouhabi H, Benariba F. A unique association of bifacial weakness, paresthesia and vestibulocochlear neuritis as post-COVID-19 manifestation in pregnant women: A case report. Pan Afr Med J 2021;38:30.
66. Garcia JJ, Turalde CW, Bagnas MA, Anlacan VM. Intravenous immunoglobulin in COVID-19 associated Guillain-Barré syndrome in pregnancy. BMJ Case Rep 2021;14:e242365.
67. Marchand G, Patil AS, Masoud AT, Ware K, King A, Ruther S, *et al*. Systematic review and meta-analysis of COVID-19 maternal and neonatal clinical features and pregnancy outcomes up to June 3, 2021. AJOG Glob Rep 2022;2:100049.
68. Wang X, Chen X, Zhang K. Maternal infection with COVID-19 and increased risk of adverse pregnancy outcomes: A meta-analysis. J Matern Fetal Neonatal Med 2022;35:9368-75.
69. Piekos SN, Roper RT, Hwang YM, Sorensen T, Price ND, Hood L, *et al*. The effect of maternal SARS-CoV-2 infection timing on birth outcomes: A retrospective multicentre cohort study. Lancet Digit Health 2022;4:e95-104.
70. Matar R, Alrahmani L, Monzer N, Debiane LG, Berbari E, Fares J, *et al*. Clinical presentation and outcomes of pregnant women with coronavirus disease 2019: A systematic review and meta-analysis. Clin Infect Dis 2021;72:521-33.
71. Pathirathna ML, Samarasekara BPP, Dasanayake TS, Saravanakumar P, Weerasekara I. Adverse perinatal outcomes in COVID-19 infected pregnant women: A systematic review and meta-analysis. Healthcare (Basel) 2022;10:203.
72. Omar M, Youssef MR, Trinh LN, Attia AS, Elshazli RM, Jardak CL, *et al*. Excess of cesarean births in pregnant women with COVID-19: A meta-analysis. Birth 2022;49:179-93.
73. Metz TD, Clifton RG, Hughes BL, Sandoval GJ, Grobman WA, Saade GR, *et al*. Association of SARS-CoV-2 infection with serious maternal morbidity and mortality from obstetric complications. JAMA 2022;327:748-59.
74. Gandhi AM, Ganatra AM, Tank P. Preliminary results from FOGSI's national registry on pregnancy with COVID-19. J Obstet Gynaecol India 2021;71:361.
75. Flaherman VJ, Afshar Y, Boscardin WJ, Keller RL, H Mardy A, Prahl MK, *et al*. Infant outcomes following maternal infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): First report from the pregnancy coronavirus outcomes registry (PRIORITY) study. Clin Infect Dis 2021;73:E2810-3.
76. Mullins E, Hudak ML, Banerjee J, Getzlaff T, Townson J, Barnette K, *et al*. Pregnancy and neonatal outcomes of COVID-19: Coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. Ultrasound Obstet Gynecol 2021;57:573-81.
77. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, *et al*. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID multinational cohort study. JAMA Pediatr 2021;175:817-826.
78. Carrasco I, Muñoz-Chapuli M, Vigil-Vázquez S, Aguilera-Alonso D, Hernández C, Sánchez-Sánchez C, *et al*. SARS-COV-2 infection in pregnant women and newborns in a Spanish cohort (GESNEO-COVID) during the first wave. BMC Pregnancy Childbirth 2021;21:1-10.
79. Vouga M, Favre G, Martinez-Perez O, Pomar L, Acebal LF, Abascal-Saiz A, *et al*. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. Sci Rep 2021;11:13898.
80. McClymont E, Albert AY, Alton GD, Boucoiran I, Castillo E, Fell DB, *et al*. Association of SARS-CoV-2 infection during pregnancy with maternal and perinatal outcomes. JAMA 2022;327:1983-91.
81. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, *et al*. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. BMJ 2020;369.
82. Overtoom EM, Rosman AN, Zwart JJ, Vogelvang TE, Schaap TP, van den Akker T, *et al*. SARS-CoV-2 infection in pregnancy during the first wave of COVID-19 in the Netherlands: A prospective nationwide population-based cohort study (NethOSS). BJOG An Int J Obstet Gynaecol 2022;129:91-100.
83. Donati S, Corsi E, Maraschini A, Salvatore MA. SARS-CoV-2

infection among hospitalised pregnant women and impact of different viral strains on COVID-19 severity in Italy: A national prospective population-based cohort study. BJOG 2022;129:221-231.
84. Balachandren N, Davies MC, Hall JA, Stephenson JM, David AL, Barrett G, *et al*. SARS-CoV-2 infection in the first trimester and the risk of early miscarriage: A UK population-based prospective cohort study of 3041 pregnancies conceived during the pandemic. Hum Reprod 2022;37:1126-33.
85. Palomo M, Youssef L, Ramos A, Torramade-Moix S, Moreno-Castaño AB, Martinez-Sanchez J, *et al*. Differences and similarities in endothelial and angiogenic profiles of preeclampsia and COVID-19 in pregnancy. Am J Obstet Gynecol 2022;227:227.e1-16.
86. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: A systematic review and meta-analysis. Am J Obstet Gynecol 2022;226:68-89.e3.
87. Mahajan NN, Ansari M, Gaikwad C, Jadhav P, Tirkey D, Pophalkar MP, *et al*. Impact of SARS-CoV-2 on multiple gestation pregnancy. Int J Gynecol Obstet 2021;152:220-5.
88. Blitz MJ, Gerber RP, Gulersen M, Shan W, Rausch AC, Prasannan L, *et al*. Preterm birth among women with and without severe acute respiratory syndrome coronavirus 2 infection. Acta Obstet Gynecol Scand 2021;100:2253-9.
89. Mahajan NN, Pednekar R, Gaikwad C, More P, Pophalkar M, Kesarwani S, *et al*. Increased spontaneous preterm births during the second wave of the coronavirus disease 2019 pandemic in India. Int J Gynecol Obstet 2022;157:115-20.
90. Oakley LL, Örtqvist AK, Kinge J, Hansen AV, Petersen TG, Söderling J, *et al*. Preterm birth after the introduction of COVID-19 mitigation measures in Norway, Sweden, and Denmark: A registry-based difference-in-differences study. Am J Obstet Gynecol 2022;226:550.e1-550.22.
91. De Curtis M, Villani L, Polo A. Increase of stillbirth and decrease of late preterm infants during the COVID-19 pandemic lockdown. Arch Dis Child Fetal Neonatal Ed 2021;106:456.
92. Hui L, Marzan MB, Potenza S, Rolnik DL, Pritchard N, Said JM, *et al*. Increase in preterm stillbirths in association with reduction in iatrogenic preterm births during COVID-19 lockdown in Australia: A multi-centre cohort study. Am J Obstet Gynecol 2022;227:491.e1-17.
93. Stenton S, McPartland J, Shukla R, Turner K, Marton T, Hargitai B, *et al*. SARS-COV2 placentitis and pregnancy outcome: A multicentre experience during the Alpha and early Delta waves of coronavirus pandemic in England. EClinicalMedicine 2022;47:101389.
94. Dubucs C, Groussolles M, Ousselin J, Sartor A, Van Acker N, Vayssière C, *et al*. Severe placental lesions due to maternal SARS-CoV-2 infection associated to intrauterine fetal death. Hum Pathol 2022;121:46-55.
95. Mahajan NN, Gaikwad C, Tayshete R, Saldanha C, Pednekar R, Mahale SD, *et al*. Increased stillbirth rate during the second wave of COVID-19 pandemic in India. Eur J Obstet Gynecol Reprod Biol 2021;266:191-2.
96. Vesce F, Battisti C, Crudo M. The inflammatory cytokine imbalance for miscarriage, pregnancy loss and COVID-19 Pneumonia. Front Immunol 2022;13:861245.
97. Gajbhiye RK, Tilve A, Kesarwani S, Srivastava S, Kore SJ, Patil K, *et al*. Increased rate of miscarriage during second wave of COVID-19 pandemic in India. Ultrasound Obstet Gynecol 2021;58:946-9.
98. Mahajan NN, Pophalkar M, Patil S, Yewale B, Chaaithanya IK, Mahale SD, *et al*. Pregnancy outcomes and maternal complications during the second wave of coronavirus disease 2019 (COVID-19) in India. Obstet Gynecol 2021;138:660-2.
99. Pednekar R, Kore SJ, Sankalecha S, Kulkarni G, Athavale M, Kumbhar P, *et al*. Impact of both the waves of COVID-19 pandemic on ectopic pregnancy in India. J SAFOG 2021;13:403-6.
100. Enhancing Response to Omicron SARS-CoV-2 Variant. Available from: https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states [Last accessed on 2022 Jun 09].
101. Mahajan N, Kesarwani S, Salunke C, Kumbhar P, Yenkure P, Shaikh J, *et al*. Clinical Presentation, Pregnancy Complications and Maternal Outcomes of SARS-CoV-2 Infection in Pregnant Women During the Third Wave of COVID-19 in Mumbai, India. Int J Gynecol Obstet 2022:1-6. Doi: 10.1002/ijgo.14348.
102. Adhikari EH, SoRelle JA, McIntire DD, Spong CY. Increasing severity of COVID-19 in pregnancy with Delta (B.1.617.2) variant surge. Am J Obstet Gynecol 2022;226:149-51.
103. Adhikari EH, MacDonald L, SoRelle JA, Morse J, Pruszynski J, Spong CY. COVID-19 cases and disease severity in pregnancy and neonatal positivity associated with Delta (B.1.617.2) and Omicron (B.1.1.529) variant predominance. JAMA 2022;327:1500-2.
104. Vousden N, Ramakrishnan R, Bunch K, Morris E, Simpson NAB, Gale C, *et al*. Severity of maternal infection and perinatal outcomes during periods of SARS-CoV-2 wildtype, alpha, and delta variant dominance in the UK: Prospective cohort study. BMJ Med 2022;1:e000053.
105. Engjom HM, Ramakrishnan R, Vousden N, Bunch K, Morris EP, Simpson N, *et al*. Severity of Maternal SARS-CoV-2 Infection and Perinatal Outcomes during the Omicron Variant Dominant Period: UK Obstetric Surveillance System national Cohort Study. medRxiv; 2022. Available from: https://www.medrxiv.org/content/early/2022/03/09/2022.03.07.22271699.abstract [Last accessed on 2022 Jun 08].
106. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, *et al*. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. Lancet 2020;395:809-15.
107. Shende P, Gaikwad P, Gandhewar M, Ukey P, Bhide A, Patel V, *et al*. Persistence of SARS-CoV-2 in the first trimester placenta leading to transplacental transmission and fetal demise from an asymptomatic mother. Hum Reprod 2021;36:899-906.
108. Dumont S, Balduyck J, Reynders M, Vanwalleghem L, Lebbe B. Acute SARS-CoV-2 alpha variant infection leading to placental insufficiency and fetal distress. J Med Virol 2022;94:1196-200.
109. Argueta LB, Lacko LA, Bram Y, Tada T, Carrau L, Rendeiro AF, *et al*. Inflammatory responses in the placenta upon SARS-CoV-2 infection late in pregnancy. iScience 2022;25:104223.
110. Ferraiolo A, Barra F, Kratochwila C, Paudice M, Vellone VG,

Godano E, *et al*. Report of positive placental swabs for sars-cov-2 in an asymptomatic pregnant woman with covid-19. Medicina (Kaunas) 2020;56:306.
111. Hsu AL, Guan M, Johannesen E, Stephens AJ, Khaleel N, Kagan N, *et al*. Placental SARS-CoV-2 in a pregnant woman with mild COVID-19 disease. J Med Virol 2021;93:1038-44.
112. Lokken EM, Huebner EM, Taylor GG, Hendrickson S, Vanderhoeven J, Kachikis A, *et al*. Disease severity, pregnancy outcomes, and maternal deaths among pregnant patients with severe acute respiratory syndrome coronavirus 2 infection in Washington State. Am J Obstet Gynecol 2021;225:77.e1-77.e14.
113. Siqueira ST, De Souza EK, Martins-Filho PR, Silva JR, Gurgel RQ, Cuevas LE, *et al*. Clinical characteristics and risk factors for maternal deaths due to COVID-19 in Brazil: A nationwide population-based cohort study. J Travel Med 2022;29:taab199.
114. Moghadam SA, Dini P, Nassiri S, Motavaselian M, Hajibaba M, Sohrabi M. Clinical features of pregnant women in Iran who died due to COVID-19. Int J Gynaecol Obstet 2021;152:215-9.
115. Gargari SS, Rahmati N, Fateh R, Khandani A, Nikfar S, Ghafouri-Fard S. Investigation of maternal and perinatal outcome in a population of Iranian pregnant women infected with COVID-19. Sci Rep 2022;12:9815.
116. Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, *et al*. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. Int J Infect Dis 2022;116:38-42.
117. Mndala L, Monk EJM, Phiri D, Riches J, Makuluni R, Gadama L, *et al*. Comparison of maternal and neonatal outcomes of COVID-19 before and after SARS-CoV-2 omicron emergence in maternity facilities in Malawi (MATSurvey): Data from a national maternal surveillance platform. Lancet Glob Health 2022;10:E1623-31.
118. Mendez-Dominguez N, Santos-Zaldívar K, Gomez-Carro S, Datta-Banik S, Carrillo G. Maternal mortality during the COVID-19 pandemic in Mexico: A preliminary analysis during the first year. BMC Public Health 2021;21:1297.
119. Lumbreras-Marquez MI, Campos-Zamora M, Seifert SM, Kim J, Lumbreras-Marquez J, Vazquez-Alaniz F, *et al*. Excess maternal deaths associated with coronavirus disease 2019 (COVID-19) in Mexico. Obstet Gynecol 2020;136:1114-6.
120. Ríos-Silva M, Murillo-Zamora E, Mendoza-Cano O, Trujillo X, Huerta M. COVID-19 mortality among pregnant women in Mexico: A retrospective cohort study. J Glob Health 2020;10:020512.
121. Torres-Torres J, Martinez-Portilla RJ, Espino-y-Sosa S, Estrada-Gutierrez G, Solis-Paredes JM, Villafan-Bernal JR, *et al*. Comorbidity, poverty and social vulnerability as risk factors for mortality in pregnant women with confirmed SARS-CoV-2 infection: Analysis of 13 062 positive pregnancies including 176 maternal deaths in Mexico. Ultrasound Obstet Gynecol 2022;59:76-82.
122. Thoma ME, Declercq ER. All-cause maternal mortality in the US Before vs during the COVID-19 pandemic. JAMA Netw Open 2022;5:e2219133.
123. Siegel M, Critchfield-Jain I, Boykin M, Owens A. Actual racial/ethnic disparities in COVID-19 Mortality for the non-hispanic black compared to non-hispanic white population in 35 US States and their association with structural Racism. J Racial Ethn Health Disparities 2022;9:886-98.
124. Khoiwal K, Agarwal A, Mittal A, Gaurav A, Chawla L, Mundhra R, *et al*. The lethal effect of the second wave of COVID-19 on pregnant women: A matter of concern. Int J Gynecol Obstet 2022;156:178-81.
125. Singh V, Choudhary A, Datta MR, Ray A. Maternal and neonatal outcome of pregnant women with SARS-CoV-2 infection during the first and second wave of COVID-19 in a tertiary care institute in Eastern India. Cureus 2022;14:e22360.
126. Sahin D, Tanacan A, Anuk AT, Sinaci S, Besimoglu B, Oluklu D, *et al*. Comparison of clinical features and perinatal outcomes between pre-variant and post-variant periods in pregnant women with SARS-CoV-2: Analysis of 1935 cases. Arch Gynecol Obstet 2022;306:1939-48.
127. Tekin AB, Yassa M, İlter PB, Yavuz E, Önden B, Usta C, *et al*. COVID-19 related maternal mortality cases in associated with Delta and Omicron waves and the role of lung ultrasound. Turk J Obstet Gynecol 2022;19:88-97.
128. Scheler CA, Discacciati MG, Vale DB, Lajos GJ, Surita FG, Teixeira JC. Maternal deaths from COVID-19 in Brazil: Increase during the second wave of the pandemic. Rev Bras Ginecol Obstet 2022;44:567-72.
129. Ilter PB, Prasad S, Mutlu MA, Tekin AB, O'Brien P, von Dadelszen P, *et al*. Maternal and perinatal outcomes of SARS-CoV-2 infection in unvaccinated pregnancies during Delta and Omicron waves. Ultrasound Obstet Gynecol 2022;60:96-102.
130. Ilter PB, Prasad S, Berkkan M, Mutlu MA, Tekin AB, Celik E, *et al*. Clinical severity of SARS-CoV-2 infection among vaccinated and unvaccinated pregnancies during the Omicron wave. Ultrasound Obstet Gynecol 2022;59:560-62.
131. Wells CR, Galvani AP. The global impact of disproportionate vaccination coverage on COVID-19 mortality. Lancet Infect Dis 2022;22:1254-5.
132. Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, *et al*. Vertical transmission of coronavirus disease 2019: A systematic review and meta-analysis. Am J Obstet Gynecol 2021;224:35-53.e3.
133 Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, *et al*. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine 2020;25:100446.
134. Mand N, Iannaccone A, Longardt AC, Hutten M, Mense L, Oppelt P, *et al*. Neonatal outcome following maternal infection with SARS-CoV-2 in Germany: COVID-19-related obstetric and neonatal outcome study (CRONOS). Arch Dis Child Fetal Neonatal Ed 2021;107:454-6.
135. Salvatore CM, Han JY, Acker KP, Tiwari P, Jin J, Brandler M, *et al*. Neonatal management and outcomes during the COVID-19 pandemic: An observation cohort study. Lancet Child Adolesc Health 2020;4:721-7.
136. Oncel MY, Akın IM, Kanburoglu MK, Tayman C, Coskun S, Narter F, *et al*. A multicenter study on epidemiological and clinical characteristics of 125 newborns born to women infected with COVID-19 by Turkish neonatal society. Eur J Pediatr 2021;180:733-42.
137. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RR, *et al*. Pregnancy outcomes among women with and without severe acute respiratory syndrome

coronavirus 2 infection. JAMA Netw Open 2020;3:e2029256.
138. Chamseddine RS, Wahbeh F, Chervenak F, Salomon LJ, Ahmed B, Rafii A. Pregnancy and neonatal outcomes in SARS-CoV-2 infection: A systematic review. J Pregnancy 2020;2020:4592450.
139. Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, *et al.* Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: A prospective national cohort study using active surveillance. Lancet Child Adolesc Health 2021;5:113-21.
140. Dileep A, ZainAlAbdin S, AbuRuz S. Investigating the association between severity of COVID-19 infection during pregnancy and neonatal outcomes. Sci Rep 2022;12:3024.
141. More K, Chawla D, Murki S, Tandur B, Deorari AK, Kumar P. Outcomes of neonates born to mothers with coronavirus disease 2019 (COVID-19)-National neonatology forum (NNF) India COVID-19 registry. Indian Pediatr 2021;58:525-31.
142. Iftimie S, López-Azcona AF, Vallverdú I, Hernández-Flix S, de Febrer G, Parra S, *et al*. First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. PLoS One 2021;16:e0248029.
143. Malik S, Jain D, Bokade CM, Savaskar S, Deshmukh LS, Wade P, *et al*. Outcomes in neonates born to mothers with COVID-19 during the second wave in India. Eur J Pediatr 2022;181:3537-43.
144. Krubiner CB, Faden RR, Karron RA, Little MO, Lyerly AD, Abramson JS, *et al*. Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response. Vaccine 2021;39:85-120.
145. Fell DB, Dhinsa T, Alton GD, Török E, Dimanlig-Cruz S, Regan AK, *et al*. Association of COVID-19 vaccination in pregnancy with adverse peripartum outcomes. JAMA 2022;327:1478-87.
146. Prasad S, Kalafat E, Blakeway H, Townsend R, O'Brien P, Morris E, *et al*. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. Nat Commun 2022;13:2414.
147. Shook LL, Kishkovich TP, Edlow AG. Countering COVID-19 vaccine hesitancy in pregnancy: The 4 Cs. Am J Perinatol 2022;39:1048-54.

How to cite this article: Zala S, Munshi H, Mahajan NN, Surve S, Gajbhiye R. Impact of COVID-19 pandemic on maternal and neonatal outcomes: A narrative review and evidence from the PregCovid registry. J Reprod Healthc Med 2023;4:2.