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Maternal Mortality in COVID Pandemic Era

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Abstract: ***Background: COVID 19 pandemic is a crisis of global proportions which has transformed the perspective of the entire world. The pandemic has affected maternal and neonatal health adversely. COVID 19 infection has an effect on various organs of the body increasing the risk of morbidity and mortality and it needs research to know the effect of the virus and also to ascertain the cause of the death. This study aims to evaluate maternal mortality in COVID pandemic era. Method: This is a prospective study which was carried out in the department of obstetrics and gynecology, Civil Hospital, Ahmedabad. The maternal patients coming to CHA with the clinical picture highly suggestive of COVID irrespective of RTPCR status were taken in this study. From these patients, few patients with alternate diagnosis were not included in this study. The study population was followed during their course of treatment to know the maternal and neonatal outcome. A proforma will be used for patients' details. Data will be compiled and analyzed. Result: Overall incidence of mortality amongst COVID positive patients in the given study population of 89 patients was found to be 12.3% (N=11). Out of 89 patients taken in this study 85 patients were RTPCR positive and 4 patients were found to be negative on RTPCR report but clinical and radiological pictures were strongly suggestive of COVID pneumonitis. The most common presenting complaint is fever seen in 53.9% patients. Other complaints were cough (25.8%), sore throat (13.4%), breathlessness (8.9%), diarrhoea (2.2%).19% of the patients in this study had presented without any complaints. Approximately 26.9% patients in this study developed complications. Most common complication found in patients infected with COVID was ARDS/pneumonitis (63%) in this study. Other compilations were DIC (14.8%), AKI (11.1%), hepatic failure (7.4%) and cardiac disease (3.7%) in this study. Conclusion: In the beginning of the COVID-19 pandemic, there was a perception that COVID-19 infection involves lungs primarily but later it was seen that multiple system involvement was attributable to the cytokine storm. AKI and other complications were attributable to past/ present/ subclinical COVID-19 infection and were also observed in RTPCR negative patients, indicating that RTPCR was not the basis of treatment during the pandemic but the clinical symptoms were found to be more reliable. The diagnosis of pneumonitis was delayed in antenatal patients as radiological investigations were avoided and hence these patients presented in the later stages of the disease leading to increased mortality in COVID-19 pandemic era. Thus it is best to take appropriate measures to prevent COVID-19 infection. This study observed absence of vertical transmission from mother to fetus and hence neonates were allowed to breastfeed from their mothers. There was no need for isolation of the neonate from the mother with COVID-19 infection.***

Keywords: Mortality, morbidity, AKI, DIC, FEVER

1. Introduction

COVID 19 pandemic is a crisis of global proportions which has transformed the perspective of the entire world. When the pandemic began the evolution and spread of the virus was uncertain. The emergencies were tackled as much as possible by conservative approach. Nevertheless, childbirth cannot be delayed indefinitely. As the virus is new, little is known about its effects on pregnant women. Given the propensity of the virus to affect large numbers, the chance of pregnant women getting infected is inevitable. Concurrent with the sharp increase in the number of infections, the number of pregnant women and children with COVID-19 had increased during the pandemic which was a matter of concern. The knowledge regarding management plans of pregnant women with or suspected COVID-19 needs to be present in the maternal health care providers. This is of paramount importance because our preparedness at this level will pave the way for a protected future for both mother and child.

Coronavirus (CoV) family consists of viruses that cause common cold but can sometimes cause severe diseases such as Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS-CoV) and currently SARSCoV-2[7]. The causative agent for COVID-19 is a new strain of coronavirus named as SARS-CoV-2 and was first discovered in humans in Wuhan, China in 2019. The World Health Organization has declared COVID-19 as a pandemic. According to the latest reports, COVID-19 virus is mainly transmitted through respiratory droplets and contact. SARS-CoV-2 is a new virus and so not much is studied about its effects on pregnant women. ***According to the American College of Obstetricians and Gynecologists, there is no data on COVID-19 to suggest that pregnant women are at higher risk of getting the virus as compared to non pregnant women[13].***

The mean incubation period of COVID-19 is 5-7 days. Most people who are infected will show features latest by 11 days of exposure [8]. Most pregnant women will have mild to moderate flu-like symptoms of cough, sore throat and fever. Few may have difficulty in breathing or shortness of breath. These have been classified as features of severe acute respiratory illness (SARI) by WHO. Pregnant women especially those associated with medical diseases (diabetes, asthma, renal disease etc) may present with pneumonia and marked hypoxia. Immunocompromised and elderly pregnant women may present with atypical features such as fatigue, malaise, body ache and gastrointestinal symptoms like nausea and diarrhea. COVID-19 primarily affects lungs but it can also involve various other organs thus it can cause serious long term complications for the patients. Various long term effects of COVID 19 are still being studied.

Severe morbidity and mortality were reported primarily among pregnant women in the second and third trimesters of pregnancy. Morbidity and mortality will rely on the

combination of transmissibility, severity and a rapid person to person transmission. Mortality rates help us identify the severity of disease, identify at risk populations and evaluate the quality of healthcare. Therefore research regarding mortality rates becomes important for the community. Maternal mortality is an indicator of access and quality of women's health care.

During the recent pandemic it was found that there was an increase in the number of sudden/ unexplained maternal mortality which can be due to various reasons like a past history of COVID disease, sub clinical COVID 19 infection or undiagnosed COVID 19 infection. Thus indicating that COVID 19 infection has an effect on various organs of the body increasing the risk of morbidity and mortality and it needs research to know the effect of the virus and also to ascertain the cause of the death.

2. Materials and Method

This is a prospective study which was carried out in the department of obstetrics and gynecology, Civil Hospital, Ahmedabad. The maternal patients coming to CHA with the clinical picture highly suggestive of COVID irrespective of RTPCR status were taken in this study. From these patients, few patients on investigations were found to have alternate diagnosis and hence these patients were excluded. But few patients in spite of having RTPCR negative had radiological picture suggestive of COVID and those were included in this study. The study population was followed during their course of treatment to know the maternal and neonatal outcome. A proforma will be used to record information such as maternal age, parity, gestational age at presentation, history of presenting and past illness, history of contact or family history and obstetric history. After that, general physical, abdominal and pelvic examinations will be carried out. Investigations and management will be carried out in accordance with standardized department protocol. Details of labour, whether it will be spontaneous or induced, and method of induction and mode of delivery will be recorded. Maternal and fetal outcomes will be noted. In case of maternal mortality the cause of death will be evaluated and if it has any association with past history of COVID-19 or systemic changes related to COVID 19 will be evaluated. Data will be compiled and analyzed.

3. Results

Overall incidence of mortality amongst COVID positive patients in the given study population of 89 patients was found to be 12.3% (N=11). Out of these 11 mortality, 9 mortality occurred in the postnatal period and 2 were antenatal mortality. Out of 89 patients taken in this study 85 patients were RTPCR positive and 4 patients were found to be negative on RTPCR report but clinical and radiological pictures of RTPCR negative patients included in this study were strongly suggestive of COVID pneumonitis.

Out of 89 patients, 16 (14.83%) patients were referred from various hospitals.

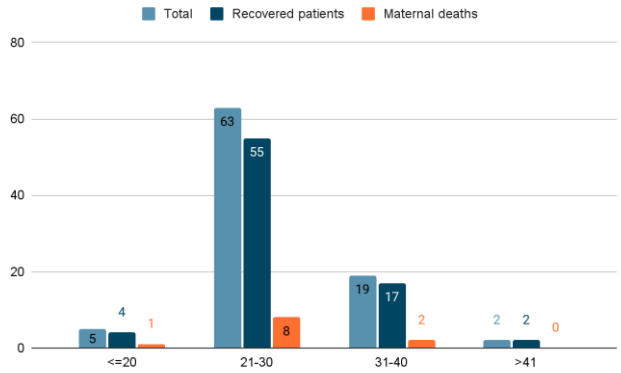

Figure 1: Age wise distribution of patients in the given study population and the number of patients who recovered or the maternal deaths that occurred

Thus indicating that the rate of mortality in age group <=20 years is 20%, amongst patients 21-30 years is 12.6%, amongst patients in 31-40 years is 10.5%.

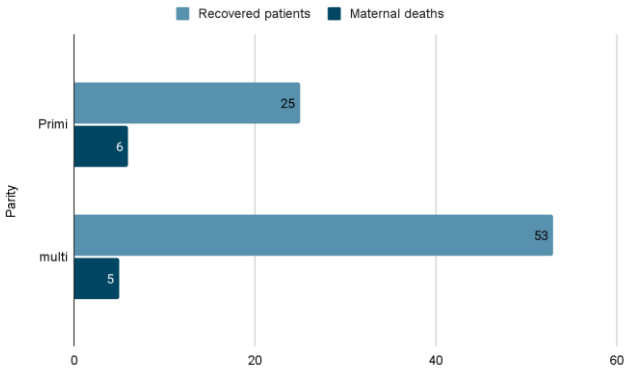

Figure 2: Parity in recovered patient and maternal death

In this study, 54 5% of the total mortality occurred in the primi patients while 45.5% mortality occurred in the multigravida patients.

Table 1: Gestational age at the time of admission

Gestational age on admission	Recovered patients (N=78)	Maternal deaths (N=11)
Ectopic pregnancy	3 (3.8%)	0
<32 weeks	8 (10.2%)	2 (18.18%)
33-36 weeks	8 (10.2%)	2 (18.18%)
>36weeks	48 (61.5%)	7 (63.6%)
Post partum	11 (14.1%)	0

In this study, 18.18% maternal mortality had occurred in patients at <32 weeks gestation and 32-36 weeks gestation each, 63.6% maternal mortality were at gestation >36 weeks.

Table 2: Mode of delivery

Mode of delivery in this pregnancy	Recovered patient (N=78)	Maternal deaths (N=11)
FTND/PTVD	25 (32%)	2 (18.18%)
LSCS	38 (48.7%)	6 (54.54%)
Operative vaginal delivery	0	1 (9.0%)
Laparotomy for ectopic pregnancy	3 (3.8%)	0
Patients discharged antenatally	12 (15.3%)	-
Antenatal maternal deaths	-	2 (18.18%)

12 (15.3%) patients in the study population were discharged during the antenatal period post recovery and 2 (18.18%) patients underwent maternal deaths in the antenatal period.

Out of the total 9 mortality that occurred in the postnatal patients, 2 (22.2%) mortality followed vaginal delivery, 66.6% mortality followed after cesarean section and 11.1% mortality followed operative vaginal delivery. ***Thus indicating that there is increased risk of maternal mortality in patients following cesarean section.***

Table 3: Neonatal outcomes

Neonatal outcome	No. of neonates
Live births	60
NICU Admission from the live births	9
IUD/SB/abortus	15

In this study, there were 60 (67.4%) live births and 15 (16.8%) were IUD/SB.

All of these neonates born to mothers infected with COVID-19 were tested for COVID-19 by RTPCR on the day of birth and on day 3. All the neonates had tested negative for COVID-19. Thus indicating that there is absence of vertical transmission.

Table 4: COVID-19 positive and symptomatic patients

COVID-19 positive	No. Of cases	Percentage
Symptomatic	72	89.80%
Asymptomatic	17	19.10%

In this study, 89.8% patients were symptomatic while 19.1% patients were asymptomatic.

Table 5: Complaints in COVID-19 patients and its prevalence in this study

Chief complaints	Prevalence
Fever	53.90%
Cough	25.80%
Sore throat	13.40%
Breathlessness	8.90%
Diarrhea	2.20%
Asymptomatic patients	19%

Majority of the maternal patients whether antenatal or postnatal suffered through mild or moderate infection. ***The most common presenting symptoms were fever (53.9%), sore throat (13.4%), cough (25.8%), breathlessness (8.9%), diarrhea (2.2%) and 19% patients were asymptomatic.***

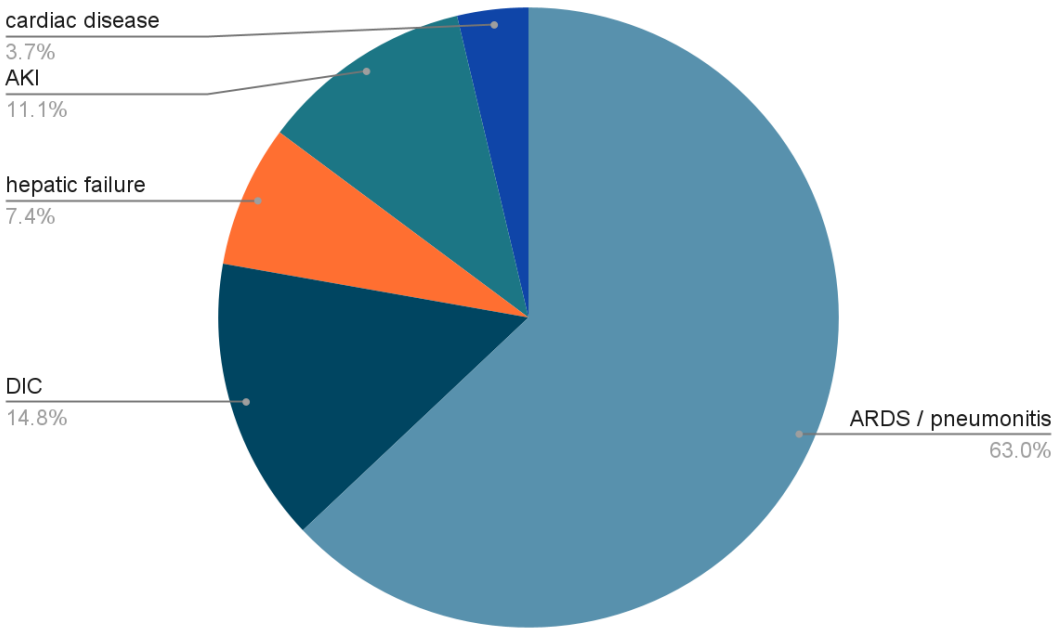

Figure 3: Maternal complications

Approximately 26.9% of patients in this study developed complications. From that few of the patients recovered with the ongoing treatment but 12.3% patients succumbed to COVID infection. ***Most common complication in patients infected with COVID was ARDS / pneumonitis (63%).*** Other complications were DIC (14.8%), AKI (11.1%), hepatic failure (7.4%) and cardiac disease (3.7%) in this study.

Table 6: Maternal complications and their outcome

Maternal complications	*Recovered patients (N=16)*	*Maternal deaths (N=11)*
ARDS/ Pneumonitis	15 (93.75%)	2 (18.18%)
DIC	1 (6.25%)	3 (27.2%)
AKI	0	3 (27.2%)
Hepatic failure	0	2 (18.18%)
Cardiac disease	0	1 (9%)

Thus it can be concluded that the most common complication was pneumonitis but it showed the maximum rate (93.75%) of recovery while the most lethal complications were AKI and DIC as they had the maximum mortality i. e. 27.2% each.

Table 7: Outcome of patients with DIC and AKI

	Outcome of patients with DIC (N=4)	Outcome of patients with AKI (N=3)
Recovered patients	1 (25%)	-
DIC with superimposed AKI	3 (75%)	-
AKI followed by respiratory failure	-	3 (100%)

In this study, there were 75% patients with DIC who developed superimposed AKI and succumbed to it while all the patients developing AKI developed respiratory failure and succumbed to it.

Table 8: Outcome of the anticoagulant therapy

Inj LMWH administration (N=14)	Recovered patients (N=10)	Maternal deaths (N=4)
In pts with Altered coagulation profile (N=10)	9 (90%)	1 (10%)
In pts diagnosed with DIC (N=4)	1 (25%)	3 (75%)

The patients who developed complications were seen to have altered d dimer and fibrinogen levels requiring the necessity for anticoagulant therapy. It was found that the coagulation profile was altered in 14 (15.7%) patients, necessitating the need for administration of INJ. LMWH (low molecular weight heparin) 5, 00, 000 IU subcutaneously in these 15.7% patients.

In this study, after the administration of the anticoagulant therapy in patients with altered coagulation profile 90% patients recovered and 10% patients succumbed. While from the patients diagnosed with DIC, after LMWH administration 25% patients recovered while 75% succumbed. This indicates that there is significantly increased risk of maternal mortality in patients with DIC in spite of LMWH administration.

COVID-19 INFECTION AND AKI

During the COVID pandemic it was observed that the patients developing AKI into the postpartum period had significantly increased. Most of them were due to clinical COVID-19 infection. Few of these patients developing AKI in the pandemic era did not have a past history of COVID-19 infection hence this can be attributed to the subclinical COVID-19 infection where the virus might have invaded the kidneys. ***Thus it was concluded that the rise in the cases of AKI in the COVID pandemic era was due to the unknown subclinical COVID-19 infection in the past where the virus might have invaded the kidney but no signs or symptoms of AKI seen. But later in times of stress in the postpartum period the damage to the kidneys may be aggravated and was manifested as AKI. Thus indicating a strong association between COVID-19 infection and AKI.***

Pregnant women with COVID-19 are at risk of developing AKI which needs to be differentiated from other causes of pregnancy related AKI. Pregnancy related hemodynamic changes involving the kidney makes the women vulnerable to develop AKI. AKI in a patient with COVID-19 can be attributed to multiple etiologies. SARSCOV-2 can cause direct damage to tubular injury or can indirectly lead to AKI secondary to cytokine storm. Fever and tachypnea may contribute to volume depletion with the need for judicious fluid resuscitation to prevent hypervolemia. Intrarenal etiologies such as pre-eclampsia, thrombotic microangiopathies, peripartum sepsis, acute cortical necrosis, acute pyelonephritis, flare from underlying glomerulonephritis such as lupus nephritis or progression of chronic kidney disease should also be included in the differential diagnosis for kidney dysfunction in patients with COVID-19. Diuretics should be used judiciously to prevent volume depletion.

For patients with SARS-CoV-2 infection, renal injury mainly manifests as increased serum creatinine, variable degrees of proteinuria and hematuria and radiographic abnormalities of the kidneys. The pathophysiology of AKI in COVID-19 is complex, suggestive of a biphasic pattern with volume responsive AKI occurring in early stages of the disease and kidney injury occurring in later stages of the disease. Acute tubular injury in the setting of creatinine elevation is reversible with appropriate care such as aggressive fluid management. Nutritional and fluid support, avoidance of nephrotoxins, maintenance of oxygenation saturation, and hemodynamic stability were useful for the management of AKI.

During this time, COVID-19 patients with AKI had a significantly higher mortality rate when compared to COVID-19 patients without AKI. Thus, AKI is a major negative prognostic factor in COVID-19 patients with dire need of prevention and management of AKI in this susceptible population.

Patients with COVID-19 should be monitored for early evidence of AKI so that preventive measures can be taken to avoid AKI.

4. Discussion

The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been growing at an accelerating rate. The increasing mortality rate warrants identification and protection of the vulnerable populations in society. Pregnancy makes the mother more vulnerable to severe infections. Anatomical changes such as an increase in the transverse diameter of the thoracic cage and an elevated level of the diaphragm and decrease maternal tolerance to hypoxia. Lung volume changes and vasodilation can further predispose to mucosal edema and increased secretions in the upper respiratory tract. In addition, alterations in cell-mediated immunity contribute to the increased susceptibility of pregnant women to be infected by intracellular organisms such as viruses. With regard to the fetus and the newborn, the immaturity of the innate and adaptive immune systems makes them highly susceptible to infections. .

In this study of 89 pregnant females infected with COVID-19 infection suggested that most of the pregnant females have mild to moderate form of infection. Most of these recover with the primary treatment. Only a few patients develop the specific maternal complications i. e 26.9% patients. Most common complication was ARDS/COVID pneumonitis. Other complications were DIC, AKI, hepatic failure, cardiac disease. This study further suggests that SARS COV 2 not only involves the lung but also other systems in the body like GIT leading to diarrhea, nausea, vomiting; renal leading to AKI (acute kidney injury), haematuria, proteinuria; cardiac leading to myocarditis, cardiac arrhythmias, cardiogenic shock, myocardial infarction; endocrine system leading to hyperglycemia; haematological system-altered coagulation profile, thrombocytopenia. This multiple system involvement in COVID- 19 infection was attributable to ***cytokine storm.***

Thus due to haematological system involvement in COVID infection further aggravates the already existing hypercoagulable state of pregnancy leading to increased risk of thrombo embolic complications. This is due to an altered coagulation profile in some patients, leading to mostly an increase in the D-dimer and fibrinogen which further necessitates the anticoagulant therapy with INJ. LMWH (low molecular weight heparin) 5, 000IU subcutaneously.

14 patients (15.7%) of patients had altered coagulation profile indicating the involvement of the haematological system or can be an early indicator of the onset of DIC.

Most maternal deaths in this study were seen to be due to the development of pneumonitis. Of the 11 maternal deaths, 9 were postnatal and 2 were antenatal deaths. In the 2 antenatal maternal deaths that occurred in this study it was seen that the cause of death for both the patients was pneumonitis. This indicated that in the antenatal patients the treatment and diagnosis of pneumonitis is challenging. This is because of the adverse effect on the fetus of the radiological investigation. ***The diagnosis of pneumonitis is delayed in the antenatal period as CT SCAN / x-ray can not be done in the antenatal patients. Thus lung involvement in the antenatal patients is indicated by the development of severe symptoms which usually occurs in the later stage of the disease***. The risk of maternal deaths was high in antenatal patients also due to the limited literature available on the safety of various newer drugs in pregnancy.

From the patients included in this study 4 patients were found to be RTPCR negative, 3 patients had died and 1 patient recovered. In this study it was seen that in spite of RTPCR being negative the clinical signs and symptoms and the CT scan were strongly suggestive of COVID pneumonitis in these 4 patients. This suggests to us that the RTPCR report was false negative. False negative reports can be due to less sensitive testing methods and improper collection of swabs. ***Thus establishing a fact that if RTPCR is negative it does not necessarily exclude COVID-19 infection. So if a patient presents with strong clinical suspicion for COVID in this pandemic era, in spite of RTPCR being negative, the patient should undergo further investigations and should be treated as COVID positive unless proven otherwise.***

There was a higher rate of cesarean section in patients infected with COVID 19 which wasn't merely due to infection but the fact that mode of delivery in current pregnancy depends on the past obstetric history of the patient.

No adverse neonatal outcome was noted in neonates which can be attributed to the COVID infection. Most of the neonates were with their mother, but a few were taken to NICU. The most common reason for NICU admission in neonates is prematurity and low birth weight. ***Majority of the neonates born to a COVID positive mother were not found to have COVID- 19 infection. Thus it suggested absence of vertical transmission of infection from mother to fetus. Neonates are allowed to breastfeed from their mothers. Having COVID-19 infection is not a contraindication to breastfeeding. It is not advisable to isolate the neonate from the mother with COVID 19 infection.***

Regarding breast feeding, COVID 19 women are educated about hygiene, social distancing, wearing facemask while feeding are explained. According to G. A. Ryan et al study there is no evidence of virus in breast milk secretion till now and the benefits of breastfeeding seem to outweigh any potential risks of transmission of virus through breast milk. Hence breastfeeding is recommended to all COVID 19 women.

5. Conclusion

In the beginning of the COVID-19 pandemic, there was a perception that COVID-19 infection involves lungs primarily but later on as the spread of the infection increased rampantly and patients presented with various symptoms it indicated ***multiple system involvement*** in COVID infection in this study. This multiple system involvement was attributable to the ***cytokine storm.*** Most of the patients developed AKI which was attributable to past/ present COVID-19 infection or past unknown subclinical COVID-19 infection. AKI and other complications were also observed in RTPCR negative patients, indicating that RTPCR was not the basis of treatment during the pandemic but the clinical symptoms were found to be more reliable. In this study it was also observed that the diagnosis of pneumonitis was delayed in antenatal patients as radiological investigations were avoided and hence these patients presented in the later stages of the disease when symptoms develop or with a more severe form of disease which was the reason of increased mortality in COVID-19 pandemic era. Thus it can be concluded that it is best to take appropriate measures to prevent COVID-19 infection. This study observed absence of vertical transmission from mother to fetus and hence neonates were allowed to breastfeed from their mothers. There was no need for isolation of the neonate from the mother with COVID-19 infection.

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