

Critically ill Covid-19 in pregnancy: Case series from a tertiary care centre in South India; Review of literature

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INTRODUCTION

It is well understood by now that the infection caused by SARS-CoV -2 is not limited to pneumonia or ARDS but can evolve into a multisystem disorder. Initial evidence and meta-analysis had an impression that antenatal women are not at an increased risk as compared to their non-pregnant peer. But recent growing data suggests that pregnant women are at an increased risk of severe illness as compared with non-pregnant women particularly in the later pregnancy (1). Although, overall risk of mortality remains very low, approximately 1 % (2). Risk factors like maternal age of 35 years or older, ethnic minority backgrounds, BMI above 25 kg/m², pre-pregnancy co-morbidities like diabetes or hypertension, socioeconomic deprivation and being a healthcare worker or in other public-interacting occupations appear to be associated with increased rate of infection and hospitalization (1,3).

Along with maternal morbidity COVID-19 infection also increased perinatal morbidity and mortality, where evidence suggest that it can be associated with double risk of stillbirth and an increased incidence of small-for-gestational-age babies, though the overall rate of stillbirth is small. Although, preterm birth rate in women with symptomatic COVID-19 appears to be two to three times higher than the background rate; contributed mainly by iatrogenic preterm births (1).

METHODOLOGY

A prospective cohort study of antenatal women with critical covid-19 was conducted at KIMS Health hospital of Kerala from 1st JULY 2020 to 31st June 2021. Categorization of cases into Severe Covid -19 and Critical Covid-19 was done as per the criteria provided by NIH (4) where Severe disease is defined as – Respiratory frequency >30 breaths per minute, SaO₂ <94 percent on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300, or lung infiltrates >50 percent. **Critical illness** refers to Respiratory failure, septic shock, and/or multiple organ dysfunction. Analysis was done including presentation, demographic data, diagnosis, disease progression, and treatment outcome in total 7 cases critical Covid-19 in pregnancy.

Results

In our series, age group of all affected women was between 20 to 30 years. All had symptomatic presentation at admission with fever being the most common symptom. In our series of cases, 5 out of seven antenatal women were in third trimester, two in second trimester. Four of these were delivered by caesarean section in view of maternal refractory respiratory distress in third trimester. One underwent spontaneous preterm vaginal delivery after recovery. One had recovered and continued pregnancy had a full-term vaginal delivery with average for gestational age baby. One had mild covid-19 at the time of term vaginal delivery and progressed to critical disease in the postpartum period despite thromboprophylaxis. All of them required invasive ventilation in view of ARDS and most of them had multisystem inflammatory disorder and one patient required ECMO. Cardiac involvement was noted in two patients having cardiomyopathy. There was one maternal mortality. Rest all the patients were discharged without much residual comorbidities. (Table 1)

Discussion

Critical care management of obstetrical patients with COVID-19 should generally be guided by the same principles as for the nonpregnant adult population and is determined by effective multidisciplinary care involving low threshold for admission, invasive ventilation and regular monitoring. The vulnerability of progression to critical disease of a pregnant women with Covid-19 is attributed to the physiological respiratory and immunity changes. Various registry data shows that pregnancy is associated with increased need for ICU care and organ support (25,26,27). According to the PregCOVID living systematic review of 192 cohort studies on pregnancy outcomes in covid-19 across hospitalized patients during the first wave, the need for ICU admission, need for invasive mechanical ventilation, and need for ECMO was twice as compared to the non-pregnant women of similar age (1). Pregnant individuals with COVID-19 in pregnancy required 3.73 days longer hospitalization than those pregnant without COVID-19 (1).

Risk factors for developing critical covid-19 include hypertension (17%), Diabetes (8%), cardiovascular diseases (5%), respiratory system disease (2%), BAME, obesity, advanced maternal age, immunosuppressive drugs and infections (3). Still care of pregnant woman with critical covid-19 poses lots of management dilemmas to the treating clinicians. In view of less available experience of pandemic management, evolving data and changing guidelines, it is important to keep updating the management strategies and involve multidisciplinary inputs. Still the most common dilemmas of management which we will be addressing here will include The data is presented on basis of case series, trials and interim management guidelines available. New aspects of disease pathology are continuously evolving and so are the treatment modalities.

Though initially there was a mixed data on findings that pregnancy is associated with increased need for ICU admission, by now it is well known that pregnancy increases the probability of hospital admission and intensive care (5,6). In cases of covid-19 induced acute respiratory failure requiring invasive mechanical ventilation, principles of care and monitoring of pregnant patients should be similar to that of the pregnant women without COVID-19. (7). Oxygen should be titrated to ensure saturations of 94–98%. This cut-off is based on animal studies where a lower oxygen saturation has been shown to cause changes in foetal heart rate and middle cerebral artery circulation (8). The level should be maintained with the aid of non-rebreather mask, non-invasive positive airway pressure (e.g. continuous positive airway pressure [CPAP]), intubation and Intermittent positive-pressure ventilation (IPPV), and or extracorporeal membrane oxygenation (ECMO) as and when appropriate. A low threshold for intubation and anticipation of difficult intubation is advised, in view of the pregnancy associated physiologic and anatomic changes. Thus, calling for indulgence and attempt by the experts. Typically, intubation is considered when there is increased oxygen requirements i.e. >15 L / minute by common nasal cannula or mask or > 40 to 50 L/minute by high-flow nasal cannula or >60% fraction of inspired oxygen (FiO₂) by a Venturi mask to maintain an oxygen saturation of equal to or more than 95% by transcutaneous pulse oximeter. Another indication included inability of a patient to protect the airway due to altered mental status.

Routine computerized before considering intubation is not to be considered, though can be considered in certain circumstances. Monitoring of response with X-ray and abdominal shield may be of assistance. In all our patients an early resort to invasive ventilation was sought in case of deterioration on clinical or imaging grounds.

Prone positioning was initially opposed and contraindicated in later gestations, but has now been considered useful in improving lung compliance by releasing the diaphragmatic and aortocaval compression. (9-12). Though interference with foetal monitoring is to be considered and most of the recommendations are for consideration till 26-28 weeks. Later as per the feasibility of neonatology care settings, delivery considerations are given more weightage as compared to maneuvers like proning (9). It can be considered in postpartum period safely.

Corticosteroids act by refining the inflammatory response and thereby decreasing the concentration of circulating proinflammatory mediators like tumour necrosis factor-alpha (TNF -alfa), interleukin-1 (IL-1) and interleukin-6 (IL-6). They control inflammation by causing immunosuppression; as such, they have a role in managing patients experiencing ARDS. (13,14). The RECOVERY trial deduced that low-dose dexamethasone (6 milligrams) reduced mortality by up to one-third among COVID-19 patients on mechanical ventilation and one-fifth among those who received supplemental oxygen. Though no benefit was noted in the group without oxygen support. Also, it has shown promising results in successful and early cessation of invasive mechanical ventilation (15). The RCOG recommends that pregnant women with moderate-to-severe COVID-19 should receive oral prednisolone or intravenous hydrocortisone (2) for a total of 10 days or up to discharge from hospital, whichever is sooner. In all our patients we considered a low threshold for starting steroids. When foetal lung maturity was the indication intramuscular route for dexamethasone was considered followed by transition to intravenous route for steroids. Earlier in accordance with the guidelines, methylprednisolone was considered later with the emergence of new evidence, intravenous dexamethasone was considered. Those who recovered soon, switching to oral steroids was considered (3). In our patients in third trimester were given steroids for lung maturity of foetus but delivery was not delayed for completion of course. All the five babies born preterm required NICU admission and respiratory assistance as well. All the babies were screened for covid-19 and were negative. All the babies were discharged healthy after variable stay duration.

It is now well established that thrombosis is associated with Covid-19 infection and micro thrombosis is perhaps the major cause for the disease related organ dysfunction, morbidity and mortality. Pregnancy and Covid-19 can have additive thrombotic effects. Servante et al did a meta-analysis and concluded that pregnancy in Covid-19 is associated with increased risk of coagulopathy and thromboembolism. Early diagnosis of the condition would be useful in the identification of women at risk of clinical deterioration. (16) All pregnant women should be considered a candidate for thromboprophylaxis, unless there is a contraindication (bleeding disorders, active bleeding etc). Though thrombocytopenia has been found to be associated in Covid-19 acute illness, thromboprophylaxis has been advised by various management guidelines keeping a safety net platelet count criteria of 50,000/cumm. There has been a debate over consideration of therapeutic versus prophylactic anticoagulation. NIH had in their press release recommended therapeutic dose to be associated with decreased need for life support in hospitalized patients. But results of various randomized controlled trials (RAPID, mPRCT collaborating REMAP-CAP, ATTACC, and ACTIV-4A) and thus guidelines from ASH, RCOG recommend that therapeutic anticoagulation is not superior to prophylactic anticoagulation in covid-19 with organ support. MDT input should be considered to decide upon optimum dosage taking into consideration weight and history of thrombotic events or other predisposing factors. Therapeutic doses of LMWH should be employed when VTE is suspected until objective testing can be undertaken.

In our cases also, anticoagulation was offered in all critical Covid-19 antenatal women. We followed the state guidelines recommending therapeutic dose of anticoagulation in critical Covid-19.

Individualized decision regarding timing and mode of delivery is to be taken in each case. Critical Covid-19 is not an indication for delivery. Requirement of an invasive ventilation or ECMO solely should not be considered as a criterion for delivery. But delivery should be considered in cases of clinical deterioration and when improvement in lung mechanics is expected by decompression of abdominal cavity pressure diaphragm especially after 32 weeks of gestation. Other factors playing a key-role in deciding timing of delivery include maternal medical and/or obstetrical comorbidities like pre-eclampsia, gestational age, and foetal indications. A shared decision should be made along with the multidisciplinary team including critical care and respiratory medicine experts and neonatologists. In our patients, 4 women delivered while on invasive ventilation in view of refractory maternal respiratory distress. 2 recovered and delivered later and one had delivered normally during mild illness, but later progressed to critical Covid-19.

There is a clear statement from the US National Institute of Health addressing that pregnant women should not be denied potentially effective treatments for COVID-19 with severe acute respiratory failure fearing the theoretical risks of fetal safety.

Tocilizumab, the monoclonal IL-6 inhibitor, has been shown to improve outcomes, in hospitalised patients with hypoxia (oxygen saturation below 92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein at or above 75 mg/l) and also survival benefits (2). There is limited data describing tocilizumab for use in pregnant women with COVID-19; however, safety of the medication is established by its long-term use in pregnant women with rheumatic disease with no increase in birth defects or miscarriage. Encouragingly, results from the RECOVERY trial (17). Jorgensen C et al in their assessment on tocilizumab in pregnancy and concluded that available data though does not raise serious safety signals, they have significant limitations and are thus not sufficient to delineate the complete spectrum of potential adverse outcomes that may be associated with exposure of the drug in pregnancy and lactation (28).

Remdesivir initially gained popularity, but interim results of the WHO Solidarity trial (29) have reported that the antiviral agent remdesivir had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay, in hospitalised patients with COVID-19. As the safety of remdesivir in pregnancy is largely unknown, consideration is to be given only for patients who are stable but not improving and strongly to be considered in those who are deteriorating (3).

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial has demonstrated that the investigational antibody combination developed by Regeneron reduces the risk of death when given to patients hospitalised with severe COVID-19 who have not mounted a natural antibody response of their own. The treatment uses a combination of two monoclonal antibodies (casirivimab and imdevimab, known as REGEN-COV in the US)

Monoclonal antibodies to be considered in pregnant patients with comorbidities and who do not require oxygen support to prevent progression of disease.

Conclusion

Early recognition of clinical deterioration, low threshold for ICU admission and invasive ventilation, timely decision of delivery can go far way optimizing maternal and perinatal outcome. Multidisciplinary team involvement is of utmost importance. Intubation by experienced personnel in view of anticipated difficult airway. Steroids, Tocilizumab to be considered in case of clinical deterioration at the earliest. Steroids for lung maturity to be considered but not to delay delivery for completion of course. A conservative approach for management in second trimester as evacuation of uterine cavity is not expected to add much to improving lung compliance. In third trimester to consider early delivery to help relieving pressure on diaphragm. Updation of management policies is a continuing process in this era of evolving evidence, thus improvising practices and quality of care delivered. Though involvement of pregnant women in clinical trials is surrounded by ethical restrictions, such studies, if done, can add to more appropriate management, rather than extrapolation of results from data on non-pregnant peers.

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- Ethical Approval – This study has been conducted according to institutional ethical standards.

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