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Preeclampsia-Like Syndrome in COVID-19– Deceptive Clinical Scenarios

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ABSTRACT

Background: COVID-19 and preeclampsia both are multisystemic diseases and both can have presentation as hypertension, proteinuria, and hepatic and renal dysfunction. Thus, creating deceptive clinical scenarios for diagnosis as well as management.

Cases: We report two cases of COVID-19 infection in pregnant women with secondary features of proteinuria, and significant hepatic dysfunction and hypertension. Despite presentation as severe preeclampsia, conservative management was adopted in view of consideration of Preeclampsia-like syndrome with COVID-19. Both pregnancies continued till term and gave birth to healthy babies.

Conclusion: In pregnancies complicated with COVID-19 infection, it is very important to consider the entity of preeclampsia-like syndrome as it can change the management drastically and has implications for both the mother and the baby.

Keywords: COVID-19, SARS-CoV-2, Preeclampsia-like syndrome

INTRODUCTION

The evidence in literature now suggests that COVID-19 in pregnancy predisposes to increased risk of severe and critical disease, including the need for intensive care unit care and mechanical ventilation, and overall mortality compared with women outside pregnancy [1,2]. This is also now well proven that apart from the respiratory system, SARS Cov -2 (severe acute respiratory syndrome coronavirus 2) virus can affect other systems as well. It can even present with Hypertension, proteinuria, and hepatic dysfunction and thus, mimic the clinical picture of preeclampsia. Also, SARS-CoV-2 infection and preeclampsia have common pathophysiological characteristics creating diagnostic and well as management dilemmas [3].

We report two cases of pregnant women with onset of features of preeclampsia on the background of COVID-19 infection and shall discuss the differential diagnosis, investigations, and management strategy.

CASE 1

26 –years-old primigravida was admitted at 27^{+4} weeks of gestation with symptoms of fever, cough and worsening dyspnoea since three days. Her vital signs were temperature 38.8°C, heart rate 110 beats per min, blood pressure 130/85 mm Hg, respiratory rate 32 breaths per minute, and oxygen saturation (SpO2) 89% in room air. On physical examination, there were bilateral basal crepitations with soft and non-tender abdomen. COVID-19 infection was confirmed by an RTPCR of the nasopharyngeal swab. Based on her vital parameters and need for oxygen supplementation, she was categorized as having severe COVID-19 pneumonia with ARDS (acute respiratory distress syndrome). She was admitted to the intensive care unit and required intubation with mechanical ventilation as her Oxygen saturation didn't improve with non-invasive modalities. Baseline laboratory investigations revealed hemoglobin of 102 g/L, White blood cell count of 18200/cumm, Platelet count of 155000/cumm, and normal liver enzymes [AST and ALT] and creatinine. Obstetric ultrasound revealed an active fetus, with normal growth and Doppler flows. She was started on a prophylactic dose of low-molecular-weight heparin as per interim institutional guidelines. On day 2 of admission, she developed features of persistent hypertension (BP 170/110 mmHg), thrombocytopenia (Platelet count 85000/cumm), transaminitis with aspartate aminotransferase (AST), and alanine aminotransferase (ALT) of 138 IU/L and 161 U/L respectively and Urine Protein-creatinine ratio of 1.2mg/mmol, consistent with severe preeclampsia. Lactate Dehydrogenase (LDH) was 310 IU/L. Diagnosis of Preeclampsia-like syndrome was made in view of normal renal function and lack of signs of placental insufficiency and presence of symptoms in the background of COVID-19. Hence after a Multidisciplinary opinion involving critical care medicine, maternal-fetal medicine, obstetrician, and infectious disease teams, it was decided to manage the case conservatively and not to embark on termination of pregnancy. Though she received intramuscular betamethasone for enhancing fetal lung maturity in view of the risk of anticipated preterm delivery. It was followed by intravenous dexamethasone.

ARDS was managed with invasive mechanical ventilation, Remdesivir, Tocilizumab, Broad spectrum Antibiotics, and high doses of IV Steroids [As per the interim institutional protocols]. Remdesivir was stopped after 3 doses as AST/ALT increased to more than 200IU/L. Blood pressure was controlled with titrated doses of oral Labetalol and Nifedipine. Monitoring of vital signs and strict charting of input and output was done. Fetal heart rate was monitored by Doppler and later by NST (Non-stress test). Transaminitis and proteinuria improved with the resolution of respiratory distress. Also, the platelet counts improved. She was gradually weaned off to room air after 8 days of intubation. A follow-up scan after recovery at 30 weeks showed a fetus with normal growth, liquor, Doppler and activity. Maternal and fetal follow-up continued throughout the pregnancy. She landed up in spontaneous labor and delivered a healthy female baby of weight 3.4 kg at 38 weeks.

CASE 2

A 34-years-old G2P1L1 at 32 weeks of gestation presented with fever and dry cough for 2 days and mild dyspnoea. SARS-CoV-2 infection was detected on RTPCR screening at admission. She was a known case of chronic hypertension with blood pressure well controlled on two antihypertensives and no features of superimposed preeclampsia till last week's antenatal visit. On evaluation, her vital signs were Temperature of 37.6°C, heart rate of 98 beats per min, blood pressure 128/84 mm Hg, respiratory rate of 20 breaths per minute, and oxygen saturation (SpO2) was 93% in room air. On examining her physically, respiratory sounds were

bilaterally clear with the relaxed uterus. She was categorized as moderate COVID-19; and was managed symptomatically along with thromboprophylaxis and Oxygen supplementation. Investigations on day 2 revealed new onset significant proteinuria [Urine protein creatinine ratio 1.5 mg/mmol] with altered liver enzymes [AST 118 IU/L and ALT 143 IU/L] and thrombocytopenia [platelet counts 78000/cumm]. LDH was 680 IU/L. Peripheral smear was not suggestive of hemolysis. Obstetric ultrasound showed normal growth, liquor, and Doppler parameters for the fetus. Admission Non-stress test was reactive. Hence in the background of the absence of significant worsening of hypertension and normal fetal parameters, a provisional diagnosis of Preeclampsia-like syndrome was made. After inputs from the multidisciplinary team, it was decided to go ahead with conservative management. Blood pressure was maintained within the normal range on her previous antihypertensive dosage. She required Oxygen supplementation with a face mask at 4L/min.

Over the next few days, her dyspnoea resolved, with normalization of oxygen saturation on room air Once she improved symptomatically, proteinuria and deranged laboratory values came to normal. Maternal-fetal monitoring continued, and she delivered a healthy male baby of 3.2 kg at 39 weeks. During the postpartum period, her antihypertensives were down titrated and blood pressure was maintained within normal range.

DISCUSSION

It is now well established that the multisystem involvement of the COVID-19 pandemic is far beyond the usual clinical manifestations of any other viral respiratory infection [4]. Though COVID-19 is primarily an infection of the respiratory system, it can have other systemic features as well, more importantly, hypertension, thrombocytopenia, nephropathy, endocrinopathy, and hepatic injury [5-8]. New-onset hypertension and hepatic and renal dysfunction have been well documented as presenting features of COVID-19 and are associated with poor prognosis [9-11]. These also constitute the diagnostic features of Preeclampsia syndrome in pregnancy [12]. It is also now known that the etiopathogenesis of the SARS-CoV-2 virus is based on cell entry through angiotensin-converting enzyme 2 (ACE2) receptor and Transmembrane protease, serine 2 (TMPRSS2), which is expressed in many extra-pulmonary tissues like placenta, vascular, endothelium, brain, renal, hepatic and endocrine tissue as well. Thus, resulting in disturbances of the renin-angiotensin system (RAS) and leading to symptoms of vasoconstriction and subsequent organ injury. On the other hand, preeclampsia also has similar manifestations of endothelial dysfunction due to imbalances in angiogenic and antiangiogenic factors resulting in increased blood pressure, proteinuria, thrombocytopenia, and hepatic and renal dysfunction. Placental insufficiency is an important association with preeclampsia. Therefore, the increased prevalence of preeclampsia amongst women with COVID-19 that has been documented in the literature might be due to misdiagnosis, as COVID-19 and preeclampsia have overlapping and coincidental clinical features [13]. Thus, it is possible that some of those cases were wrongly diagnosed as severe preeclampsia and potentially contributed to the high incidence of iatrogenic preterm delivery in mothers with COVID-19 [1,2].

Mendoza et al stated that COVID-19 in pregnancy can develop a Preeclampsia-like syndrome by inducing a pro-inflammatory state. In their study of 34 cases (8 with Severe COVID-19), five (11.9%) pregnant women developed signs and symptoms of preeclampsia including hypertension, proteinuria, thrombocytopenia, and elevated liver enzymes. However, only one amongst them had abnormal values of sFlt-1/PlGF (soluble fms-like tyrosine kinase-1 and Placental Growth Factor) ratio and Uterine artery mean pulsatility index (PI). One case

remained pregnant after recovery from severe pneumonia and had a spontaneous resolution of the Preeclampsia-like syndrome. They proposed that Preeclampsia-like syndrome can be distinguished from actual Preeclampsia by using laboratory parameters like sFlt-1/PlGF ratio and LDH and Doppler assessment of Uterine artery mean PI. Preeclampsia-like syndrome might not be an indication for earlier delivery in itself since it might not be a placental complication and could resolve spontaneously after recovery from severe pneumonia [14]. First reported by Mendoza et al, some more case reports have been published mentioning the occurrence of Preeclampsia-like syndrome in pregnancy with COVID-19, usually moderate to severe cases [3,4,15,16].

Farahani et al, Sohal et al and Karimi et al [16-18] reported tonic-clonic seizures associated with cytokine storm of severe COVID-19 infection in the peripartum period. These seizures were resistant to magnesium sulfate. Thus, they proposed that in COVID-19, Magnesium sulfate may not provide prophylactic protection against seizures as it does in severe preeclampsia. They concluded that COVID-19 infection can resemble clinical presentation of pregnancy-associated hypertensive disorders and CNS manifestations too. Thus, a cautious approach is required for the management of pregnancies with suspected preeclampsia coexisting with SARS-CoV-2 infection. Data regarding the effects of COVID-19 on pregnancy and vice versa continue to get accumulated and updated with the emergence of newer strains of the virus.

Preeclampsia and COVID-19 are well considered as prothrombotic states. COVID-19 placentas have shown a higher prevalence of decidual arteriopathy and also fibrosis is a salient pathologic feature of preeclamptic placentas [19]. Although clinical features of hypertension, proteinuria, severe hepatic and renal dysfunction, and proteinuria could all be related to COVID-19, a possible diagnosis of preeclampsia needs to be ruled out. Levels of PlGF, a placental angiogenic marker, and sFlt-1, an antiangiogenic factor, are altered in preeclampsia. Preeclampsia is characterized by low-levels of PlGF and a high sFlt-1/PlGF ratio. Thus, high PlGF levels >100 pg/mL can be used to distinguish between these 2 entities [20]. sFlt-1/PlGF values of ≥85 (at <34 weeks) or ≥110 (at ≥34 weeks) are considered highly suggestive of underlying placental disease [21-24]. Furthermore, the establishment of a correct diagnosis is required as preeclampsia with severe features would require different management, including treatment with magnesium sulfate and, antihypertensives, ultimately, preterm delivery, with the potential for significant neonatal complications secondary to prematurity. Whereas women with preeclampsia-like syndrome associated with COVID-19 can be managed conservatively and symptoms of Preeclampsia resolve with improvement in clinical features of COVID-19 infection.

CONCLUSION AND CLINICAL IMPLICATIONS

Thus, it appears very important for healthcare providers to be aware of the existence of such a clinical entity as the management of both conditions is different. Inadvertent errors in the interpretation of clinical and laboratory pictures can lead to unnecessary iatrogenic surgical intervention for the mother and prematurity for the baby. Therefore, it is extremely important to monitor pregnancies with suspected pre-eclampsia with extreme caution, especially with a co-existing severe or critical COVID-19.

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