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Correspondence

Concurrence of COVID-19 infection & dengue in pregnancy at a tertiary care centre in northern India

Sir,

Dengue has spread globally in a rapid manner and it is estimated that over half of the world's population lives in dengue endemic areas[1]. The WHO has reported that about 400 million people get infected annually, of which around 100 million people show clinical manifestations and about 40,000 of them die of severe dengue[2]. Most of the Indian States are dengue endemic with the presence of multiple serotypes and have a higher case fatality rate of 3-5 per cent as compared to Southeast Asian countries which is one per cent[3]. Wong *et al*[4] have stated that early detection and treatment reduces fatality from 20 to <1 per cent. Complications of dengue in pregnancy have not been extensively studied. Literature on its co-infection with COVID-19 during pregnancy is meagre. An increased risk of oligohydramnios, pre-term labour and maternal haemorrhage has been observed[5].

This is a descriptive, retrospective study of three pregnant women who were co-infected with dengue and COVID-19 during its first wave, between October to November 2020. They were admitted at the Postgraduate Institute of Medical Education & Research, Chandigarh, a tertiary care centre. It was an attempt to study the foeto-maternal outcome of this co-infection. The comparison of the foeto-maternal outcomes was done with respect to a study by Brar *et al*[6]. The details of the three patients are depicted in the Table.

Case 1, a 22 yr old primipara following spontaneous vaginal delivery at 36 wk at a primary health centre was referred to us on post-natal day zero with post-partum haemorrhage in shock. She delivered a stillborn baby. Maternal resuscitation and cervical exploration with repair of a cervical tear of about 2 cm was done. Severe thrombocytopaenia and grossly deranged liver function were detected (Table). She was screened and tested for COVID-19 by RT-PCR (BGI and Target – ORF gene, India) as per the existing ICMR guidelines at that point in time and found to be COVID positive[7].

In addition, she was subjected to dengue testing in view of unexplained thrombocytopenia, severe transaminitis and deranged renal function. She turned out NS1 antigen positive. Supportive management and evaluation continued; she required invasive ventilation in view of acute respiratory distress syndrome (ARDS). Unfortunately, she succumbed on postnatal day 14 due to multi-organ dysfunction leading to intracranial haemorrhage and hepatic encephalopathy.

Case 2, a 34 yr old multiparous woman presented at 37 wk with a diagnosis of dengue with high-grade fever and petechial rashes. She tested positive for dengue NS1 antigen and IgM antibody. Her COVID-19 report also came positive along with severe thrombocytopenia and deranged liver function (Table). She required administration of intravenous immunoglobulin in view of refractory thrombocytopaenia (Figure). Further evaluation ruled out secondary haemophagocytic lymphohistiocytosis. She went into spontaneous labour and delivered vaginally. She had post-partum haemorrhage which was managed with uterotonics and uterine tamponade by Bakri balloon catheter. An improvement was noted in the platelet count post-delivery. Both mother and neonate were discharged after one week.

Case 3, a 29 yr old multiparous woman was referred at 36 wk with dengue NS1 antigen-positive status. She had a history of fever and headache for a week. Her evaluation showed COVID-19-positive status and thrombocytopaenia (Table). Over a period of time, she became dyspnoeic and her chest radiograph showed left pleural effusion. Broad-spectrum antibiotics were

Table. Socio-demographic, clinical characteristics, and managment of the three pregnant women co-infected with COVID-19 and dengue

Parameters	Case 1	Case 2	Case 3
Age (yr)	22	34	29
Parity	P1L0	G3P2L1	G3P2L1
Gestation (wk)	36	37	36
Presenting complaint	Post-natal day 0 with PPH	High-grade fever and petechial rashes since one week	Fever since one week, headache and vomiting since two days
Condition at admission	Drowsy	Conscious and oriented	Conscious and oriented
PR (bpm)	110	100	96
BP (mmHg)	80/40	100/70	100/70
SpO_2 (room air; %)	80	95	97
Temperature (°F)	98	101	102
COVID report	Positive	Positive	Positive
Nature of RT-PCR sample	Nasopharyngeal	Nasopharyngeal	Nasopharyngeal
C_T value	17	15	20
Dengue report	Positive	Positive	Positive
Type of test (ELISA based)	NS1 antigen positive	NS1 antigen and IgM antibody positive	NS1 antigen positive
Number of days after onset of fever when dengue testing was done	No history of fever	Five days	Six days
Comorbidities			
Pre-eclampsia/hepatitis	None	None	None
Others (diabetes/autoimmune disease/heart disease)	None	None	None
Laboratory parameters			
Hb (g/dl)	10.9	8.3	9.9
PCV (%)	32	24	27
TLC (ul)	61,000	4310	7800
Platelet count (ul)	18,000	5000	86,000
LFT			
Total bilirubin/unconjugated bilirubin (g/dl)	6.1/5	22/19	0.4/0.2
AST/ALT (U/l)	7241/1989	92/74	81/48
Urea (mg/dl)/creatinine (g/dl)	37/1.2	11/0.8	10/0.3
aPTT/prothrombin index (%)	28/72	30/85	32/100
Procalcitonin	2	8.3	0.47
Hepatitis A/hepatitis E virus	Negative	Negative	Negative
Serum ammonia (umol/l)	161	Not done	Not done
Blood/urine culture	sterile	sterile	sterile
Chest X-ray changes	None	None	Left pleural effusion
Treatment			
Hydration	Yes	Yes	Yes
Multiple blood transfusions	Yes	Yes	No
Steroid	No	No	No

Contd...

Parameters	Case 1	Case 2	Case 3
IVIG	No	Yes	No
Antibiotics	Yes	Yes	Yes
Mechanical ventilation	Yes	No	No
Mode of delivery	Vaginal	Vaginal	Vaginal
Status of neonate	Still born, 2.4 kg	Live born, 3 kg	Live born, 2.2 kg
Neonatal dengue	Not tested	Negative	Negative
Platelet count at discharge (ul)	69,000	130,000	110,000
Maternal status at discharge	Expired on post-natal day 14	Stable on post-natal day 6	Stable on post-natal day 5

PR, pulse rate; BP, blood pressure; SpO_2, oxygen saturation; RT-PCR, reverse transcriptase-polymerase chain reaction; C_T value, cycle threshold value; NS1 antigen, non-structural protein 1 antigen; Hb, haemoglobin; PCV, packed cell volume; TLC, total leucocyte count; LFT, liver function test; AST, aspartate transaminase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin clotting time; IVIG, intravenous immunoglobulin; IgM, immunoglobulin M

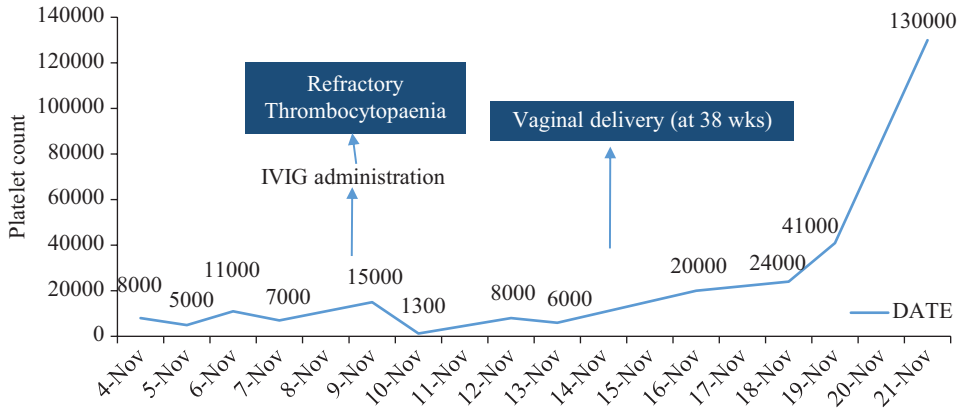

Figure. Platelet count trend in case 2, co-infected with COVID-19 and dengue showing refractory thrombocytopaenia despite multiple platelet transfusions as well as intravenous immunoglobulin administration. Improvement in platelet count was noted post-delivery.

administered along with supportive care. She delivered spontaneously at 37 wk, and there was gradual improvement of her respiratory symptoms within a week following which she was discharged.

From the analysis of these three patients, it was observed that the presence of dual infection had adverse foeto-maternal outcomes in the form of abnormal laboratory parameters, *i.e.* thrombocytopenia, transaminitis and deranged renal functions. In case profile 1, the presentation of shock was not well explained with only traumatic post-partum haemorrhage caused by the small cervical tear which was not bleeding profusely. She had associated multi-organ dysfunction, particularly acute liver and kidney injury, leading to third space loss as a result of which she succumbed. Case profile 2 had refractory thrombocytopenia requiring multiple transfusions along with intravenous immunoglobulins. With supportive care, she responded and was discharged in a stable condition. Case 3 patient also had the third space loss in the form of pleural effusion requiring supplemental oxygen. The obstetrical complication encountered in all three cases was post-partum haemorrhage.

There are pathophysiological similarities between severe dengue and COVID-19 such as plasma leakage, thrombocytopenia and coagulopathy. Both dengue virus (DENV) and SARS-CoV-2 activate immune cells releasing inflammatory cytokines such as interleukin-6 and tumour necrosis factor[8-10]. The cross-reactivity of immune responses is an emerging problem as the coronavirus may be affected by pre-existing DENV antibodies via antibody-dependent enhancement[11,12].

According to a prospective, observational study of 44 isolated dengue-infected pregnant women by

Brar *et al*[6], the severity of thrombocytopenia was not as much as seen in our patients. None of them had refractory thrombocytopenia as was seen in case 2. Our findings were in alignment with other limited studies which have been published on this co-infection. Irwinda *et al*[5] reported a pregnant woman with this coinfection. Haemorrhagic manifestations were seen, and she succumbed to death due to multi organ failure, similar to what we had observed in our case 1 patient. Mahajan *et al*[13] have reported that patients who have mild-to-moderate symptoms of COVID-19 infection create a diagnostic dilemma because co-infections can be easily misdiagnosed in such cases as late-onset SARS-CoV-2 infection while they actually may be symptoms of endemic illnesses such as dengue requiring a different management approach. This misdiagnosis can lead to life threatening foeto-maternal complications. Verduyn *et al*[14] have reported a non-pregnant woman with this co-infection and hypothesized that the symptoms are likely to be more severe and clinical diagnosis becomes difficult in endemic countries where the viruses may coexist.

Overlapping features of both infections create management challenges and highlight the importance of prognostication as dual infection seems to cause higher foeto-maternal morbidity and mortality. Fluid resuscitation, replacement of blood components, antibiotics and steroids in the form of dexamethasone in patients with severe respiratory symptoms are advocated[15].

Studies have also reported on the implications for the newborn. According to a case report of a pregnant woman with dengue by Morgan-Ortiz *et al*[16], one should be alert to the possibility of dengue infection in an endemic area. Rarely, vertical transmission can occur resulting in primary congenital dengue of severe haemorrhagic form.

Basurko *et al*[17] studied a cohort of 54 dengue infected pregnant women during the epidemic in French Guinea. The mother-to-child transmission rate was 18.5-22.7 per cent which occurred in early as well as late gestation. Of the 52 births, three neonates presented with warning signs needing platelet transfusions. Hence, vertical transmission of dengue is not negligible. It is more frequent when mother gets infected later during pregnancy, nearing delivery. In our study, the two surviving infants were tested negative for neonatal dengue.

The major limitation of this study was that the observations were made based on the analysis of only three co-infected pregnant women. Analysis of higher number of co-infected patients is needed for substantial evidence. More large-scale, prospective studies are required to confirm the foeto-maternal implications of this co-infection.

To conclude, clinical diagnosis of COVID-19 and dengue co-infection during pregnancy is difficult. High degree of clinical suspicion is required to proactively investigate the presence of this co-infection if a pregnant woman presents with acute febrile illness, thrombocytopenia with bleeding manifestations and other organ dysfunction. Timely diagnosis and management can help in mitigating complications and salvaging the mother and foetus.

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