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Case Report

Paediatrics Section

Perinatal Acute Kidney Injury in a Preterm Neonate Associated with Maternal COVID-19 Infection: A Case Report

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ABSTRACT

Effect of Perinatal maternal Coronavirus Disease-2019 (COVID-19) on growing foetus is not fully understood. There are early reports of biochemical Acute Kidney Injury (AKI) in the foetus with maternal COVID-19 infection. Present case is the first clinical case of perinatal AKI in a preterm neonate associated with maternal severe COVID-19. Preterm baby (34+4 weeks) was born to mother having COVID-19 pneumonia with raised inflammatory markers. She had history of decrease foetal movements and anhydraminos a day prior to delivery. Baby showed signs of AKI in form of weight gain, oedema and hypertension with initial serum creatinine of 3.54 mg/dL and blood urea of 95.2 mg/dL at 48 hours of age. Subsequently baby showed diuresis and improving Renal Function Tests (RFT). The foetal AKI resulted in anuria followed by anhydraminos with postnatal recovering AKI; even though the baby tested negative for COVID-19 RT-PCR, The baby did not have any clinical or biochemical evidence of asphyxia or sepsis. Possible explanation could be foetal renal hyoxic ischaemic insult due to Vasomotor Nephropathy (VMNP) or AKI due to cytokine storm in mother or direct viral injury to developing kidneys without nasopharyngeal colonisation.

Keywords: Coronavirus disease -2019, Cytokine storm, Kidney developmental toxicity, Vasomotor nephropathy

CASE REPORT

A 22-year-old female was admitted, at 34+4 weeks of gestational age with the complaints of mild grade fever (<99.5°F), intermittent in nature two days before delivery along with cough and breathlessness for last 4-5 days. Breathlessness was initially present on exertion but later progressed to breathlessness at rest one day before admission. On admission the patient's Heart Rate (HR) was 84 beats/min, Respiratory Rate (RR) of 26 breaths/min, SpO_2 on room air- 92% and on oxygen it was 97%. The patient required oxygen support. Her C-Reactive Protein (CRP) was increased to 210 mg/dL, serum ferritin levels were 900 ng/mL, D-dimer test was positive with value >500 ng/mL and RFTs were normal. The patient's pharyngeal swab tested positive for COVID-19 by RT-PCR method and was diagnosed with pneumonia. Her IL-1β, IL-6, and TNFα levels were not tested.

The patient was treated with oxygen by nasal prongs, tablet azithromycin, amoxycillin-clavulanic acid and paracetamol. Steroids were not given prior to delivery. No contact history was present. The patient had no co-morbidities. Perception of decreased foetal movement was present from 24-36 hours prior to delivery which were less than three in 24 hours. Obstetric ultrasound done 24 hours prior to delivery showed anhydraminos with Amniotic Fluid Index (AFI) of 1 with intrauterine growth restriction/IUGR (32+6 weeks by scan and 34+4 weeks by dates). Previous ultrasound done 20 days back was normal (AFI-11). There was no history of any Non-Steroidal Anti-Inflammatory Drug (NSAID) or Angiotensin Converting Enzyme (ACE) Inhibitor intake, no history of trauma and no history of leaking of amniotic fluid. There was no evidence of foetal distress. Non stress test was reassuring.

Female baby with birth weight 1719 grams was delivered by Emergency Lower Segment Caesarian Section (LSCS). APGAR was seven and eight at one and five minutes, respectively. Baby was admitted to Neonatal Intensive Care Unit /NICU for observation. From day one baby was started on full tube feeds. Baby was clinically stable on admission. Baby passed urine within first 12 hours and urine output was 2.1 mL/kg/hour during first 24 hours. Baby developed weight gain and puffiness on day two with impaired RFTs in next 48 hours. Laboratory tests done at 48 hours showed impaired RFT with creatinine levels of 3.54 mg/dL, blood urea level was 95.2 mg/dL, serum sodium was 129 mEq/L. serum potassium was 6.4 mEq/L, Complete Blood Cell (CBC) count was normal with haemoglobin of 16.8 mg/dL, leucocyte count of 10460 cells/microlitre and platelet count of 2.63 lac/microlitre. Baby had hypertension; Non

Invasive Blood Pressure (NIBP) recorded was above 95th centile (systolic/diastolic/mean value- 95/44/54mmHg) on day three of life. Urinary sodium and creatinine were 31 meq/L and 29.15 meq/L, respectively. Urine routine examination was normal. This was followed by weight loss and diuresis by day six of life. Fractional excretion of sodium was- 2.9 (value >1 is seen in intrinsic renal failure) and renal failure index/RFI was 3.75 suggestive of intrinsic renal failure. (Renal failure index= urine sodium×plasma creatinine/urine creatinine, value of more than 1 is seen in intrinsic renal failure) [1]. Venous blood gas done on day three was (pH-7.26, HCO3- 12.4, PcO_2- 27.3, BE of -14.6) suggestive of metabolic acidosis.

Pharyngeal swabs of baby tested negative for COVID-19 done on day two and on day six of life. Sepsis was ruled out both clinically and by sepsis screen which was normal. And baby did not receive any antibiotics during the hospital stay. Ultrasound (abdomen+KUB) showed evidence of renal parenchymal disease with loss of corticomedullary differentiation without hydronephrosis or obstruction. Kidney size was 4×2.2 cm on right side and on left it was 4.2×1.9 cm. Serial renal functions showed improving trend [Table/Fig-1]. Baby was given oral sodium correction with 0.2cc concentrated ringer lactate in each feed for hyponatremia and kaexylate enema 1 g/Kg dose was given thrice a day for 3 days for hyperkalemia from day of life three to day of life five. No anti-hypertensives were given. Baby was normotensive by day 10 and discharged on day 11. Placental examination was grossly normal. Histopathological examination and Immunoglobulin levels IgG and IgM for COVID-19 were not done as the facility for testing was not available at the time. The baby had in-utero AKI that resulted in anuria followed by anhydraminos with postnatal recovering AKI. The plausible explanation could be VMNP and consequently renal hypoxic ischaemia. Other possibilities could be cytokine storm in mother or direct viral injury to foetal kidney without nasopharyngeal colonisation. The final diagnosis is perinatal AKI as a result of maternal COVID-19 infection. Other differentials like sepsis, NSAIDS, leaking fluid and obstructive uropathy in baby were ruled out.

Day of life	Creatinine levels (mg/dL)	Blood urea nitrogen (mg/dL)
Day 2	3.54	95
Day 4	3.02	85
Day 7	1.56	53
Day 9	1.0	34.4

[Table/Fig-1]: Serial trends of creatinine and blood urea nitrogen levels in the neonate.

Her RFT and repeat USG KUB done at the time of follow-up at one month after discharge were normal. Baby's growth and development were normal at nine months during follow-up.

DISCUSSION

This is the first case of perinatal AKI in a preterm from India to be reported having an association with maternal COVID-19 infection antenatally. Since, it is a novel and new finding with potential future bearing in clinical practice we feel it is imperative to report this rare case.

The baby had in-utero AKI that resulted in anuria followed by anhydraminos with postnatal recovering AKI. Possible explanation could be VMNP following ischaemic hypoxic insult antenatally. AKI due to cytokine storm in mother or direct viral injury to developing kidneys without nasopharyngeal colonisation could be other possibilities.

These reports demonstrate that Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-Cov-2) infection can cause inflammatory and vascular changes in the placenta. Non infectious inflammation causes similar placental endothelial damage and thrombi in Multisystem Inflammatory syndrome in Children (MIC).

Inflammatory, thrombotic, and vascular changes in placenta could have also led to ischaemic hypoxic insult antenatally [2]. Microscopic examination of placenta however could not be done due to logistic reasons. Gross placental examination is insufficient to pick the above changes.

Inflammatory nature of SARS-CoV-2 infection during pregnancy leads to adverse obstetric and neonatal events. Activation of Toll Like Receptor-4 (TLR-4) pathways is postulated in COVID-19 infection in mother and chorioamniotis leading to high oxidative stress, causing glomerular and tubular damage with neonatal hyperoxia-induced kidney injury [2].

In COVID-19 pregnancy, host response to infection stimulates invariably production of proinflammatory cytokines, like Interleukin (IL-1β), IL-6, and Tumour Necrosis Factor-α (TNF-α), which can cross the placental barrier due to the phenomenon of cytokine storm [3]. Foetal inflammatory response could cause a cascade of events leading to foetal kidney damage even without direct viral infection [2].

The foetus in case of maternal COVID-19 is susceptible to develop VMNP leading AKI antenatally and perinatally by mechanisms leading to ischemia, hypotension and hypoxia secondary to placental involvement [4].

Zimmerman P and Curtis N, analysed nine case series. Most common neonatal complication was respiratory distress or pneumonia [5]. Non specific symptoms are common in neonates like temperature instability, fever, rashes, thrombocytopenia accompanied by abnormal liver function [6].

The AKI which was traditionally known as actue renal failure is suspected if the plasma creatinine is more than 1.5 mg/dL for 48 hours or rise of creatinine more than 0.3 mg/dL/day or Serum creatinine is above maternal levels for 5-7 days

[1]. serum creatinine is known to rise for 48 hours after birth in premature neonate [6]. However, the levels observed in this baby were way higher than normal ranges.

A recently published study showed findings corroborative of the present observation where in COVID-19 infection in mother in the last trimester was found to have been associated with foetal kidney developmental injury, as proved by increased cystatin C and β2-microglobulin in all the 22 neonates enrolled in the study irrespective of their PCR or antibody status [7]. This was the first and only study published internationally to have identified this important evidence. The present case report is first case report to identify clinical AKI in a preterm neonate born to mother with perinatal COVID-19 infection.

Histopathological examination of placenta, amniotic fluid examination and COVID-19 antibody titre levels could not be done here due to logistic reasons. Since COVID-19 infection in baby could not be proved therefore cause and effect relation cannot be conclusively proved or disproved.

CONCLUSION(S)

Perinatal COVID-19 infection in mother might affect foetal kidneys indirectly. Since nephrogenesis is incomplete before 36 weeks' gestation, it is postulated that insults like foetal VMNP or maternal cytokine storm could lead to foetal AKI. This could lead to foetal anuria and anhydraminos antenatally with postnatal recovering AKI. One must monitor renal function in a newborn born to mother with severe antenatal COVID -19 infection, since the evidence of foetal renal involvement is new and evolving. More studies are required to understand foetal effects of COVID-19 during pregnancy.

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