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Unusual presentation of Foetal Inflammatory Response syndrome(FIRS) secondary to Maternal SARS-CoV-2 infection- Case Series.

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Abstract:
Amid the coronavirus disease 2019 pandemic, uncertainty exists about the potential for vertical transmission from mothers infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the foetus in utero. Vertical transmission of SARS-CoV-2 is still under investigation. In this case series, we aim to demonstrate the occurrence of a foetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection resulting in neonatal morbidity. We describe an infant of a SARS-CoV-2–positive mother with varied clinical presentations and elevated levels of inflammatory markers, all of which are consistent with a systemic inflammatory response. The unusual presentations are hypertension with idiopathic hyperkalemia, supraventricular tachycardia and late onset fever and rash. Although all 3 neonates recovered completely from the condition, the exact mechanism is still unknown. Several studies have hypothesised as placenta being a nidus for the inflammation secondary to the maternal SAR-CoV2 infection in mother, in absence of vertical transmission in neonates.

Keywords: *SARS-CoV2, Foetal Inflammatory Response Syndrome, Supra-ventricular tachycardia, Hypertension, ARDS.*

Abbreviations: SARS-CoV2, FIRS-Foetal Inflammatory Response Syndrome), SVT-Supra-Ventricular Tachycardia, IL-6 – Interleukin 6.

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I. CASE 1

A late preterm (34 weeks), 2.4kg, male neonate born vaginally to 20yrs old mother through registered pregnancy. Mother was infected with SARS-CoV-2, 2 days before delivery. Antenatal history and USG scans did not reveal any abnormality. Neonate cried immediately after birth, had respiratory distress requiring mechanical ventilation. X-ray chest done suggestive of Hyaline membrane disease, received 1 dose of Surfactant. Post surfactant respiratory distress reduced. Oropharyngeal swab for SARS-CoV2 was done on day 2, which was negative. By day 3, baby had increased respiratory distress, requiring invasive mechanical ventilation. Repeat x-ray chest was done, which did not reveal any abnormality. Considering it as sepsis, antibiotics were started and Septic screen was sent which showed positive CRP, TLC-16300/ mm, Platelets-28000/mm and IL-6 as 268.6pg/ml. Blood culture was sterile. So a diagnosis of Foetal inflammatory syndrome was made and Intravenous Immunoglobulin @1gm/kg/d for 2 days was given. Meanwhile mechanical ventilation was continued. Follow-up CBC on day 5 showed improvement in the form of rising platelets and reduction in levels of IL-6 to 18pg/ml. Nasopharyngeal swab for SARS-CoV2 was done on day 5 was negative. Baby was extubated on day 6 of life to CPAP at 5lit/min. Orogastric feeds started and gradually increased as per tolerance. The Oxygen requirement reduced gradually. Baby had tachycardia on day 12 of life with heart rate around 230/min, haemodynamically stable. ECG was suggestive of supra-ventricular tachycardia. Serum electrolytes showed hyperkalemia, which was persistent, requiring daily k-bind sachets orally. Urine potassium was within normal limits. Direct renin activity and serum aldosterone levels were within normal levels CPK-MB, Trop-T, CRP was negative. Tachycardia responded to inj. Adenosine. Heart rate reduced to 150/min. 2D-ECHO did not reveal any abnormality. His blood pressure recordings were persistently higher 109/57mmhg (MBP-71) when compared with gestational age and weight parameters. (Expected values - Systolic 40-75mmhg and diastolic 20-50mmhg). So, Tablet Nifedipine was started and dose titrated based on the response of blood

pressure. Tab. Hydrochlorothiazide started with dose of 1mg/k/d, due to partial response to Tab. Nifedipine. Blood pressure reading gradually reduced to 78/45mmhg at discharge. Meanwhile a workup for hypertension was done, Renal functions, urine routine microscopy, ultrasound abdomen done to look for renal malformations, did not reveal any abnormality. 17-OHP levels to rule out congenital adrenal hyperplasia was normal. To summarize, this neonate had foetal inflammatory response in the initial days of life with unexplained hyperkalemia and hypertension which may be a transient phenomenon owing to unexplained effects of maternal COVID-19 infection. ROP examination did not reveal any abnormality. OAE hearing screen revealed bilateral pass.

	Day 1	Day 3	Day 6	Day 10	Day 13	Day 14	Day 15
Hb(gm%)	14	14.7	11.8	12.5			
Pcv (%)	39	40	36	37			
Tlc (/cmm)	10800	16300	13800	22600			
Platelets(/cmm)	220000	28000	74000	260000			
Neutrophils (%)	60	60	73	40			
Lymphocytes(%)	38	28	25	59			
CRP	Negative	Positive		Negative			
IL-6(pg/ml)	-	268.8	18	-			
Sr. electrolytes Na K	-			135 5.9	138 7.3	130 4.9	138 5.5
Blood culture		Sterile		Sterile			

Table 1- Haematological changes in case 1

II. Case 2

A full-term male neonate with birth weight 2.9kg was born to 24 years female who was infected with SARS-CoV2, 8 days before delivery, through 2nd degree consanguineous marriage, registered pregnancy. Baby was delivered by normal vaginal delivery, did not cry after birth, liquor was meconium stained, required bag and mask ventilation. Baby was immediately shifted to NICU, due to severe respiratory distress, requiring mechanical ventilation. Xray chest was done, s/o B/L atelectasis. He developed signs of PPHN on day 2 (SP02 in Rt UL-99%, SPO2 in LL-90%). Hence started with Tablet Sildenafil, and Milrinone infusion. On day 3, baby had persistent desaturation, Xray chest was done s/o ARDS. Hence given inj dexamethasone and inj Lasix for next 3 days and sildenafil was stopped. Inj. magnesium sulfate was given as continuous infusion for 2 days. With all above measures baby improved gradually. Meanwhile oropharyngeal swab for SARS-CoV2 was negative. Considering it as sepsis, antibiotics were upgraded and blood cultures sent. IL-6 was 10 pg/ml and CRP was positive, Blood culture was sterile. (25/7/21) On day 10 baby had fever, rash all over body, with raised IL-6 of 646pg/ml, positive CRP, with raised WBC count and thrombocytopenia. COVID Ig-G antibodies were non-reactive. Considering the diagnosis of Foetal inflammatory response syndrome, Started with inj methylprednisolone for 3 days and IVIG 1gm/kg/d for 2 days. CBC showed an improvement. IL-6 levels came down. Meanwhile he received TPN during the period of ventilation. He was extubated on day 16 to nasal CPAP. Orogastric feeds were started on 18. Gradually oxygen requirement reduced. He was shifted to oxygen by nasal prongs by day 30 of life. On day of life 33, baby had 3 episodes of tonic clonic convulsions, requiring inj phenobarbitone, although metabolic profile, septic screen and CSF examination was normal. After a seizure free duration of 3 days, injection phenobarbitone was shifted to oral phenobarbitone. Due to prolonged oxygen support, x-ray chest was done, which was suggestive of chronic lung disease. Hence, inj Dexamethasone was started according to DART regimen. Gradually the oxygen requirement reduced by day 40. Baby was then started on spoon feed trial followed by breastfeeding. Baby was successfully discharged on day 49 of life, with no signs of Retinopathy of prematurity. Hearing screening revealed left ear as pass.

	Day 1	Day 7	Day 12	Day 13	Day 20	Day 26	Day 33

Hb(gm%)	14.3	11.5	13.4	11.5	9.4	11.1	12
Pcv (%)	46	37	40	36	27	33	36
Tlc (/cmm)	13400	30000	26000	32800	17200	8300	9700
Platelets(/cmm)	1.5 L	1.9L	40,000	38000	1.3L	2.2	2.5L
N (%)	84	80	70	70	80	59	60
L (%)	14	15	28	28	14	40	28
CRP	Negative	Negative	Positive	Positive		Negative	Negative
IL-6(pg/ml)	-	-	-	646	11.43	7.05	-
Blood culture	Sterile	Sterile		Sterile	Sterile		Sterile
D-dimer		Negative		Positive	Positive	Negative	Negative

Table 2- Haematological changes in case 2

III. Case 3

A male neonate delivered at 31weeks, with birth weight of 1.7kg by LSCS due to premature rupture of memebrane of 12 hours and bad obstetrics history. This neonate was born to 30 years old female who had fever and cough 3 days before delivery. She was tested positive for COVID-19, 2 days before delivery. Baby cried immediately after birth. Baby had severe respiratory distress after birth. Chest xray was suggestive of hyaline membrane disease. Hence was given inj surfactant 7ml by INSURE technique with CPAP. Baby was hemodynamically stable till day 3 of life. On day of life 4 baby had poor peripheral perfusion with tachycardia. He was mechanically ventilated for resistant shock. Considering as late onset sepsis, antibiotics were graded up. Required inotropes noradrenalin and dobutamine for septic shock. Blood markers were suggestive of probable sepsis, with sterile blood culture. Antibiotics were stopped after 5 days. Perfusion gradually improved, and inotropes tapered and stopped. He was extubated on day of life 5. Meanwhile oropharyngeal swabs for SARS-CoV2 was done on day 2 and day 5, which were negative. He was started on OGT feeds. On day of life 11, baby had tachycardia with HR of 240/min and respiratory fatigue. Antibiotics were started after taking blood culture, suspecting sepsis. Baby was mechanically ventilated and antibiotics were started. ECG was done suggestive of supraventricular tachycardia. Inj Adenosine was given followed by Tab Propanolol. Tachycardia gradually reduced. 2D-Echo was done, which was normal with CPK-MB of 45 IU/L. Septic screen was done which showed a high CRP of 116.9mg/l and IL-6 of 84 pg/ml. Considering it as foetal inflammatory syndrome, inj. Methylprednisolone was started with 2gm/kg/d for 3 days and stopped. Baby improved clinically and extubated to CPAP on day of life 13. Baby was started on OGT feeds from day 14 and gradually increased to full feeds over 5 days. Baby could maintain his SPO2 on room air by day 17. Tab propranolol was tapered and stopped by day 20 with stable Heart Rate. Baby was started on spoon feeds from day of life 22, with nutritional supplements. Discharged on day of life 30 after successful weight gain with no ROP. Hearing screening revealed right ear pass.

	Day 1	Day 4	Day 8	Day 11	Day 14	Day 16	Day 21
Hb(gm%)	11.5	10.5	12.5	12.5	-	9.2	9.6
Pcv (%)	36	34	37	37	-	27	28
Tlc (/cmm)	6600	6300	7400	4600	-	9000	10000
Platelets(/cmm)	3.2 l	3.7l	2.7 L	2.0 L	-	1.5l	4.1l
N (%)	69		60	60	-	60	54
L (%)	28		38	38	-	38	45
CRP(mg/l)	Negative	31.1	<2.5	116.9	76.1	28.9	Negative
IL-6(pg/ml)			-	84	8.2		-
Blood culture	-	Sterile		Sterile	Sterile		-

D-dimer	Negative	-	-	>600ng/ml		Negative	-
LFT (SGPT/SGOT)	-						
2D-ECHO- No abnormality detected							
CSF- no abnormality detected							
ROP- Not detected							

Table 3- Investigations in case 3

IV. Discussion

Benjamin J F Huntley et al studied the frequency of maternal and neonatal complications, as well as maternal disease severity, in pregnancies affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. With data from early in the pandemic, it is reassuring that there are low rates of maternal and neonatal mortality and vertical transmission with SARS-CoV-2 [1]. The literature published thus far indicates that SARS-CoV-2 is not acquired via vertical transmission. However, there is a paucity of information regarding other potential fetal effects resulting from exposure to SARS-CoV-2 in utero. [2][3][4]. In our cases, all the mothers were infected with SARS-CoV2 in late third trimester. Sam Schoenmakers et al concluded that **maternal SARS-CoV-2** infection during the third trimester of pregnancy led to an adverse neonatal outcome based on a placental inflammatory reaction with subsequent dysfunction of the placenta[5].

Diriba K, et al studied the effect of maternal SARS-CoV2 on preterm birth. This meta-analyses indicates that the incidence of preterm birth at 37 weeks' gestational age is increased in women infected with SARS-CoV-2.[6][7] Additionally, a higher rate of perinatal fetal distress and admission to the NICU has been identified in neonates born to mothers infected with SARS-CoV-2.[6[[8] Out of 3 neonates in our study, 2 were born preterm.

Fetal inflammatory response syndrome (FIRS) is a condition defined by systemic inflammation in the fetus, a rapid increase of pro-inflammatory cytokines into the fetal circulation (including interleukin-1 and interleukin-6), as well as a cellular response (such as increased neutrophils, monocyte/macrophages, and T cells) and the presence of funisitis. FIRS can lead to death and multisystem organ damage in the fetus and newborn. [9]. FIRS is also associated with a neonatal systemic inflammatory response, which manifests as clinically suspected neonatal sepsis with negative blood and cerebrospinal fluid cultures [10][11][12]. In our cases each of them had a rapid rise of Interleukin 6 levels as well as CRP in neonatal blood, which initially was thought due to neonatal sepsis. In all cases the blood cultures and cerebrospinal fluid cultures were sterile.

The combination of meconium stained amniotic fluid and FIRS had a higher frequency of meconium aspiration syndrome than those without FIRS [13]. They proposed a chain of events in that meconium (with its proinflammatory properties), when aspirated before birth and combined with a foetal systemic inflammatory response involving the fetal lungs, can predispose to meconium aspiration syndrome [13,14,15], which subsequently developed Chronic lung disease, requiring injection Dexamethasone.

The first and third case in our series was born preterm requiring Surfactant. According to The Watterberg hypothesis intra-amniotic inflammation/infection is associated with a decreased rate of RDS (early protective effect) but an increased rate of BPD. In our case 2 neonates had signs of Hyaline membrane disease requiring surfactant, which is in contrast to the Watterberg hypotheses.

FIRS is associated with systolic and diastolic dysfunction, which was originally attributed to the presence of circulating myocardial depressant factors and, more recently, to direct effects of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [16]. The pattern of myocardial depression is characterized by left ventricular dilation, decreased left ventricular ejection fraction, and a normal or increased cardiac index [15]. In 2 out of three cases, we observed supraventricular tachycardia, with no underlying cause, with no systolic or diastolic dysfunction on 2D-ECHO..

Shim et al. reported that elevated umbilical cord plasma IL-6 and high CRP concentrations in the immediate neonatal period were significantly associated with neonatal hearing screening test failure in a cohort of 127 premature infants [17]. These results suggest that a fetal inflammatory response may increase the risk of hearing loss. In our case, although we did not test umbilical cord plasma IL-6, all three had high CRP values. All three neonates reported to have unilateral/ bilateral hearing loss.

Inflammatory mediators in the amniotic fluid may predispose preterm foetuses to impaired renal function during the postnatal period and increased risk of hypertension and renal dysfunction in later life [18,19]. Case 1 developed an altered handling of electrolytes by kidney leading to hyperkalaemia and hypertension requiring a constant potassium binders and antihypertensives.

Fetal systemic inflammation is associated with an increased risk of ROP.[20,21] In our study 2 cases were born preterm, but did not show any evidence of ROP

FIRS is defined by elevated interleukin 6 (IL-6) concentrations (11 pg/mL) and is often associated with leukocytosis and neutrophilia. FIRS is also associated with increased fetal plasma concentrations of tumor necrosis factor receptors and CRP. [22, 23] In all our cases, IL-6 was raised with values 268.8 pg/ml, 646pg/ml, 84pg/ml respectively. As quantitative CRP is not done at our institute, qualitative CRP was done which showed a positive report in all 3 cases. These findings, in addition supraventricular tachycardia, late onset fever and rash and multiorgan involvement are more indicative of FIRS, which we hypothesize was secondary to exposure to maternal SARS-CoV-2 infection in utero and can occur in the absence of proven vertical transmission.

The initial study of the hematologic profile in FIRS reported that affected foetuses had a higher median corrected white blood cell count and corrected neutrophil count than unaffected fetuses.[23] Neutrophilia (neutrophil count >95th percentile for gestational age) was found in 71% (30/42) of cases, while neutropenia (neutrophil count < 5^{th} percentile for gestational age) found in 4.8%. In our study, case 1 and case 2 had higher corrected WBC, with neutophilia while case 3 showed leucopenia. All 3 cases showed a severe thrombocytopenia, which is in contrast to the study of hematologic profile of fetus with systemic inflammatory response syndrome, which showed no effects on platelet count. This can be due to an an inflammatory reaction due to SARS-CoV2 infection in mother.

There is also increasing awareness of a SARS-CoV-2–related hyperinflammatory syndrome in pediatric patients, now termed multisystem inflammatory syndrome in children (MIS-C).[24,25] Diagnostic criteria for MIS-C includes the following:

• fever, laboratory evidence of inflammation, and evidence of clinically severe illness with multisystem (≥2) organ involvement requiring hospitalization;

• no alternative plausible diagnoses; and

• RT-PCR, serology, or antigen test positive for current or recent SARS CoV- 2 infection or COVID-19 exposure within the 4 weeks before onset of symptoms.

In all 3 patients, RT-PCR antigen test and serology both were negative hence, diagnosis of MIS-C was ruled out. Literature on MIS-C reveals a variety of hematologic abnormalities. We suspect that the late-onset thrombocytopenia seen in all three neonates was secondary to an inflammatory response associated with systemic exposure to maternal viral infection. Thrombocytopenia has been described in other cases of SARS-CoV-2 infection.

Preterm labour in the setting of infection results from the action of pro-inflammatory cytokines secreted by the mother and/or fetus in response to intra-amniotic infection. [26] In 2 of our cases, maternal SAR-COV2 infection has triggered preterm labour, leading to preterm births.

Gomez et al have studied the effects of FIRS on neonatal morbidity. Multivariate analysis showed that FIRS was an independent predictor of severe neonatal morbidity after adjusting for gestational age, the obstetrical cause of preterm delivery (preterm labour or preterm PROM), clinical chorioamnionitis, presence of microorganisms in the amniotic cavity, and amniotic fluid IL-6 results.[27].

All 3 patients, in our case series, developed respiratory morbidity and cardiovascular manifestations. 1 case developed neurological manifestation in the form of convulsions. We propose that FIRS secondary to antenatal maternal SARS-CoV-2 infection explains the neonatal morbidity seen in these cases

V. Conclusion

Effect of maternal SARS-CoV2 on neonates is still under study. FIRS in neonates born to mothers can have varied presentations with multisystemic presentations. In all the three cases series reported, each fulfilled the criteria to label as FIRS as laid down by AAP. The effects can be explained by the unknown effects of SARS-CoV2 on placenta. All the above cases responded well to the IV Immunoglobulins and steroids. With early suspicion for diagnosis, we can get good outcomes with no mortality. Needs more case reports focussing on diagnosis of FIRS.

Limitations

We did not evaluate the presence of the virus in amniotic fluid, cord blood, or placental tissue, which could clarify the possibility of vertical transmission. Additionally, IL-6 levels were not obtained from the amniotic fluid or the fetal plasma, which would have further examined the diagnosis of FIRS.

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Conflicts of interest
There are no conflicts of interest.