Multisystem Inflammatory Syndrome in Neonates (MIS-N) in very-preterm quadruplets born to a mother with SARS CoV-2 infection in Colombo, Sri Lanka

***Sangeetha Wickramaratne[1], Nalin Gamaathige[1], Nishani Lucas[1,2]**

Sri Lanka Journal of Child Health, 2022; **51**(2): 310-312
DOI: http://dx.doi.org/10.4038/sljch.v51i2.10148
(Key words: Multisystem inflammatory syndrome in neonates, MIS-N, Quadruplet, Very-preterm, Covid-19)

Introduction

Multisystem Inflammatory Syndrome in Neonates (MIS-N) secondary to maternal SARS-CoV-2 is characterized by a severe illness needing hospitalization with the presence of inflammation and multiorgan involvement in the absence of an alternative diagnosis[1]. We report the world's first case of quadruplets born to a SARS CoV-2 positive mother at 30 weeks of gestation, where all 4 babies displayed evidence of MIS-N.

Case report

A 25-year-old primigravida, with an unremarkable medical history, was admitted with respiratory symptoms of one day duration at a period of gestation (POG) of 28-weeks. She had a contact history of SARS-CoV-2 infection nine days prior to admission and was found to be positive for the SARS-CoV-2 antigen on admission, which was confirmed with a polymerase chain reaction (PCR). Fetal ultrasound scan revealed normal Doppler flow with age-appropriate growth as shown in table 1.

Table 1: ***Fetal ultrasound findings at 30 weeks of gestation***

Fetal ultrasound finding	Quadruplet 1	Quadruplet 2	Quadruplet 3	Quadruplet 4
Biparietal diameter	29+4	29+6	31+4	32+6
Head circumference	29+6	29+4	31+3	31+6
Abdominal circumference	29+2	29+5	30+2	29+1
Femur length	29+0	29+4	32+5	30+4
Estimated fetal weight (g)	1500	1400	1700	1420

**All measurements except the estimated fetal weight are given as gestational age in weeks and days, where the raw values have been converted to the gestational age, according to fetal growth charts at the time of the fetal ultrasound by the obstetric team*

Deterioration in the mother's condition requiring multiple blood product transfusions led to early delivery at 30+2 weeks POG following administration of intramuscular dexamethasone and intravenous magnesium sulphate. Live quadruplets, (Q1, Q2, Q3, Q4) were born, via planned caesarean section with birth weights of 1.608kg, 1.110kg, 1.222kg, 1.356kg from Q1-4 respectively. They did not require resuscitation and were managed with continuous positive airway pressure (CPAP) in the delivery room due to respiratory distress noted soon after birth, with separate T-piece equipment for each baby to avoid cross infection. Q4 needed intubation 20 minutes after birth due to apnoea. Q1, Q2 and Q3 were managed only with CPAP and were weaned off to room air by day 03. Q4 needed invasive ventilation for 47 hours and was weaned off to room air by 93 hours of life. None of the babies needed surfactant. Chest x- rays were unremarkable without features of surfactant deficient lung disease or SARS CoV-2 pneumonia.

Cord blood samples were negative for SARS-CoV-2 Polymerase Chain Reaction (PCR) and specific antibodies including Immunoglobulin G (IgG) at birth. Nasopharyngeal swabs were negative for antigen within 24 hours. Peripheral blood samples for SARS CoV-2 specific antibodies, including IgG titres, at 24 and 72 hours, were also negative.

Lactate dehydrogenase (LDH) levels (1115, 1477, 1350 and 1340 U/L) were increased on day one in Q1-4 respectively and gradually normalized by day 09 (normal range <450U/L).

Nucleated red blood cell percentage / White blood cell ratios (normal range 0.2-0.5%) were very high in all babies 3.65, 18.96, 6.92 and 107.7 (Q1-Q4),

[1]*De Soysa Hospital for Women, Colombo, Sri Lanka,* [2]*Department of Paediatrics, University of Colombo, Sri Lanka*
**Correspondence:* shyamisw@gmail.com
https://orcid.org/0000-0002-7782-4134

(Received on 28 March 2022: Accepted after revision on 02 April 2022)

The authors declare that there are no conflicts of interest
Personal funding was used for the project.

with highest values seen in Q4 who was also the sickest. Blood cultures and C-reactive protein (CRP) were negative.

Metabolic acidosis was noted over the first 48 hours with pH of 7.1, 7.2, 7.2, 7.1 and base excess of -15.2, -12.4, -15, -18 mmol/L, in Q1–4 respectively; this was managed with fluid resuscitation alone. Lactate levels were normal.

Serum creatinine levels were increased (96.8, 104.9, 123.9, 118.5 micromol/L in Q1–4 respectively) on day 02 and gradually normalized by day 07 (normal <44 micromol/L). Urine output remained normal at 1-3ml/kg/hour. Hyponatraemia was noted from day 01, dropping to the lowest on day 03 (125, 129, 128, 124 mmol/l in Q1–4 respectively) and normalizing by day 09, following sodium supplementation. Serum potassium and calcium levels were normal.

Increased serum aspartate transaminase (AST) (70, 94, 76, 61 U/L in Q1–4 respectively) (normal <40U/L), seen on day 01 gradually normalized by day 09. Prolonged Activated Partial Thromboplastin Time (APTT) 53.8, 80.3,79.9 and 52.9s (normal range 37.3–48.5s) and Prothrombin Time (PT) 14.6, 15.8, 20.1, 16 seconds (normal range 11.3-14.4 seconds) in Q1-4 respectively were seen in all babies on day 01 and normalized following transfusion of fresh frozen plasma. Echocardiographic evaluations, including coronary arteries, were found to be normal.

Expressed breastmilk via orogastric tube was started soon after birth. Kangaroo mother care was commenced by day 03. All babies achieved their birth weight by 10-12 days and were discharged with normal neurodevelopment on day 16.

Discussion

The overall rate of neonatal infection in pregnancies complicated with SARS-CoV-2 is less than 5%[1,2,3,4]. The risk of neonatal infection is higher when mothers developed SARS-CoV-2 disease near the time of delivery[2] as in this case. Rate of vertical transmission during the 3rd trimester has ranged from 3.2%-9.7% depending on the test method used[5]. According to the definition proposed by Blumberg D, *et al*[7] negative peripheral blood and nasopharyngeal aspirate for SARS-CoV-2 RT-PCR, with negative SARS-CoV-2 specific Immunoglobulin M (IgM) antibodies at 24 and 72 hours proved absence of vertical transmission in the quadruplets.

These quadruplets born at 30 weeks POG, had grown appropriately for their gestation, and completed antenatal steroids, had well expanded lungs, without evidence of surfactant deficient lung disease or respiratory acidosis. Yet they needed respiratory support in the form of CPAP/invasive ventilation. Their prematurity did not account for the requirement of respiratory support, evident metabolic acidosis, renal impairment, elevation of AST, LDH, APTT or PT levels.

Elevation of LDH seen on day 01 provided the laboratory evidence of ongoing inflammation for MIS-N[1]. Involvement of three organ systems namely renal, hepatic and haematological systems denoted by elevated creatinine, metabolic acidosis, hyponatraemia, elevated AST with elevated APTT and PT in addition to illness that warranted respiratory support and intensive care evidenced the clinical criteria for MIS-N. Normal antenatal Doppler assessment, normal Apgar scores, normal postpartum neurology with normal calcium levels were supportive towards the absence of perinatal hypoxia[1,7,8,9]. Sterile blood cultures and negative CRP excluded sepsis. Presence of laboratory evidence of inflammation with required clinical criteria on day 01 of life in the absence of an alternate diagnosis in these quadruplets born to a SARS-CoV-2 positive mother fulfil the criteria for MIS-N as suggested by Pawar R, *et al*[1].

In conclusion, it is important to evaluate babies born to SARS-CoV-2 positive mothers for MIS–N, as it is associated with increased morbidity and mortality.

References

1. Pawar R, Gavade V, Patil N, Mali V, Girwalkar A, Tarkasband V, *et al.* Neonatal Multisystem Inflammatory Syndrome (MIS-N) associated with prenatal maternal SARS-CoV-2: A case series. *Children* 2021; **8**(7): 572. https://doi.org/10.3390/children8070572 PMid: 34356552 PMCid: PMC8305422

2. FAQs: Management of infants born to mothers with suspected or confirmed Covid-19 [Internet]. Services.aap.org. 2021 [cited 2 August 2021]. Available from: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/

3. Covid-19 Clinical management: living guidance [Internet]. Who.int. 2021 [cited 2 August 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1

4. Ma X, Zhu J, Du L. Neonatal management during the Coronavirus Disease (Covid-19)

outbreak: The Chinese Experience. *NeoReviews* 2020; **21**(5): e293-e297. https://doi.org/10.1542/neo.21-5-e293 PMid: 32358142

5. Cases, Data, and Surveillance [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2 August 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/special-populations/pregnancy-data-on-covid-19/what-cdc-is-doing.html

6. Kotlyar A, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology* 2021; **224**(1): 35-53. https://doi.org/10.1016/j.ajog.2020.07.049 PMid: 32739398 PMCid: PMC7392880

7. Blumberg D, Underwood M, Hedriana H, et al. Vertical transmission of SARS-CoV-2: What is the optimal definition? *American Journal of Perinatology* 2020; **37**(8): 769-72. https://doi.org/10.1055/s-0040-1712457 PMid: 32503058 PMCid: PMC7356079

8. Boskabadi H, Zakerihamidi M, Sadeghian M, et al. Nucleated red blood cells count as a prognostic biomarker in predicting the complications of asphyxia in neonates. *Journal of Maternal-Fetal and Neonatal Medicine* 2016; **30**(21): 2551-6. https://doi.org/10.1080/14767058.2016.1256988 PMid:27809621

9. Hypoxic-Ischemic Encephalopathy Workup: Approach considerations, laboratory studies, imaging studies [Internet]. Emedicine.medscape.com. 2021 [cited 11 August 2021]. Available from: https://emedicine.medscape.com/article/973501-workup#c4