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Duyongco VLL, Bael VG, Kimseng KJN, Pasco CAMD, Tan ACC. Clinical Profile and Course on Follow-Up of Newborns of SARS-CoV-2 Positive Mothers
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ORIGINAL ARTICLE

CLINICAL PROFILE AND COURSE ON FOLLOW-UP OF NEWBORNS OF SARS-CoV-2 POSITIVE MOTHERS

Vivien Lorraine L. Duyongco, MD, Victora G. Bael, MD, Karen Joy N. Kimseng, MD, Cleo Anna Marie D. Pasco, MD and Aimee Cristine C. Tan, MD
Chong Hua Hospital Mandaue
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ABSTRACT

Objective: This study aims to determine the clinical profile and course on follow-up of newborns delivered to a SARS-CoV-2 positive mother from two private tertiary hospitals.

Methodology: This is a retrospective, cross-sectional study. A chart review of all neonates delivered to SARS-CoV-2 positive mothers was conducted. Subsequent interview was done to determine their clinical course and neurologic status at 3-, 6-, 9-, 12-, and 15-month-old. Data collected was presented as frequencies, percentages, or proportions.

Results: Out of the 67 newborns born to SARS-CoV-2 positive mothers, three neonates tested positive for SARS-CoV-2. All three were delivered to mothers with mild symptoms, were full term, with good APGAR score and appropriate for gestational age. One was eventually intubated and managed as COVID-19 confirmed critical. Among the SARS-CoV-2 negative newborns, majority had an unremarkable neonatal outcome. Thirty-six neonates were available for follow-up: 1 expired due to aspiration pneumonia at 2 months of age, 4 were readmitted for pneumonia, UTI, acute gastroenteritis, and cow's milk allergy. Twenty-one had infection at one point prior to this study follow-up but were all mild not requiring admission. Two had abnormal head size, while 2 had developmental delay, these 4 infants with neurological findings on follow-up were all RT-PCR negative at birth.

Conclusion: Maternal COVID-19 infection does not necessarily result to a neonatal infection. For those neonates with mild symptoms, SARS-CoV-2 causality could not be established. On follow-up, there were a few who developed significant problems that have long-term implications in the overall growth and development of the child.

KEYWORDS: *Maternal COVID-19 infection (SARS-CoV-2 positive mother), Neonatal outcome, Long-term follow-up*

Correspondence:
Dr. Vivien Lorraine L. Duyongco
Email: vivienduyongco@gmail.com

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INTRODUCTION

A novel pathogenic coronavirus named, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19) was first identified in Wuhan City in China, as the cause of a rapidly spreading pneumonia. It initially resulted to an epidemic in China, that eventually spread to other countries, resulting to a pandemic as declared by the World Health Organization (WHO).[1,2]

According to the Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) study by the Pediatric Infectious Disease Society of the Philippines (PIDSP) majority had mild symptoms with 42.1% and a few died (8.2%).[3] In the interim guidelines on COVID-19 of PIDSP, it showed a local data with greater number of mortalities seen in neonates and toddlers from 0-4 years old age group, comprising 54.8%.[4] The risk of developing COVID-19 during the perinatal period is relatively still unknown.[5] Vertical transmission of the SARS-CoV-2 may occur in a minority of cases, where the virus was also detected in other specimens like the cord blood (3.6%), placenta (7.7%), recto-anal swab (9.7%) and serology (3.7%).[6] In comparing symptomatic versus asymptomatic SARS-CoV-2 positive mothers, those who are symptomatic were more likely to have premature deliveries resulting to their newborns requiring intensive care.[7,8]

There is limited evidence on the impact of SARS-CoV-2 virus infection on children, especially in infants born to positive mothers and their long-term sequelae. The outcome of neonates delivered to SARS-CoV-2 positive mothers are unlikely to be directly related to the virus itself, studies showed that maternal comorbidities may have contributed to their adverse outcomes.[9] But for those SARS-CoV-2 positive neonates, they may show typical mild to moderate symptoms like fever, hyperbilirubinemia, cough, respiratory distress, and pneumonia.[7,10] However, data on the long-term follow-up of these newborns is scarce.

This study aims to determine the clinical profile and course on follow-up of the newborns delivered to SARS-CoV-2 positive mothers in private tertiary institutions from April 2020 to May 2021.

METHODOLOGY

Study design

This is a descriptive, retrospective study with 2 components. Data on maternal and neonatal demographics, their clinical profile, and the neonatal outcomes were retrieved through chart review. Information on the clinical course on follow-up of the study population was gathered through a cross-sectional survey by phone interview.

Study setting

The study was conducted in two private tertiary hospitals.

Study population

Purposive sampling was employed to include all subjects, who fulfilled the inclusion criteria. The newborns included in this study were all the neonates of SARS-CoV-2 positive mothers delivered from April 2020 to May 2021. Data from neonates of SARS-CoV-2 negative mothers or those who refused to undergo RT-PCR were not included in the study. Those without consent from the mother or attending physician and those lost to follow-up were likewise not included.

Data collection and analysis

The researcher coordinated with the pediatric residents of the two private tertiary hospitals for the list of all mothers, who delivered in their institutions from April 2020 to May 2021. The researcher only included those mothers who tested positive on RT-PCR for SARS-CoV-2 regardless of gestational age on testing. No a priori sample size computation was done since the exact incidence of the neonatal condition is not definite.

The mothers of the identified subjects were initially informed through text message and phone call regarding the study. Verbal informed consent, along with the rest of the interview were obtained, conducted, and documented. In addition, a soft copy of the informed consent was sent to their email or messaging application and was sent back to the researcher with an electronic signature attached for filing. In the preferred language of the mother (English, Filipino or Cebuano dialect), the actual interview included questions on: 1) clinical signs and symptoms that developed after hospital discharge, 2) any hospital readmissions, and 3) developmental milestones achieved by the infant at 3, 6, 9, 12 and 15 months of age as applicable to their chronological age during the interview. They were categorized as such based on the Denver chart. The developmental milestones can be assessed by direct observation of the examiner or reported by a primary caregiver based on four domains (gross motor, fine motor, language, and personal/social). For this study, the researcher collected the data through phone interview with questions guided by the Denver chart. The corresponding developmental age of the subjects was based on the report by the primary caregiver. The results of the evaluated milestones were reviewed and corroborated by a pediatric neurologist. In instances where there was discordance of results, the primary caregiver was re-interviewed for clarifications in the presence of pediatric neurologist. These neurodevelopmental milestones were then recorded as developmental quotients, which are computed by dividing the developmental age based on the Denver II developmental screening test by their chronological age on assessment. Data collected from chart review using the data collection tool and from the phone interview were encoded in Microsoft Excel spreadsheet and summarized as frequencies, percentages, or proportions.

Ethical Consideration

The research protocol was submitted to the Institutional Review Board (IRB) of the hospital before the commencement of the study.

The investigators have no conflicts of interest. There was no funding obtained for this study. The primary investigator safeguarded the rights and preferences of each newborn and his/her respective mother all throughout the duration of the study. Anonymity was ensured on all electronically gathered data, as well as the printed records. Informed consent was obtained prior to the start of the phone call interview.

All electronically gathered patient information were saved onto the investigator's laptop and were transferred to a password-protected hard drive. The hard drive and hard copies of files are kept in a drawer under lock and key with the author having sole access. At any time, data gathered will not be disclosed for use outside the scope of this study. After 5 years, all data will be appropriately discarded.

RESULTS

Out of the 1,924 mothers, only sixty-seven mothers had positive SARS-CoV-2 RT-PCR results. Only 36 mothers gave their consent to be interviewed regarding the course on follow-up of their children. One of the infants expired at 2 months of age and was assessed only up to that age, thus, she was not included in the assessment of neurodevelopmental outcome. Thus, only 35 were followed-up and included until their corresponding age during the time of interview.

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Table 1. Demographic profile of SARS-CoV-2 positive mothers

Variables		n= (67)	%
Age (years) *Mean age 31 years old*	≤ 17	0	0
	18 – 34	51	76
	≥35	16	24
Marital Status	Single	29	43.3
	Married	38	56.7
Ethnicity	Filipino	67	100
Residence	Urban	42	63
	Rural	25	37
Educational Attainment	College Graduate	47	70
	College Level	6	9
	High School Graduate	3	4.5
	High School Level	0	0
	No data available	11	16.4
Income	Above Minimum	40	60
	Minimum	13	20
	Below Minimum	2	3
	No data available	12	17

Sixty-seven mothers confirmed positive for SARS-CoV-2 RT-PCR were included in the study. Seventy-six percent were under the low-risk reproductive age with mean age of 31 years old, with the range of 20 to 43 years old.

Majority were married and resided in urban areas. Most of them were college graduates earning above minimum income.

Table 2. Clinical profile of SARS-CoV-2 positive mothers

Variables		n= (67)	%
Obstetric Score	Primigravid	29	43
	Multigravid	38	57
Trimester Infected	First	1	1.5
	Second	0	0
	Third	66	98.5
COVID Symptoms			
Number of symptoms present	Asymptomatic	50	75
	1 symptom	1	1
	More than 1 symptom	16	24
Symptoms present*		17	25
	Fever	7	
	Cough	7	
	Coryza	7	
	Body Malaise	5	
	Anosmia / Ageusia	4	
	Sore Throat	2	
	Dyspnea	1	
Maternal Comorbidities**		39	58
	Gestational Diabetes Mellitus	17	
	Urinary Tract Infection	11	
	Bronchial Asthma	6	
	Gestational Hypertension / Pre-eclampsia	4	
	Coronary Artery Disease	3	
	Hypothyroidism	3	
	Hyperthyroidism	1	
	Bacterial Vaginosis	1	
	Uterine Atony	1	
No Maternal Comorbidities		28	42

**1 patient may have one or more symptoms*
***1 patient may have one or more comorbidities*

Fifty-seven percent were multi-gravid, 98.5% were infected with SARS-CoV-2 during the third trimester and majority of them (75%) were asymptomatic. Symptoms include fever, cough, and coryza. Thirty-nine mothers (58%) had comorbidities which included gestational diabetes mellitus, followed by urinary tract infection, bronchial asthma, and gestational hypertension.

Table 3.1. Demographics of neonates born to SARS-CoV-2 positive mothers

Variables		COVID Positive (n= 3)	COVID Negative (n= 45)	No RT-PCR (n= 19)	Total Newborns (n=67)
Gender	Male	1 (33%)	18 (40%)	8 (42%)	27 (40.3%)
	Female	2 (66 %)	27(60%)	11 (58%)	40 (59.7%)
Mode of Delivery	Spontaneous Vaginal Delivery	2 (66%)	26 (58%)	11 (58%)	39 (58%)
	Cesarean Section	1 (33%)	19 (42%)	8 (42%)	28 (42%)
Maturity	Preterm	0	7 (16%)	1 (5%)	8 (12%)
	Full term	3 (100%)	38 (84%)	18 (95%)	59 (88%)
APGAR Score	Good (7 – 10)	3 (100%)	44 (98%)	17 (89%)	64 (95.5%)
	Moderate (4 – 6)	0	1 (2%)	2 (11%)	3 (4.5%)
	Severe (0 – 3)	0	0	0	0
Ballard Score	28 and below	0	1 (2%)	0	1 (1.5%)
	32 to 35 6/7	0	1 (2%)	0	1 (1.5%)
	34 to 36 6/7	0	4 (9%)	0	4 (6%)
	37 and above	3 (100%)	39 (87%)	19 (100%)	61 (91%)
Birthweight (grams)	≤ 1,000	0	0	0	0
	1,000 – 1,499	0	1 (2%)	0	1 (1.5%)
	1,500 – 2,499	0	11 (24%)	2 (11%)	13 (19.4%)
	≥ 2,500	3 (100%)	33 (73%)	17 (89%)	53 (79%)
Classification	Small for gestational age	0	4 (9%)	2 (11%)	6 (9%)
	Appropriate gestational age	3 (100%)	40 (89%)	17 (89%)	60 (90%)
	Large for gestational age	0	1 (2%)	0	1 (1%)

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Three neonates were positive for SARS-CoV-2 naso/oropharyngeal RT-PCR swabs. They were all delivered to mothers with COVID-19 mild pneumonia with unremarkable maternal history, except for one mother who had gestational diabetes requiring insulin. Majority were born full term via normal spontaneous delivery, with good APGAR score, mean age of gestation at 38 weeks and weight of 2,885 grams, appropriate for gestational age.

Eight were born preterm, out of the eight mothers with preterm baby-one had severe COVID-19 disease, two with moderate disease while the rest of the five had mild symptoms. Three of them were delivered via primary cesarean section secondary to the following: preeclampsia, non-reassuring fetal heartbeat pattern and maternal morbidity with COVID-19 infection. Majority had a good APGAR score, but the neonate from the mother with severe COVID-19 had a low APGAR score (1, 7, 7). Meanwhile the newborn delivered from a mother with moderate COVID-19 infection had an APGAR score of 5, 8.

At 24 to 48 hours of life, RT-PCR was obtained from forty-eight (72%) newborns. The 19 (28%) newborns did not undergo RT-PCR as 3 mothers refused to have their neonates swabbed, while the remaining 16 mothers were cleared from the infection after completing 14 days isolation prior to the delivery. Out of these 19 mothers, only 4 of them had mild respiratory symptoms. Regardless of the RT-PCR result, or if an RT-PCR was obtained or not, all newborns delivered from SARS-CoV-2 RT-PCR positive mothers are included in the study.

Three of the newborns had positive RT-PCR test and the rest of the forty-five (67%) were negative. Two of the COVID-19 positive neonates were delivered via normal spontaneous delivery, while one via primary cesarean section secondary to maternal morbidity. These three newborns were full term, with good APGAR score, 38-39 weeks age of gestation, average weight of 2,970 grams and appropriate for gestational age.

Table 3.2. Clinical profile of neonates born to SARS-CoV-2 positive mothers

Variables		COVID Positive (n= 3)	COVID Negative (n= 45)	No RT-PCR (n= 19)	Total Newborns (n= 67)
Number of symptoms present	Asymptomatic	1 (33.3%)	23 (51%)	15(79%)	39 (58%)
	One symptom	1 (33.3%)	6 (13%)	3 (16%)	10 (15%)
	More than one symptom	1 (33.3%)	16 (36%)	1 (5%)	18 (27%)
Signs and Symptoms*	Jaundice	1	13	3	17
	Tachypnea	1	13	2	16
	Alar flaring	1	4	0	5
	Chest Retractions	1	5	0	5
	Desaturations	1	3	0	4
	Cyanosis	0	3	0	3
	Poor suck	1	1	0	2
	Seizure	0	1	0	1
	Vomiting	0	1	0	1
	Hypoglycemia	0	1	0	1
	Elevated CRP	0	3	0	3
Comorbidities**		2 (66.6%)	22 (49%)	4 (21%)	28 (42%)
	Neonatal Pneumonia	0	6	0	6
	Neonatal Sepsis	1	4	0	5
	Hyperbilirubinemia	0	3	2	5
	Transient Tachypnea of the Newborn	0	4	0	4
	Premature Rupture of Membranes	1	3	0	4
	Respiratory Distress Syndrome	0	2	1	3
	Cardiac Problem (First Degree AV block, Mobitz type II)	0	1	0	1
No Comorbidities		1 (33.3%)	23 (51%)	15(79%)	39 (58%)

*1 neonate may have one or more signs and symptoms
**1 neonate may have one or more comorbidities

Among the 42% newborns who were symptomatic, the majority had more than 1 symptom present. It was noted that jaundice was the most common manifestation, followed by tachypnea, alar flaring, and chest retractions. Six of the newborns developed neonatal pneumonia, followed by neonatal sepsis and transient tachypnea of the newborn.

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The majority of those with negative and no RT-PCR taken were asymptomatic. Of the three COVID-19 positive newborns, one was asymptomatic. The one who was born to a mother with a history of PROM for 19 hours presented with jaundice alone. The third COVID-19 positive neonate, however, had respiratory and septic manifestations. She was eventually assessed to have had critical COVID-19.

Table 4. Management and outcome of neonates

Variables		COVID Positive (n= 3)	COVID Negative (n= 45)	No RT-PCR (n= 19)	Total Newborns (n= 67)
Number of Interventions	None	1 (33.3%)	21 (47%)	14(74%)	36 (54%)
	One intervention	1 (33.3%)	9 (20%)	4 (21%)	14 (21%)
	More than one Intervention	1 (33.3%)	15 33%)	1 (5%)	17 (25%)
Interventions Given (n= 31)*	Antibiotics	2	14	0	16
	Antiviral	1	0	0	1
	Immunoglobulin	1	0	0	1
	Monoclonal antibody	1	0	0	1
	Steroid therapy	1	0	0	1
	Phototherapy	1	13	2	16
	Oxygen Inhalation	1	13	1	15
	CPAP	0	1	0	1
	Intubation	1	2	0	3
Length of Hospital Stay	1 to 2 days	1	11	9	21
	3 to 4 days	0	15	4	19
	5 to 7 days	1	10	3	14
	More than 7 days	1 *(32 days)*	9	3	13
Average Hospital Stay (days)		13	6.5	4	

*1 neonate may have one or more interventions

Forty-six percent of the newborns needed at least 1 to 2 interventions. The remaining 54% received no intervention during the initial admission. The length of hospital stay was longest among the COVID-19 positive newborns who stayed in NICU with an average of 13 days. For those with negative and no RT-PCR taken, they stayed in the hospital for less than a week.

The determinants of the length of hospital stay were mainly the interventions required or mode of delivery aside from the neonate's symptomatology. One COVID-19 positive neonate was asymptomatic and stayed in NICU for 2 days. The other SARS-CoV-2 positive newborn, who stayed for 5 days, had history of maternal premature rupture of membranes for 19 hours and was given antibiotics. The third newborn with critical COVID-19 was born preterm, had neonatal sepsis initially presenting with temperature instability, early jaundice, and respiratory distress. She had a positive blood culture growth of Methicillin Resistant *Staphylococcus epidermidis (MRSE)*. She was eventually intubated at 13 days of life and stayed in the NICU for 32 days but was discharged improved.

Table 5.1. Clinical manifestations on follow-up of neonates from SARS-CoV-2

Variables		COVID Positive (n= 2)	COVID Negative (n= 25)	No RT-PCR (n= 9)	Total Newborns (n= 36)
Number of symptoms present	Asymptomatic	1 (50%)	9 (36%)	5 (56%)	15 (42%)
	One symptom	1 (50%)	4 (16%)	2 (22%)	7 (19%)
	More than one symptom	0	12 (48%)	2 (22%)	14 (39%)
Symptoms*	Fever	0	14	3	17
	Cough	0	9	2	11
	Coryza	0	7	0	7
	Abnormal head size - Benign External Hydrocephalus - Scaphocephaly	0 0	0 1	1 0	1 1
	Vomiting	0	1	0	1
	Bloody stools	1	0	0	1
	Rashes	0	1	0	1
Month symptoms manifested	0 to 3	1	2	1	4
	4 to 6	0	6	1	7
	7 to 9	0	2	1	3
	10 to 12	0	6	1	7
	13 to 15	0	0	0	0

*1 neonate may have one or more symptoms

Out of the 67 newborns, only 36 were included in the follow-up study due to the inability to contact the parents with invalid contact numbers. Out of the 36 mothers who consented for the interview, 58% of the neonates developed at least 1 to 2 symptoms during the course on follow-up. Most of them had fever, cough, and coryza.

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Two neonates had abnormal head size during their follow-up at 2 months of age. Most of these symptoms were seen at 4-6 and 10-12 months of age, and none were reported at 13-15 months. For the 2 patients who presented with abnormal head size at 2 months of age, a magnetic resonance imaging (MRI) was done. The female patient had a benign external hydrocephalus, while the male patient showed obliteration of the sagittal suture that is related to the scaphocephaly. Both were advised to have a close monitoring for developmental delays or episodes of seizure of which none were seen during the follow-up interview.

Two out of the 3 COVID-19 positive newborns were available for follow-up. The critical COVID-19 neonate had bloody stools at 2 months of age, and this was due to cow's milk allergy. The other neonate remained asymptomatic.

Table 5.2. Hospital readmission of neonates born to SARS-CoV-2 positive mothers

Variables	COVID Positive (n= 2)	COVID Negative (n= 25)	No RT-PCR (n= 9)	Total Newborns (n= 36)
I. Asymptomatic	1 (50%)	9 (36%)	5 (56%)	15 (42%)
II. Symptomatic	1 (50%)	16 (64%)	4 (44%)	21 (58%)
A. Readmitted	1	2	1	4
Pediatric Community Acquired Pneumonia	0	0	1	1
Urinary Tract Infection	0	1	0	1
Cow's Milk Allergy	1	0	0	1
Acute Gastroenteritis	0	1	0	1
B. Not readmitted	0	13	3	16
C. Expired				
Asphyxia 2° to Aspiration Pneumonia	0	1	0	1

Four (11%) of the 36 newborns were admitted due to the following reasons: cow's milk allergy at 2 months old, pediatric community acquired pneumonia at 6 months old, urinary tract infection at 6 months old, and acute gastroenteritis at 11 months old.

All of these readmissions had no SARS-CoV-2 RT-PCR done, were all managed accordingly by their pediatricians. The neonate, who was admitted for cow's milk allergy and was provided supportive care, was one of the COVID-19 positive newborns. One infant, whose mother had moderate COVID-19 infection, died at 2 months of age due to asphyxia secondary to aspiration pneumonia but no RT-PCR was taken to confirm if it was related to COVID-19 infection.

Table 5.3. Developmental Quotient (DQ) on follow-up

Chronologic Age	n	Developmental Quotient		
		<1	1	>1
1 to 3 mos	35	0	35	0
4 to 6 mos	35	0	34	1
7 to 9 mos	27	0	25	2
10 to 12 mos	26	0	26	0
13 to 15 mos	21	2	19	0

*Developmental Quotient (Developmental age / Chronological age)
<1 = Delayed
1 = At par with age
>1 = Advance for age

Out of the 36 infants followed-up, the one who expired was not included in the neurodevelopmental milestones assessment. Table 5.3 shows the developmental quotient based on the Denver scale II of the 35 neonates. Based on the findings, majority of the subjects were at par with age. From the 3 neonates, who developed ahead of their age, two had negative RT-PCR, while one had no RT-PCR taken. The three who were advance for age: 2 were able to hold feeding bottle and transfer objects from hand to hand at 6 months of age. One neonate on follow-up at 7 months old was noted to sit without support and stand-alone while holding on to a chair. However, all 3 were at par with age upon reaching 15 months old. Two infants at 13-15 months were noted to have some degree of delay. One had expressive language delay while the other had both gross motor and expressive language delay. Both had tested negative for COVID-19 RT-PCR.

DISCUSSION

In this study, the maternal and neonatal demographic and clinical profile of newborns born to SARS-CoV-2 positive mothers were presented. According to a study in the Journal of Maternal and Child Health, extremes of ages are associated with several complications. If the mother is too young, from ages 11 to 18 years old, it is deemed prone to preterm delivery, mild pre-eclampsia and infections like chorioamnionitis and endometritis. For mothers above the age of 35, the risk for preterm delivery is imminent and they are more prone to hypertension with superimposed preeclampsia, and severe preeclampsia, but were noted to have a decreased risk for chorioamnionitis. Older women above 40 years old are at greater risk for preeclampsia that results in poor fetal growth and fetal distress.[11] The safest pregnancy and childbirth occur in women from ages 20-35 because of the reproductive age risk of complications is lower.[12] In this study, the majority (76%) were all within the low-risk reproductive age, and only a few (24%) were in the older age group above 35 years old. Although the majority was within the low-risk population, most of these mothers (58%) had 1 or 2 maternal comorbidities. Although the age of the COVID-19 positive mothers would classify their pregnancy as low risk, the presence of some comorbidities could have led to the development of symptoms in their neonates that required some degree of intervention beyond the scope of neonatal COVID-19 infection. This could explain why some neonates required treatment even if their SARS-CoV-2 RT-PCR results were negative. Living environment and socio-economic income in the Philippines has been a great challenge for most Filipinos pre-pandemic. More so during the pandemic, that it burdens not only the economic aspect but also the accessibility to health care facilities with new health protocols implemented. The socio-economic status of the mothers has implications likewise on their level of education.

According to Silva, et al., maternal education is associated with fetal growth. They found out that low maternal education led to slower fetal head growth.[13] In this study, most mothers were college graduates, with above minimum income, and currently residing in urban areas. Thus, they had adequate prenatal care with easy accessibility to health care facilities resulting in most neonates being full term, with appropriate weight for age, and a good APGAR score. Their level of education and socio-economic status could have also played a part to the low number of mothers getting infected with the SARS-CoV-2 during their pregnancy, as they would have better understanding of the significance in abiding to the standard health protocols. At the same time for those who were SARS-CoV-2 positive, they have better access to health care facilities capable of managing COVID-19, hence probably resulting also to better neonatal outcome.

Findings by Sulastri, et al. also showed the relevance of the number of pregnancies (gravida) to the development of complications. Repeated pregnancy and childbirth result in damage to the walls of the blood vessels in the uterus, causing a decrease in elasticity of tissues due to repeated stretching that may cause abnormal fetal and placental growth. It also showed increased risk (0.156 times more) for anemia and pre-eclampsia in multigravida women.[12] In this study, majority of mothers were multigravid, but only one was documented to have had uterine atony, though this did not affect neonatal outcome. By being multigravid, this can disrupt the uterine circulation leading to less optimal fetal growth. This may have contributed to why six neonates were small for gestational age and fourteen weighed below 2,500 grams.

In our study sites, protocol does not include testing SARS-CoV-2 of the placenta and amniotic fluid. The newborns are swabbed at 24 hours of life to determine if they are COVID-19 positive especially if the mother is documented to have SARS-CoV-2. A repeat swab at 48-72 hours of life is performed especially for those newborns with symptoms.

Though there were 3 neonates who tested positive for SARS-CoV-2 in their nasal and oropharyngeal swab, establishing an intrauterine transmission could not be done with the lack of testing of the placenta and the amniotic fluid for the presence of the virus in these specimens.

A study by Elhalik, et al. in Dubai, the clinical profile of 36 newborns from SARS-CoV-2 positive mothers showed that all newborns were stable and asymptomatic. Majority were term, with a median gestational age of 37 weeks and a weight of 2,985 grams.[14] This showed almost similar results with our study, they had two SARS-CoV-2 positive neonates and one neonate with an inconclusive report. All their neonates including those who were positive were asymptomatic with no mortality. In comparison to our study, with three SARS-CoV-2 positive neonates and only one was asymptomatic. One of our positive neonates was born preterm had a critical COVID-19 infection. In the study of Elhalik, et al., 25 out of 36 neonates they followed up showed that all neonates were healthy and in good condition, as compared to the results of our follow-up study with the majority being symptomatic at one point and with one mortality. However, they have no information on neurodevelopmental status of their patients since their study focused on respiratory and infectious diseases.

According to the Philippine Society of Newborn Medicine, neonates born to SARS-CoV-2 positive mothers should be started with antibiotics, like ampicillin and gentamicin, if there is high consideration for bacterial pneumonia or sepsis.[15] In this study, 16 were started with antibiotics as they had neonatal pneumonia and neonatal sepsis and completed the antibiotics for at least 7 days.

In a study by Bender, et al. of adult COVID-19 patients presenting with jaundice, there was higher risk for mortality. The main reason identified was due to liver dysfunction that was associated with sepsis, severe systemic inflammation and hypoxic/ischemic hepatitis.[16]

Among the 67 neonates included in our chart review, 16 underwent phototherapy. Their jaundice was secondary to neonatal comorbidities, which included neonatal sepsis, neonatal pneumonia, and hyperbilirubinemia secondary to breastfeeding jaundice. All of them had good outcome though.

The World Health Organization recommends supplemental oxygen therapy immediately for patients with respiratory distress and hypoxemia for timely respiratory support.[17] Out of the 67 newborns included in the study, 15 were given supplemental oxygen as they manifested with tachypnea, alar flaring, chest retractions, desaturations, or cyanosis. One out of the 8 preterm neonates was hooked to continuous positive airway ventilation (CPAP) due to severe transient tachypnea of the newborn. All these neonates had improvement of symptoms and were eventually discharged.

For severe cases, invasive ventilation is recommended to protect the lung from respiratory failure with use of low tidal volume and higher PEEP levels.[18] For the 3 neonates who were intubated, two were preterms with negative RT-PCR and one was a term neonate with COVID severe symptoms. The first neonate was a 32-week-old preterm delivered by a multiparous mother (G7P7 (6107)) with COVID-19 moderate infection with comorbidities including gestational diabetes and chronic hypertension. The patient was delivered via STAT primary cesarean section secondary to severe preeclampsia and had an APGAR score of 5 and 8, weighing 1,200 grams, and her RT-PCR result was negative. She had respiratory distress syndrome (RDS), was intubated and was given surfactant. She was eventually extubated and was discharged after 35 days. However, at 2 months of age, the patient expired due to aspiration pneumonia. She was dead upon arrival at the emergency room, but no RT-PCR was taken to confirm COVID-19 infection. The second neonate was a 29-week-old preterm delivered to a gravida 2 mother with COVID-19 severe infection. She was in respiratory distress with episodes of desaturations; thus, she was intubated and underwent STAT primary cesarean section.

The neonate had an APGAR score of 1, 7, and 7 and weighed 1,750 grams. She was intubated and given surfactant at 6 hours of life. Chest x-ray showed reticulo-granular pattern with air bronchograms suggestive of respiratory distress syndrome and RT-PCR was also negative. She was also discharged after 35 days. The third intubated neonate was born to a gravida 1 mother with no comorbidities and with mild COVID-19 infection. The baby had episodes of thermal instability and early jaundice. Her RT-PCR at 24 hours of life showed positive for SARS-CoV-2. The blood culture was positive for MRSE and was treated with antibiotics. She then developed signs of respiratory distress and was intubated at 13th day of life. She was managed with intravenous immunoglobulin, dexamethasone, remdesivir and tocilizumab. She was extubated after 15 days and was discharged at 32 days old. She was readmitted at 2 months old due to cow's milk allergy.

Long term follow-up of children born to COVID-19 positive mothers is lacking. Information on whether they will develop persistent or permanent complications has not yet been determined. This paper describes 36 neonates with data after discharge from their initial admission at birth. Though 64% of this population developed symptoms beyond the neonatal age, majority of the problems maybe unrelated to their initial exposure to the SARS-CoV-2, but instead reflects the typical risk of any infant being exposed to pathogens or stressors. COVID-19 infection cannot be totally ruled out since these patients did not have an RT-PCR swab to detect SARS-CoV-2 infection during their readmissions. The observed increased frequency of infections documented beyond 6 months of age among our subjects is consistent with the decrease in maternal immunoglobulins during this time. Three out of 4 subjects who were readmitted were due to infections like pneumonia, acute gastroenteritis and urinary tract infection occurring beyond 6 months of age.

A direct causality from the SARS-CoV-2 exposure cannot be established for the two infants who developed abnormal head size as they were both asymptomatic with negative RT-PCR at birth. The abnormal head size was an incidental finding during their follow-up at the OPD at 2 months of age.

Neurodevelopmental assessments entail detailed and comprehensive evaluation to help recognize future neurologic sequelae that can be prevented if there is early detection. The most widely used tool for screening is the Denver Developmental Screening Test (Denver Scale II). The results are then presented as developmental quotient which are based from raw scores that is calculated to measure the competence level of the child.[19] Majority of the subjects, who were followed-up are at par with age, except for 2 who were noted to have some degree of delay. It can be noted that 2 out of the 3 neonates who tested positive for SARS-CoV-2 have normal neurodevelopmental status. The one remaining COVID-19 positive newborn cannot be contacted and was not included in the follow-up study.

In the study of Chakravarty, et al., neurological symptoms like anosmia, ageusia, headaches, delirium, stroke and seizures may occur as there are several suggested mechanism for SARS-CoV-2's entry to the central nervous system by penetrating the blood brain barrier.[20] This further supports the involvement of neurologic manifestations seen in SARS-CoV-2 positive patients, but the direct impact of COVID-19 infection on infants born to SARS-CoV-2 positive mothers still warrants further investigation as the varied findings demonstrated in several study could not be directly linked to the eventual neurodevelopmental status of the infant.

In a similar study from Kuwait by Ayed, et al., they assessed the neurodevelopmental status of newborns of SARS-CoV-2 positive mothers using the ASQ-3 scoring during their follow-up at 10-12 months corrected age.

Out of the 298 infants involved in the study, it was documented that 10% of these infants showed developmental delays. Only 2 were positive for COVID-19 and both had normal ASQ-3 scores.[21] Those with developmental delays were noted higher among those mothers who had the COVID-19 infection during the first and second trimesters and born less than 31 weeks' gestation.[21] Similar with our study, the majority of those mothers in their study were infected during the third trimester. The 2 infants in our study who had developmental delay were born term from mothers with mild COVID-19 symptoms. Both of these infants were SARS-CoV-2 negative.

In another study by Zeng, et al. in Wuhan, China, out of the 72 newborns from SARS-CoV-2 positive mothers, five newborns tested positive for COVID-19. Out of these 5 neonates, three had abnormal MRI findings showing an abnormality in white matter signal w/ delayed myelination, delayed myelination and brain dysplasia, and abnormal signal in the bilateral periventricular areas. No abnormal physical growth seen in these newborns. The 2 other COVID-19 positive neonates did not show significant changes in their MRI findings.[22] In contrast to our study where the neurodevelopmental delay and abnormal head size were all seen in COVID-19 negative newborns. The two SARS-CoV-2 positive newborns in our study were at par for age. Only the 2 newborns with abnormal head size underwent an MRI and did not show similar findings as with the study of Zeng, et al. The 2 neonates showed benign external hydrocephalus and scaphocephaly. Both neonates are at par for developmental milestones for age. The fetal inflammatory response (FIRS) due to the maternal COVID-19 infection may have contributed to the neurologic manifestations seen in several studies of newborns from SARS-CoV-2 positive mothers. The increase of interleukin-6 (IL-6) may induce adverse neurological sequelae such as autism, psychosis, and sensory deficits later in life.

The direct involvement of SARS-CoV-2 with these varied findings is not yet established, however, long-term investigation is warranted as the neurological development of any child is of outmost importance.

CONCLUSION

The clinical profile of mothers in this study indicated that they had adequate support, preparedness, and access to health care during their pregnancy and during their COVID-19 infection. Maternal COVID-19 infection does not, however, necessarily result to a neonatal infection. For those neonates who developed mild symptoms while admitted, causality in relation to SARS-CoV-2 could not be established as several other risk factors were notably present. On follow-up, there were a few who developed significant problems like abnormal head size and developmental delays. These manifestations, however, have important long-term implications in the overall growth and development of a child, that further investigation to determine relationship of these clinical outcomes with maternal COVID-19 is warranted.

RECOMMENDATIONS

In dealing with a new disease like COVID-19, it is important to allocate resources for further studies with focus on the neurodevelopmental assessment of children with COVID-19 or born to SARS-CoV-2 positive mothers. A follow-up study with a larger population to include those from government hospitals may yield more information. The maternal vaccination status and occupational exposure may also be added in future research as they are potential risk or preventive factors that could affect neonatal outcome. Subsequent research with a case-control study design may be advisable to eliminate the confounders that were noted in this study.

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