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Neonatal outcomes of pre-diagnosed COVID-19 positive mothers in Nigeria

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Abstract

Introduction: *COVID-19 infection affects all age groups including newborns, however, literature is scarce on the fetal and neonatal outcomes of babies exposed in-utero, especially in Africa. The objective of this study was to document the perinatal outcomes of COVID-19 pregnancies and deliveries that occurred during the pandemic in Nigeria.* ***Methods:*** *this study was a descriptive review of the delivery and management of COVID-19 exposed newborns delivered at our hospital between April and July 2020 during the novel coronavirus disease pandemic in Nigeria.* ***Results:*** *nine women pre-diagnosed with COVID-19 infection and admitted into the COVID-19 isolation ward delivered between April 2020 and July 2020. Eight of them gave birth to live babies (including a set of twins) while one delivery was a stillbirth. The mean maternal age was b32.6±6.5 years. The mean gestational age of the live infants was 38.1±1.2 weeks. All the live deliveries were by caesarean section. Mothers received mental health and emotional support as needed pre- and post-delivery. The mean birth weight of the infants was 3107.8±203.7g. The babies had no symptoms associated with COVID-19 and all tested negative to serial reverse transcription polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 infection. All the babies were breastfed, and breast milk samples tested were also negative for the virus.* ***Conclusion:*** *the risk of vertical transmission appears to be low in third-trimester COVID-19 maternal infection, and the perinatal outcomes of babies exposed to SARS-CoV-2 appear favorable. This finding should aid the holistic care and counselling of families with pregnant women who test positive for COVID-19 and guide policy formulations.*

Introduction

The COVID-19 pandemic that is currently ravaging the world has left many deaths in its path. COVID-19, a viral illness caused by SARS-CoV-2 was first reported in Wuhan, Hubei province of China in late 2019 [1,2]. Since its characterization, the scourge has affected more than 22 million people all over the world leaving hundreds of thousands of deaths in its wake within a very short period of seven months [3]. The COVID-19 like other coronaviruses characteristically infect the type II pneumocytes with destruction and apoptosis of affected cells leading to diffuse alveolar damage with severe inflammatory changes [4] and micro thrombi formation in small blood vessels [5]. This manifests as severe acute respiratory distress syndrome (ARDS). The disease seems to be more severe in the elderly and the immunocompromised [6]. Pregnant women and their newborns were among those thought to be most at risk of severe disease from infections due to their depressed immunity. However, reports from published literature indicates that COVID-19 manifestations in pregnant women are not different from what is seen in non-pregnant sufferers [7,8]. Based on documented evidence of other SARS illness, the viral affectation may lead to premature delivery, miscarriages and stillbirths [9,10]. A review of available evidence by Parazzini *et al*. [11] showed low frequency of these complications.

The virus is transmitted via droplet inhalation to close contacts of affected individuals and through fomites [12-14]. Vertical transmission has not been established [8,11,15]. However, many newborns have been documented to be infected with the virus during the perinatal period [16]. Neonatal disease manifestation ranges from low-grade fever, symptoms of pneumonia and respiratory distress syndrome to deranged liver enzymes, disseminated intravascular coagulopathy, septic shock and

death [11]. Alfaraj *et al*. [10] in China and Igbal *et al*. [17] in the US did not document any neonatal complications in perinatal COVID-19 exposed babies [10,17]. Literature is scarce on perinatal COVID-19 exposure and newborn affectation in Africa. Available data on neonatal outcomes of maternal infection with SARS-CoV-2 are limited, most are results from studies with small sample sizes and with diverse, often conflicting conclusions [18,19], making them difficult to interpret and use for health policy decisions in our settings. There has been no documentation on newborn COVID-19 infection or exposure from any facility in Nigeria. This study, therefore, aimed to document and expand the literature with data obtained from Nigeria with a series of COVID-19 pregnancies and deliveries that occurred at our facility from April to July 2020. Our findings also aimed to strengthen the evidence for or against vertical transmission of SARS-CoV-2 infection in the newborn and contribute to discussions related to perinatal COVID-19 transmission.

Methods

This study was a descriptive review of the delivery and management of COVID-19 exposed newborns delivered at the COVID-19 isolation center from April 2020 to July 2020 during the pandemic of the novel coronavirus disease in Nigeria. Following the designation of our facility as an isolation center for COVID-19 in April, it quickly became a COVID-19 delivery center for most diagnosed COVID-19 positive pregnant women. A maternal and newborn team of care providers was formed to care for these women and their infants through pregnancy and delivery using the established protocol on maternal and newborn guidelines on COVID-19 infection [20]. Perinatal mental health and emotional support were provided to mothers with counselling via telemedicine with focus on their own mental health and also on the management of their newborns post-delivery. After delivery, they were required to wear a face mask and observe hand hygiene during breastfeeding and maintain social distancing when not breastfeeding.

Only newborns of mothers with COVID-19 infection who presented and delivered at the center between April and July 2020 were included in this study. Maternal and infant data such as maternal age, COVID-19 infection status, PCR results, parity, gestational age, baby´s sex, APGAR score at birth, baby´s RT-PCR results of amniotic fluid, cord blood, placental tissue, nasopharyngeal swabs and mother´s breast milk samples were collected prospectively. The baby´s nasopharyngeal swab and the breast milk samples were taken after 36 hours of life following the unit protocol [20]. Samples for routine blood workup before discharge such as complete blood count, electrolytes, urea and creatinine and serum bilirubin levels were also collected and analyzed. The data were extracted into Excel and simple descriptive statistics were employed to report the findings utilizing means and standard deviations for continuous variables. Categorical variables were shown as frequencies and percentages in the tables. Ethical approval for this study was obtained from the institution´s Health Research and Ethics Committee (HREC).

Results

From April 2020 to July 2020, nine pregnant women with COVID-19 infection were delivered following their admission into the isolation ward for COVID-19. Eight of them delivered live babies (7 singletons and one set of twins) while one delivery was a stillbirth. All but one of the deliveries were via caesarean section (CS). Seven of the deliveries had obstetric indications for CS such as >1 previous scar, fetal distress and maternal ill health (two mothers were very ill and had to be emergently delivered). One mother voluntarily opted for CS at admission. The baby that was a stillbirth was delivered vaginally at 33 weeks gestational age. Table 1shows the baseline characteristics of the live newborns and their mothers. The mean maternal age was 32.6±6.5 years. All the infants were of term gestation except the infant of one of the mothers with severe symptomatic COVID-19 infection and the stillborn. Both had to be delivered at 36- and 33-weeks gestation respectively due to

deteriorating maternal health and fetal distress in one and antepartum hemorrhage and fetal demise in the other. The mean birth weight of the infants was 3107.8±203.7g. All the infants were commenced on breastfeeding as soon as the mother recovered sufficiently from the effects of anesthesia post-surgery. Babies were commenced on infant formula if the mother was unable to commence breastfeeding within 90 minutes of delivery. All the mothers were supported to breastfeed. Only two mothers were too ill to establish breastfeeding within 24 hours of delivery. Infants and their mothers were nursed in the same room during the post-natal period while maintaining two meters apart when mother was not breastfeeding. Mothers wore face masks during any interaction with the babies.

Table 2 shows the RT-PCR results of all the samples collected during the perinatal period. All the mothers tested positive to COVID-19 pre-delivery. None of the babies´ samples were RT-PCR positive to SARS-CoV-2. In mothers who provided breast milk samples, none of the breast milk samples tested positive to SARS-CoV-2. The only baby tested for antibodies to SARS-CoV-2 showed strong positivity to IgG at birth, but a repeat sample at 36 hours was weakly positive. All the babies were stable with no signs or symptoms of COVID 19 during their hospital stay. All were discharged, after 72 hours of birth according to the unit´s protocol for discharge. Table 3 shows the results of routine blood work up for the newborns before discharge. All the parameters were essentially normal according to reference standards used [21]. None of the newborns had significant jaundice before discharge. All the infants were followed up in the routine baby clinic, and all were doing well. Maternal emotional support was provided and mother infant bonding encouraged for long term mental health.

Discussion

This study set out to document the neonatal outcome of maternal COVID-19 infection in Nigeria. Our findings showed no evidence of vertical transmission of SARS-CoV-2 among our study participants and this suggests predominantly favorable fetal and neonatal outcomes for infants exposed to maternal COVID-19 in-utero. One baby was stillborn following antepartum hemorrhage in the mother though no autopsy was carried out to determine the possible cause of death in the baby. Of the nine live babies examined in this study, none of them was tested positive to SARS-CoV-2 using the RT-PCR analysis. Different fetal and neonatal samples were tested for the virus and all returned negative. This is similar to the reports by different researchers in other climes that reported negative results in infants exposed to maternal COVID-19 in utero [11,17,22]. Schwartz *et al.* [22] in his analysis of 38 pregnant women with COVID-19 infection and their newborn infants concluded that there is no evidence that SARS-CoV-2 undergoes intrauterine or trans-placental infection from pregnant women to their fetuses. The lack of virologic evidence of vertical transmission in our cohort of infants with perinatal exposure to COVID-19 further strengthens the doubt on whether neonates can be vertically infected.

Several studies have documented virus-specific immunoglobulin as possible surrogates for congenital infection, although the clinical utility of this is yet to be established [23,24]. The only baby that was tested for antibodies to SARS-Cov-2 in our cohort showed strong positivity to IgG at birth but a repeat sample after 36 hours showed rapid diminution of the antibodies in the baby´s circulation. The IgM and RT-PCR were however negative at birth and 36 hours for this baby. Zeng *et al.* [23], in a case series, reported on mothers with mild clinical manifestations that had a caesarean delivery in negative-pressure isolation rooms under strict measures to prevent transmissions. The infants were isolated from mothers immediately after delivery. All the six infants in the series demonstrated detectable levels of IgG and IgM to SAR-CoV-2 in serum samples collected at birth, with two of them having abnormally high titers of both IgG and IgM antibodies although none of their RT-PCR of nasopharyngeal specimens was positive and

they all remained asymptomatic during the study duration [23]. The presence of high levels of antibodies in the infants´ blood specimen suggests intrauterine exposure or infection, although a lack of specificity and sensitivity in these tests and cross-reactivity makes these testing methods unreliable [25].

There is a lot of uncertainty regarding the possibility of vertical transmission of COVID-19 with available studies giving conflicting information on the possibilities of intrauterine transmission of the infection. There are several case reports of neonates who have tested positive for SARS-CoV-2 after delivery [7,8,11,26,27]. Trippella *et al*. [26] in a systematic review reported 16 neonates who were positive for the virus in the neonatal period. Similarly, a cohort study from the UK [27] reported six neonates who were positive for the virus within 12 hours of birth. In all these studies, the timing and mode of transmission of the virus to the infants were not clear. Although, the UK study [27] did not mention which specimens that were RT-PCR positive but they reported that the cord blood and placental tissues were not analyzed. In the study by Trippella *et al*. [26], only nasopharyngeal and anal swab samples were positive, thus raising further doubt as to the possibility of vertical transmission of the virus to these infants. There have been reported mental health distress amongst mothers due to the uncertainties of their individual outcomes along with the outcomes of their unborn babies [28,29]. Our team in anticipation of this potential anxiety ensured an emotional support team provided counselling to the participants´ mothers pre and post-delivery. This appeared to have further assisted the mothers through the peripartum process. Adequate counselling has been recommended as part of routine perinatal maternity care in the COVID-19 pandemic [30].

COVID-19 in pregnancy may be associated with serious fetal consequences. Richtmann *et al*. [31] in a case series from Brazil reported five fetal deaths at 21-38 weeks´ gestation in women with mild to moderate COVID-19 disease with no other obstetric disorder. They found intense placental inflammatory reaction in all the five cases and this was determined to be a direct effect of the SARS-CoV-2 virus on placental tissue. Similar findings of villitis and intervillitis with intense neutrophilic and lymphocytic infiltration, described as villitis of unknown aetiology, was reported in a second-trimester miscarriage in a woman with mild COVID-19 in France [32]. Although SARS-CoV-2 was detected in the placental tissue, the virus was not detected in the amniotic fluid sample [32]. None of our patients´ placental tissues, amniotic fluid or skin surface swabs tested positive to SARS-CoV-2. The present study recorded two preterm deliveries with one of the deliveries being a stillbirth. Preterm birth and stillbirths were also reported by other researchers elsewhere [11,26,31,33,34]. In a systematic review of nine studies with a total of 92 COVID-19 pregnancies, Smith *et al*. [33] reported a higher incidence of preterm births, low birth weight, cesarean section, and neonatal intensive care unit (NICU) admission in COVID-19 pregnancies compared to the general population. Dashraath *et al*. in a study with pooled data from nine studies documented stillbirth/miscarriage in 2% of 55 pregnancies in COVID-19 positive women [34]. Like other studies [26,33] our study also reported a high incidence of cesarean delivery. All the mothers with live births in our study were delivered via cesarean section due to obstetric indications and the mother´s preference in one case.

Cesarean section in mothers with COVID-19 infection has been reported from several studies with the indication for surgery being preeclampsia, fetal distress, history of previous cesarean sections, and unknown risk of intrapartum mother-to-child transmission of SARS-CoV-2 by vaginal delivery [18,19,26,33,35]. There has been no documentation of the precise risk posed by mode of delivery on SARS-CoV-2 infection in the newborn. Therefore, the impact of the mode of delivery on the risk of vertical transmission of SARS-CoV-2 in perinatally-exposed infant still needs to be further examined in future studies. Breastfeeding is the cornerstone of infant and young child survival, nutritional, cognitive and mental development.

Early initiation of breastfeeding has been shown to have positive effects on the neonate when started within an hour after birth. Our cohort of newborn was commenced on breastfeeding as soon as the mother was stable enough after surgery to breastfeed. Nearly all established some breastfeeding within 24 hours of delivery. Several concerns have been raised as to whether the COVID-19 virus can be transmitted from the mother to her newborn after birth, through breastfeeding. All the breast milk samples collected from the mothers of our cohort were all negative for the COVID-19 virus. We encouraged rooming-in of our mother-infant dyad with the maintenance of social distancing when not breastfeeding. The WHO recommended that breastfeeding must be based on a full consideration of not only the potential risks of COVID-19 infection of the infant but also the risks of morbidity and mortality associated with not breastfeeding and the inappropriate use of infant formula milk [36]. The benefits of breastfeeding to promote health and development are important especially when health and other community services are themselves disrupted or limited due to the pandemic. None of our babies showed any ill effects from breastfeeding.

In a recently published observational cohort study on neonatal management and outcomes during the COVID-19 pandemic, Salvatore *et al.* [18] noted that perinatal transmission of COVID-19 is unlikely to occur if correct hygiene precautions are instituted and adhered to. In their study, 68 neonates who were breastfed and roomed-in with their mothers, were tested for SAR-CoV-2 by RT-PCR on nasopharyngeal swabs taken at 24 hours, 5-7 days, and 14 days of life, and the babies were clinically evaluated by telemedicine at 1 month of age. They reported that the prospective RT-PCR for SARS-CoV-2 was negative in all the neonates at 1 week and 2 weeks of life. None of the neonate had symptoms of COVID-19 as of 1 month of age. Their findings and our data support the literature and strongly suggest that perinatal transmission of COVID-19 is unlikely to occur if correct hygiene precautions are undertaken, allowing for breastfeeding and mother-neonate bonding to be promoted. Our study findings also suggest that fetal and neonatal outcomes appear good for infants exposed to maternal COVID-19 infection, although our data only included pregnant women infected in their third trimesters and all had caesarean deliveries. It remains unknown whether infection in the first or second trimesters would increase the risk of adverse fetal and neonatal outcomes or whether the mode of delivery will have any impact on the risk of vertical transmission of COVID-19 infection. Further studies are needed to ascertain the possible long-term infant and early childhood outcomes and the potential sequelae that may emanate from SARS-CoV-2 exposure and infections in the newborn period. Thus, careful monitoring and follow up of these infants through childhood is warranted and should be encouraged.

Limitations: this study is a case series with small sample size and insufficient statistical power that can be used to make any clinical inferences. However, the findings from this study have generated hypotheses that can be tested in future robust and well-controlled studies. In addition, all the mothers in this series were infected in the third trimester of pregnancy and thus may not allow the evaluation of the impact of first and second trimesters COVID-19 infection on perinatal outcome. The possible contribution of COVID-19 infection as the cause of death in the fetus that was stillborn could not be ascertained as no autopsy was carried out and no post-mortem samples were collected for RT-PCR for SARS-CoV-2. Finally, all the neonates that were examined in this series were delivered via caesarean section and thus the possible influence of the mode of delivery on perinatal outcomes and the risk of vertical transmission of SARS-CoV-2 cannot be accurately assessed in our current study.

Conclusion

This study documented no evidence of vertical transmission of SARS-CoV-2 infection in infants exposed to maternal COVID-19 infection in utero. The risk of vertical transmission appears to be low

in third-trimester COVID-19 maternal infection, and fetal and neonatal outcomes of babies exposed to SARS-CoV-2 appears favourable. The risk can further be reduced if the mother observes all other precautions of prevention of the infection such as hand washing, use of hand sanitizers and face masks when attending to the baby. The finding of this study can aid holistic care and counselling of families and individual pregnant women who test positive for COVID-19 and guide policy formulations. However, a larger cohort of pregnant women that included infections in the first and second trimesters and with different modes of deliveries still need to be further studied.

What is known about this topic

- *COVID-19 can affect all age groups including newborns;*
- *There is scanty evidence for perinatal COVID-19 transmission and infection in the newborns.*

What this study adds

- *This study provides objective evidence that the risk of vertical transmission of SARS-CoV-2 is low in third-trimester COVID-19 maternal infection;*
- *This study also highlights that rooming-in and breastfeeding can be safe in babies exposed to maternal COVID-19 infection at birth in resource limited settings.*

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors have made substantial contributions to this manuscript, which include the design, data collection and analysis, interpretation of data, drafting and editing the article, and final approval for publication. BN contributed to the study development including concept and design, participated in the acquisition of data, project administration, data analysis and drafted the original manuscript. IF, CM, KO, AO, IA, YO, TA and JO: investigation, methodology, project administration, manuscript draft, review and editing. GO, ND, RD, MR, OO, RA, RD and OS: data curation, investigation, methodology, reviewed and edited the manuscript. SA, BA and CE: Conceptualization, investigation, validation, manuscript writing, review, and editing. All authors revised the manuscript for intellectual content and approved the final version to be published.

Tables

Table 1: baseline characteristics of the mothers with live births and their infants

Table 2: the RT-PCR results of different neonatal samples

Table 3: results of routine blood work up of infants´ pre-discharge

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Table 1: baseline characteristics of the mothers with live births and their infants		
Parameter	**Frequency (%) N=9**	**Mean (±SD)**
Maternal characteristics (n=8)		
Mean age (years)		32.6±6.5
Mean parity		2.0±1.0
COVID-19 symptoms at delivery		
Yes	1(12.5)	
No	7 (87.5)	
Gestational age (completed weeks)		38.1±1.2
Preterm (<37 weeks)	1(11.1)	
Early term (37-38 weeks)	4(44.4)	
Full term (39-40 weeks)	4(44.4)	
Late term (41-<42 weeks)	0(0.0)	
Post term (≥42 weeks)	0(0.0)	
Baby's characteristics		
Sex		
Male	5(55.6)	
Female	4 (44.4)	
APGAR score (median)		
1-minute		9
5-minutes		10
Birth anthropometry		
Mean birth weight		3107.8±203.7
Mean length		46.1±1.4
Mean head circumference		34.6±1.0

Table 2: the RT-PCR results of different neonatal samples		
Sample/Specimen	**Number tested**	**RT-PCR result (%)**
Cord blood	6	Negative (100)
Amniotic fluid/skin surface swab	9	Negative (100)
Placental tissue	7	Negative (100)
Nasopharyngeal swabs at ≥36 hr of life	9	Negative (100)
Breast milk	3	Negative (100)

Table 3: results of routine blood work up of infants' pre-discharge	
Parameters	**Mean ±SD of patient's values**
Haematologic	
PCV (%)	43.1±2.5
WBC (/mm^3)	12,493±1849
Platelets ($x10^9$/L	252,357±75,129
Chemistry (reference range in newborn)	
Na^+	139.9±4.3 (130-145 mmol/L)
K^+	4.9±0.3 (3.7-5.9 mmol/L)
$HCO3^-$	18.1±2.0 (17-24 mmol/L)
Cl^-	104.9±4.2 (97-108 mmol/L)
Urea	2.3±1.2 (0.7-6.7 mmol/L)
Creatinine	48.9±14.4 (27-88 µmol/L)