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Impact of SARS-CoV-2 Infection during Pregnancy and Perinatal Outcome: Findings from Private Hospitals at Dhaka, Bangladesh

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Abstract

Introduction: *The pandemic novel corona virus (SARS-CoV-2) infects pregnant women and affects pregnancy outcome. The perinatal outcome of COVID positive pregnancies attended at private hospitals during the last epidemic peak at Dhaka is unknown. The purpose of the study was to evaluate perinatal outcome among COVID positive and COVID negative pregnant women who delivered in the 2 study hospitals at Dhaka during the last epidemic wave.*

Methods: *This retrospective study was conducted in 2 eminent private medical college& hospitals in Dhaka,namely Popular medical college &hospital (PMCH) and Greenlife medical college hospital (GLMC) over a period of 3 months from July 2021 to September 2021. COVID positive and COVID negative pregnant women who delivered in the study hospitals during the study period were included in this study. Outcome variables were COVID related maternal morbidity mortality, rate of caesarean delivery, stillbirth, preterm birth, low birth weight, neonatal COVID-19 positivity, neonatal death.*

Results: *This study included 60 COVID positive and 60 COVID negative pregnant cases. COVID positive pregnant women delivered at earlier gestational age (weeks) than COVID negative cases(34.46±3.58 vs 36.50±3.20; p=0.001) .Among COVID infected pregnancies,severe disease was observed in 15%; O2 support was needed in 68.3% and ICU admission required in 16.7% cases.The caesarean delivery rate ((93.3% vs 80%; p-.032) and preterm delivery rate (63.3% vs 35%; p-.002) were significantly higher among COVID positive cases. About 8.3% COVID affected pregnancies ended up with stillbirth.Maternal death rate due to COVID related complications was 5%.Proportion of low birth weight (LBW) was significantly more in infected pregnancies (65% vs 35%; p 0.001).No newborn from COVID positive mother was tested positive by RT-PCR at 24 hours of age.*

Conclusion: *SARS-CoV-2 infection during pregnancy cancause moderate to severe disease requiring ICU admission and maternal death in 5% among COVID positive cases .It gives rise to more still birth, preterm birth, increasing number of LUCSand LBW. However maternal to neonatal transmission is not evident at 24-hour RT-PCR testing.*

Keywords: *COVID-19, Neonate,Pregnancy, Outcome, Private hospital, Bangladesh*

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Introduction

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is proven to be the biggest public health crises of recent times; as per the World Health Organization's (WHO) update dated 11 February 2022, there have been 404,910,528 confirmed cases and 5,783,776 deaths, worldwide.[1]

Pregnant women and babies may be more vulnerable to COVID-19. The physiologic changes of pregnancy affect the cardiorespiratory and immunological systems, this could result in a different response to SARS-CoV-2 infection.[2] In 2020,a systematic review shows pregnant woman have a higher risk of severe COVID-19 infection than non-pregnant women.[3]

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According to the World Health Organization (WHO), certain host factors like older age, overweight , pre-existing medical disorders like hypertension and diabetes increase the risk of severe COVID-19 in pregnancy [4]. When compared to non COVID, research in pregnant women found that COVID-19 is linked to preeclampsia, stillbirth, and premature delivery and when compared to asymptomatic COVID-19, symptomatic COVID-19 was linked to a higher risk of cesarean delivery and premature birth. [5]Also SARS –COV-2 infection has been associated with 10% death rate in the general population and up to a 25% mortality rate in pregnant women. [6]

Evidence regarding maternal to neonatal transmission of COVID-19 infection is lacking; several samples from COVID-19 infected women, including amniotic fluid, cord blood, newborn throat swabs, and **breast milk** tested were negative for the virus. [7,8] Furthermore, there is presently no proof that the virus can induce fetal abnormality. Preterm labor delivery has been reported in women with COVID19, although it is unclear if the preterm birth was caused by another factor or occurred spontaneously. [7]

COVID-19 disease in neonates is quite rare. [9,10] The first instance of covid-19 in a newborn was discovered in China on February 1, 2020,.[11] Subsequently newborn test result positive rate of 3.1 percent to 9.1 percent was reported in systematic analyses of case series of women with SARS-CoV-2. [12-14]Still there is scarcity of data regarding maternal to neonatal transmission of COVID-19, based on accumulating evidence, World Health Organization(WHO)promoted rooming-in and breastfeeding with precautions. [15]

In Bangladesh, the estimated number of birth during COVID-19 pandemic is 2.4 million .[16] Due to lack of records, the exact number of COVID 19-positive pregnant women in Bangladesh is unknown. Earlier in pandemic, the economic effect of the Covid-19 epidemic on health-care organizations has raised fears of service interruption. Disruption of maternal and neonatal health care, particularly in developing countries, might result in poor birth outcomes.[17]

Since the identification of 1st case in March 2020 [18] and speedy growth in the number of infected patients with a remarkable mortality rate, COVID-19 infection became a health concern in Bangladesh. Although government adopted preventive strategies strongly, health care facilities were not prepared enough to manage huge number of COVID positive patients at the outset. The COVID dedicated hospitals and other COVID units of COVID non-dedicated government hospitals were overwhelmed with evolution of community transmission of pandemic status. Some private hospitals played a remarkable role for treating the COVID affected patients including COVID affected pregnant women during the last epidemic peak. There are published data on outcome of COVID positive pregnancies treated in Government hospitals.[19] But there is scarcity of data from private hospitals in this regard. The study was planned to assess and compare perinatal outcome **among** COVID positive and negative pregnancies managed in 2 eminent private hospitals at Dhaka, Bangladesh.

Methods

This retrospective study was conducted in two eminent private medical college hospitals in Dhaka city, Popular Medical College Hospital (PMCH) and Greenlife Medical College Hospital. Since COVID outbreak in Bangladesh on 8thMarch 2020, these 2 private hospitals took the lead to provide care to all categories of COVID patients besides government hospitals. The study was conducted after approval from the institutional review board(IRB).

This study included COVID positive and COVID negative pregnant women who got admitted, delivered and both mothers and babies managed at the study hospitals in postnatal period between , July 2021 to September, 2021.COVID positive or negative pregnant women with incomplete data and who did not deliver in the study hospitals were excluded from the study. Maternal COVID positive status was confirmed by real time polymerase chain reaction (RT-PCR) for SARS-CoV-2 done in nasopharyngeal swab. Control were selected as 1 to 1 ratio from delivery registers of non-COVID pregnant women who delivered close to the delivery time of COVID-positive case. All maternal data were obtained from clinical records from the department of obstetrics and gynecology (ObGyn) and from intensive care unit for those who required intensive care support. Regarding antenatal corticosteroid (ACS) , any women who received incomplete or complete dose of dexamethasone as recommended for preterm or other high risk delivery or dexamethasone received as part of management of COVID infection were considered positive for receiving ACS. For non-admitted newborns, data were gathered from maternal postnatal clinical records and for newborns requiring admission in neonatal intensive care unit (NICU), data were taken from neonatal case sheets. For case definitions and clinical severity assessment WHO[20] and National Guideline of Bangladesh for COVID-19[21]was followed. Purposive sampling techniques was used.

All newborn delivered by COVID positive pregnant women were tested for COVID infection by RT-PCR for COVID-19; oropharyngeal and nasopharyngeal swab was collected following standard technique by skilled technician of RT-PCR lab after 24 hours of age. The test was done in the RT-PCR laboratory of Popular Medical College and Green Life Medical College Hospital.

All maternal and neonatal data were collected using a structured questionnaire.Outcome was described as maternal disease severity, COVID related maternal outcome, caesarean delivery rate, pregnancy outcome as stillbirth, preterm birth, low birth weight, neonatal COVID-19 positivity, neonatal death.

Statistical analysis

After collection data was compiled in personal computer, edited. Data was analyzed using the statistical package for social sciences (SPSS) version 21. Quantitative data was expressed as mean and standard deviation and categorical data was presented as frequency and percentage. All quantitative variables were compared by unpaired *t*-test; categorical variables were compared by Chi-square test or Fisher's exact test. $P < 0.05$ was considered as significant. Logistic regression mode was used to find out the association between neonatal outcome and COVID positive pregnancy.

Results

There were total 213 deliveries in the 2 study hospitals during the study period . Of them 60 were COVID-19 positive giving the frequency of 28.2% of COVID positive delivery in the study hospitals. These 60SARS-COV2 infected pregnant patientsand 60 non-infected pregnant women delivered during the study period were enrolled in this study.More than fifty percent (51.7%) of the COVIDinfected mothers were primi in comparison to non-infected mothers (38.8%).Mean weeks ± SD of gestational age between the two groups were significantly different at the time of delivery (34.46±3.58 Vs 36.50±3.20; p=0.001). Mean gestational age at COVIDpositive test result was 35.45±3.53wks.There was no significant difference in the frequencies of co-existent obstetric and medical complications between COVID infected and non-infected groups. Higher number of mothers (33.3% vs 26.7%, p 0.426) received antenatal corticosteroid in the COVID infected pregnancies.About 93.3% COVID positive pregnant women underwent lower uterine caesarean section (LUCS) compared to 80% in COVID negative pregnant women and this finding was statistically significant.(p 0.032). Preterm delivery was also significantly higher among COVID positive women(63.3%) compared to COVID negative women(35%) with p-value 0.002). Still birth rate was higher(8.3%) in COVID infected cases than non-infected cases (5%).(Table:1)

Table -I

Maternal demographics and clinical characteristics among COVID-19 positive and negative cases

Variables	COVID Positive N=60	COVID Negative N=60	p-value
Age, mean ± SD	31.61 ±4.02	30.20 ±3.92	0.89
Primipara	31(51.7)	23(38.3)	.142
ANC n%	53(88.3)	55(91.7)	.543
Gestational age (mean± SD) at delivery	34.46±3.58	36.50±3.20	.001
Gestational age when COVID positive status detected, wk (mean ± SD)	35.45±3.53		
Antenatal steroid n (%)	20(33.3)	16(26.7)	.426
PROM	5(8.3)	3(5.0)	.464
PIH	18(30.0)	14(23.3)	.409
Gestational DM	14(23.3)	10(16.7)	.361
Other medical disorder	9(15.0)	6(10.0)	.408
LUCS	56(93.3)	48(80)	.032
Post-partum complications	3(5.0)	5(8.3)	.464
Multiple fetus	4(6.7)	7(11.7)	.343
Still born	5(8.3)	3(5)	.464
Preterm delivery	38(63.3)	21(35)	.002

Values are presented as number (%) or mean± standard deviation. quantitative variables were compared by unpaired t-test; categorical variables were compared by Chi-square test or Fisher's exact test. $P < 0.05$ considered as significant. PIH-Pregnancy induced hypertension, PORM- premature rupture of membranes, LUCS- Lower uterine cesarean section.

Of the total 60 infected women, 15% presented with severe disease ; majority (46.7%) were asymptomatic or with mild symptoms. (Figure: 1)

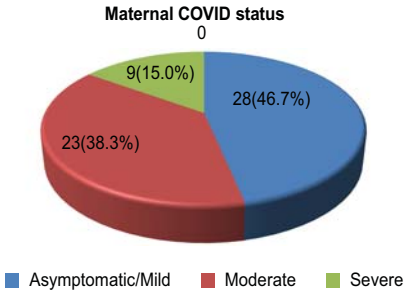

Fig.-1: *Disease severity classification among COVID positive pregnant women (n=60)*

COVID-19 infection in pregnant women caused complications (Table:2). Oxygen requirement was observed in 68.3% infected mothers.; oxygen delivery device was nasal canula (33.3%) followed by high flow nasal canula (14.9%)and rebreather mask (9.99%).There was a need for ICU admission in 10 (16.7%) infected mothers. Three COVID infected (5%) mothersdied after delivery due to COVID related complication.

Meanbirth weight(gram ±SD) of newborns from COVID positive and COVID negative mother were2355±425 and 2758±455 respectively and the difference was statistically significant (p 0.000)(Table:3). Significantly higher number of neonates wereborn pretermby COVID infected mothers compared to neonates born to COVID negative mother (65% vs 35%; p- 0.001). The number of male babies delivered by COVID infected mothers was less than non-infected mothers. The 5-minutes APGAR score and the requirement of bag mask ventilation (BMV) at birth did not differ between the 2 groups. About 53.7% newborns required admission in neonatal intensive care unit in COVID positive mothers.The neonatal morbidities were not different between the groups.Higher number of newborns from COVID infected mothers required oxygen (36.4% vs 21.1%) and their mean (day ±SD)hospital stay was also higher (8.29 ± 5.04vs 6.82±3.94) but these differences were not significant statistically.However, no baby born to COVID positive mother were tested COVIDpositive at 24-hour sample.Alsothere was equal number of neonatal death (01) in both groups. The cause of death in COVID infected delivery was extreme prematurity (27 weeker) LBW (760gram) with RDS .

Table-II

Oxygen Requirement and outcome among COVID positive pregnant women

Variables	COVID positive N=60	Frequency (%)
Maternal Oxygen Requirement	41	68.3
Nasal canula	20	33.31
Mask	1	1.66
Rebreather mask	6	9.99
HFNC	9	14.9
CPAP	2	3.33
MV	3	4.99
Maternal ICU admission	10	16.7
Maternal death related to COVID complications	3	5

Values are presented as number (%)

Table-III

Neonatal demographics and clinical characteristics between 2 groups

Variables	COVID positive N=60	COVID negative N=60	p-value
Birth wt, mean± SD,	2355±425	2758±455	**.000**
Low birth weight	39(65)	21(35)	**.001**
Male	26(43.3)	33(55)	.201
Apgar at 5 min, mean± SD	7.56±2.61	7.88±2.24	.478
Bag mask ventilation	13(21.7)	8(13.3)	.230
RT-PCR for SARS-CoV-2 Positive	0		
Need for NICU admission	29(53.7)	21(36.2)	.063
PNA	12(21.8)	8(14)	.282
Neonatal sepsis	5(9.1)	4(7)	.687
RDS	8(14.5)	5(8.8)	340
Congenital pneumonia	6(10.9)	8(14)	.617
TTN	6(10.9)	11(19.3)	.216
Jaundice	18(32.7)	13(22.8)	.241
O2 therapy	20(36.4)	12(21.1)	.073
Neonatal Death	1(1.7)	1(1.7)	.073
Hospital stay, mean± SD,day	8.29 ± 5.04	6.82±3.94	.089

Quantitative variables were compared by unpaired t-test; categorical variables were compared by Chi-square test or Fisher's exact test. P < 0.05 considered as significant. PNA-Perinatal asphyxia, RDS-Respiratory distress syndrome, TTN-Transient tachypnea of newborn

Logistic regression model showed no significant association be-tween LUCS, preterm delivery and newborns' low birth weight and the pregnant women's COVID-19 status(Table: 4).

Table -IV

Logistic regression model for caesarean delivery, preterm birth and low birth weight among COVID positive and COVID negative pregnancy.

Variables	OR	95% CI	p-value
LUCS	.338	.098-1.168	.086
Preterm	.505	.197- 1.296	.155
Low birth weight	.468	.182-1.202	.115

Statistical test by binary logistic regression

Discussion

This retrospective study included 60 COVID positive pregnant women and 60 COVID negative pregnant women. Considering the total number of deliveries in the study hospitals COVID- 19 infection rate was 28.2% among pregnant women delivered at the epidemiological peak of July to September 2021.

This finding differs with 2 reports from other country where the prevalence of COVID-19 in pregnant women was found 13.2 and 15.5% .[22,23]COVID-19 infection was noted very low (3%) in pregnant women in a study conducted in an inner city African-Americans (AA) population.[24]

The different rates of COVID-19 spread and intensity in different global regions at different times might explain the different rate in the incidence of infection among pregnant women.

This study showed about 51.7% women are primipara. COVID infected women delivered at significantly earlier mean gestational age than non-infected women. COVID positive mothers mostly underwent LUCS which differed significantly from non-infected mothers. Postoperative complications and pregnancy associated complications were comparable between the groups.

Another study conducted in Bangladesh showed, LUCS deliveries were more common (71.4%) among COVID-19-positive pregnant women than among COVID-19-neg-ative women (42.1%) which was close to our study.[19] Another study showed thatmode of delivery was LUCS in 79% cases and 57.9% women delivered before completion of 37 weeks. [25]

A systemic review published in 2021 showed, among the 522 patients who delivered successfully, 328 (62.84%) women delivered by caesarean and 135 (23.94%) mothers were reported associated comorbidities during pregnancy.[26]Some authors also reported LUCS was the preferred mode of delivery among COVID positive mothers.[27]Della Gatta et al in a systematic review reported that 90.2% of women with COVID-19 delivered via C-section .[28]The reason for this high incidence of LUCS may be due to more aggressive management of labor and delivery during the onset of the pandemic.

In the present study still birth delivery was more among the COVID-19-positive women (8.3%) than among the COVID-19-negative women (5%) in this study. Similar findings were also found by Masud SB et al.[19]

One important finding in this study was significantly high preterm delivery rate (63.3% vs 35% ; p-.002) in COVID positive pregnancies.

In 2020, a systemic review of nineteen studies of China, Canada, USA having 41 hospitalized COVID positive pregnant women show that the most common adverse pregnancy outcome was preterm birth <37 weeks, occurring in 41.1% of cases.[29]

We found 46.7% mothers were asymptomatic or had mild symptoms and only 15% of mothers had severe symptoms in this study. About 16.7% needed ICU admission. Higher number of asymptomatic cases were also noted in some other study. REF Sayeed et al also found 51 mothers (75%) to have mild, 9 mothers moderate (13%) and 8 mothers (12%) severe disease .[30]A study conducted on 258 pregnant women, 206 (79.8%) pregnant women had mild to moderate disease, 43 (16.7%) had severe disease, and 9 (3.5%) were in the critical stage of the disease.[31]

In this study, we found about 16.7% mother needed ICU admission and 68.3% COVID positive woman needed oxygen therapy. Three (5%) mothers died due to COVID related complications.

A report published by the Centers for Disease Control and Prevention (CDC) in June 2020 showed that preg-nant women with COVID-19 are likely to require more intensive care unit (ICU) support, suggesting that chiildbearing women are more vulnerable to have serious is-sues with COVID-19 . [32]

In this study higher numbers of COVID positive mothers suffered from PIH, GDM and other medical disorders although not significant statistically. A multinational cohort study conducted by Villar J et al shows women with a COVID-19 diagnosis had higher rates of pregnancy-induced hypertension (RR, 1.46; 95% CI, 1.05-2.02) and infections requiring antibiotics (RR, 3.38; 95% CI, 1.63-7.01), and there was an association with a greater risk of admission to ICU/high-dependency unit (RR, 5.04; 95% CI, 3.13-8.10). [33]

A systematic review and meta-analysis done in 2021, which shows comparison of Covid-19 with no infection and they found that SARS-CoV-2 infection in pregnancy was associated with preterm birth (OR 1.82, 95% CI 1.38 to 2.39; $I2$ = 64%; 18 studies) stillbirth (OR 2.11, 95% CI 1.14 to 3.90; $I2$ = 24%; 6 studies), ICU admission (OR 4.78, 95% CI 2.03 to 11.25; $I2$ = 76%; 5 studies). [34]

In this study due to COVID related complications 3(5%) mothers died after delivery. In another study conducted in Bangladesh also showed higher number (94%)of recovery and discharge and fewer death among COVID infected pregnant cases. [30]

According to our study, we found significant association between newborns' low birth weight and the COVID-19 status of pregnant women compared to COVID negative women. COVID positive women delivered low birth weight baby in 65% cases, whereas in COVID negative women it was only 35%. (p-.001) In a systematic review involving 10 000 pregnancies, LBW occurred in 25% of pregnancies (95% confidence interval [CI] 16–37, $p < 0.001$).[35] Though many studies did not find any relation with LBW babies. [19,27,36]

Considering increasing rate of COVID infection among pregnant woman, mother to child transmission became a vital issue with emergence of COVID pandemic. Though till date there is insufficient evidence of vertical transmission of COVID-19.Data on vertical transmission of SARS-CoV-2 are inconsistent. Many reports found no evidence of vertical transmission in a variety of samples, including amniotic fluid, cord blood, neonatal throat glands, placental cotton swabs, genital fluid, and breast milk samples from infected mothers.[14, 37-39]

Although mode of acquiring infection is uncertain, newborn can be infected as was evident from the first case reported in China on first February 2020.[9] In the current study all neonates tested negative for RT-PCR for SARS-CoV-2. Zhang L, et al also confirmed the identical result among 18 neonates delivered by 18 pregnant COVID-19 ladies and none of them found to be positive for SARS-CoV-2.[40]Another study conducted in Bangladeshi s [30] also found that among fifty-one neonates, only 41 (80%) completed RT-PCR test and all were negative.

Our study showed that about 53.7% neonates needed NICU admission. Neonatal complications were almost similar in both groups. One neonate in each group died in this study. Allotey et al reported 33% (95% confidence interval 24% to 43%; 41 studies, 3323 women) of intensive care admission of neonates born to women with COVID-19.[5] From the study in Bangladesh regarding neonatal outcome, 48 (94.2%) were term baby, 3 (5.8%) preterm, neonatal pneumonia was present in 1 (1%), neonatal hyperbilirubinemia in 3 (6%).[30] Less morbidity accounted for favorable outcome of neonates among pregnant COVID-19 women.

The immaturity of neonatal immune system, passive transfer of maternal IgG antibodies and lower ACE2 expression may lead to reduced inflammation, mild illness, and faster recovery infants and children compared to adults.[41,42]A systematic review by Zaigham M, Andersson also described favorable neonatal outcome.[43] Schwartz DA in their analysis of 38 infected pregnancies, did not find any evidence for intrauterine transmission.[44]

On the contrary, Rahman M et al [45] in a study found that out of 1714 admitted neonates, 32 (2%) cases were COVID-19 positive. Khalil et al in a systemic review with a high risk of bias included 2567 pregnant women reported a rate of 1.4% neonatal SARS-CoV-2 positivity, which is certainly infrequent, but leads to think that in utero and intrapartum vertical transmission might be possible. [46]Angelidou A et al in their study among the 255 mother-newborn from 11 hospitals in Massachusetts, found a 2.2% test result positivity rate in neonates who underwent SARS-CoV-2 testing during birth hospitalization.[47]In a systemic review,555 neonates were included. Almost all neonates (549, 98.92%) received the test for SARS-CoV-2, in which 18 were tested positive as the rate is 3.28%.[22]

Logistic regression model for caesarean delivery, preterm birth and low birth weight among COVID positive and COVID negative pregnancy shows no significant relation among them.

Conclusion

From this study, it can be concluded that SARS-CoV-2 infection during pregnancy can cause moderate to severe disease requiring ICU admission and maternal death. It can give rise to more still birth, preterm birth, increasing number of LUCS and LBW. However maternal to fetal/neonatal transmission is not evident at 24-hour RT-PCR testing.

Recommendation

Evidence from other studies for increasing perinatal/ neonatal COVID-19 urges the need for rapid identification and management COVID-19 though we did not find such positive finding in our study.

A large-scale prospective study with adequate samples are needed to identify the factors affecting maternal disease severity, pregnancy and neonatal outcome.

Limitation

Neonatal COVID testing was done only at 24 hours of age.

The study addressed the COVID-19 in pregnant women at an epidemiological peak from July to September 2021 which might not be a true estimate of the disease profile.

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