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NEONATAL OUTCOMES AND VERTICAL TRANSMISSION IN COVID-19 INFECTED PREGNANT WOMEN; A SYSTEMATIC REVIEW

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ABSTRACT

Objective: to review the probable vertical transmission and neonatal outcomes in confirmed COVID-19 pregnant women. **Methods:** Google Scholar, Science Direct, and PubMed were searched for qualified articles describing neonatal outcomes and the chances of perinatal transmission in COVID-19 pregnant women through the period from 1 January to 20 June 2020. A systematic review was done. **Results:** Nineteen articles were found eligible, investigated 125 neonates. Ten neonates (8%) confirmed to be infected, preterm delivery occurred in 33 neonates (26.4%), NICU admission (17, 14.8%), low birth weight <2500g (13, 11.3%), lung radiographic imaging suggestive for COVID-19 (14, 11.2%), and finally death (1, 0.8%). **Conclusion:** Although no evidence yet confirms COVID-19 vertical transmission, its potential occurrence should be taken into account as suggested by many studies. Good neonatal outcomes in general showing not to be significantly affected, despite the fact that COVID-19 perinatal infection can lead to neonatal deleterious outcomes.

INTRODUCTION

The latest coronavirus (SARS-CoV-2) disease was called Coronavirus Disease 19 (COVID-19) in accordance with the name given by the World Health Organization (WHO) and it is indicated to be a pandemic (1). The COVID-19 is spreading rapidly around the globe and leading to severe acute respiratory syndrome (2). Although our knowledge about the disease is being continuously updated by COVID-19 data, extensive understanding about pregnancy continues to be scarce. (3) There is a still controversy about COVID-19 perinatal outcomes in neonates. Contrary to other credible evidence on neonatal outcomes (4). Negative impacts on infants have been argued by many reports, these include fetal distress, respiratory distress, thrombocytopenia usually with liver dysfunction, or rather death (5). There is increasing concern about the probability of COVID-19 transmission vertically from the pregnant woman to the fetus, even though the existing proof is uncertain. (6). During the vaginal delivery, contact of the neonate with the vagina and rectum can occur, and this may lead to vertical transmission as is already established for many pathogens(1). Recently, the first probable vertical transmission has been documented to happen throughout normal vaginal delivery of confirmed COVID-19 pregnant that had positive swab samples for SARS-CoV-2 from rectum and stool (7). This implies that during vaginal delivery, SARS-CoV-2 can get into the neonate's nasopharynx, leading to possible infection (1). While in cases of cesarean sections (CS), despite the sterile conditions and the extreme precautions during

the delivery and after, but still COVID-19 transmitted to the newborns which largely suggests intrauterine vertical transmission (8,9). Accordingly, we implemented a systematic review to recapitulate the post delivery outcomes of the neonates and potential vertical transmission in confirmed COVID-19 pregnant women.

METHODS:

A search for articles was conducted in Google Scholar, Science Direct, and PubMed for published qualified articles through the timeframe 1 January-20 June 2020. The search was done in accordance with Medical Subject Headings (MeSH) terms, these included: "pregnancy," "pregnant women," "neonates," "COVID-19," "vertical transmission" and "coronavirus infections". Also, the references of the recognized articles were manually searched. Clinical studies, letters, and case reports or series describing neonatal outcomes and the chances of vertical transmission were screened. A systematic review has been carried out in compliance with the criteria of the Preferred Reporting Items for Systemic Assessment and Meta-Analysis (PRISMA). The following details had been extracted for each article: the last name of the first author; country; year; COVID-19 pregnant women number included; the age of gestation at the birth time; delivery method; neonatal outcomes (gender, weight, preterm delivery, 1 and 5-minute Apgar score (Appearance, Pulse, Grimace, Activity, and Respiration score), neonatal symptoms, COVID-19 swab, lung radiographic imaging results, need to neonatal intensive care unit (NICU) and symptoms).

RESULTS

Our search resulted in the identification of 32 articles, while the manual references search has resulted in 13 additional articles. After eligibility screening by reviewing abstracts and methods; 26 articles have been excluded (the reasons either to be a review article or the neonatal outcomes were not included in details). The remaining 19 articles are found to be eligible; they include research articles, letters, and case reports or series. These articles investigated the possibility of vertical transmission and newborn outcomes in 125 neonates from 124 pregnant women confirmed to be COVID-19 infected.

The PRISMA flow diagram of this study is represented by the figure (1). Delivery details and neonatal outcomes are listed in detail in the table (1). Ten neonates out of 125 were tested positive for COVID-19 by swab tests. Nine of them were delivered by cesarean section (CS), eight required NICU admission, seven had symptoms, five had positive lung radiographic imaging and finally, four neonates were preterm. Notably, 9 neonates who had negative COVID-19 swab but still had positive lung radiographic imaging results ranging from mild to severe findings in addition to several symptoms. The symptoms developed in 30 newborns were variable. These include vomiting (12, 9.6%), abdominal distention (11, 8.8%), (8, 6.4%) for each fever and shortness of breath (SOB), (4, 3.2%) for each pneumonia symptoms and cyanosis, (2, 1.6%) for each of hypoglycemia, respiratory difficulties and asphyxia and (1, 0.8%) for each cough and rash with edema. One neonate had severe complications (increased heart rate, gastrointestinal bleeding, disseminated intravascular coagulation (DIC), shock and organ failure), this neonate died eventually (5).

DISCUSSION

Pregnancy is a condition of suppressed immunity that renders pregnant women increasingly susceptible to viral disease, even in cases of seasonal influenza the morbidity is significantly higher. Consequently, the COVID-19 outbreak can lead to significant implications for them (25). Pregnant women could be more vulnerable to infections in the respiratory tract and pneumonia relative to non-pregnant women and less hypoxia tolerant due to pregnancy-related physiological changes, such as diaphragm inflation, increased oxygen use, airway edema, and immunity changes associated with pregnancy (26). Vertical transmission indicates the movement of a virus from pregnant woman to infant over the pre- and post-labor phase. It involves transmission by placental blood or germ cells during gestation, through the birth channel in delivery, childbirth and postnatal nursing (5). In the current review, ten out of 125 neonates from COVID-19 confirmed mothers got the virus. The studies included infected neonates suggest that there is possible intrauterine transmission occurred, because the 9 deliveries done by CS were under strict sterile conditions and precautions.

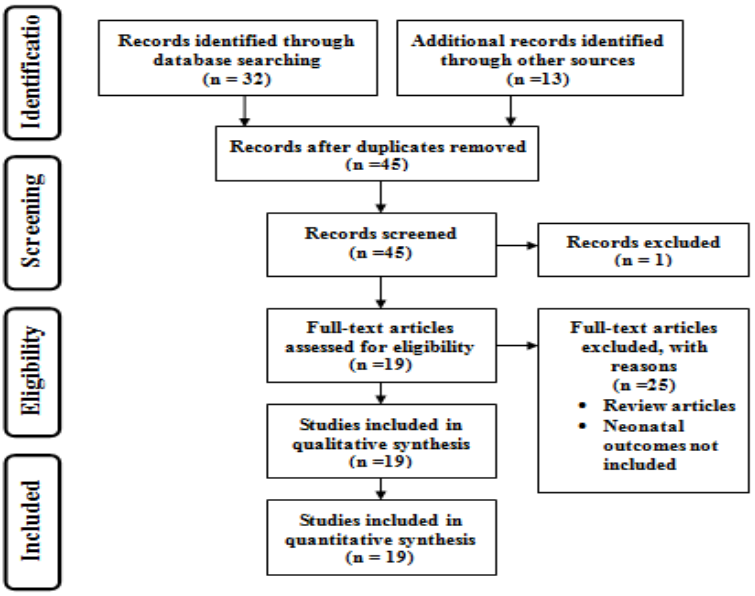

Fig. 1: PRISMA flow diagram

Table 1: Delivery details Neonatal outcomes

		Zhu *et al* (5) n=10	Chen *et al* (6) n=5	Wang *et al* (8) n=1	Sun *et al* (9) n=3	Liu *et al* (10) n=51	Yang *et al* (11) n=7	Cao *et al* (12) n=10	Kirts-man *et al* (13) n=1	Alzam -ora *et al*(14) n=1	Hu *et al*(15) n=7
Gestational Age (GA)	< 37 weeks 37-40 weeks >40 weeks	6 4 0	0 4 1	0 0 1	2 1 0	6 39 6	4 3 0	3 5 2	1 0 0	1 0 0	0 5 2
Delivery method	C/S NVD	7 3	2 3	1 0	3 0	51 0	7 0	8 2	0 1	1 0	6 1
Preterm delivery	Yes No	6 4	0 5	0 1	2 1	6 45	4 3	3 7	1 0	1 0	0 7
Gender of neonates	Female Male	2 8	NP	0 1	0 3	27 24	3 4	NP	0 1	0 1	1 6
Neonatal weight	<1500 g 1500-2500 g >2500 g	0 7 3	0 0 5	0 0 1	NP	0 4 47	0 1 6	0 2 8	0 0 1	0 0 1	0 0 7
Mean Apgar score	1 minute 5 minute	8.6 9.4	10 10	8 9	5.6 7.3	8.9 9.9	8.3 9.3	8.6 10	9 9	6 8	7.9 8.9
COCID_19 swab results	Positive Negative Not done	0 9 1	0 5 0	1 0 0	1 2 0	0 51 0	0 6 1	0 4 6	1 0 0	1 0 0	1 6 0
Lung radiographic imaging	Positive Negative Not done	7 3 0	0 0 5	1 0 0	1 0 2	0 51 0	0 0 7	0 0 10	0 0 1	0 1 0	0 7 0
NICU admission	Yes No	0 10	0 5	0 1	2 0	0 51	5 2	5 5	1 0	0 1	1 6
Symptoms	Yes No	9 1	0 5	0 1	1 2	10 41	1 6	0 10	1 0	1 0	0 7
Deaths	Yes No	1 9	0 5	0 1	0 3	0 51	0 7	0 10	0 1	0 1	0 7

Data expressed as frequencies and percent except for Apgar score that is represented as means.
NP: not provided, g:gram.

Table 1: Delivery details Neonatal outcomes (continue)

		Zama-niyan *et al* (16) n=1	Polónia-Valente *et al* (17) n=1	Zeng *et al*(18) n=3	Yu *et al* (19) n=7	Chen *et al*(20) n=9	Fan *et al*(21) n=2	Xiong *et al* (22) n=1	Khan *et al*(23) n=3	Wang *et al*(24) n=1	Total n=115
Gestational Age (GA)	< 37 weeks 37-40 weeks >40 weeks	1 0 0	0 1 0	1 0 2	0 5 2	4 5 0	1 1 0	0 1 0	1 2 0	1 0 0	33 (26.4%) 72 (57.6%) 20 (16%)
Delivery method	C/S NVD	1 0	0 1	3 0	7 0	9 0	2 0	0 1	0 3	1 0	107 (85.6%) 18 (14.4%)
Preterm delivery	Yes No	1 0	0 1	1 2	0 7	4 5	1 1	0 1	1 2	1 0	33 (26.4%) 92 (73.6%)
Gender of neonates	Female Male	1 0	1 0	0 3	NP	NP	2 0	0 1	NP	0 1	37 (29.6%) 53 (42.4%), NP (35, 28%)
Neonatal weight	<1500 g 1500-2500 g >2500 g	0 1 0	0 0 1	0 1 2	0 0 7	0 3 6	0 0 2	0 0 1	0 0 3	0 1 0	0 (0%) 20 (16%) 102 (81.6%), NP (3, 2.4%)
Mean Apgar score	1 minute 5 minute	8 9	9 10	NP	9 10	8.7 9.8	9 10	9 10	8.7 9.7	9 10	8.7±0.85 (mean±SD) 9.7±0.66 (mean±SD)
COCID_19 swab results	Positive Negative Not done	1 0 0	0 1 0	3 0 0	1 2 4	0 9 0	0 2 0	0 1 0	0 3 0	0 1 0	10(8%) 102 (81.6%) 13 (10.4%)
Lung radiographic imaging	Positive Negative Not done	0 0 1	0 0 1	3 0 0	1 6 0	0 0 9	1 0 1	0 0 1	0 0 3	0 1 0	14 (11.2%) 63 (50.4%) 48 (38.4%)
NICU admission	Yes No	1 0	0 1	3 0	3 4	0 9	0 2	0 1	0 3	1 0	22 (17.6%) 103 (82.4%)
Symptoms	Yes No	1 0	0 1	3 0	1 6	0 9	2 0	0 1	0 3	0 1	30 (24%) 95 (76%)
Deaths	Yes No	0 1	0 1	0 3	0 7	0 9	0 2	0 1	0 3	0 1	1 (0.8%) 124 (99.2%)

Data expressed as frequencies and percent except for Apgar score that is represented as means.
NP: not provided, g:gram, SD: standard deviation

Additionally the neonates were separated from the mothers directly after birth and did not received breastfeeding (8,9,14–16,18,19), according to recommendations stated that for neonates born to COVID-19 women whether they are suspected or confirmed cases, isolation is obligatory for minimum of two weeks post delivery and avoiding breastfeeding to prevent contact with the mothers(27). Most of the studies with positive neonates stated that the placental, cord blood, and amniotic fluid swabs show to be negative for COVID-19 except one which revealed positive amniotic fluid sample(16). Although no contact with vaginal fluids because the membrane was intact, one neonate in this review who was delivered by normal vaginal delivery tested COVID-19 positive, suggesting congenital infection(13). Moreover, a research proved the presence of viral RNA in two samples taken from the

placental fetal side with the neonates revealed positive swabs after birth, which highly support the potential vertical transmission in the uterus (28). Two studies support the potential vertical transmission as they confirmed the existence of viral specific antibodies (IgM and IgG) in samples of newborns' blood delivered from COVID-19 mothers instantly after birth (29,30). Another study supposed that a relatively low viral load may lead to a false negative results as a result of limited detection rates of the current testing methods, so negative swab results does not exclude COVID-19 infection (8), this highlights the results of 2 neonates (the second neonate in one study (9), and the first neonate in another (21)) in this review who had negative swab results despite of having a positive lung radiographic imaging results and the symptoms highly suggestive of COVID-19 infections. Additionally, some routes by which SARS-CoV-2 can possibly lead to fetal intrauterine infection suggested by a research that has shown that one of the COVID-19 virus responsive cells' surface receptor is the angiotensin-converting enzyme 2 (ACE2), and it is expressed in the placenta. Then again, barrier disruption of the placenta caused by extreme hypoxemia in COVID-19 infected pregnant patients may also be a possible mode that SARS-CoV-2 may result in vertical transmission (31). When investigating the neonatal outcomes, there was a high incidence of preterm birth as a result of different indications, most of them are not related to the respiratory condition of the mother (27, 23.5%), followed by NICU admission (17, 14.8%) and low birth weight of less than 2500 gram (13, 11.3%). In addition to a considerable number of neonates who had various symptoms ranging from mild to severe (21, 18.3%), though not all the symptoms can be correlated with COVID-19 but still may be as a result of the mother condition, a study showed that the negative neonatal outcomes cannot confirmed to be attributed to COVID-19 infections (3). Apgar score was generally good in all studies included in this review except one, in which one neonate found to have an Apgar score value of 3 and 5 at one and five minutes respectively (9). One neonatal death occurred in a study after multiple organ failure and DIC (5). Overall, COVID-19 disease in pregnancy is thought to have a deleterious impact on neonatal outcomes but still no confirming evidence (11). While for COVID-19 positive neonates, their outcomes and prognosis were good and this is consistent with many studies that showed that infected neonatal status was mild as compared to adults, their recovery and virus shedding were faster with improved prognosis (11,32).

CONCLUSION

Conclusively, despite the fact that the vertical transmission in not confirmed by evidence yet, there are various research findings that support its occurrence even if it occurs with low rates, and its possibility should be taken into account during delivery and immediately after. General neonatal outcomes were good and seem to be not highly affected by maternal infections; still the perinatal infection with COVID-19 can cause serious consequences on infants, leading to preterm labor, fetal distress, respiratory distress, and even death.

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