SARS-CoV-2 Vertical Infection of Newborns

Subjects: Pediatrics

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Severe acute respiratory syndrome virus 2 (SARS-CoV-2), the virus that causes 2019 coronavirus disease (COVID-19), has been isolated from various tissues and body fluids, including the placenta, amniotic fluid, and umbilical cord of newborns. Much scientific effort has been directed toward studying SARS-CoV-2, focusing on the different features of the virus, such as its structure and mechanisms of action. In addition, a great deal of emphasis has been placed on creating reliable diagnostic techniques and different drugs or vaccinations for treating COVID-19 disease.

Keywords: pregnancy ; SARS-CoV-2 ; COVID-19 ; vertical transmission

1. Introduction

In the last two decades, coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) have caused the outbreak of various diseases with high contagion and increased risk for human lives [1][2][3].

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2, has gained an unprecedented magnitude, generating a global public health crisis that could also have side effects on future generations. In this context, the scientific community's effort worldwide has focused on unraveling the different aspects of this new SARS variant, including its structure and mechanisms of action. In contrast, much attention has been given to developing accurate diagnostic tools, drugs, and vaccines to diagnose, prevent, and treat COVID-19 [3][4].

Coronaviruses are members of a family that includes enveloped viruses that replicate in the cytoplasm of host cells, including pets, farm animals, birds, and humans, leading to respiratory and gastrointestinal manifestations [4][5]. Even though SARS-CoV-2 infection is instead associated with the host respiratory system, the lungs are not the only organs that can be affected. By dissemination through the bloodstream, other tissues are susceptible to SARS-CoV-2 infection by the expression patterns of the ACE2 receptor. Consequently, the digestive, neurological, and cardio-vascular systems can be affected, as well as the kidney, liver, and placenta [6][7][8].

SARS-CoV-2 infection's impact on pregnancy and the effects of the virus on newborns diagnosed with COVID-19 have raised many questions related to the mode of transmission from mother to fetus [6]. However, despite histomorphological and ultrastructural changes in the placentas of COVID-19-positive mothers, only a small percentage of newborns were found to be infected at birth, and no teratogenic effect of COVID-19 infection has been reported [9].

2. Maternal-Fetal-Neonatal SARS-CoV-2 Transmission

2.1. Vertical vs. Congenital Transmission of SARS-CoV-2

Vertical transmission is the transfer of the pathogen from the mother to the fetus. The infection can occur during pregnancy (via the transplacental route), during birth (when the fetus is in contact with the mother's reproductive tract), or during breastfeeding. Congenital infections are vertically transmitted from mother to fetus during pregnancy, birth, or breastfeeding. Although the two terms are similar, they are frequently used ambiguously in the literature. Some articles, for example, refer to congenital infections as strict in-utero exposure and vertical infections as strict intrapartum exposure.

Furthermore, a positive RT-qPCR SARS-CoV-2 result from the neonate's NPS (nasopharyngeal swab) in the first minutes after birth does not rule out contamination or horizontal transmission, so it should not solely be considered a diagnostic tool for vertical transmission [10].

It is essential to properly diagnose vertical transmission, as it has both short-term and long-term consequences for the baby. That is why standard classification systems should be followed when analyzing the three types of congenital

transmission [11].

2.2. Proposed Criteria for Diagnosing Vertical Transmission

2.2.1. Classification Criteria Defined by World Health Organization

According to the World Health Organization (WHO), one must meet three criteria to prove the IUE (intrauterine exposure) of SARS-CoV-2 [12]. Firstly, the infection must be confirmed in the mother during pregnancy. Secondly, fetal exposure to SARS-CoV-2 in utero must be evidenced by a positive RT-PCR result in samples such as amniotic fluid or the placenta. If this cannot be performed, specific immunoglobulins A or M in neonatal blood at birth is another sign of intrauterine exposure. Samples from the upper respiratory tract can be collected on the newborn's first day. Thirdly, the persistence of the infection or an immune response must be documented, either through RT-PCR or the detection of IgA or IgM in the first two days of life. IUE can be classified as confirmed, possible, unlikely, or indeterminate based on these three criteria. The intrauterine transfer is classified only as possible if the persistence of the immune response can be proven from a sample that is not sterile. To differentiate between IUE and IPE, the WHO recommends serial detection of IgM and IgG antibody in the neonate [12]. In cases of intrauterine fetal death, the maternal–fetal transfer of the SARS-CoV-2 virus can be confirmed with the condition that the virus is evidenced in the fetal tissue using RT-PCR techniques or in situ hybridization methods [12].

2.2.2. Classification System Proposed by the Nordic Federation of Societies of Obstetrics and Gynecology

The Nordic Federation of Societies of Obstetrics and Gynecology (NFSOG)proposed a simpler classification system, described in the paper of Shah et al. [13]. To confirm an intrauterine fetal infection with the SARS-CoV-2 virus, one should have either a positive RT-PCR from an amniotic fluid sample (in the case of a cesarean section) or from umbilical cord blood at the time of birth or a positive RT-PCR from neonatal blood drawn within the first 12 h of delivery. According to him, a positive RT-PCR in an NPS at birth and on the second day of life can only demonstrate IPE (intrapartum exposure) in the newborn. To confirm the IUE in a stillbirth, RT-PCR or viral growth from fetal or placental tissue should be performed, or viral particles should be detected using electron microscopy.

2.3. Rates and Statistics Concerning the Vertical Transmission

Vertical transmission is a reality, as studies have shown that the SARS-CoV-2 virus is present in newborns' placentas, amniotic fluid, and umbilical cord [14][15]. The question remains as to how frequently it occurs and what are the potential risk factors for mother-to-fetus virus transmission. There is a paucity of literature when looking for studies that use the proper diagnostic criteria for vertical transmission [16]. In her study of 42 neonates, Sevilla-Montoya found 5 cases (11.9%) where vertical transmission is possible [17]. Kotlyar reports 3.2% (27/936) of neonates with positive RT-PCR NPS within the first 48 h of life and two cases where viral particles were identified at the level of the placenta, hence demonstrating IUE [18]. Another study that involved 70 neonates born from infected mothers concluded that in 5 cases (7.1%), the vertical transmission was considered possible [19]. Upon investigating the presence of IgM antibodies in neonates born from infected mothers, Massalha reports a rate of 3% of vertical transfer [20]. A study that included 14 positive women (7 at delivery) detected one case where the placenta, amniotic fluid, and umbilical cord blood were positive and another with a positive nasopharyngeal aspirate at birth and 48 h later [21]. Finally, using NFSOG classification system, Jeganathan reported confirmed vertical transmission in 0.3% of cases, probable vertical transmission in 0.5% of cases, and possible vertical transmission in 1.8% of cases [9].

2.4. Intrauterine Fetal Exposure to SARS-CoV-2

2.4.1. Placental Infection with SARS-CoV-2

There is still much to understand about the mechanism of coronavirus transmission from mother to fetus; however, for transplacental transmission to occur, the virus must first be circulating in the bloodstream of the infected pregnant woman. It will enter the placenta's fetal side through the uterine arterioles before moving on to the chorionic villus and spreading throughout the developing fetus [22]. There may be an association between the duration of viral exposure in utero and neonatal SARS-CoV-2 status. A more extended period of viral exposure may increase the likelihood of neonatal infection [23]. In addition, a high viral load combined with severe inflammation can result in viremia in a neonate [24]. The presence of the angiotensin-converting enzyme-2 (ACE2) receptor, as well as transmembrane serine protease 2 (TMPRSS2), are essential as they promote viral activation in the host cell and, thus, infection [9]. According to some studies, the two receptors are widely distributed in specific cell types of the maternal-fetal interface [25]. Although more abundant in the last trimester of pregnancy, the number of receptors may vary between women, some studies suggesting that there may also be a deficiency in the co-expression of the ACE2 receptor and the TMPRSS2 protease [26][27]. This feature may be

attributed to genetic peculiarities and could explain why vertical transmission is so uncommon [28]. Nonetheless, other proteins such as CD147, DPP4, GRP78, L-SIGN, and DC-SIGN may facilitate viral binding and seem to be directly involved in the passage of the SARS-CoV-2 virus through the placenta [29]. Infection of the placenta does not necessarily mean an infection of the fetus, indicating that even though it is not entirely effective, the placental barrier is a significant factor in the low likelihood of COVID-19 vertical transmission [29]. According to Mourad, proteins such as IFITM (Interferon-induced transmembrane protein) 1 and IFITM3 are involved in the trophoblastic immune response and may promote placental protection against SARS-CoV-2 [30]. On the other hand, a homozygous SNP rs12252-C mutation of the IFITM3 increases the risk of SARS-CoV-2 placentitis [31].

Extensive destruction of the syncytiotrophoblast, either through the direct cytotoxic effect or indirectly through circulatory disturbances, can promote the virus's spread in the villous stroma and its subsequent entry into the bloodstream of the fetus [32].

2.4.2. Fetal Infection with SARS-CoV-2

Regarding fetal coronavirus tropism, studies show that ACE2 and TMPRSS2 are found in the fetus's smooth cardiac muscle (with a high density, particularly at the level of cardiomyocytes), lung, and liver. The levels of ACE2 are reported to be especially high in fibroblasts and hepatocytes. ACE2 and TMPRSS2 were also detected in the fetal lungs, both in the epithelial and arterial endothelial cells. This route could explain the possibility of fetal intrauterine lung infection [33]. So far, the brain has been considered an invulnerable organ because of the absence of ACE receptors in the white and grey matter; however, current research indicates that the virus can be found in the choroid plexus of adults as well as fetal brains. From this perspective, the choroid plexus can be an entry point for an invasion of the central nervous system [34].

2.4.3. Intrapartum Fetal Exposure to SARS-CoV-2

Intrapartum exposure can occur after contact with maternal blood, vaginal secretions, or feces. In a study that included 80 women with confirmed COVID-19 infection (RT-PCR from an NPS), 12.5% presented positive vaginal RT-PCR results, and 7.5% had a positive rectal swab [35]. The possibility of neonatal infection during the intrapartum period needs to be considered, mainly if an aspirate was positive after birth. However, the likelihood of vaginally delivered newborns developing COVID-19 has not increased [36][37]. It has been proposed that vaginal microbiota can influence the ascension of the coronavirus, but more research is needed to confirm this [38].

3. Review of Available Evidence on Neonatal Outcome in Case of Vertical Transmission

Numerous studies follow the outcome of pregnancies with maternal SARS-CoV-2 infection. Chi et al. reported an 8.8% rate of positive neonates at birth [39]. However, because the criteria for vertical infection are rarely investigated in extensive studies, this type of infection cannot be included or excluded. Clinical data showed a positive outcome in most infants who tested positive for SARS-CoV-2 [40]. While most newborns with a positive SARS-CoV-2 test at birth do not exhibit any clinical abnormalities, some babies do exhibit mild to severe clinical disease. According to Garcia, fever is the most typical symptom, followed by respiratory and gastrointestinal symptoms. Lethargy is the leading neurological symptom that may be present. Although rare (6.8%), cardiovascular symptoms can severely impact the neonate [21].

Ishqeir et al. observed a threefold increase in persistent pulmonary hypertension in patients born to positive mothers [41]. Other studies report shock, arrhythmias, and even thrombosis in positive neonates [42]. Last but not least, a higher stillbirth rate was observed during the pandemic, particularly in mothers with SARS-CoV-2 infection compared to non-infected mothers (5 vs. 3 per 1000 births, $p = 0.003$) [43].

3.1. Review Approach and Methods

Researchers conducted a scoping review to determine the outcome of newborns where vertical transmission was at least possible according to the WHO and NFSOG criteria. The study was performed according to the PRISMA extension for scoping reviews (PRISMA ScR) guidelines and the Joanna Briggs Institute Reviewers' Manual for scoping reviews [44][45]. Whenever possible, the search was performed based on the PICO framework: (P) participants—pregnant women; (I) investigated condition—SARS-CoV-2 positive; (C) comparison—SARS-CoV-2 negative; (O) outcome—newborn outcome [46].

Two search engines were used: PubMed/MEDLINE and Google Scholar. The following keywords were used: ('COVID*' OR 'SARS-CoV-2*') AND ('vertical transmission' OR 'in-utero transmission' OR 'congenital transmission' OR 'placental

infection'). The search period was from 1 January 2020 to 1 November 2022. Reference lists of all identified sources were searched for additional sources.

No limit or restriction was imposed in regard to the type of study: all types of evidence are to be taken into consideration. Eligible publications comprised the following categories: systematic reviews, case reports and case studies, articles that describe vertical transmission at a molecular level, case–cohort studies, case–control studies, longitudinal cohort studies, cross-sectional studies, descriptive studies, and studies based on surveys. Systematic studies were excluded to avoid the risk of entering a case multiple time.

The studies were identified by two separate researchers who screened the articles and excluded the duplicates in the first stage. Next, abstracts of all potentially relevant papers were individually examined for suitability.

The following inclusion criteria were used to determine the eligible articles:

- Application of the standard criteria (the WHO or NFSOG criteria) in the attempt to diagnose vertical transmission;
- Delivery after 20 weeks of gestation;
- Delivery using strict infection control and prevention practices;
- Mother–neonate separation at least for 24 h after birth.

All disagreements were resolved by consensus or a third senior researcher was called in to settle.

In determining the type of classification, researchers followed an adapted table that comprised the WHO and NFSOG criteria. There is a slight discrepancy between the two used classification systems. WHO proposed a classification system that includes confirmed, possible, and unlikely possibilities, while the NFSOG classification system includes confirmed, probable, possible, unlikely, and uninfected cases. To avoid confusion, probable and possible cases classified according to the NFSOG system were grouped under the heading of possible.

Quality assessment was conducted based on the criteria proposed by Murad et al. [47] for the case or case series reports. For the clinical studies, the quality was assessed based on Newcastle–Ottawa Scale Coding Manual [48].

3.2. Review Results

The following data were extracted: first author, number of eligible patients in the report, maternal clinical status at the moment of delivery, presence of maternal severe COVID-19 disease, type of vertical transmission according to the WHO or criteria of NFSOG, gestational age at delivery, type of delivery (for live births), neonatal outcome (live birth/stillbirth), presence of any symptoms that could raise the suspicion of SARS-CoV-2 neonatal infection in the first 24 h, neonatal evolution during hospitalization as well as maternal evolution and maternal clinical status at the moment of neonatal discharge.

3.2.1. Possible Association between Vertical Transmission and Adverse Neonatal Outcome

Out of the 75 included cases, there were 32 (42.6%) stillbirths [32][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67]. Nineteen neonates (25.3%) presented no symptoms at birth or during hospitalization [21][25][68][69][70][71][72][73][74][75][76][77][78]. Twenty four neonates had symptoms of COVID-19 disease (32%) [79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95]. While most cases (75%) were classified as confirmed vertical transmission, the rest could only be classified as possible vertical transmission.

3.2.2. Livebirths Characteristics

In two cases, the livebirth neonates resulted from multiple pregnancies (1 pair of twins and one pair of triplets), and the rest of the neonates resulted from singleton pregnancies. Gestational age at birth ranged from 25 to 40 weeks in the symptomatic newborns and 29 to 40 weeks in the asymptomatic newborns, with a median of 32 in both groups.

The Apgar score ranged from 4 to 10 in asymptomatic neonates, while in the symptomatic neonates, the Apgar score ranged from 2 to 10. In both groups, the Apgar score median was 9. Overall, 14 infected newborns were delivered by c-section due to signs of fetal distress. In addition, three neonates were delivered by c-section due to severe maternal COVID disease.

3.2.3. Symptoms of SARS-CoV-2 in Neonates Classified as Confirmed/Possible Vertical Transmission

Nineteen authors described symptomatic neonates in which vertical transmission was either confirmed or possible.

Symptomatic neonates experienced most frequently acute respiratory distress in the first 24 h, which evolved in 10 cases in neonatal pneumonia [81][82][85][86][87][88][89][92][95]. Aside from pneumonia, three neonates presented encephalitic symptoms, hypotonia, gastrointestinal symptoms, or mild cutaneous erythema [82][83][86]. Only one case of isolated fever was reported [84]. Hematologic abnormalities were described in five neonates. Zaigham reported a neonate with thrombocytopenia that normalized four days after birth [53]. Kirtsman reported a neonate with neutropenia, and Sukhikh reported a newborn with disseminated intravascular coagulation and congenital anemia [83][87]. Lymphopenia and neutropenia were also reported [94][95]. While four newborns with hematologic abnormalities were classified only as probable IUE, in Sukhikh's report transplacental transfer was confirmed. One neonate had hypothermia, feeding difficulties, and multiple hypoglycemic episodes [83]. The multi-system inflammatory syndrome was present in one newborn with confirmed IPE [92]. Neurologic abnormalities (axial hypertonia, opisthotonos, and hypotonia) were present in three neonates with confirmed IUE [15][89][96]. COVID-19 was responsible for the death of three neonates on the first, fourth and seventeenth day of life. The first two newborns were delivered in the second trimester of pregnancy at 25, respectively, 26 weeks, while the third was delivered at 34 weeks of gestation. All three cases were diagnosed with congenital pneumonia [81][87][95]. While in the twenty-five-week-old newborn, vertical transmission was confirmed at birth, the 26th-week neonate was initially classified only as probable vertical transmission. Postmortem investigation of the neonatal fetal lung demonstrated the SARS-CoV-2 virus in the alveolar macrophages and the pneumocytes (IHC) [81]. The third case of neonatal death remained only a possible vertical transmission as a neonatal autopsy report was not published [95] Except for two newborns who presented neurologic symptoms, clinical evolution improved in all the newborns (respiratory, gastric, and hematologic symptoms have subsided).

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