Chapter

Perinatal COVID-19 Pandemic: Short- and Long-Term Impacts on the Health of Offspring

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Abstract

Currently, the consequences of coronavirus disease 2019 (COVID-19) in children of mothers affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy are unknown. In addition to pregnancy risks, the impact of COVID-19 on the health of these children can occur in the short, medium, and long term. Initial data reveal a low risk of vertical transmission during the third trimester of pregnancy and through breastfeeding. However, despite this low risk, cases of neonatal COVID-19 have already been reported in the literature. Historically, other viral infections during pregnancy have been associated with an increased risk of neuropsychiatric diseases in the offspring of affected pregnant women, even in the absence of fetal infection. This study aimed to review the impact of viral infections on the offspring of mothers affected in the perinatal period and discuss and determine measures for the possible consequences of COVID-19 in the offspring of pregnant women infected with SARS-CoV-2.

Keywords: COVID-19, SARS-CoV-2, vertical transmission, perinatal infection, offspring

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 11, 2020 [1]. The infection rate caused by the virus increased exponentially in 2020 until March 13, 2021, registering 119,165,535 confirmed cases and 2,641,567 deaths [2].

Pregnant and puerperal women have been considered groups at risk of morbidity and mortality since the beginning of the COVID-19 pandemic because of the physiological and immunological changes that can increase the risk of complications in respiratory infections and the knowledge of unfavorable outcomes in pregnant women and their newborns in infections caused by other coronaviruses, SARS, Middle East respiratory syndrome, and influenza [3–6].

Some adverse outcomes of SARS-CoV-2 infection observed during pregnancy include admission to the intensive care unit (ICU) or death. However, the clinical evolution of COVID-19 in most women is not serious, resembling the general population [7, 8].

Initially, there was no evidence of vertical transmission due to COVID-19 during pregnancy [3, 5, 6]. During the pandemic, several studies concluded that there was this possibility [9, 10], with one confirmed case of vertical transmission occurrence [11]. However, all of them suggested that further studies should be conducted on the subject, as it is a recent disease and the number of participants in the published studies is small.

There is strong evidence that other viral infections cause neurological and behavioral changes in the fetus, such as the influenza virus related to schizophrenia [12]. Other viral infections, such as the Zika virus (ZIKV), can cause malformations, including microcephaly [13].

Therefore, outpatient monitoring of children exposed to the SARS-CoV-2 virus during pregnancy is vital to understand the impacts of the disease on the growth and development of these children.

A narrative review was carried out using the keywords: COVID-19, SARS-CoV-2, vertical transmission, perinatal infection and offspring. In addition to the search for other viral infections: influenza, herpes simplex, rubella, cytomegalovirus and human immunodeficiency virus (HIV). The authors searched the Pubmed, Medline, and Google Scholar databases, reviewed the available articles, and determined which articles were most relevant to the project.

2. Other viral infections during pregnancy and their consequences on the fetus and offspring

2.1 Influenza

Pregnancy is a risk factor for infection by the influenza virus. During the 1918 (Spanish flu) and 1957 (Asian flu) pandemics, mortality in pregnant women was high. During the 1918 pandemic, a 27% mortality rate was recorded, and in 1957, it corresponded to 50% of deaths in women of reproductive age [14]. In seasonal influenza periods, an increased risk of hospitalization was observed in pregnant women at any stage of pregnancy, even without associated comorbidities [15].

There were higher rates of premature births, small for gestational age newborns, and stillbirths in hospitalized pregnant women than those in outpatient treatment [16]. Regarding the occurrence of malformations in the fetuses, the possibility of its teratogenic effect with the occurrence of neural tube defects, cleft lip and palate, and congenital heart disease was evaluated. A direct effect of the virus was unlikely to be the cause of these malformations, since control of fever with antipyretics, and the use of periconceptional folic acid in pregnant women with influenza reduced the risk of these malformations in their offspring (**Table 1**) [17].

Influenza infection in the first trimester of pregnancy increased the risk of schizophrenia by seven times. There was no increased risk in the other trimesters of pregnancy, according to a nested case–control study of 64 participants who were born from 1959 to 1966 and had psychiatric disorders 30 to 38 years later [12].

A cohort study of 196,929 children conducted in California did not find an increased risk of autism spectrum disorder (ASD) in offspring of pregnant women with influenza. In addition, there was no statistically significant relationship of ASD in children whose mothers received influenza vaccination in the first trimester [18].

Viral disease	Clinical manifestation
Influenza	Premature birth, small for gestational age newborns, stillbirths, pregnant woman hospitalization, fetus malformation, schizophrenia
Rubella	Congenital rubella syndrome (CRS), abortion, stillbirth, restricted urterine growth
Herpes simplex	Triad: cutaneous, neurological and ophthalmic symptoms
CMV	Intrauterine growth restriction, hepatosplenomegaly, microcephaly, chorioretinitis, petechiae, jaundice, thrombocytopenia, anemia
HIV infection	Miscarriages, stillbirths, perinatal mortality, intrauterine growth restriction, low birth weight, chorioamnionitis
Zika virus	Intrauterine growth restriction, small for gestational age, brain malformation, microcephaly, eye and hearing abnormalities, hypospadias, cryptorchidism, micropenis
COVID-19	Intense inflammatory response and placenta hypoxia can lead to abortions, pre-eclampsia, prematurity, IUGR

Table 1.
Clinical manifestations of conceptuses resulting from the infection of pregnant women by viral disease.

2.2 Herpes simplex virus (HSV)

There are two types of herpes viruses: HSV-1 and HSV-2. The latter is predominantly sexual and the etiologic agent of 70–85% of neonatal infections. Although transplacental or upward transmembrane transmission of HSV from the mother to the fetus during pregnancy is uncommon (about 5%), the rate of perinatal transmission during labor and delivery is 80–90%. The risk of neonatal infection is higher in HSV infections that start in late pregnancy (30–50%) than in early pregnancy (1%) [19, 20].

Intrauterine infection is clinically present in the fetus as a characteristic triad of cutaneous (vesicles, erosions, and scars), neurological (intracranial calcifications, microcephaly, and meningoencephalitis), and ophthalmic symptoms (microphthalmia and chorioretinitis). The clinical manifestations of neonatal peripartum and postpartum infection are found in the skin, eyes, and/or mouth (45%) and central nervous system (CNS; 30%) or as disseminated infection (25%). Regarding mortality and neurological prognosis, mortality is higher in disseminated infection cases (approximately 30%), and a worse neurological prognosis occurs in cases with CNS involvement (50%). In the treatment of neonatal HSV, high doses of intravenous acyclovir are indicated, which improves the prognosis and reduces the occurrence of neurological sequelae and delayed child development (**Table 1**) [19, 21].

2.3 Rubella

It is an acute viral disease caused by the RNA Rubella virus of the Togaviridae family. Its clinical characteristics in healthy adults are often self-limited and include low fever, maculopapular rash, lymphadenomegaly, and oropharyngeal pain. The rates of asymptomatic cases range from 25–50% [22].

In pregnancy, maternal infections can determine a poor prognosis for the conceptus, especially when it occurs in the first trimester of pregnancy, which can result in congenital rubella syndrome (CRS), abortion, stillbirth, congenital malformations, and restricted uterine growth of the conceptus. The chances of malformation are 81% and 25% in the first and second trimesters, respectively. Rubella immunization is considered the best measure to combat this infection in the

world. CRS has already been significantly eliminated in the USA; however, it cannot be said that it has been completely controlled, since outbreaks are still reported around the world [14].

Rubella virus infection findings can be found from prenatal life to later manifestations after the child's birth and development. Among them, it can cause ocular alterations (cataract, microphthalmia, glaucoma, pigmentary retinopathy, and chorioretinitis), cardiac malformations (peripheral pulmonary artery stenosis, patent duct artery, or ventricular septal defects), and CNS alterations (microcephaly). Children who survive the neonatal period may have severe developmental disabilities (e.g., visual and hearing impairments) and an increased risk of developmental delay, even autism. In the long term, congenital rubella infection may determine an increased risk of endocrinopathies, such as thyroiditis and insulin-dependent diabetes mellitus (**Table 1**) [23, 24].

2.4 Cytomegalovírus (CMV)

CMV, like other viruses in the Herpesviridae family, causes a primary infection and remains latent in the body. Primary infection is generally harmless, but it can be fatal in immunocompromised patients and cause serious fetal damage due to vertical transmission, which can occur intrauterine during childbirth through cervical and blood secretions and postnatally through breastfeeding. Thus, identifying infection in pregnant women is important [25].

In 1–4% of pregnant women, seroconversion to CMV occurs, with most women being seropositive before pregnancy, which does not prevent the infection in about 60% of babies during pregnancy. In newborns, 0.2%–2.5% are infected in utero, and most are asymptomatic (90–80%). About 10–20% of neonates have symptoms at birth, such as intrauterine growth restriction (IUGR), hepatosplenomegaly, microcephaly, chorioretinitis, petechiae, jaundice, thrombocytopenia, and anemia. Of them, 20–30% progress to death, mainly from disseminated intravascular coagulation, liver dysfunction, or bacterial infection. Even asymptomatic children at birth can present sequelae of neurological development, such as mental retardation, motor impairment, sensorineural hearing loss, or visual impairment (**Table 1**) [26, 27].

2.5 Human immunodeficiency viruses (HIV)

Vertical transmission by HIV can occur during pregnancy, childbirth, and during breastfeeding. Test implementation for HIV detection in prenatal care, antiretroviral therapy (ART) use during pregnancy and by the newborn after birth, elective cesarean delivery indication, and breastfeeding contraindication reduce the risk of HIV transmission to the baby from 40% to less than 1% in the USA [28].

Children exposed but not infected to HIV during pregnancy have a worse prognosis than those who are not since their mothers are more likely to have low CD4+ cell counts, detectable viremia, and higher morbidity. In addition, the effects on fetal development due to maternal immune dysfunction and the potential dysfunction of hereditary mitochondria in the fetus due to the exposure of women with HIV in early childhood to ART are unknown [29]. Adverse results in pregnancy associated with HIV infection can result in miscarriages, stillbirths, increased perinatal mortality, IUGR, low birth weight, and chorioamnionitis [30]. In symptomatic pregnant women, an increase in premature births has been observed (**Table 1**) [28].

2.6 Zika virus (ZIKV)

ZIKV is a flavivirus transmitted by mosquitoes, mainly by *Aedes aegypti*, and became a major human pathogen during the 2015 pandemic. Although 80% of infected cases are asymptomatic, it can cause adverse results in pregnancy, such as congenital Zika syndrome [31], which presents as microcephaly associated with other brain malformations that can result in severe mental retardation, motor impairments, and eye and hearing abnormalities. In addition, other malformations were observed, such as hypospadias, cryptorchidism, and micropenis [13]. ZIKV infection in mothers during the first trimester is more likely to affect the CNS since this period is vital for neurological development [32].

One cohort study evaluated 244 pregnant women with confirmed ZIKV infection during pregnancy and reported that 223 (91.4%) babies were born alive. Of these, 216 babies had clinical follow-up after birth, of which 130 (60%) children had blood and/or urine samples obtained for ZIKV detection using the real-time polymerase chain reaction (RT-PCR) technique. Results revealed that 13% of the children who underwent brain imaging exams had structural brain abnormalities such as microcephaly, 5.5% who underwent ophthalmological evaluation had ocular changes, and 12.1% who underwent additive evaluation had an abnormal result. In addition, 7.7% were born small for gestational age, which may be associated with IUGR. Meanwhile, 19% who underwent neurological exams had an abnormality in the first 6 months of life. Neurodevelopment assessments carried out after 1 year of age showed that 13.2% had severe developmental delay (**Table 1**) [33].

3. What we know about COVID-19 during pregnancy and the prognosis of the fetus and offspring

At the beginning of the pandemic, the clinical manifestations of COVID-19 in pregnant women and babies were unknown. Some studies concluded that the evolution of SARS-CoV-2 infection in pregnant and nonpregnant women was similar [6, 34]. A case–control study compared the clinical evolution of COVID-19 between pregnant women with and without COVID-19 and observed that pregnant women with mild symptoms of COVID-19 have a similar evolution to those without the disease. However, pregnant patients with severe or critical illness have worse results. The risk factors for a worse maternal and neonatal outcome include black and Hispanic race, advanced maternal age, obesity, comorbidities (diabetes mellitus and chronic hypertension), and admission to the COVID-19-related antepartum [35].

Immune responses in pregnancy induce that pregnancy is a risk factor for SARS-CoV-2 infection. In both normal and COVID-19-infected pregnancies, maternal immune responses occur as a result of decreased lymphocytes, inhibitory natural killer cell receptor activation such as NKG2A, and increased inflammatory cytokines (interferon-ɣ, interleukin (IL)-2, IL-6, IL-7, IL-10, and tumor necrosis factor-α) [36, 37]. In addition, the angiotensin-converting enzyme 2 is the receptor for SARS-CoV-2 and is widely expressed in the female reproductive system (ovary, uterus, vagina, and placenta) and fetal tissues; therefore, vertical transmission of COVID-19 is possible [38, 39].

The fetuses of mothers infected with SARS-CoV-2 may be exposed to an intense inflammatory response, which can induce placental or fetal damage. Nonspecific anatomopathological changes were observed in SARS-CoV-2 infected placentas, and the most common finding was poor placental perfusion on the maternal side due to maternal hypoxia secondary to severe pulmonary infection by COVID-19.

Both maternal immune response and poor placental perfusion can result in abortions, pre-eclampsia, prematurity, and IUGR [37, 40].

A study that evaluated the fetal inflammatory response in newborns of mothers infected with COVID-19 in the third trimester observed an increase in IL-6 in the fetuses, which may determine adverse sequelae of neurological development, including autism, psychosis, and long-term sensorineural deficits. However, longitudinal studies are needed to validate these associations (**Table 1**) [37, 41].

Only one study confirmed the vertical intrauterine transmission. In the case report described by Vivanti et al., the pregnant woman was in her last trimester of pregnancy (35 weeks) when she developed symptoms and was diagnosed with COVID-19. Cesarean delivery was indicated because of fetal distress. The conceptus was resuscitated at birth and transferred in invasive mechanical ventilation to the ICU. The virus was investigated and detected by RT-PCR from the amniotic fluid, placental tissue, bronchoalveolar lavage fluid, blood, and nasopharyngeal and anal swabs. The conceptus evolved with neurological manifestations similar to those described in adult patients with COVID-19 [11].

A review study evaluated 108 pregnant women confirmed with COVID-19 and found that 86 had pregnancy resolution. Of the newborns, 75 were tested for SARS-CoV-2 using RT-PCR, and only one was positive (1.3%). The test was collected at 36 h of life. The patient presented a good clinical evolution with reports of lymphopenia and increased liver enzymes in laboratory tests. The average gestational age of the 86 pregnancies evaluated was 36 weeks and 1 day. One baby died at birth (1.1%), and one pregnancy resulted in intrauterine death (1.1%). In both cases, the mothers had severe COVID-19. Seven babies (8.1%) required admission to the neonatal ICU [42].

A study of nine case series and two case reports evaluated 65 mothers confirmed for COVID-19 and 57 newborns. The report revealed that 31% of cases had fetal distress, and 38% of pregnant women had a premature birth. Neonatal complications were breathing difficulties or pneumonia (18%), low birth weight (13%), skin rash (3%), disseminated intravascular coagulation (3%), asphyxia (2%), and perinatal death (3%). Twenty-seven newborns underwent RT-PCR for SARS-CoV-2 by nasopharyngeal swab. Of them, four were positive: one newborn was healthy, and three had pneumonia and positive results on nasopharynx and anal swabs on days 2 and 4 of life. The question remains whether some of the maternal and neonatal complications reported are due to the virus and not iatrogenic, for example, the indication for cesarean delivery determining premature birth [43].

The infection by the SARS-CoV-2 virus presents neurological manifestations, which can be a consequence of cardiorespiratory failure and metabolic abnormalities triggered by the infection, direct invasion of the virus, or an autoimmune response to the virus. Among the neurological symptoms observed were headache, ageusia, anosmia, dizziness, myalgia/myositis, and stroke [44, 45]. The effects of this neurotropism of the virus should be investigated in children, especially in newborns whose mothers were infected during pregnancy, since its consequences on children's neurological development are unknown. In addition, the effects of infection according to the trimester of pregnancy are unknown, leaving doubt about the prognosis of children of mothers infected in the first trimester, in relation to other periods of pregnancy (**Table 2**).

International Health Security, also called "global health security" or "public health security", has as its main objective to maintain humanity's well-being through prevention. Its focus is not only on diseases (infectious, chronic), it also encompasses social determinants of health, bioterrorism, climate change, cybersecurity in health and other situations.

COVID-19 study	Neonate clinical manifestation
Wong YP, Khong TY, Tan GC, 2021	Poor placenta perfusion: abortions, pre-eclampsia, prematurity and IUGR
Cavalcante M, Cavalcante C, Sarno M, Barini R, Kwak-kim J, 2021	
Wong YP, Khong TY, Tan GC, 2021	Increase in IL-6: autism, psychosis and long-term sensorineural deficits
Liu P, Zheng J, Yang P, Wang X, Wei C, Zhang S, et al., 2020	
Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al., 2020	Conceptus evolved with neurological manifestations similar to those described in adults patients with COVID-19
Zaigham M, Andersson O, 2020	Outcome of death at birth and intrauterine death of fetuses from mothers confirmed for COVID-19
Zimmermann P, Curtis N, 2020	Fetal distress, premature birth, breathing difficulties, pneumonia, low birth weight, skin rash, disseminated intravascular coagulation, asphyxia and perinatal death

Table 2.
Studies that evaluated the clinical manifestations in newborns born to mothers confirmed with COVID-19.

COVID-19 is a threat to international health security, as it has repercussions in all aspects of human health, physical, social and mental well-being, as the disease causes death, sequelae, compromised mental health and social of individuals.

In children, in addition to the impact of the absence of face-to-face classes in schools and social interaction, the impact of intrauterine SARS-CoV-2 infection on their neurological and body development is still uncertain. Being an item of extreme importance to International Health Security.

4. Conclusion

It is vital to monitor the growth and proper development of children exposed to COVID-19 during pregnancy since whether or not vertical transmission occurs is still uncertain, and if confirmed, fetal prognosis should be improved through diagnosis to determine early consequences. Several viral infections during pregnancy can compromise the health of the fetuses in the short, medium, and long term.

Conflict of interest

The authors declare no conflict of interest.

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