

COVID-19 and pregnancy: clinical outcomes and scientific evidence about vaccination

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Abstract. – Pregnant women and their infants are at high risk to develop a severe COVID-19, with increased rates of hospitalisation to intensive care units, need for mechanical ventilation and mortality. Preterm birth, fetal vascular malperfusion, and premature rupture of membrane have been the most reported adverse pregnancy outcomes and these effects have been especially associated with the onset of the disease at early gestational age. The early expression of ACE2 and TMPRSS2 in human embryos has been proven, determining an increased susceptibility to SARS-CoV-2. Preterm infants born to women infected by SARS-CoV-2 have a higher risk of need for specialist neonatal care with prolonged hospitalization. Moreover, inflammation of developing embryos could cause long-term defects, regardless of vertical transmission of SARS-CoV-2. Due to Maternal Immune Activation (MIA), in utero inflammation is associated with neurodevelopmental, cognitive and psychiatric disorders in affected offspring. Despite risks that COVID-19 could induce in pregnancy, there are not many published data describing the safety and/or efficacy of COVID-19 vaccines in pregnant women, commonly not included in vaccine research. The evidence from the few pregnant women unintentionally enrolled in clinical trials and vaccinated suggests that COVID-19 vaccines, both based on mRNA and viral vectors, do not pose significant risks to the fetus or breastfeeding infants. Moreover, human studies using mRNA-based vaccines against Zika virus, influenza, and rabies have reported good safety and immunogenicity during pregnancy. In this review, we evaluate the role of COVID-19 in adverse pregnancy and neonatal outcomes and the need to vaccinate pregnant women.

Key Words:

COVID-19, Pregnancy, Neonates, Vaccination, Short and long-term effect in neonates.

Introduction

The Coronavirus Disease-2019 (COVID-19) pandemic continues to have a huge impact on humanity not only in terms of morbidity and mortality but also in social, psychological, and environmental terms^{1,2}. This has attracted the interest in many fields of medicine and biology. The interaction between COVID-19 and pregnancy has been studied by numerous research groups worldwide, because pregnant women and their infants are considered a high-risk group due to the effects of the infection during and after pregnancy³. Pregnant women affected by COVID-19 have an increased risk of developing a severe illness compared with nonpregnant ones, and they have an increased rates of hospitalization in intensive care units, need for mechanical ventilation, and mortality⁴. These findings are similar to those observed during other respiratory viral infections in pregnancy, such as influenza A/H1N1^{5,6}, Severe Acute Respiratory Syndrome (SARS)⁷, and Middle East Respiratory Syndrome (MERS)⁸.

Many types of publications on COVID-19 in pregnancy have risen very quickly. A meta-analysis including 61 studies with a total of 790 pregnant women affected by COVID-19 and 548 neonates, reported adverse pregnancy outcomes, such as fetal vascular malperfusion, premature rupture of membranes and preterm birth, in 27% of the cases. These effects were present especially when the infection was acquired at earlier gestational age and preterm birth was three times more frequent in symptomatic compared to asymptomatic women⁹. The Centers for Disease Control and Prevention (CDC) conducted a surveillance including 598 pregnant women affected by labo-

ratory confirmed COVID-19 infection and found a rate of preterm births (< 37 weeks) of 12.6%, which was higher compared to that generally observed in the US (approximately 10% in 2018)¹⁰. Preterm birth can be due to premature rupture of membranes, an adverse pregnancy outcome increased in women infected with COVID-19^{11,12}. A higher incidence of fetal malperfusion, including thrombosis, poor placental vasculature development with fibrin deposition, have been observed in pregnant women affected by COVID-19¹³. Pregnant women are at higher risk for thromboembolic complications due to the increased blood concentration of coagulation factors and the acquisition of COVID-19 infection, enhancing hypercoagulability, putting pregnant women at even greater risk for thromboembolism¹⁴. In addition, preeclampsia, occurring in approximately 6-8% of all pregnancies, shares several features with COVID-19 including hypertension, thrombocytopenia and immune dysregulation^{15,16} that are strongly related with high morbidity and mortality in COVID-19 patients^{17,18}. Pregnant women affected by severe COVID-19 disease have preeclampsia-like symptoms without having increased levels of markers for preeclampsia, suggesting that systemic inflammation of COVID-19 mimics the clinical features of preeclampsia^{19,20}.

SARS-CoV-2 has not been systematically found in the placentas of mothers infected with COVID-19 and only very few neonates with a SARS-CoV-2-positive placenta were positive for the virus. Moreover, they did not present any congenital defects, suggesting that some protective placental mechanisms, among which the presence or absence of certain receptors/pathways, could play an important role²¹.

In this review, we provide an overview of the existing literature about the role played by COVID-19 infection in adverse pregnancy and neonatal outcomes while also evaluating the scientific findings about the need to vaccinate pregnant women.

Immune Characteristics of Pregnancy

During the first 3 months of intrauterine life, when the different steps of embryogenesis take place, many factors can perturb the delicate equilibrium that allows for fetal development and, consequently, some crucial immunological changes occur in pregnancy. Overall, during the implantation of the blastocyst in the receptive endometrium, a pro-inflammatory setting is ongoing. Conversely, as pregnancy and fetal growth

proceed, an anti-inflammatory profile is established, with the prevalence of type 2 helper T cells (Th2). Finally, during the last part of pregnancy and until childbirth, a switch back to pro-inflammatory status occurs²².

Innate immunity in pregnancy plays a key role in the maternal-fetal interface. In the first trimester peripheral NK (pNK) cells and decidual NK (dNK) cells account for 5-30% and for $\geq 70\%$ of total circulating lymphocytes²³. These immune cells decrease with the progression of gestational age. Specifically, dNK cells have low cytotoxicity, since they recognize non-classical HLA on the extravillous trophoblast, leading to the subsequent process of immunotolerance. Macrophages have an immunomodulatory M2 phenotype and phagocytotic activity of apoptotic cells throughout pregnancy. They also secrete proangiogenic factors, such as Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and remodeling factors, such as Matrix Metalloproteinase (MMP)-3 and MMP-9, helping extravillous trophoblast invasion and spiral artery remodelling²⁴. In pregnancy, Dendritic Cells (DCs) are reduced in number and maturity, since immature DCs secrete low levels of pro-inflammatory cytokines (IFN- γ and IL-12) and present a low expression of classic HLA-DR antigens. However, in response to a viral infection, innate immune cells, such as NK, monocyte, and plasmacytoid DCs stimulate an efficient cytokine response²⁵. Moreover, intracellular Toll-like Receptors (TLRs) 3, 7, 8, and 9 are largely expressed at the maternal-fetal interface in the syncytial trophoblast and amniotic layer^{26,27}. T and B cells are decreased and the capacity of naïve T cells to differentiate into mature TH cells is compromised²⁸. Finally, the syncytiotrophoblast, the external layer of the chorionic villi in direct contact with maternal blood, produces and secretes antimicrobial molecules and cytokines (IFN-III, IFN-I) that counteract infections and are the hallmark of placental antiviral defence²⁹⁻³³.

Role of Placenta In SARS-CoV-2 Transmission

SARS-CoV-2 infects pneumocytes by binding to the receptor Angiotensin-Converting Enzyme 2 (ACE2), a molecule expressed in respiratory and intestinal systems, placenta, ovaries, vagina, and uterus³⁴. After viral adhesion by the outer viral spike (S) protein, cell entry occurs by the priming of the S protein by Transmembrane Serine Protease 2 (TMPRSS2)^{35,36}. The cellular presence of both ACE2 and TMPRSS2 allows the SARS-CoV-2 infection³⁷. In the fetus, ACE2 is present in

kidney, ilium, and rectal cells from as early as 15 weeks, while it is slightly detectable at 15 weeks in lungs. Placental cytotrophoblast and syncytiotrophoblast express ACE2 starting in the seventh week of pregnancy, suggesting that SARS-CoV-2 could cross the placenta at any gestational age³⁸. A research³⁹, performed on surplus In Vitro Fertilization (IVF) human embryos to assess ACE2 and TMPRSS2 co-expression up to day 14, has revealed the expression of these genes, proving an increased susceptibility to SARS-CoV-2 in the early stages of embryonic development.

The placental barrier protects the fetus from maternal infections⁴⁰. However, vertical viral transmission can occur. Some viruses cause apoptosis with direct damage to chorionic villi cells and disruption of the protective syncytiotrophoblast layer, as well as damage to placental vascularization. This can determine viral spread through the infected maternal endothelium to the extravillous trophoblast. Moreover, passage of infected maternal immune cells through the syncytiotrophoblast and swallowing or suction of infected amniotic fluid are involved in fetal viral acquisition^{41,42}. Placental infection by SARS-CoV-2 has been confirmed by the detection of viral mRNA or mature virions in the syncytiotrophoblast layer^{43,44}. However, considering that the viral load of SARS-CoV-2 in the blood is around 1%, the infection of the syncytiotrophoblast seems to be low⁴⁵.

Another mother to child transmission of SARS-CoV-2 can occur during childbirth through the vaginal canal^{46,47}. It is still uncertain if neonates positive for SARS-CoV-2 have been infected during pregnancy, childbirth or after birth. Neonates born to SARS-CoV-2 infected women had high IgG and, more rarely, IgM levels against the virus. Unlike IgG, the higher molecular weight of IgM prevents their transplacental crossing and the IgM presence is highly suggestive for fetal production in response to viral infection^{48,49}. A summary of the scientific evidence about the vertical transmission of SARS-CoV-2 is reported in Table I.

Outcomes of SARS-CoV-2 Infection in Pregnancy and Neonates

Potential mechanisms involved in the maternal transfer of SARS CoV-2 to the infant are intrauterine transmission through transplacental crossing of viruses from maternal to fetal blood; ingestion/inhalation of contaminated amniotic fluid (actually less likely); intrapartum transmission after contact with maternal secretions or feces; and postpartum transmission after contact with an infected mother, relatives or healthcare workers (probable mode of transmission before the beginning of vaccination campaigns for this staff)^{41,42,50-52} (Figure 1).

Postpartum transmission from an infected mother is more probable from respiratory secre-

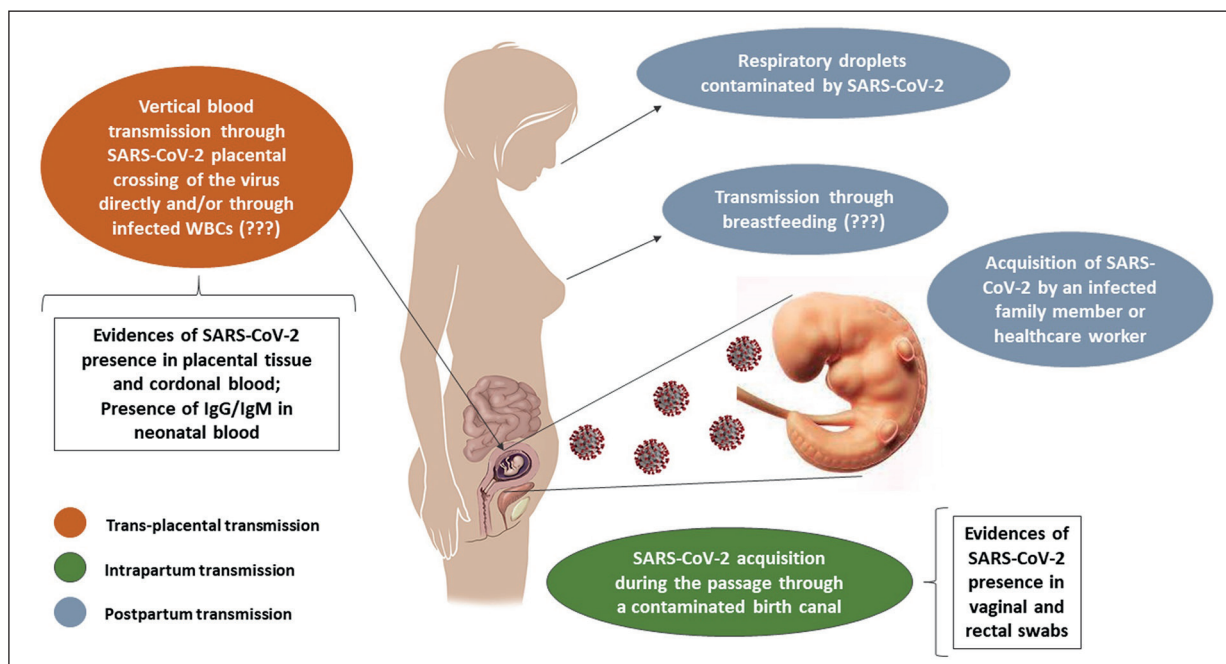


Figure 1. Possible modalities involved in the transmission of SARS-CoV-2 from mother to infant. WBCs: white blood cells.

Table I. Summary of the scientific evidence about the vertical transmission of SARS-CoV-2.

Authors 2020	Study description	Main findings
Alzamora et al ¹⁵⁰	Case report of a diabetic COVID-19 infected pregnant woman with rapid respiratory failure and necessity to mechanical ventilation.	Emergency caesarean section with preterm birth and isolation of the neonate with no contact to the mother. Neonatal nasopharyngeal swab on day 1 was positive for SARS-CoV-2 detection (RT-PCR) while the detection of IgG/IgM SARS-CoV-2 was negative. Possibility of perinatal transmission.
Breslin et al ¹⁴⁵	Case series including 43 COVID-19 infected pregnant women.	All the tested neonates resulted negative for COVID-19 and none of them had IgG/IgM SARS-CoV-2 on day 1 of life.
Chen et al ¹⁴⁶	Original research including 9 COVID-19 infected pregnant women.	All nine patients had a caesarean section. No stillbirths and neonatal asphyxia. Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six patients were tested for SARS-CoV-2, and all samples tested negative for the virus.
D a s h r a t h et al ¹⁴⁷	Review including 55 case studies of COVID-19 infected pregnant women and 46 neonates.	No evidence of vertical transmission.
Di Mascio et al ¹⁴⁸	Systematic review of 19 studies including 79 pregnant women of which 41 tested positive for SARS-CoV-2 and the others for MERS-CoV or SARS-CoV.	In COVID-19-positive women, the most common adverse outcome was preterm birth (41%), with death in 7%. Some outcomes were better for SARS-CoV-2 infected women than SARS or MERS infected ones, incl. rates of ICU admission (9.3% vs. 44.6% vs. 53.3%), need for mechanical ventilation (5.4% vs. 40.9% vs. 40%) and maternal death (0% vs. 28.6% vs. 25.8%). The study did not report information about vertical transmission.
Dong et al ¹⁴⁸	Case report of a preterm birth via caesarean section in a SARS-CoV-2 positive woman.	RT-PCR on multiple neonatal swabs performed for 16 days resulted all negative indicating no vertical transmission. However, presence of high level of IgG, IgM, white blood cells and IL-6 in neonatal blood until day 14.
Dubey et al ⁹	Systematic review and meta-analysis of case series and case reports	The C-section rate in infected patients was unusually higher than uninfected pregnant women. Preterm birth, low birth weight and other adverse pregnancy outcomes are commonly observed in COVID-19 patients. 1% (six neonates) prevalence of neonatal COVID-19.
Karimi-Zarchi et al ¹⁴⁹	Review including 31 COVID-19 positive pregnant women	All the neonates resulted negative for the detection of SARS-CoV-2. Two of the women died for complication linked to the COVID-19 infection.
Kirtsman et al ¹⁵⁰	Case study of a COVID-19 positive pregnant woman	Despite the neonate was born via caesarean section with no direct contacts with the mother before the collection of nasopharyngeal swabs, the latter resulted SARS-CoV-2 positive on days 1, 2 and 7 of life. Placenta resulted positive as well as neonatal plasma and stool.
Liu et al ¹⁵¹	Original research including 15 COVID-19 positive pregnant women	10 childbirths via caesarean section and 3 preterm childbirths. No evidence of neonatal asphyxia, neonatal death, stillbirth, or abortion.
Patanè et al ¹⁴⁴	Case series including 22 COVID-19 positive pregnant women	Of all the 22 tested neonates, 2 were positive for the detection of SARS-CoV-2 in nasopharyngeal swab with RT-PCR. The virus was also detected on placental tissues.
Peng et al ¹⁵²	Case report of a COVID-19 pregnant woman with preterm birth via caesarean section	Despite the neonate presented symptoms of a mild respiratory distress, the detection of SARS-CoV-2 in neonatal swab and bronchoalveolar lavage fluid, and in amniotic fluid and genital maternal secretion were negative. No evidence of a vertical transmission.
Schwartz et al ⁷⁰	Review about the effects of SARS, MERS and COVID-19 on pregnancy outcomes (literature describing 38 COVID-19 infected Chinese pregnant women and their neonates)	All tested neonates and some placentas were negative using RT-PCR tests. No evidence of vertical transmission.
Vivanti et al ¹⁵³	Case reported of a COVID-19 infected pregnant woman	Neonate born with caesarean section. SARS-CoV-2 detection was positive on amniotic fluid collected both before and after membrane rupture. Neonatal nasopharyngeal and rectal swabs, blood and bronchoalveolar lavage resulted positive. On the third day of life, the neonate was irritable with poor feeding and opisthotonos but CSF was negative to the SARS-CoV-2 detection.

Table Continued

Table I. (Continued). Summary of the scientific evidence about the vertical transmission of SARS-CoV-2.

Authors 2020	Study description	Main findings
Yu et al ¹⁵⁴	Retrospective, single-centre study including 7 COVID-19 infected pregnant women	All the patients had caesarean. The outcomes of the pregnant women and neonates were good. Three neonates were tested for SARS-CoV-2 and one neonate was infected with SARS-CoV-2 36 h after birth.
Zamaniyan et al ⁴²	Case report of a COVID-19 infected pregnant woman	The neonate was preterm and the childbirth was via caesarean section. On day 1, the neonate resulted negative for the detection of SARS-CoV-2 but further tests in blood and amniotic fluid resulted positive, indicating a vertical transmission of the infection. The women died 11 days after the childbirth for complication linked to the COVID-19 infection.
Zeng et al ⁴⁹	Case series including 6 COVID-19 infected pregnant women.	RT-PCR on neonatal swabs resulted all negative. Significantly high levels of serum antibodies (especially in two of them) and IL-6.
2021		
Bwire et al ¹⁵⁵	Systematic review of 33 articles and a total of 205 infants born to COVID-19 positive mothers	6.3% of the infants tested positive for COVID-19 virus at birth. IgG/IgM were detected in 90% infants who tested negative for COVID-19 virus with antibody titres much higher for IgG than IgM. Evidence of low possibility of vertical transmission of COVID-19.
Chi et al ¹⁵⁶	Systematic review of 230 pregnant women infected with COVID-19 and their 156 infants.	A total of 34.62% of the pregnant patients had obstetric complications and 24.74% of neonates were premature. Five neonates' throat swab tests of SARS-CoV-2 were positive while for eight of them with negative throat swab tests, three had both elevated IgM and IgG against SARS-CoV-2. Nucleic acid tests of vaginal secretions, breast milk, amniotic fluid, placental blood, and placental tissues were negative.
Ciapponi et al ¹⁵⁷	Overview of 66 systematic reviews	The most frequent maternal outcomes were C-section (23-96%) and preterm delivery (14-64%). Most of their neonates were asymptomatic (16-93%) or presented fever (0-50%), low birth weight (5-43%) or preterm delivery (2-69%). The risk of congenital transmission or via breast milk was estimated to be low, but close contacts may carry risks.
De Medeiros et al ¹⁵⁸	Systematic review and meta-analysis 70 studies included 10,047 pregnant women with COVID-19	The most adverse outcomes were delivered preterm (24%) and caesarean delivery (42%). There were 108 maternal mortalities (2%) and 50 abortions (5%). The neonatal outcomes included foetal distress (11%), birth weight (15%), APGAR <7 (19%), admission to the neonatal intensive care unit (28%), and foetal mortality (2%).
Dhir et al ⁶³	Systematic review of 86 publications (45 case series and 41 case reports) including 1992 COVID-19 infected pregnant women and 1141 neonates	281 (25%) neonates were preterm, and caesarean section (66%) was the preferred mode of delivery. Overall, 58 neonates were reported with SARS-CoV-2 infection (4 had a congenital infection), of which 29 (50%) were symptomatic (23 required ICU) with respiratory symptoms being the predominant manifestation (70%). No mortality was reported in SARS-CoV-2-positive neonates.
Jafari et al ¹⁵⁹	Meta-analysis including 128,176 non-pregnant patients (228 studies) and 10,000 pregnant patients (121 studies) with confirmed COVID-19 infection	Caesarean delivery, low birth weight and preterm birth are more probable in pregnant women with COVID-19 than uninfected those. The most prevalent neonatal complications are neonatal intensive care unit admission, foetal distress and low birth weight. The rate of vertical transmission was 5.3%, and the rate of positive SARS-CoV-2 test for neonates born to mothers with COVID-19 was 8%
Lassi et al ¹⁶⁰	Systematic review and meta-analysis of 62 studies and 31,016 COVID-19 infected pregnant women	Among neonates, 23.4% were preterm (<37 weeks), 16.6% were low birth weight, and 23.7% were admitted to neonatal ICU. A total of 21 stillbirths (1.6%) and 24 neonatal deaths (1.6%) were recorded, while 50 babies (3.5%) were COVID-19 positive. The risk of preterm birth was almost 2.4 folds among women with severe COVID-19.
Wei et al ¹⁶¹	Systematic review and meta-analysis of 42 studies involving 438,548 pregnant women	COVID-19 was associated with preeclampsia, preterm birth and stillbirth, gestational diabetes and low birth weight.

tions while there is no evidence that SARS-CoV-2 can be transmitted through breastfeeding. The positive effect of breast milk in providing protective antibodies against infectious agents, including SARS-CoV-2, is well known and it far overcomes the potential transmission risk, also given the less serious COVID-19 burden in infants⁵³⁻⁵⁵. International and national scientific societies, including the WHO and American Association of Pediatrics, support breastfeeding during the pandemic⁵⁶. Actually, SARS-CoV-2 infection is more likely acquired by neonates *via* horizontal transmission from contact with infected respiratory secretions from the mother and others, emphasizing the maintaining of appropriate hygiene during contact with a neonate.

Fetal malperfusion and premature rupture of membranes, can be responsible for adverse neonatal outcomes in infants born to women infected with SARS-CoV-2, regardless of whether the infection is transmitted from mother to fetus^{57,58}. A meta-analysis⁵⁹ including 342,080 pregnant women showed that neonates born to women infected with SARS-CoV-2 had a 2-fold higher risk of death compared to those born to uninfected women (aOR of 2.21). In women with and without laboratory-confirmed SARS-CoV-2 infection the risk of preterm birth was 5.8% *vs.* 12.1% (aOR, 2.17), of preeclampsia or eclampsia was 3.9% *vs.* 2.5% (aOR, 1.55), and of emergency caesarean delivery was 27.6% *vs.* 18.5% (aOR, 1.63), with a parallel reduction of spontaneous vaginal delivery (49.2% *vs.* 54.6%; aOR, 0.80). SARS-CoV-2-infected pregnant women were at increased risk for a longer hospital stay after delivery (25.8% *vs.* 17.0%; aOR, 1.57) and re-hospitalization within 6 weeks after birth (4.3% *vs.* 3.1%; aOR, 1.39). Concerning infants, those born to women with laboratory-confirmed SARS-CoV-2 infection had a higher risk of neonatal adverse outcomes (aOR, 1.45), need for specialist neonatal care (aOR, 1.24), and prolonged neonatal hospitalization after birth (aOR, 1.61). This was reported for preterm infants while the only adverse outcome reported in term infants born to infected women was a prolonged hospital stay after birth (21.1% *vs.* 14.6%; aOR, 1.61).

In the systematic review and meta-analysis performed by Di Toro et al⁶⁰ including 1,100 women, of which 588 (53.5%) were registered as COVID-19 cases, only five maternal deaths and three stillbirths were reported (one case was not COVID-19-related, while in the other two, the role of the infection was unclear). Moreover, in

17 studies involving 684 neonates, the rate of preterm delivery (mean gestational age of 35.74 weeks) was assessed to be 23% while in fourteen studies (217 neonates) the mean birth weight was 3144.71 g.

Immature immune system, passive transfer of maternal IgG antibodies through placental circulation and breastfeeding, and lower ACE2 expression compared to adults, can result in a low level of inflammation with a mild level of illness in SARS-CoV-2-infected neonates and children⁶¹. However, neonates can be affected by more severe disease than older children, so SARS-CoV-2-positive neonates should be clinically monitored and isolated^{51,62}. The infection can have an early onset (between 2 and 7 days after birth) caused by perinatal transmission (intrapartum or more commonly immediately after birth). Infected neonates are asymptomatic in 20% of cases⁶²⁻⁶⁴ or have mild symptoms (rhinorrhea and cough) in 40-50% of cases^{65,66} and/or fever in 15-45% of cases^{63,66,67}. However, moderate to severe symptoms, such as respiratory distress, lethargy, vomiting and diarrhea, and clinical evidence of multiorgan failure, have also been observed^{65,68}. Management of symptomatic COVID-19-positive neonates requires respiratory support for respiratory distress⁶⁹.

Symptomatic neonates are often diagnosed beyond 5 to 7 days after birth (late-onset neonatal COVID-19)⁶⁵, confirming the major role of postnatal transmission, even if intrapartum exposure to maternal infected secretions and body fluids can contribute⁴¹. In the first 2 days of life, during hospitalization, many affected neonates had negative RT-PCR tests and then had to be readmitted with symptoms suggestive of COVID-19⁷⁰. In the study of Gale et al⁶⁵ on affected neonates the most common symptoms were lethargy, hyperthermia, cold, mild respiratory symptoms, apnea, poor appetite, and vomiting. One-third of them required respiratory support and supplemental oxygen. In 26% of cases the mothers were positive for SARS-CoV-2, while in 52% a close contact with an infected adult was confirmed. Similar symptoms and radiographic findings with worsening illness were reported by others^{71,72}. Infants aged < 1 month have a 3-fold higher risk of need for critical care⁷⁰.

Leukocytosis, thrombocytopenia, and elevated lactate and C-reactive protein levels have been observed⁷³. Disseminated intravascular coagulation has also been reported⁶⁸. In the case of symptomatic infection, management is especially support-

ive and includes supplemental oxygen, respiratory support, fluid resuscitation, and temperature control. Currently, the use of antiviral drugs and steroids is controversial. Remdesivir was used in a 22-day-old infant with severe late-onset COVID-19 who well tolerated the treatment and clinically improved⁷⁴, and in a 4-day-old infant who continued to get worse despite treatment. He received dexamethasone and convalescent plasma, required invasive ventilation until 13 days of age and finally improved⁵².

Potential Long-Term Effects of Maternal COVID-19 Infection In Infants

While adverse obstetric and neonatal outcomes are clearly highlighted, other potential adverse outcomes are still only hypothesized as they manifest later. The morbidity and lethality of SARS-CoV-2 infection is partly due to host defense mechanisms, such as an abnormal inflammatory response to the virus, i.e., cytokine storm syndrome (CSS), mainly driven by overproduction of IL-6^{75,76}. While inflammatory and thrombotic placentas cause the early adverse effects, inflammation in developing embryos and fetus could cause long-term defects, regardless of vertical transmission of SARS-CoV-2. Due to Maternal Immune Activation (MIA), in utero inflammation is associated with neurodevelopmental, cognitive and psychiatric disorders in affected offspring^{77,78}. The transplacental passage of maternal cytokines damages the delicate neurodevelopmental process that begins in the first weeks of gestation. Fetal neuroinflammation causes microglial activation and changes in macrophage function, modifying neuronal migration, axonal and dendritic growth, programmed cell death, synaptogenesis, myelination and pruning (i.e., modelling/synaptic refinement)⁷⁹⁻⁸¹. Impaired neurodevelopment has cognitive and psychiatric long-term implications, and reduces the quality of life, causing autism spectrum disorder (ASD) and neuropsychiatric disorders, such as Schizophrenia (SCZ) and anxiety (AD), mood (MD) and impulse control disorders (ICD).

Epidemiological studies and case reports have highlighted the strong association between viral infection in pregnancy and the onset of both ASD and psychiatric disorders, such as SCZ in the offspring, making similar effects for the COVID-19 pandemic more than plausible⁸²⁻⁸⁵. In addition to cytomegalovirus⁸⁶, polyomaviruses⁸⁷, rubella, measles and mumps⁸⁸, for which vertical transmission of the infection is proven, respiratory viruses, such as influenza viruses, are also linked to

autism⁸² and SCZ⁸³. *In vivo* studies, have proved that poly-inosinic acid:poly-cytidylic (Poly I:C), mimicking single-stranded RNA viruses recognized by TLR-3 of the host's innate immune cells, induced MIA in pregnant mice. Due to the activation of the transcriptional factor NF- κ B, MIA caused behavioral abnormalities in offspring with features similar to those of ASD and SCZ^{82,89,90}. Despite the low invasiveness of influenza viruses, the host's innate immune response promotes the onset of CSS, which contributes to severe influenza complications that are not limited to the lungs. In a mouse pregnancy model, the influenza virus disrupted the delicate and interconnected cytokine and hormonal signaling pathways, damaging placental and fetal tissue⁹¹. Also, fetal inflammation induced by maternal inoculations of LPS has important unfavorable effects on brain development, underlying the neurobehavioral deficits reported in humans and animals exposed to prenatal pro-inflammatory conditions⁹².

All that would seem to give biological plausibility to the population-based cohort study of Atladóttir et al⁹³ that reported a 2-fold increased risk of autism after self-reported gestational influenza. Similar data were obtained by Deykin and MacMahon⁸⁸ (1979) but were not confirmed by Zerbo et al⁹⁴ that, however, observed an increased risk of autism when fever occurred during pregnancy.

The above highlights the need for long-term follow-up of the largest number of subjects in utero exposed to SARS-CoV-2 during the pandemic to assess the earliest signs of cognitive and behavioral deficits. In addition to longitudinal cohort studies aimed to assess a possible increase in neuropsychiatric disorders, in subjects in utero exposed to SARS-CoV-2, it is necessary to implement preclinical studies to develop treatments to contain and/or delay the onset of these highly impactful long-term disorders.

COVID-19 Vaccination In Pregnant And Lactating Women

Infectious risk is one of the most important issues regarding the health of pregnant women and their infants, and some vaccines are strongly recommended in this category. Since 2012, the Advisory Committee on Immunization Practices (ACIP) has recommended the tetanus-diphtheria-acellular pertussis (Tdap) immunization for pregnant women between 27 and 36 weeks of gestation⁹⁵. The CDC recommends immunization against seasonal influenza^{96,97}. In Italy, the last National Plan for Vaccine Prevention 2017-2019

included pregnant women among at-risk groups recommending influenza and pertussis vaccinations⁹⁸. However, pregnant women are one of the most vaccine hesitant categories⁹⁹. A continuous health education on the importance of vaccine prevention in pregnancy is crucial for healthcare professionals, especially those directly involved in the care of pregnant women¹⁰⁰. Some studies¹⁰¹⁻¹⁰³ have shown that vaccine hesitancy can be effectively counteracted with health education campaigns addressed to the general population and especially parents and healthcare workers.

Nanovaccinology is one of the most promising future weapons in the fight against infectious diseases¹⁰⁴. The highly safe and effective licensed mRNA COVID-19 vaccines are lipid nanoparticle-formulated, nucleoside-modified RNA (modRNA) vaccines encoding the SARS-CoV-2 full-length spike (S) protein¹⁰⁵. Despite the risks and consequences that COVID-19 infection could induce in pregnancy and the availability of safe and effective COVID-19 vaccines, there are few published data on COVID-19 vaccine in pregnant women due to the fact that they are commonly not included in vaccine research, especially for safety and responsibility concerns¹⁰⁶⁻¹¹⁰. At the moment, over 300 clinical trials evaluating new drugs and vaccines for COVID-19 are in progress, all excluding pregnant women¹¹¹. To remedy this lack of precious information, in 2018, the Food and Drug Administration (FDA) provided some consideration to include pregnant women in clinical trials¹¹². The Task Force on Research Specific to Pregnant Women and Lactating Women recommends the inclusion of these categories in clinical trials, unless there are scientific reasons proving their exclusion¹¹³. Despite these recommendations, this population continues to be excluded from clinical trials.

Pfizer/BioNTech, Moderna, and Janssen reported data on their vaccines' animal Developmental and Reproductive Toxicology (DART) studies that have found no safety problems and no adverse effects on female reproduction, fertility, fetal, embryonal or postnatal development and miscarriage¹¹⁴⁻¹¹⁹. Preliminary human studies using mRNA-based vaccines against the Zika virus, influenza, and rabies have reported good safety and immunogenicity during pregnancy¹²⁰⁻¹²⁶.

Very few pregnant women were unintentionally vaccinated, because they were enrolled in clinical trials of vaccines by Pfizer/BioNTech, Moderna and Janssen. The Pfizer/BioNTech and Moderna vaccine trials reported miscarriage only

in the placebo group. The Janssen vaccine trial reported one spontaneous abortion in the vaccine group compared to placebo, one incomplete abortion in the placebo group, two elective abortions in the placebo group, and one ectopic pregnancy in the vaccine group^{118,127}.

On 18 February 2021, Pfizer announced a global phase 2/3 randomized, placebo-controlled, observer-blind trial to evaluate the safety, tolerability, and efficacy of its vaccine in pregnant women. The trial includes 4,000 healthy women vaccinated between 24 and 34 weeks of pregnancy¹²⁸. Similarly, Moderna has announced a prospective observational study to evaluate obstetric, neonatal, and infant outcomes and has created a registry that monitors pregnancy outcomes in women exposed to the Moderna COVID-19 vaccine during pregnancy¹²⁹. Current ongoing studies about COVID-19 vaccine on pregnant and lactating women are summarized in Table II.

The United Kingdom has also created a similar registry that shows no safety concerns related to COVID-19 vaccination¹³⁰. Another important initiative on a voluntary base with the creation of a smartphone-based app called "v-safe", in which pregnant women report adverse events following COVID-19 vaccination, has been adopted by the CDC. So far, over 50,000 pregnant women have adhered, showing no serious vaccine-related adverse events¹³¹.

Gray et al¹³² carried out a prospective cohort study, including 131 reproductive age vaccinated women (with 84 pregnant and 31 lactating women) and reported that mRNA-based COVID-19 vaccines elicited vigorous humoral immunity with reactogenicity similar to that observed in non-pregnant women. The transmission of protective antibodies to neonates *via* the placenta and breast milk is also reported.

Shimabukuro et al¹³³ analyzed the data of 35,691 pregnant women adhering to surveillance registries on the safety of mRNA COVID-19 vaccines in pregnancy, such as "v-safe" and the Vaccine Adverse Event Reporting System (VAERS). The most common local and systemic reactions after vaccination, especially after the second dose, were pain at the site of injection, fatigue, headache, and myalgia. Similarly, to non-pregnant women, less than 1% of the participants reported a temperature > 38°C on day one after the first dose and 8.0% after the second dose. Only a slightly higher frequency of nausea and vomiting after the second dose was observed in pregnancy.

Table II. Current ongoing studies about COVID-19 vaccine efficacy on pregnant and lactating women.

	Study title	Type of study	Description of the study	Participants	Status	Study period
Pfizer-BioNTech SE ¹⁶²	Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older	Interventional (Clinical Trial)	“A Phase 2/3, randomized, placebo-controlled, observer-blind study evaluating the safety, tolerability, and immunogenicity of 30 µg of BNT162b2 or placebo administered in 2 doses, 21 days apart, in approximately 700 healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks’ gestation. Participants will be randomized 1:1 to receive BNT162b2 or placebo (saline)”	700 participants	Recruiting	February 16, 2021 October 15, 2022
Moderna ¹⁶³	Moderna mRNA-1273 Observational Pregnancy Outcome Study	Observational (Cohort study)	“The Moderna COVID-19 Vaccine Pregnancy Registry will collect and analyze information on the potential impact of exposure to the Moderna COVID-19 vaccine on pregnancy and birth outcomes”	1000 participants	Recruiting	September 1, 2021 January 6, 2024
Janssen Vaccines & Prevention B.V. ¹⁶⁴	An Open-label, Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.COV2.S in Healthy Pregnant Participants	Interventional (Clinical Trial)	“The purpose of this study is to assess the safety and reactogenicity of Ad26.COV2.S administered intramuscularly (IM) as a 1-dose schedule at the standard dose level, or 2-dose schedule at a lower dose level, at a ratio of approximately 325:75 adult participants (regardless of serostatus), during the second and/or third trimester of pregnancy and (potentially) post-partum; to assess the humoral immune response in peripheral blood of adult participants to Ad26.COV2.S administered IM as a 1-dose, or 2-dose schedule, during the second and/or third trimester of pregnancy, 28 days after the first vaccination and 14 days after the second vaccination”	400 participants	Recruiting	August 27, 2021 September 18, 2024

Some studies^{134,135} suggest that COVID-19 vaccines, both based on mRNA nanoparticles and viral vectors, had no significant risks to the fetus or breastfeeding infants, even in the absence of certain data on whether vaccine particles cross the placenta and penetrate the fetal organism. Specifically, with regard viral vector vaccines, the FDA specifies that non-replicating adenovirus 26 (Ad26) used as the vector for Janssens' COVID-19 vaccine showed no substantial clinical evidence, based on data from ongoing and completed clinical trials, including COVID-19, HIV, and Ebola vaccines administered to pregnant women, which demonstrated an acceptable safety and reactogenicity profile^{136,137}. Research on lipid nanoparticle-based vaccines suggest that the nanostructures cannot cross the placenta^{138,139}. IgA elicited by vaccination are present in breast milk, providing protection to infants¹⁴⁰⁻¹⁴¹. IgA titers in breast milk 3 to 4 weeks after mRNA-based COVID-19 vaccines were similar to those present in women that were affected by COVID-19 infection¹⁴⁰. Finally, the efficient transplacental transfer of anti-COVID-19 spike antibodies after antenatal vaccination with the Pfizer/BioNTech vaccine was reported¹⁴¹.

From the analysis of the safety surveillance registries, including “v-safe” and the Vaccine Adverse Event Reporting System (VAERS), Shimabukuro et al¹³³ reported that pregnancy loss occurred in 13.9%, preterm birth in 9.4% and small size for gestational age in 3.2%. However, no neonatal deaths were reported. From the analysis of the VAERS, reporting data of 221 pregnancy-related adverse events, spontaneous abortion was the most frequently observed, with a reported absolute number of 46 cases. However, similar results have been reported by studies on pregnant women conducted before the COVID-19 pandemic¹⁴²⁻¹⁴⁴.

Conclusions

The COVID-19 pandemic has upset the world, and human beings are paying a heavy toll worldwide. Vaccination is the most important means of controlling the spread of this new enemy and it is crucial to safeguard all vulnerable populations, such as pregnant and lactating women and their neonates. To protect these vulnerable groups both from short-term and long-term effects, it is important to prioritize their involvement in clinical vaccination trials. Furthermore, considering the role of healthcare workers in the spread of a pre-

ventive culture and acceptance of preventive measures, performing health education campaigns specifically addressed to this working category is a cornerstone in helping pregnant women to undergo vaccination.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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