European Review for Medical and Pharmacological Sciences 2022; 26: 2610-2626

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

A. FACCIOLÀ[1], C. MICALI[2], G. VISALLI[1], E. VENANZI RULLO[2], Y. RUSSOTTO[2], P. LAGANÀ[1], A. LAGANÀ[1,3], G. NUNNARI[2], A. DI PIETRO[1]

[1]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[2]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[3]Multi-Specialist Clinical Institute for Orthopaedic Trauma Care (COT), Messina, Italy

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 pregnancy[3]. 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 mortality[4]. 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 women[9]. The Centers for Disease Control and Prevention (CDC) conducted a surveillance including 598 pregnant women affected by labo-

Corresponding Author: Emmanuele Venanzi Rullo, MD; e-mail: evenzirullo@unime.it

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-19[13]. 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 thromboembolism[14]. 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 role[21].

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 occurs[22].

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 ≥ 70% of total circulating lymphocytes[23]. 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 remodelling[24]. 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 response[25]. 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 compromised[28]. 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-l) that counteract infections and are the hallmark of placental antiviral defence[29-33].

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 uterus[34]. 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 infection[37]. 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 age[38]. A research[39], 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 infections[40]. 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 low[45].

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-

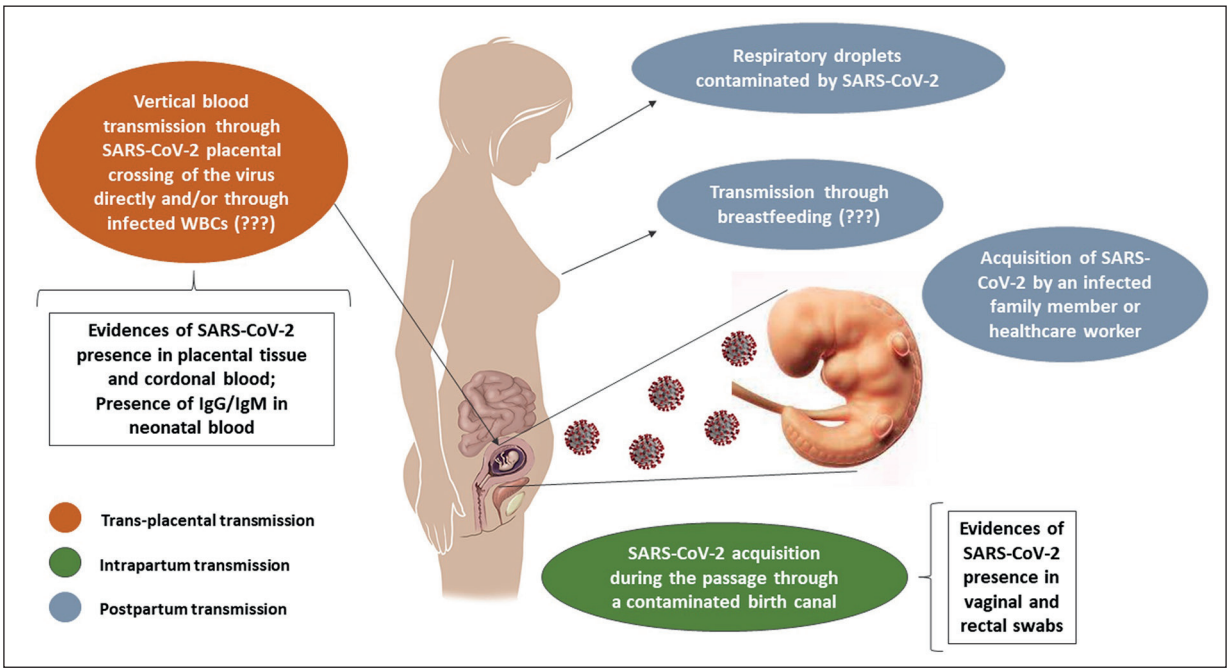

Figure 1. Possible modalities involved in the transmission of SARS-CoV-2 from mother to infant. WBCs: white blood cells.

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

Authors 2020	Study description	Main findings
Alzamora et al[50]	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.
Dashraath 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[48]	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[44]	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 infants[53-55]. International and national scientific societies, including the WHO and American Association of Pediatrics, support breastfeeding during the pandemic[56]. 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-analysis[59] 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 al[60] 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 children[61]. 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 cases[62-64] 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 distress[69].

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 contribute[41]. 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-19[70]. In the study of Gale et al[65] 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 care[70].

Leukocytosis, thrombocytopenia, and elevated lactate and C-reactive protein levels have been observed[73]. Disseminated intravascular coagulation has also been reported[68]. 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 improved[74], 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 improved[52].

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 plausible[82-85]. In addition to cytomegalovirus[86], polyomaviruses[87], rubella, measles and mumps[88], for which vertical transmission of the infection is proven, respiratory viruses, such as influenza viruses, are also linked to autism[82] and SCZ[83]. *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-κB, 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 tissue[91]. Also, fetal inflammation inducted 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 conditions[92].

All that would seem to give biological plausibility to the population-based cohort study of Atladóttir et al[93] that reported a 2-fold increased risk of autism after self-reported gestational influenza. Similar data were obtained by Deykin and MacMahon[88] (1979) but were not confirmed by Zerbo et al[94] 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 gestation[95]. 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 vaccinations[98]. However, pregnant women are one of the most vaccine hesitant categories[99]. 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 women[100]. Some studies[101-103] 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 diseases[104]. 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) protein[105]. 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 concerns[106-110]. At the moment, over 300 clinical trials evaluating new drugs and vaccines for COVID-19 are in progress, all excluding pregnant women[111]. To remedy this lack of precious information, in 2018, the Food and Drug Administration (FDA) provided some consideration to include pregnant women in clinical trials[112]. 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 exclusion[113]. 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 miscarriage[114-119]. Preliminary human studies using mRNA-based vaccines against the Zika virus, influenza, and rabies have reported good safety and immunogenicity during pregnancy[120-126].

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 pregnancy[128]. 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 pregnancy[129]. 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 vaccination[130]. 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 events[131].

Gray et al[132] 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 al[133] 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 infants[140-141]. 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 infection[140]. Finally, the efficient transplacental transfer of anti-COVID-19 spike antibodies after antenatal vaccination with the Pfizer/BioNTech vaccine was reported[141].

From the analysis of the safety surveillance registries, including "v-safe" and the Vaccine Adverse Event Reporting System (VAERS), Shimabukuro et al[133] 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 pandemic[142-144].

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 preventive 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.

Funding

This research received no external funding.

References

1) Pedrosa AL, Bitencourt L, Fróes ACF, Cazumbá MLB, Campos RGB, de Brito SBCS, Simões E, Silva AC. Emotional, Behavioral, and Psychological Impact of the COVID-19 Pandemic. Front Psychol 2020; 11: 566212.
2) Facciolà A, Laganà P, Caruso G. The COVID-19 pandemic and its implications on the environment. Environ Res 2021; 201: 111648.
3) Cabinet Office. Guidance. Staying alert and safe (social distancing). Coronavirus (COVID-19) Guidance and support. 2020. Available online: https://www.gov.uk/government/publications/staying-alertand-safe-social-distancing/staying-alert-and-safe-social-distancing.
4) Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, Woodworth KR, Nahabedian JF, Azziz-Baumgartner E, Gilboa SM, Meaney-Delman D. CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1641-1647.
5) Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, Lindstrom S, Louie JK, Christ CM, Bohm SR, Fonseca VP, Ritger KA, Kuhles DJ, Eggers P, Bruce H, Davidson HA, Lutterloh E, Harris ML, Burke C, Cocoros N, Finelli L, MacFarlane KF, Shu B, Olsen SJ. Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009; 374: 451-458.
6) Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Louie J, Doyle TJ, Crockett M, Lynfield R, Moore Z, Wiedeman C, Anand M, Tabony L, Nielsen CF, Waller K, Page S, Thompson JM, Avery C, Springs CB, Jones T, Williams JL, Newsome K, Finelli L, Jamieson DJ. Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus

illness among pregnant women in the United States. JAMA 2010; 303: 1517-1525.

7) Wong SF, Chow KM, de Swiet M. Severe Acute Respiratory Syndrome and pregnancy. BJOG 2003; 110: 641-642.
8) Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection During Pregnancy: Report of Two Cases & Review of the Literature. J Microbiol Immunol Infect 2019; 52: 501-503.
9) Dubey P, Reddy SY, Manuel S, Dwivedi AK. Maternal and neonatal characteristics and outcomes among COVID-19 infected women: an updated systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2020; 252: 490-501.
10) Delahoy MJ, Whitaker M, O'Halloran A, Chai SJ, Kirley PD, Alden N, Kawasaki B, Meek J, Yousey-Hindes K, Anderson EJ, Openo KP, Monroe ML, Ryan PA, Fox K, Kim S, Lynfield R, Siebman S, Davis SS, Sosin DM, Barney G, Muse A, Bennett NM, Felsen CB, Billing LM, Shiltz J, Sutton M, West N, Schaffner W, Talbot HK, George A, Spencer M, Ellington S, Galang RR, Gilboa SM, Tong VT, Piasecki A, Brammer L, Fry AM, Hall AJ, Wortham JM, Kim L, Garg S. COVID-NET Surveillance Team. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 d COVID-NET, 13 states, March 1-August 22, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1347-1354.
11) Yan J, Guo J, Fan C, Juan J, Yu X, Li J, Feng L, Li C, Chen H, Qiao Y, Lei D, Wang C, Xiong G, Xiao F, He W, Pang Q, Hu X, Wang S, Chen D, Zhang Y, Poon LC, Yang H. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol 2020; 223: 111.e1-111.e14.
12) Salem D, Katranji F, Bakdash T. COVID-19 infection in pregnant women: Review of maternal and fetal outcomes. Int J Gynaecol Obstet 2021; 152: 291-298.
13) Smithgall MC, Liu-Jarin X, Hamele-Bena D, Cimic A, Mourad M, Debelenko L, Chen X. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. Histopathology 2020; 77: 994-999.
14) Benhamou D, Keita H, Ducloy-Bouthors AS. Coagulation changes and thromboembolic risk in COVID-19 obstetric patients. Anaesth Crit Care Pain Med 2020; 39: 351-353.
15) Lockwood CJ, Yen CF, Basar M, Kayisli UA, Martel M, Buhimschi I, Buhimschi C, Huang SJ, Krikun G, Schatz F. Preeclampsia-related inflammatory cytokines regulate interleukin-6 expression in human decidual cells. Am J Pathol 2008; 172: 1571-1579.
16) Ciobanu AM, Colibaba S, Cimpoca B, Peltecu G, Panaitescu AM. Thrombocytopenia in pregnancy. Maedica (Bucur) 2016; 11: 55-60.
17) Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, Stamatelopoulos K, Dimopoulos MA, Caforio ALP, Georgiopoulos G. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. Eur J Clin Invest 2020; 50: e13362.
18) Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta 2020; 506: 145e148.
19) Mendoza M, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, Lopez-Martinez RM, Balcells J, Fernandez-Hidalgo N, Carreras E, Suy A. Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study. BJOG 2020; 127: 1374e1380.
20) Rolnik D. Can COVID-19 in pregnancy cause pre-eclampsia? BJOG 2020; 127: 1381.
21) Auriti C, De Rose DU, Santisi A, Martini L, Piersigilli F, Bersani I, Ronchetti MP, Caforio L. Pregnancy and Viral Infections: Mechanisms of Fetal Damage, Diagnosis and Prevention of Neonatal Adverse Outcomes From Cytomegalovirus to SARS-CoV-2 and Zika Virus. Biochim Biophys Acta Mol Basis Dis 2021; 1867: 166198.
22) Lv D, Peng J, Long R, Lin X, Wang R, Wu D, He M, Liao S, Zhao Y, Deng D. Exploring the Immunopathogenesis of Pregnancy With COVID-19 at the Vaccination Era. Front Immunol 2021; 12: 683440.
23) Gaynor LM, Colucci F. Uterine Natural Killer Cells: Functional Distinctions and Influence on Pregnancy in Humans and Mice. Front Immunol 2017; 8: 467.
24) Ning F, Liu H, Lash GE. The Role of Decidual Macrophages During Normal and Pathological Pregnancy. Am J Reprod Immunol 2016; 75: 298-309.
25) Le Gars M, Kay AW, Bayless NL, Aziz N, Dekker CL, Swan GE, Davis MM, Blish CA. Increased Proinflammatory Responses of Monocytes and Plasmacytoid Dendritic Cells to Influenza A Virus Infection During Pregnancy. J Infect Dis 2016; 214: 1666-1671.
26) Wagner H. The immunobiology of the TLR9 subfamily. Trends Immunol 2004; 25: 381-386.
27) Bryant AH, Menzies GE, Scott LM, Spencer-Harty S, Davies LB, Smith RA, Jones RH, Thornton CA. Human Gestation-Associated Tissues Express Functional Cytosolic Nucleic Acid Sensing Pattern Recognition Receptors. Clin Exp Immunol 2017; 189: 36-46.
28) Pazos M, Sperling RS, Moran TM, Kraus TA. The Influence of Pregnancy on Systemic Immunity. Immunol Res 2012; 54: 254-261.
29) King AE, Paltoo A, Kelly RW, Sallenave JM, Bocking AD, Challis JRG. Expression of natural antimicrobials by human placenta and fetal membranes. Placenta 2007; 28: 161-169.
30) Bayer A, Delorme-Axford E, Sleigher C, Frey TK, Trobaugh DW, Klimstra WB, Emert-Sedlak LA, Smithgall TE, Kinchington PR, Vadia S, Seveau S, Boyle JP, Coyne CB, Sadovsky Y. Human trophoblasts confer resistance to viruses implicated in perinatal infection. Am J Obstet Gynecol 2015; 212: 71.e1-71.e8.

31) Bayer A, Lennemann NJ, Ouyang Y, Bramley JC, Morosky S, Marques ET Jr, Cherry S, Sadovsky Y, Coyne CB. Type III interferons produced by human placental trophoblasts confer protection against Zika virus infection. Cell Host Microbe 2016; 19: 705-712.

32) Corry J, Arora N, Good CA, Sadovsky Y, Coyne CB. Organotypic models of type III interferon-mediated protection from Zika virus infections at the maternal-fetal interface. Proc Natl Acad Sci USA 2017; 114: 9433-9438.

33) Wells AI, Coyne CB. Type III interferons in antiviral defenses at barrier surfaces. Trends Immunol 2018; 39: 848-858.

34) Salamanna F, Maglio M, Landini MP, Fini M. Body Localization of ACE-2: On the Trail of the Keyhole of SARS-CoV-2. Front Med (Lausanne) 2020; 7: 594495.

35) Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181: 271-280.e8.

36) Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The Trinity of COVID-19: Immunity, Inflammation and Intervention. Nat Rev Immunol 2020; 20: 363-374.

37) Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARSCoV-2 and Coronavirus Disease 2019: What We Know So Far. Pathogens 2020; 9: 231.

38) Faure-Bardon V, Isnard P, Roux N, Leruez-Ville M, Molina T, Bessieres B, Ville Y. Protein expression of angiotensin-converting enzyme 2, a SARS-CoV-2-specific receptor, in fetal and placental tissues throughout gestation: new insight for perinatal counseling. Ultrasound Obstet Gynecol 2021; 57: 242-247.

39) Weatherbee BA, Glover DM, Zernicka-Goetz M. Expression of SARS-CoV-2 Receptor ACE2 and the Protease TMPRSS2 Suggests Susceptibility of the Human Embryo in the First Trimester. Open Biol 2020; 10: 200162.

40) Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, Critchley HOD. Pregnancy and COVID-19. Physiol Rev 2021; 101: 303-318.

41) Blumberg DA, Underwood MA, Hedriana HL, Lakshminrusimha S. Vertical Transmission of SARS-CoV-2: What is the Optimal Definition? Am J Perinatol 2020; 37: 769-772.

42) Zamaniyan M, Ebadi A, Aghajanpoor S, Rahmani Z, Haghshenas M, Azizi S. Preterm Delivery in Pregnant Woman with Critical COVID-19 Pneumonia and Vertical Transmission. Prenat Diagn 2020; 40: 1759-1761.

43) Algarroba G, Rekawek P, Vahanian SA. Visualization of SARS-CoV-2 Virus Invading the Human Placenta Using Electron Microscopy. Am J Obstet Gynecol 2020; 223: 275-278.

44) Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, Mangili G, Arosio M, Cornolti G. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gynecol MFM 2020; 2: 100145.

45) Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020; 323: 1843-1844.

46) Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of Coronavirus Disease 2019 (COVID-19) on Maternal, Perinatal and Neonatal Outcome: Systematic Review. Ultrasound Obstet Gynecol 2020; 56: 15-27.

47) Yang Z, Liu Y. Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. Am J Perinatol 2020; 37: 1055.

48) Dong L, Tian J, He S, Zhu C, Wang J, Liu C, Yang J. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. JAMA 2020; 323: 1846-1848.

49) Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, Long X. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA 2020; 323: 1848-1849.

50) Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol 2020; 37: 861-865.

51) Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020; 145: e20200702.

52) Hopwood AJ, Jordan-Villegas A, Gutierrez LD, Cowart MC, Vega-Montalvo W, Cheung WL, McMahan MJ, Gomez MR, Laham FR. Severe Acute Respiratory Syndrome Coronavirus-2 Pneumonia in a Newborn Treated with Remdesivir and Coronavirus Disease 2019 Convalescent Plasma. J Pediatric Infect Dis Soc 2021; 10: 691-694.

53) Cheema R, Partridge E, Kair LR, Kuhn-Riordon KM, Silva AI, Bettinelli ME, Chantry CJ, Underwood MA, Lakshminrusimha S, Blumberg D. Protecting breastfeeding during the COVID-19 pandemic. Am J Perinatol 2020. Online ahead of print.

54) Lackey KA, Pace RM, Williams JE, Bode L, Donovan SM, Järvinen KM, Seppo AE, Raiten DJ, Meehan CL, McGuire MA, McGuire MK. SARS-CoV-2 and human milk: What is the evidence? Matern Child Nutr 2020; 16: e13032.

55) Stuebe A. Should infants be separated from mothers with COVID19? First, do no harm. Breastfeed Med 2020; 15: 351-352.

56) American Academy of Pediatrics. Breastfeeding guidance post hospital discharge for mothers or infants with suspected or confirmed SARS-CoV-2 infection. 2021. Available online: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/breastfeeding-guidance-post-hospital-discharge/

57) Bellos I, Pandita A, Panza R. Maternal and perinatal outcomes in pregnant women infected by

SARS-CoV-2: A meta-analysis. Eur J Obstet Gynecol Reprod Biol 2021; 256: 194-204.

58) Norman M, Navér L, Söderling J, Ahlberg M, Hervius Askling H, Aronsson B, Byström E, Jonsson J, Sengpiel V, Ludvigsson JF, Håkansson S, Stephansson O. Association of Maternal SARS-CoV-2 Infection in Pregnancy With Neonatal Outcomes. JAMA 2021; 325: 2076-2086.

59) Gurol-Urganci I, Jardine JE, Carroll F, Draycott T, Dunn G, Fremeaux A, Harris T, Hawdon J, Morris E, Muller P, Waite L, Webster K, van der Meulen J, Khalil A. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. Am J Obstet Gynecol 2021; 225: 522.e1-522.e11.

60) Di Toro F, Gjoka M, Di Lorenzo G, De Santo D, De Seta F, Maso G, Risso FM, Romano F, Wiesenfeld U, Levi-D'Ancona R, Ronfani L, Ricci G. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clin Microbiol Infect 2021; 27: 36-46.

61) Rawat M, Chandrasekharan P, Hicar MD, Lakshminrusimha S. COVID-19 in newborns and infants-low risk of severe disease: silver lining or dark cloud? Am J Perinatol 2020; 37: 845-849.

62) Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, Vidal E, Cogo P. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr 2020; 179: 1029-1046.

63) Dhir SK, Kumar J, Meena J, Kumar P. Clinical features and outcome of SARS-CoV-2 infection in neonates: a systematic review. J Trop Pediatr 2021; 67: fmaa059.

64) Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, Aveni K, Yazdy MM, Harvey E, Longcore ND, Barton J, Fussman C, Siebman S, Lush M, Patrick PH, Halai UA, Valencia-Prado M, Orkis L, Sowunmi S, Schlosser L, Khuwaja S, Read JS, Hall AJ, Meaney-Delman D, Ellington SR, Gilboa SM, Tong VT. CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. COVID-19 Pregnancy and Infant Linked Outcomes Team (PILOT). Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1635-1640.

65) Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, Sharkey D, Doherty C, Mactier H, Kurinczuck JJ. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health 2020; 5: 113-121.

66) Raschetti R, Vivanti AJ, Vauloup-Fellous C, Loi B, Benachi A, De Luca D. Synthesis and systematic review of reported neonatal SARSCoV-2 infections. Nat Commun 2020; 11: 5164.

67) De Bernardo G, Giordano M, Zollo G, Chiatto F, Sordino D, De Santis R, Perrone S. The clinical course of SARS-CoV-2 positive neonates. J Perinatol 2020; 40: 1462-1469.

68) Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta 2020; 507: 167-173.

69) De Luca D. Managing neonates with respiratory failure due to SARS-CoV-2. Lancet Child Adolesc Health 2020; 4: e8.

70) Schwartz DA, Mohagheghi P, Beigi B, Zafaranloo N, Moshfegh F, Yazdani A. Spectrum of neonatal COVID-19 in Iran: 19 infants with SARS-CoV-2 perinatal infections with varying test results, clinical findings and outcomes. J Matern Fetal Neonatal Med 2020; 1-10. Online ahead of print.

71) Coronado Munoz A, Nawaratne U, McMann D, Ellsworth M, Meliones J, Boukas K. Late-onset neonatal sepsis in a patient with Covid-19. N Engl J Med 2020; 382: e49.

72) Precit MR, Yee R, Anand V, Mongkolrattanothai K, Pandey U, Dien Bard J. A case report of neonatal acute respiratory failure due to Severe Acute Respiratory Syndrome Coronavirus-2. J Pediatric Infect Dis Soc 2020; 9: 390-392.

73) Oncel MY, Akın IM, Kanburoglu MK, Tayman C, Coskun S, Narter F, Er I, Oncan TG, Memisoglu A, Cetinkaya M, Oguz D, Erdeve O, Koc E. Neo-Covid Study Group. A multicenter study on epidemiological and clinical characteristics of 125 newborns born to women infected with COVID-19 by Turkish Neonatal Society. Eur J Pediatr 2021; 180: 733-742.

74) Wardell H, Campbell JI, VanderPluym C, Dixit A. Severe acute respiratory syndrome coronavirus 2 infection in febrile neonates. J Pediatric Infect Dis Soc 2020; 9: 630-635.

75) Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis. Rev Med Virol 2020; 30: 1-9.

76) Trovato M, Sciacchitano S, Facciolà A, Valenti A, Visalli G, Di Pietro A. Interleukin-6 signalling as a valuable cornerstone for molecular medicine (Review). Int J Mol Med 2021; 47: 107.

77) Chudnovets A, Lei J, Na Q, Dong J, Narasimhan H, Klein SL, Burd I. Dose-dependent structural and immunological changes in the placenta and fetal brain in response to systemic inflammation during pregnancy. Am J Reprod Immunol 2020; 84: e13248.

78) Lu-Culligan A, Iwasaki A. The Role of Immune Factors in Shaping Fetal Neurodevelopment. Annu Rev Cell Dev Biol 2020; 36: 441-468.

79) Choi BR, Kim DH, Back DB, Kang CH, Moon WJ, Han JS, Choi DH, Kwon KJ, Shin CY, Kim BR, Lee J, Han SH, Kim HY. Characterization of White Matter Injury in a Rat Model of Chronic Cerebral Hypoperfusion. Stroke 2016; 47: 542-577.

80) Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK. Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. Exp Neurol 2018; 299: 241-251.

81) Barichello T, Simoes LR, Quevedo J, Zhang XY. Microglial Activation and Psychotic Disorders: Evidence from Pre-clinical and Clinical Studies. Curr Top Behav Neurosci 2020; 44: 161-205.

82) Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci 2003; 23: 297-302.

83) Tochigi M, Okazaki Y, Kato N, Sasaki T. What causes seasonality of birth in schizophrenia? Neurosci Res 2004; 48: 1-11.

84) Werenberg Dreier J, Nybo Andersen AM, Hvolby A, Garne E, Andersen PK, Berg-Beckhoff G. Fever and infections in pregnancy and risk of attention deficit/ hyperactivity disorder in the offspring. J Child Psychol Psychiatry 2016; 57: 540-548.

85) Lombardo MV, Moon HM, Su J, Palmer TD, Courchesne E, Pramparo T. Maternal immune activation dysregulation of the fetal brain transcriptome and relevance to the pathophysiology of autism spectrum disorder. Mol Psychiatry 2018; 23: 1001-1013.

86) Yamashita Y, Fujimoto C, Nakajima E, Isagai T, Matsuishi T. Possible association between congenital cytomegalovirus infection and autistic disorder. J Autism Dev Disord 2003; 33: 455-459.

87) Lintas C, Altieri L, Lombardi F, Sacco R, Persico AM. Association of autism with polyomavirus infection in postmortem brains. J Neurovirol 2010; 16: 141-149.

88) Deykin EY, Macmahon B. Viral exposure and autism. Am J Epidemiol 1979; 109: 628-638.

89) Meyer U. Prenatal poly(I:C) exposure and other developmental immune activation models in rodent systems. Biol Psychiatry 2014; 75: 307-315.

90) Garcia-Valtanen P, van Diermen BA, Lakhan N, Lousberg EL, Robertson SA, Hayball JD, Diener KR. Maternal host responses to poly(I:C) during pregnancy leads to both dysfunctional immune profiles and altered behaviour in the offspring. Am J Reprod Immunol 2020; 84: e13260.

91) Littauer EQ, Esser ES, Antao OQ, Vassilieva EV, Compans RW, Skountzou I. H1N1 influenza virus infection results in adverse pregnancy outcomes by disrupting tissue-specific hormonal regulation. PLoS Pathog 2017; 13: e1006757.

92) Ghiani CA, Mattan NS, Nobuta H, Malvar JS, Boles J, Ross MG, Waschek JA, Carpenter EM, Fisher RS, de Vellis J. Early effects of lipopolysaccharide-induced inflammation on foetal brain development in rat. ASN Neuro 2011; 3: e00068.

93) Atladóttir H, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: An exploratory study. Pediatrics 2012; 130: e1447-e1454.

94) Zerbo O, Iosif A-M, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. J Autism Dev Disord 2013; 43: 25-33.

95) Advisory Committee on Immunization Practices. ACIP Recommendations. 2021. Available online: https://www.cdc.gov/vaccines/acip/recommendations.html

96) Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women — advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep 2012; 62: 131-135.

97) Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices—United States, 2013–2014. MMWR Morb Mortal Wkly Rep 2013; 62: 1-43.

98) Di Pietro A, Visalli G, Antonuccio GM, Facciolà A. Today's vaccination policies in Italy: The National Plan for Vaccine Prevention 2017-2019 and the Law 119/2017 on the mandatory vaccinations. Ann Ig 2019; 31: 54-64.

99) Strassberg ER, Power M, Schulkin J, Stark LM, Mackeen AD, Murtough KL, Paglia MJ. Patient attitudes toward influenza and tetanus, diphtheria and acellular pertussis vaccination in pregnancy. Vaccine 2018; 36: 4548-4554.

100) Visalli G, Facciolà A, Mazzitelli F, Laganà P, Di Pietro A. Health education intervention to improve vaccination knowledge and attitudes in a cohort of obstetrics students. J Prev Med Hyg 2021; 62: E110-E116.

101) Jarrett C, Wilson R, O'Leary M, Eckersberger E, Larson HJ. SAGE Working Group on Vaccine Hesitancy. Strategies for addressing vaccine hesitancy - A systematic review. Vaccine 2015; 33: 4180-4190.

102) Facciolà A, Visalli G, Orlando A, Bertuccio MP, Spataro P, Squeri R, Picerno I, Di Pietro A. Vaccine hesitancy: An overview on parents' opinions about vaccination and possible reasons of vaccine refusal. J Public Health Res 2019; 8: 1436.

103) Abdullahi LH, Kagina BM, Ndze VN, Hussey GD, Wiysonge CS. Improving vaccination uptake among adolescents. Cochrane Database Syst Rev 2020; 1: CD011895.

104) Facciolà A, Visalli G, Laganà P, La Fauci V, Squeri R, Pellicanò GF, Nunnari G, Trovato M, Di Pietro A. The new era of vaccines: the "nanovaccinology". Eur Rev Med Pharmacol Sci 2019; 23: 7163-7182.

105) Tregoning JS, Brown ES, Cheeseman HM, Flight KE, Higham SL, Lemm NM, Pierce BF, Stirling DC, Wang Z, Pollock KM. Vaccines for COVID-19. Clin Exp Immunol 2020; 202: 162-192.

106) Spong CY, Bianchi DW. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. JAMA 2018; 319: 337-338.

107) Beigi RH, Krubiner C, Jamieson DJ, Lyerly AD, Hughes B, Riley L, Faden R, Karron R. The need

for inclusion of pregnant women in COVID-19 vaccine trials. Vaccine 2021; 39: 868-870.

108) Bianchi DW, Kaeser L, Cernich, AN. Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines. JAMA 2021; 325: 1041-1042.

109) Klein SL, Creisher PS, Burd I. COVID-19 vaccine testing in pregnant females is necessary. J Clin Invest 2021; 131: e147553.

110) Riley LE, Jamieson DJ. Inclusion of Pregnant and Lactating Persons in COVID-19 Vaccination Efforts. Ann Intern Med 2021; 174: 701-702.

111) Mullard A. Flooded by the torrent: The COVID-19 drug pipeline. Lancet 2020; 395: 1245-1246.

112) Food and Drug Aministration. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trial. 2018. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnant-women-scientific-and-ethical-considerations-inclusion-clinical-trials

113) HHS Task Force on Research Specific to Pregnant Women and Lactating Women. Report to Secretary, Health and Human Services Congress; 2018. Available online: https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf

114) American College of Obstetricians & Gynecologists. Vaccinating Pregnant and Lactating Patients against COVID-19. 2020. Available online: https://www.acog.org/en/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-Pregnant-and-Lactating-Patients-Against-COVID

115) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC. C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383: 2603-2615.

116) Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech B, McGettingan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T. COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384: 403-416.

117) Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, McCullough MP, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott A, Flach B, Doria-Rose NA, Corbett KS, Morabito KM, O'Dell S, Schmidt SD, Swanson II PA, Padilla M, Mascola JR, Neuzil KM, Bennett H, Sun W, Peters E, Makowski M, Albert J, Cross K, Buchanan W, Pikaart-Tautges R, Ledgerwood JE, Graham BS, Beigel JH. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020; 383: 1920-1931.

118) Food and Drug Aministration. Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Announcement. 2021. Available online: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announceme

119) Centers for Disease Control and Prevention. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine—United States 2021. Available online: https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e1.htm

120) Alberer M, Gnad-Vogt U, Hong HS, Mehr KT, Backert L, Finak G, Gottardo R, Bica MA, Garofano A, Koch SD, Fotin-Mleczek M, Hoer I, Clemens R. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: An open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet 2017; 390: 1511-1520.

121) Richner JM, Himansu S, Dowd KA, Butler SL, Salazar V, Fox JM, Julander JG, Tang WW, Shresta S, Pierson TC, Ciaramella G, Diamond MS. Modified mRNA Vaccines Protect against Zika Virus Infection. Cell 2017; 168: 1114-1125.e10.

122) Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines-A new era in vaccinology. Nat Rev Drug Discov 2018; 17: 261-279.

123) Feldman RA, Fuhr R, Smolenov I, Mick Ribeiro A, Panther L, Watson M, Senn JJ, Smith M, Almarsson Ö, Pujar HS, Laska ME, Thompson J, Zaks T, Ciaramella G. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019; 37: 3326-3334.

124) Maruggi G, Zhang C, Li J, Ulmer JB, Yu D. mRNA as a Transformative Technology for Vaccine Development to Control Infectious Diseases. Mol Ther 2019; 27: 757-772.

125) Zhang C, Maruggi G, Shan H, Li J. Advances in mRNA Vaccines for Infectious Diseases. Front Immunol 2019; 10: 594.

126) Craig AM, Hughes BL, Swamy GK. Coronavirus disease 2019 vaccines in pregnancy. Am J Obstet Gynecol MFM 2021; 3: 100295.

127) Food and Drug Aministration. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020: FDA Briefing Document, Pfizer-BioNTech COVID-19 Vaccine. 2021. Available online: https://www.fda.gov/media/144245/download

128) BioNTech. Pfizer and Biontech Commence Global Clinical Trial to Evaluate COVID-19 Vaccine in Pregnant Women. 2021. Available online: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate

129) Moderna, Frequently Asked Questions: What Is Known about the Safety of the Vaccine for Special

Populations (Children, Pregnant Women, Elderly People)? 2021. Available online: https://www.modernatx.com/covid19vaccine-eua/providers/faq#patient-vaccination

130) GOV-UK, COVID-19: The Green Book, Chapter 14a. 2021. Available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/984310/Greenbook_chapter_14a_7May2021.pdf

131) National Center for Immunization & Respiratory Diseases, COVID-19 Vaccine Safety Update Advisory Committee on Immunization Practices (ACIP). 2021. Available online: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

132) Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, Baez AM, Shook LL, Cvrk D, James K, De Guzman R, Brigida S, Diouf K, Goldfarb I, Bebell LM, Yonker LM, Fasano A, Rabi SA, Elovitz MA, Alter G, Edlow AG. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol 2021; 225: 303.e1-303.e17.

133) Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, Marquez PL, Olson CK, Liu R, Chang KT, Ellington SR, Burkel VK, Smoots AN, Green CJ, Licata C, Zhang BC, Alimchandani M, Mba-Jonas A, Martin SW, Gee JM, Meaney-Delman DM. The CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med 2021; 384: 2273-2282.

134) Society for Maternal Fetal Medicine, Society for Maternal-Fetal Medicine (SMFM) Statement: SARS-CoV-2 Vaccination in Pregnancy. 2020. Available online: https://s3.amazonaws.com/cdn.smfm.org/media/2591/SMFM_Vaccine_Statement_12-1-20_(final).pdf.

135) Academy of Breastfeeding Medicine. ABM STATEMENT-Considerations for COVID-19 Vaccination in Lactation. 2020. Available online: https://www.bfmed.org/abm-statement-considerations-for-covid-19-vaccination-in-lactation.

136) American College of Obstetricians & Gynecologists. COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care. 2020. Available online: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care.

137) Food and Drug Aministration, Moderna COVID-19 Vaccine. 2021. Available online: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine.

138) Refuerzo JS, Alexander JF, Leonard F, Leon M, Longo M, Godin B. Liposomes: A nanoscale drug carrying system to prevent indomethacin passage to the fetus in a pregnant mouse model. Am J Obstet Gynecol 2015; 212: 508.e1-508.e7.

139) Rasmussen SA, Kelley CF, Horton JP, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) Vaccines and Pregnancy: What Obstetricians Need to Know. Obstet Gynecol 2021; 137: 408-414.

140) Perl SH, Uzan-Yulzari A, Klainer H, Asiskovich L, Youngster M, Rinott E, Youngster I. SARS-CoV-2-Specific Antibodies in Breast Milk After COVID-19 Vaccination of Breastfeeding Women. JAMA 2021; 325: 2013-2014.

141) Rottenstreich A, Zarbiv G, Oiknine-Djian E, Zigron R, Wolf DG, Porat S. Efficient maternofetal transplacental transfer of anti- SARS-CoV-2 spike antibodies after antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Clin Infect Dis 2021; 73: 1909-1912.

142) Ferré C, Callaghan W, Olson C, Sharma A, Barfield W. Effects of Maternal Age and Age-Specific Preterm Birth Rates on Overall Preterm Birth Rates-United States, 2007 and 2014. MMWR Morb Mortal Wkly Rep 2016; 65: 1181-1184.

143) Boghossian NS, Geraci M, Edwards EM, Horbar JD. Morbidity and Mortality in Small for Gestational Age Infants at 22 to 29 Weeks' Gestation. Pediatrics 2018; 141: e20172533.

144) Panagiotakopoulos L, McCarthy NL, Tepper NK, Kharbanda EO, Lipkind HS, Vazquez-Benitez G, McClure DL, Greenberg V, Getahun D, Glanz JM, Naleway AL, Klein NP, Nelson JC, Weintraub ES. Evaluating the Association of Stillbirths After Maternal Vaccination in the Vaccine Safety Datalink. Obstet Gynecol 2020; 136: 1086-1094.

145) Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, Ring L, Landau R, Purisch S, Friedman AM, Fuchs K, Sutton D, Andrikopoulou M, Rupley D, Sheen JJ, Aubey J, Zork N, Moroz L, Mourad M, Wapner R, Simpson LL, D'Alton ME, Goffman D. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM 2020; 2: 100118.

146) Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J, Yang H, Hou W, Zhang Y. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395: 809-815.

147) Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020; 222: 521-531.

148) Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati, M, Vecchiet J, Nappi L, Scambia G, Berghella V, D'Antonio F. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020; 2: 100107.

149) Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalili SR, Behforouz A, Ferdosian F, Bahrami R. Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review. Fetal Pediatr Pathol 2020; 39: 246-250.

150) Kirtsman M, Diambomba Y, Poutanen SM, Malinowski AK, Vlachodimitropoulou E, Parks WT, Erdman L, Morris SK, Shah PS. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ 2020; 192: E647-E650.

151) Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, Zheng C. Pregnancy and Perinatal Outcomes of Women with Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. Am J Roentgenol 2020; 215: 127-132.

152) Peng J, Li R, Yin H, Tang F, Xie H, Li M, Zhao Y. A case report of a pregnant woman infected with coronavirus disease 2019 pneumonia. Medicine (Baltimore) 2020; 99: e21335.

153) Vivanti AJ, Deruelle P, Picone O, Guillaume S, Roze JC, Mulin B, Kochert F, De Beco I, Mahut S, Gantois A, Barasinski C, Petitprez K, Pauchet-Traversat AF, Droy A, Benachi A. Follow-up for pregnant women during the COVID-19 pandemic: French national authority for health recommendations. J Gynecol Obstet Hum Reprod 2020; 49: 101804.

154) Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, Liu Y, Xiao J, Liu H, Deng D, Chen S, Zeng W, Feng L, Wu J. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis 2020; 20: 559-564.

155) Bwire GM, Njiro BJ, Mwakawanga DL, Sabas D, Sunguya BF. Possible vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19: A living systematic review. J Med Virol 2021; 93: 1361-1369.

156) Chi J, Gong W, Gao Q. Clinical characteristics and outcomes of pregnant women with COVID-19 and the risk of vertical transmission: a systematic review. Arch Gynecol Obstet 2021; 303: 337-345.

157) Ciapponi A, Bardach A, Comandé D, Berrueta M, Argento FJ, Rodriguez Cairoli F, Zamora N, Santa María V, Xiong X, Zaraa S, Mazzoni A, Buekens P. COVID-19 and pregnancy: An umbrella review of clinical presentation, vertical transmission, and maternal and perinatal outcomes. PLoS One 2021; 16: e0253974.

158) De Medeiros KS, Sarmento ACA, Costa APF, Macêdo LTA, da Silva LAS, de Freitas CL, Simões ACZ, Gonçalves AK. Consequences and implications of the coronavirus disease (COVID-19) on pregnancy and newborns: A comprehensive systematic review and meta-analysis. Int J Gynaecol Obstet 2021. Online ahead of print.

159) Jafari M, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, Basirjafari S, Mohammadi M, Rasmussen-Ivey C, Razizadeh MH, Nouri-Vaskeh M, Zarei M. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. Rev Med Virol 2021; 31: 1-16.

160) Lassi ZS, Ana A, Das JK, Salam RA, Padhani ZA, Irfan O, Bhutta ZA. A systematic review and meta-analysis of data on pregnant women with confirmed COVID-19: Clinical presentation, and pregnancy and perinatal outcomes based on COVID-19 severity. J Glob Health 2021; 11: 05018.

161) Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ 2021; 193: E540-E548.

162) U.S. National Library of Medicine, 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. 2021. Available online: https://clinicaltrials.gov/ct2/show/NCT04754594.

163) U.S. National Library of Medicine, Moderna COVID-19 Vaccine mRNA-1273 Observational Pregnancy Outcome Study. 2021. Available online: https://clinicaltrials.gov/ct2/show/NCT04958304

164) U.S. National Library of Medicine, An Open-label, Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.COV2.S in Healthy Pregnant Participants. 2021. Available online: https://clinicaltrials.gov/ct2/show/NCT04765384.