

Review

# Viral Infection, COVID-19 in Pregnancy and Lactating Women: What Is Known?

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**Abstract:** Introduction. Viral infections during pregnancy have always been considered to cause complications and adverse events and birth defects during pregnancy. In particular, we do not have any therapeutic or preventive tools aimed at protecting the mother and fetus during the gestational period during pandemics. Methods. The studies were identified by using the PubMed database published until 30 April 2021. The search was performed by using the following keywords: viral infection, SARS-CoV-2, COVID-19, vaccine, pregnancy, gestational period, pandemics, vaccination, complication, adverse events, drugs. Results. It has been reported that viral infections are considered to cause complications and adverse events during pregnancy. In this regard, pregnancy is associated with higher mortality rates and complications during viral infections. In fact, maternal immunization represents a unique approach to protect newborns from several infectious diseases. Conclusion. European Board and College of Obstetrics and Gynecology (EBCOG) and International public health institutions (WHO, CDC) report the recommendations about the use of vaccines during pregnancy.

**Keywords:** viral infection; SARS-CoV-2; COVID-19; vaccine; pregnancy; mortality; gestational period; pandemics; vaccination; complication; adverse events; drugs



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## 1. Introduction

Viral infections during pregnancy have always been considered to cause complications and adverse events and birth defects during pregnancy. In the real world to date, unfortunately, we do not have any therapeutic or preventive tools aimed at protecting the mother and fetus during the gestational period during pandemics. In particular, from the data available so far, the epidemiology and symptoms of COVID-19 disease in pregnancy appear to be similar to the general population. It has been reported that vertical transmission of the SARS-CoV-2 virus is possible, although, to date, it is still considered a rare event. It is conceivable that most pregnant patients infected with the COVID-19 virus have mild or moderate flu symptoms. More serious symptoms, such as pneumonia, in fact, seem to be more common in the elderly population or in subjects suffering from chronic diseases. As a precaution, pregnant women are considered the most vulnerable, in particular in the first trimester during embryogenesis and for symptomatic patients. This is because, although there are no data relating to greater risk, not all the potential effects that the virus could cause on the body of a pregnant woman are known. At the moment, there are no data to indicate whether spontaneous birth is preferable in case of coronavirus infection (suspected or confirmed) than a cesarean section. However, in the event of breathing difficulties that make it necessary to deliver the baby as soon as possible, a cesarean is recommended. Waterbirth is not recommended in case of coronavirus infection (suspected or confirmed). Actually, there is no report that the virus can be transmitted through breastfeeding. Furthermore, breastfeeding is preferable and has numerous benefits for the newborn's immune system. The aim of our narrative review is to

describe the therapeutic or preventive tools for the mother and fetus during the gestational period and, in particular during the COVID-19 pandemic.

## 2. Methods

This is a narrative review. The studies were identified by using the PubMed database published until 30 April 2021. The search was performed by using the following keywords: viral infection, SARS-CoV-2, COVID-19, pregnancy, gestational period, pandemics, vaccination, complication, adverse events, drugs. Clinical trials, retrospective, and prospective studies were included. Two authors (T.C. and P.C.) reviewed all study abstracts. Studies were included if they described the characteristics of viral infection in pregnancy. Studies written in languages other than English were excluded. All selected studies were qualitatively analyzed. The work is aimed at discussing the most recent acquisitions regarding the relationship between COVID-19 and pregnancy. Given the growing increase in literary work on this subject, it is clear that it is necessary to deal with each appearance. The maximum number of works to be included in the bibliography has been set at 150 citations.

## 3. Pathogenesis of Viral Infections in Pregnancy

Viral infections during pregnancy have always been considered to cause complications and adverse events and birth defects during pregnancy, in particular in symptomatic patients and in the first trimester during embryogenesis [1]. In the real world to date, unfortunately, we do not have any therapeutic or preventive tools aimed at protecting the mother and fetus during the gestational period during pandemics. On the other hand, it has been reported [1] that viruses rarely cross the placental barrier. However, when this happens, and the virus reaches the fetus, it can cause serious birth defects. The maternal–fetal interface plays a decisive role in the prevention of the diffusibility of viruses in the fetal microenvironment since it includes cells that contribute to the correct development of the fetus. The maternal interface is constituted by the stroma of the uterus. This consists of decidual cells, immune cells including NK lymphocytes, cells of the monocyte-macrophage lineage, cells dendritic cells (DCs) specializing in the capture of antigens from viral exposure, and regulatory T cell (Treg) cells, which constitute a cell population that suppresses other immunocytes and mediates peripheral tolerance. The fetal interface is made up of placental villi, which contain fetal blood vessels, cytotrophoblasts, and the multinucleated syncytiotrophoblast in direct contact with maternal blood. Of these tissues, the extravillous trophoblast is in direct contact with the decidua cells, including maternal immune cells, endothelial cells, and saprophytic microorganisms present in the uterine ecosystem. Due to this complexity of the anatomical and organizational system of the maternal–fetal cell system, viruses can gain access within the decidua and placenta by the lower reproductive tract or for hematogenous transmission [1–3]. Viral tropism for the decidua and placenta depends on the intensity of the viral entry receptor expression and the maternal immune response. The virulence of the virus and the correct activation of these defense factors vary according to the type of cell affected and the gestational age. Therefore, the virus–host interaction during pregnancy is complex and variable. After access to the upper reproductive tract, viral tropism for the decidua and placenta depends both on the intensity of the viral entry receptor expression by the cellular component of these issues and on the maternal immune response induced in response to the virus. The virulence and the correct activation of these defense factors vary according to the type of cell affected and the gestational age. In particular, they largely depend on changes in the uterine environment and the efficiency of maternal immunity. To this regard, innate immune cells, including NK lymphocyte cells, dendritic cells, and macrophages, and the maternal humoral response play a fundamental role in the regulation and control of infection and, consequently, in determining the severity of the infectious process. The innate immune cells present at the maternal–fetal interface engulf the viral complexes and can kill infected cells, while antibodies facilitate viral clearance. Unlike non-pregnant women, during pregnancy the function of the innate immune system at the uterine level

is influenced and regulated by the fetoplacental unit. In summary, the viral route of transmission, the abundance of permissive cell types (which change with gestational age), and maternal immune function all influence viral infections at the maternal–fetal interface. Taking into account all explained elements and considering that pregnant women have been carefully observed during the COVID-19 pandemic, pregnancy-specific immune adaptation is known to increase the risk for infections. Recent evidence indicates that even though most pregnant women have a mild or asymptomatic course, a severe course of COVID-19 and a higher risk of progression to diseases have also been described, along with a heightened risk for pregnancy complications. Yet, vertical transmission of the virus is rare, and the possibility of placental SARS-CoV-2 infection as a prerequisite for vertical transmission requires further studies [4].

#### 4. Viral Infection and Maternal Health

The higher mortality in pregnancy, during viral infection, is not well defined [5]. Unfortunately, little is known about the role of the mother's response to viral pathogens during pregnancy. Probably, the placental response to the virus is directly responsible for the severity of the disease. In particular, it has been reported that the placenta is a crucial mediator of the maternal response to viral infection [6,7]. Pregnant women have higher mortality rates associated with varicella virus infection, with a high risk of having a clinical course that can be complicated by pneumonia during pregnancy [5–10]. This infection is more likely to cause death [11,12]. Furthermore, H1N1 influenza virus infections are particularly dangerous for pregnant women, as they develop more severe flu-related complications that in some cases lead to increased hospitalization and death [13–17]. The most common virus identified to date at the maternal–fetal interface is CMV, a member of the Herpesviridae family. CMV interacts with ubiquitously expressed heparin sulfate on the cell surface and then penetrates cells via interactions with integrin subunits [18,19]. Roles for other receptors, such as EGFR and PDGFR- $\alpha$ , have also been reported, but those findings have been contradicted, and the role of these receptors in CMV infection remains disputed [20,21]. Cytomegalovirus (CMV) infection can affect pregnant women because the virus resides in the faeces, blood, urine, and vaginal, oral-pharyngeal, and cervical secretions. The disease is transmitted through direct contact with the infected person (rarely through objects). Most of the time, the disease begins with no symptoms or with modest symptoms such as a slight fever and a sense of fatigue. Having contracted the disease does not produce immunity. In fact, once the activity phase of the virus ceases, the cytomegalovirus assumes latent stability within the organism. In a situation where the immune defenses are insufficient, the virus can reactivate. CMV in pregnancy is extremely common, but the product of conception can in rare cases be severely damaged. The interest in pregnancy in this type of infection is due to the possibility of transmission of the infection from the mother to the fetus. This can occur mainly through the blood, which crossing the placenta, can carry the virus from the mother to the fetus. Fetal cytomegalovirus infection does not usually cause miscarriage or malformations but can lead to disease affecting various fetal organs. More frequently, it can cause intrauterine growth retardation of the fetus, liver pain and microcephaly. In severe cases, children who actually contract the disease from their mother may die within months of birth or suffer permanent damage of varying degrees. Another member of the Herpesviridae family, herpes simplex virus (HSV), is estimated to infect the decidua and/or placenta in 6 to 14% of pregnancies [21,22] and, like CMV, is more likely to be identified in the decidua than in the placenta [21,23]. Deciduitis and villitis have been described in relation to HSV infections [24], which may explain the association between primary maternal infection with HSV and increased risk of miscarriage and fetal death [25]. Heparan sulfate, herpesvirus entry mediator A (HveA), HveB, and HveC are the entry receptors for HSV-1 and -2. They are not expressed on the surface of the syncytiotrophoblast but are expressed on the extravillous trophoblast [26]. Finally, there is growing evidence suggesting that the placental response to viruses is directly responsible for disease severity. For example, pregnant women infected with

Lassa fever had higher mortality rates than non-pregnant women with the infection. The Lassa virus replicates at very high levels in the placenta [27], and the risk of maternal death increases with the length of gestation, [28] and the size of the placenta. Furthermore, evacuation of the uterus significantly improves the mother's chances of survival. Since the placenta regulates the maternal immune system and can itself respond to pathogens it is probably an important mediator of the maternal response to viral infection, regardless of whether the placenta is directly infected [7].

## 5. COVID-19 Virus Infection

Coronavirus is a linear stranded RNA virus [29–31]. The envelope of the coronavirus is composed of bilayer lipids and is provided with some spiny processes on the outside of the crown-like membrane. The coronavirus genome size is 26–32 kb, and its structure is highly conserved. About 67% of its genome is used to encode replication enzymes [32,33]. It has been reported that SARS-CoV-2 enters the host cell by binding its S proteins to ACE2 receptors located on the surface of the host cells, with the affinity between SARS-CoV-2 and ACE2 being 10–20 times higher than that of SARS-CoV-1 [34]. After, the virus uses the cell's protein synthesis system to produce replicas, other structural proteins, and helper proteins. On 30 January 2020, COVID-19 was declared a public health emergency by the WHO. The new coronavirus is described as SARS-CoV-2, known as “severe acute respiratory syndrome coronavirus 2” [35]. During pregnancy, women require great attention due to the physiological changes that make them more susceptible to the virus [36]. Therefore, it is crucial to know why pregnant women are at increased risk during infectious disease and to plan appropriate management.

## 6. Pathophysiology of COVID-19 Infection in Pregnancy

We report the physiological changes in the respiratory, circulatory, secretory, and immune systems during pregnancy.

### 6.1. Changes in the Respiratory System

In the first trimester of pregnancy, progesterone and muscle relaxants induce the relaxation of the muscle-ligamentous structures [37]. These anatomical modifications and the reduced compliance of the chest wall induce a reduction of 20 to 30% of the functional residual capacity [38]. However, high levels of progesterone stimulate the respective receptors in the hypothalamus, increasing the Tidal volume by 50% compared to non-pregnant women [39]. In addition, progesterone-mediated changes in the nasal mucosa can lead to the adhesion of viruses such as SARS-CoV-2 in the upper respiratory tract [40,41]. Additionally, physiological changes in pregnancy increase the severity of the disease [42]. In fact, even the presence of adjustments in the cardiovascular and circulatory functions of pregnant women, such as increased oxygen consumption, or reduced functional residual capacity, could worsen the severity of hypoxic respiratory insufficiency in women affected by SARS-CoV-2 infection [43]. In this regard, during virus infection, increases in the pulmonary vascular resistance can consequently lead to acute pulmonary hypertension, and therefore heart failure [44].

### 6.2. Changes in the Immune System

The pregnant woman will undergo a series of immune changes that can increase the susceptibility of the mother to infectious diseases [45,46]. Danza et al. observed that the total number of CD3+ T cells decreased during pregnancy [47]. In addition, the increase in estrogen and progesterone in the first trimester of pregnancy induces a reversible involution and hypofunction of the thymus, with a decrease in CD4+ and CD8+ T cells [48]. This is associated with changes in the number and function of NK and CD4+ cells in the pregnant woman, as well as a reduction in the immunological response of T cells [49]. However, this can influence a higher incidence of infectious diseases [50,51] and the susceptibility of pregnant women with the COVID-19 virus [52].

### 6.3. ACE2 Expression Increased during Pregnancy

ACE has been considered a key regulator of blood pressure in mammals [53]. The ACE receptor, present in two different isoforms: ACE1 and ACE2, capable of lysing a bioactive angiotensin II peptide with vasodilatory activity and effect on systemic blood pressure [54]. Recent studies have shown that ACE2 is the access that SARS-CoV-2 uses to enter into host cells, and the upregulation of ACE2 could increase the susceptibility of COVID-19 [55]. Studies have shown that smoking and pregnancy lead to an increased expression of ACE2 at the cellular level, and susceptibility to SARS-CoV-2 infection is increased [56]. However, it has been reported that an increase in ACE2 levels is able to regulate blood pressure during pregnancy. Furthermore, ACE2 is involved in post-infection regulation, including immune response, cytokine secretion, and viral genome replication [57]. Several reasons exist to explain the possible vertical transmission in the case of COVID-19. First of all, there is the marked tissue tropism of COVID-19, largely related to the binding of the angiotensin-converting enzyme 2 (ACE2) receptor to entry in the host cells. ACE2 is expressed in the placenta [58], and its presence was found in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle from both primary and secondary villi [59]. A recent systematic review also found evidence that ACE2 is expressed in gynecologic organs such as the ovary, uterus, and vagina [60]. Overall, ACE2 expression is present in numerous tissues that are directly involved with the developing pregnancy. These data were further supported by the discovery of single-cell RNA sequencing analysis that found ACE2 expression in stromal, perivascular, placental, and decidual cells at the maternal–fetal interface [61]. Several authors suggested that viral entry into placenta cells may still occur using a combination of ACE2 and an atypical cell entry mediator [62]. In addition, concerning vertical transmission, the presence of immunoglobulin M (IgM) antibodies was demonstrated in neonates born to mothers who had positive results for COVID-19 [63,64]. Moreover, several recent case reports provided evidence that COVID-19 can infect the placenta, as confirmed by the presence of SARS-CoV-2 viral RNA and protein in the placenta and evidence of virions found within the syncytiotrophoblast [65–67]. The best evidence to date for transplacental transmission of SARS-CoV-2 was seen in the case report by Vivanti et al. [68], which showed not only viral RNA and protein in the placenta, but also viral RNA in the amniotic fluid and neonatal blood sampled at birth. Data are emerging for a number of cellular mediators/receptors that may also facilitate host cell infection by SARS-CoV-2, including CD147, glucose-regulated protein 78 (GRP78), angiotensin II receptor type 2 (AGTR2), the receptor for advanced glycation end products (RAGE), heparan sulfate, sialic acids, and neuropilin-1 (NRP1). Among them, NRPs are highly conserved, non-tyrosine kinase single transmembrane glycoproteins that are expressed in all vertebrates and are primarily co-receptors for various molecules (e.g., semaphorins and vascular endothelial growth factors). (VEGF) NRPs are involved in several physiological processes, including cell proliferation, angiogenesis, vascular permeability, immune function, neuronal development, and axon control [69].

## 7. Effects of Viral Infection on the Fetus

No evidence has been found that the development of a COVID-19 infection in the third trimester of pregnancy can lead to serious adverse outcomes [70,71]. Chen et al. [71] demonstrated, in COVID-19 positive mothers, that the screening tests for the virus were negative. Although there is no reported evidence of vertical transmission, the mother's immune response to viral infection tends to promote an inflammatory response, and it is characterized by an increase of inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF- $\alpha$  [72]. It has been reported that the increase of these cytokines is able to create malformations and morphological alterations of the circulatory system [73–75]. It has recently been proposed that COVID-19 results in systemic endothelial damage that, in adults, predisposes to the development of or exacerbation of already existing hypertension and other cardiovascular diseases and results in a severe COVID-19 course [76–79]. In particular, COVID-19 frequently induces hypercoagulability with both microangiopathy

and local thrombus formation [80]. Pregnant women represent an especially vulnerable population given their hypercoagulable state, with associated unique conditions. Hypertensive disorders of pregnancy are a group of conditions. The pathogenesis of these disorders is not well understood. However, systemic endothelial dysfunction, vascular hypoperfusion, and a systemic proinflammatory state have been implied as potential etiologies or components of the disease pathophysiology, especially in cases of pre-existing hypertension, obesity, or diabetes [81]. Of note, a narrative review found several cohort studies and case reports describing an association between maternal COVID-19 infection and placental's, such as evidence of maternal vascular hypoperfusion, particularly maternal vessel injury and intervillous thrombi. One may speculate that COVID-19 may result in the activation of endothelial damage pathways predisposing to the development of hypertensive disorders of pregnancy with associated adverse maternal and neonatal outcomes (i.e., prematurity, growth restriction) over the long term. Taking into account the various evidence of the present of COVID-19 viral RNA in numerous fetal or neonatal sources, and positive serology, vertical transmission of COVID-19 is highly likely. These data suggest that maternal COVID-19 infection, in the third trimester, appears to be associated with low rates of vertical transmission (approximately 3.2%) without significant consequence to the newborns. This low rate is consistent with recent transcriptomic data showing that placental cells co-expressing ACE2 and TMPRSS2 proteins required for SARS-CoV-2 viral cell entry are rare [45]. However, numerous questions remain to be addressed concerning the vertical transmission of this novel coronavirus. These include whether the virus can cross the placenta in utero and cause an infection in fetal tissues. Furthermore, it is necessary to understand whether susceptibility varies by gestational age and whether there is a gestational age at which the virus is more likely to infect and cross the placenta. When taking into account the pieces of evidence exposed in the report, several points still remain obscure. In particular, one example is regarding the risk of teratogenic effects of placental infection occurring in the first trimester. In addition, the possibility to determine whether there are any non-teratogenic fetal effects that can be reconditioned as effects of COVID-19 infection on the uterine vasculature and placental tissue (i.e., growth restriction; placental abnormalities such as, infarction, or stillbirth; hypertensive disorders of pregnancy). Finally, it was not clearly understood if the transmission of COVID-19 in newborns depends on the severity of the maternal disease or correlates with the clinical course. Further larger-scale studies are needed ideally across numerous countries to answer these questions. Therefore, some authors suggest the need for effective treatment in pregnant women infected with SARS-CoV-2 in order to prevent more serious effects on the future development of the mother and fetus [82]. It was also observed that the risk of spontaneous abortion and preterm birth is not increased in women who developed the infection in the third trimester of pregnancy [83,84]. An Egyptian study [84] described cases of maternal placenta with hydropic degeneration in women affected by the virus [82]. The recommendation for clinical practice is to test for SARS virus in women diagnosed with hydatiform mole [85]. It was shown that women diagnosed with COVID-19, compared to uninfected pregnant women, had a substantially higher risk of serious pregnancy complications, including preeclampsia/eclampsia/HELLP syndrome, ICU admission or referral to a level of higher care and infections requiring antibiotics, as well as preterm labor and low birth weight. The risk of maternal mortality was 1.6%, which is 22 times higher in the group of women diagnosed with COVID-19. These deaths were particularly more frequent in less developed regions, which implies that when health systems and especially critical care services are insufficient or unable to cope with an excessive increase of hospitalization, COVID-19 in pregnancy can be lethal. Reassuringly, we also found that asymptomatic women diagnosed with COVID-19 had similar outcomes to women without a COVID-19 diagnosis, with the exception of preeclampsia. In fact, it was shown that women diagnosed with COVID-19, already at high risk of preeclampsia and COVID-19 due to pre-existing overweight, diabetes, hypertension, and chronic heart and respiratory diseases, had an almost four times greater risk of developing preeclampsia/eclampsia, which may reflect the known association

with these comorbidities and/or the acute kidney injury that may occur in patients with COVID-19 [86]. Therefore, surgery should be delayed for at least 7 weeks after SARS-CoV-2 infection to reduce the risk of postoperative mortality and pulmonary complications. Furthermore, patients still symptomatic  $\geq 7$  weeks after SARS-CoV-2 infection and undergoing surgery also have an increased mortality rate. Decisions should be tailored to each patient, as the possible benefits of delaying surgery for at least 7 weeks after the diagnosis of SARS-CoV-2 must be balanced against the potential risks of delay. In particular, would advise caution [87] in performing surgical interventions in the early stages of infection, and therefore having to perform a cesarean prematurely puts the mother at a higher risk of complications and serious maternal and fetal mortality. Birth assistance paths during the pandemic were immediately created. In particular, a study [88] was conducted describing the tracing and control operations of positive people and their contacts. Recommended measures include testing for all contacts of identifiable positive subjects; use of masks by all staff; continuous monitoring of sick leave, both of internal and external staff, for example, those in charge of laundry or catering services; measures to ensure social distancing in all common environments; checks to verify compliance with hygiene and continuous staff training on prevention measures; direct and transparent communications to both healthcare personnel and patients. In many hospitals, the indicated outpatient services are normally guaranteed both in the consultatory/territorial service and in the context of hospital birth points. The precautions are taken to reduce the risk of contagion in carrying out the necessary and urgent diagnostic and instrumental services (ultrasound, cardiotocography, etc.), such as environments and equipment used, use of personal protective equipment for the staff and for the pregnant woman who has to perform the examination.

## 8. Care of Pregnant Patients with COVID-19

With regard to COVID-19 infection in pregnancy, it has been seen that the presence of any symptoms can be associated with an increase in morbidity and mortality. In particular, the rates of serious pregnancies and neonatal complications were higher in women who presented with fever and dyspnea, and if these symptoms had been present for several days. The risks of serious neonatal complications, including hospitalization in the NICU for 7 days or more, as well as the summary score of severe neonatal morbidity and its individual components, were also substantially higher in the group of women diagnosed with COVID-19. The increased neonatal risk remained after adjustment for previous preterm birth and preterm birth in index pregnancy; therefore, a direct effect on the newborn from COVID-19 is likely [86]. The pregnant woman with COVID-19 shows, in most cases, typical symptoms of upper respiratory tract involvement and general symptoms that simulate mild or moderate cases of cold or flu. However, cases have been reported with the rapid development of respiratory symptoms requiring hospitalization in infectious diseases, up to sub-intensive support. Signs of SARS-CoV-2 pneumonia were present in 45.2% of patients with predominantly mild to moderate clinical pictures, although some women were admitted to intensive care. The authors conclude by stating that cesarean delivery should be reserved for women with severe respiratory impairment, confirming a low risk of intrapartum transmission of the SARS-CoV-2 virus. A multicentric study [87] found that patients operated on within 6 weeks of SARS-CoV-2 diagnosis had an increased risk of 30-day postoperative mortality and 30-day postoperative pulmonary complications. These risks decreased at baseline in patients who underwent surgery  $\geq 7$  weeks after being diagnosed with SARS-CoV-2. These results were consistent in both low-risk (age  $< 70$  years, ASA 1–2 physical status, minor surgery) and high-risk (age  $\geq 70$  years, ASA 3–5 physical status, major surgery) subgroups. In conclusion, attention was immediately paid to the organizational aspects in order to properly maintain essential services for reproductive health during the emergency caused by the pandemic. The need to remain unaltered the standards of care for pregnancy, childbirth, and the puerperium, services for contraception and voluntary termination of pregnancy as well as those for sexually transmitted diseases, prevention, and support for women victims of violence, has favored that every hospital on

an international scale endows itself with appropriate diagnostic and therapeutic pathways even in the epic pandemic [88–90]. A multicentric study showed the importance of SARS-CoV-2 vaccination to the prevention of COVID-19-related postoperative complications and deaths [91]. It is likely that SARS-CoV-2 vaccination could prevent tens of thousands of postoperative deaths linked to COVID-19, especially in particular situations such as pregnancy. However, this could still face numerous obstacles related to vaccine supplies which are limited in most countries, especially developing countries, and due to the delay in starting the vaccination campaign. Furthermore, most governments are giving priority to vaccination of the population groups at the highest risk of mortality, and therefore pregnant women are excluded from this. Only when vaccines are administered to a larger and younger population will there be a decrease in the risk of maternal–fetal complications and lethality, a reduction in postoperative or neonatal intensive care pulmonary complications, thus reducing overall healthcare costs [92].

## 9. COVID-19 Infection, Pregnancy, and Therapy

There are a few aspects in relation to the pharmacological treatment of COVID-19 infection during pregnancy (Table 1). During pregnancy, pregnant women are at increased risk for severe COVID-19. Given the changes to the cardiopulmonary and immune systems, pregnant women with COVID-19 were more likely to be hospitalized and at increased risk of intensive care unit (ICU) admission and receipt of mechanical ventilation compared with non-pregnant women of reproductive age. Although vaccination is underway in many countries, pregnant women are often advised against it due to missing data on safety and efficacy during pregnancy. Medications that are already available to treat other conditions are presently being studied in clinical trials as potential treatments for COVID-19 [93]. Aspects relating to the pharmacological treatment of COVID-19 infection during pregnancy are poorly dealt with in the literature due to the scarce evidence available.

**Table 1.** Aspects in relation to the pharmacological treatment of COVID-19 infection during pregnancy.

| Risk Related COVID-19                                                                                                | Vaccine in Pregnancy                                 | Medications               |
|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|---------------------------|
| Severe COVID-19<br>Hospitalized<br>Increased risk for intensive care unit (ICU) admission and mechanical ventilation | Missing data on safety and efficacy during pregnancy | Scarce evidence available |

### 9.1. Steroids

Dexamethasone was associated with increased risks of prematurity and major congenital malformation MCM [93]. Palmsten et al. [94] showed that oral corticosteroid use during pregnancy was associated with a doubling of the risk of preterm birth in women with rheumatoid arthritis recruited within teratogen information services (MotherToBaby). Early pregnancy corticosteroid use has also been associated with increased risk of MCM [94–99], but no orofacial defect with dexamethasone use was reported in more recent pregnancy studies [100].

### 9.2. Azithromycin

Azithromycin use was associated with an increase in the risk of MCM. A recent population-based cohort study, using data from the Clinical Practice Research Datalink in the United Kingdom, has shown that use of macrolide antibiotics, including erythromycin, clarithromycin, or azithromycin during pregnancy was associated with an increased risk of overall major congenital malformations in children [101]. Similarly, a population-based cohort study using data from the Swedish Medical Birth Register has shown an association between early pregnancy erythromycin use and infant cardiovascular defects [102].

### 9.3. Heparin

Our findings on antithrombotics (mostly heparins) use and pregnancy are different from what has been published recently. The increased prevalence of adverse fetal/infant outcomes, including death, prematurity, and MCM, have been reported following heparin use [103]. However, in another more recent study performed by Shlomo et al. [104], no associations were found within an Israeli cohort of pregnant women. While heparin does not appear to cross the placenta, it may affect embryo and fetal development through interactions with the trophoblast and placental vasculature. Differences between the results found by Berard et al. [93] and those from Shlomo et al. [104] could be partly explained by their lack of adjustment for potential confounders such as gestational hypertension and diabetes, indications for heparin use, and lifestyles such as tobacco and alcohol use.

### 9.4. Chloroquine, Chloroquine Phosphate, and Hydroxychloroquine

The use of chloroquine [105] during pregnancy would have a minimal effect on gestation without reports of fetal damage in the main registers held by the WHO [106,107]. Hydroxychloroquine also appears to have a safety profile in pregnancy in the absence of significant increases in congenital diseases. Based on this evidence, hydroxychloroquine also appears to have an excellent safety profile in pregnancy in the absence of significant increases in congenital diseases or malformations, stillbirths, and prematurity [108]. In addition, chloroquine and potentially hydroxychloroquine are genotoxic [109]. In other situations (other dosages, other durations of treatment, other indications), their benefit/risk balance is not established yet. In the case of exposure during pregnancy, as a precaution, careful ultrasound monitoring, increased vigilance at birth (especially in case of prematurity), and ophthalmological monitoring of the child should be recommended [109]. Although these available medications are being considered as treatments for COVID-19, caution is warranted in pregnancy.

### 9.5. Interferon

Interferon (IFN- $\alpha$  and IFN- $\beta$ ) has been considered among the main and potential agents capable of suppressing the inflammatory response induced by COVID-19, interfering with viral replication by discarding pre-existing data on the efficacy of the molecule on other viruses. The antiviral effect of interferon has been demonstrated in subjects with SARS-CoV [110,111]. In pregnancy, interferon may be associated with the onset of primary thrombocytopenia, and therefore some authors [110,111] have conducted a meta-analysis to see if this condition may be an adverse effect on pregnant women. The results showed that the interferon did not significantly increase the risk of malformations. Therefore, in the case of COVID-19 during pregnancy, interferon could be effective and safe.

### 9.6. Antivirals

Lopinavir/ritonavir is an antiviral, ritonavir-boosted protease inhibitor. Ritonavir improves its pharmacokinetic profile, and by inhibiting cytochrome P450, isoenzyme 3A4 slows the metabolism of lopinavir and increases its pharmacological exposure. The association has proved effective in the treatment of HIV. Currently, lopinavir/ritonavir is recommended in many treatments [112–114]. During pregnancy, there are no studies about the use of these drugs in women with COVID-19. Berard et al. [93] and Powis et al. [114], investigating the association between indinavir, lopinavir/ritonavir, raltegravir, and saquinavir (HIV drugs) used during pregnancy, demonstrated an increased risk of prematurity, low birth weight, and small for gestational age. This drug may play a role in the treatment of COVID-19 during pregnancy. Remdesivir inhibits viral replication by competing with endogenous nucleotides for incorporation into replicating viral RNA via RNA-dependent RNA polymerase (RdRp). Remdesivir undergoes rapid metabolic conversion by intracellular kinases to its active nucleoside metabolite triphosphate (GS-443902) [115]. It was effective for severe COVID-19 in adults, but data in pregnant women

are limited to a single study that demonstrated that recovery rates were high with a low rate of serious adverse events [116,117].

### 9.7. Monoclonal Antibody Therapy

Tocilizumab is an IL-6 receptor inhibitor agent. However, data on the safety of tocilizumab in pregnant women and their newborns are few. Tocilizumab has shown no harmful effects in COVID-19 infected pregnant women and needs close monitoring [118]. Current management is largely focused on supportive care and the prevention of complications. In critically ill patients with COVID-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival, and mimicked the benefit of mechanical ventilation [118].

## 10. The Management of SARS-CoV-2 in Neonatal Intensive Care Units

Breindhal et al. [41] reported for the purposes of optimal hospitalization management, non-separation of the family unit is recommended. It is also very clear that other hospitalized boys and girls, their parents, and staff must be safeguarded. Therefore, strict adherence to preventive measures by parents and the use of PPE by staff must be of primary importance for the safety of the entire department, including the safety of operators and their families, while maintaining a high quality of care.

## 11. SARS-CoV-2 Infection and Breastfeeding

The WHO has expressed a favorable position regarding breastfeeding in the case of a suspected or confirmed mother. This position is justified by the fact that the virus was not detected in the breast milk, and there is no evidence of its transmission through breastfeeding. Furthermore, infants appear to be at low risk of COVID-19 infection. However, of the few confirmed cases in young children, most only had a mild or asymptomatic disease. It is well known that breastfeeding and skin-to-skin contact significantly reduce the risk of death. Therefore, the evidence confirms that the benefits of breastfeeding outweigh the potential risks of transmission of SARS-CoV-2 infection [45].

## 12. Vaccine and Pregnancy

It has been reported that maternal immunization is a crucial approach to protect newborns and young infants [119–121]. In this regard, vaccinations are an important topic in pregnant women. In particular, it has been reported that inactivated vaccines can be given before, during, and after pregnancy. Live vaccines should be given at least one month before pregnancy and avoided during pregnancy [122,123]. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine should be indicated between 27 and 36 weeks of gestation [121–123]. In particular, the Tdap vaccine should be administered immediately postpartum in any woman who has not previously received it. The hepatitis B (HBV) vaccine should be prescribed to pregnant women at higher risk of exposure to HBV. Live, attenuated influenza, measles, mumps, rubella (MMR) vaccine, varicella vaccines, human papillomavirus (HPV) and herpes zoster (HZV) vaccines are not recommended in pregnant women. The World Health Organization recommends the administration of the influenza vaccine in healthy women who are in the II or III trimester of pregnancy or with concomitant chronic conditions in any stage of gestation [70]. In relation to the SARS-CoV-2 vaccine, no data are available, but it is recommended in pregnancy at-risk [121–123]. In April 2021, the JCVI recommendation for pregnant women reported that the offered COVID-19 vaccination at the same time as the rest of the population is to be welcomed. The timing of the first dose should be decided on an individual basis. In particular, women at the highest risk may wish to have it as early as possible in pregnancy, and others may choose to wait until the end of the first trimester if they have concerns about the early gestation period. It should be before the third trimester as this is the time of the greatest COVID-19 risk.

### 13. Conclusions

In Table 2, we report the current recommendations for immunization during pregnancy. Viral infections during pregnancy have always been considered to cause complications and adverse events during pregnancy and birth defects. The higher mortality in pregnancy, during viral infection, is not well defined. Unfortunately, little is known about the role of a mother's response to viral pathogens during pregnancy. The pregnant woman will undergo a series of immune changes that can increase the susceptibility of the mother to infectious diseases. Medications that are already available to treat other conditions are presently being studied in clinical trials as potential treatments for COVID-19 [93]. Aspects relating to the pharmacological treatment of COVID-19 infection during pregnancy are poorly dealt with in the literature due to the scarce evidence available. In relation to the SARS-CoV-2 vaccine, no data are available, but it is recommended in pregnancy at-risk. Future studies are needed to confirm these data. Maternal immunization can improve maternal and child health. It has been reported that it can reduce maternal and infant morbidity and mortality. European Board and College of Obstetrics and Gynecology (EBCOG) and the International public health institutions (WHO, CDC) recommended the use of vaccines during pregnancy. Future studies are needed to confirm these data.

**Table 2.** Current recommendations for immunization during pregnancy [121–123] (modified).

| Population                    | Vaccine                                                                                                         | Type of Vaccine                                                           |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| <i>All pregnant women</i>     | Influenza<br>Tetanus Diphtheria, and<br>acellular Pertussis<br>COVID-19                                         | Inactive<br>Toxoid, Inactive<br>Current vaccine                           |
| <i>Pregnant women at risk</i> | Hepatitis A e B<br>Meningococcal<br>Pneumococcal<br>Human Papilloma Virus<br>Tetanus and Diphtheria<br>COVID-19 | Inactive<br>Inactive<br>Inactive<br>Inactive<br>Toxoid<br>Current vaccine |
| <i>Postpartum</i>             | Measles, Mumps, and Rubella<br>Varicella                                                                        | Live<br>Live                                                              |

### 14. Take Home Messages

1. There are still no certain data on whether pregnancy increases susceptibility to COVID-19. Although the data were initially unclear whether pregnant people are at increased risk for serious complications from COVID-19, other evidence suggests an increased risk.
2. Intrauterine transmission of SARS-CoV-2 has been documented [6], but appears to be rare. The reasons for this are unknown but may be related to the decreased expression of the ACE2 receptor and the TMPRSS2 serine protease that are required for SARS-CoV-2 cell entry. The role of other molecules such as neuropilin-1 (NRP1), has recently been demonstrated.
3. Several pregnancy outcome studies suggest that premature birth may occur more often among babies born to individuals with COVID-19, although the results have been inconsistent.
4. Hospitalization in an intensive care unit, invasive ventilation, extracorporeal membrane oxygenation, and death were all more likely among pregnant people than among non-pregnant women of reproductive age.
5. Transmission via breast milk appears to be unlikely.
6. Almost all vaccines are allowed during pregnancy if the benefits are expected to outweigh the potential risks, with the exception of live attenuated vaccines, which are contraindicated due to the theoretical risks of the virus crossing the placenta and

infecting the fetus. Therefore, pregnant women who meet the criteria for receiving the COVID-19 vaccine can choose to be vaccinated.

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