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RESEARCH ARTICLE

The Management of Covid-19 Infection in Pregnancy and Puerperium: From the World View to the Italian Reality

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ABSTRACT

Coronavirus disease 2019 (Covid-19) is characterized by severe acute respiratory syndrome and is an emerging disease. Considering the changes in maternal physiological and immune function during pregnancy, pregnant women may be at increased risk of being infected with Covid-19 and developing more complicated clinical events. Vertical transmission of the Covid-19 virus is possible although to this day 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 and therefore isolation and limitation of contact are recommended. At the moment there are no data to indicate whether spontaneous delivery is preferable in case of coronavirus infection (suspected or confirmed) to a cesarean section. However, in case of breathing difficulties that require delivery as soon as possible, a cesarean section is recommended. There is no evidence that the virus can be transmitted through breast milk. Furthermore, breastfeeding is preferable and has numerous benefits for the newborn's immune system. Since pregnant people appear to have a high risk of becoming seriously ill if they have an infection, vaccination is particularly important. In addition, there is evidence that vaccinated people have a lower risk of baby problems, such as stillbirth.

Keywords: management, COVID-19, viral infection, SARS-CoV-2, pregnancy, gestational period, pandemics, vaccination, complication, adverse events, and drugs

Background

Viral infections during pregnancy have always been considered to cause complications and adverse events during pregnancy and birth defects. It is also well known that viral infections affecting cells that are at the interface of the maternal-fetal circuit can affect the placental function, to the point of causing complications of the pregnancy itself with a higher incidence of spontaneous, delayed, or incomplete abortions, intrauterine growth of the fetus or a higher incidence of preterm delivery. 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 regulation of the correct functioning of the maternal immune system, and the protection against all microorganisms^{1, 2}. Coronaviruses are viruses with a nucleocapsid, non-segmented, single-stranded ribonucleic acid (RNA) envelope that can cause clinical changes ranging from the simplest such as a common cold syndrome to severe fetal disease. Studies have confirmed that both SARS-CoV-2 and SARS-CoV-1 enter the host cell by binding their S proteins to ACE2 receptors located on the surface of the host cells. Furthermore, electron microscopy studies demonstrated for the first time the molecular structure of the neocoronavirus protein S and found that the affinity between neocoronavirus and ACE2 was 10 ~ 20 times higher than that of SARS-CoV-1^{3, 4}. After the protein S binds to the ACE2 receptor, it is cleaved in the S1 region by the TMPRSS2 cell proteases to expose the fusion region located in the S2 region, thus facilitating the fusion of the virus envelope and cell membrane system, aiding the nucleocapsid viral to enter the cytoplasm⁵⁻⁷. Pregnant women are at high risk for viral infectious diseases, which have been shown to be closely related to physiological changes in the respiratory, circulatory, secretory, and immune systems during pregnancy. Recent studies have shown that ACE2 is the access that Covid-19 uses to enter host cells and the upregulation of ACE2 could increase the susceptibility of Covid-19⁵. Studies have shown that smoking and pregnancy lead to an increased expression of ACE2 at the cellular level and therefore in pregnant women, especially smokers, the susceptibility to Covid-19 infection is increased⁵. Studies speculate that an increase in ACE2 level is able to regulate blood pressure during pregnancy and this adaptation could be a favourable condition for Covid-19 infection. Furthermore, ACE2 is not only a receptor but is also involved in post-infection regulation, including immune response, cytokine secretion, and viral genome replication⁶.

There are limited reports on the impact of Covid-19 during pregnancy. As a result, the potential effects on fetal and neonatal outcomes are unclear, and the various national health systems have urgently had to establish maternal care pathways for the management of pregnant women with Covid-19, parallel to those used for follow-up of pregnant women not affected by covid-19. The purpose of this study was to compare the various experiences on the management of pregnancy during the Covid-19 pandemic coming from the world panorama of scientific literature matured during these years, with a model of pregnancy management developed in the context of the Italian territory.

Methods

This is a narrative review that compares the main scientific evidence gained in the experience of the management of pregnancy and the puerperium during the pandemic linked to Covid-19 with the protocols used in the Italian health reality in order to manage with a high profile of effectiveness and safety. The studies were identified by using the PubMed database, published until 31st July 2022. The search was performed by using the following keywords: viral infection, SARS-CoV-2, Covid-19, pregnancy, gestational period, pandemics, vaccination, complication, adverse events, and drugs. Clinical trials, and retrospective and prospective studies were included. Two authors (T.C. and P.C.) reviewed all study abstracts. Studies were included if describe the characteristics of viral infection in pregnancy. Studies written in languages other than English were excluded. All selected studies were qualitatively analysed. 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 word limit to be included in the bibliography has been set at 150 citations.

Clinical manifestations

The clinical manifestations of covid-19 infection can be extremely variable and depend on the viral load and the immunological status of the host during the infection. The infection can also run for the entire period of positivity to covid-19 in an asymptomatic or pauci-symptomatic manner or to have serious manifestations. The most common clinical symptoms of Covid-19 in the general population are fever (91%), cough (67%), fatigue (51%), and dyspnea (30%)⁸. Fever (68%) and cough (34%) are also the most common symptoms in pregnant women with Covid-19, with other

symptoms including dyspnoea (12%), diarrhoea (6%), and general malaise (12%)⁹. Based on the severity of the disease, Covid-19 is classified as mild (symptomatic or mild pneumonia), severe (tachypnoea ≥ 30 breaths/min or oxygen saturation $\leq 93\%$ at rest or PaO₂/FiO₂ < 300 mmHg), and critical (respiratory failure requiring endotracheal intubation, shock or other organ failure requiring intensive care), accounting for 81%, 14% and 5% of cases in the general population, respectively¹⁰. The World Health Organization reported a large cohort study of 147 pregnant women with Covid-19, only 8% and 1% were seriously and severely ill, respectively¹¹. This suggests that most women pregnant with Covid-19 have milder symptoms than the general population. Another study also reported that pregnant women with Covid-19 pneumonia had a milder illness and good recovery¹². In pregnant women who develop Covid-19 pneumonia, early data showed a similar intensive care unit hospitalization rate for non-pregnant women, but higher rates of preterm and cesarean delivery. The mortality rate for Covid-19 was 25%, compared to just 1% for Covid-19. However, it is important to consider when discussing covid-19 infection outcomes the negative impact pre-pregnancy conditions such as high blood pressure and diabetes can potentially have as they can be decisive on the outcome of Covid-19 in pregnant women¹³.

Healthcare organization for the management of pregnant patients with suspected or claimed Covid-19 infection

The recent outbreak of a novel coronavirus isolated in Wuhan (China) in late 2019 Covid-19 among other clinical and public health issues, also raises those relating to the organization of the perinatal network in relation to the management of infection in pregnancy, to the possible maternal-infant transmission of the infection, before, during, and after childbirth and at the safety of the joint management of pregnant-newborn and breastfeeding, subject of this document. In Italy, the definition of the case was implemented by the ministerial circular DGPRES 7922 of 09.03.2020 "COVID2019. Update"¹⁴. The definition of the Covid-19 infection case was based on the information available and subsequently revised based on the evolution of the epidemiological situation and scientific knowledge was gradually available. Generally, the diagnostic and therapeutic path of pregnant women generally followed that of the general population. On the basis of it, the pregnant women to the attention of the health system have been divided into three groups.

- *Suspected case of Covid-19 requires diagnostic testing.* These are people with an acute respiratory infection (sudden onset of at least one of the following signs and symptoms: fever, cough, and difficulty in breathing), with no possibility of another aetiology fully explaining the clinical presentation, with a history of travel or residence in a country/area where local transmission is reported during the 14 days prior to the onset of symptoms (especially in the early stages of the pandemic); or, people with any acute respiratory infection in close contact with a probable or confirmed case of Covid-19 in the 14 days prior to the onset of symptoms; or finally people with a severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease - e.g. cough, respiratory distress), requiring hospitalization and without another aetiology that fully explains the clinical presentation.
- *Probable case.* A suspected case whose test results for Covid-19 are questionable or inconclusive using specific Real-Time PCR protocols for Covid-19 at the Regional Reference Laboratories detected or is positive using a pan-coronavirus test.
- *Confirmed case.* A case with a laboratory confirmation was carried out at the Institute's reference laboratory, Health Superior for Covid-19 infection, regardless of clinical signs and symptoms.

Pregnant women, as we have already reported, are generally considered to be at greater risk of developing respiratory systems tract infections that can have severe evolutions requiring management appropriate when they access the health facility with respiratory symptoms. The obstetric emergency room (or the acceptance of any emergency room) at the birth point has provided an area of triage reserved for pregnant women with suspicion of covid-19 infection, ensuring a place of isolation (room with bathroom) and trained staff, equipped with personal protective equipment; Each birth point has set up a path for the hospital management of suspected or ascertained cases for obstetric care for any situations in which there is a contraindication to transfer of the pregnant woman. In particular, it was prepared by path for assistance obstetrician for a vaginal birth or cesarean section and for the puerperium, which includes the protection of the pregnant woman, the unborn child, and health workers.

Follow-up of pregnant women with Covid-19 infection

There is currently no data on first trimester Covid-19 infections, so the effect of Covid-19 on the foetus in the first trimester is unknown. From the data available in the literature in the first trimester of pregnancy some cases of spontaneous abortions were found especially in pre-vaccination epics and cases of elective termination in pregnancy while in the other cases the pregnancies were carried to term without any complication for the mother and for the fetus¹⁵. Also, for what concerns the second and third trimester of pregnancy Lam et al.¹⁶ observed that pregnant women with lung disease attributable to Covid-19 infection had a higher rate of maternal mortality, intubation, and ICU admission than non-pregnant women with the same pulmonary condition, but that transmission virus to the child was quite rare¹⁷. Additional complications such as miscarriage, preterm delivery, and small-for-gestational-age infants have also been reported. On the contrary, the results of another study showed the absence of increased risks of spontaneous abortion and preterm birth in pregnant women infected with Covid-19¹⁷. Many systemic infections and inflammatory states are associated with preterm births, and preterm births have been reported in women infected with Covid-19. However, most of them have been reported in China, which has a different medical system, and it is still unclear whether the virus caused these premature births or was iatrogenic due to maternal or fetal distress or other indications¹³. Data obtained in the years following the first scientific evidence shows that, although it appears that Covid-19 is rarely transmitted transplacental to the foetus, there is more and more evidence that is accumulating that Covid-19 infection during pregnancy is associated with a series of adverse pregnancy outcomes¹⁸. A systematic review and meta-analysis of relatively high-quality studies with appropriate comparison groups found an increased risk of preeclampsia, preterm birth, and stillbirth among pregnant people with Covid-19 infection compared to those without infection¹⁹. Among pregnant people with Covid-19, the severe disease has been associated with preeclampsia, preterm birth, gestational diabetes, and low birth weight compared to those with mild disease¹⁹. Two studies published after the meta-analysis found similar results^{20,21}.

Delivery

In general, the coexistence of a Covid-19 infection is not an indication to anticipate or delay childbirth and should not be considered an element

capable of altering neither the timing nor the methods of delivery. However, in some cases where delivery is not medically indicated, it may be delayed until the mother tests negative for Covid-19 to reduce the likelihood of transmission to the newborn²². Several studies have been performed to demonstrate the passage of Covid-19 from the bloodstream of the infected mother through the umbilical cord to the baby but none of these studies have shown the presence of the virus in umbilical cord blood, placenta, and/or amniotic fluid^{23, 24}. For this reason, Covid-19 infection is not an indication in the strict sense of a cesarean section. Delivery mode and timing should be individualized based on disease severity, existing comorbidities, and obstetric indications. However, the babies of most pregnant women with Covid-19 have been reported to be delivered by cesarean section. It is not clear, however, whether the indications for cesarean section were due to maternal health conditions with severe impairment or related to fetal suffering such as conditions of fetal hypoxia caused by maternal Covid-19 or other contingent causes. As regards the delivery methods, it has been clarified that both regional anaesthesia and general anaesthesia can be considered, depending on the clinical condition of the patient^{25,26}. However, regional anaesthesia is preferable to reduce the risk to the staff of having contact with infected biological materials²⁶.

The hospital management of pregnant patients with suspected or overt respiratory symptoms of Covid-19 can be summarized in different scenarios, as reported:

1. Pregnant Not in Travel Accessing Hospital with Respiratory Symptoms.

The General Emergency Department carries out the pre-triage assessments, shares with the infectious specialist the possible execution of the nasopharyngeal swab and asks for gynaecological-obstetric consultancy in the PS. The dedicated on-call gynaecologist (identified at each shift) will go to the emergency room, will wear the specific individual protection devices for dressing (provided by the First Aid staff), and will perform the specific assessment. If a pregnant patient is clinically stable: the gynecologist completes the obstetric-gynaecological evaluation (Obstetric examination, especially ultrasound evaluation; trans-vaginal ultrasound is preferable. Avoid, as far as possible, cardiotocography; if necessary, obtain and use a dedicated cardiotocograph). In the case of a negative swab, if the pregnant woman had been kept in the "dedicated room" of the Birth Center because she needed a brief observation and/or hospitalization, it is possible to transfer the

pregnant woman to an obstetric hospitalization to continue hospitalization as per standard path, otherwise if not in need of observation she can be discharged normally. In the case of a positive swab, it is possible to continue, if necessary, brief observation and/or hospitalization, or with transfer to Infectious Diseases, if a bed is available and if obstetric-gynaecological conditions do not contraindicate a transfer. In this case, the pregnant woman will be able to enjoy obstetric-gynaecological assistance guaranteed in Infectious Diseases by the obstetric-gynaecological team. In case of lack of a bed in Infectious Diseases, or in the event that the clinical conditions of the pregnant woman contraindicate the transfer to another ward, the pregnant woman remains hospitalized under obstetrics, in a "dedicated room". The referring Gynaecologist Doctor of the case will take care to contact the Infectious Disease Doctor for the specific consultations necessary during the hospitalization. If the pregnant woman is sent to her home, she will be evaluated by an infectious disease specialist and will be contacted by telephone, according to the provisions of each local health company.

2. Pregnant In Labor/ Delivery

The patient can be transferred directly from the General Emergency Department (if in advanced labour/expulsive period) or from the "dedicated room" in Obstetrics to the "dedicated labour room" in the Delivery Room. The Gynaecologist doctor contacts the Infectious Disease Doctor for a consultation. For the need for continuous monitoring, the following must be identified: "dedicated cardiotocograph and ultrasound system" to be placed "dedicated labour room". During the whole phase of labour and the puerperium, the pregnant woman will have to keep the mask and sanitize her hands with alcoholic gel. At the time of birth, the newborn will be entrusted to the neonatology team (Neonatologist and Neonatology Nurse) The neonatology team wears the following personal protective equipment for low-risk dressing but with an FFP2 mask, overshoes, (an FFP2 mask in anticipation of the possible need for neonatal resuscitation), cap, eye protection, disposable overcoat, disposable gloves). In the event of a need for neonatal resuscitation, the newborn is brought by the neonatal team to the dedicated neonatal island, present in the ad hoc area of the Birth Center. In the case of a physiological newborn that does not require resuscitation, the newborn inside the incubator is transferred to the neonatal clinic and placed in isolation. In the presence of an ascertained case,) of positivity to Covid-19 in the pregnant woman, the

execution of the nose and oropharyngeal swab is also agreed with the Infectious Doctor on the newborn (first swab at birth and second swab at a distance of 48-72 hours). If the first swab of the newborn is negative, the newborn remains in isolation until the outcome of the second swab. If the second swab is also negative, the newborn can be permanently removed from isolation. In the case of a pathological newborn, dedicated assistance will also become medical.

New-borns and Breastfeeding

From the data available in the literature, only a small fraction of newborns had a positive swab for Covid-19, although none of them showed severe symptoms of infection. This positivity was resolved in the course of a few days without leaving any sequelae^{27, 28}. There was no difference between neonates in the positivity rate between trans-vaginal births versus those born by cesarean section²⁹. These data, therefore, suggest that the newborn is fairly protected from Covid-19 infection while it is difficult to establish whether the newborns were infected by maternal-fetal transmission and by iatrogenic causes. About 20% of newborns were born premature, but this data is obtained from deliveries performed hastily in pregnant women in critical conditions or with severe respiratory failure. Instead, as regards Covid-19 infections in the newborn in the perinatal period, it can be said with certainty that most of them were caused by exposure to infected caregivers. Some studies have shown that breastfeeding is to be considered safe since the presence and replicative activity of Covid-19 in breast milk were not detected³⁰⁻³². The literature agrees in underlining those mothers who wish to breastfeed directly must adhere to scrupulous health and hygiene rules, which include hand hygiene, and the use of masks during breastfeeding, as an infected mother can transmit the virus through droplets. respiratory during breastfeeding. No increase in late postnatal transmission (defined as occurring after three days of life) associated with breastfeeding has been found with careful attention to health and hygiene standards, however, this risk was increased when infants were not. were separated from infected mothers after birth^{33,34}. This possible increase in risk must be placed in relation to the known benefits of the mother-infant bond during breastfeeding. Most guidelines support infant rooming-in with an infected mother, particularly when the mother is afebrile and asymptomatic^{35,36}.

Healthcare organization for the management of puerpera, the newborn, and breastfeeding

Whenever possible, the option to be preferred is that of the joint management of mother and newborn, to facilitate interaction and the initiation of breastfeeding. If the mother is positive and has a frankly symptomatic respiratory infection (with fever, cough, and respiratory secretions), mother and newborn are temporarily separated, pending the negativization of the laboratory test (RNA-PCR) for coronavirus; if the test is Positive, the mother and newborn continue to be managed separately; if the test is negative, the rooming-in for mother-infant is applicable, given the normal prevention of airborne respiratory diseases. The decision to separate or not mother-infant was in any case taken for each individual couple taking into account the information-consent of the parents, the logistical situation of the hospital, and possibly also the local epidemiological situation relating to the spread of Covid-19. About breastfeeding and nutrition, in the event of the separation of the newborn from the mother, the use of freshly squeezed breast milk was favoured, while the pasteurization of breast milk was not taken into consideration. The compatibility of breastfeeding with drugs possibly administered to women with Covid-19 was assessed on a case-by-case basis.

Medical treatment of pregnant women with Covid-19 infection

As for the treatment of pregnant women suffering from Covid-19 virus infection, the data are very reassuring as they have access to monoclonal antibodies and antiviral agents deemed safe and approved by the various agencies for the use of drugs. Monoclonal antibodies have been authorized for the treatment of symptomatic Covid-19 patients at high risk of progression to severe Covid-19 and/or hospitalization and because pregnancy is a particular clinical condition with a high risk of clinical progression, pregnant patients are among those who can benefit from the administration of monoclonal antibodies on an outpatient basis^{35,36}.

Although corticosteroids can delay the clearance of the virus from the body and are associated with an increased risk of morbidity and mortality in patients with Covid-19, they have been approved to promote fetal lung maturation in order to reduce morbidity and mortality. preterm neonatal delivery in pregnant women with Covid-19. Dexamethasone is recommended for pregnant women with Covid-19 who are mechanically ventilated or require supplemental oxygen; Anticoagulant prophylaxis is recommended for

hospitalized patients. Although other therapeutic options for Covid-19 are being evaluated, many clinical trials for new therapeutic agents exclude pregnant people^{35,36}. Magnesium sulphate is used for neonatal neuroprotection and eclampsia prophylaxis. The benefits of therapy must be weighed against the potential risks of maternal respiratory depression. A high fever during pregnancy may be associated with an increased risk of congenital abnormalities, including neural tube defects and spontaneous abortion during organogenesis in the first trimester. Among antipyretics, Paracetamol can be safely prescribed and may reduce the risks during pregnancy associated with exposure to fever. In general, it can be said that all effective treatments should not be withdrawn based on pregnancy status^{35,36}.

COVID-19 vaccination in pregnant and lactating females

The American College of Obstetricians and Gynaecologists (ACOG) and the CDC strongly recommend vaccinating pregnant and lactating people. The CDC specifies that any currently licensed vaccine can be given to pregnant or lactating people, with no preference for the type of vaccine³⁷⁻³⁸. Furthermore, the ACOG guidelines do not indicate a preference for the type of vaccine or the timing of vaccination during pregnancy³⁸. In a preliminary analysis of pregnant people who received an mRNA vaccine, no worrying safety signs were observed. In terms of vaccine efficacy, studies indicate that administration of mRNA vaccines results in a robust maternal humoral response. Regarding the safety profile of vaccines, although there were some small differences, the same adverse events and the same presence were observed in pregnant versus non-pregnant women and therefore it can be said that there were no differences. significant in vaccine reactogenicity in the two groups considered. Pregnant people had slightly higher rates of injection site pain and slightly lower rates of headache, myalgia, chills, and fever than non-pregnant women. Regarding vaccines other than those with mRNA technology, the safety data mainly concern Johnson & Johnson-Janssen (adenoviral vector) and are much more limited because it was authorized for use at a later time, and have been far fewer vaccines belonging to this pharmaceutical class have been administered. Therefore, although no signs of poor safety have been detected in pregnancy, data on these vaccines currently available during pregnancy are limited. More information on birth outcomes is needed, particularly among people vaccinated in early pregnancy. Cases of venous thrombosis with

thrombocytopenia have been reported following vaccination with the Oxford AstraZeneca adenoviral vaccine (UK, Sweden), available in several countries outside the US³⁹. After a careful review of the risks and benefits of vaccination, the CDC and the FDA have reaffirmed its use in all people aged ≥ 18 and issued a warning that rare clotting events may occur after vaccination, among women aged 18 to 49⁴⁰. Doctors should ensure that women under the age of 50 are aware of the risk of this rare adverse event and that other Covid-19 vaccines are available for which this risk has not been seen. Although the overall risk of thrombosis is increased during pregnancy and after delivery, the mechanism underlying thrombocytopenia linked to these vaccines is distinct from pregnancy-associated thrombosis and, therefore, there is no specific concern for pregnant women compared to non-pregnant women of the same age group⁴¹. However, the use of mRNA vaccines rather than adenoviral vaccines is preferably recommended on the basis of these safety concerns⁴². There are no known or theoretical risks of vaccination when it comes to vaccinating lactating people. High titers of vaccine-induced antibodies against Covid-19 have been found in breast milk^{43,44}. However, it is not known whether this is related to the protection of the breastfed baby.

Conclusions

There is limited data on the impact of Covid-19 on pregnant women and their babies. Most pregnant women with Covid-19 have only mild symptoms, however, special attention should be paid to those with underlying illnesses, as they are at greater risk of developing serious illnesses than the general population and which a high miscarriage rate. In women with severe Covid-19

disease or severe respiratory insufficiency, cesarean section is indicated because of maternal hypoxemia since it also affects the oxygenation of the foetus. Intrauterine transmission of Covid-19 appears to be rare and this is likely related to low levels of Covid-19 viremia and reduced co-expression of ACE2 and TMPRSS2 required for entry of Covid-19 into cells of the placenta. With regard to the treatments commonly used for the treatment of Covid-19 infection and its prevention through the use of vaccines, it can be said that at present there have been no concerns about safety or doubts about their effectiveness. Despite reports of rare clotting events in vaccinated people, there is no particular concern for people with a prothrombotic state, including pregnancy. Furthermore, the available data suggest that vaccination during pregnancy and breastfeeding is associated with the transmission of antibodies to the foetus, although the level of protection provided to the baby is unknown. It is now common opinion that Covid-19 infection can become endemic. Furthermore, in full agreement with what was expressed by the recent revision of Jamieson and Rasmussen¹⁸, globalization with the increasing connection and displacement of millions of people around the world, the serious and devastating climate changes, and the increasing exploitation of environmental resources often practiced for profit, they are causing a constant approach of human settlements with wildlife habitats, causing the emergence of possible other infections with disastrous global effects. As with any segment of the population, it is also important for pregnant women to capitalize on scientific knowledge and apply it to improve planning and response to emerging infections in the future.

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