Obstetric issues raised by SARS-CoV-2 infection

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ABSTRACT

Background and Purpose: Available information on the occurrence of adverse events in pregnancy in women affected by coronavirus (CoV) disease 2019 (COVID-19) is currently scarce and based on data from other CoV-related infections (severe acute respiratory syndrome [SARS] and Middle East Respiratory Syndrome [MERS]) during pregnancy.
Methods: In this context, cases of miscarriage, premature birth and low birth weight have been reported. Furthermore, the development of fever during the first trimester of pregnancy can increase the risk of fetal damage. To date, it is unclear whether the new coronavirus can cross the transplacental barrier, and thus result in vertical transmission. Some unproven cases of newborns who tested positive for the virus shortly after birth have been reported, but validated data are needed to understand how these babies were infected and whether or not the virus can be transmitted during pregnancy.
Results: In the limited series of cases reported in the literature, there are no reports of presence of the virus in amniotic fluid or in neonatal blood taken from the umbilical cord in women with clinical symptoms of COVID-19 in pregnancy. There are no data regarding differences in transmission of the infection based on the method of delivery. Current data show that SARS-CoV-2 has not been detected in breastmilk.
Conclusions: At present, in the presence of stable maternal conditions, there are no contraindications to vaginal delivery, and therefore there is no elective indication for cesarean section in women suffering from COVID-19. In view of the undoubted benefits of breastfeeding, and in accordance with current recommendations, breastfeeding must be started and/or maintained, directly on the breast or with manually or mechanically expressed milk.

KEYWORDS

Coronavirus, pregnancy, delivery, breastfeeding.

Introduction

Emerging infections, many zoonotic, are caused by a variety of pathogens with global distribution. Previously rare pathogens have emerged, and global travel facilitates their rapid spread. Human encroachment on remote areas has led to contact with zoonotic diseases never before characterized. Although systematic study of rare outbreaks can be challenging, knowledge of emerging pathogens and their effects on women is accumulating [1]. The new severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, in the Chinese province of Hubei, in late 2019 [2]. After the Chinese epidemic, Italy quickly became one of the European countries with the largest number of clinical cases. The situation evolved rapidly, and on March 11th, 2020, the World Health Organization (WHO) declared the state of pandemic.

On the basis of limited data and examples of previous coronavirus (CoV) cases (SARS-CoV and Middle East Respiratory Syndrome [MERS]-CoV) and a small number of CoV disease 2019 (COVID-19) cases, pregnant women are believed to be at greater risk than the general population: in fact, worse outcomes have been demonstrated in terms of mortality, intensive care admission and morbidity compared with infections in the general population [3, 4]. Previously, the 2009 flu epidemic linked to the H1N1 virus showed that pregnant women are a population at risk of viral respiratory infections, with increased unfavorable outcomes, both maternal and neonatal [5]. Albeit in the absence of conclusive information about the susceptibility of pregnant women to the new SARS-CoV-2 pathology, the data available to date seem to indicate that it is similar to that of the general population [6]. The lack of accurate and validated data on COVID-19 has made it possible to postulate only dynamic hypotheses so far, which are sometimes updated from day to day.

The issues of greatest concern for better management of SARS-CoV-2 infection in pregnant women and newborns include infection diagnostic criteria, inspection precautions, drug treatment options, indications for and methods of termination of pregnancy, postpartum fever, breastfeeding considerations, mode of mother-to-child transmission, neonatal isolation, and advice on neonatal nursing [7].

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This paper aims to give a short overview of the main obstetric issues related to this new infectious disease, with the aim of setting out current experience and opinion.

Methods

We conducted a brief review of the main papers on this topic starting from the first reports of the disease to the end of June 2020, with the aim of offering some recommendations based on the literature.

Results

Pregnancy

At the moment, very little is known about SARS-CoV-2 infection, particularly with respect to its pathogenic effect on pregnant women and infants. Currently, available information on the occurrence of adverse events in pregnancy in women with COVID-19 is scarce and based on data from other CoV-related infections (SARS and MERS) during pregnancy [8]. In this context, cases of miscarriage, premature birth, or low birth weight have been reported, but it is not clear whether these are linked to the infection itself or to other coexisting factors. Furthermore, the development of fever during the first trimester of pregnancy can increase the risk of fetal damage.

During the implantation period, a significant proportion of embryos are lost; less than half of clinically established pregnancies eventually reach full term without obstetric complications. A significant proportion of pregnancy losses is associated with immune etiologies, including autoimmune and cellular immune abnormalities. Although an autoimmune etiology such as anti-phospholipid antibodies (APAs) has been reported to induce placental infarct and thrombosis at the maternal-fetal interface, APAs induce inflammatory immune responses as well. These responses, such as increased proportions of natural killer (NK) cells and T helper 1 (Th1)/T helper 2 (Th2) cell ratios in peripheral blood, are related to recurrent pregnancy loss and multiple implantation failures. Systemic and local inflammatory immune responses seem to be induced by activation of toll-like receptors (TLRs) by infectious agents, fetal cell debris, or gonadotropin-releasing hormone agonists, etc. Cellular activation of T and NK cells leads to a pro-inflammatory cytokine storm and consequently, placental infarction and thrombosis. Potential application of anti-inflammatory therapeutic agents for the prevention of pregnancy losses should be further explored [9]. The incidence of preterm birth in developed countries has risen in recent decades. Underlying causes of this enigmatic pregnancy complication are numerous, yet infectious agents that induce dysregulation of immunity at the maternal-fetal interface are among the most probable causes of preterm birth. In particular, two situations related to maternal infections are associated with the triggering of unscheduled inflammatory sequences deleterious to the maternal-fetal balance necessary to maintain pregnancy. The first concerns the role of TLRs as sentinels of uterine immunity in the context of response to pathogens. Particular TLR activations lead to differential immune cascades that induce preterm birth. Second, two alternative routes of pathogenic entry may prove to be critical for inducing preterm birth via a cytokine storm or a secondary and currently unknown cell-mediated mechanism of uterine inflammation. Pathways underlying the activation of adverse and diverse immune responses to foreign agents may result in preterm birth [10].

To date, it is unclear whether the virus is able to cross the transplacental barrier, and thus result in vertical transmission. Some unproven cases of newborns who tested positive for the virus shortly after birth have been reported, but validated data are needed to understand how these babies were infected and whether or not the virus can be transmitted during pregnancy. The limited series of cases reported in the literature did not detect, in women with clinical symptoms of COVID-19 in pregnancy, the presence of the virus in amniotic fluid or in neonatal blood taken from the umbilical cord. In the literature, we have a series of 19 cases of pregnant women and infants of mothers with clinical symptoms of COVID-19 where the virus was not detected in amniotic fluid or in neonatal blood drawn from the umbilical cord, and so far, no maternal death has been reported [11, 12]. Swabs and histopathological examination of 3 placentas of infected mothers were negative for the virus and, for the moment, we have no evidence of transmission through the birth canal [13]. In a single case, possible intrauterine or intrapartum maternal-fetal vertical transmission has been reported, but expert opinion is that the fetus is unlikely to be infected in pregnancy [14].

Although a Chinese case report describing a suspected vertical transmission of SARS-CoV-2 infection could not be confirmed due to late execution of the neonatal oropharyngeal swab, performed 36 hours after birth, evidence continues to accumulate against vertical transmission of SARS CoV-2 from mother to infant [15]. A retrospective analysis of the clinical documentation of 9 women with confirmed diagnosis of COVID-19 pneumonia undergoing cesarean section in China did not find any vertical transmission of the infection from mother to infant. Attempts to detect the virus in amniotic fluid, umbilical cord blood, and oropharyngeal swab samples of newborns were consistently negative [16]. In another work, the authors describe the clinical, laboratory, and virological data of 38 Chinese women who contracted COVID-19 during pregnancy and confirm the absence of transplacental transmission of the infection [17]. An interesting work published in the journal "Viruses" reviews the evidence on CoV infections in pregnancy and highlights how the limited knowledge available is drawn from the SARS and MERS epidemics, responsible for serious maternal and neonatal outcomes both in terms of morbidity and mortality. The authors point out that no vertical transmission has ever been demonstrated for the two CoVs responsible, respectively, for the SARS and MERS epidemics, contrary to what was seen with Zika virus and Ebola virus infection [18].

A Consensus and other papers summarize indications on perinatal and neonatal management for prevention and control of SARS-CoV-2 infections [14, 19, 20]. A recent Italian work describes the use of pulmonary ultrasound as an imaging diagnostic technique in the clinical evaluation of SARS-CoV-2-infected women with respiratory complications [21]. The authors describe the possible use of the technique in clinical practice

by obstetricians/gynecologists. Another work summarizes the clinical recommendations on prevention and management of COVID-19 in pregnancy and reviews the main organizational and welfare criticalities of the condition, emphasizing the need and urgency to collect and disseminate epidemiological data on the infection in pregnancy during the current pandemic [22].

More and more studies are demonstrating the absence of vertical mother-child transmission during pregnancy and breastfeeding [23-25]. Fan *et al*. present two cases of mothers affected by COVID-19 during the third trimester of pregnancy [26]. Samples of maternal serum, cord blood, placental tissue, amniotic fluid, vaginal swab, breastmilk, and naso/oropharyngeal swab were collected from the mothers and the newborns. With the exception of the mothers' nasopharyngeal swabs, which were positive, the other analyzed elements were all negative. Although the babies were separated from their mothers immediately after birth, the authors provide evidence of a low risk of intrauterine vertical transmission and suggest the possible protective effect on infants of maternal antibodies transmitted through milk, although in these two cases breastfeeding was discouraged to avoid close contact.

Delivery

At present, in the case of stable maternal conditions, there are no contraindications to vaginal delivery. There are no data indicating differences in transmission of the infection based on the method of delivery, and therefore there is no elective indication for cesarean section in women suffering from COVID-19; the current indications for cesarean section remain valid [27].

Through a retrospective review of the medical records of 17 SARS-CoV-2-positive Chinese women undergoing cesarean section, Chen and collaborators describe epidural and general anesthesia as safe and effective for patients and infants [28].

Postpartum and breastfeeding

Current data show that SARS-CoV-2 has not been detected in breastmilk. In view of the undoubted benefits of breastfeeding, and in accordance with current recommendations, breastfeeding must be started and/or maintained, directly on the breast or with manually or mechanically expressed milk [8, 29]. To reduce the risk of transmission from mother to baby, which occurs via aero-transmitted droplets emitted through coughs and/or sneezing, it is recommended to adopt preventive measures such as hand hygiene before each feed or breast expression, and the use of a mask during feeding, in addition to the recommendations for cases requiring temporary separation of mother and child [30].

More and more authors are confirming the indication for breastfeeding by mothers, be they symptomatic or asymptomatic, and suspected or known to be infected with SARS-CoV-2. Writing in "The Lancet", Favre *et al*. advised against breastfeeding [31]. Responding, in this regard, to a comment by Schmid *et al*. [32], Baud reviews the authors' initial position in the light of new available information [33]. The new indications include delayed cord clamping and non-removal of caseous varnish for up to 24 hours after birth. Breastfeeding during maternal COVID-19 is no longer contraindicated and the appropriate hygiene measures should be adopted. They also recommend, in cases where mother-baby separation is necessary, expression of breastmilk. The interim guidance of the Inter-Agency Standing Committee (IASC) on the COVID-19 epidemic and more general situations of emergency indicates that affected women should continue breastfeeding because the child who has already been exposed to the virus through the mother and/or family will benefit most from direct breastfeeding. Therefore, any interruption of breastfeeding can actually increase the baby's risk of being infected or getting seriously ill [34]. Some Chinese authors continue to recommend mother-infant separation "for at least two weeks", advising against direct breastfeeding, to "minimize the risk of viral transmission by avoiding close and prolonged contact with the infected mother". On the contrary, the WHO, the British Royal Colleges, and the Centers for Disease Control and Prevention (CDC) confirm the indication for breastfeeding [35-37].

With respect to the postpartum period, the WHO recommends that "mothers and children should be enabled to remain together and practice skin-to-skin contact, kangaroo care, and to remain together and practice rooming-in throughout the day and night, especially immediately after delivery and during the start of breastfeeding" [38]. The Royal Colleges indicate that healthy women and their children, who do not otherwise require neonatal care, should remain together in the immediate postpartum period. In addition, the WHO and the Royal College of Obstetricians and Gynecologists (RCOG) offer this same information on their websites, also to women and the general population, through a series of questions and answers [39, 40]. In the latest version of its interim indications, the Italian Society of Neonatology (SIN) suggests that, whenever possible, mother and child should be managed jointly, in order to facilitate interaction and the start of breastfeeding; if the mother is symptomatic and with a compromised clinical picture, the mother and her child are transiently separated. The decision as to whether or not to separate them must, in any case, be made for each individual situation, taking into account "the informed consent of the mother, the logistical situation of the hospital, and possibly also the local epidemiological situation relating to the spread of SARS-CoV-2". In the event of separation of the infant from the mother, the use of freshly expressed breastmilk is recommended, for which pasteurization is not indicated [41]. Several Italian newspapers have reported cases of infants born to SARS-CoV-2-positive mothers who were born healthy and breastfed directly at the breast.

The Italian Regions are developing their own indications and care pathways for pregnant women and women who have recently given birth with SARS-CoV-2 infection. There are differences, in particular, in the management of the immediate postpartum period. These differences can be linked to local, logistical and organizational factors, as well as to the epidemiological situation of the different affected areas. Another aspect of maternity care is that of territorial services and the support networks available to women, both of which are playing an increasingly important role during the COVID-19 epidemic. Among strategies aimed at reducing women's visits to hospital facilities and thus their risk of contagion, the Italian Society of Obstetric-Gynecological-Neonatal Sciences (SISOGN) has recommended the reinforcement of postnatal protected discharge strategies for both mother and child, and of clinical

activities and home support for the obstetric-neonatal area [42]. They also recommend the reinforcement of teleassistance services (ideally via video calls) and provision of the necessary counseling opportunities in relation to specific information and support needs. The same strategies can be successfully adopted both during pregnancy (for example, by offering individual or group childbirth preparation sessions) and in the puerperium and lactation period. Numerous healthcare companies have activated childbirth and postnatal assistance and support services, based on video calls and home visits; however, information relating to the availability of these services is not always readily accessible to users. Some healthcare companies provide peer support groups, which, in line with the Child Friendly Communities promoted by the United Nations Children's Fund (UNICEF), are an integral part of locally available support. A network of mother-to-mother support groups also gives new mothers the opportunity to participate, for free, in individual or group remote meetings (video calls or web meetings) [43, 44].

A first systematic literature review on COVID-19 in newborns and children has now been published. The authors selected 45 relevant articles and letters [45]. Of all COVID-19 cases, 1-5% concern children, who have a less serious clinical course than the adult population. The most frequent symptoms are fever and respiratory problems, which rarely evolve into pneumonia. Inflammatory markers are also less frequently altered than in adults. Therapy involves oxygen administration, inhalations, nutritional support, and hydro-electrolyte balance control. The authors conclude that COVID-19 in children has a better course and prognosis than in adults and that deaths are extremely rare.

Recommendations

Uncontrolled information on the SARS-CoV-2 epidemic has led to the spread of incorrect and sometimes alarming suggestions. For Italian women, obstetricians and gynecologists are the reference figures in the maternity care pathway, and, from their privileged vantage point, these professionals are called upon to disseminate scientifically validated and accredited information. As there are currently no tools, such as a vaccine, to counter COVID-19, pregnant women and those around them must necessarily refer to the indications of the Italian Ministry of Health, which are based on the common hygiene rules of primary prevention: frequent and thorough handwashing, avoidance of contact with people who are sick or have symptoms related to respiratory diseases, and avoidance of crowded places [46]. It is, in any case, always advisable to comply with ministerial indications and regional health institutions in the event of symptoms of respiratory diseases. In this current phase of uncertainty, no one is able to provide conclusive recommendations for SARS-CoV-2-positive mothers and/or mothers with clinical symptoms of COVID-19. The clinical, organizational and logistics management of this population represents a challenge for health services that are already at full stretch managing the emergency [47].

The CDC has issued two documents with the aim of offering organizational instructions to healthcare facilities that provide obstetric care for pregnant women with a confirmed or suspected diagnosis of COVID-19. These instructions concern inpatient wards, obstetric triage, labor-birth units, and finally the management of discharge of the mother-child dyad [6, 48]. The main points, summarized, are the following:

1) activate basic and refresher training for all healthcare personnel in order to encourage correct adherence to infection control practices and the use of personal protective equipment (PPE);
1) healthcare professionals must promptly inform infection control personnel at their facility about the arrival of a pregnant woman with confirmed or suspected SARS-CoV-2 infection;
2) place the patient with confirmed or suspected SARS-CoV-2 infection in isolation; if this is not possible, ensure transfer to another health facility to ensure isolation;
3) offer a dedicated physical and logistical pathway for labor/delivery;
4) children born to mothers with confirmed SARS-CoV-2 infection should be considered suspected cases and undergo diagnostic testing; therefore, children should be isolated according to the infection prevention and control guidelines for people under investigation;
5) to reduce the risk of mother-to-infant transmission of the virus causing COVID-19, facilities should consider temporarily separating (separate rooms) the mother with a confirmed or suspected diagnosis of COVID-19 until such time as it is possible to suspend any precautions for transmission prevention; and
6) discharge for women and newborns after childbirth should follow the recommendations described in the CDC documents.

On March 21st, 2020, the RCOG, in collaboration with the Royal College of Midwives (RCM), Royal College of Paediatrics and Child Health (RCPCH), Public Health England (PHE), and Health Protection Scotland (HPS), released the fourth update of a document on COVID-19 and pregnancy [35]. The main change was the introduction, in the document, of a short section dealing entirely with the care of women in pregnancy after a period of isolation due to suspected symptoms or following recovery from a confirmed SARS-CoV-2 infection.

On March 24th, 2020, the "Saperidoc" website devoted a detailed page to the topic "COVID-19 in pregnancy, delivery, and puerperium", with the subtitle: "Information on the new SARS-CoV-2 and on the management of pregnant women and their infants with suspected or confirmed diagnosis of COVID-19" [49]. The page offers interesting in-depth insights aimed at healthcare professionals and, as usual, material aimed at women. The latter include indications for women in pregnancy with the description of the care pathways offered by facilities, counseling information material aimed at the general public, useful also for health centers, a section on remote support resources (in the form of self-help groups and psychological support through toll-free numbers), and a map of free remote support, curated by the Italian Breastfeeding Movement (MAMI), aimed at pregnant women and mothers who wish to breastfeed. The last section is also devoted to the topic of "staying at home with children" and includes suggestions and indications pro-

vided by the Center for Child Health of Trieste, a section of games, reading material and music, developed in collaboration with the Cultural Association of Pediatricians, and an advice section for parents and future parents entitled: "The (precious) time of CoV".

An emerging chapter in the new CoV literature concerns the role and needs of professional health workers involved in the pandemic emergency. A "British Medical Journal" (BMJ) piece, published on March 23rd, taking up RCOG recommendations, addresses the issue of health workers who are professionally exposed to the risk of contracting the disease during pregnancy [50]. Another recent work addresses the issue of the COVID-19 pandemic from the maternal-fetal medicine professionals' perspective and offers operational indications on preventing the spread of infections and protecting pregnant patients, suggesting a review of the schedule of prenatal visits and appointments for ultrasound or cardiotocographic checks, and suggesting a policy for outpatient services [51]. Also, the interim guidance of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) offers indications for the management of SARS-CoV-2-positive women during pregnancy and puerperium [52]. In view of the high contagiousness of the virus and the high risk of transmission of the infection by medical staff in close contact with patients, a work published in Chinese and focusing on the operative setting in cases of emergency cesarean section recommends the adoption of strict protection measures [53]. The indications provide the establishment of a solid management system, the establishment of effective disinfection and isolation measures, and rigorous implementation of operational procedures to prevent iatrogenic transmission of the new CoV.

Conclusions

The COVID-19 pandemic is a public health emergency requiring significant changes to obstetric and gynecological healthcare delivery in order to minimize the risk of transmission to healthy patients and healthcare workers [54, 55].

Pregnancy management is unchanged in terms of clinical and instrumental checks. The possibility of postponing deferrable checks in order to minimize contacts should be favored, giving documentary evidence in the medical records. Table 1 lists the situations in which this is not possible. Pregnant women are a population at risk of respiratory infections. Strict compliance with contagion risk prevention rules is required, as it is for the general population (spacing of at least one meter, frequent handwashing, etc.). Strict compliance with recommended vaccinations (whooping cough and flu) is necessary. Women must be informed that partners may not attend instrumental visits/examinations, except in particular situations to be evaluated with the physician/midwife or decided on the basis of specific regional/company indications. Mask wearing by women and health professionals during any clinical and instrumental investigation is advisable. Respect must be ensured for the woman's choice of maternity care (hospital, consultancy,

Table 1 Obstetric/gynecological procedures that cannot be postponed according to the Italian Ministry of Health.

Obstetrics	1) blood chemistry tests provided in attachment 10.B of the PMD January 12th, 2017; 1) first obstetric visit to be performed within 12 weeks as per ISS guideline for physiological pregnancy; 2) urgent obstetric visits for: a) uterine contractions; b) threatened miscarriage; and c) risk of preterm birth. 3) combined aneuploidy screening test (if required by the SSR); 4) first trimester obstetric ultrasound; 5) fifth month morphological ultrasound; 6) third trimester obstetric ultrasound only if there are risk factors such as gestational diabetes, growth retardation, previous cesarean section, hypertension, etc.; 7) hospital high-risk pregnancy clinic procedures (where obstetric examinations and ultrasounds will be carried out); 8) prenatal diagnosis (villocentesis, amniocentesis, and related tests); 9) monitoring of fetal well-being (cardiotocography, etc.); 10) vaginal-rectal swab search for GBS at 37 weeks; 11) microbiological samples for suspected vulvar-vaginal infection; 12) pharmacological and non-pharmacological techniques for the control of pain in labor; 13) postpartum visit; and 14) psychological counseling if there are risk factors for pregnancy or puerperium; it is recommended to run childbirth preparation courses exclusively online.
Gynegocolgical	16) Certificate of VTP with ecodatation; 17) VTP; 18) gynecological examinations for: a) abnormal bleeding; b) hemorrhages; c) significant pelvic pain; and d) acute vulvar-vaginal infections. 19) gynecological ultrasound for oncological suspicion. 20) second-level colpo-cytological screening for patients at increased risk of cervical cancer (H-SIL, AGCs, etc.); 21) hysteroscopies for suspected cancer; 22) ART procedures exclusively for patients already in treatment who must be submitted to oocyte retrieval and ET.

PMD: Italian Prime Ministerial Decree, ISS: Italian Higher Health Institute, SSR: Regional Health Service, GBS: group B Streptococcus, VTP: voluntary termination of pregnancy, H-SIL: high-grade squamous intraepithelial lesion, AGCs: abnormal glandular cells, ART: assisted reproductive technology, ET: embryo transfer

freelance, private). Online birth preparation courses, accessible to all pregnant women, whatever their chosen maternity care pathway, should be offered. Pregnant working women must be guaranteed the full range of protections, including home/smart working for activities that can be carried out at home or remotely.

At childbirth centers, the pathway of care for women with negative clinical-anamnestic triage and/or with negative tests and that of women with documented or suspected SARS-CoV-2 infection must be clearly separated. Clinical-anamnestic triage for the identification of possible cases is of fundamental importance. The use of rapid tests or buffers for all suspected cases or, better still, for every woman is advisable, as is mask wearing by women and healthcare workers during labor. The use of PPE during the expulsion phase is advisable, due to the increase in aerosol-producing maneuvers; the use of PPE is also recommended during labor and delivery, both spontaneous and by cesarean section, in women with documented or suspected SARS-CoV-2 infection. The use of labor wards accessed by numerous women should be avoided. The presence of the partner (or another trusted person chosen by the woman) during labor and childbirth is desirable, subject to adequate clinical-anamnestic triage, respect for distances and use of PPE. In women with negative clinical-anamnestic triage and/or with negative tests, skin-to-skin contact and umbilical cord clamping procedures should not be modified. In women with documented or suspected SARS-CoV-2 infection, early clamping is recommended and skin-to-skin contact should be avoided. During the hospitalization period, there should be no visitors, except for special situations (minors or women with physical/mental disability). As for the partner, the identification of pathways allowing parental contact is desirable. Early discharge is advisable, providing the necessary protections and obstetric assistance and advice is available, both in the local area and at home, or via telephone. The usefulness of breastfeeding is reiterated in all cases, including women with documented or suspected infection by SARS-CoV-2, if maternal conditions permit (i.e. the woman is not symptomatic or is pauci-symptomatic) [56].

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