Coronavirus disease 2019 (COVID-19) and human pregnancy: a scoping review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by infection with a coronavirus (SARS-CoV-2). Pregnant women show mild or moderate symptoms, with 5% presenting as severe pneumonia. The prevalence and evolution of COVID-19 in pregnancy, including the risk of maternal death, are similar to what is observed in the general population. Radiography, computed tomography or ultrasound imaging examinations are pivotal for the diagnosis and performed when there is clinical suspicion of COVID-19 pneumonia. Lab findings include lymphocytopenia, thrombocytopenia, leukopenia, and elevation of D-dimer and ferritin. To date, there is no specific treatment or vaccination for COVID-19. Clinical management of pregnant woman is also similar to that of the general population, with prophylactic antibiotic treatment for bacterial pneumonia and oxygen support. Thromboprophylaxis should be indicated in severe cases, given that pregnancy is a hypercoagulable state that may be exacerbated by COVID-19. Hospital management should focus on treating the mother and protecting the newborn and the healthcare personnel. As regards COVID-19 and perinatal outcomes, premature deliveries are mainly associated with iatrogenic pregnancy termination through cesarean section aimed at conserving maternal well-being. To date, vertical transmission to the fetus has not been demonstrated, either intrauterine or through the birth canal. The virus has not been detected in vaginal fluids, or in breast milk. Breastfeeding may be allowed depending on maternal and neonatal health status. Although there are still many open issues, scientific information related to pregnancy and COVID-19 is being updated continuously.

KEYWORDS

Coronavirus, COVID-19, pregnancy, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by an RNA virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has genetic similarities with other coronaviruses such as the bat coronavirus (Bat-CoV), SARS-CoV-1, and the Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. The latter two have the ability to infect humans. Cases of SARS-CoV-1 were initially diagnosed between 2002 and 2004 and this is currently considered an eradicated virus, whereas MERS-CoV-1 was initially identified in 2012, and some cases are still reported in Saudi Arabia [2]. Neither of these viruses reached pandemic status, but in 2013 the WHO declared MERS-CoV a global threat [3]. Although the new virus is more contagious than the previous ones, the average mortality is lower for SARS-CoV-2 (3-4%) than for SARS-CoV-1 (10%) and MERS-CoV (37%) [4-6]. At the time of writing, we are facing a very rapid spread and a continuous increase in the number of COVID-19 cases worldwide, although some countries, such as China, South Korea and Japan, are controlling new cases and beginning to lift restrictions. Contrary to this, other areas, such as the USA, Central and South America and the Caribbean, are just starting to report increases in their numbers of cases. However, the number of cases does not seem to be the most reliable parameter for measuring the magnitude of viral spread, since up to 86% of carriers of the virus are asymptomatic and were probably not reported as a clinical problem [7]. Furthermore, the lack of reliable tests, the low capacity of each country to perform tests, and the rate of false negatives due to low quality test reagents, do not allow a precise estimation of the evolution of the pandemic [8,9].

Article history
Received 12 May 2020 – Accepted 18 May 2020

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General aspects of COVID-19

COVID-19 pneumonia has similar clinical characteristics to pneumonia produced by bacteria or other viruses. The faster

spread of SARS-CoV-2, as compared to other coronaviruses such as SARS-CoV-1, appears to be related to the fact that it is thousands of times more contagious, with a basic reproduction ratio of 2.5 [10,11]. Interestingly, unlike SARS-CoV-1, it not only multiplies in the lungs, but also replicates actively in the throat during the first week when symptoms appear [12].

SARS-CoV-2 has an incubation period of 5-6 days [13], after which various complaints may occur: anosmia, headache, myalgia, gastro-intestinal symptoms, cough, fever, dyspnea and pneumonia being some of the most important [14]. Severe disease occurs more frequently in patients with associated comorbidities (obesity, hypertension, chronic obstructive pulmonary disease, diabetes mellitus) and higher mortality rates (up to 15%) have been observed in men aged 80 years or over [15-17]. Mortality rates will also depend on available local health resources at a given moment, which in turn will depend on the speed of action regarding disease prevention or control [18]. The clinical picture is associated with a cytokine storm with overproduction of tumor necrosis factor, interleukin (IL) 6, and IL-1β. The massive inflammatory response is associated with multiorgan lesions (heart, liver, kidneys among others) that, at the same time, potentiates the inflammatory reaction and impairs anticoagulant mechanisms. Cases with severe pneumonia show microthrombosis, disseminated intravascular coagulation, and multiorgan failure with raised D-dimer concentrations (a poor prognostic feature). Disseminated intravascular coagulation is common in non-survivors [19].

Although the most prevalent general COVID-19 symptoms include respiratory difficulty, cough, myalgia, and loss of appetite, some mild to moderate cases may frequently report olfactory and gustatory dysfunction. A multinational European study analyzed these symptoms in the general population using olfactory and gustatory questionnaires based on the smell and taste component of the Questionnaire of Olfactory Disorders-Negative Statements [20]. Facial pain and nasal obstruction were the most frequent disease-related otorhinolaryngological symptoms. Olfactory and gustatory dysfunctions were reported by 85.6% and 88.0% of patients, respectively. A significant association was found between the two disorders. Olfactory dysfunction appeared before the other symptoms in 11.8% of cases. Among the 18.2% of patients who did not present nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic. The early olfactory recovery rate was 44.0%, and sudden anosmia or ageusia may be suggestive of COVID-19. However, there is no information about these symptoms in pregnant women.

Cutaneous manifestations of COVID-19 have also been reported [21]. Vesicular eruptions appear early in the disease, in some cases even developing before other symptoms. Other patterns appear later in the disease evolution, such as acral areas of erythema-edema, usually asymmetrical, with some vesicles or pustules with small red or purple spots caused by bleeding under the skin. Other lesions include small macropapules, sometimes around hair follicles or similar to pityriasis rosea. Itching was very common for urticariform (92%) and for maculopapular (57%) lesions [21].

SARS-CoV-2 during pregnancy

The respiratory system is more vulnerable in pregnant women than in the general population [22]. Like the rest of the population, pregnant women can become infected with both SARS-CoV-1 and 2, and with MERS-CoV [23-24]. However, no increased susceptibility to coronavirus infection has been demonstrated during pregnancy [25] and the clinical evolution is similar to that seen in non-pregnant women of similar age [26]. During pregnancy, maternal dominant T-helper 2 (Th2) protects the fetus, whereas the Th1 response (increase of interleukin 1) is associated with higher mortality risk among those with COVID-19 [27]. Respiratory failure progresses rapidly among pregnant women with involvement of the cardiorespiratory system [22]. Despite the fact that data on these aspects are accumulating, there is no specific information on the real incidence of COVID-19 during pregnancy.

Clinical characteristics during pregnancy and perinatal outcomes

A high rate of maternal fatalities has been described in pregnant women infected with SARS-CoV-1 and MERS-CoV (up to 25% and 35% respectively) [28,29]. This figure seems to be much higher than what is currently described for SARS-CoV-2. The clinical course of pregnant women with COVID-19 has been reported to be generally mild to moderate, fever and cough being the two most frequent symptoms [23,30]. Only 5% of cases were severe [31-33]. Therefore, pregnant women do not seem more susceptible to COVID-19 or more likely to develop severe pneumonia [34]. In general, the perinatal prognosis will depend on prematurity, often due to iatrogenesis, and on maternal well-being at the end of the pregnancy.

Qiancheng *et al*. [26] reported a retrospective study of the severity of COVID-19 in pregnant (n=28) and non-pregnant (n=54) women of similar reproductive age hospitalized at the Central Hospital of Wuhan during a two-month period in 2020. They determined that there was no risk of viral vertical transmission during the third trimester of pregnancy including during vaginal delivery. Comorbidities were not frequently reported in either of the two groups. The majority of women were classified as having moderate pneumonia: 85.7% of the pregnant women, and 98% of the non-pregnant ones. Only 2 pregnant women and 1 non-pregnant woman had severe pneumonia. The authors acknowledged among the limitations of the study that (i) more severe patients might have been admitted to other hospitals, other than the study center, and (ii) the pregnant women studied were infected with SARS-CoV-2 in the late stage of pregnancy, and the probability of vertical transmission during the first half of pregnancy could not be assessed.

A retrospective study analyzed the clinical records of pregnant women with COVID-19 pneumonia treated at 25 hospitals in China between January 20 and March 24, 2020. Possible vertical transmission of the virus was studied by testing for SARS-CoV-2 in amniotic fluid, cord blood, and neonatal pharyngeal swab samples [35]. All tests were negative and there were no cases of fetal death. In addition, vaginal secretion samples were collected from the lower third of the vagina upon admission and were negative.

Zaigham and Andersson [30] performed a systematic review of peer-reviewed publications both in English and Chinese to summarize the clinical manifestations of 108 pregnancies with COVID-19, as well as maternal and perinatal outcomes. Cases of SARS-CoV-2 infection were confirmed by a laboratory test (reported in 18 articles). Women started to have symptoms in the third trimester of gestation, fever (68%) and coughing (34%) being the most frequent. Women presented lymphocytopenia (59%) and elevated C-reactive protein (CRP) (70%). Delivery by cesarean section was performed in 91% of gravidas. Three maternal intensive care unit admissions were noted but there were no maternal deaths. One neonatal death and one intrauterine death were reported. The authors concluded that although the majority of mothers were discharged without major complications, severe maternal morbidity and perinatal deaths as a result of COVID-19 were also reported. Vertical transmission of COVID-19 could not be ruled out. Careful monitoring of pregnancies with COVID-19 and measures to prevent neonatal infection are required.

Di Mascio *et al*. [23] performed another systematic review of pregnancy and perinatal outcomes of 79 coronavirus spectrum infections, particularly SARS-COV-2. Pneumonia was diagnosed in 91.8% of cases, the most common symptoms being fever (82.6%), cough (57.1%) and dyspnea (27.0%). For all coronavirus infections, the rate of miscarriage was 39.1%; the rate of preterm birth < 37 weeks was 24.3%), while premature prelabor rupture of membranes was reported in 20.7%, preeclampsia in 16.2%, and fetal growth restriction in 11.7%. Delivery was by cesarean section in 84% of women; perinatal death occurred in 11.1%, and 57.2% of newborns were admitted to the neonatal intensive care unit (NICU). When focusing on COVID-19 infections, the most common adverse pregnancy outcome was preterm birth < 37 weeks, occurring in 41.1% (95% CI 25.6-57.6) of cases, while the rate of perinatal death was 7.0% (95% CI 1.4-16.3). None of the 41 assessed newborns showed clinical signs of vertical transmission.

Elshafeey *et al*. [36] reported a systematic review and meta-analysis of COVID-19 during pregnancy and childbirth. They summarized the clinical presentation and obstetric outcomes of 33 studies including data from 385 cases of which 14 (3.6%) were severe and 3 (0.8%) were critical. These 17 women were admitted to the intensive care unit; 6 of the 17 were mechanically ventilated and one case died. A total of 252 women gave birth, 175 (69.4%) by cesarean section and 77 (30.6%) through vaginal delivery. Outcomes for 256 newborns included four reverse-transcription polymerase-chain-reaction (PCR) positive cases, two stillbirths, and one neonatal death. The authors concluded that the clinical characteristics and severity of the disease were similar to what is observed in non-pregnant women or men. In addition, the review of 256 newborns showed that 8 were admitted to the NICU (3.1%), 3 needed neonatal mechanical ventilation (1.2%), 12 had respiratory distress syndrome (4.7%), 3 had pneumonia (1.2%), and 3 disseminated intravascular coagulation (1.2%). Mortality occurred in 3 cases and there were two stillbirths involving two critical women (one case of maternal mortality and one woman on extracorporeal membrane oxygenation). In addition, there was one early neonatal death, which occurred due to complications of prematurity following cesarean delivery at 34 weeks after antepartum hemorrhage.

Respiratory assessment

Chest radiography, computed tomography (CT) and/or chest ultrasound of patients with COVID-19 pneumonia are very important for early diagnosis and follow-up. Radiographic images of these patients show increased opacities with bilateral lower lobe predominant distribution, whereas lung ultrasound shows thickened pleural lines and patchy consolidations, and CT shows consolidations [14,37-39]. These findings were consistent with the experience reported by Peng *et al*. [40] and Poggiali *et al*. [41], confirming the important role of lung ultrasound in the management of patients with SARS-CoV-2, given that it allows rapid diagnosis and monitoring of COVID-19 pneumonia and its evolution toward acute respiratory distress syndrome (ARDS) in critically ill patients. Ultrasound chest exam may be preferred in pregnant women. As mentioned above, this shows thickened pleural lines and patchy consolidations. These types of image have repeatedly been reported by radiologists as a fundamental part of the early diagnosis and monitoring of the effects of treatment in COVID-19 pneumonia [37,38].

Laboratory findings and diagnostic test during pregnancy

Laboratory test findings include lymphocytopenia, thrombocytopenia, leukopenia, and elevation of D-dimer and ferritin [14]. Lymphocytopenia (59%) and elevation of CRP (70%) are among the most frequent laboratory abnormalities observed in gravidas [30]. In pregnancy, D-dimer cannot be considered a marker of severity due to its physiological elevation during gestation [42].

Xu *et al*. [17] reported retrospective results of five pregnant women at > 34 weeks' gestation with a positive PCR test for SARS-CoV-2. These women displayed lymphopenia (<1.1 × 10^9/L) and eosinopenia (<0.02 × 10^9/L) at the onset of fever. The timing of eosinopenia largely matched that of lymphopenia. Lymphopenia and eosinopenia persisted until the patients' illness clinically and radiographically improved after antiviral/antibacterial treatment. In contrast, leukopenia was observed in only one patient, while all the women had anemia, decreased albumin, and increased CRP and D-dimer levels.

Diagnostic tests performed for SARS-CoV-2, antibodies and/or PCR, whether antepartum, intrapartum or postpartum, will depend on the possibilities of each center or healthcare system. However, given the possibility of false negatives it is important also to take into account the symptoms of the patient [43]. This approach would allow us to classify them as confirmed, possible, improbable, or uninfected, and act accordingly.

Based on data from several publications, Sethuraman *et al*. [44] have described how to interpret diagnostic tests used for SARS-CoV-2 and suggest more test to be done. Despite this, they specify that the reported time intervals should be considered approximations and may in fact vary overtime. Thus, their suggestion is only applicable if patients are proactively followed since the time of exposure, which is not easy in clinical practice, and expensive when taking into account all the techniques required and all the settings involved. The most commonly used and reliable test for diagnosis of COVID-19 has been the reverse-transcription polymerase PCR test, performed from nasopharyngeal swabs or other upper respiratory tract specimens, including throat swabs or, more recently, saliva samples. The

virus can be detected at day 1 of symptoms and peaks within the first week of symptom onset; the positivity declines by 3 weeks and from then on it becomes undetectable. A "positive" PCR result reflects only the detection of viral RNA and does not necessarily indicate the presence of viable virus.

Management of COVID-19 and pregnancy

The initial management of COVID-19 pregnant cases was not associated with severe maternal morbidity or mortality. However, more recent reports suggest that a subset of pregnant women may suffer organ failure or even die. Pregnant women have a state of increased thrombin and prothrombin secretion that enhances the thrombosis risk when they are affected by COVID-19. Hospital management should be focused on treating the mother and protecting the newborn and health personnel. In general, management is also extrapolated from that used for the general population, and consists of monitoring vital signs, oxygen therapy, monitoring fetal well-being and prophylactic antibiotic use for bacterial pneumonia. Some centers have used antiviral therapies (i.e. lopinavir, ritonavir and hydroxychloroquine) but, to date, there is no clear evidence of their effectiveness.

A prophylactic dose of a low molecular weight heparin (LMWH) is recommended for hospitalized patients with COVID-19 to prevent venous thromboembolism, and a treatment dose of LMWH is contemplated for those with significantly raised D-dimer concentrations due to concerns of thrombin in the pulmonary circulation; LMWH also has anti-inflammatory properties that might be beneficial in COVID-19 patients. The International Society of Thrombosis and Hemostasis has generated a simple algorithm for the management of COVID-19 coagulopathy [45]. The use of LMWH has been recommended in all such patients [46]. This body of evidence should be considered by obstetricians caring for pregnant women affected by COVID-19. A coagulation profile to detect the presence of subclinical disseminated intravascular coagulation and the use of LMWH for the prevention of thromboembolic disorders should be considered and discussed between clinicians and patients [46].

Miscarriage and preterm birth risk

Although miscarriage and second trimester losses have been described in SARS-CoV-1 and MERS-CoV infected pregnancy [28,47], no direct association could be demonstrated [48]. To date, the relationship with SARS-CoV-2 has not been demonstrated either [32], although the first case of perinatal mortality in a premature newborn has already been described [30]. A recent systematic review by Di Mascio *et al*. [23] reported that coronavirus infected pregnant women (including SARS-CoV-1, SARS-CoV-2 and MERS-CoV) present miscarriages, prematurity, probably due to iatrogenesis, and perinatal death among the > 90% who also had pneumonia. As regards the relationship between SARS-CoV-2 and preterm birth, this event has been mainly associated with iatrogenesis, being due to the termination of pregnancy to maintain maternal well-being [23,49]. The risk of fetal hypoxia is probably secondary to maternal hypoxia due to COVID-19 pneumonia, rather than to direct viral involvement which has not been demonstrated.

New information has come from a single pregnant woman with symptomatic COVID-19 associated with severe preeclampsia and placental abruption, in whom viral presence was demonstrated by molecular and immunohistochemical assay and electron microscopy [50]. SARS-CoV-2 was localized in the maternal interphase of syncytiotrophoblastic cells, suggesting that in some gravidas the virus can affect the placenta.

Delivery

During the pandemic, it is important perform a PCR screening at delivery in order to know who is virally active for the SARS-CoV-2. This is necessary to improve the clinical care of pregnant women and newborns, and to protect healthcare personnel, who must also be equipped with personal protective equipment (PPE). If screening is not possible, the decision to take these protective measures would have to be based on the presence of symptoms compatible with the disease. Caution should also be exercised with asymptomatic cases who had symptoms in the past two weeks, who recently had a risky contact, or who are under viral screening. At the time of delivery, pregnant women with COVID-19 may have evident clinical symptoms of the respiratory syndrome and PPE must be worn to assist them. However, there are also cases without clinical symptoms or signs of the disease who may subsequently be diagnosed with COVID-19. Managing every type of patient as a high-risk case may generate huge healthcare costs.

Vintzileos *et al*. [51] screened, for COVID-19 immune status, 161 pregnant women admitted to the labor and delivery area. They found that 19.9% were COVID-19 positive (32/161 patients). Of these, 34% (n=11) were asymptomatic and 66% (n=21) were symptomatic. The authors reported several findings related to routine COVID-19 testing: (i) routine testing would have shown the need for PPE use in an additional 21 (asymptomatic) patients; (ii) there were 5 patients with clinical symptoms who had a negative test; (iii) testing would increase by 10% the identification of infected gravidas (16/161); and (iv) all 32 COVID-19-positive mothers had negative COVID-19 tested neonates. Maternal testing during labor makes it possible to identify gravidas needing to be cared for using PPE, and to better allocate clinical resources such as chest imaging, oxygen use, and transfers to negative-pressure rooms. In addition, testing may overcome the problem of mothers tending to "downplay"/deny their symptoms in order not to be separated from their newborns. This type of study should be confirmed in different clinical scenarios and countries.

All healthcare personnel attending women in active labor should wear full PPE. Ashokka *et al*. [45] have given some general/standard recommendations about maternal care during delivery to reduce the risk of infection. Due to the possibility of viral dissemination during intense exhaling related to the pain of active labor, early epidural analgesia for pain control should be considered. Advanced ventilatory and circulatory support, in an intensive care unit, should be provided, by specialists, to cases presenting with severe complications such as pneumonia, ARDS, and multi-organ dysfunction syndrome..

Up to 93% of described COVID-19 pregnancy cases have

been delivered by cesarean section, the majority due to the effects of COVID-19 during gestation and the risk of impaired fetal well-being [30,52]. In other cases cesarean section has been indicated for maintenance of maternal well-being, which can lead to iatrogenic prematurity [23,24,49]. In some elective cases its justification should be questioned [53].

Puerperium and vertical transmission

The first series of pregnant SARS-CoV-2 cases failed to demonstrate vertical transmission to the fetus, either intrauterine or through the birth canal. Furthermore, the virus has not been detected in vaginal fluid or in maternal milk [24,54-58], although it appears to have been detected in stool [9].

Six newborns with elevated IgG antibodies in the blood and some cases with elevated IgM have been described, although none of these cases yielded a positive PCR test [59,60]. There is a need for more correlational studies. There is one case in which SARS-CoV-2 was diagnosed by PCR in a newborn at 36 hours of life, but the authors themselves indicated that although this could be a case of vertical transmission, confirmation was not possible and this possibility still needs to be confirmed [61]. Rodrigues *et al*. [62] carried out a systematic review of 30 original studies without language restriction, and irrespective of study quality. These studies reported 182 deliveries resulting in one stillbirth and 185 live births. In all cases amniotic fluid, placenta and/or cord blood were analyzed and found to be negative for COVID-19. In addition, breast milk samples from 13 mothers showed no evidence of presence of the virus.

Breastfeeding may be allowed depending on maternal and neonatal health status, and its prohibition should be decided on an individual case basis, after discussion with a physician (infectious disease specialist) and neonatologist [63].

Future directions

COVID-19 has changed the way medical practice should be addressed in the near future. There is no specific treatment for COVID-19 and current management is focused on maintaining ventilatory and cardiovascular functions and preventing thromboembolism. For the moment, there is no clear evidence for any specific coronavirus antiviral therapy. Future progress may be related to the development of a specific vaccine to prevent the infection.

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Funding information: *this review was partially supported by the Sistema de Investigación y Desarrollo and the Vice-Rectorado de Investigación & Postgrado of the Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador.*
Conflict of Interest: *None*

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