

A Review of Sars-Cov-2 Infection in Pregnancy: What We Know So Far

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ABSTRACT

Coronavirus infection (COVID-19) in pregnancy is highly relevant due to the impact on maternal and fetal health, it is caused by SARS-CoV-2, which has a high morbidity and mortality rate worldwide. It is important to evaluate pregnant patients who are identified as suspicious, to make an accurate and timely diagnosis, to implement correct follow-up and adequate therapeutic management to reduce associated complications and adverse perinatal outcomes.

Objective: Execute a detailed and updated review of the causal agent, pathophysiology, diagnostic methods, treatment, maternal and fetal repercussions, via of delivery and whether there is evidence of vertical transmission.

Method: A search of literature published in English and Spanish was carried out in databases such as PubMed / MEDLINE, MDconsult, HSTAT, Internet Grateful Med, using the keywords: Coronavirus, pregnancy, SARS-CoV-2, treatment, vertical transmission. From the information obtained, 88 articles were selected, which were classified and used as support to do this review.

Results: Studies and available evidence, reviews, and recommended guidelines for the evaluation of patients with COVID-19 are discussed, mainly those that provide valuable data regarding the diagnosis, monitoring and management of this infection.

Conclusion: Information is limited and much remains to be studied about vertical transmission and perinatal outcomes. There is no evidence to support that pregnancy increases the susceptibility to get COVID-19. More studies are necessary to know the behavior of the infection in pregnancy, for a better approach, diagnosis and treatment.

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Introduction

The rapid spread around the world of SARS-Cov-2 infection, also known as COVID-19, currently represents one of the biggest public health issues. The World Health Organization (WHO) declared the pandemic on March 11 2020 and by June 1 its spread has been reported in 216 countries, with a total of 6,057,853 infected and 371,166 deaths, which indicates a world mortality rate that exceeds 6% [1].

There is limited information about this infection and its behavior during pregnancy. However, pregnant women are considered a population at risk since pregnancy represents a vulnerable state to the natural evolution of this disease, due to changes in the immune system, respiratory physiology adaptation and possibility of vertical transmission [2].

Despite the fact that its origin was in China, the United States

of America is the country with the highest number of cases worldwide, followed by Russia and the United Kingdom. There are several clinical elements that are fundamental in the evaluation of suspicious patients and their diagnostic and therapeutic approach. That is why both national and international medical institutions as well as experts in obstetrics and fetal medicine are providing their recommendations as a tool for health professionals, given the increase in cases of COVID-19 during pregnancy. There are still questions that represent a great challenge for obstetric doctors, but one priority is to avoid or reduce contagion in pregnant patients and provide medical care and safe prenatal control in both cases; suspected or confirmed. Infection continues to expand in our country and work is needed to understand what this represents in the latent risk of maternal and perinatal death [3].

This review aims to present the most relevant and up-to-date data available, in relation to the precise diagnosis and treatment of COVID-19 in obstetric patients, as well as to assess and evaluate its impact on perinatal outcomes.

Background

The era of human coronavirus began in the United Kingdom in 1965 when British researchers extracted a virus directly from tissue culture of patients with common cold, they named it B814 [4]. After that, in 1966 HCoV-229E virus was identified, HCoV-OC43 in 1967, HCoV-NL63 in 2004 and HCoV-HKU1 in 2005, which cause the common cold with mild symptoms. However, there are two highly pathogenic and transmissible viruses, the severe acute respiratory syndrome coronavirus (SARS-CoV) reported in 2002 in China and the Middle East respiratory syndrome coronavirus (MERS-Cov) detected in 2012 in Saudi Arabia, with a lethality of 10.5 and 34.4% respectively. All of them of zoonotic transmission [5]. On December 31, 2019 in Wuhan China, 27 cases of pneumonia of unknown etiology with severe symptoms were reported. On January 7, 2020, the discovery of the new virus was reported, using bronchoalveolar lavage samples from patients infected with the use of real-time polymerase chain reaction (RT-PCR) and viral culture, which was originally called “new coronavirus 2019” (nCoV-2019). Classified within the genus Beta coronavirus (β CoV) [6]. Two days later the first death was reported in that country. On January 12, the analysis of the viral genome was published and it concluded to be 96% identical to the bat coronavirus genome. In addition of having high structural similarity with SARS-CoV, for which it was renamed SARS-CoV-2 [7].

On January 13, the first case outside China was confirmed, registered in Thailand which then spread to Europe, with a large number of positive cases and deaths in countries like Italy and Spain. The United States reported its first case on January 20 in a patient who had returned from Wuhan. On February 11 the name of the disease officially changed to COVID-19 (Coronavirus Infection Disease). By March 11, the virus had spread to 143 countries and the WHO declared COVID-19 as a pandemic [8].

In Mexico, the Institute of Diagnosis and Epidemiological References (InDRE) reported the first positive case of COVID-19 on February 28, in a patient with a history of a recent trip to Italy. As of June 1, 2020 the figure in the national territory is 93,435 confirmed cases and 10,167 deaths, with a current case fatality rate greater than 10% [9].

The infection in pregnancy was first disclosed in a study published on February 12 by Chinese researches involving 9 obstetric patients from a hospital in Wuhan, with the objective of evaluating the risk of vertical transmission [10]. In our country by the second week of April, the first cases were reported during pregnancy and since 2 deaths on April 9. In May 17, Lumbreras and collaborators reported maternal mortality, demographics and clinical characteristics from COVID-19 in Mexico. They identified 308 confirmed cases in pregnant women, with 7 maternal deaths with a case fatality rate of 2.3%. In their report they described that patients with an average age of 37 years and a higher prevalence of diabetes and obesity. Of the 7 cases of maternal death, only two received intensive care and only one received mechanical ventilation. In the 301 cases with maternal survival, a high prevalence of obesity, high blood pressure, diabetes, smoking and asthma was found. The average age was 30 years old. Of these patients, 87 of them (28.9%) required hospitalization, 8 patients (2.7%) were admitted to intensive care unit and only one patient required mechanical ventilation [11]. On June 1, a total of 560 confirmed cases were reported from which 18 were fatal due to COVID-19, with a case fatality rate of 5%. Data truly alarming for the obstetric population [12-13].

Coronavirus SARS-CoV-2

The SARS-CoV-2 virus is a new strain identified in humans. It belongs to the Coronaviridae family, named after the appearance of their surface which resembles a crown shape under electron microscope. They are enveloped, single-stranded, positive sense RNA viruses, possessing the largest genome of RNA viruses with a size of 32 kilobases, each virion up to 90nm. It encode structural proteins that participate in viral transcription and replication: spike glycoprotein (S), envelope (E), membrane (M), nucleocapsid (N) and hemagglutinin esterase (Figure 1) [14]. It shares 7 non-protein Structural with the SARS-CoV virus, with 82% nucleotide identity. According to the International Committee on Virus Taxonomy, they belong to the order *Nidovirales*, *Coronaviridae* family, *Coronavirinae* subfamily, consisting of four genera, *Alphacoronavirus* (α CoV), *Betacoronavirus* (β CoV), *Gammacoronavirus* (γ CoV) and *Deltacoronavirus* (δ CoV) [15-16].

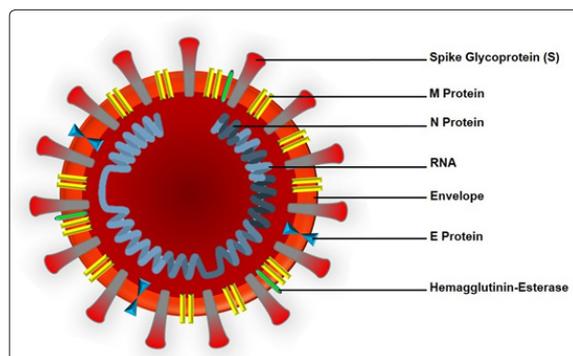


Figure 1: SARS-CoV-2 viral structure

Protein S has a receptor binding domain (RBD, Receptor- Binding Domain), typical of SARS- related coronavirus, this domain binds to the receptor for angiotensin-converting enzyme 2 (ACE-2) expresses mainly in type II alveolar epithelial cells and in extra pulmonary tissues such as heart, kidneys, and gastrointestinal tract, which facilitates viral entry into target cells [17]. Recent studies demonstrated that the SARS-Cov-2 RBD mutation increased the affinity for ECA-1 in 18 humans compared to SARS-CoV [18].

Phylogenetic analysis of coronavirus has identified that α CoV and β CoV originated in bats and rodents, infecting only mammals, and can cause respiratory, gastrointestinal, neurological, and hepatic infections, while γ CoV and δ CoV originated in avian species have not been identified in humans yet [19]. Meanwhile, SARS- CoV-2 studies have revealed that RBDs are a mutated version of the recognized RaTG13 virus in bats. After mutating, it is believed that it infects other animals such as ferrets and pangolins which later spread to the general population, including pregnant women (Figure 2). Some studies recognize the pangolin as an intermediate host, however, the exact origin is still unknown [20].

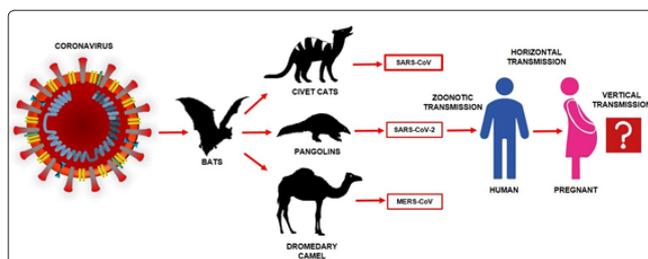


Figure 2: Transmission mechanism

Recently it has been described that the virus has evolved and four lineages called G,S,V,O have been defined, usually in groups called A,B,C and O of others. A phylogenetic tree is a scheme that tells the story, shows the common ancestor and how a species diversifies depending on the variations in its sequences. A lineage is a branch of the phylogenetic tree of a species. Around 17,205 SARS-CoV-2 sequences have been identified in patients from all over the world, which has allowed to study the associated virus variations according to the geographical site. The variant of group A, corresponding to lineage G, was the one identified in Wuhan, and regions such as Japan, the United States and Australia. Group B or S lineage, also found in Wuhan, the United States, Canada, Italy, Germany and France. Finally, group C or lineage V, is found in Italy, Switzerland, England, the United States, Singapore and South Korea. Lineages A and B circulate in Mexico and are believed to be of European origin. The importance lies in the fact that the variant is much more efficient in the process of replication and adaptation to a specific population. In addition, these variations could be related to the severity of the disease, especially if the infection is caused by more than one variant [21].

Physiopathology

SARS-COV-2 is known as lethal secondary to the damage produced in the organism, starting with massive alveolar injury and ending in progressive respiratory failure. Different studies report that the pathogenic action will depend on the affected tissue, mainly the virus has the ability to cause respiratory syndromes to enter and replicate inside respiratory epithelial cells, contact of glycoprotein S with ECA-2 receptor is essential [22,23]. Which is essential in the transmission capacity of the virus, it is divided into 2 domains: S1 and S2, and its function lies in receptor binding and membrane fusion respectively. As already mentioned, ACE-2 works as a receptor for SARS-CoV and is expressed in different parts of the body such as: intestines, heart, kidneys and lungs, this last one through type II pneumocytes and macrophages [25]. Meanwhile, coronavirus use receptors such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPPA) [24], SARS CoV-2 glycoprotein S shows 10 to 20- fold higher affinity for ECA-2 receptors than SARS CoV, which results in its easy spread [20].

In order for the infection to take place, it is essential that the viral content is deposited in the cytosol of the host cell, this occurs after the fusion of the membrane in which a plasma membrane-associated type II transmembrane serine protease (TMPRSS2) participates and is activated when ACE-2 is coupled to the glycoprotein S [23]. This results in an inflammatory cascade initiated by antigen presenting cells (APCs) which play a major role in performing 2 decisive steps: the first is the presentation (IL-12) and further stimulating Th1 cells. These last cells stimulate CD8 and T-Killer (Tk) cells by attacking cells that express the foreign antigen. Finally, B cells are stimulated by Th1 cells with the purpose of producing specific antibodies against the antigen [20].

The binding of glycoprotein S to the ACE-2 receptors of host cells occurs mainly in the lower respiratory tract, instead of the upper airway, which justifies that the maximum viral elimination is greater on the tenth day of the disease [26-27].

Both the severity and the lethality of the disease are the result of the hyperinflammatory state produced by SARS-Cov-2. Autopsy reveal high concentrations of circulating inflammatory cytokines and chemokines, deep lymphopenia, and infiltrated mononuclear cells in specific organs such as: lungs, heart, spleen, lymph nodes and kidney [28].

Clinical Presentation

Multiple studies have reported the clinical presentation, where it can be seen that although there are variations, the main symptoms and clinical signs are usually the same. It is important to mention that since it is relatively a new disease, the clinical picture is also new, so it is essential to understand the symptoms in the general population and in pregnant women [29].

For example, in general population Xu et al., analyzed 50 patients with confirmed COVID-19 cases and symptoms included fever (42%), cough (20%), expectoration (14%), fatigue (16%), headache (10%), gastrointestinal complaints (2%), respiratory difficulty (8%) and muscle pain (16%). [29] Tian analyzed 262 confirmed COVID-19 RT-PCR cases in China and symptoms included fever(82%), cough (46%), fatigue (26%), respiratory distress (7%) and headache (6%). In severe cases, respiratory distress was present in 32.6% of patients [30].

According to Wang, although fever is the most common symptom, the absence of fever in cases of COVID-19 is more common than in SARS-CoV and MERS-CoV infection [31]. In Tian's investigation, the average incubation time was approximately 7 days. The median time from the disease onset to the hospital visit and from hospital visit until the confirmation of the case was 4.5 and 2.1 days respectively [30]. Most common symptoms included fever (83%), cough (82%) and dyspnea (31%) [32]. The complete clinical manifestation has not yet been clarified, due to the variety of reported symptoms in mild to severe cases, even the cases that result in death [33]. Several studies conclude that in pregnant patients the difference in clinical presentation is no exception, in a systematic review of 18 studies composed of 114 pregnant women conducted by Yang, the most common symptoms were fever (87.5%) and cough (53.8%), the least common included fatigue (22.5%), diarrhea (8.8%), dyspnea (11.3%), sore throat (7.5%) and myalgia (16.3%). Two asymptomatic patients were admitted and a few days later they developed typical symptoms. Most patients (96.5%) were categorized as mild or regular type illness at their admission [34-35]. In a cohort study of pregnant women with severe or critical infection from COVID-19 conducted at 12 institutions in the United States and published on May 8, admission generally occurred 7 days after the onset of symptoms, the stay in-hospital was 6 days on average for seriously ill patients and 12 days in critical patients. Critically ill women had a higher rate of Acute Respiratory Distress Syndrome (ARDS) and one case of cardiac arrest was presented, but there were no cases of cardiomyopathy. 50% of hospitalized women terminated their pregnancy, generally in the third trimester and there were no perinatal deaths. Pre-existing comorbidities were: 25% lung disease, 17% heart disease and the average BMI was 34kg/cm.2 Gestational age at the onset of symptoms was a mean of 29±6 weeks and at hospital admission was 30±6 weeks [36].

Diagnosis

The correct performance of diagnostic tests for SARS-Cov-2 continues to evolve, currently the 2 most commonly used types of tests are nasopharyngeal swab RT-PCR and the IgM and IgG enzyme-linked immunosorbent assay (ELISA). Clear knowledge and understanding of the nature of these methods is essential, as well as the interpretation of the findings and how the results may vary over time (Figure 3). Most patients with SARS-CoV-2 infection test positive for IgG within 10 to 20 days after the onset of symptoms, however, the clinical value of the antibody test has not yet been fully substantiated, even in pregnant women nor in the general population. Unfortunately, the sensitivity and specificity of these tests are still being studied, but there are studies

that report low sensitivity of up to 48%, and high specificity of even 100% depending on the test. Due to variations in values between studies, the estimated time intervals should be considered as approximations and the probability of detection of SARS-CoV-2 infection will be presented qualitatively. Detection only occurs if patients receive proactive follow-up from the moment of exposure [37].

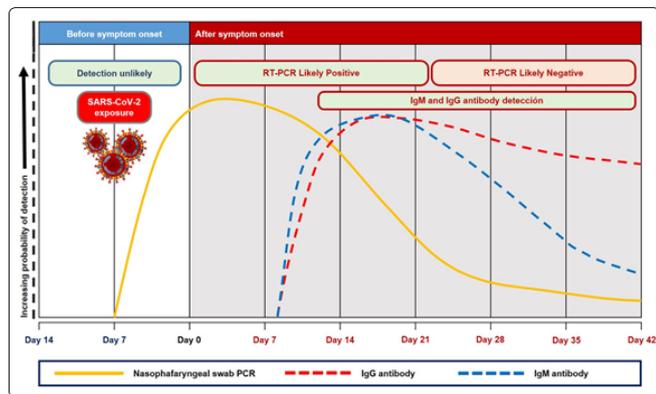


Figure 3: Antibody response against SARS-CoV-2. Modified from: Sethuraman N, Stanleyraj S, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA 2020

In patients with suspected infection, other nucleic acid-based procedures are RT-PCR in sputum and in lower respiratory tract secretions obtained by bronchoalveolar lavage. [38-40] Clinically, nucleic acid-based methods are sensitive but prone to false positives. Therefore, it is suggested to combine the two methods to improve the precision in COVID-19 detection [41-43].

Antibody testing in pregnant women can have two possible advantages: identification of cured (IgG positive) women who never underwent RT-PCR and women still at risk of infection (negative IgM and IgG). Despite the controversial information, applying the rapid antibody test first would be ideal. If this is IgG positive, the next step would be to perform RT-PCR by nasopharyngeal swab and consider the patient as COVID-19 positive until the test result is available. Positive patients should be isolated and hospitalization should be reserved until having RT-PCR results. If it is not feasible to postpone hospitalization due to obstetric causes, the patient will enter the COVID area and will be treated as positive COVID-19 [44].

Evidence on vertical transmission and during lactation

A mystery to date has been whether there is vertical transmission of SARS-CoV-2 during pregnancy to the fetus and what mechanism would be by which this occurs. Most of the reported studies describe cases of women in China. According to Chen in his study on clinical characteristics and intrauterine vertical transmission in pregnant patients in Wuhan, he reported 9 patients who had a cesarean section in the third trimester, all of them with pneumonia and empirical antibiotic therapy, 8 of them with characteristic changes in Computerized Axial Tomography (CAT). Samples of amniotic fluid, umbilical cord blood and pharyngeal samples were taken from neonates, in addition to breast milk, in which the virus was not detected. Based on the above, it was concluded that there is no evidence to suggest that the development of SARS-CoV-2 pneumonia in the third trimester had any adverse events outcomes in neonates or fetal infection by vertical transmission [10].

Matching with Liu's study, which reported 3 cases in Wuhan of pregnant patients who were infected with SARS-CoV-2 during the third trimester with ages between 30 to 24 years and positive

by RT-PCR, fever or cough and changes in tomography, resulting in two caesarean sections and one delivery. With swabs of the 3 infants being negative, as well as milk samples, vaginal mucosa and placenta without evidence of the virus [45].

On another hand, Zhu reported 9 patients, 7 caesarean sections and 2 deliveries, whose samples collected from neonates between 1 and 9 days after birth were negative [46].

In contrast, Dong's study reported a case of a newborn with elevated IgM antibodies to SARS-CoV-2 born to a mother with COVID-19, 2 hours after birth, the mother always wore a N95 mask and was not in contact with the newborn. No evidence of infection was found in vaginal secretions [47].

The Italian Society of Neonatology recommends both suspected or confirmed identified women with SARS-CoV-2 to breastfeed under strict control measures [48]. Furthermore, the Centers for Disease Control and Prevention (CDC) issue preventive recommendations such as hand washing, the proper use of masks and cleaning of milk jugs or bottles [49].

Currently, the knowledge about the clinical impact of COVID-19 on maternal, fetal and placental aspects is limited. It is a controversial topic and it is unknown if there is vertical transmission of the virus, as well as its frequency. We found literature that does not support the intrauterine transmission mechanism of SARS-CoV-2 and its presence in neonates could be a result of the mother's postpartum respiratory transmission route.

Treatment

Despite the severity of the pandemic and the progressive increase in scientific production, combined with the short time of evolution and the sufficient symptoms, little is still known about the effectiveness of therapeutic options to decrease mortality and slow the progression of the disease to severity stages. Currently, the best strategy for treatment for confirmed COVID-19 patients is purely supportive, including oxygen therapy and antibiotic treatment [50]. In addition, many patients have received compassionate therapy including antiretrovirals, antiparasitic agents, anti-inflammatory compounds, and convalescent plasma [51]. There are no randomized studies in pregnant patients, there are only a series of cases, so we will address proposed treatments for COVID-19 and if they are safe to use during pregnancy. Recommendations, clinical practice guidelines and procedures to minimize nosocomial transmission are under evaluation, there are several studies about medications in progress to develop targeted treatment [52].

Antivirals

In past epidemics of betacoronavirus, several antivirals were tested, including ribavirin, interferon, lopinavir-ritonavir, darunavir-cobicistat, some of them with promising in vitro results [53].

On May 1, 2020 the FDA issued an emergency use authorization to allow the administration of remdesivir as treatment in critical hospitalized patients with COVID-19 [54]. This is a prodrug of a nucleotide analog that is metabolized intracellularly to an adenosine triphosphate analog that inhibits viral RNA polymerases. It was initially introduced as a treatment for Ebola, which in vitro studies showed activity against SARS-CoV-2. In a compassionate use study by Grein et al [55] 53 patients were treated with remdesivir, 40 (75%) received 10-day treatment, 10 (19%) 5-9 days, and 3 (6%) less than 5 days. The dose was 200 mg IV the first day and 100 mg IV daily for 10 days thereafter. 34 of them were under assisted mechanical ventilation and 19 with supplemental oxygen

only, concluding that remdesivir may have benefit for patients with critical COVID-19, but randomized studies are required. Currently, several investigations in phase 3 are being carried out, which will help us define this agent's role in COVID-19 [56]. Compassionate use in pregnant patients is approved, although there are no studies to support it.

Another medication more studied is lopinavir/ritonavir, in which the preliminary report of a systematic review for COVID-19, which is still in process for publication, concludes efficacy in reducing ARDS, nosocomial infection and death, so it could have a positive effect on reducing mortality and ARDS. In a rapid synthesis update of pharmacological treatment, several studies were analyzed and the effectiveness and safety of antivirals in SARS, MERS, COVID-19 and nonspecific coronavirus infections were evaluated, without finding evidence for or against treatment with ribavirin, oseltamivir, lopinavir-ritonavir, in decreasing admission rates to the Intensive Care Unit (ICU) for patients with SARS and MERS infections (21 studies). Referring to mortality (40 studies), none of the drugs showed significant differences [57]. There is no contraindication for use in pregnancy, although it is category C.

Arbidol, is an antiviral approved in Russia and China used in influenza treatment, it has no significant adverse effects. A retrospective cohort study compared arbidol plus empirical treatment versus empirical treatment alone, finding discrete improvement in virological conversion, tomographic findings, and oxygen requirement, mainly in cases with mild and moderate disease, although in severe cases no advantages or changes were found [58]. In another series of cases (7 participants), in which all patients received antiviral therapy with oseltamivir, ganciclovir, nebulized interferon and arbidol, in addition to traditional Chinese medicine and antibiotics, 71% were treated with methylprednisolone after their cesarean section, without a documentation of any deleterious events to either one of the treatments [59].

Interferon

Interferon is an adjuvant treatment, they are proteins that bind to cell surfaces and initiate signaling cascades, where they regulate the transcription of genes by interferons, in viruses such as hepatitis B and C [60]. although their use by the *Surviving Sepsis guide* does not recommend its use, the Wuhan University makes a slight recommendation in favor, at a dose of 5 million international units 2 times a day in mists [61]. However, toxicity is considerable including severe cytopenias, hepatotoxicity, neuropsychiatric events, risk of developing infection or life-threatening ischemia, especially in combination with ribavirin. This combination is not associated with improvement in mortality or improvement in viral load in a retrospective analysis of patients infected with MERS-CoV who started therapy upon admission to the ICU from 1 to 3 days [62]. Several combinations of ribavirin, interferon and other antivirals are in the process of clinical trials. There is limited data for use during pregnancy.

Chloroquine and Hydroxychloroquine

They are antimalarial drugs, with anti-inflammatory and immunomodulatory activity. In February 2020 Wand and colleagues demonstrated highly effective in vitro activity of chloroquine against SARS-CoV[63]. This justified the use of 500 mg every 24 hours orally, and multiple studies were started in China during this pandemic. But hydroxychloroquine has better tolerance than chloroquine, which is why its long-term use has been chosen

in rheumatological diseases, Yao et al. carried out an in vitro comparative study of these two drugs to compare its lung activity. Hydroxychloroquine was shown to be more potent in Vero cells than chloroquine against SARS-CoV-2 [64].

Gautret reported his experience with hydroxychloroquine at a 200 mg dosage every 8 hours,[65] he evaluated 36 patients (20 hydroxychloroquine and 16 controls) who were COVID-19 positive and had also taken a nasopharyngeal sample in the first 6 days of treatment. He demonstrated that hydroxychloroquine (14/20, 70%) was superior to the control group (2/16, 12.5%; p=0.001) in eradicating SARS-CoV-2 from nasopharynx. Azithromycin was prescribed to 6 patients to avoid bacterial infections and they found that viral eradication was significantly higher (6/6, 100%) compared to those who only received hydroxychloroquine (8/14, 57%). Although they are very promising results, we have to take into account that they did not report any clinical results, in addition the sample is very small, the potential for toxicity and the need for specific treatment against this pandemic, there are not enough studies that support this therapy. Chloroquine toxicity and the need for monitoring electrocardiographic to rule out QTc prolongation or bradycardia, investigating and minimizing the clinical situations that may lead to these adverse effects happening, [66] this studies should focus on hydroxychloroquine, which is a much safer medication. There is no contraindication for its usage during pregnancy.

Corticosteroids

The usage of glucocorticoids has been shown to improve oxygenation and achieve rapid resolution of chest abnormalities in SARS patients [67]. In a retrospective cohort study, where the use of methylprednisolone at a dose of 1 to 2 mg/kg/day for variable time in patients with COVID-19 was shown to reduce the possibility of case progression of mild or moderate to severe [68]. The most frequent methylprednisolone dosage was 40 mg to 80 mg/day. *Surviving Sepsis* gives a slight recommendation for the corticosteroids usage and patients with ventilatory failure associated with acute respiratory distress syndrome, and in patients with refractory shock to intravenous fluid management and intravenous vasopressors [69]. Wuhan University also makes a slight recommendation in favor of the usage of methylprednisolone in patients with rapid disease progression, with severe manifestations, where it improved symptoms and disease progression.

Oxygen Therapy

As we mentioned before, the guides from both Wuhan University and the *Surviving Sepsis Guide*, recommend oxygen therapy according to the severity of hypoxia where the strongest recommendations are to start supplemental oxygen if peripheral SO_2 is less than 90% and in case of acute hypoxemic respiratory failure, maintain SO_2 below 96% [61-69].

In addition, a retrospective multicenter study found that the index oxygenation was better in severe patients (>100 mmHg) than in critically ill patients (<100 mmHg), which was evident in 86.6% of severe patients were treated with nasal cannula and only 13.64% needed a high-flow cannula, while critically ill patients, 13.33% required a high-flow cannula, 60% required IMV, and 26.6% NIMV, therefore the most critical patients with the worst prognosis have higher oxygen requirements [70].

Resuscitation with intravenous fluids

Both guidelines recommend restrictive resuscitation with

intravenous fluids (mainly crystalloids), because high volumes can worsen the pulmonary edema degree, prolong days on the ventilator, ICU stay, and increase mortality in patients with ARDS [61-69].

Other treatments

Convalescent plasma does not have enough evidence to allow its use. Two studies in China treated patients with COVID-19 with convalescent serum. The results were that there were no serious adverse effects, the 10 patients improved in symptoms (cough, dyspnea, fever, and chest pain) in an average of 1 to 3 days after the transfusion, also demonstrated radiological improvement of lung lesions. In the second study, 5 patients under ventilation invasive mechanics reported improvement after convalescent plasma transfusion, evidenced the withdrawal of mechanical ventilation, reduction in viral load, improved oxygenation and clinical stabilization. Doses of 200 to 500 ml (4-5 ml/kg) are recommended. Although no serious side effects have been seen,

safety and efficacy testing, testing and trials are still pending to be realized in randomized clinicians [71-72].

Gamma globulin IV does not have sufficient evidence to determine its efficacy in COVID-19 treatment for patients, since it was administered in combination with other medications and in selected cases, generally more serious or critical patients [73].

There is insufficient evidence to recommend specific pharmacological treatment for COVID infection in pregnant women, beyond the recommendations associated with oxygen therapy as needed according to hypoxia, vasoactive support and antibiotic if necessary, no adverse events have been reported in the aforementioned schemes of antivirals or immunomodulators. The American College of Obstetricians and Gynecologists (ACOG) proposed an evaluation and outpatient treatment algorithm for pregnant women with suspicion or confirmation of COVID-19 (Figure 4) [74].

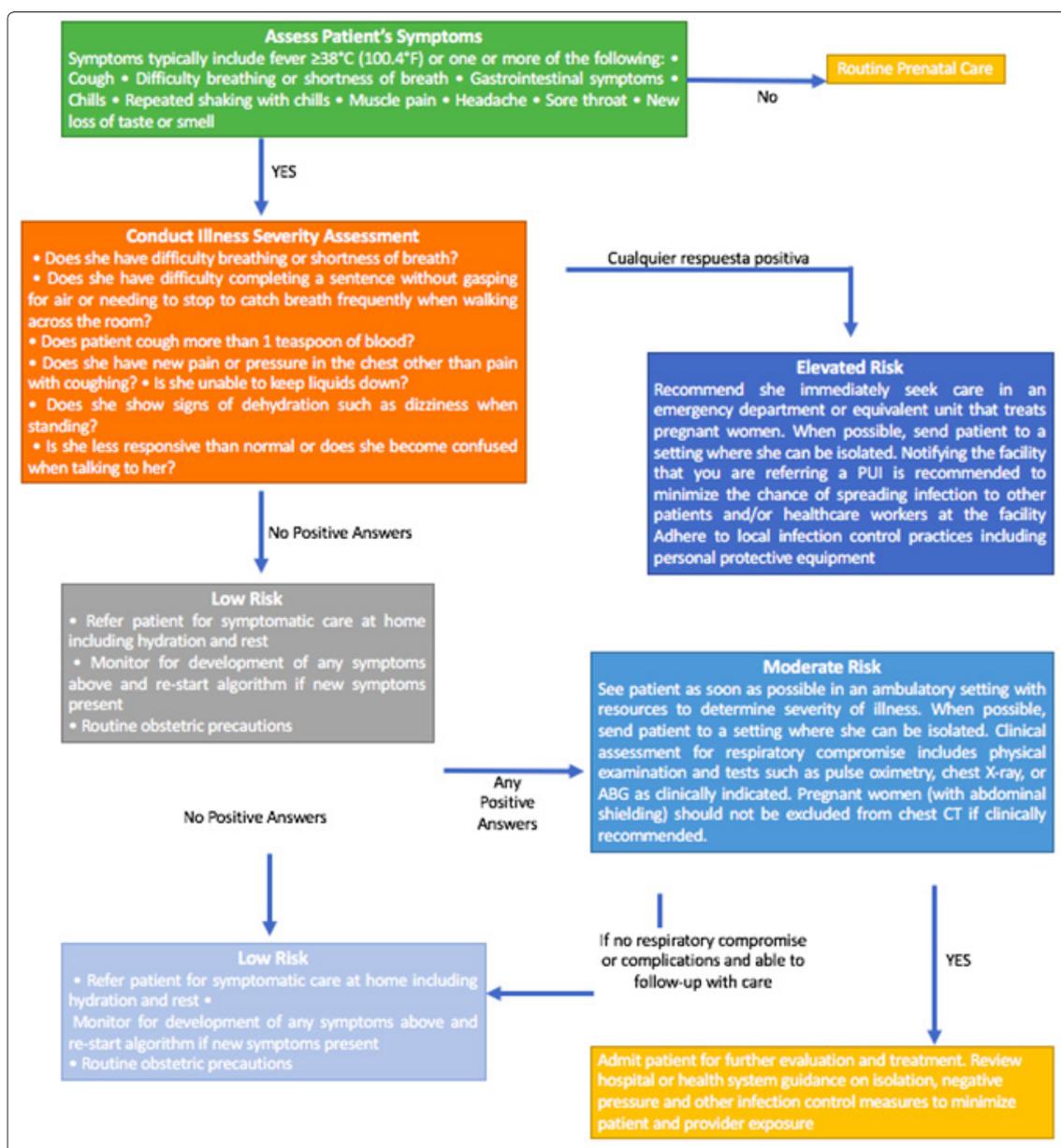


Figure 4: Outpatient assessment and management for pregnant women with suspected or confirmed Novel Coronavirus (Covid 19). Adapted from: The American College Of Obstetricians and Gynecologists / Society for Maternal-Fetal Medicine

Perinatal Outcomes

Maternal Outcomes

There is not much information known about the adverse effects and maternal impact of SARS-CoV-2. However, most reports are based on the great similarity between the genomic sequence of SARS-CoV-2 and SARS-CoV, so we can use the studies carried out in the latter, to know what we can expect from the new coronavirus, although transmission and propagation between these viruses have been shown to occur in different ways.

Coronaviruses have been responsible for pandemics such as SARS over the past two decades, with a 10.5% fatality rate [75] and in pregnant women it has been shown to be up to 25%. There is also MERS with a 34.4% fatality rate and in pregnancy up to 37% [76]. A systematic review of 6 studies mentioned that SARS-CoV-2 infection is associated with high risk of preterm delivery (41.1%), pre-eclampsia (13.6%), delivery via cesarean section and perinatal death (7%) [77].

Physiological adaptation in pregnant women predisposes to a more severe course of pneumonia. When specifically studying women with this diagnosis, Liu reported a study of 15 patients in whom changes in the CT were studied. At first, opacities in polished glass were observed, progressing to consolidations and finally remitting in 10 patients. Pregnancy did not exacerbate the severity of pneumonia in these patients [78].

In a systematic review of patients without comorbidities, the majority of which had infection during the third trimester, only 1 of 51 presented the severe type. The delivery route was cesarean section, the indication of which is not entirely clear, the majority of them were preterm, which could be a consequence of elective intervention after diagnosis [79].

In a publication that included 38 pregnant women with COVID-19, of whom 37 had infection confirmed by RT-PCR, no cases of severe pneumonia or maternal death were reported. Although there were comorbidities in some of them, some of which were of obstetric etiology, it did not result in maternal deaths [80]. The Pierce-Williams study, previously commented, is one of the most recent studies and it covered 64 patients, the maternal impact was that the severely ill had a high rate of acute respiratory failure and there was a case of cardiac arrest, but without cases of cardiomyopathy or maternal deaths [36].

Fetal Outcomes

As there is not much maternal evidence available, there is also little information about fetal impact. So likewise, the experience reported in studies of other coronaviruses in previous pandemics supports current medicine to evaluate possible outcomes in the fetus.

A study by Wong in women with SARS in Hong Kong evaluated perinatal outcomes in the period from February 1st to July 31st, 2003. Of 7 patients, 4 presented spontaneous abortion during the first trimester, which is attributed to hypoxia caused by SARS-related acute respiratory distress [81].

Another study made in China in 2003 by Zhang, included 5 pregnant women. The 5 infants were clinically evaluated and none presented evidence of SARS infection at birth [82]. In Hong Kong, Yan and colleagues did another study on 5 infants whose mothers were infected with SARS-CoV, who underwent multiple examinations including serial RT-PCR, viral cultures and neonatal serological titers; and all were negative. None of the 5 neonates

developed any clinical sign or symptoms of infection or respiratory compromise [83].

Looking into new evidence regarding SARS-CoV-2 infection, Shek retrospectively reviewed the clinical records of 116 pregnant women with SARS-CoV-2 pneumonia from 25 hospitals in China from January 29 to March 24 2020, that were included in 4 small series of cases previously done. During the review of records, no fetal risks were identified, but it was found that of the 100 infants of infected mothers, there was one case of severe neonatal asphyxia and one case of neonatal death. 86% of the newborns were tested for SARS-CoV-2 viral nucleic acid by pharyngeal swab, and all results were negative. Umbilical cord blood was examined in 10 of the neonates and amniotic fluid was collected at the time of birth, both of which were also negative for SARS-CoV-2 [84].

In Chen's study, it was concluded that there is currently no evidence to suggest that the development of COVID-19 pneumonia in the third trimester of pregnancy leads to the occurrence of severe outcomes in neonates or fetal infection. In this study one of the infants weighed 1880 grams at birth, with a gestational age of 36 weeks. But in this case the mother started with pneumonia symptoms 3 days before her hospital admission for COVID-19 and she also develops preeclampsia, so it was concluded that it was a case of fetal growth restriction associated with preeclampsia, and that it was not a consequence of SARS-CoV-2 infection. Another important finding was that the 9 neonates had Apgar at 8 minutes and at 5 minutes at 9 and some at 10. One of the infants had a slight increase in cardiac enzymes on the day of birth, but without clinical signs. None of the neonates required special pediatric treatment [84].

At Wuhan Children's Hospital, Zeng carried out a study in a cohort of 33 neonates, born to mothers with COVID-19, of whom only 19 had been examined. Of those 19, 3 were SARS-CoV-2 positive, and their mothers had positive RT-PCR. These 3 neonates are male, with adequate weight at birth and no data of asphyxia at birth. Among the symptoms and complications that they developed, 2 of them presented only fever and pneumonia, and the other presented pneumonia, respiratory distress, dyspnea, cyanosis, and food intolerance. Although there are other studies in which tests carried out on amniotic fluid, cord blood and breast milk report negative results, it cannot be safely stated that there is no vertical transmission due to the results found in neonates in this cohort [85].

There is a case report by Wang of a newborn son of a woman living in Wuhan, who underwent a cesarean section at 40 weeks of pregnancy for probable viral pneumonia. The newborn did not have contact with its mother after birth, never developed signs of COVID-19 or clinical deterioration. However, 36 hours after birth, SARS-CoV-2 infection was confirmed. The clinical manifestations of both patients were mild with a satisfactory prognosis. The timing of infection acquisition on the neonate is controversial [86].

Childbirth and Delivery Method

Different guidelines mention that the delivery method for patients with COVID-19 who are in labor and are symptomatic or that are with mild, stable symptoms and without contraindication for vaginal delivery and without fetal deterioration, should continue labor. In these patients, continuous cardiotocography should be used, ideally neuraxial analgesia should be administered, the number of vaginal evaluations should be minimized, amniotomy should be performed, the expulsive period should be shortened and instrumented delivery should be considered. Early cord clamping

should be done to avoid any risk of transmission from the mother to the newborn.

If the patient deteriorates or presents severe symptoms or alterations of the fetal state, regardless of gestational age, individualized assessment should be made taking into consideration risks and benefits of continuing labor or immediate delivery via cesarean section. The latter should be considered only if it will help the efforts of medical personnel to improve the clinical condition of the patient. If the patient goes into labor, with COVID-19 confirmed or suspected and both the mother and infant are clinically stable, there is no indication to urge the delivery or to perform a cesarean section.

Preferably, delivery should occur electively when the patient has or develops a negative test after a SARS CoV 2 infection. Abdominal delivery is only recommended in the presence of obstetric contraindications to vaginal delivery or due to obstetric indications. An important aspect is to emphasize that regardless of the delivery method, all protection measures must be taken, both by medical personnel and for the mother and newborn, too [87- 88].

Conclusion

The COVID-19 pandemic has spread at a rapid rate. Being its origin in China and its epicenter in Europe, it has ended up affecting around more than 200 countries in the world, with an increased alarming rate of infected cases and deaths. Through time, there are reported new findings that change the course of medical action. Information regarding pregnancy is limited and much remains to be studied about vertical transmission and perinatal outcomes. A great question has been raised about its management, but based on previous experiences with SARS, MERS and other respiratory infections, attempts have been to replicate or improve the treatment. There is no doubt that the evidence will be updated quickly and daily, and therefore, we are going to count on better recommendations regarding the detailed obstetric evaluation and correct management of the infection in these patients. There is no evidence to support that pregnancy increases the susceptibility to COVID-19. However, it is a global challenge for obstetricians and maternal fetal specialists to obtain the best benefits and achieve satisfactory perinatal outcomes. In Mexico it is necessary to carry out precise studies to know the exact behavior of the infection in our pregnant patients, this way we will begin to contribute as a country in the correct approach and diagnosis of the disease in order to provide the patients with the best possible treatment and avoid fatal outcomes or maternal and fetal adverse consequences.

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