

REVIEW PAPER

1. Paulino Vigil-De Gracia, MD., Dr. AAM Hospital Complex – Social Security Fund. Distinguished Researcher of the National Research System SENACYT, Panama
2. Gynecologist-Obstetrician, Luis "Chico Fábrega" Hospital, Santiago-Veraguas, Panama
3. Gynecologist-Obstetrician, Chief of the Department of Gynecology and Obstetrics, Dr. AAM Hospital Complex – Social Security Fund, Panama, Panama
4. Gynecologist-Obstetrician, Panama, Panama
5. Gynecologist-Obstetrician, Santo Tomás Hospital, President of the Panama Society of Gynecology and Obstetrics, Panama, Panama
6. Gynecologist-Obstetrician, José Domingo de Obaldía Hospital, David-Chiriquí, Panama
7. Gynecologist-Obstetrician, Santo Tomás Hospital, Panama, Panama
8. Gynecologist-Obstetrician, Dr. AAM Hospital Complex – Social Security Fund, Chief of SUGO, Panama, Panama

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Corresponding author:

Paulino Vigil-De Gracia, MD.

Complejo Hospitalario Dr. AAM Caja de Seguro Social, SENACYT Panamá

50766143240

pvigild@hotmail.com

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COVID-19 and pregnancy. Review and update

COVID-19 y embarazo. Revisión y actualización

Paulino Vigil-De Gracia¹, Luis Carlos Caballero², Jorge Ng Chinkee³, Carlos Luo⁴, Jaime Sánchez⁵, Arelys Quintero⁶, Jorge Espinosa⁷, Sara E. Campana Soto⁸

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ABSTRACT

Objective: To search for all the information and available evidence on infection with SARS-CoV-2, a virus that appeared during the first 4 months of 2020, and pregnancy. **Methods:** Systematic review in PubMed and Google Scholar databases until April 25, 2020. We searched for published articles related to pregnant women infected with SARS-CoV-2. There was no language restriction. The search was extended to the references of the articles found. **Results:** In pregnant women with COVID-19, more than 90% of patients evolve mildly, 2% require intensive care. One maternal death has been reported. Prematurity occurs in approximately 25% of the cases, with predominance of late preterm infants; premature rupture of membranes presents in about 9%. Perinatal mortality is lower or similar to that of the general population, and vertical transmission has not been shown. **Conclusions:** Obstetrician-gynecologists must prepare to attend more cases with COVID-19 and therefore they need to know this disease. COVID-19 progresses similarly in pregnant and non-pregnant women, although it is associated to prematurity. While vertical transmission has not been demonstrated, horizontal transmission during vaginal birth is very likely.

Key words: COVID-19, Pregnancy infectious complications, Maternal mortality, Perinatal mortality, Infectious disease transmission, vertical.

RESUMEN

Objetivo. Buscar toda la información y evidencia disponible sobre el SARS-CoV-2 -que surgió en estos primeros 4 meses de 2020- y el embarazo. **Metodología.** Revisión sistemática en las bases de datos PubMed y Google Scholar, hasta el 25 de abril de 2020. Se buscó artículos publicados relacionados con mujeres embarazadas infectadas con SARS-CoV-2. No hubo restricción de idioma. La búsqueda se extendió a las referencias de los artículos encontrados. **Resultados.** La enfermedad COVID-19 en mujeres embarazadas se caracteriza porque más del 90% de las pacientes evoluciona en forma leve, 2% requiere ingresar a las unidades de cuidados intensivos. Una muerte materna ha sido reportada. La prematuridad es alrededor de 25%, con predominio de recién nacidos prematuros tardíos; aproximadamente el 9% se complica con rotura prematura de membranas; la mortalidad perinatal es baja o similar a la de la población general y no se ha demostrado la transmisión vertical. **Conclusiones.** Los ginecólogos obstetras deben prepararse para atender cada vez más casos con COVID-19 y, por lo tanto, es necesario tener su conocimiento. La enfermedad evoluciona de la misma manera que en las no embarazadas, genera mayor prematuridad, no se ha demostrado la transmisión vertical, pero hay altas posibilidades de transmisión horizontal durante el parto vaginal.

Palabras clave. COVID-19, Complicaciones infecciosas del embarazo, Mortalidad materna, Mortalidad perinatal, Transmisión vertical de enfermedad infecciosa.

INTRODUCTION

On December 31, the first case of pneumonia caused by a new coronavirus (SARS-CoV-2) was announced in the city of Wuhan, Hubei province, China. Since then, new cases have appeared all around the world, to such a degree that the World Health Organization (WHO) declared it a global pandemic on March 13^(1,2).

The available information suggests that the infection was originally zoonotic, but current transmission is through close person-to-person contact (less than 2 meters) through respiratory droplets, or by direct contact with surfaces contaminated with infected secretions. Transmission could also occur by contaminated stool. The usual incubation period is 4 to 6 days, but it can vary from 2 to 14 days.



As the number of infected increases, cases of pregnant women with COVID-19 rise. Currently, there are no controlled studies of this disease in pregnant patients, but we have found case studies, case series and reviews⁽³⁾ informing that pregnant women with COVID-19 do not tend to present serious symptoms. Until now, one maternal death has been reported, despite viral pneumonia being a leading cause of maternal mortality worldwide⁽⁴⁾. In pregnant women, COVID-19 is usually characterized by fever (77 to 85%), followed by respiratory symptoms (dry cough and dyspnea in 23%), fatigue and/or muscle pain and, less frequently, gastrointestinal symptoms like diarrhea. Leukopenia and especially lymphopenia have also been reported⁽³⁾. It remains unclear if the pulmonary compromise or the pneumonia pattern among infected pregnant women differs from the other patients. A study of 15 cases in China⁽⁵⁾ found that most infected pregnant women had mild pneumonia with the same imaging findings as the general population, which are pavement pattern and consolidations mainly in the inferior lobes from both lungs⁽⁶⁾.

As in the general population, diagnosis is done by detecting viral genome (RT-PCR)⁽¹⁻⁴⁾.

Vertical transmission is highly unlikely; it has not been shown in any case during the current COVID-19 outbreak in China⁽³⁾, nor in previous epidemics by similar coronaviruses (SARS-CoV and MERS-CoV)⁽⁷⁾. Available studies have not found the virus in genital secretions, amniotic fluid nor breast milk⁽³⁾. Reported cases of infection in newborns are probably due to horizontal transmission.

This review summarizes the findings of studies and analyses in pregnant women with COVID-19, to contribute to the knowledge and management of this group of patients.

METHODOLOGY OF THE REVIEW

We performed a systematic review in the databases PubMed and Google Scholar until April 25, 2020, searching for published articles about pregnant women infected with SARS-CoV-2, without language restriction, and extending the search to the references of the retrieved articles. The review also included pregnancy outcomes after COVID-19 was diagnosed, as well as newborn's birth, progress and outcomes. Relevant

data were extracted to a dedicated database. The protocol was registered in the research database of Panama.

DIAGNOSIS

Current methods to detect SARS-CoV-2 include:

A. Nucleic acid detection technology (RNA)

This diagnostic technology works with nucleic acid and is currently available as commercial kits. However, it has the following disadvantages: false negatives and false positives, samples for detection are easily contaminated and they require precision instruments and technical professionals. It is inconvenient to study the population at a large scale, and the technique is not viable for all hospitals. Besides, the positive rate for mild cases and for samples taken more than one week ago is low.

B. Immunodiagnosics techniques

1. Enzyme-linked immunosorbent assay (ELISA). The ELISA method is a fast, simple test that has a high sensitivity and does not require special instruments. It is particularly adequate for the serological detection of a large number of samples. Nevertheless, the purity of the antigen or of the coated antibody can seriously affect its specificity.
2. Immunogold labelling technology has become a trend in in vitro diagnostics in the last years because of its simple process that does not require special equipment nor specific operator training. Test results are intuitive and convenient for basic units and field work.

MOLECULAR METHODS

Routine confirmation of COVID-19 cases is based on detecting viral nucleic acid (RNA) by RT-PCR assays.

RNA can be extracted from the samples using any standard protocol or extraction kit. In general, the lysis step in RNA extraction inactivates any living virus, so lysates are usually considered non-infectious. Inactivation of SARS-CoV-2 by sample lysis has been confirmed in some commercial kits^(8,9).



The protocol is based on detecting two targets in the viral genome: the E gene as a first line screening assay and the RdRp gene as the confirmatory assay using probes P1 and/or P2. The E gene is specific for all viruses related to SARS-CoV-2 (SARS-CoV and bat coronaviruses), while the RdRp gene is specific for SARS-CoV-2 when tested with probe P2. The PAHO/WHO has distributed specific reagents (primers, probes and positive controls) and protocols for these assays^(8,9).

Although it is recommended to test for two different genetic targets (the E gene, followed by the RdRp gene) in order to obtain laboratory confirmation, once there is sustained transmission of coronavirus-19 within an area or country, it is not necessary to perform PCR for both genes. Diagnosis can use either the E or the RdRp gene. However, PCR for the E gene has a greater sensitivity, so the E gene is preferred for diagnosis.

Many reasons can explain a negative result in a person infected with COVID-19:

- Poor sample quality, handling, transportation
- Sampling failure, insufficient sample, presence of PCR inhibitors in the extracted RNA
- Sample collection taking place when the patient is shedding undetectable levels of the virus, for example, too early or too late in the infectious disease process.
- As with any other molecular assay, viral mutations in the regions targeted by the probes can affect detection sensitivity.

We must remember that, although this type of test is the most precise way to determine disease, its sensitivity does not exceed 60 to 70%.

ANTIGEN DETECTION

During the first days after symptom onset (between 1 and 5), viral proteins that can be detected with several tests, such as ELISA and immunofluorescence, are generated. These assays have a generally acceptable specificity (depending on the assay). Thus, a positive result can be used as a diagnostic criterion, together with case definition and the clinical and epidemiological history; it can also be used to make public health decisions, such as social isolation. Nevertheless, the dynamics of production and

secretion of these proteins (antigens) has not been established, so a negative result should not be used to rule out disease, and other criteria must be taken into account⁽¹⁰⁾. Besides, as days after infection and peak viral load pass by, sensitivity decreases.

SEROLOGIC METHODS

Assays based on the detection of IgM/IgG antibodies can be of use in the investigation of outbreaks and seroprevalence studies. Many assays that detect IgM/IgG antibodies, such as ELISA and rapid diagnostic tests, are available and commercialized for diagnosing infection by coronavirus-19. These tests can be limited by cross-reaction with other coronaviruses normally present in the community, which makes the results difficult to interpret. Besides, response and antibody production dynamics during the different phases of infection is not fully established yet, which further limits the use of these tests.

Some studies have shown that during the first 6 to 7 days since symptom onset, less than 40% of patients have detectable antibodies⁽¹¹⁾. In the same way, antibody detection after day 7 only indicates previous contact with the virus, but it does not confirm presence and active shedding of it. Detected antibodies could be the result of a previous infection and not of an acute one, which is the problem that requires diagnosis.

Many products that detect antibodies (IgM and/or IgG) induced by COVID-19 infection are being commercialized, including rapid diagnostic tests (RDT). Any test of this kind must be validated and its performance evaluated in terms of specificity and sensitivity.

These are the tests that will certainly help us assess population immunity and the duration of protection against the virus. Even today, they can help us know if there are people who were infected and did not present any symptoms.

MATERNAL COMPLICATIONS

A pregnant woman with COVID-19 implies a great dilemma for her, her relatives and, obviously, her attending physicians. Like in the general population, disease can be mild or severe. Nearly 90% of patients will present a mild form⁽³⁾, a rate comparable to that of the general population between 15 and 45 years old. The remain-



ing 10% will develop the severe form, usually with pneumonia or respiratory distress, requiring hospitalization to receive oxygen and close care. 2% will need an intensive care unit due to severe acute respiratory syndrome⁽³⁾. Until now, one scientific publication has reported one maternal death⁽¹²⁾; another publication presented a severe case without mentioning its outcome⁽¹³⁾. We consider, based on current limited data, that lethality in a pregnant woman with COVID-19 is approximately 1%. As more cases are reported, we will have a more precise idea of the course of disease and outcomes of pregnant women with COVID-19⁽¹⁴⁾.

FETAL COMPLICATIONS

Current evidence does not suggest a higher risk of abortion or early gestational loss in pregnant women with COVID-19^(3,14,15). Previous results in patients with SARS-CoV and MERS-CoV have not shown a clear causal relationship with these complications⁽⁷⁾. To date, vertical transmission has not been confirmed, so the existence of congenital defects linked to COVID-19 is unlikely^(3,14).

The main perinatal complications are those associated with prematurity, observed in 25% of the cases and especially in late preterm infants⁽³⁾. Delivery could be programmed prematurely by the attending physician, in response to the mother being infected with COVID-19. Another proposed cause of prematurity is the high rate of premature membrane rupture, 9%.

So far, there is no evidence of higher intrauterine nor postnatal mortality associated to COVID-19^(3,14,15). The reviews with the highest number of total cases (108⁽¹⁴⁾ and 83⁽³⁾ pregnant women) and the largest case series to date (118 cases)⁽¹⁵⁾ report very similar maternal and perinatal results.

CLINICAL MANAGEMENT OF THE PREGNANT PATIENT

The clinical management of the pregnant woman with COVID-19 depends on the severity of the disease, gestational age, patient conditions when delivery ensues and the delivery mode or method of termination.

Stable patients with mild disease require ambulatory care, which includes rest, temperature

monitoring, hydration and paracetamol 500 mg every 8 hours for fever, and personal and family protective measures such as hand washing, wearing a mask and isolation to the extent possible. The patient must also receive the standard obstetric recommendations given to any healthy woman, according to gestational age^(16,17).

Cases with a severe condition require hospitalization and continuous monitoring. They usually receive oxygen via nasal catheter upon need and paracetamol for fever. Antibiotics must be considered, given the possibility of additional bacterial pneumonia. Management has to be collaborative with pulmonologists and specialists in infectious diseases. In patients whose respiratory condition worsens, mechanical ventilation and their admittance to the ICU may be required; in these cases, a multidisciplinary team will be in charge. The gynecologist-obstetrician can consider performing an ultrasound to evaluate fetal wellbeing and growth, as well as electronic fetal monitoring, in accordance to gestational age and following instructions for personal protection^(16,17). In the intensive care unit, if gestational age is over 26 weeks, we suggest monitoring fetal heart rate every 8 hours with Doppler ultrasound. If gestational age is under 26 weeks, it is not justified.

CHEST RADIOGRAPHY DURING PREGNANCY

Chest imaging, especially by CT scan, is essential to evaluate the clinical state of a pregnant woman with COVID-19^(18,19). Radiation from a single chest X-ray is insignificant; the amount of radiation from a single chest CT scan or CT pulmonary angiogram is very low⁽²⁰⁾.

In a pregnant woman under suspicion of COVID-19, while a chest CT scan is regarded as an important tool to detect the disease, diagnosis can be based on chest X-ray and clinical findings alone. Informed consent must be obtained (shared decision making), and radiation shielding must be provided.

USE OF CORTICOIDS

Usually, when a patient is at risk of preterm birth, specifically between weeks 24 and 37, it is suggested to administer corticoids in a total dose of 24 mg (two doses of betamethasone or four doses of dexamethasone)⁽²¹⁾. There are no studies



about the use of corticoids in pregnant women with COVID-19 yet; however, case reports mention using them for fetal maturity^(3,15). There is no contraindication to the use of corticoids in these patients, but they must be reserved for cases with criteria of severity and a gestational age between 24 and 34 weeks, if there is a possibility of delivery within the next 7 days.

USE OF ANTI-INFLAMMATORIES, ANTIVIRALS AND OTHER DRUGS

Some guidelines and medical professionals recommend using drugs such as lopinavir/ritonavir, chloroquine, hydroxychloroquine and some other antivirals in pregnant women⁽²²⁾. Currently, there are no adequate studies assessing the efficacy of these treatments in COVID-19 patients in the general population⁽²³⁾, which is why we do not recommend their use. Besides, the systematic review of 83 pregnant women with COVID-19 reports that approximately 98% of patients did not take any of these drugs during pregnancy, with results equal or better than those of the general population^(3,15). However, if a patient is taking a drug as part of a research study with specific requirements, it is suggested that they continue to do so.

Antibiotics, especially azithromycin, can be used if recommended by the specialist in infectious diseases, particularly in severe cases, given the possibility of bacterial coinfection.

CESAREAN SECTION

Delivery in a patient with COVID-19 should preferably take place when tests are negative. Because of this, infection with COVID-19 should not be an indication for patients with a gestational age under 39 weeks; however, there are some scenarios to discuss.

For patients in the 39th week or more with history of a C-section or an obstetric indication of cesarean delivery and COVID-19, either mild or severe, C-section must take place with all the required care regarding personal protection and follow-up of mother and newborn.

In pregnancies under 39 weeks with a previous C-section or obstetric indication of C-section and COVID-19, with criteria of mild disease, the team

must wait until clinical findings disappear or improve and tests for SARS-CoV-2 turn negative.

In pregnancies under 39 weeks with a previous C-section or an obstetric indication for it and COVID-19, with criteria of severe disease, the decision to operate must be discussed with the neonatologist, the specialist in infectious diseases, the pulmonologist and the gynecologist-obstetrician. If the patient has less than 37 weeks and the clinical scenario allows it, corticoids must be administered as previously described. In some cases, the obstetric indication for C-section is a maternal condition, which may worsen during the active phase of labor.

There is no evidence that early or delayed clamping is associated with a higher risk of infection. As such, we consider that the attending professional should wait at least one minute to clamp the umbilical cord, until there is evidence suggesting the contrary. Vertical transmission of the virus has not been proven^(3,15).

DELIVERY

As described previously, the best moment for birth is when tests are negative and pregnancy is at term. In most cases, COVID-19 is considered an indication for cesarean delivery^(3,14,15). Rates of vaginal delivery are extremely low, between 7 and 11%^(3,15), possibly because of maternal condition and the limited knowledge about this disease. It should be clear that if we do not have a PCR test from a perianal swab or if its result is positive, vaginal delivery is contraindicated. At the same time, we must have all the necessary precautions to protect health professionals, mother and newborn. They must be attended under the same obstetric conditions as a patient without COVID-19, which include fetal monitoring and oxytocin if required. It is preferable to not use obstetric analgesia and, if strictly necessary, to do so in the least invasive way possible, exposing the least number of healthcare workers possible. All this must be discussed with the patient. Delayed umbilical cord clamping should be performed except for neonatal or maternal complications.

Conditions for delivery based on gestational age are the same as those for C-section, as long as vaginal birth is indicated; cervical ripening with prostaglandins can be considered.



Vaginal delivery could carry a risk of horizontal transmission to the newborn. Viral presence in stool by PCR varies from 29 to 67%⁽²⁴⁻²⁶⁾, which means that the virus can be present in the perianal area, especially during delivery, when stool can come out. At birth, the baby's face (mouth, nose) contacts the perianal area and, occasionally, also stool, so the possibility for horizontal transmission is high if these are contaminated. This obviously has to be confirmed with clinical studies. On the other hand, the outcomes of newborns horizontally infected by their mother are still unknown⁽²⁷⁾. Until clinical studies resolve these issues, cesarean section should remain as an indication for COVID-19 positive patients, unless testing for SARS-CoV-2 in the perianal area is negative.

MANAGEMENT AFTER BIRTH

After delivery, standard postpartum management should be performed in an isolation area. If the disease is mild, discharge should occur at the same time as in healthy mothers, with recommendations for social isolation at home, hydration and paracetamol for fever. Anti-inflammatory analgesics should be avoided in these patients.

If the patient has severe illness, management should continue in the hospital until the multidisciplinary team recommends discharge.

Testing for SARS-CoV-2 should be applied to all newborns of mothers with COVID-19⁽²²⁾.

The outcomes of newborns with COVID-19 are still unknown. If the PCR test from nasal swab is negative, isolation should be practiced in the same room, with at least 2 meters of distance between mother and child.

BREASTFEEDING

There is currently no evidence of the virus being found in breast milk, so this would not be a reason to suspend breastfeeding; further research is still required. It is clear that, in the scenario of an infected mother in close contact with her newborn, there is a risk of infection for the baby. Consensus among most organizations^(17,22,28) is that breastfeeding should not be forbidden as long as mother and child are in normal conditions. This is a decision that should be discussed and agreed upon with the mother⁽²²⁾.

If breastfeeding is decided and mother-child contact cannot take place, milk should be expressed following all hygiene measures and avoiding any possible contagion, and a relative or a third person should feed the milk to the infant.

ASYMPTOMATIC CASES

When there is sustained community transmission in a city or country, the chance of having asymptomatic cases is higher; among pregnant women, this probability persists. To date, we have identified three publications⁽²⁹⁻³¹⁾ that demonstrate the existence of asymptomatic pregnant patients. Combined, they present 48 cases initially admitted to the hospital without any symptoms, who later developed signs for COVID-19 and were diagnosed with the disease, during vaginal or cesarean delivery or during the immediate postpartum. Interestingly, Sutton et al.⁽³¹⁾ tested 215 patients in a maternity ward, of which 33 (15%) were positive for COVID-19. An outstanding finding of this study was that out of the 33 positive patients, 29 of them were asymptomatic on admission; in other words, 88% of COVID-19 cases had no symptoms.

Given the findings of these studies, it is necessary to attend all obstetric patients as suspect cases and to perform confirmatory tests for SARS-CoV-2 whenever possible.

CONCLUSIONS

SARS-CoV-2 is a new coronavirus that started infecting humans by the end of 2019. It has caused the WHO to declare it a global pandemic and it has affected over 3 million people, causing approximately 200 000 deaths. Pregnant women are vulnerable to infection.

Most infected patients develop a mild form. In pregnant women, less than 10% develop the severe form, and less than 2% is admitted to an ICU. Only one case of maternal death has been published.

A significant proportion of cases of COVID-19 in the third trimester result in preterm birth (25%), mainly due to maternal instability and the attending healthcare team's decision, as well as a higher frequency of premature membrane rupture. Perinatal mortality is very low. Vertical transmission has not been shown yet and cases of infected newborns seem to be caused by horizontal transmission.



There is a significant amount of asymptomatic cases seeking routine obstetric attention, so obstetric patients have to be treated as possible cases, providing the necessary protection for the healthcare team, the newborn and their families.

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