ORIGINAL ARTICLE

Placental pathology and perinatal risk during the COVID-19 pandemic

Víctor M. Vargas-Hernández, Jesús E. Luján-Irastorza and Carlos Durand-Montaño*
PRONATAL Clinic (Bité Médica Hospital), Mexico City, Mexico

Abstract

Background: *Respiratory and immune changes during pregnancy can lead to viral infections. In coronavirus disease 2019 (COVID-19), clinical characteristics and perinatal risks are difficult to assess and are relatively unknown.* **Objective:** *To review placental pathology in asymptomatic women with COVID-19, and to evaluate effects on perinatal outcomes.* **Material and method:** *Retrospective, observational, cross-sectional study that included 29 pregnant women in 2020. The women underwent COVID-19 tests and were divided in two groups: 1) control, COVID-19-negative patients, and 2) asymptomatic COVID-19-positive patients; the placentas were studied at the pathology department, and clinical data were retrieved from the electronic medical record; in addition, a literature review was carried out.* **Results:** *When the groups were compared, no differences were observed in general data and clinical characteristics. On the day of delivery, patients 2, 4, 5, 6, 8 and 9 of the COVID-19 group were between day 0 and 10.5 after having tested positive; only patients 1, 3 and 7 had overcome the infection. There was a decrease in weeks of gestation in the COVID-19 group (37.8 ± 1.8 vs. 39 ± 0.8; p ≤ 0.05). COVID-19-positive patients' placental histopathology showed a higher prevalence of thrombotic alterations in placental villi (55.5 vs. 0%).* **Conclusions:** *COVID-19 asymptomatic infection potentiates preexisting prothrombotic profile, thus increasing the risk of placental thrombosis and, potentially, of thrombosis in pregnant women.*

KEY WORDS: *COVID-19. Pregnancy. Placenta. Thrombosis.*

Patología placentaria y riesgo perinatal durante la pandemia por COVID-19

Resumen

Antecedentes: *Los cambios respiratorios e inmunitarios en el embarazo pueden conducir a infecciones virales. En la enfermedad por coronavirus 2019 (COVID-19) las características clínicas y riesgos perinatales son difíciles de evaluar y son relativamente desconocidos.* **Objetivo:** *Revisar patología placentaria en mujeres asintomáticas con COVID-19 y evaluar efectos en datos perinatales.* **Material y método:** *Estudio retrospectivo, observacional y transversal, incluye 29 mujeres embarazadas en 2020. Se realizaron prueba COVID-19 y dividieron en dos grupos: 1) control, pacientes COVID-19 negativas y 2) COVID-19 asintomáticas con COVID-19 positivo; las placentas se estudiaron en patología y los datos clínicos se tomaron del expediente electrónico; asimismo, se realizó revisión de literatura.* **Resultados:** *Al comparar grupos no se observó diferencia en datos generales y características clínicas. El día del parto, las pacientes 2, 4, 5, 6, 8 y 9 del grupo COVID-19 se encontraban entre día 0 y 10.5 después de positividad; únicamente las pacientes 1, 3 y 7 habían superado la infección. Se presentó disminución de semanas de gestación en el grupo COVID-19 (37.8 ± 1.8 vs. 39 ± 0.8; p ≤ 0.05). La histopatología placentaria en COVID-19 mostró mayor prevalencia de alteraciones trombóticas en vellosidades placen-*

Correspondence:
*Víctor M. Vargas-Hernández
E-mail: vvargashernandez@yahoo.com.mx

Date of reception: 12-07-2021
Date of acceptance: 12-08-2021
DOI: 10.24875/GMM.M21000604

Gac Med Mex. 2021;157:494-501
Contents available at PubMed
www.gacetamedicademexico.com

tarias (55.5 vs. 0%). **Conclusiones:** *La infección asintomática por COVID-19, potencializa perfil protrombótico preexistente, incrementando riesgo de trombosis placentaria y trombosis en mujeres embarazadas.*

PALABRAS CLAVE: *COVID-19. Embarazo. Placenta. Trombosis.*

Background

Coronavirus disease 2019 (COVID-19) is a respiratory condition caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus that is more contagious and infectious than SARS-CoV (2002) and Middle-East respiratory syndrome coronavirus (MERS-CoV) (2012).[1-4]

It infects epithelial cells through the angiotensin-converting enzyme 2 (ACE2), using the Spike protein.[5-7] It generates symptoms such as fever (83-98%), cough (46-82%), myalgia or fatigue (11-44%), dyspnea (31%), gastropathies (10%), hypotension (60%),[6] lymphopenia, leukopenia, thrombocytopenia, increased inflammatory cytokines, elevated cardiac biomarkers and decreased albumin.[6] Although respiratory conditions associated with COVID-19 are the focus of attention, there are studies that report ocular lesions,[7] testicular alterations,[8] ACE2 in the ovaries,[9] nervous system alterations,[10,11] thrombosis,[12] placental alterations[13] and pregnancy complications.[14,15]

In view of the foregoing, we evaluated a series of cases of asymptomatic pregnant women with COVID-19 with the purpose to analyze placental histopathological data in order to evaluate fetal effects and risks within the last trimester of pregnancy, in addition to conducting a review of recent literature.

Material and Method

Retrospective, observational, cross-sectional study that included 29 patients who attended the PRONATAL clinic (Bíte Médica Hospital, Mexico City) in 2020 for obstetric care. Clinical data were obtained from the electronic record, after informed consent was obtained.

The patients were hospitalized in the labor room for obstetric care, following the protocol implemented for the COVID-19 pandemic. It included the presentation of a COVID-19 test, not older than one week before the patient was admitted or, otherwise, if they had complications such as premature birth threat. Health personnel wore safety equipment to avoid contagion (face masks, face shields, caps, gloves, etc.), and the operating room was sanitized before and after use.[16] Two groups were formed: 1) control, which included those women who never contracted COVID-19 and 2) COVID-19, asymptomatic women with COVID-19 at third trimester of pregnancy.

COVID-19 tests (reverse transcriptase polymerase chain reaction [RT-PCR]; detection kit: Logix SmartTM Coronavirus Disease 2019 [COVID-19, InDRE validation document DGE-DSAT-03863-2020; InDRE permit document DGE-DDYR-08355-2020) were sent to the Cellular Diagnostic Center (Genes and Care, Mexico City).

The placentas were processed by Bíte Médica Pathology Department. Typical sections were fixed in formalin, processed in paraffin and stained with hematoxylin/eosin.

Data collection was carried out by nurses, physicians and a PRONATAL researcher (general data, COVID-19 test results and placental histopathology), with anonymity being protected, without the source of information being referenced and only numerical data being shown. Inclusion criteria were: COVID-19-positive asymptomatic women, full-term and preterm pregnancies. Exclusion criteria were: refusal to participate in the study, high levels of natural killer cells, tumor necrosis factor and having autoimmune diseases.

Clinical characteristics of the pregnant woman (age, weight, height, temperature, O_2 saturation, blood pressure [mmHg], heart and respiratory rate) and data of the newborn (gestational age, weight and height), are reported with the mean ± standard deviation (SD) and were analyzed using Student's t-test; on the other hand, thrombophilias, cesarean sections, deliveries and spontaneous abortions are reported as percentages and were analyzed with the chi-square test, using the SPSS statistical package, version 25.

Results

Twenty-nine women were included for obstetric care, out of which 9 were included in the COVID-19 group and 20 in the control group. Comparing both groups, no difference was observed in pregnant women general data and clinical signs (weight, height,

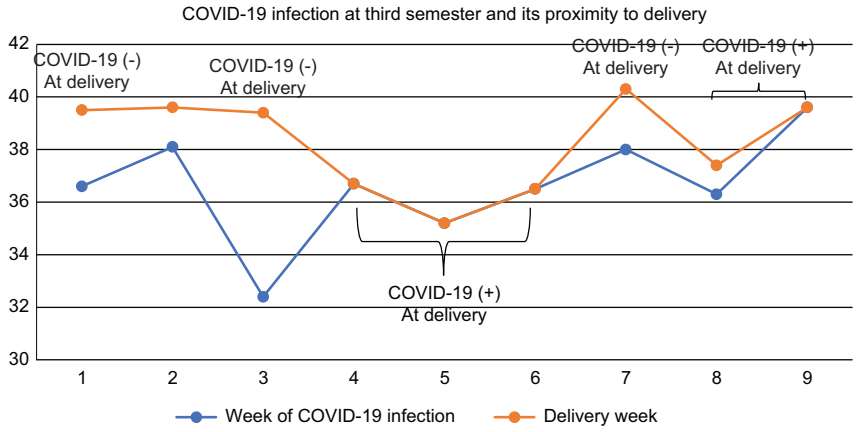

Figure 1. *Sample, weeks of gestation and delivery in relation to positive or negative COVID-19 status. COVID-19: coronavirus disease 2019.*

body mass index, temperature, O_2 saturation, blood pressure, heart and respiratory rate) (Table 1).

Regarding the COVID-19 group, on the day of delivery, patients 2, 4, 5, 6, 8 and 9 were between day 0 and 10.5 of infection, after having tested positive by the RT-PCR technique, and only patients 1, 3 and 7 had completed the quarantine period recommended for this infection (14 days) (Fig. 1).

As for the type of delivery, there was a higher prevalence of COVID-19 in cesarean sections vs. control (77.7 vs. 30%) (Tables 2 and 3). Complications such as preterm delivery (33.3%), premature placental abruption (20%), hypertension (11.1%), proteinuria (11.1%), mild preeclampsia (11.1%), oligohydramnios and fetal hypomobility (11.1%) were found in the COVID-19 group; and in the control group, placental abruption (5%) and premature rupture of membranes (5%) were observed (Tables 2 and 3). In the control group, cesarean sections were requested by the patient (10%) due to a thin uterine segment, imminence of uterine rupture and placental abruption. In addition, the prevalence of deliveries was lower in the COVID-19 group vs. controls (22.2 vs. 70%) (Tables 2 and 3). Neither group had complications in the postpartum period.

According to each patient obstetric history, the COVID-19 group had a prevalence of recurrent pregnancy loss of 44.4%, with one patient referring two induced abortions (11.1%); as for the control group, the prevalence of recurrent pregnancy loss was 10% (Tables 2 and 3).

Perinatal data showed a statistically significant decrease in the number of weeks of gestation in the COVID-19 group in comparison with controls (37.8 ± 1.8 vs. 39 ± 0.8; $p \leq 0.05$), with similar results being observed in both groups regarding birth weight (2,915 ± 535.4 vs. 3,013 ± 518.8 grams) and length (48.1 ± 2 vs. 48.5 ± 3.3 cm) (Fig. 2).

In the placental histopathological reports, COVID-19 vs. control group was found to have a higher prevalence of organized thrombi in placental villi (55.5 vs. 0%), as well as of laminated thrombus in an artery (11.1 vs. 0%), perivascular hemorrhage (33.3 vs. 0.0%), villous hemorrhage (55.5 vs. 42.1%), subchorionic hemorrhage (11.1 vs. 5.2%), retroplacental hematoma (22.5 vs. 15.7%) and stromal edema (44.4 vs. 31.5 %) (Fig. 3); in controls, villous ischemic changes

Table 1. General data and maternal signs at delivery day

	Control ($\bar{x}$ ± SD)	COVID-19 ($\bar{x}$ ± SD)	$p \leq 0.05$
N	20	9	-
Weight (kg)	72.9±11.1	74.5±9.3	-
Height (m)	1.62±0.04	1.61±0.04	-
BMI	27.6±3.3	28.5±2.5	-
Age (years)	35.8±5	35.4±4.6	-
Temperature (°C)	36.4±0.3	36.5±0.5	-
O_2 saturation	95.1±0.7	95.9±0.8	-
Blood pressure (mmHg)	1.5±0.1	1.5±0.1	-
Heart rate	81.8±13.6	86.4±8.9	-
Respiratory rate	19.7±1.3	18.7±8.4	-

SD: standard deviation; BMI: body mass index.

Table 2. Delivery characteristics (COVID-19 group)

N	Age (years)	Obstetric history	WOG	Type of delivery	Characteristics and complications
1	38	G2P1C1	39.5	Vaginal	No complications
2	35	G0	36.6	Vaginal	No complications
3	36	G0	39.4	C-section	Placental abruption
4	41	G2A2	36.7	C-section	Preterm delivery
5	39	G11A3P8	35.2	C-section	Preterm delivery
6	32	G8A6C2	36.5	C-section	Preterm delivery
7	34	G2C2	40.3	C-section	Placental abruption
8	44	G2A2 (elective)	37.4	C-section	Hypertension, proteinuria, mild preeclampsia
9	27	G3A3	39.6	C-section	Oligohydramnios and fetal hypomobility
Total	35.8±5 ($\bar{x}$ ± SD)	-	37.8±1.8 ($\bar{x}$ ± SD)	77.7% c. section	22.2% no complications, 33.3% preterm delivery, 22.2% placental abruption, 11.1% oligohydramnios, 11.1% hypomobility, 11.1% hypertension, 11.1% proteinuria and 11.1% mild preeclampsia

COVID-19: coronavirus disease 2019; WOG: weeks of gestation; SD: standard deviation.

Table 3. Delivery characteristics (control group)

N	Age (years)	Obstetric history	WOG	Type of delivery	Characteristics and complications
1	34	G3P3	37.3	Vaginal	No complications
2	44	G1A1	38.3	C-section	Elective, no complications
3	42	G0	39.3	Vaginal	No complications
4	31	G0	40.2	Vaginal	No complications
5	39	G1P1	38.5	Vaginal	No complications
6	36	G1A1	40.3	Vaginal	No complications
7	32	G0	38.6	C-section	Placental abruption
8	36	G1C1	38.2	C-section	Elective, no complications
9	31	G1P1	38.5	Vaginal	No complications
10	35	G0	40.2	Vaginal	No complications
11	39	G1C1	39.5	C-section	Thin uterine segment; no complications
12	37	G1P1	38.6	Vaginal	No complications
13	38	G2C1A1	39.5	C-section	Thin uterine segment and premature rupture of membranes
14	36	G0	39.4	Vaginal	No complications
15	43	G3A3	39.1	C-section	Thin uterine segment; no complications
16	40	G0	39.2	Vaginal	No complications
17	34	G0	38.2	Vaginal	No complications
18	29	G0	40.2	Vaginal	No complications
19	32	G0	39.4	Vaginal	No complications
20	27	G1P1	39.2	Vaginal	No complications
Total	35.4±4.6 ($\bar{x}$ ± SD)	-	39±0.8 ($\bar{x}$ ± SD)	30% C-sections	90% without complications, 5% placental abruption and 5% rupture of membranes

WOG: weeks of gestation; SD: standard deviation.

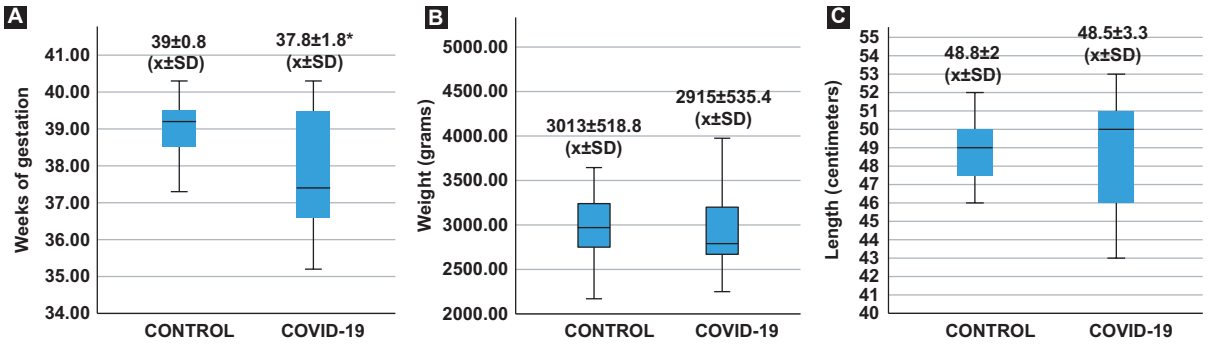

Figure 2. *Perinatal data of newborns from mothers infected with COVID-19 during the last trimester of pregnancy.* **A:** *weeks of gestation.* **B:** *birth weight.* **C:** *birth length. *Weeks of gestation statistical difference (control vs. COVID-19; p ≤ 0.05), Student's t-test. COVID-19: coronavirus disease 2019. SD: standard deviation.*

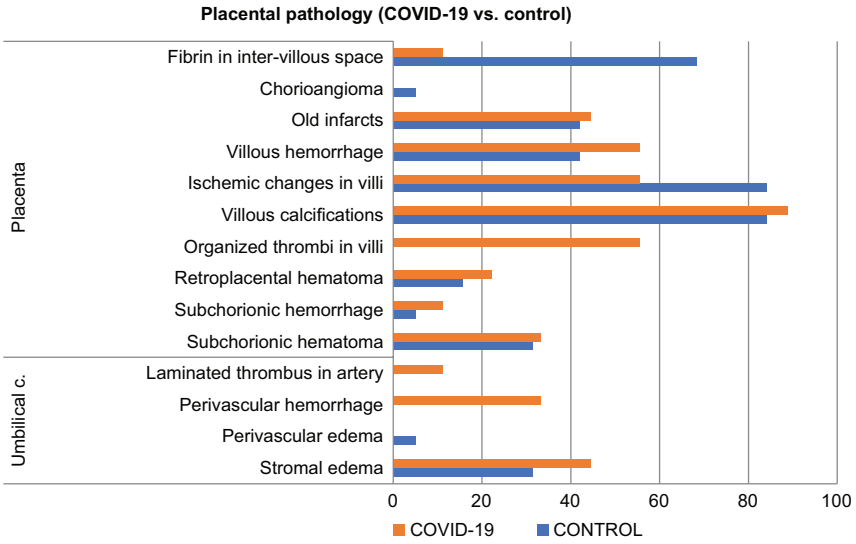

Figure 3. *Inter-villous space fibrin statistical difference (COVID-19 vs. control; p ≤ 0.05), chi-square test.*

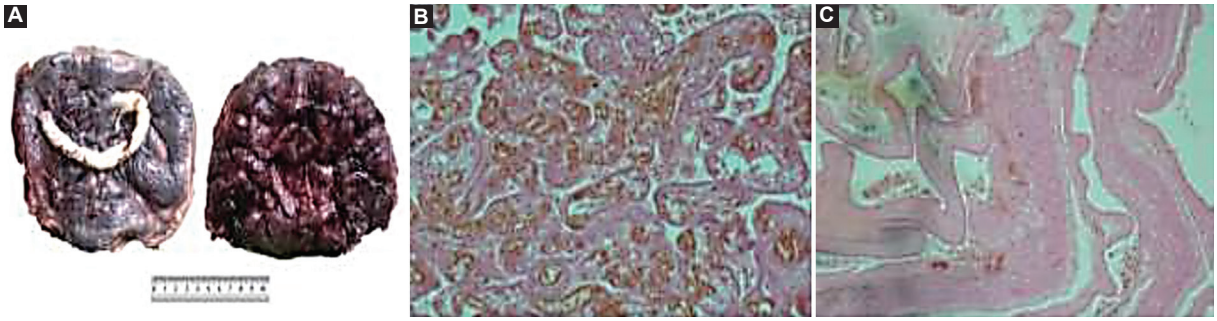

Figure 4. A: *gross description: 405-g placenta, hematic areas with 5-cm hematoma.* **B** and **C:** *microscopic description: 5-cm marginal retroplacental hematoma, organized, non-laminated thrombi, third trimester chorionic villi with calcifications on 5% of surface and ischemic changes on 10%. Similar to the other 8 examined placentas.*

were more common (84.2 vs. 55.5%), as well as the presence of fibrin in intervillous spaces (68.4 vs. 11.1%) (Fig. 3). Histopathological data of alterations in all 9 placentas are shown in figure 4.

Discussion

A previous history of some viral pathogens (cytomegalovirus, varicella zoster virus, etc.) raises concern about probable effects of SARS-CoV-2 on pregnant women and the development of the baby.[17,18]

Regarding SARS-CoV and MERS, an increase in first-trimester abortion, preterm delivery, premature rupture of membranes, intrauterine growth restriction and cesarean section rates has been reported,[19-23] with placental histopathology reporting a large amount of fibrin (intervillous and subchorionic), villous calcifications, infarcts, placental hypotrophy and thrombotic vasculopathy in some villi.[24-32] SARS-CoV-2, SARS-CoV and MERS-CoV have equivalent mechanisms of infection, which possibly results in similar maternal/fetal alterations.[33]

On the other hand, there is no conclusive evidence of SARS-CoV-2 vertical intrauterine transmission, and reported maternal/fetal complications have included intrauterine fetal distress (14%) and premature rupture of membranes (8%), and in newborns, respiratory distress (6%), gastrointestinal symptoms (4%) and fever (3%).[34] In this study, COVID-19-positive patients did not develop severe acute respiratory syndrome, with a latent and perhaps immune-compensated state being maintained.[35] The complications observed at delivery included a high rate of cesarean section (77%), preterm delivery (33.3%), placental abruption (22.2%), mild preeclampsia (11.1%) and association of oligohydramnios and fetal hypomobility (11.1%), in agreement with publications of pregnancies with severe COVID-19, which reported high rates of cesarean section, of up to 92%, and preterm delivery of 11 to 42%,[35-37] as well as comorbidities or complications such as preeclampsia, gestational diabetes, hypothyroidism, placenta previa and previous uterine surgeries.[38] In turn, COVID-19 has been predominantly localized in syncytiotrophoblast cells at maternal-fetal placental interface.[38] Furthermore, in week 27 and 39 placentas obtained from women with severe SARS-CoV-2 infection, an increase in factors that predispose to placental alterations, such as thrombosis, infarcts, and vascular wall remodeling in chorionic villi have been found.[39]

In our perinatal data, asymptomatic pregnant women with COVID-19 at third trimester were observed to experience a reduction in weeks of gestation in comparison with control women (37.8 ± 1.8 vs. 39 ± 0.8; p = 0.05). Similarly, Metz (2021), Flores (2021) and Martínez (2020) found a decrease in the number of weeks of gestation and low birth weight in patients with severe symptoms.[40-42]

In turn, this work shows an increase in organized thrombi in villi (33.3 vs. 0%) and perivascular hemorrhage (55.5 vs. 0%) in COVID-19 vs. control women, similar to studies that report placental villous infarcts (20 vs. 2%), fibrinoid necrosis (20 vs. 0%), membrane wall hypertrophy (33 vs. 4%), chorangiosis (27 vs. 5%), villous edema (27 vs. 9%), intra-villous thrombi (40 vs. 8%), fibrin (52 vs. 6%), microcalcifications (60 vs. 4%), small fibrotic villi (28 vs.0 %), villi agglutination (18 vs. 0%) and syncytial knots increase (40 vs. 2%).[38,42]

The hypercoagulation state that occurs during pregnancy could favor these alterations, in addition to the high prevalence of inherited thrombophilias in the Mexican population,[43,44] where a pro-thrombotic state induced by an increase of 36 to 43% in peripheral blood D-dimer has been observed in patients with COVID-19.[45]

The pro-thrombotic state caused by COVID-19 in pregnant women may be generated in a similar way to the deep vein thrombosis, pulmonary embolism, myocardial infarction and ischemic stroke events reported in patients with COVID-19.[46,47]

In this study, we report few cases of asymptomatic women who had a positive COVID-19 test at the end of pregnancy, which indicates that perinatal risk may already exist, as shown by the histopathological examination of the placentas of women who did not develop severe acute respiratory syndrome. Further research is required as more cases of pregnancy with COVID-19 occur in order to identify which positive asymptomatic patients are actually at perinatal risk.

Pregnant women health, regardless of whether they exhibit mild symptoms more often, even if asymptomatic, as our patients were, requires close surveillance during this pandemic and timely critical assistance in severe cases.

Limitations

The small sample size, which by itself is not significant, but coupled with studies that have been developed to date, can provide information that helps to detect alterations that could be generated by COVID-19 at delivery.

Conclusions

COVID-19 asymptomatic infection within the third trimester of pregnancy can potentiate a preexisting

pro-thrombotic profile and increase the risk of thrombosis, especially if severe acute respiratory syndrome develops, which can generate alterations such as placental abruption, preeclampsia, hemorrhages and an increase in preterm deliveries.

Funding

This research has not received any specific grant from agencies of the public, commercial or non-profit sectors.

Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-502.
2. Cui J, Li F, Shi Z. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17:181-92.
3. Aragón R, Vargas I, Miranda M. COVID-19 por SARS-CoV-2: la nueva emergencia de salud. Rev Mex Pediatr. 2020;86(6):213-8.
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-207.
5. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):e00120-27.
6. José J Elizalde-González. SARS-CoV-2 and COVID-19. A pandemic review. Med Crit 2020;34(1):53-67 doi: 10.35366/93281.
7. Collange O, Tacquard C, Delabranche X, Leonard-Lorant I, Ohana M,Onea M, et al. Coronavirus Disease 2019: Associated Multiple Organ Damage. Open Forum Infect Dis. 2020;7(7):ofaa249. doi:10.1093/ofid/ofaa249
8. Yang M, Chen S, Huang B, Zhong JM, Su H, Chen YJ, et al. Pathological findings in the testes of COVID-19 patients: Clinical implications. Eur Urol Focus. 2020;1(20):30144-9.
9. Li R, Yin T, Fang F, Li Q, Chen J, Wang Y, et al. Potential risks of SARS-CoV-2 infection on reproductive health. Reprod Biomed Online. 2020;41(1):89-95.
10. Duque J, Duque D, Pelaez F. El COVID-19 también afecta el sistema nervioso por una de sus compuertas: el órgano vascular de la lámina terminal y el nervio olfatorio. Alerta neurológica, prueba de disosmia o anosmia puede ayudar a un diagnóstico rápido. Int J Odontostomat. 2020;14(3):285-7.
11. Iadecola C, Anrather, Kamel H. Effects of COVID-19 on the nervous system. Cell Press. 2020;183:6-28.
12. Carbonell A, García A, García O, Frías M, Cabrera MA. Trombosis y COVID-19: Atención primaria clave en el abordaje interdisciplinar. Semergen. 2020;46(S1):100-1.
13. Shabes E, Mithal B, Otero S, Azad HA, Miller ES, Goldstein JA.Placental pathology in COVID-19. Am J Clin Pathol. 2020;154(1):1-10.
14. Panahi L, Amiri M, Pouy S. Risks of novel coronavirus disease (COVID-19) in pregnancy; a narrative review. Arch Acad Emerg Med. 2020;8(1):e34.
15. Johns Hopkins University & Medicine. Coronavirus Resource Center [Internet]. Johns Hopkins University & Medicine [viewed: December 28, 2020]. Available at: https://coronavirus.jhu.edu/map.html
16. Khan S, Jun L, Nawsherwan, Siddique R, Li Y, Han G, et al. Association of COVID-19 with pregnancy outcomes in health-care workers and general women. Clin Microbiol Infect. 2020;26:788-90.
17. Coyne C, Lazear H. Zika virus - reigniting the TORCH. Nat Rev Microbiol. 2016;14(11):707-15.
18. Wastnedge E, Reynolds R, van Boeckel S, Stock SJ, Denison FC, Maybin JA, et al. Pregnancy and COVID-19. Physiol Rev. 2021;101:303-18.
19. Yudin M, Steele D, Sgro M, Read SE, Kopplin P, Gough KA. Severe acute respiratory syndrome in pregnancy. Obstet Gynecol. 2005;105:124-7.
20. Wong S, Chow K, Leug T. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Obstet Gynecol. 2004;191:292-7.
21. Lam C, Wong S, Leung T. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. BJOG. 2004;111:171-4.
22. Robertson C, Lowther S, Birch T. SARS and pregnancy: a case report. Emerg Infect Dis. 2004;10:345-8.
23. Schneider E, Duncan D, Reiken M, Perry R, Messick J, Sheedy C, et al. SARS in pregnancy. AWHONN Lifelines. 2004;8(2):122-8. doi:10.1177/1091592304265557
24. Alfaraj S, Al-Tawfiq J, Memish Z. Middle East respiratory syndrome coronavirus (MERS-CoV) infection during pregnancy: report of two cases and review of the literature. J Microbiol Immunol Infect. 2019;52:501-3.
25. Jeong S, Sung S, Sung J, Ahn SY, Kang ES, Chang YS. MERS-CoV infection in a pregnant woman in Korea. J Korean Med Sci. 2017;32: 717-20.
26. Alserehi H, Wali G, Alshukairi A, Alraddadi B. Impact of Middle East respiratory syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC Infect Dis. 2016;16:105.
27. Assiri A, Abedi G, Al Masri M, Bin Saeed A, Gerber SI, Watson JT. Middle East respiratory syndrome coronavirus infection during pregnancy: a report of 5 cases from Saudi Arabia. Clin Infect Dis. 2016;63:951-3.
28. Malik A, El Masry K, Ravi M, Sayed F. Middle East respiratory syndrome coronavirus during pregnancy, Abu Dhabi, United Arab Emirates, 2013. Emerg Infect Dis. 2016;22:515-7.
29. Park M, Kim H, Choi D, Sung JH, Kim JH. Emergency cesarean section in an epidemic of the middle east respiratory syndrome: a case report. Korean J Anesthesiol. 2016;69:289-91.
30. Payne D, Iblan I, Alqasrawi S. Stillbirth during infection with Middle East respiratory syndrome coronavirus. J Infect Dis. 2014;209:1870-2.
31. Sharps M, Hayes D, Lee S, Zou Z, Brady CA, Almoghrabi Y, et al. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. Placenta. 2020;101:13-29.
32. Ng W, Wong S, Lam A, Mak YF, Yao H, Lee KC, et al. The placentas of patients with severe acute respiratory syndrome: a pathophysiological evaluation. Pathology. 2006;38(6):210-8.
33. Wong S, Chow K, Leung T, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;91(1):292-7.
34. Oliva J. SARS-CoV-2: origen, estructura, replicación y patogénesis. Alerta. 2020;3(2):79-86.
35. Akhtar H, Patel C, Abuelgasim E, Harky A. COVID-19 (SARS-CoV-2) infection in pregnancy: A systematic review. Gynecol Obstet Invest. 2020;85(4):295-306.
36. Della Gatta A, Rizzo R, Pilu G, Simonazzi G. Coronavirus disease 2019 during pregnancy: a systematic review of reported cases. Am J Obstet Gynecol. 2020;223:36-41
37. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020;99(7):823-9.
38. Mendoza M, Garcia I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, et al. Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study. BJOG. 2020;127(11):1374-80.
39. Singh N, Buckley T, Shertz W. Placental pathology in COVID-19: Case series in a community hospital setting. Cureus. 2020;13(1):e12522.
40. Flores A, Miranda J, Vega S, Valdespino Y, Helguera C, Espejel A, et al. Molecular insights into the thrombotic and microvascular injury in placental endothelium of women with mild or severe COVID-19. Cells. 2021;10(364):1-21.
41. Martínez O, Vouga M, Cruz S, Forcen Acebal L, Panchaud A, Muñoz-Chápuli M, et al. Association between mode of delivery among pregnant women with COVID-19 and maternal and neonatal outcomes in Spain. JAMA. 2020;324(3):296-9.

42. Metz T, Clifton R, Huges B, Sandoval G, Saade GR, Grobman WA, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2021;137(4):571-80.
43. Shanes E, Mithal L, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol. 2020;154:23-32.
44. Almagro D. La hemostasia en el embarazo. Revista Cubana de Hematología, Inmunología y Hemoterapia. 2000;16(2):90-8.
45. Lujan J, Durand C, Ávila F, Rebollar D. Incidence of hereditary thrombofilies in a population of Mexican women. Obstetrics & Gynecology International Journal. 2020;11(4):208-13.
46. Lippi G, Favaloro E. D-dimer is associated with severity of coronavirus disease 2019: A pooled analysis. Thromb Haemost. 2020;120(5):876-7.
47. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and antithrombotic treatment in coronavirus 2019. Thromb Haemost. 2020;120(6):949-56.