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REPERCUSIÓN DE LA INFECCIÓN POR SARS-COV-2 EN LA GESTACIÓ

ITZIAR GARCÍA RUIZ

TESIS DOCTORAL

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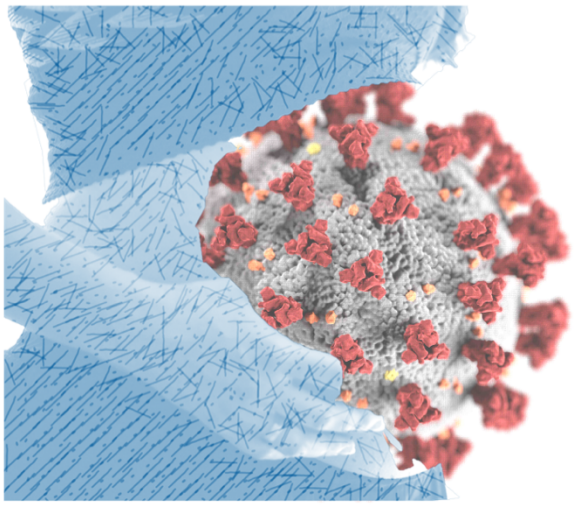

Doctoranda

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A mi padre

Gernikako arbola
da bedeinkatua
Euskaldunen artean
guztiz maitatua.
Eman ta zabal zazu
munduan frutua
adoratzen zaitugu
arbola santua

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Abreviaturas

2019-nCoV	Nuevo Coronavirus 2019
aCGH	Arrays De Hibridación Genómica Comparada
ACOG	American College Of Obstetricians And Gynecologists
ALT	Alanina Aminotransferasa
Ang I	Angiotensina I
ARN	Ácido Ribonucleico
ARN	Ácido Ribonucleico
AST	Aspartato Aminotransferasa
AT1	Receptor Tipo 1
CDC	Centers For Disease Control And Prevention
CIR	Crecimiento Intrauterino Restringido
ECA	Enzima Convertidor De Angiotensina
ECA-2	Enzima Convertidora De Angiotensina 2
ECMO	Oxigenación Por Membrana Extracorpórea
FDA	Food And Drug Administration
GESTACOVID	Grupo Colaborativo para el Estudio de la COVID-19
H1N1	Virus Influenza A
IL-6	Interleuquina 6
IMC	Índice De Masa Corporal
ISUOG	International Society Of Ultrasound In Obstetrics And Gynecology
MERS	Síndrome Respiratorio De Oriente Medio
OMS	Organización Mundial De La Salud
ORF	Marcos De Lectura Abierta
PAN-COVID	UK And Global Pregnancy And Neonatal Outcomes In COVID-19

PlGF	Factor de crecimiento placentario
RAAS	Sistema Renina-Angiotensina-Aldosterona
RBD	Receptor Celular
RT-PCR	Reacción en cadena de la Polimerasa en Tiempo Real
RTC	Complejo Replicasa Transcriptasa
SARS-CoV-2	Coronavirus De Tipo 2 Causante Del Síndrome Respiratorio Agudo Severo”
sFlt-1	Tirosina quinasa 1 soluble tipo fms
SMFM	Society For Maternal-Fetal Medicine
ssRNA	Ácido Ribonucleico De Polaridad Positiva
TBC	Tuberculosis
TMPRSS-2	Proteasa Transmembrana Serina Tipo 2
TORCH	Toxoplasmosis, Rubéola, Citomegalovirus, Herpes simple y VIH
UCI	Unidad De Cuidados Intensivos
UKOSS	United Kingdom Obstetrics Surveillance System
VEGF	Factor De Crecimiento Endotelial Vascular
VHB	Virus Hepatitis B
VMI	Ventilación Mecánica Invasiva

INTRODUCCIÓN

CRONOLOGÍA DE LA PANDEMIA

- El 31 de diciembre de 2019 las autoridades chinas informaron a la Organización Mundial de la Salud (OMS) de un elevado número de casos de neumonía de causa desconocida en la ciudad de Wuhan, provincia de Hubei, China.
- El 5 de enero de 2020 la OMS emitió su primer informe sobre el brote epidémico causado por un nuevo tipo de coronavirus.
- El 12 de enero se publicó la secuencia genética del virus, inicialmente denominado *nuevo coronavirus 2019 (2019-nCoV)*.
- El 13 de enero se confirmó el primer caso fuera de China, en Tailandia.
- El 22 de enero se confirmó la transmisión de la infección de persona a persona.
- El 30 de enero la OMS declaró el brote por el nuevo coronavirus "Emergencia de Salud Pública de Importancia Internacional".
- El 31 de enero se confirmó el primer caso en España y comenzó la primera ola o fase epidémica.
- El 11 de febrero el Comité Internacional de Taxonomía de los Virus nombró al nuevo virus, "Coronavirus de tipo 2 causante del síndrome respiratorio agudo severo" (SARS-CoV-2, en inglés), por sus similitudes con el coronavirus causante de la epidemia de Síndrome Respiratorio Agudo Grave (SARS) de 2003. Y la OMS nombró la nueva enfermedad "COVID-19".
- El 25 de febrero se confirmó el primer caso en Cataluña.
- El 11 de marzo la OMS determinó que la COVID-19 se podía considerar una pandemia por su extensa propagación geográfica.
- El 14 de marzo se decretó en España el estado de alarma.
- El 16 de marzo ingresó la primera gestante con neumonía por SARS-CoV-2 en el Hospital Vall D´Hebron.
- El 3 de abril se registraron más de 1.000.000 de infectados en todo el mundo.
- El 21 de junio de 2020 expiró el estado de alarma en España y finalizó la primera ola.

- En octubre y noviembre de 2020 tuvo lugar la segunda ola epidémica.
- El 27 de diciembre de 2020 comenzó la vacunación frente al SARS-CoV-2. Inicialmente las gestantes no se consideraron grupo prioritario para la vacunación.
- En enero de 2021 se inició la tercera ola.
- En abril de 2021 se inició la cuarta ola.
- En junio de 2021 comenzó la vacunación de la población con edad inferior a 49 años. A pesar de que la gestación no era contraindicación, los estudios de seguridad eran limitados y el porcentaje de vacunación en este grupo fue más bajo que en el resto de la población.
- En julio y agosto de 2021 se produjo la quinta ola. La proporción de gestantes con necesidad de ingreso fue la más alta de toda la pandemia. Desde las sociedades de obstetricia y ginecología se hizo un llamamiento a profesionales sanitarios y gestantes para incentivar la vacunación.
- El 1 de septiembre de 2021 se alcanzó la vacunación completa del 70% de la población adulta en España.
- Entre diciembre del 2021 y febrero del 2022 se desarrolló la sexta ola.

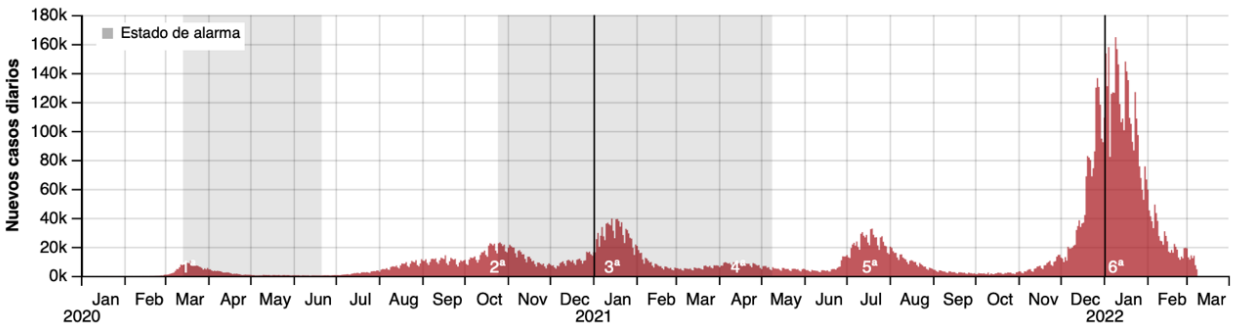

Figura 1 Casos diarios confirmados de COVID-19 en España desde enero 2020 a marzo 2022. Fuente: Web del Ministerio de Sanidad.

DESCRIPCIÓN DEL VIRUS SARS-CoV-2.

Estructura viral

El SARS-CoV-2 pertenece a la familia *Coronaviridae,* que recibe su nombre por su morfología en forma de corona al ser observados con microscopía electrónica.

Estructuralmente es un virus esférico de 80-120 nm de diámetro, constituido por una bicapa lipídica que contiene una cadena simple de ácido ribonucleico (ARN) de polaridad positiva (ssRNA) de 26-32 kilobases de longitud. Su genoma consta de 14 marcos de lectura abierta (open reading frames, ORF) que codifican 16 proteínas no estructurales (nsp 1-16) que forman el complejo de replicación, 9 proteínas accesorias (ORF) y 4 proteínas estructurales: proteína de espícula (S), proteína de envoltura (E), proteína de membrana (M) y proteína de nucleocápside (N)[1]

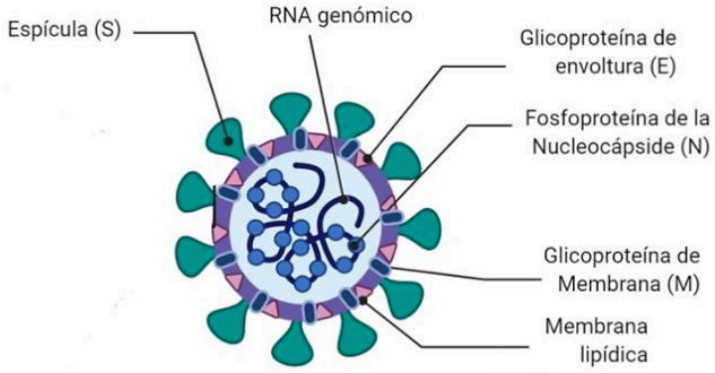

Figura 2 representación esquemática de las proteínas estructurales que conforman el SARS-CoV-2[2]

Ciclo de replicación

El dominio de unión al receptor celular (RBD) de la proteína S se une a la enzima convertidora de angiotensina 2 (ECA-2) de la célula huésped, para permitir la entrada del virus a la célula por endocitosis.

Completada esta fusión, el ARN viral queda libre en el citoplasma de la célula huésped, donde los ribosomas comienzan la traducción del ARN en las proteínas no estructurales del virus. Éstas forman el complejo replicasa transcriptasa (RTC), que se encarga de la replicación del virus y este nuevo ARN se traduce en las proteínas estructurales. Como resultado de la replicación y traducción del virus se producen nuevos viriones[1].

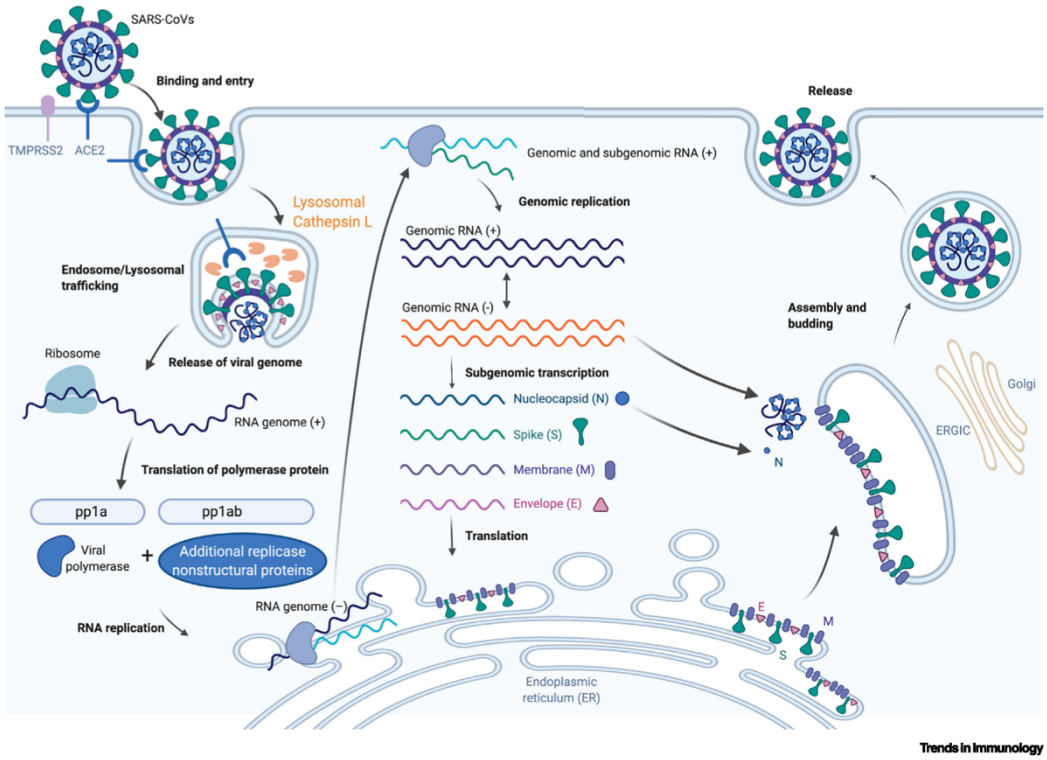

Figura 3 Ciclo de replicación del SARS-CoV-2[1]

Tropismo tisular

La afinidad del virus SARS-CoV-2 por ciertos tejidos está determinada por la proteína S. La proteína S consta de 2 subunidades que permiten el reconocimiento y la unión a la célula huésped y su invasión. La subunidad S1 contiene el RBD. La subunidad S2 permite la internalización del virus en la célula huésped mediante endocitosis, mediado por la proteasa transmembrana serina tipo 2 (TMPRSS-2). El gen que codifica la proteína S tiene una gran variabilidad y comparte menos del 75% de su secuencia con el SARS CoV. El SARS-CoV-2 tiene 10-20 veces mayor afinidad al ECA-2 que el SARS-CoV, lo que puede determinar su mayor contagiosidad[3].

El SARS-CoV-2 actúa sobre tejidos que expresan el ECA-2. El ECA-2 forma parte del sistema renina-angiotensina-aldosterona (RAAS). El RAAS es un sistema que regula la presión arterial, el volumen extracelular y el balance hidroelectrolítico. Ejerce sus funciones a tres niveles: 1) endocrino, a distancia a través de la circulación sanguínea; 2) paracrino, en el medio tisular más cercano; y 3) intracrino, regulando procesos intracelulares.

El tropismo tisular del SARS-CoV-2 está determinado por la expresión en las células huésped de ECA-2 y TMPRSS-2. El ECA-2 está presente en una proporción elevada (>1%) en tracto respiratorio inferior, pulmón, corazón, íleo, esófago, riñón y vejiga.

ECA-2 y TMPRSS-2 se expresan también en placenta y decidua y su representación se incrementa a lo largo de la gestación. En tejidos fetales se han detectado en corazón, hígado y pulmón y también su cantidad se modifica según progresan las semanas y en el periodo neonatal[4].

FISIOPATOLOGÍA

El SARS-CoV-2 produce enfermedad sistémica a través de diferentes mecanismos[5].

1. *Toxicidad viral directa.*

El SARS-CoV-2 entra en el huésped a través del tracto respiratorio superior mediante el receptor ECA-2, que se expresa en gran cantidad en endotelio vascular, epitelio respiratorio, monocitos alveolares y macrófagos. Si la enfermedad progresa, el virus continúa su replicación en el tracto respiratorio inferior.

En estudios histopatológicos se ha confirmado el tropismo del SARS-CoV-2 por tracto respiratorio, tracto gastrointestinal, riñón, miocardio y sistema nervioso. Estos hallazgos indican que la afectación multiorgánica en parte es debida a lesión tisular directa.

2. *Lesión e inflamación endotelial*

En pacientes con COVID-19 se ha identificado lesión endotelial mediada por infección (caracterizada por niveles elevados del factor Von Willebrand) e inflamación endotelial (caracterizada por la presencia de neutrófilos y macrófagos activados) en los lechos vasculares de pulmón, riñón, corazón, intestino delgado e hígado. En consecuencia, se activa la producción de trombina, se inhibe la fibrinolisis y se activa la cascada del complemento, favoreciendo el depósito de microtrombos y la disfunción endotelial. Altas concentraciones en sangre de dímero D y productos de la degradación de la fibrina se asocian a formas graves de la enfermedad[6].

3. *Desregulación del sistema inmune*

El SARS-CoV-2 infecta las células dendríticas induciendo una activación defectuosa de los linfocitos T y su apoptosis. La linfopenia es signo de mal pronóstico de la enfermedad.

Además, la infección de monocitos, macrófagos y células dendríticas resulta en la activación y secreción exagerada de interleuquina 6 (IL-6) y otras citoquinas inflamatorias desencadenando el síndrome de liberación de citoquinas o “tormenta de citoquinas”. La IL-6 estimula la liberación de factor de crecimiento endotelial vascular (VEGF) y reduce la expresión de E-caderina, provocando daño endotelial y permeabilidad vascular, mecanismos fisiopatológicos del síndrome de distrés

respiratorio agudo[7]. La elevación de marcadores inflamatorios como proteína C reactiva, ferritina, velocidad de sedimentación globular, dímero D, fibrinógeno y lactato deshidrogenasa, es predictora de enfermedad grave. Niveles altos de IL-6 en sangre también se asocian a peor pronóstico.

4. Desregulación de sistema renina-angiotensina-aldosterona

El RAAS es una compleja cascada enzimática que regula el balance hidroelectrolítico, la presión arterial, la permeabilidad vascular y el crecimiento tisular.

La disminución de la concentración de sodio en la nefrona estimula la liberación de renina, que convierte el angiotensinógeno en angiotensina I (Ang I) en el hígado. El enzima convertidor de angiotensina (ECA) convierte Ang I en Ang II. La Ang II se une al receptor tipo 1 (AT1) y produce vasoconstricción y secreción de aldosterona en la glándula suprarrenal, reabsorbiendo sodio y agua a nivel renal y aumentando la presión arterial. Además, la acción de Ang II sobre el receptor AT1 produce estrés oxidativo, inflamación, fibrosis y apoptosis celular. Esta vía está regulada por el ECA-2, que escinde la Ang I en Ang (1-9) y la Ang II en Ang (1-7), provocando efectos opuestos: vasodilatación, actividad antiinflamatoria, antifibrótica y anti-apoptosis.

La proteína S del SARS-CoV-2 compite con la Ang I y la Ang II por el receptor ECA-2, provocando un desequilibrio en el RAAS. Se incrementa la activación del eje Ang II/AT1, favoreciendo vasoconstricción, estrés oxidativo, inflamación, fibrosis y apoptosis[3].

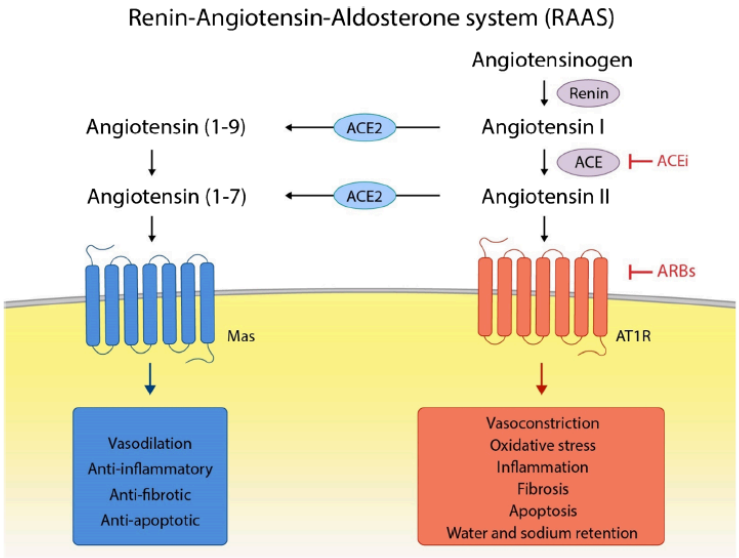

Figura 4 Mecanismos fisiopatológicos del sistema renina-angiotensina-aldosterona.[3]

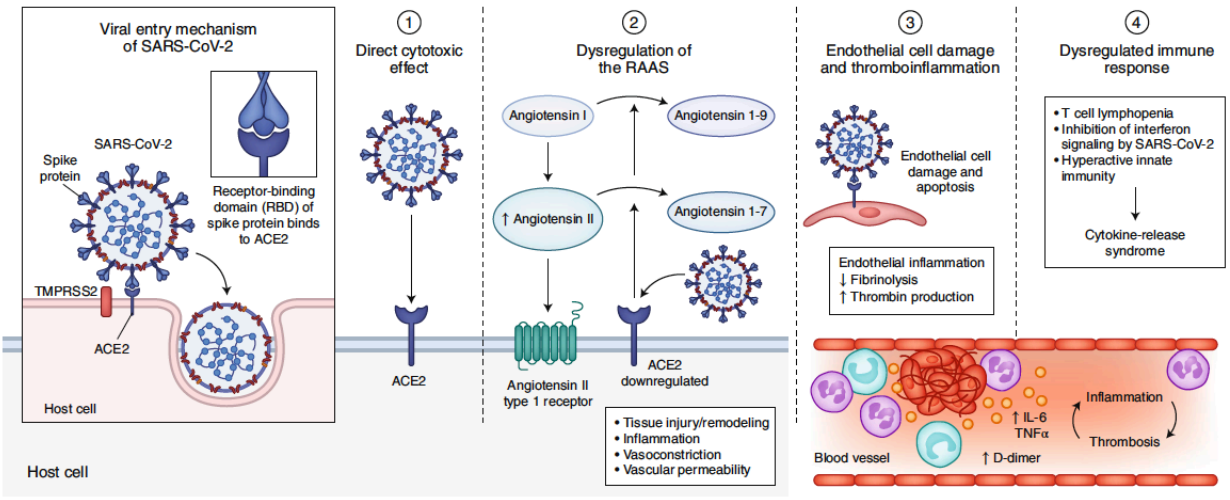

Figura 5 Mecanismos fisiopatológicos del COVID-19[5].

TRANSMISIÓN

La forma más frecuente de transmisión del SARS-CoV-2 de persona a persona es por contacto directo a través de gotas respiratorias (>5 micrones de diámetro); o aerosoles (<5 micrones de diámetro). Menos habitual por contacto indirecto a través de fómites o superficies contaminados[8,9].

Una persona infectada, al toser, estornudar hablar o exhalar, expulsa gotas respiratorias que pueden ser expelidas hasta un metro de distancia. Estas gotas se pueden posar sobre la conjuntiva o mucosas de una persona muy cercana (menos de un metro) trasmitiendo la infección. Algunas de estas secreciones respiratorias se fragmentan en partículas más pequeñas, aerosoles, que permanecen suspendidos y pueden ser transportadas por el aire distancias variables, según condiciones de temperatura, humedad y flujo de aire, propagando la infección por más tiempo y a más distancia. Las gotas respiratorias más pesadas se depositan rápidamente en las superficies más próximas contaminándolas, estos fómites actúan como vectores pasivos del virus[10].

ENFERMEDAD POR SARS-COV-2

Los síntomas más frecuentes de la infección son fiebre, astenia, tos seca, mialgia y disnea. Menos habituales son cefalea, ageusia y anosmia, dolor abdominal, náuseas, vómitos y diarrea[11]. Las manifestaciones clínicas han ido variando según las diferentes cepas del SARS-CoV-2 y también según la inmunidad poblacional.

Durante la primera ola, la mayoría de las personas con infección por SARS-CoV-2 desarrollaron enfermedad leve, el 14% requirieron ingreso hospitalario y soporte de oxígeno y el 5% ingreso en unidad de cuidados intensivos (UCI)[12].

La OMS definió las siguientes manifestaciones clínicas de la enfermedad:

1. ***Infección leve.*** Infección no complicada de vías respiratorias altas. Se caracteriza por sintomatología inespecífica como fiebre, tos con o sin expectoración, mialgias, congestión nasal, cefalea, odinofagia, anosmia y ageusia. En menor proporción de casos puede asociar sintomatología digestiva, con náuseas, vómitos y diarrea.
2. ***Neumonía.*** Signos clínicos y/o radiológicos de neumonía, pero sin necesidad de suplementación de oxígeno.
3. ***Neumonía grave.*** Frecuencia respiratoria mayor de 30 respiraciones por minuto; distrés respiratorio; o saturación O2 (FiO_2 0.21) $\leq$93.
4. ***Síndrome de distrés respiratorio agudo (SDRA).*** Radiografía o TC pulmonar que muestre opacidades pulmonares bilaterales e insuficiencia respiratoria no secundaria a fallo cardiaco o sobrecarga de líquidos.
    a. *Leve*. PaO2/FiO2: 200 mmHg – 300 mmHg (con PEEP o CPAP $\geq$ 5 cmH20, o sin ventilación)
    b. *Moderado*. PaO2/FiO2: 100 mmHg – 200 mmHg (con PEEP $\geq$ 5 cmH20, o sin ventilación)
    c. *Grave*. PaO2/FiO2: $\leq$100 mmHg (con PEEP $\geq$ 5 cmH20, o sin ventilación). En ausencia de PaO2, SpO2/FiO2 $\leq$ 315 es sugestivo de SDRA.
5. ***Sepsis.*** Disfunción orgánica que amenaza la vida causada por una respuesta desregulada a la infección

6. ***Shock séptico.*** Necesidad de vasopresores para mantener la tensión arterial media ≥65 mmHg y concentración de lactato en suero ≥2 mmol/L en ausencia de hipovolemia.[13]

Entre la aparición de los primeros síntomas y la disnea suele transcurrir una mediana de 5 días (IQR 1 – 10), al ingreso hospitalario 7 días (IQR 4 – 8) y al desarrollo del síndrome de distrés respiratorio 8 días (IQR 6 – 12)[11].

Además de las manifestaciones respiratorias, se han descrito manifestaciones sistémicas.

- ***Hematológicas:*** linfopenia, trombopenia, síndrome de liberación de citoquinas, coagulación intravascular diseminada.
- ***Cardiovasculares:*** fenómenos trombóticos arteriales y venosos, miocarditis, isquemia miocárdica, miocardiopatía de Takotsubo.
- ***Renales:*** hematuria, proteinuria, insuficiencia renal.
- ***Gastrointestinales:*** diarrea, náuseas, vómitos, dolor abdominal, anorexia.
- ***Hepatobiliares:*** Elevación de transaminasas y elevación de bilirrubina hasta tres veces por encima de los límites normales.
- ***Endocrinológicas:*** hiperglicemia, cetoacidosis.
- ***Neurológicas:*** cefalea, ageusia, anosmia, encefalopatía, accidente cerebro vascular, Guillain-Barré.
- ***Oftalmológicas:*** conjuntivitis.
- ***Dermatológicas:*** petequias, rash eritematoso, *livedo reticularis*, lesiones tipo perniosis[5].

La existencia de ciertas comorbilidades se asocia a mayor riesgo de infección. Hipertensión, diabetes mellitus, obesidad, enfermedad cardiovascular, enfermedad renal crónica, enfermedad pulmonar obstructiva crónica y consumo de tabaco son factores de riesgo de desarrollar formas más graves de la enfermedad y muerte[14].

TRATAMIENTO

Las estrategias terapéuticas tienen como objetivo el tratamiento sintomático y de soporte sistémico, la prevención de la progresión del virus y el control de la respuesta inmune exagerada.

1. *Soporte respiratorio*

Se requiere soporte respiratorio en caso de hipoxia [SatO2 (FiO2 0.21) <93%] o síntomas evidentes de distrés respiratorio. La oxigenoterapia se puede administrar, de menos a más invasivo, mediante gafas nasales, mascarillas de alto flujo, ventilación mecánica no invasiva o intubación orotraqueal y ventilación mecánica.

2. *Profilaxis y tratamiento antitrombótico*

Se ha descrito un estado de hipercoagulabilidad asociado a la COVID-19. Los pacientes que requieren ingreso en UCI presentan mayor riesgo de eventos trombóticos venosos[15]; y entre los fallecidos por neumonía se ha detectado coagulación intravascular diseminada en el 71,4%, en comparación con el 0,6% entre los supervivientes[16]. El tratamiento con heparina de bajo peso molecular disminuye el riesgo de eventos trombóticos y se asocia a menor tasa de mortalidad en subgrupos de pacientes con neumonía grave y SDRA[6,17].

3. *Tratamiento antivírico*

Lopinavir / Ritonavir. Lopinavir es un inhibidor de la proteasa y combinado con Ritonavir prolonga su vida media. Se ha utilizado en el tratamiento del VIH y parece que puede inhibir la replicación del SARS-CoV-2 in vitro. Sin embargo, su uso no ha demostrado mejoría en la evolución de la enfermedad ni en la persistencia del ARN viral[18].

Remdesivir. Pertenece al grupo de análogos de los nucleótidos. Administrado en los primeros 9 días desde el inicio de la sintomatología disminuye el tiempo de recuperación[19].

Hidroxicloroquina y Azitromicina. La Hidroxicloroquina tiene actividad antiviral e inmunomoduladora y en asociación con la Azitromicina se potencia el efecto antiinflamatorio. Sin embargo, no ha demostrado disminuir la mortalidad y su uso se asocia a alto riesgo de efectos adversos cardiacos[20].

4. *Tratamiento inmunomodulador*

Tocilizumab. Es un anticuerpo monoclonal antagonista de la IL-6. Su utilización en pacientes graves parece disminuir la mortalidad a corto plazo. El efecto inmunosupresor del Tocilizumab conlleva un riesgo significativo de sobreinfecciones[21].

5. *Tratamiento antiinflamatorio*

Corticoides. La respuesta inmunitaria exagerada participa en la fisiopatología del daño pulmonar agudo y del SDRA. El tratamiento con Dexametasona y Metilprednisolona se asocia a menor necesidad de ventilación mecánica e ingreso en UCI en pacientes con requerimientos de oxigenoterapia[22,23].

INFECCIÓN EMERGENTE EN GESTACIÓN

Las infecciones emergentes son aquéllas cuya incidencia ha aumentado en los últimos diez años o presentan la amenaza de hacerlo en un futuro próximo. Pueden tener las siguientes características:

- Infecciones completamente nuevas, como el síndrome respiratorio de Oriente Medio (MERS).
- Infecciones nuevas en un área geográfica, como la enfermedad de Chagas en Europa.
- Infecciones que reaparecen en un área geográfica, como el dengue en Florida.
- Infecciones causadas por bacterias que han adquirido resistencia a determinados antibióticos, como el *Staphylococcus aureus* resistente a meticilina[24].

Las infecciones emergentes son de especial relevancia durante el embarazo debido a que 1) las gestantes pueden tener mayor susceptibilidad a la infección y / o presentar manifestaciones clínicas más graves; 2) pueden tener repercusiones negativas en el feto o neonato; 3) la profilaxis o el tratamiento recomendado en la población general puede estar contraindicado en las gestantes[25].

Algunos ejemplos de infecciones emergentes con repercusión específica en la gestación son la infección por el virus Influenza A (H1N1) o el virus del Zika. Las gestantes con gripe A, en comparación con mujeres de edad similar no gestantes, tienen mayor riesgo de hospitalización, de ingresar en UCI y muerte[26]. Y la infección por virus Zika se puede transmitir de madre a feto provocando el síndrome congénito por el virus Zika, que se caracteriza por microcefalia y otras alteraciones neurológicas[27].

La mayoría de las infecciones por coronavirus en humanos tienen escasa repercusión clínica, sin embargo, las epidemias de SARS-CoV y MERS-CoV en los últimos 15 años han afectado de forma más grave a las gestantes, con hasta un tercio de mortalidad[28].

Ante la aparición de la infección por SARS-CoV-2, en Obstetricia se plantean tres preguntas fundamentales:

1. ¿Cómo afecta la gestación al desarrollo de la infección por SARS-CoV-2?
2. ¿Cómo afecta la infección por SARS-CoV-2 a la gestación?
3. ¿Qué consecuencias tiene la infección por SARS-CoV-2 en el feto y en el neonato?

Para intentar dar respuesta a estas preguntas en febrero de 2020 se constituyó el Grupo Colaborativo Gestacovid. Este grupo está formado por nueve hospitales de tercer nivel referentes en Obstetricia: Hospital Universitari Vall d´Hebron (centro coordinador), Hospital Universitario La Paz (Madrid), Hospital Virgen de la Arrixaca (Murcia), Hospital Universitario Cruces (Bizkaia), Hospital Clínico Universitario Lozano Blesa (Zaragoza), Hospital de Torrejón (Madrid), Hospital Universitario San Cecilio (Granada), Hospital Universitario La Fe (Valencia) y Hospital Universitario Príncipe de Asturias (Madrid).

Los objetivos principales de este grupo de trabajo se definen en el artículo **"Gestation and COVID-19: clinical and microbiological observational study (Gesta-COVID19)".**

INFECCIÓN SARS-CoV-2 EN GESTANTES

Prevalencia

La prevalencia de la infección es difícil de estimar, porque la evolución de las fases epidémicas es diferente según áreas geográficas; y porque las estrategias de cribado utilizadas varían entre los distintos países y a lo largo de la pandemia.

Allotey y col[29]. describieron la prevalencia de la enfermedad durante la primera ola (entre diciembre y junio de 2020): 7% (4-10%) si se realizaba cribado universal; 18% (10-28%) si se realizaba en base a sintomatología. Aproximadamente tres cuartas partes (74%, 51%-93% de las gestantes eran asintomáticas).

Un estudio de seroprevalencia realizado en Barcelona aplicando estrategia de cribado universal a todas las gestantes que acudían a la ecografía de primer trimestre o ingresaban de parto, entre abril y mayo de 2020, determinó una prevalencia de infección del 14%. El 60% de las gestantes eran asintomáticas, variando entre un 70% en primer trimestre de gestación y un 52% en tercer trimestre[30].

Algunos estudios sugieren mayor susceptibilidad para adquirir la infección durante la gestación. En un estudio en el que se compararon los resultados del cribado universal en pacientes que ingresaban de forma programada para cirugía y gestantes en trabajo de parto, los casos de infección asintomática eran quince veces superiores en las pacientes obstétricas, incluso ajustando en base a edad, raza y sexo[31].

Manifestaciones clínicas de la infección

Hasta la quinta ola epidémica, que finaliza en septiembre de 2021, el comportamiento clínico de la infección por SARS-CoV-2 se ajusta a las descripciones iniciales de la enfermedad.

La incidencia de infección por COVID-19 es similar a lo largo de toda la gestación[30]. Sin embargo, los casos sintomáticos y con necesidad de ingreso hospitalario se concentran en el tercer trimestre de gestación, en torno a las 34 semanas (IQR: 29-38)[30,32].

La sintomatología de la enfermedad es similar a la población general. Los síntomas más frecuentes son: fiebre (40%), tos (39%), mialgias (10%), anosmia y ageusia (15%) y diarrea (7%). En comparación con población similar no gestante, las embarazadas presentan menos fiebre y mialgias[29].

La evidencia existente sobre otras infecciones como el virus influenza A H1N1, el síndrome respiratorio agudo grave o el síndrome respiratorio de Oriente Medio, sugiere que las gestantes tienen más riesgo de desarrollar formas más graves de la enfermedad que la población general[26,33,34].

Las primeras series de casos de gestantes con COVID-19 (marzo 2020) reportan manifestaciones clínicas similares a la población general: 86% infección leve, 9,3% neumonía grave y 4,7% síndrome de distrés respiratorio agudo[35]. En mayo de 2020, el grupo United Kingdom Obstetrics Surveillance System (UKOSS) publicó una cohorte nacional prospectiva de gestantes que ingresaron con la COVID-19, detectando un porcentaje de enfermedad grave, con necesidad de ingreso en UCI y muerte, comparables a las de población general femenina en edad reproductiva[32].

Sin embargo, en agosto de 2020, con un mayor conocimiento de la enfermedad y de su abordaje terapéutico, la revisión sistemática de Allotey y col[29]. demostraron que las gestantes con COVID-19 presentaban mayor riesgo de ingreso en UCI (OR 2,13, IC95% 1,53 – 2,95), necesidad de ventilación mecánica invasiva (VMI) (OR 2,59, IC95% 2,28 – 2,94) y necesidad de oxigenación por membrana extracorpórea (ECMO) (OR 2,02, IC95% 1,22 – 3,34), respecto a mujeres de edad similar no gestantes. Y comparando con gestantes sin COVID-19, se incrementó el riesgo de muerte materna (OR 2,85, IC95% 1,08 – 7,52) y de necesidad de ingreso en UCI (OR 18,58, IC95% 7,53 – 45,82).

Los factores de riesgo asociados a manifestaciones más graves de la enfermedad y muerte son los mismos en embarazadas que en población general. La edad avanzada (≥ 35 años), la obesidad (IMC >30 kg/m^2), la hipertensión arterial, la diabetes mellitus, la enfermedad pulmonar crónica, la enfermedad cardiovascular, la enfermedad renal crónica y el consumo de tabaco se asocian a peores resultados maternos[36,37].

Complicaciones obstétricas de la infección

1. *Parto pretérmino*

El parto pretérmino es el que se produce antes de las 37 semanas de gestación. Es la principal causa de morbilidad y mortalidad perinatal y afecta a un 5-13% de las gestaciones[38]. El 30-35% de los partos pretérmino son iatrogénicos, ya sea por inducción de parto o cesárea electiva, y sus principales causas son la enfermedad hipertensiva del embarazo y el retraso de crecimiento fetal[39]. Las causas de parto pretérmino espontáneo son múltiples y entre sus principales mecanismos patogénicos destacan la infección, la inflamación, las alteraciones vasculares y los factores anatómicos[40].

Entre las gestantes con infección por SARS-CoV-2 se ha detectado una mayor tasa de parto prematuro respecto a lo esperado en la población general (OR 1,82, IC 95% 1,38 – 2,39). Además, esta diferencia se incrementa con la gravedad de la infección: comparando pacientes sintomáticas respecto a asintomáticas (OR 2,29, IC 95% 1,49 – 3,53); y enfermedad grave respecto a enfermedad leve (OR 4,29, IC 95% 2,41 – 7,63)[41]. Este aumento de la prematuridad es sobre todo de causa iatrogénica (83%, RR 1,97, IC95% 1,56 – 2,51) y las principales indicaciones de finalización de la gestación de forma prematura son: afectación materna por COVID-19, enfermedad hipertensiva del embarazo, feto pequeño para la edad gestacional y distrés fetal[42].

2. *Preeclampsia*

La preeclampsia se define por la aparición de hipertensión arterial (tensión arterial sistólica ≥140 mmHg y/o diastólica m≥90 mmHg, medida en dos ocasiones separadas al menos por 4 horas) después de las 20 semanas de gestación en una mujer previamente normotensa asociado a proteinuria; o en ausencia de proteinuria, la hipertensión asociada a plaquetopenia, insuficiencia renal, alteración de la función hepática, edema pulmonar y/o sintomatología neurológica[43].

La preeclampsia afecta al 2-8% de las gestaciones y es una de las principales causas de morbilidad y mortalidad materna, y la primera de prematuridad iatrogénica[44].

El origen de la preeclampsia es placentario. En la formación de la placenta se produce una invasión trofoblástica alterada que induce disfunción endotelial, estrés oxidativo y un estado antiangiogénico. Las consecuencias de esta alteración son hipoxia

placentaria y afectación multiorgánica, que se manifiesta clínicamente con hipertensión arterial y proteinuria, afectación hepática, insuficiencia renal y trombopenia[45].

Entre las manifestaciones extrapulmonares del COVID-19 destacan signos y síntomas comunes a la preeclampsia: proteinuria y elevación de creatinina[46]; elevación de aspartato (AST) y alanina (ALT) aminotransferasas[47]; y plaquetopenia[48].

En la primera serie de casos de gestantes con infección por SARS-CoV-2 procedente de Wuhan en enero 2020, destaca que, de nueve gestantes ingresadas por neumonía, tres presentan elevación de transaminasas y una, preeclampsia[49].

En una revisión sistemática de marzo 2020, se observó que el porcentaje de casos de preeclampsia entre las pacientes con COVID-19 era más elevado que lo esperado en la población general (proporción acumulada 14,6%, IC 95% 0,94 – 40,34)[50].

El estudio **"Preeclampsia-like síndrome induced by severe COVID-19: a prospective observational study",** se diseñó con el objetivo de analizar la prevalencia de las manifestaciones clínicas, marcadores ecográficos y bioquímicos de preeclampsia en las gestantes con infección por SARS-CoV-2 y analizar su posible asociación.

3. *Óbito fetal*

Se define óbito fetal como la ausencia de signos de vitalidad fetal a partir de las 20 semanas de gestación o ante un feto de más de 350 gramos si se desconoce la edad gestacional. En los países desarrollados los factores de riesgo asociados a óbito fetal son: factores socio demográficos, edad materna avanzada (≥ 40 años), obesidad (IMC ≥ 30 kg/m^2), diabetes pregestacional, hipertensión crónica, consumo de tabaco y gestación múltiple[51].

En enero de 2021, el registro del Reino Unido "UK and Global Pregnancy and Neonatal Outcomes in COVID-19" (PAN-COVID) y el de la Sociedad Americana de Pediatría "National Perinatal COVID-19 Registry", reportaron una proporción de óbito fetal de 1 de cada 200 gestantes con infección por SARS-CoV-2. Estas cifras son comparables a registros de estos mismos grupos en 2016 y 2014 respectivamente[52].

Una revisión sistemática posterior, de abril 2021, sí objetivó la asociación entre la infección por SARS-CoV-2 y un mayor riesgo de óbito fetal (OR 2,11, IC 95% 1,14 – 3,90), sin relacionarse con la gravedad de la enfermedad materna[41].

Khalil y col[53]. en Reino Unido, compararon la incidencia de óbito fetal en los meses previos a la pandemia, de octubre de 2019 a enero de 2020, y los primeros meses de ésta, de febrero a junio de 2020. Detectaron una mayor incidencia de óbito fetal en el segundo periodo, 9,31 frente a 2,38 por cada 1000 partos (diferencia 6,93 [IC 95% 1,83 – 12,0] por cada 1000 partos; p=0,01, sin relación con infección activa o pasada por SARS-CoV-2.

La posible asociación entre óbito fetal y COVID-19 puede ser efecto directo de la infección, o secundario al estado de pandemia y los cambios en la asistencia médica en este periodo.

El estudio "Diffuse trophoblast damage is the hallmark of SARS-CoV-2 associated fetal demise"[54] describe las características anatomopatológicas de las placentas con infección por SARS-CoV-2 y buscar una asociación con los resultados de pérdidas gestacionales.

4. Cesárea

La vía del parto en las mujeres con infección por SARS-CoV-2 no se asocia a peores resultados maternos ni neonatales[55].Desde el comienzo de la pandemia, las principales sociedades de ginecología y obstetricia han recomendado el parto vaginal y la realización de cesárea únicamente por indicación obstétrica, independientemente del estatus del SARS-CoV-2[56,57].

A pesar de esto, la tasa de cesáreas se ha visto influenciada por la infección por SARS-CoV-2.

Una revisión sistemática que incluyó 6 estudios realizados en China en el mes de marzo de 2020 describió un porcentaje de cesáreas en gestantes con infección de hasta el 91% (IC 95% 81,0 – 97,6)[50].

Una revisión posterior que recogió estudios realizados hasta mayo de 2020, la mitad en China y la otra mitad en Europa y Estados Unidos, mantiene esta tendencia. Observó un porcentaje de cesárea del 85% (IC 95% 72-94%), sin asociación con la gravedad de la enfermedad materna ni compromiso fetal[58].

Según evoluciona la pandemia estas cifras se han ido normalizando. En una revisión de enero de 2021, no se identificó mayor riesgo de cesárea en gestantes con infección (OR 1,00, IC 95% 0,82 – 1,23). Sí se observa esta diferencia en gestantes con infección sintomática en comparación con asintomáticas (OR 1,57, IC 95% 1,32 – 1,85); y más llamativo, en gestantes con enfermedad grave respecto a enfermedad leve (OR 2,58, IC 95% 1,64 – 4,06)[41].

5. *Otros*

Otras complicaciones obstétricas no han demostrado asociación significativa con la infección por SARS-CoV-2.

El porcentaje de aborto en gestantes con COVID-19 es del 15,3% (IC 95% 10,95 – 20,59)[59], similar a lo esperable en población general (10-26%)[60].

Las gestantes con diagnóstico de diabetes gestacional con necesidad de insulina presentan mayor riesgo de infección, independientemente de su índice de masa corporal[61]. Sin embargo, la infección no se relaciona con mayor riesgo de diabetes gestacional (OR 1,03, IC 95% 0,76 -1,39)[41].

La infección por SARS-CoV-2 tampoco se asocia con retraso de crecimiento fetal intrauterino (OR 2,32 IC 95% 0,26 – 21,07). Solamente en gestantes con infección grave respecto a gestantes con infección leve, se detectó mayor riesgo de neonatos con bajo peso al nacimiento (OR 1,89 IC 95% 1,14 – 3,12), en relación con prematuridad iatrogénica[41].

Manifestaciones fetales o neonatales

Transmisión vertical del SARS-CoV2

La transmisión vertical es la transmisión de una infección de madre a hijo. Esta puede ser: antenatal, periparto o postparto.

Para confirmar la posibilidad de transmisión vertical de la infección por SARS-CoV-2 son necesarios: una prueba diagnóstica fiable que confirme la infección en madre y feto o neonato; y la exclusión de riesgo de contaminación de las muestras biológicas[62].

Basándose en las definiciones de Lebech y col[63]. para la infección congénita por *Toxoplasma* sp, Shah y col[64]. desarrollaron un sistema de clasificación según la probabilidad de infección. De acuerdo con ello se establecen cinco categorías mutuamente excluyentes:

- ***Caso confirmado.*** Diagnóstico de certeza.
- ***Caso probable.*** Implica evidencia importante de infección, pero falta de diagnóstico de certeza.
- ***Caso posible.*** Es sugestivo de infección, pero con pruebas diagnósticas incompletas.
- ***Caso improbable.*** Escasa evidencia diagnóstica, pero sin poder excluir infección totalmente.
- ***No infectado.*** Diagnóstico de certeza.

Esta clasificación es dinámica, un caso puede ser incluido inicialmente en una categoría y después pasar a otra según se disponga de más información.

TABLE 1 Classification System for Maternal-Fetal-Neonatal SARS-CoV-2 Infections

Patient	Category	Case Definition
Maternal infection during pregnancy		
Symptomatic mother	Confirmed	Detection of the virus by PCR in a respiratory sample (nasopharyngeal/ nasal/ broncho-alveolar lavage)
	Possible	No testing done
	Unlikely[a]	No detection of the virus by PCR in a respiratory sample and no other cause identified
	Not infected[a]	No detection of the virus by PCR in a respiratory sample and other cause identified
Asymptomatic mother who has positive contact history	Confirmed	Detection of the virus by PCR in a respiratory sample
	Unlikely[a]	No detection of the virus by PCR in a single respiratory sample
	Not infected	No detection of the virus by PCR in two respiratory samples taken at different time points
Congenital infection with intrauterine fetal death/stillbirth		
Fetal tissues or autopsy material	Confirmed	Detection of the virus by PCR from fetal or placental tissue or electron microscopic detection of viral particle in tissue or viral growth in culture from fetal or placental tissue
	Possible	Detection of the virus by PCR in surface swab from fetus or placental swab on fetal side
	Unlikely	Detection of the virus by PCR in surface swab from maternal side of placenta only and no testing done or no detection of the virus by PCR from fetal or placental tissue
	Not infected	No detection of the virus by PCR or by electron microscopy in fetal tissue(s) on autopsy
Congenital infection in live born neonate		
Clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in umbilical cord blood[b] or neonatal blood collected within first 12 hours of birth or amniotic fluid collected prior to rupture of membrane[c]
	Probable	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) AND placental swab from fetal side of placenta in a neonate born via cesarean section before rupture of membrane or placental tissue
	Possible[a]	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) BUT presence of anti-SARS-CoV-2 IgM antibodies in umbilical cord blood or neonatal blood collected within first 12 hours of birth or placental tissue
	Unlikely	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) or umbilical cord blood, or neonatal blood collected within first 12 hours of birth or amniotic fluid AND antibody testing not done
	Not infected	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) or umbilical cord blood, or neonatal blood collected within first 12 hours of birth or amniotic fluid AND no anti-SARS-CoV-2 IgM in umbilical cord blood or neonatal blood collected within first 12 hours of birth
No clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in cord blood[b] or neonatal blood collected within first 12 hours of birth
	Probable	Detection of the virus by PCR in amniotic fluid collected prior to rupture of membrane but no detection in umbilical cord blood or neonatal blood collected within first 12 hours of birth
	Possible	Presence of anti-SARS-CoV-2 IgM in umbilical cord blood or detection of the virus by PCR in placental tissue but no detection of the virus by PCR in umbilical cord blood or neonatal blood collected within first 12 hours of birth or amniotic fluid
	Unlikely	No detection of the virus by PCR in cord blood or neonatal blood collected within first 12 hours of birth or amniotic fluid collected prior to rupture of membrane[c] AND serology not done
	Not infected	No detection of the virus by PCR in cord blood or neonatal blood collected within first 12 hours of birth or amniotic fluid collected prior to rupture of membrane[c] AND no anti-SARS-CoV-2 IgM in cord blood

TABLE 1 (Continued)

Patient	Category	Case Definition
Neonatal infection acquired intrapartum		
Clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age AND alternate explanation for clinical features excluded
	Probable	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) but not at 24-48 hours of age AND alternate explanation for clinical features excluded
	Possible	No detection of the virus by PCR in nasopharyngeal swab at birth AND detection of the virus by PCR in any of maternal vaginal/placental/cord/skin swab at birth AND alternate explanation for clinical features excluded
	Unlikely	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) OR in any of maternal vaginal/placental/cord/neonatal nasopharyngeal/skin swab at birth AND alternate explanation for clinical features not identified
	Not infected	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) OR in any of maternal vaginal/placental/cord/neonatal nasopharyngeal/skin swab at birth AND alternate explanation for clinical features identified
No clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age
	Possible	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND not at 24-48 hours
	Not infected	No detection of the virus by PCR in nasopharyngeal swab at birth AND no detection of the virus by PCR in any of vaginal swab in mother/placental swab/skin/cord swab at birth
Neonatal infection acquired postpartum		
Clinical features of infection in newborn at ≥48 hours age (parent or caregiver may or may not have SARS-CoV-2 infection or were not tested)	Confirmed	Detection of the virus by PCR in nasopharyngeal/rectal swab at ≥48 hours of birth in a neonate whose respiratory sample tested negative by PCR at birth
	Probable	Detection of the virus by PCR in nasopharyngeal/rectal swab at ≥48 hours of birth in a neonate who was not tested at birth
	Not infected[a]	No detection of the virus by PCR in nasopharyngeal/rectal swab at ≥48 hours of birth and other cause identified

Figura 6 sistema de clasificación de infección materno fetal neonatal por SARS-CoV-2[64].

A finales de marzo de 2020, Zeng y col[65]. describieron los primeros casos de posible infección neonatal por SARS-CoV-2. En una serie de 33 gestantes con COVID-19 en el momento del parto, tres neonatos resultaron positivos para SARS-CoV-2 en la prueba de reacción en cadena de la polimerasa mediante transcriptasa inversa (RT-PCR) en exudado nasofaríngeo y anal a los 2 y 4 días de vida y negativizaron a partir del día 6.

Posteriormente se describieron 5 casos de posible infección congénita: Baud[66], Penfield[67] y Algarroba[68]. En todos ellos se detectó RT-PCR SARS-CoV-2 positiva en muestras de placenta de mujeres con infección activa. Sin embargo, las muestras neonatales resultaron negativas.

En mayo de 2020, Patanè y col[69]. demostraron por primera vez infección congénita confirmada. En una serie de 22 gestantes con infección activa en el momento del parto, describieron el caso de una gestación a término con RT-PCR SARS-CoV-2 positiva en placenta y en exudado nasofaríngeo del neonato al nacimiento, a las 24 horas y a los 7 días de vida. El neonato no presentó ninguna sintomatología.

En julio de 2020, Vivanti y col[70]. publicaron un nuevo caso de infección congénita confirmada. Se trataba de una gestante de 35 semanas y 2 días que ingresó por neumonía COVID-19 sin signos de gravedad y a los tres días se finalizó la gestación mediante cesárea por monitorización fetal con signos de sufrimiento agudo. Se confirmó la presencia de virus mediante RT-PCR en muestras de líquido amniótico (obtenido inmediatamente antes de la cesárea) y placenta, y en el neonato en exudado nasofaríngeo al nacimiento, a los 3 y 18 días de vida, en lavado broncoalveolar, sangre y exudado anal. El neonato no presentó sintomatología compatible con infección respiratoria y la ecografía pulmonar no mostró signos de neumonía.

Uno de los principales objetivos del grupo Gesta-COVID19 es determinar el riesgo de transmisión vertical de la infección. En el protocolo se define un seguimiento ecográfico fetal exhaustivo durante la infección materna, la toma de muestras maternas y neonatales en el momento del parto y el seguimiento posterior del neonato.

El estudio **"Congenital infection of SARS-CoV-2 in live-born neonates: a population-based descriptive study"** está diseñado para valorar el riesgo de transmisión vertical de la infección.

Y el estudio **"Fetal transient skin edema in two pregnant women with Coronavirus Disease 2019 (COVID-19)"** describe los hallazgos ecográficos fetales en relación con infección por SARS-CoV-2 materna.

Tratamiento

Los objetivos del tratamiento en la gestante son los mismos que en la población general: tratamiento sintomático y de soporte sistémico, evitar la progresión del virus y frenar la respuesta inmune exagerada. Teniendo en cuenta que toda medida terapéutica va destinada a dos pacientes: madre y feto.

1. Soporte respiratorio

Durante la gestación se recomienda mantener los niveles de oxigenación materna más altos que en población general, para garantizar la perfusión placentaria y prevenir la hipoxemia y la acidosis fetal. El objetivo terapéutico es saturación de oxígeno ≥95%; o PaO2 >70 mmHg en caso de ventilación mecánica[71].

2. *Profilaxis y tratamiento antitrombótico*

Varias sociedades científicas recomiendan profilaxis de enfermedad tromboembólica con heparina de bajo peso molecular en gestantes con infección por SARS-CoV-2, incluso en pacientes asintomáticas[72–76]. Sin embargo, no se ha detectado mayor porcentaje de complicaciones trombóticas en gestantes con COVID-19 frente a no gestantes, a pesar de que la gestación supone un estado de hipercoagulabilidad[32].

3. *Tratamiento antivírico*

Remdesivir. Es el primer medicamento aprobado por la Food and Drug Administration (FDA) para el tratamiento de COVID-19 en niños y adultos hospitalizados. En gestantes no parece que se asocie a toxicidad fetal, pero debido a la escasa evidencia disponible en gestantes, sólo se recomienda como uso compasivo[77].

4. *Tratamiento inmunomodulador*

Tocilizumab. No parece producir efectos adversos directamente en el feto, pero por su acción inmunosupresora se asocia a riesgo de infecciones secundarias en la madre, y por lo tanto, riesgo de infección congénita en el neonato[78].

5. *Tratamiento antiinflamatorio*

Corticoides. Se recomienda el tratamiento con corticoides en gestantes que requieren suplementación de oxígeno, por su beneficio para disminuir mortalidad materna[79].En gestantes es preferible Metilprednisolona a Dexametasona para minimizar el paso a través de la barrera placentaria[75].

6. *Finalización de la gestación*

La finalización de la gestación puede ser parte de la estrategia terapéutica, al disminuir las demandas fisiológicas propias del embarazo. El momento óptimo de finalización de la gestación dependerá del balance riesgo / beneficio para madre y feto. A partir de las 32 semanas, la hipoxemia refractaria se puede considerar motivo de finalización[79].

INFECCION POR SARS-CoV-2 EN GESTANTES EN EL HOSPITAL UNIVERSITARI VALL D´HEBRON

En abril de 2020 el Hospital Universitari Vall D´Hebron se convierte en centro de referencia de toda Cataluña para gestantes que requieren ingreso por COVID-19. Se trata del único hospital de tercer nivel con UCI de adultos, UCI neonatal y Maternidad en el mismo centro, y capacidad para dar respuesta al creciente número de casos en gestantes. Esta medida permite concentrar la casuística y por lo tanto la experiencia, el conocimiento y la investigación.

Entre el 16 de marzo de 2020 y el 1 de enero de 2022, ingresaron 220 gestantes por COVID-19.

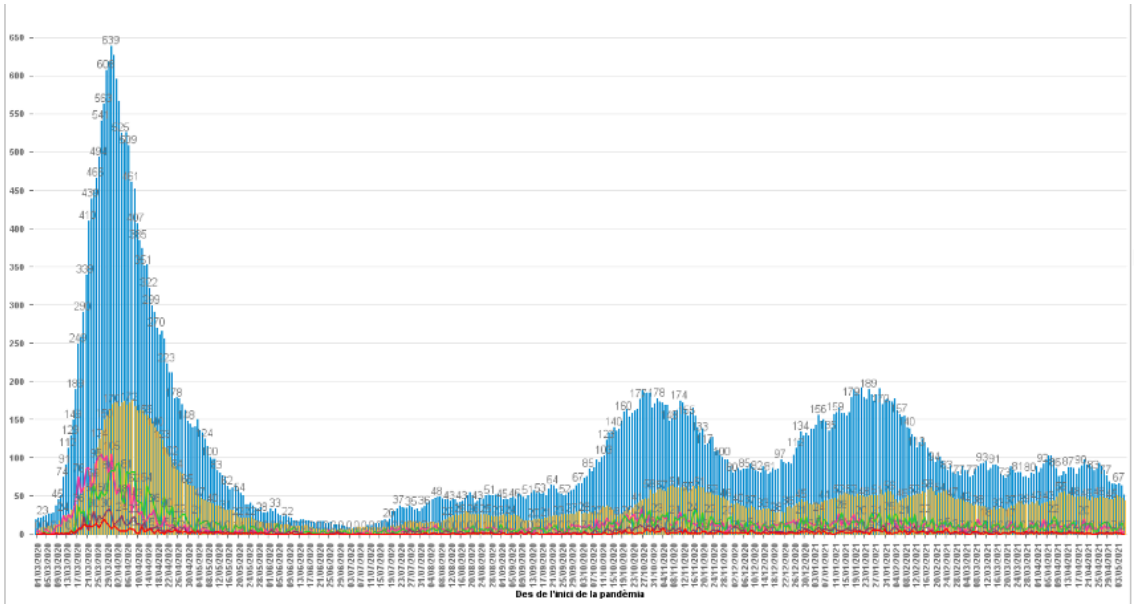

Figura 7 Distribución de los casos ingresados por COVID-19 en el Hospital Universitari Vall D´Hebron entre marzo de 2020 y enero 2022. Azul: casos totales; verde: ingreso en UCI.

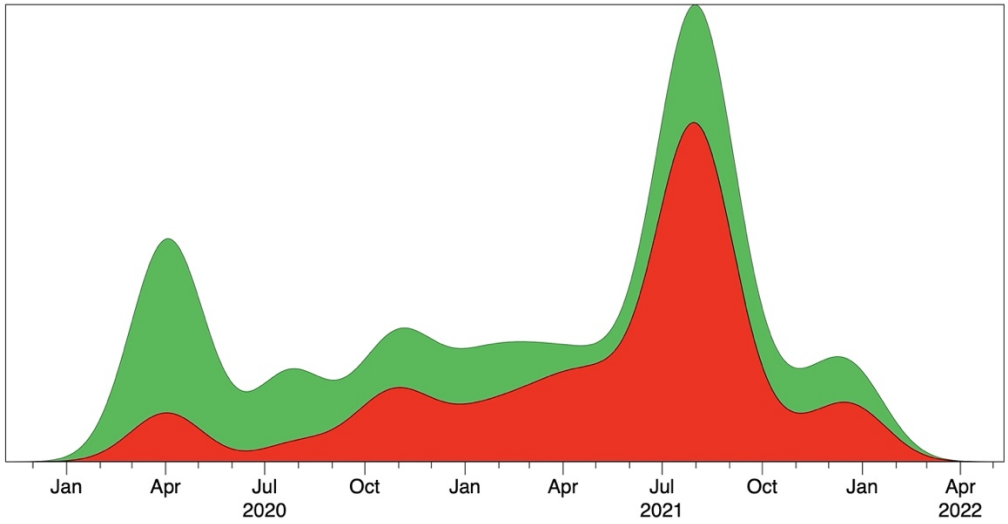

Figura 8 Distribución de los casos de gestantes que requieren ingreso por COVID-19 en el Hospital Universitari Vall D´Hebron entre marzo de 2020 y enero 2022. Verde: casos totales; rojo: ingreso en UCI.

Características	N = 220
Edad materna (años), mediana (rango)	33 (17 – 51)
Índice de masa corporal (kg/m^2), mediana (rango)	27,9 (14,8 – 44,3)
IMC ≥30, n (%)	71/206 (34,5%)
IMC ≥30 <35, n (%)	50/206 (24,3%)
IMC ≥35 <40, n (%)	12/206 (5,8%)
IMC ≥40, n (%)	9/206 (4,4%)
Origen, n (%)	
Europa	68/193 (35,2%)
Latinoamérica	63/193 (32,6%)
Sahara	40/193 (20,7%)
Asia Meridional	17/193 (8,8%)
Africa Subsahariana	5/193 (2,6%)
Tipo de gestación, n (%)	
Única	214 (97,3%)
Gemelar bicorial biamniótica	6 (2,7%)
Consumo de tabaco, n (%)	5 (2,3%)
Patología de base, n (%)	
Psiquiátrica: trastorno ansioso depresivo	10/220 (4,5%)

Hipertensión arterial	6/220 (2,7%)
Diabetes mellitus	5/220 (2,3%)
Infección crónica: VHB TBC Chagas	4/220 (1,8%) 2 1 1
Enfermedad respiratoria: asma	3/220 (1,4%)
Cardiopatía congénita	3/220 (1,4%)
Hipertrigliceridemia	2/220 (0,9%)
Manifestaciones clínicas	
Enfermedad leve	20/220 (9,1%)
Neumonía	77/220 (35,0%)
Neumonía grave (UCI)	80/220 (36,4%)
SDRA	43/220 (19,5%)
Edad gestacional al diagnóstico (semanas), mediana (rango intercuartil)	32 (25 - 35)

Tabla 1 Características demográficas y clínicas de la cohorte de 220 mujeres con infección por SARS-CoV-2 hospitalizadas en el Hospital Universitari Vall d'Hebron entre marzo de 2020 y enero de 2022

Abreviaturas: VHB, virus hepatitis B; TBC, tuberculosis; SDRA, síndrome de distrés respiratorio agudo.

Complicaciones obstétricas	53/211
Aborto <14 semanas	0
Aborto 14-22 semanas	2
Óbito fetal	1
Amenaza de parto prematuro	6
Rotura prematura de membranas <37 semanas	10
Preeclampsia	11
Diabetes gestacional	15
CIR	7
Malformación fetal: edema fetal transitorio	2
Edad gestacional al parto (semanas), mediana (rango)	39 (27 – 41)
Inicio de parto	
Espontáneo	98/210 (46,7%)
Indicado	112/210 (53,3%)
- Por COVID-19	53 (47,3%)
- Otras indicaciones	59 (52,7%)
Parto prematuro <37 semanas	51/210
- Por COVID-19	37
- Otros	14
Tipo de parto	
Vaginal	122/210 (58,1%)
Cesárea	88/210 (41,9%)

Tabla 2 Resultados gestacionales de las mujeres con infección por SARS-CoV-2 hospitalizadas en el Hospital Universitari Vall d'Hebron entre marzo de 2020 y enero de 2022.

Abreviaturas: CIR, crecimiento intrauterino restringido.

HIPÓTESIS

Las gestantes son un grupo especialmente vulnerable a las infecciones emergentes. Presentan mayor riesgo de adquirir la infección por SARS-CoV-2 y de presentar manifestaciones clínicas diferentes a la población general, complicaciones obstétricas específicas y repercusiones negativas en el neonato.

La infección por SARS-CoV-2 supone riesgo de complicaciones maternas y fetales específicas y existe riesgo de transmisión congénita.

OBJETIVOS

1. Elaborar un protocolo de diagnóstico y seguimiento de gestantes infectadas por SARS-CoV-2 y sus recién nacidos.
2. Evaluar la prevalencia de manifestaciones clínicas, marcadores ecográficos y bioquímicos de preeclampsia en las gestantes con COVID-19.
3. Valorar qué marcadores clínicos, ecográficos o bioquímicos de preeclampsia son útiles para el diagnóstico diferencial entre preeclampsia e infección por SARS-CoV-2.
4. Evaluar la posibilidad de transmisión materno-fetal de la infección por SARS-CoV-2.
5. Evaluar si existe afectación fetal durante la infección aguda por SARS-CoV-2.

ARTÍCULOS

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STUDY PROTOCOL Open Access

Gestation and COVID-19: clinical and microbiological observational study (Gesta-COVID19)

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Abstract

Background: The Coronavirus Disease 2019 (COVID-19) is a novel disease which has been having a worldwide affect since December 2019. Evidence regarding the effects of SARS-CoV-2 during pregnancy is conflicting. The presence of SARS-CoV-2 has been demonstrated in biological samples during pregnancy (placenta, umbilical cord or amniotic fluid); however, maternal and fetal effects of the virus are not well known.

Methods: Descriptive, multicentre, longitudinal, observational study in eight tertiary care hospitals throughout Spain, that are referral centres for pregnant women with COVID-19. All pregnant women with positive SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction during their pregnancy or 14 days preconception and newborns born to mothers infected with SARS-CoV-2 will be included. They will continue to be followed up until 4 weeks after delivery. The aim of the study is to investigate both the effect of COVID-19 on the pregnancy, and the effect of the pregnancy status with the evolution of the SARS-CoV-2 disease. Other samples (faeces, urine, serum, amniotic fluid, cord and peripheral blood, placenta and breastmilk) will be collected in order to analyse whether or not there is a risk of vertical transmission and to describe the behaviour of the virus in other fluids. Neonates will be followed until 6 months after delivery to establish the rate of neonatal transmission. We aim to include 150 pregnant women and their babies. Ethics approval will be obtained from all the participating centres.

Discussion: There is little information known about COVID-19 and its unknown effects on pregnancy. This study will collect a large number of samples in pregnant women which will allow us to demonstrate the behaviour of the virus in pregnancy and postpartum in a representative cohort of the Spanish population.

Keywords: SARS-CoV-2, COVID-19, Pregnancy, Vertical transmission, Amniotic fluid, Placenta, Cord blood, Breastmilk

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Background

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) was first reported in the city of Wuhan, China, in December 2019, with a rapid spread to the rest of the planet within a few weeks. Spain reported its first case of the Coronavirus Disease 2019 (COVID-19) in February, 2020 and as of December 29th 2020, almost 2 million cases have been reported [1].

Evidence regarding the effects of SARS-CoV-2 during pregnancy is conflicting: A study on pregnant women in the United States of America reported that percentages of mild, moderate and severe disease for pregnant women are similar to that of the general population (80, 15 and 5%, respectively) [2] whilst others suggest higher rates of Intensive Care Unit (ICU) admission and oxygen supplementation in pregnant women above 20 weeks' gestation compared to non-pregnant population with COVID-19 [3]. Many publications regarding the maternal-fetal effects of the virus have raised: a preeclampsia-like syndrome in women affected by COVID-19 has been described [4] and transplacental transmission and possible fetal effects of the virus have been demonstrated [5–7]. The presence of the virus in amniotic fluid and breast milk has also been reported [6, 8]. However, evidence on the effects of the SARS-CoV-2 infection during the first trimester of pregnancy is scarce, with only few publications reporting low rates of miscarriage in the first trimester [9] In our centre we have identified patients with these characteristics, the obstetric and neonatal results of which will be of utmost importance for the correct care and treatment of this disease in pregnant women. Given the little evidence published so far regarding the effects that COVID-19 can have on pregnancy and vice versa, it is essential to gather as much information as possible.

We designed an observational study in 8 tertiary care hospitals in Spain, that are referral centres for pregnant women with COVID-19 during the pandemic. The study intends to investigate both the effect of COVID-19 on pregnancy, and the effect of pregnancy status with the evolution of SARS-CoV-2 disease.

Methods/design

Design and setting of the study

This is a descriptive, multicentre, longitudinal, observational study in eight tertiary care hospitals throughout Spain, that are referral centres for pregnant women with COVID-19: Vall d'Hebron University Hospital (HUVH), Barcelona (coordinating centre); La Paz University Hospital (HULP), Madrid; Hospital Virgen de la Arrixaca (HUVA), Murcia; Hospital Universitario Cruces (HUC), Bizkaia; Hospital Clínico Universitario Lozano Blesa (HCULB), Zaragoza; Hospital de Torrejón, Madrid; Hospital Universitario San Cecilio, Granada; and Hospital Universitario La Fe, Valencia.

Given that COVID-19 is an emerging disease and our knowledge of it evolves from day to day, authors will be encouraged to add other variables to the protocol as new clinical evidence comes forward, with the commitment to notify any changes in protocol to the Ethics Committee.

Objective

To investigate both the effect of COVID-19 on pregnancy and the effect of pregnancy status with the evolution of SARS-CoV-2 disease.

Outcomes (Table 1)

Primary outcome:

- Rate of perinatal morbidity in pregnant women with COVID-19 (preterm delivery, preeclampsia, hospitalization during pregnancy, and admission to the ICU)

Secondary outcomes:

- Description of COVID-19 maternal symptoms
- Rate of maternal mortality

Table 1 Definition of primary and secondary outcomes

Primary outcome	
Preeclampsia, preterm delivery, need of hospitalization, ICU admittance	Frequency of each complication / total number of pregnant women
Secondary outcomes	
Description of COVID-19 maternal symptoms	Frequency of each symptom / Total number of pregnant women
Maternal mortality	Number of maternal deaths due to COVID-19 or any other complication during the pregnancy / Total number of pregnant women
Rate of fetal morbidity and mortality	Number of miscarriage, stillbirth, fetal malformation, intrauterine growth restriction / Total number of foetuses
Description of behaviour of the virus in biological fluids (urine, faeces, blood cord, placenta and breastmilk)	Number of positive tests / Number of tests performed (per each fluid or tissue)
Neonatal infection at 24, 48 h and 7 days	Number of newborns with positive RT-PCR in pharyngeal aspirate at 24, 48 h and at 7 days / Total number of newborns
Neonatal mortality	Number of neonatal deaths within the first 7 (early) and 28 days of life / Total number of foetuses/ newborns
Neonatal morbidity (pneumonia, NICU admission, sepsis,…)	Number of each complication / Total number of neonates

ICU Intensive Care Unit, *NICU* Neonatal Intensive Care Unit

- Rate of fetal mortality
- Rate of fetal morbidity (miscarriage, stillbirth, fetal malformation, and intrauterine growth restriction)
- Description of the behaviour of the virus in biological fluids (peripheral blood, urine, faeces, blood cord, placenta, and breastmilk) and serological response
- Rate of neonatal infection at 24, 48 h and 7 days after birth
- Rate of neonatal mortality
- Rate of neonatal morbidity (infection, pneumonia, and admission to the ICU)

Participants and processes

All consecutive pregnant women with a confirmed COVID-19 diagnosis by real-time reverse transcriptase polymerase chain reaction (RT-PCR) will be included.

Women attended in a labour ward or outpatient clinic with SARS-CoV-2 symptoms (fever, cough, dyspnoea, anosmia, ageusia, diarrhoea, fatigue, myalgias) [10] or those in close contact with a COVID-19 confirmed case, will undergo a SARS-CoV-2 RT-PCR in nasopharyngeal and oropharyngeal smears.

They will be managed according the presence of mild (fever, cough, anosmia, diarrhoea), moderate (tachypnoea >30xmin, hypoxia (saturation < 93% in room air at sea level or PAO2/FiO2 < 300 mmHg) or abnormal chest imaging (> 50% affected lung) or severe symptoms (respiratory failure, shock) [10, 11] Women with mild symptoms will be managed as outpatients and called in daily for a symptoms' evaluation until a SARS-CoV-2 RT-PCR negativization. Women requiring hospitalization (with moderate or severe symptoms) will be managed according to gestational age and symptoms until discharged from the hospital.

All women with a previous history of COVID-19 and negative RT-PCR SARS-CoV-2 will be followed monthly in the outpatient clinic until delivery and at 4 weeks postpartum.

Delivery of positive SARS-CoV-2 women will be performed according the Spanish Guidelines for COVID-19 pregnancy and delivery [12, 13]. Neonates will not be separated from their mothers but women will be instructed regarding measures to prevent contagion of their sons.

Inclusion and exclusion criteria:

- Inclusion criteria: women with SARS-CoV-2 RT-PCR during pregnancy or 14 days preconception and newborns born to mothers infected with SARS-CoV-2.
- Exclusion criteria: refusal to participate in the study, pregnant women under 18 years of age, and difficulty to understand informed consent.

Samples to be collected (Fig. 1):

- Pregnant women: SARS-CoV-2 RT-PCR in nasopharyngeal and oropharyngeal swab at first visit, weekly until SARS-CoV-2 RT-PCR negativization, delivery and postpartum; SARS-CoV-2 RT-PCR in amniotic fluid, urine, faeces, peripheral blood and serum for serologic tests, according to clinical criteria; SARS-CoV-2 RT-PCR in amniotic fluid, placenta, cord blood, and breast milk at delivery and postpartum. Serologic tests within 4–6 weeks after negative SARS-CoV-2 RT-PCR results.
- Newborns born to COVID-19 women: SARS-CoV-2 RT-PCR in nasopharyngeal aspirate, urine, and faeces after delivery. Serologic tests at delivery and after 30 days and 6 months postpartum.
- Newborns born to COVID-19 women requiring admission to the Neonatal Unit: SARS-CoV-2 RT-PCR in nasopharyngeal aspirate and tracheal aspirate (if intubated) after delivery, 24 h, 5 days, and 14 days after birth. SARS-CoV-2 RT-PCR in urine, faeces and serologic tests after delivery. Serologic tests after 30 days and 6 months postpartum.

The detection of SARS-CoV-2 RNA for any sample type will be performed by means of a commercial RT-PCR-based assay Allplex™ 2019-nCoV (Seegene, Korea). The serological study consists in the determination of specific IgG antibodies for pregnant women and specific IgG and IgM antibodies in newborns. These tests will be determined from serum samples using Liaison SARS-CoV-2 S1/S2 IgG (DiaSorin, Italy) and Liaison SARS-CoV-2 S1-RBD IgM. Both of them will be performed on the LIAISON® XL Analyzer (DiaSorin, Italy).

Data will be collected and encoded on an electronic data collection sheet (REDCap®). Each patient will have an identification number for the study. The correlation between the medical record number and the study identification number will be collected in a separate and anonymized database.

Statistics

A descriptive analysis for the primary and secondary outcomes will be carried out, calculating absolute and relative frequencies. For the maternal characteristics' description, median and interquartile range will be used for continuous variables and absolute and relative frequencies for categorical variables.

Logistic regression analysis will be used to explore the association of adverse maternal, fetal and neonatal outcomes with each specific drug used to treat COVID-19.

All analysis will be carried out with R software. Statistical significance will be set at $p < 0.05$.

	1st pregnancy assessment	Subsequent pregnancy assessments (every 4 weeks)								Delivery	Postpartum
TIMEPOINT**	*0*	*4 w*	*8 w*	*12 w*	*16 w*	*20 w*	*24 w*	*26 w*	*etc.*		*4 w*
Enrolment	X										
Informed consent	X										
INTERVENTIONS:											
Serum RT-PCR SARS-CoV-2	X									X	
Urine, feces RT-PCR SARS-CoV-2	X										
Serology SARS-CoV-2		X								X	
Ultrasound evaluation	X	X	X	X	X	X	X	X	X		
RT-PCR SARS-CoV-2 amniotic fluid, blood cord and placenta										X	
ASSESSMENTS:											
Maternal age, ethnicity, BMI, previous pregnancies, other illnesses	X										
COVID-19 symptoms	X	X	X	X	X	X	X	X	X	X	X
Outcomes: Maternal mortality, fetal-neonatal morbidity, fetal-neonatal mortality	X	X	X	X	X	X	X	X	X	X	X
ICU admittance, NICU admittance	X	X	X	X	X	X	X	X	X	X	X

Fig. 1 Gesta-COVID19 Study protocol. Pregnant women timeline (SPIRIT figure)

Sample size

Given the short evolution of this infection, this study aims to be exploratory and to make a quick characterization of the described outcomes. To this end, it has been estimated that within a period of 4 to 6 months (peak of the epidemic and subsequent months), we will be able to achieve a sample size of 150 pregnancies.

Ethics

This study was approved by the Ethics Committee of the coordinating centre (PR(AMI)181/2020) and by that of all the participating centres.

Patients will be informed about the study. Given the current situation of the pandemic and public health concerns (in order to reduce the risk of contagion), the Ethics Committee accepted to obtain oral consent from the patient and to record it in the medical history.

Discussion

The mother-foetus binomial is unique in medicine, morbidity and mortality can therefore affect both. This prospective longitudinal study aims to collect all consecutive cases of COVID-19 in pregnant women in eight referral centres throughout Spain, with the objective of defining whether the pregnancy implies a change in the prognosis of the infection, and vice versa, whether the infection impacts the pregnancy. Furthermore, we intend to assess vertical transmission.

The electronic data collection sheet, accessible via the website from eight of the main reference hospitals in Spain, will allow us to obtain a representative sample of the pregnant Spanish population.

The major strength of this study is that weekly consecutive samples of the naso / oropharyngeal smears will be obtained, allowing to infer virus clearance. Collecting

other samples apart from the naso / oropharyngeal smears (peripheral and cord blood, serum, faeces, urine, amniotic fluid, placenta, breast milk and serologic follow-up), will grant more information on the behaviour of the virus in other biological fluids and investigate whether or not there is risk of perinatal transmission.

Due to the limited information on COVID-19 in pregnancy to date, the limitation in the management and treatment of pregnant women, and the possibility of a new outbreak when confinement measures will relax, it is necessary to collect all possible evidence to establish management protocols and working dynamics to efficiently react when it happens. It is the clinicians' responsibility to be updated on COVID-19 in order to be able to offer the best care to their patients.

Abbreviations

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus Disease 2019; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; HUVH: Vall d'Hebron University Hospital; HULP: La Paz University Hospital; HUVA: Hospital Virgen de la Arrixaca; HUC: Hospital Universitario Cruces; HCULB: Hospital Clínico Universitario Lozano Blesa; RT-PCR: Real-time reverse transcriptase polymerase chain reaction; EC: Ethics Committee

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Authors' contributions

AS, IGR, MC, PGM, MAF, FC and NFH designed the study and collected samples. ES, AA, JE and TP conserved and analysed samples. NM described statistical analysis. CR, NM and EC wrote the manuscript. All authors read and approved the final manuscript.

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The study has been awarded with a Spanish Government grant (Instituto de Salud Carlos III: COV20/00188). It covers the expenses for transporting, processing and analyzing samples, database creation and maintenance, and hiring support staff.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Vall d'Hebron University Hospital Ethics Committee (EC), as the reference Ethics Committee, first approved this study. The reference number is PR(AMI)181–2020. All of the participating centres also obtained their own EC approval.
The protocol, informed consent form, participant information sheet and any applicable documents were submitted to the respective Ethics Committees and regulatory authorities, and written approval was obtained. All substantial amendments to the originally approved documents will be sent to the respective authorities for approval. The study did not begin until the approval of the EC and Director's consent was obtained. Given the current pandemic and public health concerns, it was accepted to obtain oral consent from the patients and to record it in their medical history.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. COVID-19 situation reports [Internet]. [cited 2020 Apr 18]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM. 2020;2(2):100118. https://doi.org/10.1016/j.ajogmf.2020.100118.
3. Badr DA, Mattern J, Carlin A, Cordier A-G, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol. 2020; [cited 2020 Oct 1]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002937820307766.
4. Mendoza M, Garcia-Ruiz 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 Int J Obstet Gynaecol. 2020; [cited 2020 Jun 2]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16339.
5. Garcia-Manau P, Garcia-Ruiz I, Rodo C, Sulleiro E, Maiz N, Catalan M, et al. Fetal Transient Skin Edema in Two Pregnant Women With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2020; [cited 2020 Oct 1]; Publish Ahead of Print. Available from: https://journals.lww.com/10.1097/AOG.0000000000004059.
6. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020; 11(1) [cited 2020 Oct 1]. Available from: http://www.nature.com/articles/s41467-020-17436-6.
7. Schwartz DA, Morotti D, Beigi B, Moshfegh F, Zafaranloo N, Patanè L. Confirming Vertical Fetal Infection with COVID-19: Neonatal and Pathology Criteria for Early Onset and Transplacental Transmission of SARS-CoV-2 from Infected Pregnant Mothers. Arch Pathol Lab Med. 2020; [cited 2020 Oct 1]; Available from: http://meridian.allenpress.com/aplm/article/doi/10.5858/arpa.2020-0442-SA/441323/Confirming-Vertical-Fetal-Infection-with-COVID19.
8. Costa S, Posteraro B, Marchetti S, Tamburrini E, Carducci B, Lanzone A, et al. Excretion of SARS-CoV-2 in human breast milk. Clin Microbiol Infect. 2020; 26(10):1430–2.
9. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol. 2020;56(1):15–27.
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239.
11. Documento técnico: Manejo clínico del COVID-19: atención hospitalaria. Version 18 June 2020 [Internet]. 2020 [cited 2020 Oct 7]. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf.
12. Olaso OP. Documento técnico. Manejo de la mujer embarazada y el recién nacido con COVID-19. Version 17 June 2020 [Internet]. [cited 2020 Oct 7]. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Documento_manejo_embarazo_recien_nacido.pdf.
13. Falguera G, González E, Espart L, Coll E, Martínez C, Escuriet R. Guia d'actuació enfront de casos d'infecció pel nou coronavirus SARS-CoV-2 en dones embarassades i nadons. [Internet]. [cited 2020 Oct 7]. Available from: https://scientiasalut.gencat.cat/handle/11351/4786.

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Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study

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Objectives To investigate the incidence of clinical, ultrasonographic and biochemical findings related to pre-eclampsia (PE) in pregnancies with COVID-19, and to assess their accuracy to differentiate between PE and the PE-like features associated with COVID-19.

Design A prospective, observational study.

Setting Tertiary referral hospital.

Participants Singleton pregnancies with COVID-19 at $>20^{+0}$ weeks.

Methods Forty-two consecutive pregnancies were recruited and classified into two groups: severe and non-severe COVID-19, according to the occurrence of severe pneumonia. Uterine artery pulsatility index (UtAPI) and angiogenic factors (soluble fms-like tyrosine kinase-1/placental growth factor [sFlt-1/PlGF]) were assessed in women with suspected PE.

Main outcome measures Incidence of signs and symptoms related to PE, such as hypertension, proteinuria, thrombocytopenia, elevated liver enzymes, abnormal UtAPI and increased sFlt-1/PlGF.

Results Thirty-four cases were classified as non-severe and 8 as severe COVID-19. Five (11.9%) women presented signs and symptoms of PE, all five being among the severe COVID-19 cases (62.5%). However, abnormal sFlt-1/PlGF and UtAPI could only be demonstrated in one case. One case remained pregnant after recovery from severe pneumonia and had a spontaneous resolution of the PE-like syndrome.

Conclusions Pregnant women with severe COVID-19 can develop a PE-like syndrome that might be distinguished from actual PE by sFlt-1/PlGF, LDH and UtAPI assessment. Healthcare providers should be aware of its existence and monitor pregnancies with suspected pre-eclampsia with caution.

Keywords Angiogenic factors, COVID-19, PlGF, pre-eclampsia, pre-eclampsia-like syndrome, pregnancy, SARS, SARS-CoV-2, sFlt-1.

Tweetable abstract This study shows that a pre-eclampsia-like syndrome could be present in some pregnancies with severe COVID-19.

Linked article This article is commented on by DL Rolnik, p. 1381 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16369

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Introduction

On 11 March 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic disease, given its increasing number of cases worldwide.[1] Studies have shown that the disease caused by SARS-CoV-2, named as COVID-19 (coronavirus disease 2019) typically presents with fever, dry cough and fatigue; nevertheless, up to 14% of the cases can evolve to severe pneumonia and 5% to severe acute respiratory syndrome (SARS), both requiring admission to intensive care for intensive respiratory support.[2] Whereas COVID-19 is primarily a respiratory infection, it has important systemic effects including hypertension, kidney disease, thrombocytopenia and liver injury.[3–6] As SARS-CoV-2 is believed to invade the host

through the cell entry receptor angiotensin-converting enzyme 2 (ACE2), these signs and symptoms in SARS-CoV-2 infection are thought to be due to the vasoconstriction resulting from the dysfunction of the renin-angiotensin system.[7,8] By contrast, clinical features of pre-eclampsia (PE) are mainly a consequence of the endothelial damage originated by placental oxidative stress and antiangiogenic status, which leads to the appearance of hypertension and proteinuria, elevated liver enzymes, renal failure or thrombocytopenia, among others.[9,10] An increased incidence of PE has been reported among mothers infected with SARS-CoV-2 compared with the general population.[11] Misdiagnosis, however, might have occurred in some of these cases, as COVID-19 and PE have overlapping clinical features. Therefore, differential diagnosis might be challenging in COVID-19 pregnant women presenting with hypertension and proteinuria, thrombocytopenia or elevated liver enzymes.[10] Thus, the aim of this study was to investigate the prevalence of clinical, ultrasonographic and biochemical findings related to PE in women with SARS-CoV-2 infection and to assess their accuracy in differentiating between actual PE and PE-like features associated with COVID-19.

Methods

We carried out a prospective cohort study of all consecutive pregnant women at >20 weeks of gestation who presented to the emergency department of our tertiary care center for suspicion of COVID-19 (dry cough and fever) and had laboratory-confirmed SARS-CoV-2 infection, between 13 March and 10 April 2020. Patients were not actively involved in the research.

Patients were classified in two groups: severe and non-severe COVID-19, according to the occurrence of severe pneumonia. The laboratory and clinical data were prospectively recorded in a database. The recorded data included the following: platelet count (per microlitre), D-dimer (microg/l), lactate dehydrogenase (U/l), aspartate aminotransferase (U/l), alanine amninotransferase (U/l), urine protein to creatinine ratio (mg/g), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), mean arterial pressure (mmHg), creatinine (mg/dl) and gestational age (GA) in weeks. GA to describe particular cases was expressed in weeks^{+days}. Mean arterial pressure was calculated as: 1/3 × (systolic blood pressure) + 2/3 × (diastolic blood pressure). Maternal baseline characteristics were compared between groups. In severe cases, data were analysed at three different time points during COVID-19: before, during and after intensive care unit (ICU) admission for severe pneumonia.

According to the WHO guidance, laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RTPCR) assay of nasal and pharyngeal swabs.[12]

PE was defined as new onset of high blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) or worsening of previous high blood pressure in addition to new-onset proteinuria (protein to creatinine ratio >300) or worsening of previous proteinuria, or to at least one of the following signs and symptoms of severe PE: cerebral or visual symptoms, elevation of liver enzymes to twice normal concentration, platelet count <100 000/µl, serum creatinine concentrations >1.1 mg/dl or pulmonary oedema.[10] The HELLP syndrome is frequently considered a variant of PE. Diagnostic criteria for HELLP syndrome are haemolysis with increased LDH (>600 U/l) and AST (≥70 U/l), and platelets <100 000/µl.[13]

In women with new-onset hypertension, the uterine artery pulsatility index (UtAPI) was assessed by transabdominal Doppler ultrasound and maternal serum levels of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in pg/ml were determined by means of the fully automated Elecsys assays for sFlt-1 and PlGF on an electrochemiluminescence immunoassay platform (cobas e analyzers; Roche® Diagnostics, Rotkreuz, Switzerland).[14,15] The sFlt-1/PlGF was then calculated. UtAPI above the 95th centile for gestational age, and sFlt-1/PlGF values ≥85 (at <34 weeks) or ≥110 (at ≥34 weeks) were considered highly suggestive of underlying placental disease.[16 19]

Statistical analysis

The open-source satistical software R Commander(R package version 2.3-1), which is freely available on CRAN (https://cran.r-project.org), was used for statistical analysis. Categorical data were reported as frequency and percentage, and comparisons between severity groups were estimated by Chi-square or Fisher tests, as appropriate. Continuous variables were described as median and interquartile (IQR) range and Mann–Whitney U test was used to assess differences between severity groups. The statistical significance level was set at $P < 0.05$.

Results

During the study period (31 days), 42 cases of SARS-CoV-2-infected women were identified at a median GA of 32.0 (IQR 26.0–37.5) weeks of gestation. Among them, eight (19.0%) cases developed severe pneumonia and required admission to the ICU. Median maternal age of cases with severe COVID-19 was significantly greater than in the non-severe cases (39.4 [34.2–44.5] versus 30.9 [25.0–41.8], $P = 0.006$). No other pregnancy baseline characteristics differed between severity groups. Among the eight severe cases, five (62.5%) developed PE features (new-onset hypertension and proteinuria and/or thrombocytopenia and/or elevated liver enzymes), requiring antihypertensive

drugs in all of them. No cases with diagnostic criteria for PE were found among the 34 non-severe COVID-19 women (Table 1).

Evolution of clinical and laboratory findings in the severe cases of COVID-19

Before severe pneumonia, all eight women were normotensive, had normal platelet count, liver enzymes, LDH and proteinuria, and only one case with UtAPI above the 95th centile was identified. During severe pneumonia, the most frequent findings were: elevated liver enzymes to twice normal concentrations (87.5%), proteinuria >300 mg/g (75.0%) and hypertension (62.5%) (Figure 1). No cases with creatinine >1.1 mg/dl or platelet count <100 000/μl were found; nevertheless, one case presented mild thrombocytopenia (platelet count <150 000/μl). sFlt-1/PlGF ≥85/110 and UtAPI >95th centile were present in only one woman. Only one case with LDH >600 IU/l was identified. Based on these findings, five women (62.5%) had diagnostic criteria of PE and/or HELLP syndrome. Caesarean delivery was performed during ICU stay in four cases. HELLP syndrome was the indication for delivery in case 1 (at a GA of 30^{+1}) and worsening of SARS in cases 3, 4 and 7 (at a GA of 37^{+6}, 36^{+6} and 28^{+3}, respectively). After recovery from severe pneumonia, hypertensive therapy was no longer required in all cases and only the woman who had presented with sFlt-1/PlGF >110, LDH >600 and UtAPI above the 95th centile, still met PE diagnostic criteria (more details on clinical and laboratory findings and their evolution in severe cases can be seen in Table 2 and Figure 1).

Discussion

Main findings

This study shows that 11.9% of COVID-19 pregnant women develop PE features; however, they only appeared in COVID-19 cases complicated by severe pneumonia. In this situation, PE/HELLP diagnostic criteria were found in five (62.5%) of the cases; nevertheless, abnormal angiogenic status, increased LDH and placental underperfusion could only be confirmed in one of them, which indicates that this case was probably an actual PE. These findings suggest that the signs and symptoms compatible with PE/HELLP present in four of these five cases, could be derived from the complex polypharmacy administrated or from the renal and cardiovascular dysfunction for severe SARS-CoV-2 infection. In our cohort, only one of these five cases remained pregnant after severe pneumonia recovery, and then all PE/HELLP features recovered spontaneously. PE and HELLP syndrome do not resolve spontaneously and delivery is the only definitive cure. For these reasons, we believe that the four women with PE/HELLP signs and symptoms, and normal sFlt-1/PlGF, UtAPI and LDH <600, had developed a PE-like syndrome.

Strengths and limitations

To our knowledge, this is the first study to describe the incidence of signs and symptoms of PE in a relatively large cohort of pregnancies with COVID-19 and to show that a PE-like syndrome could be induced by severe COVID-19. Furthermore, our findings are of great value to improve

Table 1. Maternal characteristics in pregnant women with COVID-19

	All patients (n = 42)	Nonsevere patients (n = 34)	Severe patients (n = 8)	P
Maternal age (years)	32.0 (26.0 37.5)	30.9 (25.0 41.8)	39.4 (34.2 44.5)	0.006
Pre-pregnancy BMI (kg/m^2)	26.2 (23.5 29.3)	26.1 (22.8 29.3)	27.9 (25.4 30.6)	0.378
Gestational age (weeks)	31.6 (25.9 36.1)	32.8 (26.7 36.1)	28.6 (22.3 32.4)	0.211
Ethnicity				
White	22 (52.4%)	19 (55.9%)	3 (37.5%)	0.304
Latin American	17 (40.5%)	12 (35.3%)	5 (62.5%)	
Others	3 (7.1%)	3 (8.8%)	0	
ART	4 (9.5%)	2 (5.9%)	2 (25.0%)	0.158
Smoking	2 (4.8%)	1 (2.9%)	1 (12.5%)	0.348
Nuliparous	20 (47.6%)	16 (47.1%)	4 (50.0%)	1.0
History of PE	0	0	0	1.0
Pre-pregnancy HTN	0	0	0	1.0
Pre-pregnancy diabetes	1 (2.4%)	1 (2.4%)	0	1.0
Chronic kidney disease	0	0	0	1.0
PE diagnostic criteria during COVID-19	5 (11.9%)	0	5 (62.5%)	<0.001

ART, assisted reproductive technology; BMI, body mass index; HTN, hypertension; PE, pre-eclampsia.
Continuous data are given as median and interquartile range. Categorical data as frequency and percentage. P-values denoted the comparison between non-severe and severe subgroups.

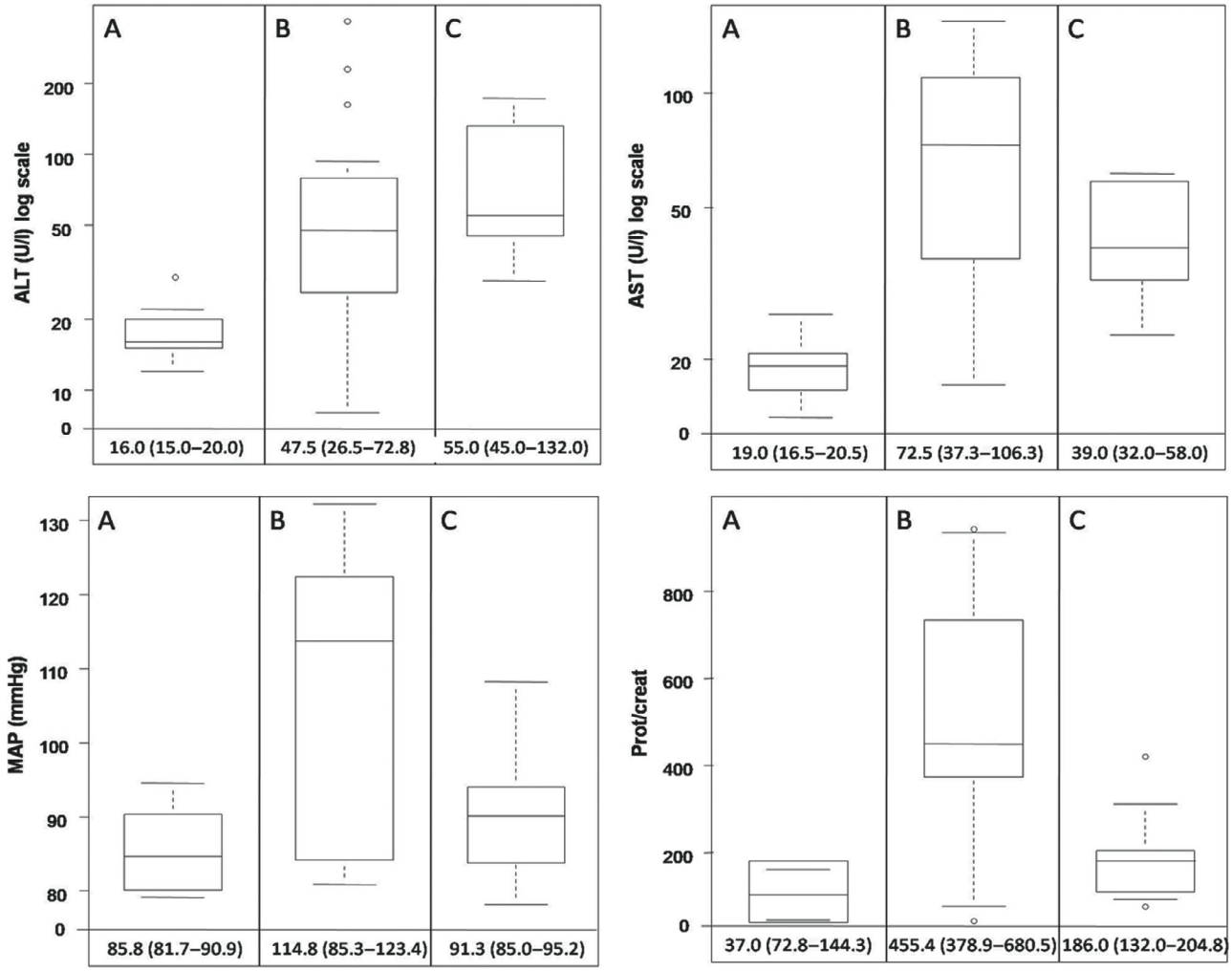

Figure 1. Evolution of ALT, AST, proteinuria and mean arterial blood pressure in pregnant women with COVID-19 before (A), during (B) and after (C) severe pneumonia. The bottom and top edges of each box represent the first and third quartiles, respectively, the band within the box represents the median value and the whiskers represent values that are 1.5 times the interquartile range. Median values and interquartile range of each variable are displayed.

maternal care of pregnancies with severe pneumonia due to COVID-19.

This study has several limitations. First, this is a small series and the results should be considered with caution. Further research is needed to better understand the systemic consequences of COVID-19 in pregnant women. Second, only four women with PE-like syndrome are reported, which could mean that our findings are not applicable to all pregnancies with severe pneumonia due to COVID-19. Third, only one of the four women who developed a PE-like syndrome remained pregnant after severe pneumonia and despite the PE-like syndrome recovering spontaneously, we cannot affirm that the three other cases did not improve due to delivery. Nevertheless, we believe that the PE-like syndrome alone may not be an obstetric indication for delivery, as it seems that it might not be a placental complication itself, but one of the clinical manifestations of severe COVID-19. Finally, although UtAPI and sFlt-1/PlGF ratio have a high negative predictive value to predict the short-term absence of PE, they are not diagnostic criteria of PE;[20,21] thus, we cannot categorically state that the case with PE features and elevated UtAPI and sFlt-1/PlGF was an actual PE and not a PE-like syndrome.

Interpretation

Several disorders have previously proved to imitate PE because they share some of the clinical and laboratory findings of patients with PE. The pathophysiologic causes of these conditions include vasospasm, platelet activation or destruction, microvascular thrombosis, endothelial cell dysfunction and reduced tissue perfusion. Some of these disorders include gestational hypertension, chronic kidney

Table 2. Clinical and biochemical pre-eclampsia-related findings in pregnant women with COVID-19 before, during and after severe pneumonia

	Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Before severe pneumonia	GA (weeks)	30^{+0}	22^{+6}	37^{+5}	36^{+4}	32^{+0}	20^{+3}	27^{+4}	20^{+1}
	SBP (mmHg)	130	120	123	117	104	135	107	116
	DBP (mmHg)	74	72	74	67	71	76	67	63
	MAP (mmHg)	92.7	88.0	90.3	83.7	82.0	95.7	80.3	80.7
	Prot/creat (mg/g)	37	180						
	AST (U/l)	17	19	15	20	26	19	23	14
	ALT (U/l)	16	30	13	26	20	12	14	22
	Platelets/μl	158 000	242 000	402 000	210 000	275 000	234 000	319 000	242 000
	LDH (U/l)								
	D-dimer (mg/ml)								
	Creatinine (mg/dl)	0.63	0.49		0.79	0.74	0.36	0.45	0.66
	UtAPI >95th centile	No	No	Yes	No	No	No	No	No
	PE/HELLP diagnostic criteria	No	No	No	No	No	No	No	No
During severe pneumonia	GA (weeks)	30^{+1}	24^{+4}	37^{+6}	36^{+5}	32^{+1}	20^{+4}	28^{+3}	20^{+2}
	SBP (mmHg)	145	168	156	155	116	115	140	108
	DBP (mmHg)	90	116	98	108	70	68	105	69
	MAP (mmHg)	108.3	133.3	117.3	123.7	85.3	83.7	116.7	82.0
	Prot/creat (mg/g)	855	622	378	514	396	49	948	130
	AST (U/l)	153	122	104	62	38	52	138	113
	ALT (U/l)	170	136	52	39	38	14	65	230
	Platelets/μl	324 000	160 000	279 000	231 000	336 000	243 000	108 000	505 000
	LDH (U/l)	482	370	672	555	517	176	463	312
	D-dimer (mg/ml)	457	2129	5065	1800	326	119	514	376
	Creatinine (mg/dl)	0.34	0.42	0.85	0.88	0.42	0.20	0.39	0.26
	Hidralazine	Yes	Yes	Yes	Yes	No	No	No	No
	Labetalol	Yes	Yes	Yes	Yes	No	No	Yes	No
	sFlt-1/PlGF	9.40	20.24	378.90	49.36	24.78	4.60	7.60	5.19
	UtAPI >95th centile	No	No	Yes	No	No	No	No	No
	PE/HELLP diagnostic criteria	Yes	Yes	Yes	Yes	No	No	Yes	No
After severe pneumonia	GA at delivery (weeks)	30^{+1}	Not delivered	37^{+6}	36^{+6}	Not delivered	Not delivered	28^{+3}	Not delivered
	Reason for delivery	HELLP		SARS	SARS			SARS	
	GA (weeks)		25.5			33.2	21.5		21.3
	SBP (mmHg)	123	132	142	115	116	108	109	110
	DBP (mmHg)	83	75	93	68	79	62	75	64
	MAP (mmHg)	96.3	94.0	109.3	83.7	91.3	77.3	86.3	79.3
	Prot/creat (mg/g)	210	183	426	83	115	83	189	128
	AST (U/l)	39	32	56	43	58		23	61
	ALT (U/l)	45	132	41	29	55		29	172
	Platelets/μl	312 000	218 000	232 000	258 000	292 000	169 000	364 000	762 000
	LDH (U/l)	222	277	692	325	211		353	192
	D-dimer (mg/ml)	617	1745	3258		454		347	470
	Creatinine (mg/dl)	0.25	0.3	0.58		0.41		0.42	0.65
	UtAPI >95th centile		No			No	No		No
	PE/HELLP diagnostic criteria	No	No	Yes	No	No	No	No	No

ALT, alanine amninotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; GA, gestational age; LDH, lactate dehydrogenase; MAP, mean arterial pressure; PE, pre-eclampsia; PlGF, placental growth factor; prot/creat; urine protein to creatinine ratio; SARS, severe acute respiratory syndrome; sFlt-1, soluble fms-like tyrosine kinase-1; UtAPI, uterine artery pulsatility index.

disease, acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, acute exacerbation of systemic lupus erythematosus, severe hypothyroidism and sepsis.[17,22,23] Differential diagnosis may be a challenge to caregivers due to the overlap of diagnostic criteria among them. Additionally, some of them are potentially life-threatening for both the mother and the fetus; thus, accurate diagnosis is important, as the management and prognosis of these conditions differ widely. Recent studies have shown that angiogenic factors support the differential diagnosis between PE and some of its imitators.[17,24,25] PlGF and sFlt-1 are placenta-related angiogenic factors that are highly specific to placental insufficiency.[26] In PE, the placenta fails properly to invade and remodel maternal uterine spiral arteries, leading to impaired perfusion and placental oxidative stress.[27,28] This condition leads to increased UtAPI and to an antiangiogenic status with increased s-Flt-1/PlGF ratio due to up-regulation of sFlt-1 and down-regulation of PlGF.[9,20] The identification of an sFlt-1/PlGF imbalance is detectable in the maternal circulation at least 5 weeks before the onset of clinical PE.[26] Thus, COVID-19 patients with normal early phase of placental implantation should have normal values of sFlt-1/PlGF and UtAPI in spite of proteinuria, thrombocytopenia, elevated liver enzymes or hypertension. This hypothesis, however, had not been previously investigated due to the very recent outbreak of the SARS-CoV-2 infection.

This study has important clinical implications, as we show that sFlt-1/PlGF, UtAPI and LDH allow PE to be differentiated from the PE-like syndrome present in some of the pregnant women with severe COVID-19. This knowledge could improve management and reduce misdiagnosis in pregnancies with severe COVID-19. In our cohort, case 1 was probably misdiagnosed as HELLP syndrome; this, in addition to the concurrence of SARS, influenced the indication of delivery. The fact that the sFlt-1/PlGF results were not available at the time of worsening of the maternal condition, and the scarce evidence available at that time of the consequences of COVID-19 during pregnancy, prompted the delivery indication at 30^{+1} weeks. After the experience with this first case, a more conservative management was adopted in the following cases that developed PE-like syndrome. Fortunately, they completely recovered after severe pneumonia and became normotensive again without any antihypertensive drugs and without being delivered.

Conclusion

Pregnant women with severe COVID-19 could develop a PE-like syndrome, which might be distinguished from actual PE by sFlt-1/PlGF, LDH and UtAPI assessment. Therefore, healthcare providers should be aware of its existence and monitor pregnancies with suspected PE with caution. PE-like syndrome might not be an indication for earlier delivery in itself, as it might not be a placental complication and could resolve spontaneously after recovery from severe pneumonia.

Disclosure of interests

Manel Mendoza and Itziar Garcia-Ruiz received lecture fees by Roche Diagnostics. The other authors have no conflicts of interest to declare. Completed disclosure of interests forms is available to view online as supporting information.

Contribution to authorship

AS and EC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EC, AS, MM and IG-R conceived and designed the study. RML-M, JB, NM and NF-H contributed to the literature research. NM, CR, PG-M and BS contributed to data collection and confirmation. MM, IG-R and AS contributed to data analysis, and MM, IG-R, AS, RMLM, JB, NF-H and EC contributed to data interpretation. MM and IG-R were in charge of writing the manuscript draft. AS and EC made substantial revisions to the manuscript. MM and IG-R contributed equally to this article. AS and EC also contributed equally to this article.

Details of ethics approval

This study was approved by the Vall d'Hebron University Hospital Ethics Committee (PR[AMI]181/2020) on 13 March 2020. Written informed consent was waived due to the rapid emergence of this infectous disease. However, verbal informed consent was obtained from all patients, which was included in the patient's medical record.

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References

1 WHO Director-General's opening remarks at the media briefing on COVID-19. 2020 [www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020]. Accessed 12 March 2020.

2 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; published online Feb 24. https://doi.org/10.1001/jama.2020.2648

3 Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. Characteristics of liver tests in COVID-19 patients. *J Hepatol* 2020; published online Apr 13. https://doi.org/10.1016/j.jhep.2020.04.006

4 Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; published online Mar 20. https://doi.org/10.1016/j.kint.2020.03.005

5 Kreutz R, Algharably EAE-H, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res* 2020; published online Apr 15. https://doi.org/10.1093/cvr/cvaa097

6 Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020;506:145 8.

7 Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, et al. Angiotensin converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system. *Circ Res* 2020; published online Apr 8. https://doi.org/10.1161/CIRCRESAHA.120.317015

8 Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020; published online Apr 15. https://doi.org/10.1161/CIRCULATIONAHA.120.047549

9 Turpin CA, Sakyi SA, Owiredu WKBA, Ephraim RKD, Anto EO. Association between adverse pregnancy outcome and imbalance in angiogenic regulators and oxidative stress biomarkers in gestational hypertension and preeclampsia. *BMC Pregnancy Childbirth* 2015;15:189.

10 American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol* 2013;122:1122 31.

11 Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID 1 19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2020). 2, 100107https://doi.org/10.1016/j.ajogmf.2020.100107

12 World HealthOrganization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. 2020 [https://apps.who.int/iris/handle/10665/330854]. Accessed 11 March 2020.

13 Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A review. *BMC Pregnancy Childbirth* 2009;9:8.

14 Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11 14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001;18:583 6.

15 Schiettecatte J, Russcher H, Anckaert E, Mees M, Leeser B, Tirelli AS, et al. Multicenter evaluation of the first automated Elecsys sFlt-1 and PlGF assays in normal pregnancies and preeclampsia. *Clin Biochem* 2010;43:768 70.

16 Gómez O, Figueras F, Fernández S, Bennasar M, Martínez JM, Puerto B, et al. Reference ranges for uterine artery mean pulsatility index at 11 41 weeks of gestation. *Ultrasound Obstet Gynecol* 2008;32:128 32.

17 Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol.* 2012;206:58.e1 8.

18 Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. *Ultrasound Obstet Gynecol* 2015;45:241 6.

19 Paules C, Youssef L, Rovira C, Crovetto F, Nadal A, Peguero A, et al. Distinctive patterns of placental lesions in pre-eclampsia vs small-for-gestational age and their association with fetoplacental Doppler. *Ultrasound Obstet Gynecol* 2019;54:609 16.

20 Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med* 2016;374:13 22.

21 1 Recommendations | PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). NICE Guidance. [www.nice.org.uk/guidance/dg23/chapter/1-Recommendations]. Accessed 28 March 2020.

22 Sibai BM. Imitators of severe pre-eclampsia. *Semin Perinatol* 2009;33:196 205.

23 Inversetti A, Serafini A, Manzoni MF, Dolcetta Capuzzo A, Valsecchi L, Candiani M. Severe hypothyroidism causing pre-eclampsia-like syndrome. *Case Rep Endocrinol* 2012;2012:586056.

24 Rolfo A, Attini R, Nuzzo AM, Piazzese A, Parisi S, Ferraresi M, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. *Kidney Int* 2013;83:177 81.

25 Hirashima C, Ogoyama M, Abe M, Shiraishi S, Sugase T, Niki T, et al. Clinical usefulness of serum levels of soluble fms-like tyrosine kinase 1/placental growth factor ratio to rule out preeclampsia in women with new-onset lupus nephritis during pregnancy. *CEN Case Rep* 2019;8:95 100.

26 Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350:672 83.

27 Hung TH, Skepper JN, Burton GJ. In vitro ischemia-reperfusion injury in term human placenta as a model for oxidative stress in pathological pregnancies. *Am J Pathol* 2001;159:1031 43.

28 Pijnenborg R, Vercruysse L, Verbist L, Van Assche FA. Interaction of interstitial trophoblast with placental bed capillaries and venules of normotensive and pre-eclamptic pregnancies. *Placenta* 1998;19:569 75.

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Research note

Congenital infection of SARS-CoV-2 in live-born neonates: a population-based descriptive study

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ABSTRACT

Objective: To evaluate the evidence of mother-to-child transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: This is a descriptive, multicentre, observational study in nine tertiary care hospitals throughout Spain. The study population was women with coronavirus disease 2019 during pregnancy. Mother-to-child transmission was defined as positive real-time RT-PCR of SARS-CoV-2 in amniotic fluid, cord blood, placenta or neonatal nasopharyngeal swabs taken immediately after birth.

Results: We included 43 women with singleton pregnancies and one with a twin pregnancy, as a result we obtained 45 samples of placenta, amniotic fluid and umbilical cord blood. The median gestational age at diagnosis was 34.7 weeks (range 14–41.3 weeks). The median interval between positive RT-PCR and delivery was 21.5 days (range 0–141 days). Fourteen women (31.8%, 95% CI 18.6%–47.6%) were positive at the time of delivery. There was one singleton pregnancy with SARS-CoV-2 RT-PCR positive in the placenta, amniotic fluid and umbilical cord blood (2.2%, 95% CI 0.1%–11.8%). Nasopharyngeal aspiration was performed on 38 neonates at birth, all of which were negative (0%, 95% CI 0%–9.3%). In 11 neonates the nasopharyngeal aspiration was repeated at 24–48 hours, and one returned positive (9.1%, 95% CI 0.2% –41.3%).

Conclusions: The presence of SARS-CoV-2 in placenta, amniotic fluid and cord blood shows that mother-to-child transmission is possible but uncommon. **Itziar Garcia-Ruiz, Clin Microbiol Infect 2021;27:1521.e1–1521.e5**

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Introduction

Physiological changes in pregnancy increase the susceptibility to infections and their severity. Moreover, maternal infections may have consequences for the offspring, as obstetric complications or congenital infections.

Clinical presentation of coronavirus disease 2019 (COVID-19) in pregnancy is similar to the general population [1], but with a significantly higher risk of Intensive Care Unit admission and invasive ventilation than in non-pregnant adults [2,3].

The likelihood of mother-to-child transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still unknown. Several studies have suggested this possibility [4–6], but most of them did not have enough evidence to demonstrate both maternal and fetal or neonatal infection.

The aim of this study was to evaluate the possibility of mother-to-child transmission of SARS-CoV-2 in a cohort of pregnant women with COVID-19.

Materials and methods

Approval for the study was obtained from the Vall d'Hebron University Hospital Ethics Committee (PR(AMI)181/2020) on 27 March 2020, and subsequently validated in the other hospitals. Informed consent was obtained from pregnant women for the collection of data and biological samples from the mother and newborn.

Study population

This sub-study of the Gesta-Covid Collaborative Group (see Supplementary material, Appendix S1) included only pregnant women with COVID-19 infection for whom amniotic fluid, umbilical cord blood and placenta samples were collected at birth. Exclusion criteria were age under 18 years, difficulty understanding informed consent and refusal to participate.

A COVID-19 confirmed case was defined as laboratory confirmation of real-time RT-PCR for SARS-CoV-2 assay of the nasal and pharyngeal swab. In probable cases (negative RT-PCR), if the symptoms had started in the last 7 days then the RT-PCR was repeated after 24 hours, otherwise a serology test was performed.

Study outcomes

The primary outcome was evidence of mother-to-child transmission, defined as positive RT-PCR of SARS-CoV-2 in amniotic fluid, cord blood, placenta or neonatal nasopharyngeal swabs taken immediately after birth [7].

Clinical data

Medical and obstetric history, exposure history and COVID-19 symptoms in the previous 14 days, physical examination, and laboratory and radiological findings were collected. COVID-19 severity was classified into three groups: mild (not requiring hospital admission), severe (pneumonia) and critical (Intensive Care Unit admission).

Data on pregnancy, gestational age at delivery, mode of delivery, indication for cesarean delivery, maternal complications and neonatal outcomes were also recorded.

Newborns were examined by a paediatrician specialized in congenital infections.

Microbiological samples collection

Nasal and pharyngeal swabs were taken from the mothers on a weekly basis until negativity.

All non-respiratory samples were collected at the time of delivery with strict aseptic techniques to avoid contamination by maternal blood or by respiratory droplets from the mother or birth attendants. The procedure is described in detail in the Supplementary material (Appendix S2).

Table 1
Baseline demographic and clinical characteristics

Maternal age (years), median (range)	33.5 (18–46)
Body mass index (kg/m^2), median (range)	26.6 (16.7–47.0)
Ethnic group, *n* (%)	
Caucasian	29 (65.9%)
Latin American	12 (27.3%)
Asian	2 (4.5%)
Black-African	1 (2.3%)
Type of pregnancy, *n* (%)	
Single	43 (97.7%)
Dichorionic diamniotic twins	1 (2.3%)
Cigarette smoker, *n* (%)	1 (2.3%)
Medical condition, *n* (%)	8 (18.2%)
Autoimmune disease	4
Asthma	1
Diabetes	1
Thrombophilia	1
Acquired heart disease	1
Clinical presentation, *n* (%)	
Mild disease	29 (65.9%)
Pneumonia	12 (27.3%)
Severe pneumonia – ICU admission	3 (6.8%)
Diagnosis, *n* (%)	
RT-PCR	33 (75%)
Serology	11 (25%)
Gestational age at diagnosis (weeks), median (range)	34.7 (14–41.3)
Interval RT-PCR diagnosis and delivery (days), median (range)	21.5 (0–141)
RT-PCR positive at delivery, *n* (%)	14 (31.8%)

Abbreviations: ICU, intensive care unit.

Results

Forty-four pregnancies with samples of placenta, amniotic fluid and umbilical cord blood collected were included in the study. There was one monochorionic twin pregnancy, in which the samples were taken from both fetuses. As a result, we obtained 45 samples. Table 1 depicts baseline demographic and clinical characteristics of the studied population and Table 2 shows pregnancy outcome.

The median gestational age at COVID-19 diagnosis was 34.7 weeks (range 14–41.3 weeks). The median interval between positive RT-PCR and delivery was 21.5 days (range 0–141 days). Fourteen women (31.8%, 95% CI 18.6%–47.6%) were still positive at the time of delivery.

Table 2
Pregnancy outcome

Gestational age at birth (weeks), median (range)	39 (28.4–41.4)
Labour onset, *n* (%)	
Spontaneous	16 (36.4%)
Elective	28 (63.6%)
For COVID-19	2[a]
Other indication	26
Preterm birth <37 weeks, *n* (%)	2 (4.5%)
For COVID-19	2[a]
Other	0
Mode of delivery, *n* (%)	
Vaginal delivery	29 (65.9%)
Caesarean section	15 (34.1%)
Pregnancy outcome, *n* (%)	
Live births	44[b]
Stillbirth	1[c]
Birthweight (g), median (range)	3440 (1000–4425)

[a] Two cases of preterm birth at 28 weeks and 3 days, and 36 weeks and 5 days, respectively, due to COVID-19 infection. In both cases, a caesarean section was performed because of the worsening maternal condition.
[b] One was a twin pregnancy.
[c] The stillbirth occurred in an asymptomatic woman who tested positive for COVID-19 at 20 weeks. The fetus was diagnosed with a macrocephaly, intracranial cyst and polyhydramnios at 30 weeks, and resulted in a stillbirth at 34 weeks. The genetic study did not show any abnormal finding, and the post-mortem examination showed central nervous system anomalies (ventriculomegaly, subependymal cysts).

One singleton pregnancy was SARS-CoV-2 RT-PCR-positive in the placenta, amniotic fluid and umbilical cord blood (2.2%, 95% CI 0.1%–11.8%) Fig. 1

Nasopharyngeal aspiration was performed on 38 neonates at birth, all of which were negative (0%, 95% CI 0%–9.3%). In 11 neonates the nasopharyngeal aspiration was repeated at 24–48 hours, and one was positive (9.1%, 95% CI 0.2%–41.3%).

Discussion

Of the 45 neonates analysed, one was SARS-CoV-2 RT-PCR-positive in the placenta, amniotic fluid and umbilical cord blood, but negative in nasopharyngeal aspirate.

To accept the possibility of mother-to-child transmission of SARS-CoV-2, there are two requirements: a confident diagnostic test to confirm maternal and fetal or neonatal infection and an adequate exclusion of contamination of the samples. In our case, both conditions were met. The mother had COVID-19 confirmed by RT-PCR with clinical symptoms at delivery, and neonatal infection was proven by the detection of SARS-CoV-2 in placenta, amniotic fluid and umbilical cord blood. Strict aseptic measures were taken to collect the samples. Contamination of the placenta can be excluded by the cytoplasmic positivity of trophoblastic cells observed with antibody against SARS-CoV-2 Figs. 2 and 3. Amniotic fluid and cord blood samples are not easily susceptible to contamination by vaginal fluid or by respiratory droplets from the mother or attendants if strict sterile collection measures are taken. Moreover, the possibility of contamination of both, taken at different times, is extremely unlikely.

Several studies reported SARS-CoV-2 RT-PCR-positive results in neonatal samples within the first hours after birth [4–6], but they did not report placenta, amniotic fluid or umbilical cord blood positive samples. The link between mother and neonate infections is during labour or postnatal, but there is no evidence of longer exposition for the fetus during pregnancy. Only six studies [8–13] and ours support the possibility of intrauterine exposure and transmission to the child.

According to Shah et al. [14] classification system, only the studies by Vivanti et al. [12], Fenizia et al. [13] and us are confirmed cases of congenital infection in a live-born neonate. Other studies [4–6,8–11] may only consider possible or even unlikely congenital

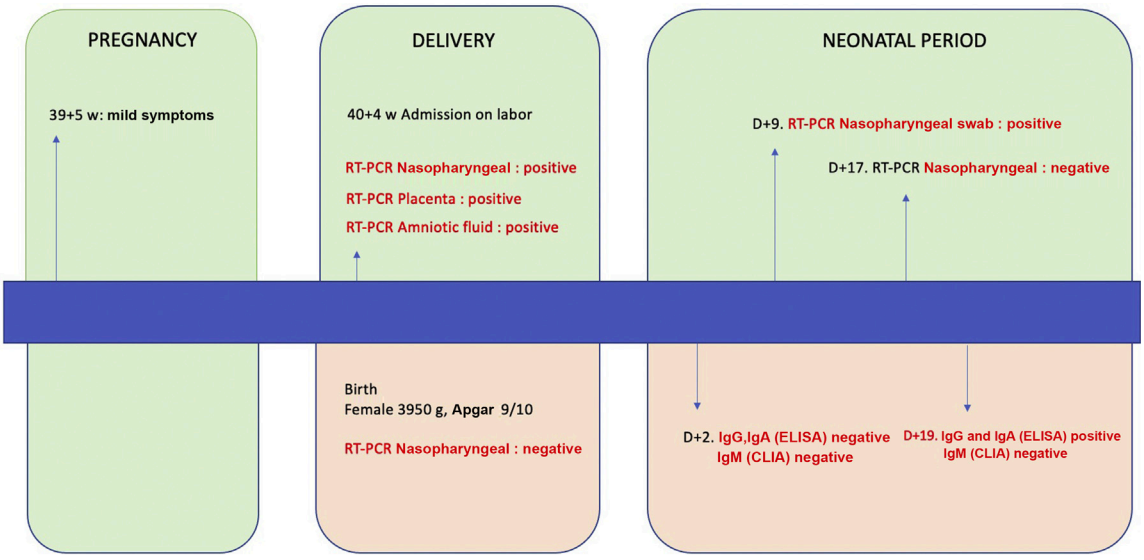

Fig. 1. Summary of the case.

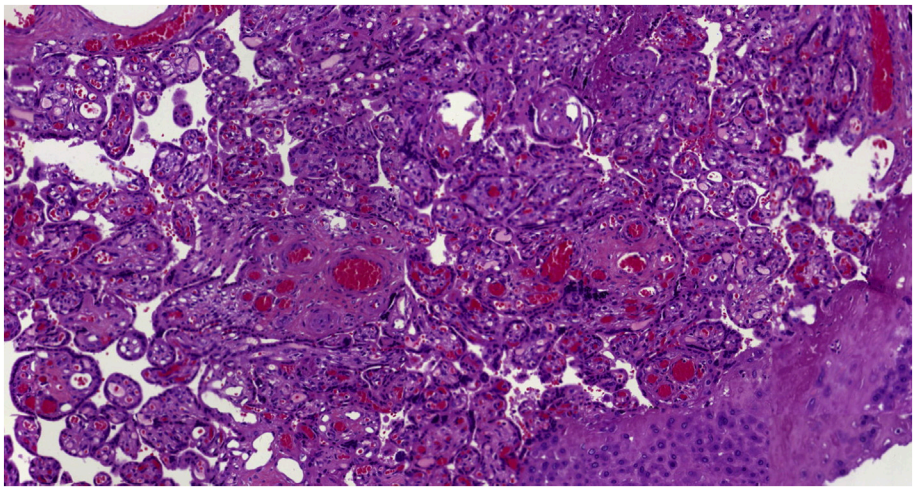

Fig. 2. Detection of SARS-CoV-2 by immunohistochemistry.

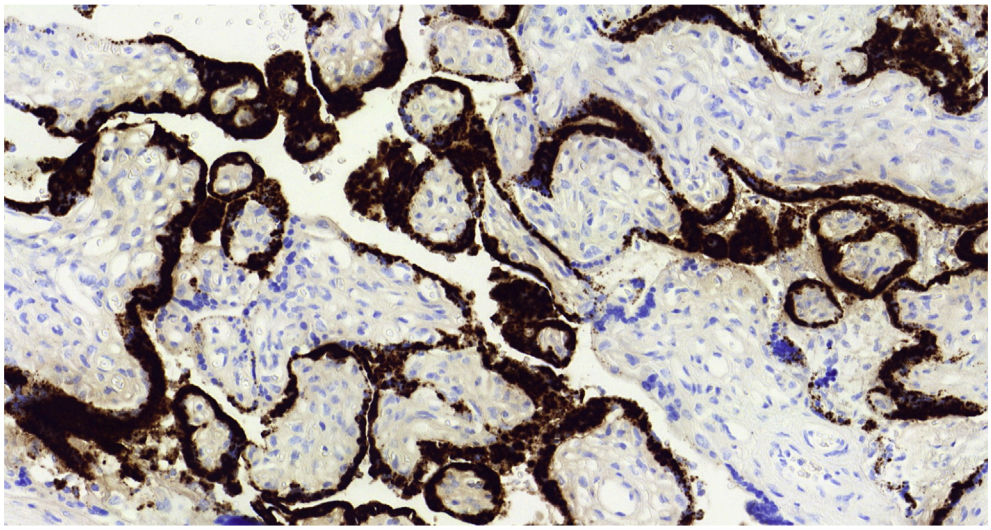

Fig. 3. Detection of SARS-CoV-2 by in situ hybridisation.

infection because there are not enough specimens from the mother or the newborn and contamination during labour or caesarean cannot be ruled out.

Our newborn nasopharyngeal RT-PCR was negative. In Vivanti et al., neonatal respiratory sample was obtained from non-bronchoscopic bronchoalveolar lavage before extubation, which is more sensitive. Testing RT-PCR in other tissues may improve the detection of the virus in neonates [15].

Neonatal antibodies were negative at birth and became positive 49 days later. It could be the response of the newborn's immune system to SARS-CoV-2 infection. However, maternal origin post-natally or cross-reactivity with non-specific antibodies can never be excluded entirely.

The sample size is small. As a result of the epidemiological time when the patients were recruited, personal protective equipment was lacking, and ethical approval was substantially delayed, making sample collection challenging. Besides, in some cases, amniocentesis was not possible because of premature rupture of membranes.

The findings of this study support the possibility of mother-to-child transmission, even it seems to be rare. A larger cohort would be necessary to accurately evaluate the rate of congenital transmission and assess the newborn's potential consequences.

Transparency declaration

The authors declare that they have no conflicts of interest.

This study was supported by a grant from Instituto de Salud Carlos III (ISCIII) COV20/00188. The funding sources were not involved in the study design, collection, analysis or interpretation of data, in the writing of the report or in the submission for publication.

Contribution to authorship

This study was conceived by IG, ES, NM and AS, who contributed to the design of the study. Collection and analysis of the data was performed by IG, BS, IF, LR, DS, MF, FC, NF, NM and AS. Analysis of

the samples was performed by ES, AA, JE and AN. Drafting the article was performed by IG, ES, NM, EC, NF and AS. All authors, IG, ES, BS, IF, LR, DS, AA, JE, MF, FC, AN, NF, NM, EC, AS and Gestacovid Collaborative Group, reviewed and agreed to the final version of the manuscript.

Details of ethics approval

This study was approved by the Vall d'Hebron University Hospital Ethics Committee (PR(AMI)181/2020) on 27 March 2020.

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Appendix

GESTACOVID COLLABORATIVE GROUP

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.06.016.

References

[1] Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol 2020. https://doi.org/10.1016/j.ajog.2020.04.014.
[2] Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020:m3320. https://doi.org/10.1136/bmj.m3320.
[3] Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1641–7.
[4] Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107.
[5] Martínez-Perez O, Vouga M, Cruz Melguizo 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;324:296–9.
[6] 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.
[7] Mahyuddin A, Kanneganti A, Wong J, Dimri PS, Su L, Biswas A, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2. Prenatal Diagn 2020. https://doi.org/10.1002/pd.5765.
[8] Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA 2020;323:2198–200.
[9] Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. Am JObstet Gynecol MFM 2020:100133. https://doi.org/10.1016/j.ajogmf.2020.100133.
[10] Algarroba GN, Rekawek P, Vahanian SA, Khullar P, Palaia T, Peltier MR, et al. Visualisation of SARS-CoV-2 virus invading the human placenta using electron microscopy. Am JObstet Gynecol 2020. https://doi.org/10.1016/j.ajog.2020.05.023.
[11] Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am JObstet Gynecol MFM 2020:100145. https://doi.org/10.1016/j.ajogmf.2020.100145.
[12] Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11. https://doi.org/10.1038/s41467-020-17436-6.
[13] Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. Nat Commun 2020;11:5128. https://doi.org/10.1038/s41467-020-18933-4.
[14] Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstet Gynecol Scand 2020;99:565–8.
[15] Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections–the state of the art. Emerg Microb Infect 2020;9:747–56.

OPEN

Case Report

Fetal Transient Skin Edema in Two Pregnant Women With Coronavirus Disease 2019 (COVID-19)

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BACKGROUND: The risk of vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remains unknown. Positive reverse-transcription polymerase chain reaction (RT-PCR) test results for SARS-CoV-2 infection in neonates and placental tissue have been reported, and immunoglobulin M antibodies have been detected in neonates born to mothers with infection.

CASES: The first case is a woman at 22 3/7 weeks of gestation with coronavirus disease 2019 (COVID-19) who was admitted to the intensive care unit. In the second case, the patient remained at home with mild symptoms, starting at 20 weeks of gestation. In both cases, fetal skin edema was observed on ultrasound examination while maternal SARS-COV-2 RT-PCR test results were positive and resolved when maternal SARS-COV-2 RT-PCR test results became negative. The RT-PCR test result for SARS-CoV-2 in amniotic fluid was negative in both cases. The two pregnancies are ongoing and uneventful.

CONCLUSION: Transient fetal skin edema noted in these two patients with COVID-19 in the second trimester may represent results of fetal infection or altered fetal physiology due to maternal disease or may be unrelated to the maternal illness.

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Teaching Point

1. Maternal coronavirus disease 2019 (COVID-19) might have an effect on the fetus during pregnancy.

Coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Spain reported its first case on January 31, 2020, and more than 241,000 confirmed cases and 27,100 deaths have been reported.[1]

Some maternal infections during pregnancy are associated with poor perinatal outcomes and fetal anomalies. In infections such as cytomegalovirus or Zika virus, gestational age at the time of maternal infection plays a role in the risk of both intrauterine infection and severe sequelae.[2,3] In SARS-CoV-2 infection, there is a paucity of reports of pregnancy outcomes with infection before the third trimester.

The risk of maternal–fetal transmission of SARS-CoV-2 infection remains controversial. Severe acute respiratory syndrome coronavirus 2 has been detected in placental swabs or biopsies in five cases, but not in amniotic fluid.[4–7] However, it is unknown whether the virus, the immune response it causes, or the gestational age at which the infection occurs may have consequences for the fetus.[8]

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Herein, we present two cases of unexplained fetal skin edema in two pregnant women diagnosed with COVID-19 during the second trimester of pregnancy.

CASE 1

A 50-year-old primigravid woman at 22 6/7 weeks of gestation presented to the emergency department at Vall d'Hebron University Hospital (Barcelona, Spain) with a 7-day history of dry cough and fever. She was living with her mother, who had tested positive for SARS-CoV-2 infection on reverse-transcription polymerase chain reaction (RT-PCR) testing. The patient was a former smoker, had no relevant medical history, and was receiving 150 mg of acetylsalicylic acid owing to a high risk of early-onset preeclampsia. Her gestation was conceived by in vitro fertilization with egg donation and had had an uneventful course. No genetic tests had been performed during the pregnancy. Physical examination revealed a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 25.4, blood pressure 125/64 mm Hg, temperature 37°C, and respiratory rate of 30 breaths per minute, with a hemoglobin saturation by pulse oximetry of 93% on room air. Blood tests performed at admission showed lymphopenia and interleukin-6 (IL-6) and D-dimer levels above the normal range (Table 1).

A chest radiograph showed conspicuous bilateral ground glass opacities, and the patient tested positive for SARS-CoV-2 infection on RT-PCR testing of oropharyngeal and nasopharyngeal swabs (Allplex 2019-nCoV assay). A COVID-19 bilateral pneumonia was diagnosed, and the patient was admitted and put on azithromycin, lopinavir-ritonavir, and hydroxychloroquine medications (day 0). Obstetric ultrasound examination at admission showed no fetal anomalies, normal Doppler parameters, and a normal amount of amniotic fluid. The day after admission (day 1), the patient's condition worsened and she was transferred to the intensive care unit (ICU), where she underwent intubation for mechanical ventilation on day 2 (23 1/7 weeks of gestation). Fetal prognosis was estimated to be poor owing to gestational age. After discussion with the mother, expectant management of the pregnancy was decided on by a multidisciplinary team (obstetricians and critical care and infectious disease specialists). Elective delivery was accorded with the patient before intubation if deterioration persisted. Blood tests were performed daily, and pro-inflammatory markers related to COVID-19 severity (IL-6 and D-dimer) were also monitored (Fig. 1).[9] The result of the SARS-CoV-2 RT-PCR test in peripheral blood was negative.

Fetal well-being scans (Siemens Acuson NX2) were conducted daily by the ICU team to check fetal heart rate and weekly by a fetal medicine specialist to assess fetal growth, Doppler parameters, and the amount of amniotic fluid and to detect any potential abnormalities. Fetal heart rate was always within the normal range, without episodes of tachycardia or bradycardia.

On day 6 (23 5/7 weeks of gestation), fetal skin edema was observed with no ascites, hydrothorax, thickened placenta, or other signs of hydrops fetalis. Edema was generalized, but it was more evident in the scalp and trunk. A detailed survey for anomalies and fetal echocardiography were performed, showing no abnormal results. The same findings persisted on day 10 (24 2/7 weeks), and no structural anomalies were found (Fig. 2). Doppler examinations of the umbilical artery, middle cerebral artery, ductus venosus, and uterine arteries were also within normal limits. Maternal indirect antiglobulin and serologic tests were obtained, being negative for cytomegalovirus, varicella zoster virus, parvovirus B19, *Toxoplasma gondii*, herpes virus, and rubella. An amniocentesis was

Table 1. Patients' Relevant Clinical Findings

Clinical Characteristics	Patient 1	Patient 2
Age (y)	50	30
Ethnicity	White	Latin American
Nuchal translucency in 1st trimester (mm)	1.28	2.3
Gestational age at COVID-19 diagnosis (wk)	22.6	20.1
Time from symptom onset to fetal edema (d)	13	10
Maternal serum IL-6* level at COVID-19 diagnosis (pg/mL)	76.47	16.22
Maternal serum D-dimer* level at COVID-19 diagnosis (ng/mL)	576	953
Gestational age at fetal edema diagnosis (wk)	23.5	21.2
Maternal serum IL-6 level at fetal edema diagnosis (pg/mL)	409.5	3.59
Maternal serum D-dimer level at fetal edema diagnosis (ng/mL)	2,190	373
Time RT-PCR remained positive for SARS-CoV-2 infection (d)	17	22
Fetal edema duration (d)	11	14
RT-PCR test result for SARS-CoV-2 in maternal serum	Negative	Negative
IL-6 level in amniotic fluid* (pg/mL)	345.18	109.4

COVID-19, coronavirus disease 2019; IL-6, interleukin-6; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Reference ranges: serum IL-6: 0–4.3 pg/mL; D-dimer: 0–243 ng/mL; IL-6 in amniotic fluid: median values ranging from 150.5 to 339 pg/mL.[10]

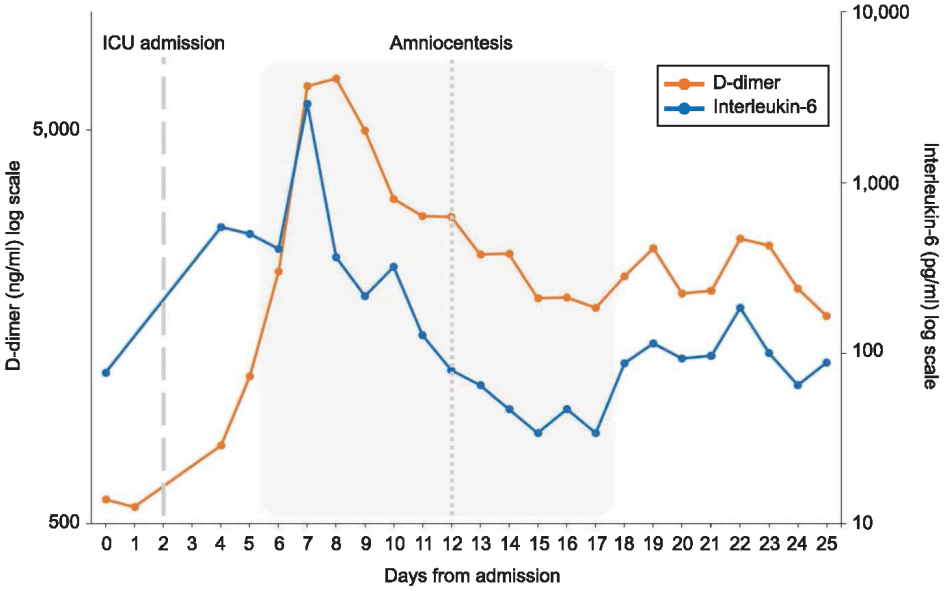

Fig. 1. Proinflammatory marker evolution during admission in case 1. Fetal skin edema was observed between days 6 and 17 and is delimited by a *grey area*. Intensive care unit (ICU) admission and amniocentesis were on days 2 and 12, respectively.

Garcia-Manau. Fetal Skin Edema in Pregnant Women With COVID-19. Obstet Gynecol 2020.

performed on day 12. The results of the genetic test (Quantitative Genomic Hybridization Array, 8 60K Agilent G4827A CGH (ISCA v2 array) were normal. The RT-PCR test result for SARS-CoV-2 in amniotic fluid was negative, and the IL-6 level in amniotic fluid was within the normal range.[10] Tests in amniotic fluid were negative for cytomegalovirus, varicella zoster virus, parvovirus B19, *T gondii*, and sexually transmitted infectious agents (*Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis, Ureaplasma parvum, Mycoplasma genitalium, Ureaplasma urealyticum*, and *Trichomonas vaginalis*).

One week later (day 17, 25 2/7 weeks of gestation), the maternal condition improved: PaO_2 progressively increased, and oxygen supplementation requirements lowered. Proinflammatory markers decreased, and the result of the SARS-CoV-2 RT-PCR test on oropharyngeal and nasopharyngeal swabs was negative. Simultaneously, the fetal edema had almost disappeared on ultrasound examination (Fig. 2).

CASE 2

A 30-year-old primigravid woman at 20 1/7 weeks of gestation with no relevant medical history presented to the emergency department (day 0) with cough and fever in the previous 48 hours. She was living with her husband and her parents, and all three had tested positive for SARS-CoV-2 infection. Her gestation had had an uneventful course. Physical examination revealed a BMI of 32, blood pressure 130/71 mm Hg, temperature of 37.5°C, respiratory rate 16 breaths per minute, and a hemoglobin saturation of 99% on room air. The results of blood tests performed at admission are shown in Table 1. Chest radiography showed no anomalies, and the patient tested positive for SARS-CoV-2 infection on RT-PCR of oropharyngeal and nasopharyngeal swabs. She was diagnosed with mild COVID-19, and she was discharged with no medication to home isolation. Maternal well-being was assessed daily by phone calls, and no deterioration requiring

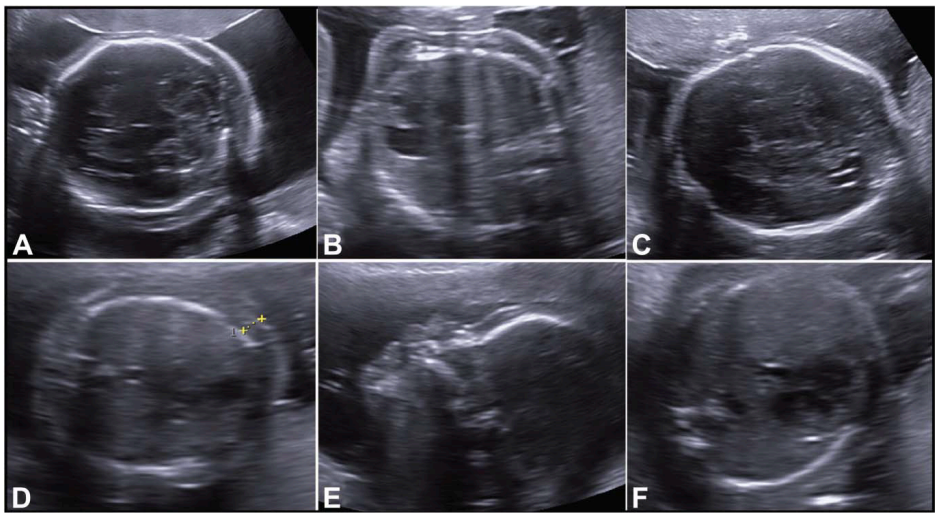

Fig. 2. Fetal skin edemas. Fetal ultrasound examinations. Case 1: skin edema in transcerebellar (**A**) and transthoracic (**B**) planes and its resolution (**C**). Case 2: skin edema in transthoracic (**D**) and midsagittal face (**E**) planes and its resolution (**F**).

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hospital admission was observed. On day 8 (21 2/7 weeks of gestation), an ultrasound examination was performed, detecting an isolated mild fetal skin edema with no other abnormalities (Fig. 2). Fetal echocardiography and Doppler parameters were also within normal limits. Fetal heart rate was within the normal range, and no episodes of tachycardia or bradycardia were recorded. Middle cerebral artery velocity was within the normal range. Maternal indirect antiglobulin and serologic tests were obtained, with negative results. Nasopharyngeal RT-PCR test results remained positive, and RT-PCR test results in peripheral blood were negative. The IL-6 level in maternal serum was within the normal range, and D-dimer levels were slightly elevated (Table 1). An amniocentesis was performed, and the RT-PCR assay of the amniotic fluid was negative for SARS-CoV-2 infection. Result s of genetic tests (Quantitative Genomic Hybridization Array) and tests for congenital infections (cytomegalovirus, varicella zoster virus, parvovirus B19, *T gondii, Chlamydia trachomatis, N gonorrhoeae, M hominis, U parvum, M genitalium, U urealyticum,* and *T vaginalis*) in amniotic fluid were negative. The IL-6 level in amniotic fluid was normal.[10] On day 22 (23 2/7 weeks of gestation), fetal edema had disappeared after the SARS-CoV-2 RT-PCR test result was negative.

At the time of submission, both women are still pregnant. Their gestations are being closely followed-up, with a complete resolution of the fetal edema, and no other fetal anomalies have been reported.

DISCUSSION

Two cases of fetal transient skin edema in pregnant women with COVID-19 in their second trimester of pregnancy are described. In case 1, the patient was admitted to the ICU and fetal edema followed a time course parallel to the maternal respiratory condition and the pro-inflammatory markers; the edema disappeared with maternal recovery. Patient 2 remained at home with mild symptoms and did not require hospital admission. Pro-inflammatory markers were lower, and the edema was milder and it also disappeared with maternal improvement. In both cases, viremia and amniotic fluid RT-PCR test results were negative for SARS-CoV-2 infection.

There is still inconclusive evidence of transplacentally acquired fetal infection reported in the literature. A study investigated the expression of SARS-CoV-2 receptors, identified as angiotensin-converting enzyme 2, in human maternal–fetal interface and the main fetal organs. The authors conclude that angiotensin-converting enzyme 2 is widely present in the human placenta and in the main fetal organs.[11] Another article describes a second-trimester miscarriage in a woman diagnosed with COVID-19 in which placental and amniotic membranes tested positive for SARS-CoV-2 infection.[6] In another study, three cases of detection of SARS-CoV-2 RNA in placental or membrane samples are also described; although none of the neonates tested positive.[4] Recently, the first two cases of positive RT-PCR test results for SARS-CoV-2 infection in mother, neonate, and placental tissues have been reported.[5] However, none of these studies demonstrate fetal abnormalities or the presence of the virus in amniotic fluid or in cord blood.

Current protocols recommend, for safety reasons, delaying ultrasound scans while pregnant women are positive for SARS-CoV-2 infection, which may result in lack of observation of transient fetal abnormalities.[12,13] However, at our center we are scanning pregnant women weekly in the framework of an Institutional Review Board–approved observational study (PR(AMI)181/2020), which includes microbiological sampling and ultrasound examinations in pregnant women with COVID-19. During the pandemic, we performed 31 ultrasound examinations on pregnant women with COVID-19, and fetal skin edema was seen in two cases (6.5%; 95% CI 1.8–20.7%).

Some patients with COVID-19 develop a rapid deterioration related to a cytokine storm syndrome due to a massive, virally driven hyperinflammation.[14,15] It has been demonstrated that maternal cytokines during pregnancy can lead to a failure in multiple fetal organ systems.[16] The fetal edema described in case 1 appeared when the highest maternal serum IL-6 concentrations were noted and while D-dimer was rapidly increasing. By contrast, its resolution was preceded by a progressive decrease in both serum IL-6 and D-dimer values; the lowest concentrations were noted when the edema had disappeared on day 17, coinciding with a negative SARS-CoV-2 RT-PCR test result (Fig. 1). In case 2, edema was observed with a low pro-inflammatory status, as IL-6 levels were within the normal range. The IL-6 levels in amniotic fluid were normal in both cases. For this reason, we believe that SARS-CoV-2 might have an effect on the fetus, regardless of the pro-inflammatory maternal profile.

Despite the overwhelming amount of data generated since the beginning of the COVID-19 outbreak, many questions about the virus–host interactions remain unanswered. Pregnant women represent a small subgroup of patients with COVID-19, and there is a dearth of data about the potential effects of the virus on the fetus.

This report has several limitations. Firstly, two cases are insufficient to draw out significant conclusions. Fetal edema is a nonspecific finding and often idiopathic. Considering other congenital infections, the

time interval from infection to fetal edema was shorter than expected, and fetal edema is not a common finding in cases of intraamniotic inflammation or chorioamnionitis. We, therefore, cannot state that fetal skin edema was caused by SARS-CoV-2 infection, despite the correlation between the disappearance of the edema and the negative test results for the virus. Secondly, the interpretation of a negative result on RT-PCR test for detection of SARS-CoV-2 infection in amniotic fluid is unknown, and the possibility of the virus testing negative in utero cannot be excluded, because this has been demonstrated for other viruses.[7,17]

To conclude, we report a fetal complication potentially related to COVID-19 in pregnant women. Given these findings and the lack of reports of COVID-19 in the first and second trimesters, a close follow-up of these pregnancies may help to understand the effect on the fetus.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Retrieved April 18, 2020.
2. Rodó C, Suy A, Sulleiro E, Soriano-Arandes A, Maiz N, García-Ruiz I, et al. Pregnancy outcomes after maternal Zika virus infection in a non-endemic region: prospective cohort study. Clin Microbiol Infect 2019;25:633.e5–9.
3. Neu N, Duchon J, Zachariah P. TORCH infections. Clin Perinatol 2015;42:77–103, viii.
4. Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of SARS-COV-2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM 2020. [Epub ahead of print].
5. Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of COVID-19: SARS-CoV-2 RNA on the fetal side of the placenta in pregnancies with COVID-19 positive mothers and neonates at birth. Am J Obstet Gynecol MFM 2020. [Epub ahead of print].
6. Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA 2020;323:2198–200.
7. Yu N, Li W, Kang Q, Zeng W, Feng L, Wu J. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. Lancet Infect Dis 2020 [Epub ahead of print].
8. Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville M, Ville Y. Evidence for and against vertical transmission for severe acute respiratory syndrome coronavirus 2. Am J Obstet Gynecol 2020;223:91.e1–4.
9. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020;95:834–7.
10. Bamberg C, Fotopoulou C, Linder M, Roehr CC, Dudenhausen JW, Henrich W, et al. Mid-trimester amniotic fluid concentrations of the proinflammatory cytokines IL-6, IL-8, TNF-α, and lipopolysaccharide binding protein in normal pregnancies: a prospective evaluation according to parity, gestational age, and fetal gender. J Perinat Med 2011;39:403–9.
11. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One 2020;15: e0230295.
12. Abu-Rustum RS, Akolekar R, Sotiriadis A, Salomon LJ, Da Silva Costa F, Wu Q, et al. ISUOG consensus statement on organization of routine and specialist obstetric ultrasound services in context of COVID-19. Ultrasound Obstet Gynecol 2020;55:863–70.
13. Bourne T, Kyriacou C, Coomarasamy A, Al-Memar M, Leonardi M, Kirk E, et al. ISUOG Consensus Statement on rationalization of early-pregnancy care and provision of ultrasonography in context of SARS-CoV-2. Ultrasound Obstet Gynecol 2020;55:871–8.
14. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
15. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the cytokine storm in COVID-19. J Infect 2020;80:607–13.
16. Yockey LJ, Iwasaki A. Interferons and proinflammatory cytokines in pregnancy and fetal development. Immunity 2018;49: 397–412.
17. Rodó C, Suy A, Sulleiro E, Soriano-Arandes A, Antón A, García-Ruiz I, et al. In utero negativization of Zika virus in a foetus with serious central nervous system abnormalities. Clin Microbiol Infect 2018;24:549.e1–3.

PEER REVIEW HISTORY

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RESULTADOS

La presente tesis está elaborada por compendio de publicaciones y está constituida por cuatro artículos.

Artículo 1. Gesta-COVID19 Collaboration Group. Gestation and COVID-19: clinical and microbiological observational study (Gesta-COVID19)

Suy A, Garcia-Ruiz I, Carbonell M, Garcia-Manau P, Rodo C, Maiz N, Sulleiro E, Anton A, Esperalba J, Fernández-Hidalgo N, Frick MA, Camba F, Pumarola T, Carreras E; Gesta-COVID19 Collaboration Group. Gestation and COVID-19: clinical and microbiological observational study (Gesta-COVID19). BMC Pregnancy Childbirth. 2021 Jan 22;21(1):78. doi: 10.1186/s12884-021-03572-4. PMID: 33482757; PMCID: PMC7820822. (Anexo 1)

El grupo de trabajo multicéntrico Gestacovid elaboró un protocolo de diagnóstico y seguimiento de gestantes infectadas por SARS-CoV-2 y sus recién nacidos, con el objetivo de investigar los efectos del virus en la gestación, y la repercusión de la misma sobre la infección.

Se definieron los criterios de inclusión y exclusión de las participantes. Se incluyeron todas las gestantes con diagnóstico de COVID-19 confirmado por RT-PCR; y se excluyeron las pacientes que denegaron consentimiento, las de edad inferior a 18 años y aquellas con incapacidad para comprender el consentimiento informado.

Se describió el seguimiento clínico así como las muestras biológicas a tomar en gestantes y neonatos.

Se especificó el análisis estadístico a realizar posteriormente con los datos obtenidos. Al tratarse de un estudio exploratorio, al inicio de la pandemia se estimó que en 4-6 meses se obtendría una muestra de 150 gestantes.

El protocolo fue aprobado por el comité de ética del Hospital Vall D´Hebron, centro coordinador del estudio (PR(AMI)181/2020).

Artículo 2. Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study

Mendoza M, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, Lopez-Martinez RM, Balcells J, Fernandez-Hidalgo N, Carreras E, Suy A. Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study. BJOG. 2020 Oct;127(11):1374-1380. doi: 10.1111/1471-0528.16339. Epub 2020 Jun 21. PMID: 32479682; PMCID: PMC7300912. (Anexo 2)

Entre el 13 de marzo y 10 de abril de 2020, 42 gestantes ingresaron por infección por SARS-CoV-2 en el Hospital Universitari Vall D´Hebron. Ocho desarrollaron neumonía grave y requirieron ingreso en UCI. De éstas, cinco presentaron signos y síntomas compatibles con preeclampsia. Previo a la neumonía por SARS-CoV-2, ninguna de ellas presentaba manifestaciones clínicas, ecográficas o analíticas asociadas a preeclampsia; salvo una con Doppler de arterias uterinas >p95

Los marcadores de preeclampsia más frecuentes entre las gestantes ingresadas en UCI por neumonía COVID-19 fueron: elevación de enzimas hepáticas (87,5%), proteinuria >300 mg/g (75,0%) e hipertensión con necesidad de tratamiento médico (62,5%). Una paciente presentó LDH de 672 UI/L. No se identificó ningún caso con creatinina >1,1 mg/dL o trombopenia <100.000 /μL. Solamente gestante con alteración del Doppler de arterias uterinas presentó ratio sFlt-1/PlGF ≥ 110. En base a estos hallazgos, cinco pacientes (62,5%) cumplían criterios diagnósticos de preeclampsia o síndrome de HELLP.

Tras la recuperación de la neumonía, todas las pacientes normalizaron la tensión arterial sin necesidad de medicación antihipertensiva y las enzimas hepáticas descendieron. Solamente la paciente que presentaba ratio sFlt-1/PlGF ≥ 110 mantuvo criterios de preeclampsia: tensión arterial >140/90 mmHg, proteinuria de 426 mg/g y LDH de 692 UI/l, que se normalizaron a los pocos días de finalizar la gestación.

Artículo 3. GESTACOVID Collaborative Group. Congenital infection of SARS-CoV-2 in live-born neonates: a population-based descriptive study

Garcia-Ruiz I, Sulleiro E, Serrano B, Fernandez-Buhigas I, Rodriguez-Gomez L, Sanchez-Nieves Fernandez D, Anton-Pagarolas A, Esperalba-Esquerra J, Frick MA, Camba F, Navarro-Jimenez A, Fernandez-Hidalgo N, Maiz N, Carreras E, Suy A; GESTACOVID Collaborative Group. Congenital infection of SARS-CoV-2 in live-born neonates: a population-based descriptive study. Clin Microbiol Infect. 2021 Oct;27(10):1521.e1-1521.e5. doi: 10.1016/j.cmi.2021.06.016. Epub 2021 Jun 19. PMID: 34153457; PMCID: PMC8213522. (Anexo 3)

Se incluyeron 43 gestaciones únicas y una gemelar con infección por SARS-CoV-2, en el Hospital Universitari Vall D´Hebron. La mediana de la edad gestacional al diagnóstico es 34,7 semanas (rango 14 – 41,3 semanas). Veintinueve pacientes (65.9%) presentaron infección leve, 12 (27,3%) neumonía y 3 (6,8%) neumonía grave con ingreso en UCI. En el momento del parto 14 pacientes (31.8%) persistían con RT-PCR SARS-CoV-2 positiva.

Se identificó un caso con RT-PCR SARS-CoV-2 positiva en las muestras de placenta, líquido amniótico y sangre de cordón umbilical (2,2% IC 95% 0,1% - 11,8%). En el resto de las pacientes todas las muestras fueron negativas.

En 38 neonatos se realizó RT-PCR de exudado nasofaríngeo tomado al nacimiento y ninguno resultó positivo.

Artículo 4. Fetal Transient Skin Edema in Two Pregnant Women With Coronavirus Disease 2019 (COVID-19)

Garcia-Manau P, Garcia-Ruiz I, Rodo C, Sulleiro E, Maiz N, Catalan M, Fernández-Hidalgo N, Balcells J, Antón A, Carreras E, Suy A. Fetal Transient Skin Edema in Two Pregnant Women With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2020 Nov;136(5):1016-1020. doi: 10.1097/AOG.0000000000004059. PMID: 32649505; PMCID: PMC7575012. (Anexo 4)

Se describieron dos casos de edema cutáneo fetal transitorio en gestantes con infección activa por SARS-CoV-2.

El primer caso se trató de una gestante que requirió ingreso por neumonía grave por SARS-CoV-2 a las 22+6 semanas de gestación. A las 24 horas de ingreso, ante empeoramiento clínico, requirió ingreso en UCI y VMI. En este momento, la valoración ecográfica fetal fue de normalidad.

Durante el ingreso en UCI se practicó ecografía fetal diaria. Al sexto día, se observó edema cutáneo generalizado, más evidente en cuero cabelludo y tronco, sin asociar ascitis, hidrotórax ni engrosamiento de la placenta. Se practicó una amniocentesis para estudio genético mediante arrays de hibridación genómica comparada (aCGH) *(Quantitative Genomic Hybridization Array, 8 60K Agilent G4827A CGH)* estudio microbiológico convencional, de infecciones de espectro TORCH y la RT-PCR SARS-CoV-2, resultando todos los estudios negativos

El edema cutáneo fetal se resolvió espontáneamente coincidiendo con la mejoría del estado materno.

El segundo caso se trató de una gestante de 20+1 semanas con infección leve por SARS-CoV-2, sin necesidad de ingreso hospitalario. Al octavo día desde el diagnóstico se detectó en el feto edema cutáneo generalizado sin otras alteraciones. Se realizó amniocentesis con estudio genético, microbiológico convencional, infecciones TORCH y RT-PCR SARS-CoV-2, que fueron negativos. En este caso también el edema fetal se resolvió espontáneamente, de forma simultánea a la recuperación materna.

DISCUSIÓN

Ante la rápida expansión de la infección, las principales sociedades científicas, International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[73], American College of Obstetricians and Gynecologists (ACOG)[80], Centers for Disease Control and Prevention (CDC)[81] y Society for Maternal-Fetal Medicine (SMFM)[82], comenzaron a publicar las primeras guías clínicas sobre SARS-CoV-2 y gestación en marzo de 2020. La SMFM aconsejó que sobre estas recomendaciones se crearan guías locales, adaptadas a las necesidades y recursos particulares y también advirtieron de la necesidad de actualización constante[83].

El grupo de trabajo Gesta-COVID19 diseñó un estudio observacional longitudinal prospectivo, para registrar los casos consecutivos de gestación y COVID-19, con el objetivo investigar los efectos de la infección en la gestación. El protocolo de este estudio se publicó en el artículo **"Gestation and COVID-19: clinical and microbiological observational study (Gesta-COVID19)**", y sirvió como documento de referencia para la elaboración del documento técnico "Manejo de la mujer embarazada y el recién nacido con COVID-19" del Ministerio de Sanidad de España[84]. y la guía clínica "Guia d'actuació enfront de casos d'infecció pel nou coronavirus SARS-CoV-2 en dones embarassades i nadons" del Servei Català de la Salut (CatSalut)[85].

Narang y col.[86], en mayo de 2020, realizaron una revisión de las principales guías clínicas publicadas, entre las que se encuentra la del CatSalut.

Todas estas guías proporcionaron recomendaciones sobre el control gestacional, la asistencia al parto y el seguimiento post parto de la población general durante la pandemia. El protocolo del CatSalut destacó por establecer recomendaciones específicas para el manejo de las gestantes con infección activa.

El hecho de disponer de un protocolo específico y actualizado en todo momento garantiza una asistencia de calidad a las pacientes, minimizando la variabilidad en la práctica clínica, un uso más racional de los recursos humanos y materiales y la homogeneidad en la evaluación de los resultados clínicos.

Esta ventaja supuso que el Hospital Universitari Vall d´Hebron se conviertiera en centro de referencia de gestantes con la COVID-19 de todo Cataluña[85]. De esta manera la mayor parte de las gestantes que requierían ingreso por infección por SARS-CoV-2 se

concentraron en nuestro hospital. La elevada casuística y la calidad de los datos recogidos, permitió la participación en los grandes registros internacionales, como el INTERCOVID, que han generado la evidencia más robusta sobre el efecto de la infección en la gestación, y de ésta sobre la propia enfermedad[42,61,87,88]

Las primeras versiones del protocolo propusieron un seguimiento muy exhaustivo, de la madre durante la infección activa y toda la gestación, y del feto y recién nacido hasta los 6 meses de vida. Ante el desconocimiento de los posibles efectos de la enfermedad, se optó por la máxima prudencia para detectar cualquier complicación. Esto supuso la identificación de complicaciones específicas como el síndrome preeclampsia-like, el edema fetal transitorio o el riesgo de transmisión congénita.

Una de las primeras observaciones del estudio Gesta-COVID19, fue una mayor frecuencia de signos propios de preeclampsia en las gestantes con enfermedad grave por SARS-CoV-2.

En el estudio **"Preeclampsia-like síndrome induced by severe COVID-19: a prospective observational study**", en una cohorte de 42 gestantes con infección por SARS-CoV-2, 8 sufren neumonía grave con necesidad de ingreso en UCI, y de éstas, 5 presentan criterios clínicos y analíticos diagnósticos de preeclampsia.

Otros estudios y revisiones sistemáticas posteriores describieron mayor riesgo de preeclampsia entre las gestantes con infección por SARS-CoV-2 [RR 1,95 (IC 95% 1,38 – 2,75)]. Esta asociación se mantuvo al ajustar por factores de riesgo conocidos de preeclampsia como obesidad, diabetes, enfermedad cardiaca, hipertensión y enfermedad renal[87]. Además, el riesgo se incrementaba con la severidad de la infección (OR 4,16, IC95% 1,55 – 11,15)[41].

Sin embargo, en nuestro estudio, se cuestiona esta asociación. Se plantea la hipótesis de que la COVID-19 en la gestación puede provocar un síndrome tipo preeclampsia, en vez de una verdadera preeclampsia. Los motivos que apoyan este argumento son los siguientes.

1. Los signos clínicos y analíticos típicos preeclampsia en las gestantes con infección por SARS-CoV-2, se han observado como manifestaciones extrapulmonares de la

infección en población general: proteinuria y elevación de creatinina[46]; elevación de aspartato (AST) y alanina (ALT) transaminasas[47]; y plaquetopenia[48].

2. De las 5 gestantes descritas en el estudio con COVID-19 y diagnóstico de preeclampsia, sólo en una se confirmó elevación de la ratio sFlt-1/PlGF y signos ecográficos de insuficiencia placentaria.
3. La única mujer que no se finalizó la gestación durante la infección, tras la recuperación de la neumonía, presentó resolución espontánea de los signos y síntomas de preeclampsia.

Estos hallazgos sugieren que la infección grave por SARS-CoV-2 en gestantes puede inducir un síndrome tipo preeclampsia, que sería una manifestación extrapulmonar más de la infección. El diagnóstico diferencial entre la COVID-19 y una preeclampsia superpuesta es fundamental, ya que el manejo y el pronóstico materno y fetal son muy diferentes.

Existen otras patologías que comparten características clínicas y analíticas con la preeclampsia y se han considerado imitadores de ésta: hígado graso del embarazo, púrpura trombótica trombocitopénica, síndrome hemolítico urémico, exacerbación del lupus eritematoso sistémico, síndrome antifosfolípido catastrófico, sepsis secundaria a herpes simple y síndrome de respuesta inflamatoria sistémica y shock séptico. Estas entidades presentan mecanismos fisiopatológicos similares: vasoespasmo, activación o destrucción plaquetaria, trombosis microvascular, disfunción endotelial y disminución de perfusión tisular[89]. Estas alteraciones también se han descrito en la fisiopatología de la infección por SARS-CoV-2 como responsables de sus manifestaciones extrapulmonares[5].

El origen de la preeclampsia es placentario. En la preeclampsia se produce una alteración en la invasión trofoblástica y remodelación de las arterias espirales uterinas, provocando disfunción endotelial, estrés oxidativo y mala perfusión placentaria. Esta situación se caracteriza por una vasoconstricción de las arterias uterinas, valorable ecográficamente por un aumento de su índice de pulsatilidad y un estado antiangiogénico con un incremento del ratio sFlt-1/PlGF[90,91].

SFlt-1 y PlGF son factores angiogénicos muy específicos de insuficiencia placentaria. El aumento de SFlt-1 y la disminución de PlGF son predictores de preeclampsia y este disbalance se puede detectar en la circulación materna hasta cinco semanas antes de la aparición clínica de la enfermedad[90].

En el estudio **"Preeclampsia-like síndrome induced by severe COVID-19: a prospective observational study**", se hipotetiza que el ratio de factores angiogénicos y el Doppler de las arterias uterinas, marcadores específicos de insuficiencia placentaria, pueden ser útiles para el diagnóstico diferencial entre la preeclampsia y las manifestaciones extrapulmonares de la propia infección por SARS-CoV-2.

En gestantes con diagnóstico de preeclampsia con signos de gravedad: tensión arterial ≥160/110, trombopenia, elevación enzimas hepáticos, insuficiencia renal, edema pulmonar o sintomatología neurológica, está indicada la finalización de la gestación a partir de las 34 semanas, o independientemente de las semanas de gestación en caso de inestabilidad materna o fetal[43].

En gestantes con infección por SARS-CoV-2 y que presenten estos criterios diagnósticos, si se descarta la preeclampsia sobreañadida, se puede realizar un manejo expectante de la gestación, condicionando la finalización del embarazo sólo a la evolución de la infección. Con la resolución de la COVID-19, los signos y síntomas de preeclampsia también se normalizan, sin comprometer el estado materno ni aumentar la prematuridad fetal[92,93].

Se requieren más estudios para comprender la relación entre el síndrome preeclampsia-like y la COVID-19. El estudio de las placentas de estas gestantes puede ser útil para esclarecer su fisiopatología.

En el estudio "Diffuse trophoblast damage is the hallmark of SARS-CoV-2 associated fetal demise"[54] se describen las características anatomopatológicas de las placentas de gestantes con infección por SARS-CoV-2.

Las primeras series de casos en las que se estudiaron las placentas muestran hallazgos anatomopatológicos inespecíficos y sin relación con los resultados neonatales[94–96]. Estos casos estaban seleccionados por la positividad materna a SARS-CoV-2, pero no se valoró la afectación placentaria.

En nuestro estudio[54] se describió una lesión trofoblástica específica, caracterizada por la necrosis del trofoblasto velloso y el colapso del espacio intervellositario. Estos hallazgos solo estaban presentes en placentas en las que se confirmó la positividad a SARS-CoV-2 mediante técnicas de inmunohistoquímica, hibridación in situ y RT-PCR.

El tipo de lesión placentaria puede guardar relación con el riesgo de transmisión vertical. En mujeres con COVID-19 y placenta negativa para SARS-CoV-2, la descripción anatomopatológica de estas placentas era muy heterogénea: signos de malperfusión vascular materna o fetal, lesiones inflamatorias como corioamnionitis o villitis o ausencia de alteraciones. Sin embargo, en los casos de infección placentaria confirmada por inmunohistoquímica, hibridación in situ o RT-PCR, es en los que se detectó lesión trofoblástica específica[97].

La extensión de la afectación placentaria puede estar relacionada con los resultados perinatales. En nuestro estudio[54], los cinco casos que presentaban necrosis difusa más extensa se asociaron a óbito fetal y en dos de ellos se confirmó RT-PCR positiva en tejido fetal. Otros estudios también asociaron lesión trofoblástica a pérdida gestacional[97].

Estos hallazgos proporcionan una primera aproximación para comprender el riesgo de transmisión vertical de la infección por SARS-CoV-2 y sus mecanismos patogénicos.

En el estudio **"Congenital infection of SARS-CoV-2 in live-born neonates: a population-based descriptive study"**, se confirma la posibilidad de transmisión vertical de la infección.

Zeng y col[65]. son los primeros autores en describir la infección neonatal precoz, abriendo la posibilidad de la transmisión vertical de la infección. Presentaron el caso de tres neonatos con RT-PCR SARS-CoV-2 positiva en exudado nasofaríngeo y anal a los 2 y 4 días de vida y negativización a partir del día 6. Siguiendo los criterios de Shah y col. no se pudo confirmar infección congénita, porque no había muestra del neonato al nacimiento (nasofaríngea, sangre de cordón, líquido amniótico o placenta). Únicamente

con las muestras nasofaríngeas y anales positivas a los dos días de vida, no se puede excluir la posibilidad transmisión horizontal postnatal.

Otros estudios describieron muestras neonatales positivas para SARS-CoV-2 en las primeras horas del nacimiento[32,98,99]. Pero tampoco presentan resultados de placenta, líquido amniótico o sangre de cordón umbilical, por lo que la transmisión pudo ser intraparto o postparto pero no hay evidencia suficiente para confirmar transmisión durante la gestación.

En comparación con los casos previos, en nuestro estudio se confirmó el caso de una mujer con sintomatología compatible y RT-PCR nasofaríngea positiva en el momento del parto y el neonato RT-PCR positiva en líquido amniótico, sangre de cordón umbilical y placenta. Según la clasificación de Shah y col[64]. nuestro caso cumple criterios de infección congénita confirmada.

La toma de las muestras maternas y neonatales se realizó con estrictas medidas de asepsia. La muestra de líquido amniótico se obtuvo por amniocentesis en el momento del parto, previo a la amniorrexis, y la sangre de cordón umbilical tras el nacimiento del neonato. Con los equipos de protección individual utilizados por todo el personal sanitario involucrado en el parto y las medidas de asepsia generales, es muy difícil la contaminación de las muestras por fluidos vaginales o aerosoles. Incluso, aunque esto fuera factible, la posibilidad de contaminación de ambas muestras, tomadas en momentos distintos, es extremadamente improbable.

Nuestros hallazgos son compatibles con los de otros estudios[70,100]. El caso descrito por Vivanti y col[70]. presenta todavía evidencia más robusta de transmisión vertical, porque detectó RT-PCR positiva en muestra nasofaríngea neonatal, en comparación con el nuestro, que resulta negativo. En nuestro caso esta muestra se tomó exudado nasofaríngeo en el momento del nacimiento, sin embargo, en el estudio de Vivanti la muestra procede de lavado broncoalveolar, que resulta más sensible. La toma de muestras de diferentes tejidos puede mejorar la tasa de detección de la infección[101].

Los hallazgos de este estudio demuestran la posibilidad de transmisión madre – feto de la infección por SARS-CoV-2. Son necesarias series de casos más grandes para evaluar la tasa de transmisión y los posibles efectos en feto y neonato.

En nuestra experiencia no hemos hallado repercusiones fetales o neonatales de la infección, salvo dos casos de edema fetal transitorio, que se describen en el estudio **"Fetal transient skin edema in two pregnant women with Coronavirus Disease 2019 (COVID-19)".**

Martinez-Varea y col[102]. describieron un caso de edema fetal transitorio en una gestante con infección leve en tercer trimestre. Aunque no disponían de estudio de líquido amniótico ni de la placenta para descartar otras causas. Rodrigues y col[103]. y Popescu y col[104]. describieron dos casos de hydrops fetal a las 25 y 34 semanas respectivamente que finalizaron en óbito fetal. En ninguno de los dos se realizó estudio de líquido amniótico para descartar infección TORCH o alteraciones genéticas, pero en ambos se confirmó RT-PCR SARS-CoV-2 positiva en placenta.

Es posible que no existan series más largas de edema fetal transitorio debido a que la mayoría de las guías clínicas[56,73,82], durante las primeras olas de la pandemia, recomendaban posponer hasta 14 días los controles ecográficos en las pacientes con infección, por lo que es probable que los casos se hayan infradiagnosticado.

Siguiendo el protocolo descrito previamente[105], en el Hospital Universitari Vall d´Hebron se creó una consulta específica de COVID-19 y gestación para visitar semanalmente a todas las gestantes con infección activa hasta la negativización de la RT-PCR nasofaríngea. En todas las visitas se realizó ecografía fetal completa. Este seguimiento tan exhaustivo permitió detectar los dos casos descritos y dos más posteriores no recogidos en este artículo.

En la literatura no se han descrito otras manifestaciones ecográficas fetales en relación con la infección por SARS-CoV-2 en la gestación.

Ante este hallazgo, la primera hipótesis es que el edema fetal sea un signo de infección congénita. Sin embargo, el estudio de líquido amniótico para SARS-CoV-2 resultó negativo, y aunque no estaba disponible en el momento de la publicación del artículo, posteriormente se confirmó que el estudio de placenta fue también negativo. El resultado de ambas gestaciones han sido dos neonatos sanos con RT-PCR nasofaríngea al nacimiento negativa.

Otra hipótesis es que sea una repercusión de la tormenta inflamatoria de citoquinas materna, propia de la COVID-19[106], ya que está demostrado que la respuesta inmune inducida por patógenos puede derivar en complicaciones fetales[107]. En el primer caso, la elevación de IL-6 en sangre materna coincidió con la aparición del edema fetal, y su descenso con la resolución. Sin embargo, en el segundo caso los niveles de IL-6 se mantuvieron en rango de normalidad en todo momento.

Son necesarios más estudios para esclarecer si existen repercusiones fetales por la infección materna.

LÍNEAS DE INVESTIGACIÓN

Tras más de dos años desde el inicio de la pandemia, con un conocimiento cada vez mayor de la enfermedad y sobre todo con la aparición de las vacunas, la situación en nuestro medio se ha estabilizado. Sigue habiendo casos de COVID-19 en gestantes, pero la mayoría son cuadros leves. Se ha normalizado la atención de estas pacientes en todos los centros sanitarios, salvo los casos graves que requieren ingreso, que siguen beneficiándose de la atención en centros de referencia.

A pesar de esta normalización de la enfermedad, sigue habiendo muchos interrogantes sobre la afectación del SARS-CoV-2 en la gestación.

Nuestro grupo de trabajo ha seguido investigando sobre el síndrome tipo preeclampsia asociado a la infección por SARS-CoV-2.

Una de las posibles hipótesis sobre esta asociación es que la preeclampsia y la COVID-19 comparten factores de riesgo asociados a daño endotelial, como obesidad, hipertensión arterial, diabetes o edad materna. El estudio "**Shared risk factors for COVID-19 and preeclampsia in the first trimester: An observational study"**[108] compara los factores de riesgo maternos valorados en el despistaje de preeclampsia en primer trimestre en gestantes con COVID-19 y una cohorte de gestantes sanas.

Se ha realizado un estudio sobre el impacto de la COVID-19 en las características patológicas de las placentas, con resultados pendientes de publicación.

Y se acaba de publicar el artículo **"Confirmation of preeclampsia-like syndrome induced by severe COVID-19: an observational study"**[109], confirmando el planteamiento del **"Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study"**[110], en una cohorte mayor de pacientes.

Estos trabajos forman parte de otra tesis doctoral por compendio de artículos.

Otra línea de investigación y tesis doctoral trata sobre los efectos de la infección por SARS-CoV-2 durante la gestación en el crecimiento fetal y en el desarrollo neurológico fetal y neonatal.

También se han desarrollado trabajos sobre el impacto psicológico del SARS-CoV-2 en la gestación, **"Psychological impact and social support in pregnant women during lockdown due to SARS-CoV2 pandemic: A cohort study"**[111]; y en el propio personal sanitario **"Impact of simulation-based teamwork training on COVID-19 distress in healthcare professionals"**[112].

CONCLUSIONES

1. La elaboración de un protocolo específico para el manejo de la gestante con infección por SARS-CoV-2 permite una asistencia de calidad a las pacientes, minimizar la variabilidad en la práctica clínica, un uso racional de los recursos y evaluar de manera homogénea los resultados clínicos.
2. El 62.5% de las gestantes con COVID-19 grave tratadas en el Hospital Universitari Vall d'Hebron entre marzo y abril de 2020 presentaron signos y síntomas propios de preeclampsia. Los hallazgos más frecuentes fueron elevación de enzimas hepáticas (87.5%), proteinuria (75%) e hipertensión arterial (62.5%).
3. La ratio de factores angiogénicos sFlt-1/PlGf y el Doppler de las arterias uterinas son marcadores útiles para el diagnóstico diferencial entre preeclampsia y síndrome preeclampsia-like secundario a COVID-19.
4. La transmisión materno-fetal de la infección por SARS-CoV-2 es posible, aunque muy poco frecuente.
5. La infección por SARS-CoV-2 en la gestación puede producir edema fetal transitorio, sin repercusión posterior en los recién nacidos.

BIBLIOGRAFÍA

1. Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol. 2020;41:1100-15.
2. Sebastia Portales N. SARS-CoV-2: origen zoonótico y transmisión a otras especies animales. 2021.
3. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. European Journal of Clinical Microbiology & Infectious Diseases. 2021;40:905-19.
4. Li Q, Chen L, Yang Z, Ye Z, Huang Y, He M, et al. Metabolic effects of bariatric surgery in type 2 diabetic patients with body mass index < 35 kg/m2. Diabetes Obes Metab. 2012;14:262-70.
5. Gupta A, Madhavan M v., Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017-32.
6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of Thrombosis and Haemostasis. 2020;18:1094-9.
7. Moore JB, June CH. Cytokine release syndrome in severe COVID-19 2020.
8. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395:514-23.
9. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. New England Journal of Medicine. 2020;382:1564-7.
10. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res. 2020;188.
11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - Journal of the American Medical Association. 2020;323:1061-9.
12. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239-42.
13. WHO 2020 s. f.
14. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020;13:1833-9.
15. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020;191:148-50.
16. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18:844-7.
17. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020;76:122-4.

18. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New England Journal of Medicine. 2020;382:1787-99.
19. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. New England Journal of Medicine. 2020;383:1813-26.
20. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients with COVID-19 in New York State. JAMA - Journal of the American Medical Association. 2020;323:2493-502.
21. Snow TAC, Saleem N, Ambler G, Nastouli E, Singer M, Arulkumaran N. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. Intensive Care Med. 2021;47:641-52.
22. Papamanoli A, Yoo J, Grewal P, Predun W, Hotelling J, Jacob R, et al. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. Eur J Clin Invest. 2021;51.
23. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients with Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2020;324:1307-16.
24. Rasmussen SA, Hayes EB. Public Health Approach to Emerging Infections Among Pregnant Women. Am J Public Health. 2005;95.
25. Meaney-Delman DM, Jamieson DJ, Rasmussen SA. Addressing the effects of established and emerging infections during pregnancy. Birth Defects Res. 2017;109:307-10.
26. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. Am J Obstet Gynecol. 2011;205:10-8.
27. Rodó C, Suy A, Sulleiro E, Soriano-Arandes A, Maiz N, García-Ruiz I, et al. Pregnancy outcomes after maternal Zika virus infection in a non-endemic region: prospective cohort study. Clinical Microbiology and Infection. 2019;25:633.e5-633.e9.
28. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222:521-31.
29. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. The BMJ. 2020;370.
30. Crovetto F, Crispi F, Llurba E, Figueras F, Gómez-Roig MD, Gratacós E. Seroprevalence and presentation of SARS-CoV-2 in pregnancy. The Lancet. 2020;396:530-1.
31. Kelly JC, Raghuraman N, Carter EB, Palanisamy A, Stout MJ. Preprocedural asymptomatic coronavirus disease 2019 cases in obstetrical and surgical units. Am J Obstet Gynecol. 2021;224:114-6.

32. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. The BMJ. 2020;369.
33. Lam CM, Wong SF, Leung TN, Chow KM, Yu WC, Wong TY, et al. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. BJOG. 2004;111:771-4.
34. Babarinsa IA, Okunoye GO, Odukoya O. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in pregnancy – An overview. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2021;263:171-5.
35. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM. 2020;2.
36. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Morbidity and Mortality Weekly Report Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status-United States. 2020.
37. Galang RR, Newton SM, Woodworth KR, Griffin I, Oduyebo T, Sancken CL, et al. Risk Factors for Illness Severity Among Pregnant Women With Confirmed Severe Acute Respiratory Syndrome Coronavirus 2 Infection—Surveillance for Emerging Threats to Mothers and Babies Network, 22 State, Local, and Territorial Health Departments, 29 March 2020–5 March 2021. Clinical Infectious Diseases. 2021;73:S17-23.
38. Valle L, Carreras E, Fetal M, Goya M, Pratcorona L, Merced C, et al. Articles Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. The Lancet. 2012;379:1800-6.
39. Valencia CM, Mol BW, Jacobsson B, Simpson JL, Norman J, Grobman W, et al. FIGO good practice recommendations on modifiable causes of iatrogenic preterm birth. International Journal of Gynecology and Obstetrics. 2021;155:8-12.
40. Romero R, Dey SK, Fisher SJ. Preterm labor: One syndrome, many causes. Science (1979). 2014;345:760-5.
41. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: A systematic review and meta-analysis. CMAJ. 2021;193:E540-8.
42. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and Neonatal Morbidity and Mortality among Pregnant Women with and without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. 2021;175:817-26.
43. American College of Obstetricians and Gynecologists. Task Force on Hypertension in Pregnancy, American College of Obstetricians and Gynecologists. Hypertension in pregnancy. s. f.
44. Duley L. The Global Impact of Pre-eclampsia and Eclampsia. Semin Perinatol. 2009;33:130-7.

45. Roberts JM, Hubel CA. The Two Stage Model of Preeclampsia: Variations on the Theme. Placenta. 2009;30:32-7.
46. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97:829-38.
47. Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. Liver International. 2021;41:20-32.
48. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clinica Chimica Acta. 2020;506:145-8.
49. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One. 2020;15.
50. di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2.
51. Metz TD, Berry RS, Fretts RC, Reddy UM, Turrentine MA. Management of Stillbirth: Obstetric Care Consensus No, 10. Obstetrics and gynecology. 2020;135:e110-32.
52. Mullins E, Hudak ML, Banerjee J, Getzlaff T, Townson J, Barnette K, et al. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. Ultrasound in Obstetrics and Gynecology. 2021;57:573-81.
53. Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the Incidence of Stillbirth and Preterm Delivery during the COVID-19 Pandemic. JAMA - Journal of the American Medical Association. 2020;324:705-6.
54. Garrido-Pontnou M, Navarro A, Camacho J, Crispi F, Alguacil-Guillén M, Moreno-Baró A, et al. Diffuse trophoblast damage is the hallmark of SARS-CoV-2-associated fetal demise. Modern Pathology. 2021;34:1704-9.
55. Omar M, Youssef MR, Trinh LN, Attia AS, Elshazli RM, Jardak CL, et al. Excess of cesarean births in pregnant women with COVID-19: A meta-analysis. Birth. 2022;49:179-93.
56. Coronavirus (COVID-19), pregnancy and women's health | RCOG s. f.
57. COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics | ACOG s. f.
58. di Toro F, Gjoka M, di Lorenzo G, de Santo D, de Seta F, Maso G, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2021;27:36-46.
59. Cavalcante MB, de Melo Bezerra Cavalcante CT, Cavalcante ANM, Sarno M, Barini R, Kwak-Kim J. COVID-19 and miscarriage: From immunopathological mechanisms to actual clinical evidence. J Reprod Immunol. 2021;148.
60. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstetrics and gynecology. 2018;132:e197-207.
61. Eskenazi B, Rauch S, Iurlaro E, Gunier RB, Rego A, Gravett MG, et al. Diabetes mellitus, maternal adiposity, and insulin-dependent gestational diabetes are

associated with COVID-19 in pregnancy: the INTERCOVID study. Am J Obstet Gynecol. 2022;227:74.e1-74.e16.
62. Mahyuddin AP, Kanneganti A, Wong JJL, Dimri PS, Su LL, Biswas A, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2s. Prenat Diagn. 2020;40:1655-70.
63. Lebech M, Joynson DHM, Seitz HM, Thulliez R, Gilbert RE, Dutton GN, et al. Classification System and Case Definitions of Toxoplasma gondii Infection in Immunocompetent Pregnant Women and Their Congenitally Infected Offspring. vol. 15. 1996.
64. Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstet Gynecol Scand. 2020;99:565-8.
65. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal Early-Onset Infection with SARS-CoV-2 in 33 Neonates Born to Mothers with COVID-19 in Wuhan, China. JAMA Pediatr. 2020;174:722-5.
66. Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-Trimester Miscarriage in a Pregnant Woman with SARS-CoV-2 Infection. JAMA - Journal of the American Medical Association. 2020;323:2198-200.
67. Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM. 2020;2:100133.
68. Algarroba GN, Rekawek P, Vahanian SA, Khullar P, Palaia T, Peltier MR, et al. Visualization of severe acute respiratory syndrome coronavirus 2 invading the human placenta using electron microscopy. Am J Obstet Gynecol. 2020;223:275-8.
69. Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019–positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020;2.
70. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020;11.
71. Eid J, Stahl D, Costantine MM, Rood KM. Oxygen saturation in pregnant individuals with COVID-19: time for re-appraisal? Am J Obstet Gynecol. 2022;226:813-6.
72. Health Q. Maternity and Neonatal Clinical Guideline Maternity care for mothers and babies during the COVID-19 pandemic. s. f.
73. Poon LC, Yang H, Lee JCS, Copel JA, Leung TY, Zhang Y, et al. ISUOG Interim Guidance on 2019 novel coronavirus infection during pregnancy and puerperium: information for healthcare professionals. Ultrasound in Obstetrics and Gynecology. 2020;55:700-8.
74. Donders F, Lonnée-Hoffmann R, Tsiakalos A, Mendling W, de Oliveira JM, Judlin P, et al. ISIDOG recommendations concerning COVID-19 and pregnancy. Diagnostics. 2020;10.
75. D'Souza R, Ashraf R, Rowe H, Zipursky J, Clarfield L, Maxwell C, et al. Pregnancy and COVID-19: pharmacologic considerations. Ultrasound in Obstetrics and Gynecology. 2021;57:195-203.

76. RECOMENDACIONES SOBRE PROFILAXIS ETV en embarazo y puerperio durante la pandemia COVID-19. s. f.
77. Lampejo T. Remdesivir for the treatment of COVID-19 in pregnancy. J Med Virol. 2021;93:4114-9.
78. Jiménez-Lozano I, Caro-Teller JM, Fernández-Hidalgo N, Miarons M, Frick MA, Batllori Badia E, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study. J Clin Pharm Ther. 2021;46:1062-70.
79. Vaught J. Society for Maternal-Fetal Medicine Management Considerations for Pregnant Patients With COVID-19 Developed with guidance from Torre Halscott, MD, MS. s. f.
80. COVID-19 | ACOG s. f.
81. COVID-19 during Pregnancy | CDC s. f.
82. Boelig RC, Saccone G, Bellussi F, Berghella V. MFM guidance for COVID-19. Am J Obstet Gynecol MFM. 2020;2.
83. Boelig RC, Manuck T, Oliver EA, di Mascio D, Saccone G, Bellussi F, et al. Labor and delivery guidance for COVID-19. Am J Obstet Gynecol MFM. 2020;2.
84. Manejo de la mujer embarazada y el recién nacido con COVID-19. s. f.
85. Servei Català de la Salut. Guia d'actuació enfront de casos d'infecció pel coronavirus SARS-CoV-2 en dones embarassades i nadons. 2020.
86. Narang K, Ibirogba ER, Elrefaei A, Trad ATA, Theiler R, Nomura R, et al. SARS-CoV-2 in pregnancy: A comprehensive summary of current guidelines. J Clin Med. 2020;9.
87. Papageorghiou AT, Deruelle P, Gunier RB, Rauch S, García-May PK, Mhatre M, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. Am J Obstet Gynecol. 2021;225:289.e1-289.e17.
88. Giuliani F, Oros D, Gunier RB, Deantoni S, Rauch S, Casale R, et al. Effects of prenatal exposure to maternal COVID-19 and perinatal care on neonatal outcome: results from the INTERCOVID Multinational Cohort Study. Am J Obstet Gynecol. 2022;227:488.e1-488.e17.
89. Sibai BM. Imitators of Severe Pre-eclampsia. Semin Perinatol. 2009;33:196-205.
90. Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating Angiogenic Factors and the Risk of Preeclampsia. vol. 12. 2004.
91. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol. 2012;206:58.e1-58.e8.
92. Federici L, Picone O, Dreyfuss Di, Sibiude J. Successful continuation of pregnancy in a patient with COVID-19-related ARDS. BMJ Case Rep. 2020;13.
93. Naeh A, Berezowsky A, Yudin MH, Dhalla IA, Berger H. Preeclampsia-Like Syndrome in a Pregnant Patient With Coronavirus Disease 2019 (COVID-19). Journal of Obstetrics and Gynaecology Canada. 2022;44:193-5.
94. Sharps MC, Hayes DJL, 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.
95. Baergen RN, Heller DS. Placental Pathology in Covid-19 Positive Mothers: Preliminary Findings. Pediatric and Developmental Pathology. 2020;23:177-80.

96. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental Pathology in COVID-19. Am J Clin Pathol. 2020;154:23-32.
97. Schwartz DA, Morotti D. Placental pathology of covid-19 with and without fetal and neonatal infection: Trophoblast necrosis and chronic histiocytic intervillositis as risk factors for transplacental transmission of sars-cov-2. Viruses. 2020;12.
98. Martínez-Perez O, Vouga M, Cruz Melguizo 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 - Journal of the American Medical Association. 2020;324:296-9.
99. 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. Clinical Microbiology and Infection. 2020;26:788-90.
100. Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. Nat Commun. 2020;11.
101. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections–the state of the art. Emerg Microbes Infect. 2020;9:747-56.
102. Martínez-Varea A, Desco-Blay J, Monfort S, Hueso-Villanueva M, Perales-Marín A, Diago-Almela VJ. Transitory Fetal Skin Edema in a Pregnant Patient with a Mild SARS-CoV-2 Infection. Case Rep Obstet Gynecol. 2021;2021:1-4.
103. Rodrigues ML, Gasparinho G, Sepúlveda F, Matos T. Signs suggestive of congenital SARS-CoV-2 infection with intrauterine fetal death: A case report. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2021;256:508-9.
104. Popescu DE, Cioca A, Muresan C, Navolan D, Gui A, Pop O, et al. A case of covid-19 pregnancy complicated with hydrops fetalis and intrauterine death. Medicina (Lithuania). 2021;57.
105. Suy A, Garcia-Ruiz I, Carbonell M, Garcia-Manau P, Rodo C, Maiz N, et al. Gestation and COVID-19: clinical and microbiological observational study (Gesta-COVID19). BMC Pregnancy Childbirth. 2021;21.
106. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. Journal of Infection. 2020;80:607-13.
107. Yockey LJ, Iwasaki A. Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development. Immunity. 2018;49:397-412.
108. Serrano B, Mendoza M, Garcia-Aguilar P, Bonacina E, Garcia-Ruiz I, Garcia-Manau P, et al. Shared risk factors for COVID-19 and preeclampsia in the first trimester: An observational study. Acta Obstet Gynecol Scand. 2022;101:803-8.
109. Serrano B, Bonacina E, Garcia-Ruiz I, Mendoza M, Garcia-Manau P, Garcia-Aguilar P, et al. Confirmation of preeclampsia-like syndrome induced by severe COVID-19: An Observational Study. Am J Obstet Gynecol MFM. 2022:100760.
110. Mendoza M, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, et al. Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study. BJOG. 2020;127:1374-80.
111. Brik M, Sandonis MA, Fernández S, Suy A, Parramon-Puig G, Maiz N, et al. Psychological impact and social support in pregnant women during lockdown due to SARS-CoV2 pandemic: A cohort study. Acta Obstet Gynecol Scand. 2021;100:1026-33.

112. Beneria A, Arnedo M, Contreras S, Pérez-Carrasco M, Garcia-Ruiz I, Rodríguez-Carballeira M, et al. Impact of simulation-based teamwork training on COVID-19 distress in healthcare professionals. BMC Med Educ. 2020;20.