REVIEW

Immunological and physiopathological approach of COVID-19 in pregnancy

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Abstract
Coronavirus disease-2019 (COVID-19) related to Coronavirus-2 (SARS-CoV-2) is a worldwide health concern. Despite the majority of patients will evolve asymptomatic or mild-moderate upper respiratory tract infections, 20% will develop severe disease. Based on current pathogenetic knowledge, a severe COVID-19 form is mainly a hyperinflammatory, immune-mediated disorder, triggered by a viral infection. Due to their particular immunological features, pregnant women are supposed to be particularly susceptible to complicate by intracellular infections as well as immunological disturbances. As an example, immune-thrombosis has been identified as a common immune-mediated and pathogenic phenomenon both in COVID-19, in obstetric diseases and in COVID-19 pregnant women. According to extensive published clinical data, is rationale to expect an interference with the normal development of pregnancy in selected SARS-CoV-2-infected cases, mainly during third trimester.
This manuscript provides insights of research to elucidate the potential harmful responses to SARS-CoV-2 and /or other coronavirus infections, as well as bidirectional interactions between COVID-19 and pregnancy to improve their respective management.

Keywords COVID-19 · Immune-mediated · SARS-CoV-2 · Pregnancy outcome · Placental disease · Hyperinflammation · Obstetric disorder · Viral infection

Abbreviations
ACE-2 Angiotensin-converting enzyme-2
ADE Antibody dependent enhancement
ADRS Acute distress respiratory syndrome
Ang Angiotensin
APC Antigen-presenting cells
aPL Antiphospholipid antibodies
BNP B-type natriuretic peptide
MAC Membrane attack complex (C5-9)
COVID-19 Coronavirus disease 2019
DAF Decay-accelerating factor
HLA Human leucocyte antigen
HELLP Hemolysis, elevated liver enzymes, low-platelet count

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Introduction

The coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), was first described as an epidemic in China (Wuhan, Hubei province) in December 2019 [1]. Only 3 months later, the World Health Organization (WHO) declared the outbreak a global pandemic [2] and a public health emergency of international concern due to its highly contagious nature, and its morbidity and mortality rates, which could rise up to 3–4% [2, 3].

SARS-CoV-2 is the seventh and the larger type of enveloped simple strained RNA coronavirus species that has been demonstrated to be able to infect humans [4]. The Severe Acute Respiratory Syndrome coronavirus 1 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are two zoonotic coronaviruses that were responsible for epidemic outbreaks with a great local impact in 2002 in China, and in 2012 in Saudi Arabia, respectively [5]. Their global impact, however, was relatively low. COVID-19, by contrast, has spread rapidly worldwide, becoming a global health threat. A low rate of previously exposed individuals in different communities, and the antigenic diversity among coronaviruses, could explain the explosive COVID-19 outbreak [6]. Researchers have struggled to understand the diversity in the molecular pathways of the human hosts’ immune system responses to SARS-CoV-2 [5–7].

SARS-CoV-2 infection has a triggering role of the immune system. For this reason, pregnant women are of special interest, due to their unique immunological temporary features. This manuscript summarizes existing literature of the molecular mechanisms that may be underlying in the obstetric manifestations of pregnant women infected with SARS-CoV-1, MERS-CoV or SARS-CoV-2.

COVID-19: an immunological disorder underlying a clinical disease

Like in SARS-CoV-1 and MERS-CoV, COVID-19 features a range in symptoms from: asymptomatic or mild upper respiratory tract infections (80%); through flu-like syndromes to systemic inflammatory responses, undergoing more complicated forms of the disease, like severe bilateral pneumonia (15%); to Severe Acute Respiratory Syndrome (SARS) and/or multisystemic involvement (5%) requiring admission to intensive care units (ICU) for continuous and invasive support [8, 9]. Adults, specifically older men with comorbidities such as obesity, high blood pressure, cardiovascular or chronic lung diseases, are more likely to suffer severe life-threatening forms of COVID-19, that eventually lead them to death [8, 9].

A five-stage model has been proposed to explain the clinical spectrum of COVID-19 disease. These stages correlate with a direct viral effect to triggered responses of both the innate and adaptive immune systems [1, 9, 10]. The different stages are represented in Fig. 1.

Incubation and early infection. Stage 0 and Stage 1

SARS-CoV-2 infection is transmitted person-to-person, airborne or via direct contact, nasal and oropharyngeal mucosa being the main entrance path of the virus into the human host. The mechanism of SARS-CoV-2 that makes host cell entry possible, is the Spike protein (S protein) on the envelope that binds to a cell membrane receptor, angiotensin converting enzyme (ACE) homolog 2 (ACE2), which is a part of the renin–angiotensin–aldosterone system (RAS). The S protein is cleaved into S1 and S2 by a human cell-derived protease (proteolytic enzyme). S1
binds to its receptor, ACE2. The other fragment, S2, is cleaved by transmembrane protease, serine 2 (TMPRSS2), a human cell surface serine protease, resulting in membrane fusion [11, 12]. SARS-CoV-2, thusly, infects ACE2 cells, which include mainly oral mucosa, lungs, alveoli, kidney, liver, intestinal and all endothelial cells [12, 13]. After entering the cells, the viral RNA genome is released into the cytoplasm and is translated into polyproteins and structural proteins, and then, the viral genome begins to replicate [14]. The mature virion enters the endosome and interacts with toll-like receptors (TLR) from the immune cells to stimulate downstream inflammatory and clot pathways. Despite sharing almost 70% of the amino acid sequences of SARS-CoV-1, and having the same functional receptor (ACE2), SARS-CoV-2 is more contagious than SARS-CoV-1 and MERS-CoV [5, 15]. It has two main genomic polymorphisms; the newest and the most predominant one, L type (~70%) is meant to be more aggressive, and spreads quicker than others [14, 16, 17]. One possible explanation is that in SARS-CoV-2 infection, the IFN-I type response, -a protective pathway through infected cells usually modulate innate immune responses, promoting balanced antigen presentation and natural killer cell functions, while reducing proinflammatory cytokine production- [18], is suppressed, and therefore viruses rapidly replicate [7, 19].

**Primary inflammatory responses. Infection/pulmonary phase. Stage 2**

These primary inflammatory responses are mainly driven by active viral replication. The cellular effectors of the innate immune system are mainly macrophages and neutrophils that massively respond by producing reactive oxygen species (ROS), viral antigenic peptides, and specific tissue matrix metalloprotease (MMP). The core activity of innate immune system in this stage, is the release of pro-inflammatory cytokines like pro-IL-1β [20] that is cleaved by caspase-1 and converted into active mature IL-1β. This is the very first mediator of lung inflammation and the ensuing epithelial and endothelial cell apoptosis, vascular leakage and tissue damage [8, 20]. After the innate system, the adaptive immune system rapidly comes onto the scene through antigen-dependent lymphocyte activation by antigen presenting cells (APC) bearing viral antigenic peptides on human leukocyte antigens (HLA) molecules. Some gene polymorphisms, i.e., mannose-binding lectin (MBL) expressed in the virus that determine pattern recognition receptors (PRR), could define the different responses in the host [21]. The APC-viral antigen complexes are recognized by virus-specific cytotoxic T lymphocytes (CTLs), which are mediated by virus-specific B and T cells (CD8+, CD4+), secreting at different times typical of viral-induced patterns of neutralizing antibodies (IgM and IgG) [7, 21]. Besides these inflammatory responses, a persistent waste of active macrophages, neutrophils and lymphocytes still remain,
boosting pyroptosis and apoptosis of the infected cells. The massive viral entry causes ACE2 downregulation and shedding, reducing Ang-1–7 synthesis while shifting to an increase of ACE1 activity, increasing Ang II and turning to vasoconstriction, inflammation and vascular permeability. After entering the cells, the viral RNA genome is released into the cytoplasm and is translated into polyproteins and structural proteins, after which the viral genome begins to replicate. The mature virion enters the endosome and interacts with toll-like receptors (TLR) from the immune cells to stimulate downstream inflammatory and clot pathways. The viral nuclear integration could induce protein expression in the infected cells that would contribute to enhance the inflammatory response and cell damage both directly and indirectly, increasing procoagulant tissue factor and inflammatory cell adhesion and attraction proteins (E-selectine, ICAM, VCAM), as well as reducing HO/CO or NOs that would contribute to vasoconstriction, tissular hypoxia and underperfusion. The primarily inflammatory responses are driven by the innate immune system activation consisting in a massive invasion of neutrophils, monocytes and macrophages that release different pro-inflammatory cytokines and other proteins and molecules responsible to induce cell apoptosis and pyroptosis, leading to a different grade of tissue and organ damage. Simultaneously, adaptive immune system comes on the scene through antigen-dependent lymphocyte activation by antigen presenting cells (APC) bearing viral antigenic peptides on human leukocyte antigens (HLA) molecules. APC-viral antigen complexes are recognized by virus-specific B and T cells (mainly CD8+), secreting at different times, Th1 profile cytokines, which, reinforce previous inflammation, as well as Th2 adaptive humoral response by typical viral- induced pattern of neutralizing antibodies (Nab) IgM and IgG. In some cases, the appearance of Nab not only cannot limit viral replication, but trigger an hyperimmune response, owing to antibody dependent enhancement inflammatory pathways (ADE) that perpetuate responses from macrophages and Th1-lymphocyte, releasing a cytokine storm composed by IFN-α, IFN-γ, IL-1β, IL-2, IL-6, IL-12, IL-8, TNF-α etc. and more pro-inflammatory proteins like monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP-1α), or MMP(tissue matrix metallopro- tease). Additionally, these secondary inflammatory responses include antibody-dependent cell-mediated cytotoxicity, Ag-Ab immunocomplexes-mediated inflammatory pathways, including transient aPL-, and complement pathway hyperactivation that contributes to increasing tissue damage and hypoxia by releasing antiangiogenic factors (sFLT-1, sENG) and inducing platelet aggregation and clot cascade hiperactivation leading to thrombotic events.
Secondary inflammatory responses. Hyperinflammatory phase. Stage 3

In some cases, the appearance of Nab not only limits viral replication, but can also trigger a hyperimmune response. Antibody-dependent cellular cytotoxicity (ADCC) and complement pathway hyperactivation, contribute to an increase in tissue injury. In addition, both platelet and clot cascade hyperactivation give way to thrombotic events. The main underlying known mechanism, antibody-dependent enhancement (ADE), is able to up-modulate the immune response, regardless of virus triggering [25, 26]. ADE perpetuates inflammatory responses from macrophages and Th1-lymphocyte by releasing a cytokine storm, composed of IFN-α, IFN-γ, IL-1β, IL-2, IL-6, IL-12, IL-18, IL-33, protein 10, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP-1α), and tumour necrosis factor-alpha (TNF-α), among others [9, 10, 27]. This hyperinflammatory state can cause the host to suffer from a disseminated intravascular coagulation (DIC), in context of multi-organic failure that, in refractory catastrophic situations, result eventually in death [28].

Immune protection. Post infectious phase. Stage 4

The majority of infected patients are able to limit the situation and to overcome the disease. Thus, the underlying pro-inflammatory and clot pathway hyperactivation gradually returns to basal status. Clinically, this stage lasts 2–6 weeks, with some residual symptoms. Preliminary data suggest that at least 15–20% of cases with pulmonary or systemic involvement will have residual lesions, i.e., pulmonary fibrosis or heart conditions. Some dynamic models of SARS-CoV-2 assume that infection could induce immunity to reinfection for at least 1 year; although, the protective role of the immune response and the timescale of the protection, still remain unclear [29, 30]. Relapsing severe forms of COVID-19 patients have been reported, pointing out the question if the presence of naturally acquired antibodies against SARS-CoV-2, -or exposure to other previously coronaviruses- would bestow cross-protection or would be a harmful trigger through ADE in further contacts [31].

Considering the above, COVID-19 creates a great challenge to the immune system. The newness of SARS-CoV-2 makes all populations immunologically susceptible. Pregnant women, because of their particular and temporary immunological features, deserve special attention. The Fig. 2 represents all the hypothetical pathogenic pathways that could operate in a COVID-19 affected pregnancy.

Covid-19 and pregnancy

Immunological and physiological characteristics of pregnancy

Rather than immunosuppression, a successful pregnancy requires a robust, dynamic and responsive immune system [32]. The mother has to tolerate the implantation of a semi-allogeneic or allogeneic foetus in the womb, while preserving the ability for protection against microbial challenges. A precise timing of local and systemic immunological events occurs throughout pregnancy [33].

At first, the embryo implantation and placentation benefit from a pro-inflammatory state; after that, an anti-inflammatory state permits cell clearance, angiogenesis, and fetal growth; and finally, a second pro-inflammatory state progressively prepares for the initiation of parturition in the third trimester until birth [32, 33]. Overall, the events that facilitate immune tolerance, are led by hormonal inputs, i.e., human chorionic gonadotropin (hCG) and progesterone [34]. These events include indoleamine-2,3-dioxygenase (IDO) secretion by the placental trophoblast, the monocyte-macrophages activation in decidua and the reduction of tryptophan catabolism [35]. Simultaneously, HLA-mediated recognition promotes the endogenous STAT5ab signalling across multiple T cell subsets, including Treg cells (CD25 + FoxP3 +), naive and memory CD4 + and CD8 + T cells, and γδ T cells.

Treg cells are crucial effectors, mostly but not only, in the peri-implantation period down-regulating the T-cell aggressive responses. Uterine NK (uNK) cells, which are non-cytotoxic but proangiogenic, accumulate in the decidua (15% of all cell types), while decreasing in the maternal circulation [36, 37]. They are activated by KIR receptors [38, 39]. The relationship between different maternal KIR genotypes and haplotypes and fetal HLA haplotypes, are crucial to tolerate the semiallogeneic fetus. On the other hand, the maternal innate immune system, through peripheral natural killer (pNK) cells, as well as monocytes and macrophages, will recognize and phagocytose eventual pathogens as a protective mechanism to systemic infections [40, 41]. Simultaneously, the systemic adaptive immune responses are down-regulated but keeps humoral Th2/cellular Th1 balanced, according to pro-inflammatory or anti-inflammatory pregnancy demands [33].

Besides the immunological aspects, physiologic maternal adaptations determine and increase susceptibility and severity of microbial infection throughout pregnancy [42, 43]. Oxygen consumption increases in pregnant women. The physiologic diaphragm elevation that prompts a restriction in lung expansion, as well as the hormone induced oedema of upper respiratory tract mucosa, render them highly sensitive
to hypoxia and particularly vulnerable to respiratory pathogens [43].

Given this scenario, it is rational to think that any event, such as a highly immunogenic viral infection like SARS-CoV-2, could interrupt the normal course of pregnancy. Some studies point to the involvement of COVID-19 in a deregulation of the Treg/Th17 cell ratio toward an increase in Th17 cells, resulting in uncontrolled systemic inflammation. Thus, in SARS-CoV-2–infected pregnant women, Treg/Th17 cell imbalance might be potentially associated with adverse pregnancy outcomes such as pregnancy loss, preterm birth, and PE [44]. Different outcomes can be expected according to individual immune susceptibility and the gestational age at the onset of infection, which might bidirectionally determine both obstetric complications and duration, and/or severity of the infectious disease.

**Previous and current coronavirus infection experience in pregnant women**

SARS-CoV-2 infection in pregnant women could entail obstetric complications, and pregnancy can influence the course of the COVID-19 disease in the mother. Obstetric complications in COVID-19 could be induced by both direct viral effect (ACE2 receptors, viral replication) and the subsequent hyperinflammatory responses. There is current evidence suggesting that pregnant women have been specially affected by viral infections and suffer greater virus-associated morbidity and mortality than non-pregnant women [45].

Pneumonia arising from any infectious aetiology is an important cause of morbidity and mortality among pregnant women [46]. Classically, pneumonia was one of the most common causes of indirect maternal death [46, 47]. Mortality rate of the 1918 influenza pandemic was 26% of the general population, but 37% among pregnant women [48]. On the basis of data from twentieth century, approximately 25% of pregnant women with all-cause pneumonia will need to be hospitalized in intensive care units (ICU) and will require ventilatory support [47–50]. During the pandemic H1N1 influenza virus in 2009 pregnant women were, more than four times, more likely to be admitted to hospital than the general population [51].

Data from previous experiences in the SARS-CoV-1 and MERS-CoV epidemics, showed around 50% of pregnant women who developed SARS were admitted to the ICU, and around 33% of them required mechanical ventilation with a mortality rate as high as 25% [52]. According to data from the first studies of COVID-19 in China amongst pregnant women, the clinical characteristics of pneumonia were similar to those of non-pregnant adult patients, with a prevalence of severe cases of 1–8% and a mortality rate of 1% [53, 54]. Certainly, current data show similar prevalence of mild and severe COVID-19 cases among pregnant women compared to general population. However, they advertise that pregnant women should be considered as a high risk group of pulmonary status worsening, mainly those cases with added comorbidities (asthma, obesity, diabetes) and during third trimester [55–59].

Regarding obstetric outcomes, previous studies showed that SARS-CoV-1 and MERS-CoV infections caused a higher incidence of maternal morbidity and poor obstetric outcomes such as preterm birth, IUGR, intrauterine death or neonatal death [60–63]. The first studies on perinatal morbidity and mortality and COVID-19 infection, reveal that all pregnant women, but mainly those in the third trimester, may be particularly vulnerable to suffer obstetric complications such as foetal loss, stillbirth, intrauterine growth restriction (IUGR) and preterm delivery [54, 63]. These statements, however, should be taken with caution, as they come from a series of low numbered cases and retrospective case–control studies published mainly in China during the first wave of the pandemic.

One of the first systematic review and meta-analysis published on pregnancy outcomes in mothers infected with coronavirus (SARS-CoV-1, MERS-CoV and SARS-CoV-2), preterm birth was the most common adverse pregnancy outcome [64]. Foetal loss, pre-eclampsia (PE), caesarean section and perinatal death (7–11%) were also more common, than in unaffected pregnancies. The mode of delivery in the majority of cases with pneumonia was caesarean section (~80%) [28, 64]. In that study, the authors warn that adverse outcomes when focusing on COVID-19 could be overestimated as a result of either a limited follow-up periods to recruit data, or misdiagnosis or iatrogenic acts due to the lack of experience in the clinical features of the novel virus [64]. A possible overestimation of the risk magnitude of obstetric complications in COVID-19 pregnancies could be partially related to the bias and the relative low level of evidence of first case reports and case series, published by a stressed scientific community, committed to publish clear data to provide knowledge to approach the overwhelming outbreak period of the pandemic. Since then, much data regarding the impact of COVID-19 in pregnancy has been accumulated [58, 65–67]. To date, data available about the consequences of COVID-19 in pregnancy outcomes state that preterm delivery and fetal distress are the main adverse outcomes observed in symptomatic COVID-19 pregnancies in the third trimester and at delivery [59, 65–67]. The effects of SARS-CoV-2 in the first and second trimesters deserve specific studies to elucidate the contribution of the infection in complications such miscarriage, pre-eclampsia or IUGR showing variable and inconclusive incidence among published studies [65, 67–71].
Hypothesis on the influence of SARS-CoV-2 infection in obstetric immune pathways

First and third trimester

A state of mild systemic activation of the innate immune system and inflammation exists in the first but especially in the third trimester [72]. In these periods, an increased number of monocytes and granulocytes are found in maternal blood, releasing inflammatory cytokines, i.e., IL-8, TNF-a, IL-6, by dendritic cells (DC), compared to non-pregnant women [72, 73]. Cytokine storm has been documented as a key pathogenic immune mechanism in SARS-CoV-2 infection. The infection, therefore, could induce a more severe inflammatory state in pregnant women, that might explain an eventual higher incidence of first and third trimester outcomes like miscarriage [65, 74, 75], and preterm deliveries [76].

During the period from the third trimester to delivery, COVID-19 leads to an increased incidence of premature rupture of membranes, fetal distress and preterm labour [67, 76]. The higher incidence of these complications might be due both the need for reduce the mechanical limitation of thoracic expansion, and to improve maternal oxygenation, as well as the inflammatory response of the maternal multi-organ disease [56, 57, 65, 67].

Second trimester

During the second trimester, the low-level inflammatory state combined with skewing towards humoral immunity is thought to allow foetal growth. Th1 cell-mediated immunity is, somewhat compromised, increasing the susceptibility of pregnant women to viral and intracellular bacterial infections [32, 77]. This scenario allows researchers to speculate on the effect of SARS-CoV-2 in shifting immune responses towards a rejection of the fetal-placental unit or even foetal compromise, resulting in variable manifestations of placental inflammation related diseases such as IUGR and PE [78–80], or foetal demise and foetal structural defects [81, 82]. The mother’s response to infection tends to promote the fetus inflammatory response, which is defined as the fetal inflammatory response syndrome (FIRS) [83], characterized by high levels of inflammatory cytokines in placenta. These cytokines have been shown to affect the central nervous system and circulatory system and tend to cause fetal abnormal morphology in animal models, including ventricular expansion and bleeding [84, 85]. Even in human studies, a maintained hyperinflammatory environment during pregnancy would have a deleterious effect mostly on the neurodevelopment of the fetus, leading to potential neuronal dysfunctions in their postnatal life [86].

Despite SARS-CoV-2 virions have been detected in placental and foetal membranes [87, 88], the harm of the foetus in a COVID-19 pregnant mother is not expected to be exerted by a direct action of the virus, as vertical transmission in the amniotic fluid has not been clearly proved [54, 89–92]. A range of 2% to 4% of pooled proportion of SARS-CoV-2 viral RNA test in neonatal nasopharyngeal swab resulted positive in recent published studies, even after having ensured no physical contact between the mother and the newborn. Despite the fact that not only nasopharyngeal swabs but umbilical cord, urine and rectal samples have tested positive suggesting a possible vertical transmission, no evidence of the presence of the virus in the amniotic fluid has been reported [92, 93].

An indirect foetal harm by immune responses induced by SARS-CoV-2 should not be excluded. For many viral diseases (SARS-CoV-1, MERS, influenza virus, Ebola virus, and Zika virus) it is well known that viral RNA can be detected in patients long after the disappearance of the virus. The immune system can neutralise viruses by lysing their envelope, aggregating virus particles; thus, the presence of nucleic acid alone, cannot be used to define viral shedding or infective potential, but could induce antibodies to be able to neutralise or enhance ADE [94]. ADE responses upregulating the immune-mediated cytokine storm described in severe and relapsing COVID-19 cases, have been similarly described in other positive ssRNA viruses, like flaviviruses such as Zika virus [95]. Recently, data of the human plasma with subneutralising antibody levels against flaviviruses with capacity to promote Zika virus pathogenicity in adult mice and foetal demise during pregnancy were reported [31, 96]. For these reasons, both foetuses and newborns of SARS-CoV-2-infected mothers, should be accurately evaluated.

Immune-thrombosis in COVID-19 pregnancies

Immune-thrombotic mechanisms operate as the basis in almost all placental-related complications such as recurrent miscarriage (RM), abruptio placentae, placental insufficiency or foetal death. Pregnancy is a physiologically hypercoagulable state [97] with raised coagulation factors, including fibrinogen and FVIII, and markers of clot activation, i.e., D-dimer and decreased fibrinolytic proteins, such as protein S [97–99]. These particular conditions could be aggravated in an infectious context. Severe SARS-CoV-2 infection induces immune-mediated mechanisms, hypercoagulability and up-regulation of the complement pathway. Coagulopathy results from concurrent activation of the clot and fibrinolytic cascades, causing both thrombus and clotting factor consumption. Thus, manifestations can be either thrombotic or haemorrhagic. Venous and arterial thrombosis have been reported in both COVID-19 patients [100–102], and pregnant women [103]. Coagulopathy complications,
thrombosis apart, have been reported similarly in pregnant women and in the general population [104]; however, pregnant women deserve closer surveillance since they are more likely to suffer from thrombotic-haemorrhagic catastrophic events [97, 98].

A quite low mortality rate has been reported since the COVID-19 outbreak [56, 65, 67, 105, 106]. Along with specific case series of maternal deaths [107, 108], a systematic review on maternal mortality summarizes that the acute respiratory distress syndrome (ARDS) and severity of pneumonia were considered as the leading causes of all maternal mortalities [58]. Except for some cases of maternal deaths related to thrombotic complications [58, 109], scarce publications has delved into a potential implication of haemorrhagic o thrombotic events implicated in the referred COVID-19 maternal deaths. Microvascular thrombosis in the pulmonary system, -led by immunothrombosis phenomena-, and immobility due to hospitalization-associated venous thromboembolism are the two distinct mechanisms that could affect in those cases with a worst evolution of COVID-19 pregnant women [110–112]. Inflammation targeting, clot pathway involvement and thrombosis should be investigated further in all maternal death cases [106, 110, 113].

**Learning from placenta histology**

Despite being considerably scarce, valuable information comes from the histological analysis of the placentas of SARS-CoV-1 and SARS-CoV-2-infected mothers [114–116] that contributes to the understanding of the viral pathogenicity during pregnancy. In general terms, placentas of SARS-CoV-1 pregnancies infected during the first trimester of pregnancy were found to be normal. By contrast, those infected in the second or third trimester were clearly abnormal. Beyond acute or chronic signs of amniotic inflammation, the prevalent histopathological findings were marked signs of abnormal maternal vessels showing subchorionic and intervillous fibrin deposits, as well as extensive foetal thrombotic vasculopathy with areas of avascular chorionic villi, suggesting vascular malperfusion. A recent publication related to placental pathology of five full-term births to COVID-19 patients shows an histology indicative of fetal vascular malperfusion characterized by focal avascular villi and thrombi in larger fetal vessels [113].

Interestingly, villitis, the microscopic finding of inflammation of the chorionic villi that is the histologic hallmark of many maternal haematogenous infections transmitted through the placenta to the foetus [117], was not identified in these placentas. Overall, thrombotic and/or microangiopathic traits seemed to prevail over chorioamnionitic ones. Only in one reported case of second trimester miscarriage in a pregnant woman with SARS-CoV-2 infection [118], placental studies demonstrated mixed inflammatory infiltrates and unspecific increased intervillous fibrin deposition and funisitis; however, no bacteria or fungi were identified in placental PCR or cultures.

Histological findings in SARS-CoV-1 and SARS-CoV-2 placentae share some characteristics with those of pregnant women with obstetric antiphospholipid syndrome (OAPS) [119]. Therefore, COVID-19 infection and the presence of aPL might have a synergistic effect, inducing both inflammation and thrombosis. Antiphospholipid syndrome (APS) is considered a prothrombotic disorder [120]; however, in OAPS subset, rather than thrombotic, the main pathogenic mechanisms triggered by aPL are those related with inflammation [79–81]. Moreover, viral infections as a trigger to synthesize aPL has already been reported [121, 122]. Acute viral infections can be frequent triggers of catastrophic antiphospholipid syndrome (CAPS) (24%) [123, 124], an infrequent and severe clinical subset of APS presenting in ≈1% of cases. Only one paper has been published regarding aPL in the context of severe COVID-19 disease [125]. Similarly, other cases have also been recruited (Estève-Valverde E, Aljotjas-Reig J: unpublished results). Some argue that transient non-pro-thrombotic antibodies can arise in patients with critical illness and various infections. It is difficult to dismiss their potential harmful effect in severe medical conditions, like severe COVID-19, that present similar characteristics as CAPS. Recently, a European Multicentre Registry endorsed by the EUROFORUM projects to recruit cases of COVID-19 patients with thrombosis and aPL positivity (COVIDAPS) has been started (Aljotjas-Reig J: personal communication).

**Complement system role**

**Complement role in COVID-19**

The complement system is a protein-composed mediator -([C1 to C9]- of the innate immune system that promotes inflammation, defends against bacterial infections, and often neutralizes infectious viruses [126]. Its classical pathway is triggered by Ag-Ab complexes, and its alternative pathway by specific surface antigens and molecules. Other activators such as coagulation factors FXa, FXIa and plasmin, that can cleave both C5 and C3, have been reported [127]. These pathways converge on a common via. The common pathway includes production of C3a and C5a inflammatory mediators, C3b-initiated pathogen opsonisation, and ends in formation of the C5b-9 membrane attack complex (MAC) that lyses targeted cells, resulting in cell death [128, 129]. Complement activation has polarized effects: towards protective-tolerogenic-defender functions or life-threatening responses, like in autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA)
The complement system role in the pathogenicity of previous coronavirus epidemic diseases has already been described. In SARS-CoV-1-infected mice lacking C3, thus unable to activate the common complement pathway, a less severe respiratory dysfunction was observed, as well as lower cytokine levels despite equal viral loads [129]. Similarly, in the murine model of MERS-CoV infection, increased levels of C5a and C5b-9 were found in sera and lungs of sick mice [130, 131]. When blocking C5a protein with specific antibodies, an improvement of lung damage besides lower cytokine production and viral replication were seen [132]. According to all these data, hyperactivation of the complement system in SARS-CoV-2 infection, as a powerful inducer of the hyperinflammatory state, could be compellingly suggested [131, 132]. Widespread complement activation, with C3 deposition in lung biopsies and increased C5a serum levels of COVID-19 patients have already been reported [133]. Excessive complement activation is clearly recognized to be involved in diffuse thrombotic microangiopathy, as seen in organ dysfunction syndromes such as atypical haemolytic uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP) and CAPS [134–136]. Likewise, in other well-known hyperinflammatory and hyperferritinaemic disorders, -see Table 1-, like haemophagocytic syndrome (HPS) and macrophage activation syndrome (MAS), a hyperactivation of the complement system has also been recognized to be essential to induce tissue damage [137–139]. The current similarities between these syndromes and the severe life-threatening COVID-19 forms, reinforce the role of complement hyperactivation as one of the most harmful molecular pathways in the pathogenesis of the disease.

Complement role in pregnancy

Autoantibody-mediated complement pathway hyperactivation, has been widely described in several pregnancy complications [140–142]. Thus, besides strategic HLA-G exposition, T cells suppression and uNK-specific activity, a tight regulation of complement system activation is essentially needed to achieve a successful tolerant environmental in the fetal-maternal interface [143, 144]. The specific role of C1q, synthesised in extravillous trophoblast, and widely distributed in human decidua, has been studied [145]. To achieve a simultaneous balanced control between required inflammation and immune-protection against infection, trophoblast secrete C3a, C4a, and C5a [146, 147]. This regulation necessarily involves placental complement inhibitors, such as decay-accelerating factor (DAF) and membrane cofactor protein (MCP), that are expressed throughout gestation, protecting from preterm delivery among other adverse events [148, 149]. The opposite scenario appears when uncontrolled complement activation, -conditioned by gene polymorphism, (mainly in sperm genes) [150, 151], ethnicity, acquired mutations [152, 153], infections or presence of aPL [154, 155]-, determines disabling placental immune regulation, leading to abnormal pregnancy outcomes like RM, IUGR, or PE.

Preterm birth

Studies in mice models of preterm birth, reported high C5a deposits and macrophage releasing MMP, collagen degradation and increased cervical distensibility after an administration of low-dose intravaginal endotoxin. These observations were reverted after progesterone treatment. Activation of complement entail uterotonic properties that have been tested through C5a- C5aR interaction, leading to preterm birth [156]. By contrast, the labour at term is not mediated by inflammatory molecules and cells or complement activation, but by MMP and other active products released from cervical fibroblasts and columnar epithelial cells [157].

In addition to immaturity-related risks of preterm birth, both inflammatory and/or infectious insults that can occur during pregnancy have deleterious effects on the foetus. Several studies show a strong association between intrauterine inflammation or infection and the following complement hyperactivation, causing foetal and newborn brain abnormalities and neuronal injuries, respectively [158, 159]. Some illustrative studies in mice models demonstrated that the length of axons of cortical neurons of preterm mice exposed to C5a deposits was considerably reduced, compared with controls [160].

Preeclampsia

Pre-eclampsia is another obstetric disorder where complement activation appears to play an important

| Table 1 Hyperferritinemia-related disorders |
|------------------------------------------|
| Adult Still’s disease                     |
| Systemic lupus erythematosus              |
| Vasculitis                                |
| Lymphoma                                  |
| Catastrophic antiphospholipid syndrome    |
| Biological compound anti-CD28 treatment   |
| Haemophagocytic syndrome                  |
| Macrophage activation syndrome            |
| SARS-CoV-2 infection (COVID-19)           |

SARS-CoV-2 severe acute respiratory syndrome related to coronavirus-2
COVID-19 coronavirus disease 2019

*aCluster differentiation*
role. Despite an open discussion on the role of circulating complement levels to predict obstetric outcomes [161–164], complement component tissue deposits have been observed in embryo implantation sites of pre-eclamptic mice models, and in focal or diffuse staining patterns in the placenta of women with PE and IUGR [165–167]. The complement hyperactivation acts as a strong inflammatory insult, leading to functional deficiency of free vascular endothelial growth factor (VEGF) while increasing levels of soluble VEGF receptor 1 (sVEGFR-1, or sFlt-1), a strong anti-angiogenic molecule, enhancing organ underperfusion and defective placental development [168–170], which have been proved to be the origin of Preeclampsia [171–173]. A clear restoration of this essential angiogenic imbalance, (reducing sFlt-1 as well as increasing VEGF), has been observed after complement inhibition treatment [169, 174].

Preeclampsia is a disease characterized by increased levels of anti-angiogenic factors sensitive to hypoxia produced by the placenta to the detriment of angiogenic ones [172, 173, 175]. However, the diagnostic criteria is still based on clinical and laboratory data, and not includes these biochemical markers. Several disorders have previously proved to imitate PE from clinical and analytical point of view, including COVID-19 [176]. Recent studies have reported PE/HELLP facts in pregnant women with severe forms of COVID-19 despite showing a normal angiogenic status and placental perfusion [68, 71]. The role of the inflammatory pathways triggered by the virus should be investigated in these specific cases.

Recurrent miscarriage. Recurrent miscarriage in obstetric antiphospholipid syndrome In previous studies, up to 20% of miscarriages and fetal losses not mediated by autoantibodies were associated with hypocomplementemia [177]. According to the newest data, the main role of complement-mediated injuries in trophoblast and placenta causing embryo or foetal loss, is thought to be through aPL [154, 155, 178, 179]. Murine models have widely demonstrated the hyperactivation of complement in both pro-inflammatory and pro-thrombotic events involved in obstetric complications seen in OAPS [155, 179], where the main clinical outcomes are RM, foetal death, PE, premature births or IUGR [178, 180, 181]. Using human or animal aPL monoclonal antibodies, the increased foetal death and embryo resorption seen in transferred pregnant mice were attributed to hyperactivation of the classical complement pathway acting as key mediators of foetal injury. Complement activation (via C3a, C5a, and MAC) cooperates not only in triggering a local inflammatory process, but eventually, leading to placental thrombosis [141, 142, 180], through stimulus of the expression of tissue factor (TF) or CD142, a powerful activator of extrinsic clot cascade [179]. The usefulness of therapeutic molecules aimed to complement inactivation in human models reinforces the complement roles in many human obstetric immune-mediated diseases [182–184].

Complement pathway and its hypothesized role in COVID-19 pregnancies

Considering the endothelial injury as a hallmark of COVID-19, SARS-CoV-2 infection during pregnancy could induce or even aggravate complement activation, involving obstetric complications like RM or PE. As previously mentioned, microangiopathic syndromes, such as aHUS, TTP, acute fatty liver of pregnancy (AFLP) or CAPS, can complicate pregnancy. All these syndromes share common pathogenic mechanisms like vasospasm, platelet activation or destruction, microvascular thrombosis, endothelial cell dysfunction, and reduced tissue perfusion [176]. Some of them have been identified in severe COVID-19 cases. Therefore we can infer that, in the context of the SARS-CoV-2 pandemic, COVID-19 disease might be considered a potential cause of placental-related disorders, and even become part of the list of PE imitators [176], challenging physicians and specialists to be faced with difficult differential diagnosis see Table 2.

Role of ACE2 and RAS in COVID-19 pregnancies

Role of ACE2 in pregnancy

RAS has a major role in regulation of vascular tone and cardiovascular haemodynamics. RAS has two main metabolic axis from angiotensinogen to angiotensin I, showing opposite effects: ACE1/angiotensin II (AngII) axis, and ACE2/

| Table 2  | Preeclampsia imitators |
|----------|------------------------|
| HELLP syndrome | Acute fatty liver of pregnancy |
| Systemic lupus erythematosus with nephritis | Catastrophic antiphospholipid syndrome |
| Renal thrombotic microangiopathy related to aPL | Systemic vasculitis |
| Systemic sclerosis: renal crisis | Atypical hemolytic uremic syndrome |
| Thrombotic thrombocytopenic purpura | Sepsis |
| Disseminated viral diseases, i.e. herpes virus, CMV, SARS-CoV-2 | Drugs: gemcitabine; quinidine, cyclosporine A, thienopyridines |
| Others: necrotizing pancreatitis, pheochromocytoma, cocaine abuse, paroxysmal nocturnal hemoglobinuria |

aPL antiphospholipid antibodies, HELLP haemolysis, elevated liver enzymes, low platelet count, CMV cytomegalovirus, SARS-CoV-2 severe acute respiratory syndrome related to coronavirus-2
endothelial dysfunction, vascular reactivity, and angiogenic processes. Animal models have shown that Ang receptor type 1–AAs (AT1R-AAs) increase RAS activation, thus increasing inflammation and vasoconstriction. Autoantibodies like AT1R-AAs, that emulate AngII, autoimmune/alloimmune phenomena have been described in conditions of immune system dysregulation [199].

Peptides, particles, and RAS mRNAs of the ischaemic and nephrotic syndrome [185, 186]. A balanced RAS activation is one of the cornerstones of the haemodynamic regulation during pregnancy, while contributing to maintain a normal, or even decreased blood pressure, in a progressive increasing volaemia [187]. In normal pregnancy, estrogens induce a shift in metabolic pathways of angiotensin peptides in a tissue-specific manner. A physiological enhancement of ACE2 increases the expression of the vasodilator Ang (1–7) [188–190]; this effect counteracts the elevation of tissue and circulating Ang II levels leading to a vasoconstrictor effect, while amplifying a vasodilator component [191].

The vasodilator actions of Ang (1–7) have not only been reported in vascular beds of systemic maternal circulation, but in feto-maternal interface, thereby releasing nitric oxide, kinins, and prostaglandins [192]. Studies in both human and mouse models have demonstrated a wide and dynamic expression of RAS effectors in maternal–fetal interface. In early gestation, pro-renin receptor and the AngII type 1 receptor (AT1R) have been localized in extravillous trophoblast cells, suggesting a balancing role in trophoblast migration [192–194], while correlating with a high expression of VEGF [194]. These findings, along with the expression of ACE2 in syncytiotrophoblasts and Ang 1–7 releasing into the fetal–maternal vascular endothelium, targeting maternal, placental and foetal vessels in a dynamic process throughout pregnancy, suggest that the RAS regulation pathway to be likely important in both placental angiogenesis and maintained maternal vascular tone [194–196].

All RAS components, both systemic and tissue-based (renal and uteroplacental) are involved in hypertension-related disorders during pregnancy [197]. A dysregulation of systemic and renal RAS, results in cardiovascular dysfunction and electrolyte imbalance as well as variable PE syndrome showing hypertension, oedema and proteinuria [197, 198]. In abnormal placentation, the situation is aggravated due to the hypersecretion of RAS proteins/angiotensin (Ang) peptides, particles, and RAS mRNAs of the ischaemic and underperfused placenta [196, 197]. In addition, an underlying autoimmune/alloimmune phenomena have been described through autoantibodies like AT1R-AAs, that emulate AngII actions, thus increasing inflammation and vasoconstriction [199]. Animal models have shown that AT1R-AAs increase sensitivity to AngII and are able to activate complement C3aR pathways that release antiangiogenic factors, such as sFlt-1 [174, 199] that increase placental oxidative stress, endothelial dysfunction, vascular reactivity, and angiogenic imbalance. All these phenomena are the primary mechanisms in placental related diseases, like early and severe PE, and IUGR [173, 200]. RAS peptides and AT1R-AAs were only seen if clinical PE was present (late-onset hypertension and proteinuria), but not in early stages of the disease, suggesting a later-clinical role of RAS imbalance, rather than an early-genesis role of PE [201].

Hypothesized role of ACE2 and RAS in COVID-19 pregnancies

Differences in ACE2 expression could correlate with a different susceptibility to SARS-CoV-1 infection [202], and therefore, to SARS-CoV-2 displaying COVID-19 in different forms of severity. The expression levels of ACE2/TMPRSS2 among fetal-maternal interface, may vary among pregnancy forms [203]. SARS-CoV-2 could trigger RAS dysfunctions when ACE2 binds during pregnancy, causing variable organ injuries [204–207] -as seen in other adult patients- as well as in placenta, due to systemic haemodynamic disturbances. This occurs not only in the mother, but also in the fetus [165], since ACE2 is expressed in fetal endothelial cells and fetal organs too. ACE2 is present in the fetal heart, liver and lungs, but not in the kidneys. This fact could explain the observation that SARS-CoV-2 is not excreted in urine, and thus, unable to detect viral RNA in amniotic fluid [54, 208].

SARS-CoV-2 induced downregulation and shedding of ACE2 reducing Ang 1–7, could have a non-despicable role in some trophoblast/placental or haemodynamic-related obstetric complications such as miscarriage or PE, respectively. While some studies reported a higher incidence of miscarriage and PE among COVID-19 pregnant women compared to the general population [54, 64, 209], others concluded that there is not an increased risk of obstetric complications [173, 200]. Generally, on the basis of current data, many authors argue with weak evidence of a causal association between SARS-CoV-2 infection and obstetric complications, stating that further investigations are needed. Hypertension, kidney disease, thrombocytopenia or liver injury are frequently seen in moderate to severe COVID19 cases [205, 206, 210, 211]. If they occur during pregnancy, patients could fulfill complete or incomplete clinical and/or laboratory PE or HELLP syndrome criteria [71]. To make a true diagnosis, deeper investigation should be executed, and thus, an appropriate care management [71, 200, 212, 213].
Role of natriuretic peptides B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP)

Role of NT-proBNP in COVID-19

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are natural inhibitors of RAS and the sympathetic nervous system (SNS). The main, but not only source of BNP, is ventricular myocardium. BNP is synthesized as a prohormone (proBNP) cleaved in circulation into the active BNP, and the inactive NT-proBNP [214]. The main stimulus for increased BNP and NT-proBNP is myocardial wall stress, as a result of an adaptive mechanism to cardiac walls elongation after variations of haemodynamic parameters, to prevent cardiac insufficiency. The physiological effects of BNP are manifold and comprise natriuresis/ diuresis and induce peripheral vasodilatation. NT-proBNP has a greater half-life with higher serum values, and thus, becomes a better marker for any relevant cardiac overload in chronic heart failure. Between 8–28% of COVID-19 patients show evidence of cardiac injury with elevated troponin and natriuretic peptides [204, 215]. Some data support NT-proBNP as an independent risk factor for in-hospital death in patients with severe COVID-19 disease [216]. The predictive value of increased BNP and NT-proBNP in plasma was already recognized as cardiovascular endpoints in patients and all-cause death in the general population [217].

NT-proBNP in pregnancy and in COVID-19 pregnancies

Corin, the type II transmembrane serine protease enzyme that is in charge of cleaving with proBNP in BNP and NT-proBNP, has been expressed mainly in the heart and in the pregnant uterus [218]. In mice models, both delayed trophoblast invasion and impaired spiral artery remodeling, as well as high blood pressure and proteinuria, were found in pregnant rats lacking corin. There is an association of NT-proBNP levels with RAS component levels in pregnant women [219]. Some studies have focused on the increased circulating levels of natriuretic peptides in pregnant women suffering from PE, mainly in its early and severe form [219–221]. PE involves a failure of the maternal cardiovascular system to adapt to the demands of pregnancy, therefore a cardiac origin of NT-proBNP was first attributed. Considering that PE is mainly a placental mediated disease, in which an inflamed and underperfused placenta release diverse antiangiogenic factors into the maternal circulation (sFlt1, soluble Endoglin (sENG)) [173, 200], the hypothesis of a partial placental origin of the elevated levels of BNP/NT-proBNP was first suspected, and further confirmed, when NT-proBNP protein was observed in maternal spiral arteries and in syncyiotrophoblasts, in preeclamptic placent al samples [222]. Interestingly, some antiangiogenic factors present in women with PE have also been observed in non-pregnant women suffering from myocardial diseases [175]. Many authors, therefore, have studied the potential cardiovascular strain of PE, and its repercussion in cardiovascular morbidity and mortality in later life [223, 224]. The potential use of natriuretic peptides such as NT-proBNP in the assessment of hypertensive pregnancy disorders, is due to cardiovascular alterations that have been considered to have a non-despicable role in their physiopathology. As PE is mainly an angiogenic inflammatory disorder, current evidence supports that NT-proBNP could be useful to assess a cardiovascular strain but, on contrary to antiangiogenic factors (sFlt1, sENG), does not seem to improve the diagnostic of PE [225]. Data from severe COVID-19 patients show that increased levels of NT-proBNP could be related to cardiac and renal injury, and systemic inflammation [175]. The significance of increased levels of NT-proBNP in COVID-19 pregnant patients has not yet been evaluated. Given that, higher NT-proBNP levels should be outlined in pregnant women, mainly in those affected with moderate-severe COVID-19, showing PE or PE like syndrome, to establish their role as a current cardiac stress marker, or even as a marker for the risk of cardiovascular repercussion later in life.

Final remarks

The global strike of the COVID-19 pandemic has challenged the scientific community with a struggle to understand the complexity of its pathophysiological mechanisms. The whole population is susceptible to sicken. Pregnant women, however, deserve particular attention. Severe COVID-19 is mainly an immune-mediated disorder triggered by the SARS-CoV-2 infection that, in context of pregnancy could bring about several complications. Not only those related to lung and multiorgan damage, but also placental injury, mainly due to an excessive hyperinflammation and, frequently, hypercoagulation owing to thrombosis. Immune-thrombosis contains a wide spectrum of pathological mechanisms that have been proven to be involved in the aetiology of many placental-related disorders such as RM, PE, IUGR or preterm birth. Pathogenetic mechanisms of pregnancy complications such as complement activation, release of pro-inflammatory cytokines, antigen–antibody abnormal responses, prothrombotic phenomena or endothelial-vascular dysregulation are similar to those involved in immune-mediated severe forms of COVID-19. Given that SARS-CoV-2 has come to stay, obstetricians and immunologists, as well as all medical specialists, should be encouraged to keep collecting disease outcomes in the context of pregnancy, to elucidate the potential harmful responses to SARS-CoV-2.
and/or other coronavirus infections, as well as research on actual bidirectional interactions between COVID-19 and pregnancy, that can interfere with their respective outcomes.

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Declarations

Conflict of interest Raquel Ferrer-Oliveras declares that she has no conflict of interest. Manel Mendoza declares that he has no conflict of interest. Sira Capote declares that she has no conflict of interest. Jaume Alijotas-Reig: manuscript writing and editing, critical revision of the final content. All authors have approved the final version of the manuscript.

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