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COVID-19 and pregnancy: Lessons from 2020^{☆,☆☆}

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ABSTRACT

The outbreak and spread of the coronavirus disease 2019 pandemic has led to an unprecedented wealth of literature on the impact of human coronaviruses on pregnancy. The number of case studies and publications alone are several orders of magnitude larger than those published in all previous human coronavirus outbreaks combined, enabling robust conclusions to be drawn from observations for the first time. However, the importance of learning from previous human coronavirus outbreaks cannot be understated. In this narrative review, we describe what we consider to be the major learning points arising from the SARS-CoV-2 pandemic in relation to pregnancy, and where these confound what might have been expected from previous coronavirus outbreaks.

1. Background

The risk posed by viral pneumonia to pregnant populations in particular has been recognised as early as the 1957 coronavirus pandemic and the H1N1 2009 influenza pandemic [1,2]. Human coronaviruses (HCoV) have generally been considered to lead to mild illness, however the first two decades of the 21st century have proved this assumption wrong. The characteristics of each HCoV outbreak: namely their scale and the general case fatality ratio (CFR), have largely determined the extent to which the impact on pregnancy was studied. The severe acute respiratory syndrome coronavirus 1 virus (SARS-CoV-1) is the most closely related microorganism to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3] and was the first 21st century HCoV epidemic, initially identified in February 2003 in China [4], with a CFR of around 10% in people aged <60 [5]. The Middle East respiratory syndrome coronavirus (MERS-CoV) was first reported in Saudi Arabia in 2012 [6] with a CFR of 33% [7]. MERS has therefore only been reported in few nations, particularly in the Arabian Peninsula with more recent outbreaks occurring in other countries (mainly Korea in 2015) [6].

SARS-CoV-2 infection or coronavirus disease 2019 (COVID-19) was first diagnosed in China in November 2019 and declared a pandemic on March 11th, 2020 [8]. Analysis of data from early cases showed the average time for a person to infect the next to be shorter than the incubation period (up to 14 days on SARS-CoV-2 compared to 7 and 6 days for SARS-CoV-1 and MERS-CoV, respectively) and that infection could occur from asymptomatic individuals. These characteristics resulted in an infected population that has been hard to assess, requiring large-scale prospective sampling and screening and enabled the SARS-CoV-2 epidemic to develop into a pandemic very quickly compared to previous HCoV epidemics [9].

2. Pregnancy, HCoV and maternal risks; what we have learnt from the 2020 pandemic

It is reported that 66–88% of pregnant patients infected by SARS-CoV-2 are asymptomatic, similarly to the general population [10–13], and most pregnant women who do have overt clinical manifestations only have mild cold or flu-like symptoms [14]. This quickly highlighted the importance of triage tools and SARS-CoV-2 screening on hospital

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admission. However, most available studies only consider symptomatic pregnant patients with serologic/reverse transcription-PCR (RT-PCR) evidence of infection, and control groups of asymptomatic patients are often not available to study. This is a significant limitation to many of the studies conducted in the first months of the pandemic.

At the start of the pandemic, information on pregnancy and perinatal outcomes in coronaviruses (SARS-CoV-1 and MERS) was scarce. The biggest case series on MERS-CoV in pregnancy was a study from Saudi Arabia published in 2016 with 5 cases of pregnant women affected by MERS [15,16]. For SARS-CoV-1, the numbers were slightly higher for a total of 20 pregnancies [16]. This state of affairs has been reversed for SARS-CoV-2, case rates and the previous knowledge of the harmful effects of HCoV on maternal outcomes leading to an exponential increase in the number of publications treating COVID-19 in pregnancy.

2.1. HCoV and changes during pregnancy

During pregnancy, respiratory and cardiovascular function, production of coagulation factors and immunological competence undergo changes that may alter HCoV maternal disease progression, as extensively studied during the 2020 SARS-CoV-2 pandemic [17]. The immune system changes during pregnancy to allow for the growth of a semi-allogenic fetus. There is a shift in CD4+ T cells towards Th2 phenotype, a decrease in natural killer (NK) cells, a decrease in circulating plasmacytoid dendritic cells (pDCs), an increase in progesterone levels and modifications of the innate immune system [17].

It is well known that HCoVs are mainly transmitted by droplet, airborne and fomite transmission [18] and infect pneumocytes through the angiotensin-converting enzyme 2 (ACE2) receptor. These mechanisms have been studied in greater detail with SARS-CoV-2. A protease (transmembrane serine protease 2, TMPRSS2) aids with host cell entry. The virus causes pyroptosis of the host cell and an inflammatory response which varies in intensity among individuals, potentially culminating in multisystem organ failure [17]. In fact, that the life-threatening clinical consequences of the infection are a reflection of the activity of the host's cytokine storm response rather than damage exerted by the microorganism itself became apparent in the first few months of the pandemic [19], and it is perhaps not surprising therefore that dexamethasone has been found to be an effective treatment for COVID-19 disease [20]. Prednisolone is the preferred choice in pregnant women, due to its limited transplacental transfer, thus avoiding the effects on the fetus of repeated high dose steroids [21]. The question of how much tropism coronaviruses have for cells other than pneumocytes is still open; in MERS-CoV cases as opposed to SARS CoV-1, severe renal damage was diagnosed in more than 50% of cases after the incubation period [22,23], leading to the suggestion of a new target site in the renal tissue. The presence of ACE2 and TPRSS2 on trophoblast cells was also investigated during the first months of the 2020 pandemic [24–26].

Pregnant patients are more vulnerable to pulmonary infections as there is a physiological elevation of the diaphragm; the end-expiratory abdominal pressure rises, increasing the negative pressure within the pleural cavities that keeps the alveoli from collapsing. There is a partial closure of the smaller airways, a reduction of functional residual capacity, a decrease of the expiratory reserve volume and therefore, ultimately, an increased susceptibility to pulmonary infections [27]. Patients manifesting more severe coronavirus symptoms are subject to the development of pulmonary damage after pulmonary infection resulting in a clinical picture known as acute respiratory distress syndrome (ARDS). The causal trigger is the pulmonary endothelial cell dysfunction that follows pneumocyte damage. It is still unclear if the peripheral vasodilation that physiologically occurs during pregnancy has any role in ARDS development [17].

In addition to respiratory modifications, the coagulation status of pregnant patients is swayed towards hypercoagulability; patients affected by SARS-CoV-2, are known to be more exposed to thromboembolic complications than the general population and guidelines

recommend anticoagulation for all hospitalised SARS-CoV-2 positive patients [11]. Although no reports on thrombotic events in pregnancies complicated by SARS-CoV-1 or MERS-CoV are available, they have been reported in the general population [28]. From a pregnancy management point of view, current guidelines recommend thromboprophylaxis for all pregnant women admitted to hospital with confirmed or suspected SARS-CoV-2 infection (provided the patient does not have thrombocytopenia) and a low threshold for investigating potential thromboembolic complications [11].

2.2. Risk factors for poor maternal outcomes in SARS-CoV-2 positive patients: relationship between ethnicity and maternal outcomes

The first UK Obstetric Surveillance System (UKOSS) report investigated the characteristics of hospitalised women during the first months of the pandemic [14]. Over half were “black or other minority ethnic group”, and this was also confirmed in a systematic review of international papers [29], establishing the greater risk of hospitalization for this population. Of note, we cannot compare this finding with what previously learnt from the other HCoV as these affected mainly patients from Asian and Middle Eastern geographical regions.

2.3. Other risk factor for adverse maternal outcomes

Other noticeable risk factors to consider when managing pregnancies complicated by COVID-19 are those that lead to a baseline increase in endothelial dysfunction, such as obesity, hypertension and diabetes. Vitamin D deficiency has been thought to play a role in progression in disease progression, although its supplementation in SARS-CoV-2 positive pregnant patients is not based on robust evidence [14].

2.4. HCoV maternal manifestations

As expected, given the tropism HCoV have for pneumocytes, a strong association between HCoV infection and **pneumonia** has been recorded in the literature (up to 88.9% in SARS-CoV-1 and 71.4% in MERS-CoV) [30]. Although the correlation initially appeared to be less pronounced for SARS-CoV-2 infections in a UK national population cohort study (24% of hospitalised women with confirmed SARS-CoV-2 infection [14]), the strength of the association was found to increase to up to 89% in a systematic review of hospitalised patients [31]. MERS-CoV may also present with pleural effusion (33–50% of cases) [22] in contrast to SARS-CoV 1 and 2, where this is rarely reported [30].

While **fever, cough and fatigue** are generally common in HCoV pregnant patients, ranging from 50 to 78% in MERS-CoV to 80–97% in SARS-CoV-1 [30], the incidence is lower in SARS-CoV-2. In a UK population of non-hospitalised pregnant patients with confirmed infection from the PAN-COVID registry [32], 38.4% had a fever, 37.2% had a cough and 14% reported fatigue. Similarly, the prevalence of **dyspnea** was reported being 50% for MERS and up to 90% in SARS-CoV-1, but only in 22.1% of SARS-CoV-2 infected patients, while **myalgia** was reported in 37.5% of MERS affected pregnant patients and up to 72.7% of SARS patients compared to 9.7% of SARS-CoV-2 patients [30].

Pregnancy induced hypertension (PIH) and pre-eclampsia (PET) are characterised by underlying endothelial cell dysfunction, similar to the effect SARS-CoV-2 mainly has on the pulmonary endothelium. As a result, pregnancies complicated by pre-eclampsia could be expected to be at increased risk for HCoV related complications (and vice versa) [30]. In reality, the incidence of PIH and PET in pregnancies complicated by a COVID-19 diagnosis remains unelucidated, as the PANCOVID [32] data showed no excess in PIH and PET compared to historic norms while a prospective international cohort study (INTERCOVID Multinational Cohort Study) found an increased relative risk (1.76, CI 1.27 to 2.43) for PET compared to general pregnant population [33], as did a UK based national cohort study [34].

Furthermore, we know that COVID-19 related morbidity is higher in

Table 1
Prevalence of laboratory findings in HCoV in pregnancy.

	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Leukocytosis	41.7% [30]	2% ^a [45]	28.4–41% [30]
Leukopenia	58.3% [30]	6% ^a [45]	12.6% ^a [46]
Lymphocytosis	12.5% [30]	0% ^a [45]	11.4% [30]
Lymphocytopenia	83.3% [30]	100% [30] (1 case)	49.8–63% [47]
Increased LDH	70% ^a [48]	8% ^a [45]	34.8% [30]
Increased AST	25% [30]	33.3% [30]	16.7% - 48.8% [29,30]
Increased ALT	25% [30]	33.3% [30]	18.8% - 48.8% [29,30]
Increased C-reactive protein	100% [30]	100% [30]	54–57% [29,30,47]
Thrombocytopenia	44.8% ^a [28,49]	36% ^a [49]	62.9% [29]
Increased D-dimer	45% ^a [28,49]	Not available	46.4% [50,51]

(ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH lactate dehydrogenase.)

^a Data from non-pregnant patients.

pregnant patients with other risk factors for endothelial dysfunction such as raised body mass index (BMI) and pre-existing cardiac disease [14]. Whilst one woman out of 8 with MERS-CoV infection (12.5%, CI 0–53.6) developed pre-eclampsia, there were no cases with this complication in two SARS-CoV-1 infected patients reported [30]. Interestingly, fetal consequences of placental dysfunction such as intrauterine fetal growth restriction (IUGR) or small for gestational age (SGA) fetuses appear not to be increased in pregnancies complicated by SARS-CoV-2 infections [32,33], despite reports of this in the earlier stages of the pandemic [35]. There is also some suggestion that ACE2 might be expressed both by the trophoblasts and the inflammatory cells that infiltrate the placenta [36,37].

Maternal mortality appears to be less likely in SARS-CoV-2 compared to other coronaviruses; as the pandemic unfolded, it became clear that mortality during pregnancy was higher compared to non-pregnant patients [29]. Pooled percentages for maternal mortality in SARS-CoV-1 and MERS-CoV were high at 12.5% (3.3–32.9) and 40% (12.5–74.3), respectively [30]. In a systematic review from May 2020, the maternal mortality in patients with confirmed SARS-CoV-2 infection with RT-PCR was around 1% compared to a general infection fatality ratio (IFR) of 0.03% (CI 0.03–0.04) in adults aged 15–44 [38]; however, in a report on national SARS-CoV-2 registries in the UK and US (PAN-COVID and AAP-SONPM, respectively) [32] that included non-hospitalised patients the maternal mortality rate was 0.2–0.5%. This data supports the higher susceptibility of pregnant women to SARS-CoV-2 related mortality. However, the authors of this report concluded that given routine RT-PCR testing was not available at the time of recruitment, in reality the mortality rate was likely 10 fold less than reported (which is then similar in magnitude to the aforementioned general IFR [38]). Similarly, ICU admissions and need for mechanical ventilation were higher for other HCoV; nonetheless, ventilation and extracorporeal membrane oxygenation were indeed required respectively in 3% and 0.2% of SARS-CoV2 positive pregnant patients [39].

Pre-term birth (PTB) is an important concern as it appears to occur more frequently in HCoV infected patients; the pooled proportion of deliveries before 34 weeks is 33.3% (CI 14.2–38.9) in MERS-CoV and 12% (CI 3.6–31.5) in SARS-CoV-1 [30]. The PAN-COVID data shows that 16% of SARS-CoV-2 positive patients deliver preterm (before 37 weeks), which is a 60% increase compared to expected office for national statistics (ONS) data [32]; 83–94% of preterm births in SARS-CoV-2 positive patients are reported as iatrogenic [33,39] mainly due to the need of expediting delivery for maternal respiratory compromise. Whether some form of placental inflammation (potentially ACE2 expressing granulocytes [36]) is implicated in the pathophysiology underlying pre-term

labour however remains an open question. Delivery at earlier gestational ages, along with maternal respiratory compromise, also may in part explain the relatively high proportion of caesarean section deliveries in SARS-CoV-2 positive patients (47.9% in the UK PAN-COVID registry, up to 85% in other meta-analyses [31]).

2.5. Maternal laboratory findings

There is little information on laboratory findings in SARS-CoV-1 and MERS-CoV during pregnancy, while increasing data is being published with regard to SARS-CoV-2 (Table 1). Test results are generally unspecific however the most reported findings are lymphocytopenia, raised C reactive protein and raised liver function tests [29,30] although there is some discordance in the literature on the prevalence of hypertransaminasemia in COVID-19 during pregnancy [40,41].

Leukocytosis is more common in pregnant patients infected by SARS-CoV-2 compared to the general infected population, but white blood cell count does not differ between infected and non-infected pregnant patients [42]. Another known observation is that in pregnant patients, D-dimer levels are physiologically higher than in the general population. The International Society of Thrombosis and Hemostasis' recommendation to admit those with a significant D-dimer increase should be therefore reviewed in the context of each specific pregnancy case [43,44].

2.6. Fetal risks and neonatal outcome

Neonatal outcome post SARS-CoV-2 infection is generally favourable, with stillbirth numbers similar to those of the non-affected population (0.2%) [32], although there are reports of stillbirth rates being higher than expected at the height of the SARS-CoV-2 pandemic in spring 2020 [50] that are yet to be confirmed by larger studies [11]. A systematic review from May 2020 reported that no HCoV studies (including the few available cases of SARS-CoV-1 and MERS-CoV infection) stated evidence of vertical transmission [45], although the highest rates of neonatal admission and perinatal death were reported after MERS-CoV infection [30]. Vertical transmission (unclear mechanism to date) in SARS-CoV-2 is low, with positive neonatal tests present in 2% of neonates born from mothers with confirmed infection in the UK (PAN-COVID) [32] registry. This was similar to the proportion of neonatal positivity in the AAP-SONPM and is also in keeping with other observational studies [46]. SARS-CoV-2 neonates are largely asymptomatic or have self-limiting symptoms; the prevalence of poor fetal/neonatal outcomes, in fact, is very low and is probably not the result of direct CoV infection, but rather a reflection of maternal health and preterm delivery [30,45]. SARS-CoV-2 related NICU admissions in neonates was reported to be around 2% in a meta-analysis from July 2020, however, in this population the mean gestational age at delivery was 38.0 (37.6–38.4) weeks. The mode of viral transmission is still unclear, and can be hypothesised to occur in utero, during labour, through the birth canal or post-partum from contact with the positive mother or other positive hospital staff. To date, there are no contraindications to breastfeeding, skin-to-skin and delayed cord clamping provided the mother wears adequate personal protective equipment (PPEs) [11].

It would also appear that HCoV infections are associated higher rates of miscarriage compared to those of the general population [30,45]. However, no study has been able to reliably assess this for SARS-CoV-2.

2.7. Shielding and avoiding contact for women in pregnancy

In March 2020 the Royal College of Obstetricians and Gynaecologists (RCOG) published the first version of the guideline on SARS-CoV-2 in pregnancy. The main recommendations were to implement service modifications to patient care aiming to reduce the spread of SARS-CoV-2: using teleconferencing and videoconferencing, shielding pregnant patients (avoiding communal waiting areas, attending hospital in

isolated single rooms) and coordinating remote/on-site care for SARS-CoV-2 positive patients. Additionally, the RCOG recommended keeping neonates with mothers with SARS-CoV-2 infection, in contrast to the separation recommended in Chinese, Centre for Disease Control (CDC) and International Society for Ultrasound in Obstetrics and Gynaecology (ISUOG) [47] guidance at the time. Modifications to standard care were substantial and the effect on quality of maternity care is still to be fully determined [48]. Black, Asian and minority ethnic women were encouraged to have a lower threshold for seeking medical care throughout the pandemic [11].

However, when observing the reports from the intensive care national audit and research centre (ICNARC) it is interesting to note that despite these recommendations there were two subsequent higher peaks in the number of pregnant patients admitted to critical care with confirmed SARS-CoV-2 infection; in January 2021 and in July 2021 [49]. These reflect the pattern of SARS-CoV-2 positivity in the general population.

Despite JAMA publishing a study showing an unusual increase in stillbirth rate in a single UK hospital early in the 2020 pandemic [50], this risk was not borne out by a much larger study using NHS Hospital Episode Statistics (HES) for England April–June 2020 [51]. Nevertheless a concern remains about a reluctance of women to attend hospital, and obstetric staff therefore reassured and encouraged patients to seek hospital care if they had concerns for their baby [11].

We believe that although it is hard to achieve a correct balance between avoiding unnecessary hospital attendance and receiving high quality healthcare, it should be clear to women that all services in hospital are made as safe as possible by the staff and that if they have concerns about their pregnancy, these should be addressed in a timely way. Furthermore, it is safer to discuss delicate matters such as domestic violence, anxiety, and psychiatric disorders face to face rather than on a telephone call. However, routine consultations in patients classified as having a “low risk” pregnancy can be addressed virtually in order to reduce the risk of SARS-CoV-2 transmission both for healthcare workers (HCW) and patients. Moreover, given the current easing of lockdown restrictions, we would underline the importance of recommending the influenza vaccine during pregnancy as per national guidelines to avoid infection or co-infection.

3. Vaccines

Before being faced with the new COVID-19 challenge, researchers had already made some progress in investigating how to engineer vaccines for SARS-CoV-1 and MERS-CoV [52]. As a general rule during pregnancy, live attenuated vaccines like measles-mumps-rubella (MMR) are contraindicated due to the small chance of an attenuated live virus causing viremia, even though the available evidence on the outcomes of live vaccines inadvertently given during pregnancy does not reveal any major concerns [53]. The inactivated form of flu vaccination is highly recommended during pregnancy and is routinely offered to all pregnant patients during flu season.

When the SARS-CoV-2 pandemic broke out, various immunization strategies had already been explored for the other HCoV, and the propulsive financial and political forces generated by the pandemic quickly led to the development of successful messenger RNA (mRNA vaccines) and DNA viral vector vaccines. For vaccination during pregnancy, precious information came from the “v-safe pregnancy surveillance”, a US smartphone based active vaccine surveillance program that collected information regarding pregnancy status at the time of vaccination. Pregnant patients were initially excluded from pre-emergency use authorisation, however, given the very high proportion of female healthcare workforce, from December 2020 female HCW were offered vaccination, in view of pregnancy being a high-risk condition [54,55]. The “v-safe” project’s objective was to rapidly provide information on the safety of these vaccines in pregnancy [56].

It rapidly became clear that SARS-CoV-2 vaccines did not appear to

Table 2
Relevant differences for different HCoV during pregnancy.

	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Incubation period (days) [5]	2–7	5–6	7–14
Asymptomatic patients	2.3% [72]	12.5% [73]	66–88%
Ethnicities at greater risk of morbidity and mortality	Unknown – outbreaks mainly in Asia	Unknown - outbreaks mainly in Asia	Black or other ethnic minority ethnicity, [14]
Pre-existing morbidities that confer greater risk of morbidity and mortality	Older age, diabetes [74]	Male gender, older age, diabetes mellitus, heart disease, smoking [75]	Diabetes mellitus, gestational diabetes, obesity, hypertension, older age, male gender
Vaccines	Inactivated virus/DNA vaccine (all phase 1 trials) [76]	DNA vaccines/viral vector vaccines (all phase 1 trials) [76]	mRNA vaccine, DNA viral vector vaccine

cause harm to the fetus, and a new Centre for Disease Control (CDC) analysis published on August 9th 2021 [57] declared mRNA vaccines during pregnancy as being safe, in keeping with what was previously known with regard to recombinant or inactivated vaccines during pregnancy. DNA-containing viral vector vaccines were cited in an independent report by the UK government and current advice is that individuals younger than 40 years should be offered mRNA vaccines, given the evidence of an association between DNA containing viral vector vaccines and serious thrombosis in the context of thrombocytopenia [58]. The rates of other maternal and fetal outcomes after mRNA vaccine administration during pregnancy (miscarriage, PTB, SGA and major congenital anomalies) were similar to those of the general pregnant population [59].

The concern often cited on social media about immunization and its relationship to affecting fertility are difficult to explain as no vaccine has to our knowledge ever been shown to affect fertility. There is evidence that there was distrust in respect of mass vaccination programmes from the 1970s onwards in Africa leading to vaccine hesitancy [60] as vaccines were rumoured to represent a form of reproductive health control. This was most clearly brought into focus with the beliefs of parents at the onset of HPV vaccination among girls of African origin in the UK [61].

4. Neonatal immunity

Initial studies on the presence of SARS-CoV-2 antibodies in neonates born from infected mothers indicated some form of transplacental immunity but more clear evidence was lacking, and investigations on the latter post vaccine were necessary. A recent study questioned the efficiency of transplacental transfer of vaccine-induced antibodies and found that the neonatal humoral immunity generated in vaccine recipients was significantly higher than that in neonates of infected patients [62]. Boosting the maternal humoral immunity with vaccination during pregnancy for efficient neonatal passive immunity should therefore be recommended in pregnant patients with a history of SARS-CoV-2 infection even though - as previously discussed - the neonatal immune system can handle SARS-CoV-2 infection effectively [63,64], with most of the neonates testing positive on RT-PCR being asymptomatic or experiencing a very mild form of disease.

In conclusion, as reported in Table 2, our knowledge on HCoV during pregnancy has exponentially increased compared to before the SARS-CoV-2 2020 pandemic. Given the continuous evolution of the virus and the recent introduction of the mRNA vaccine for pregnant women, it is important to keep reporting pregnancy outcomes to optimally manage and counsel pregnant patients regarding SARS-CoV-2 infection.

Declaration of competing interest

None to declare.

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