Full length article

Severe acute respiratory syndrome (SARS) coronavirus-2 infection (COVID-19) in pregnancy – An overview

Wafaa Ali Belail Hammad [a], Mariam Al Beloushi [b], Badreleden Ahmed [c], Justin C. Konje [d,*]

[a] Department of Obstetrics and Gynaecology Basildon and Thurrock University Hospitals NHS Foundation Trust Nethermayne, Basildon Essex SS16 5NL, United Kingdom
[b] Women's Wellness Research Center, Hamad Medical Corporation, Doha, Qatar and Department of Obstetrics and Gynaecology, Qatar University, Doha Qata and Weil Cornell Medicine, Qatar
[c] Feto-Maternal Medicine Center, Doha Qatar and Department of Obstetrics and Gynaecology, Qatar University Doha Qata and Weil Cornell Medicine, Qatar
[d] Department of Health Sciences, University of Leicester, Leicester, UK

A R T I C L E   I N F O

A B S T R A C T

The novel severe acute respiratory syndrome (SARS) coronavirus-2 which causes COVID-19 disease results in severe morbidity and mortality especially in vulnerable groups. Pregnancy by virtue of its physiological and anatomical adaptations increases the risk of severe infections especially those of the respiratory tract. This single stranded RNA virus is transmitted by droplets as well as soiled fomites. There are various degrees of disease severity– asymptomatic, mild, moderate severe and critical. Most infections in pregnancy are asymptomatic or mildly symptomatic. For these women, the consequences on the mother or pregnancy are minimal unless they have additional risk factors such as diabetes, hypertension, cardiorespiratory disease, obesity or are of ethnic minority background. Most women with symptoms will present with fever, unproductive cough, sore throat, myalgia, nasal congestion, loss of smell and taste with associated leukocytosis and lymphopenia. Diagnosis is by RT-PCR on nasopharyngeal flocked swabs or saliva and pathognomonic features of ground-glass appearance and pulmonary infiltrates on chest X-ray or CT scans. Management in pregnancy is same as that for non-pregnant women with COVID-19. It is not an indication for elective delivery but assisted delivery in the second stage for those with moderate, severe or critical disease may be required to shorten this stage. COVID-19 is not an indication for interrupting pregnancy or caesarean section but the latter may be performed to facilitate ventilation support or resuscitation in those with severe disease. Pain relief in labour should not be different but regional analgesia is preferred for operative deliveries. Postpartum thromboprophylaxis should be considered and breast feeding encouraged with appropriate precautions to minimize vertical transmission. Pregnant and lactating women should be encouraged to receive the mRNA based vaccines as there is no evidence of adverse outcomes with these.

© 2021 Published by Elsevier B.V.

Introduction

The 2019 novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported in Wuhan, China, in December 2019 and declared a pandemic by the WHO on 23rd March 2020 [1] has infected over 179 million people and killed over 3.8 million worldwide according to the latest update from Johns Hopkins Coronavirus Resource Center [2]. The virus has spread rapidly and almost every country in the world has been affected. The disease caused by SARS-CoV-2 is known as COVID-19.

SARS-CoV-2 is a positive-sense single-stranded RNA virus of the species "severe acute respiratory syndrome-related coronavirus"

and is believed to have emerged from a bat-borne virus due to its close genetic similarity to bat coronaviruses [3–6].

COVID-19 is a multi-systemic disease with a widespread clinical spectrum – most people infected with the virus are asymptomatic but those with symptoms may manifest with mild, moderate, severe, or critical disease with a small proportion dying from the infection.

The number of people infected with SARS-CoV-2 worldwide continues to increase, although there is the expectation that widespread immunization will soon result in a steady decline. Pregnant women are at risk of this virus just as other members of the population, but they are a unique group. Altered physiology with associated mechanical changes that occur in pregnancy increase maternal susceptibility to infections. A change in the maternal immune system to prevent rejection of the semiallogenic fetus

* Corresponding author.
  E-mail address: jck4@leicester.ac.uk (J.C. Konje).

results in a state of relative immunosuppression. Several factors are responsible for this including, a shift from a cell-mediated type-1 helper to hormone-mediated type-2 helper cell response, which is more anti-inflammatory in nature, promoting the release of anti-inflammatory cytokines with concomitant suppression of the production of inflammatory cytokines and a decrease in CD4+ and CD8+ T cells – all thought to be mediated through increasing oestrogens and cortisol levels [7]. These physiological and anatomical changes predispose the mother to more severe infections that would otherwise have a mild course and furthermore have the potential to infect and cause complications in the fetus.

As our understanding of the SARS-CoV-2 and the pathogenesis of COVID-19 evolves, clinicians are undoubtedly getting better at managing the infection as well as preventing it. In this update we present a summary of our current understanding of COVID-19 in pregnancy and its management.

Pathogenesis of COVID-19

The severe acute respiratory syndrome coronoavirus-2 (SARS-CoV-2) is a novel enveloped ribonucleic acid (RNA) betacoronavirus belonging to the subfamily *Coronavirinae* in the *Coronoviridae* family. This family of viruses have a large RNA genome and therefore a propensity for genetic variation [8–10]. Within this family of viruses are four genera – *Alphacoronoavirus, Betacoronavirus, Gammacoronavirus* and *Deltacoronavirus* [11]. Other members of the family that have caused infections in humans with varying severity include the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses have four structural proteins (Fig. 1) namely spike (S) [that gives them the crown appearance from which corona is derived], membrane (M), envelop (E) and nucleocapsid (NC). The S protein is responsible for binding the virus to the host cell [12]. SARS-CoV-2 has an 80% genetic sequence similarity to that of SARS-CoV-1 and a 96.2% similarity to that of the bat coronavirus RaTG13 [13]. SARS-CoV-2 has a higher reproductive number (Ro) than SARS-CoV-1, implying that it spreads more efficiently [14].

Following exposure to SARS-CoV-2, the virus infects the hosts cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor – a membrane-bound aminopeptidase (functioning as the putative receptor). These receptors are expressed predominantly in type 2 alveolar cells of the lungs and also in several extra-pulmonary sites such as the mucosa of the oral cavity, the nasal and respiratory tract, cardiovascular and digestive systems making these susceptible to the virus [15,16]. Interestingly, these receptors have been suggested but not proven to express sexual dimorphism with cellular studies only revealing attenuation in females [17] a plausible explanation for the overall more severe morbidity and higher mortality in men than women.

Three phases have been described following SARS-CoV-2 virus infection. In the first phase, the virus binds to ACE2 receptors in the nasal epithelium where it undergoes local replication and propagation as well as infecting the epithelial cells in the conducting airways [12,18]. This phase, known as the ***asymptomatic stage*** lasts for 1–2 days [18]. Host innate immune response at this stage is limited and there are usually no symptoms. The virus can be detected at this stage by nasal rather than pharyngeal swabs and although the viral burden at this stage on the individual is low, they are infectious [12]. The next phase known as the ***invasion and infection of the upper respiratory tract stage*** involves migration of the virus from the nasal epithelium to the upper respiratory tract via the conducting airways [12] generating a greater immune response with the release of the C-X-C motif chemokine ligand 10 (CXCL10) and interferons (IFN-β and IFN-λ) from infected cells [19]. At this stage, the patient experiences fever, malaise and a dry cough which in over 80% of cases is self-limiting (i.e. do not progress beyond this stage). Diagnosis at this stage can be from nasal or pharyngeal swabs and sputum. This stage lasts for a few days only. The third stage is one with involvement of the lower respiratory tract and progression to acute respiratory distress syndrome (ARDS*)* and has been also been referred to as ***hypoxia, ground glass infiltrates and progression to ARDS stage*** [12,18]. It is estimated that about 20% (one fifth) of patients progress to this stage which is characterised by viral invasion of type 2 alveolar cells followed by replication to produce more viral nucleocapsids [12]. The pneumocytes which are now laden with SARS-CoV-2 release cytokines and inflammatory markers such as interleukins (IL-1 IL-6, IL-8, IL-12), tumour necrosis factor (TNF-α) and interferon (IFN-β and IFN-λ and CXCL10), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1a (MIP1- α). This response, referred to as the 'cytokine storm' [12,20], acts as a chemoattractant for neutrophils, CD4 + helper and CD8 + cytotoxic cells. These cells which are responsible for fighting the virus induce an inflammatory response and subsequent injury to the lungs. Infected alveolar cells undergo apoptosis and release more viruses to infect adjacent type 2 pneumocytes with loss of both type 2 and type 1 pneumocytes (type 2 are precursors of type 1) and consequently there is diffuse alveolar damage which eventually leads to acute respiratory distress syndrome (ARDS) [12].

Transmission of SARS-CoV-2 is mainly by contact of the mucosa (eyes, nose or mouth) of susceptible individuals with respiratory droplets (generated by coughing or sneezing by those infected) [21–24]. Transmission has also been reported through contacts with contaminated fomites (bedsheets, toilet seats, blankets, kitchen utensils, thermometers, stethoscopes and even currency notes) used by or on infected individuals. Such transmission occurs mainly through unwashed hands. Airborne transmission is rare but is a means of transmission in special medical procedures such as endotracheal intubation, nebulization with oxygen, open suctioning, tracheostomy, bag and mask before intubation, cardiopulmonary resuscitation and bronchoscopy [23,24]. Most transmissions occur through close contacts, defined as 15 min face-to-face contact within 2 m [25]. The transmission rate is higher in enclosed environments compared to outdoor [27–31].
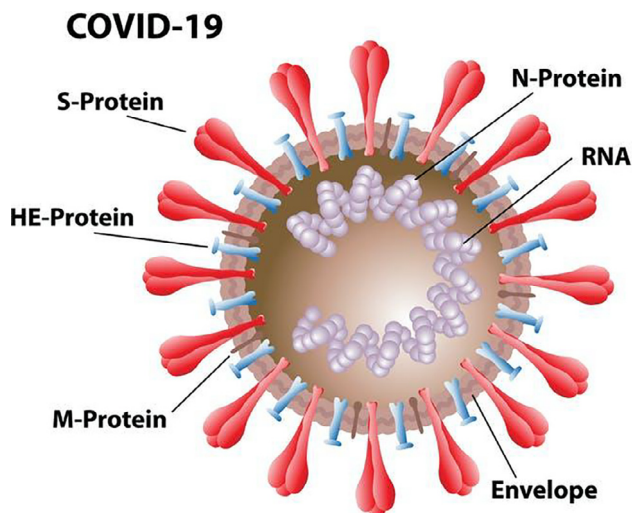

Fig. 1. Illustration of the structure of SARS2-CoV-2 (proteins and RNA) (Downloaded on-line from Shutterstock)

Clinical features of COVID-19

The incubation period (time from exposure to development of symptoms) for COVID-19 is approximately 5–6 days but can be up to 14 days [12,32–33]. It has been shown that about 97.5% of people with COVID-19 develop symptoms within 11.5 days of SARS-CoV-2 infection [32]. The peak viral load occurs at the time of symptom onset or in the first week with SARS-CoV-2 and then declines after, and by implication infectivity is highest just before or within the first five days of symptom onset [26]. Although viral RNA has been detected by RT-PCR in the upper respiratory tract for a mean of 17 days (and up to a maximum of 83 days [34], this does not equate to infectiousness as viral cultures (which truly reflect infectiousness) have rarely been positive beyond 9 days of illness [26]. This corresponds to contact tracing studies that have shown that transmission capacity is maximum in the first week of illness with no transmission documented after this period [26,35].

The clinical features of COVID-19 vary depending on the population being screened and the timing of the screening. In the non-pregnant population for example, testing most commonly occurs when patients present with symptoms or have a contact history. In pregnancy, however, screening occurs at different levels – presentation for (a) antenatal care, (b) obstetric admissions or emergency reviews, (c) assessment in labour or (d) admission for elective delivery. Most pregnant women just like the non-pregnant population are asymptomatic. The proportion who at diagnosis are asymptomatic has also been shown to vary depending on screening criteria, population studied and timing of the study. These have varied from 34% −88% [36–43]. Adhikari et al [44] found that 95% of their cohort were either asymptomatic or had mild symptoms. Universal screening of pregnant women presenting to hospitals found positive SARS-CoV-2 rates of between 3.9% and 15.6% [37–45]. In their living systematic review, Allotey et al [46] showed that 1:10 (10%) of all pregnant women attending or admitted to hospital for any reason were diagnosed with COVID-19. In the asymptomatic group 1:20 admitted or presenting to the hospital tested positive for COVID-19 [46]. These figures are comparable to those generally reported in all populations. For example, Oran and Jopol [47] in a systematic review, showed that at least a third of SARS-CoV-2 infections are asymptomatic and furthermore, up to 75% of those with a positive PCR test result and no symptoms at the time of testing when followed up longitudinally remained asymptomatic.

Of those presenting with symptoms, the most common are fever/chills and dry cough [46]. Other symptoms include shortness of breath, muscle or body aches, nausea/vomiting, headaches, sore throat, abdominal pain, chest pain, nasal congestion/rhinorrhea, tiredness, malaise, decreased smell, decreased taste and diarrhoea [38,48–50]. It would seem that pregnant women are less likely to present with fever and myalgia compared to age-matched controls [36]. Rare presentations depend on the severity of the disease and include features of multi-system failure such as those of the kidneys, liver and lungs [12]. Table 1 shows the latest prevalence of symptoms at presentation as published by the Johns Hopkins Coronavirus Resource Center [2]. These figures are not dissimilar to those in pregnant women although the proportion presenting with fever and cough are not as high as reported in the general population.

With respect to laboratory features, leukocytosis (26%) has been shown to be the most common (in 26% of cases) followed by lymphopenia (33–48.3%) [46,51]. Other laboratory abnormalities include elevated D-dimers, CRP (49%) and lactate dehydrogenase [52,53] and procalcitonin (23%) [46]. Radiologically, the most common CT findings are ground-glass opacities and bilateral infiltrates in the lungs. A *meta*-analysis of 42 studies of pregnant patients

Table 1
Comparison of the prevalence of symptoms at presentation according as reported by Zambrano et al. (73).

Symptom	% of patients pregnant presenting with this	% of non-pregnant patients presenting with this
Fever	32.0%	39.3%
Dry cough	51.3%	50.3%
Fatigue	13.5%	17.1%
Shortness of breath	25.9%	24.8%
Muscle pain or joint pains	36.7%	45.2%
Sore throat	28.4%	34.6%
Headache	42.7%	54.9%
Chills	24.4%	29.2%
Nausea or vomiting	>10%	
Nasal congestion	21.5%	24.8%
Diarrhoea	>10%	
New loss of smell or taste	21.5%	24.8%
Abdominal pain	8.4%	9.3%
Chest pain	3.5%	4.1%

Table 2
Classification of severity of COVID-19.

Category of Severity	Definition (features)
Asymptomatic	A positive SARs-CoV-2 PCR test result with no symptoms
Mild disease	Positive SARS-CoV-2 PCR test and symptoms including fever, cough (typically dry), myalgia (muscle aches) and anosmia but with no shortness of breath or abnormalities on chest imaging
Moderate disease	Positive SARS-CoV-2 PCR test with evidence of lower respiratory tract disease on assessment (clinical features including dyspnoea, pneumonia on imaging, abnormal blood gases, refractory temperature of 39.0oC or greater not alleviated with acetaminophen) and oxygen saturation of >93% on room air at sea level)
Severe disease	Positive SARS-CoV-2 PCR test with tachypnoea (respiratory rate of >30 bpm), hypoxia with oxygen saturation of <93% a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of greater than 300 or greater than 50% lung involvement on imaging
Critical disease	Positive SARS-CoV-2 PCR test associated respiratory failure (requiring mechanical ventilation or high-flow nasal cannula), septic shock and/or h multi-organ failure or dysfunction

found focal ground glass opacities and bilateral infiltrates as the most common CT abnormalities in those with mild or asymptomatic disease while all those with critical disease had diffuse ground-glass opacities with subpleural involvement and pleural effusion. These abnormal findings were present in 89% of patients, 8.9% of whom were asymptomatic at the time of imaging [53,54]. Abnormal chest X-Ray findings include bilateral pneumonia (57.9%), unilateral pneumonia (20%) and multiple patchy pulmonary infiltrates (22.7%) [46]).

There are five classes of COVID-19 disease characterized by a spectrum of clinical symptoms as shown in Table 2 [55,56].

Diagnosis

There are three approaches to making a diagnosis – viral cultures, serology (IgG and IgM) and reverse transcriptase-polymerase chain reaction (RT-PCR) also referred to as nucleic acid amplification test (NAAT).

The most reliable contemporaneous test for diagnosing SARS-CoV-2 infection is RT-PCR. This is performed on nasopharyngeal or other upper respiratory tract specimens and more recently

saliva [12,57]. Different RNA gene targets – the envelope (*env*), the nucleocapsid (*NC*), spike (*S*), RNA- dependent RNA-polymerase (*RdRp*) and *ORF1* genes [57] are employed by various manufacturers. Comparisons of the sensitivities of tests with various RNA gene targets found them to be similar [58]. Viral RNA is measured by cycle threshold (Ct) and becomes detectable as early as the first day of symptoms and achieves a peak within 7 days of symptoms onset [57]. The test reports on the number of replication cycles required to produce a fluorescent signal (Ct)–lower Ct values represent higher viral loads) [57]. A Ct value of <40 is considered a positive test. Viral RNA begins to decline by week 3 of the infection and gradually becomes undetectable. A positive RT-PCR does not indicate infectivity but simply the detection of viral RNA [59]. For example, in a small study of 9 patients after the 8th day of the illness onset, isolation of the virus by culture (which reflects infectivity) was unsuccessful [30] (supporting CDC's recommendation that healthcare workers could return to work if at least 3 days have elapsed since recovery defined as resolution of fever without antipyretics and improvement in respiratory symptoms of cough and shortness of breath or at least 10 days have passed since symptoms first appeared [60]. Nasopharyngeal flocked swabs require expertise to collect, are inconveniencing and discomforting to patients. They are also difficult to collect in special circumstances such as from those under quarantine. Using saliva has several advantages as it is non-invasive, easy to collect and well tolerated by patients. A systematic review of 16 studies in which nasopharyngeal swabs and saliva were compared showed a similar sensitivity −83.2% versus 84.8% and specificity −99.2% versus 98.9% for nasopharyngeal swabs and saliva respectively [61]. Salivary RT-PCR is therefore likely to become the primary test for diagnosis.

The presence of IgM and IgG antibodies reflects the host immune response to pathogens and is therefore conclusive evidence of infection. Antibodies to SARS-CoV-2 viruses develop 1–3 weeks after the onset of symptoms at which time evidence suggests that infectiousness is likely to be greatly decreased and that some degree of immunity from future infection has developed. IgM and IgG seroconversion occur together (i.e. they rise together) so either of them or the total could be measured [62]. IgM levels decline to reach lower levels by week 5 and almost disappear by week 7 [57] while IgG persist beyond weeks 7 [63]. Not everyone infected with SARS-CoV-2 virus will develop detectable IgG or IgM antibodies and in these individuals, the absence of detectable IgM or IgG antibodies does not therefore necessarily rule out that they could have previously been infection.

Unlike the direct detection by RT-PCR (nucleic acid amplification or antigen detection tests) that detect acutely infected patients, antibody (serological) tests determine previous infection, even if these were asymptomatic. By measuring the humoral immune response to the virus, these tests detect resolving or past SARS-CoV-2 infection but these do not replace direct detection methods as the primary tool for diagnosing active SARS-CoV-2 infection. The serological tests used either detect binding or neutralizing antibodies. The binding antibody tests use purified proteins of SARS-CoV-2 and are able to determine antibody types such as IgG and IgM. Results are generated within 30 min. Examples are the *Point-of-care (POC) tests* that detect IgG, IgM or total antibody in serum, whole blood and/or saliva [64] and the laboratory tests which use enzyme linked immunosorbent assay (ELISA) or chemiluminescent immunoassay (CIA). Neutralizing antibody detection is more cumbersome and involves the use of live viruses [65]. Studies have compared ELISA IgM directed at the nucleocapsid (NC) antigen with RT-PCR and showed its sensitivity to be much lower (51.9% vs 98.6%). RT-PCR had a higher positivity rate during the first 5.5 days but the ELISA IgM had a higher rate after 5.5 days [66]. ELISA-based IgM and IgG antibody tests have, however, been shown to have a more than 95% specificity for diagnosing SARS-CoV-2. In infected patients, most of the IgM antibodies produced are against the NC, the most abundant protein of the virus, implying that the most sensitive tests will be those against this protein. Antibodies to the receptor-binding domain S (RBD-S) protein which is the host attachment protein is more specific and are therefore expected to be neutralizing. In general, tests that detect either IgG or IgM or both have high sensitivity, however, the antibodies may cross-react with SARS-CoV-1 and possibly other coronaviruses [65]. Currently, there is no identified advantage with the assays testing for IgG, IgM or total (IgG and IgM) antibody.

Viral cultures represent the best indication of current infection and infectivity. It is the gold standard for diagnosis and will ideally inform isolation and managing contacts. In a systematic review of 14 studies of SARS-CoV-2 viral cultures from various specimens including sputum, nasal or nasopharyngeal swabs, urine, stool and environmental samples, Jefferson et al [67] stated that while this was achieved in all the studies, lack of standardized reporting and lack of RT-PCR testing against these viral cultures or infectivity in animals limit current ability to quantify the relationship between viral load and cycle threshold (Ct) and infectivity. They concluded that the lower quality of the studies limited firm conclusions and that without a uniform international standard for reporting comparative SARS-CoV-2 cultures with index test, routine viral cultures was not yet of additional benefit to diagnosis of infectivity.

With every new viral outbreak, there is always concern about mutations with the development of strains that maybe resistant to treatment or evade immunisation. A number of strains of SARS-CoV-2 have been shown to either be more infective and/or potentially not be prevented by currently available vaccines [68]. Identifying these strains is critical in planning treatment and prevention. This is achieved by next-generation sequencing (NGS) which provides an effective, unbiased way to identify new coronavirus strains [68–70]. Novel variants of the SARS-CoV-2 that have been identified include the B.1.1.7 strain [UK], B1.351 strain (S. Africa), B.1 strain (Brazil) and B.1.617.2 strain (India). While the Pfizer vaccine has been shown to be effective against the SA and UK variants [71] data remain scarce on effectivity, highlighting the need for more sequencing to detect mutations quickly and prevent the spread of new strains. NG sequencing allows labs to track the transmission routes of the virus globally, detect mutations quickly to prevent the spread of new strain types, identify viral mutations that can avoid detection by established molecular diagnostic assays, identify viral mutations that can affect vaccine potency, screen targets for possible COVID-19 therapeutics, identify and characterize respiratory co-infections and antimicrobial resistance alleles. [69–70]

Clinical course and outcomes of COVID-19 in pregnancy

Although the clinical presentation of pregnant women with COVID-19 is similar to that of non-pregnant aged matched controls and indeed several studies show a similar hospitalisation rate [72], pregnant women are at a significantly higher risk for severe outcomes compared to non-pregnant women [46,55,73]. Initial studies had shown a mixed picture – with some small international case series suggesting a similar course of illness in pregnant and non-pregnant women [74,75,76]. Most studies including large population cohorts, however, show that while critical illness is rare in pregnant women, it is slightly increased when compared to the general population [53,75–79]. In their live systematic review, Allotey et al. reported that approximately 90% of pregnant women diagnosed with COVID-19 recovered without needing to deliver [44]. Another meta-analysis of 637 pregnant women with COVID-19 found that 76.5% of patients had mild disease, 15% had severe disease, and 7.7% had critical disease at the time of

Table 3

OR for the various risk factors for hospital admission for patients with SARS-CoV-2 infection in pregnancy.

Risk factor	OR	95% CI
Black, Asian, Latino and minority ethnic background	4.49	3.37 – 6.00
Maternal age 35 years or older	1.78	1.25 – 2.55
BMI 30 kg/m2 or above	2.38	1.67 – 3.39
Pre-existing diabetes mellitus	2.51	1.31 – 4.80
Chronic hypertension	2.0	1.14 – 3.48

admission [53]. Of those with mild disease, approximately 3% went on to develop severe or critical infection [53]. The estimated mortality rates for pregnant women with COVID-19 of 0.6–2%, are comparable to the general population; those with critical disease at the time of presentation accounting for the vast majority of deaths secondary to COVID-19 [46,53]. A more recent and large population study of the clinical characteristics and outcomes of hospitalised women giving birth with COVID-19 in the USA showed that while in-hospital mortality was low, it was significantly higher in women with COVID-19 compared to those without (141; 95% CI 65–268 versus 5; 95%CI, 3.1–7.7 deaths per 100,000 women). Myocardial infarction (0.1% versus 0.004%) and venous thromboembolism (0.2% versus 0.1%; P < 0.001) rates were also significantly higher [80]. Furthermore, recent large population studies found an increased risk of severe illness and mechanical ventilation in pregnant women compared to their non-pregnant counterparts when adjusted for age, race, and co-morbidities [55,73]. Pregnant women were more likely than non-pregnant women to be admitted into an intensive care unit (10.5 vs 3.9 per 1000 cases (aRR 3.0; 95%CI 2.6–3.4), receive invasive ventilation (aRR 2.9 vs 1.1 per 1000 cases; 95%CI 2.2–3.8), receive extracorporeal membrane oxygenation (ECMO) (0.7 vs 0.03 per 1000 cases. aRR 2.4, 95% CI 1.5–4.0) and die (1.5 vs 1.2 per 1000 cases, aRR 1.7; 95% CI 1.2–2.4) [73]. The rate of intensive care admission rises with increasing gestational age, with one study reporting more than 90% of pregnant patients requiring ICU in their third trimester [53]. Increased maternal age, high body mass index, pre-existing hypertension, ethnicity (Black, Asian, Latino) and pre-existing diabetes were associated with severe COVID-19, and the presence of maternal co-morbidities was a risk factor for ICU admission and mechanical ventilation [46,53,77,81]. Several reasons have been advanced for these differences including a higher prevalence of comorbidities associated with poor COVID-19 outcomes (eg, type 2 diabetes among British South Asians), greater social deprivation, large multigenerational households, differences in occupational risk, and delayed access to health [82,83]

Table 3 shows the OR of each factor on the risk of admission with SARS-CoV-2 infection in pregnancy.

Data from various studies showed that 40% of pregnant patients who died from COVID-19 were obesity, at least 40 years old or diabetic [46,53,55,78]. Other factors that have been reported to be associated with more severe disease include a combination of elevated D-dimer and interleukin-6 levels. Turan et al found this combination to be present in 60% of severely ill and 80% of critically ill pregnant women with COVID-19, respectively [53]. Unfortunately, data on baseline levels of these laboratory variables in pregnancy were limited, making comparisons difficult. COVID-19 has also been reported to be associated with the development of cardiomyopathy in 7–33% of the general population [84,85].

Impact of COVID on pregnancy

SARS-CoV-2 infection has been shown to have adverse effects on pregnancy, with most of the data coming from infections in late pregnancy. There is some evidence, however, that miscarriages are more common in those who became ill in the first trimester compared to the second trimester, with rates of 16.1% and 3.5%, respectively [86,87]. A few studies on small numbers showed no increase in miscarriages but these were either on asymptomatic women [88,89] or non-infected women where the impact of the COVID-19 environment was the variable being investigated [90]. Whether acute maternal illness in those not needing delivery (i.e. those who recover and continue with the pregnancy) results in abnormal fetal growth, probably due to placental insufficiency such as uteroplacental vascular malperfusion, intervillous inflammation, and thrombosis of fetal intervillous vessels in maternal COVID-19 infection [77] has not been proven. Four studies found occlusive fibrin deposition and non-occlusive thrombi with placental hypoperfusion in all specimens on histopathological examinations of 14 placentas from patients with clinically mild COVID-19 [53]. Interestingly 50% of these cases were preterm deliveries and there were one each of placental abruption, second-trimester miscarriage, and small for gestational age [91–93].

Preterm (<37 weeks) birth risk has consistency been reported to be increased in women infected with SARS-CoV-2 [46,86,87]. This risk is particularly increased in mothers testing positive 0–14 days before delivery [52,77,92–95]. The largest cohort study that followed the course of 242 COVID-19 positive pregnant women and their 248 infants through the third trimester and one month postpartum [53] confirmed these findings. The PRIORITY study of 263 infants born to 179 COVID-19 mothers and 84 non-COVID-19 mothers, however, showed no increase in preterm birth, respiratory disease and NICU admission [91]. What is uncertain, is whether the higher rate of prematurity derives from a need to deliver secondary to COVID-19 related maternal complications or from effects of the disease on the pregnancy. In general rates of preterm birth and caesarean delivery are increased in COVID-19 patients regardless of the severity of disease, suggesting that these outcomes may be iatrogenic. In their meta-analysis Turan et al found that preterm delivery occurred in approximately one third of patients with COVID-19 [53] and 40% of these were early preterm deliveries (24^{+0} – 33^{+6} weeks), and 60% were late preterm deliveries (34^{+0}-36^{+6} weeks) [53]. The rates of caesarean delivery were extremely high in this meta-analysis, with reported rates of nearly 85% [92,93]. The caesarean section rates in hospitalized COVID-19 patients were much higher in initial reported rates (80–90%) but subsequent cohorts have reported much lower rates [95]. Other complications that have not been consistently found to be increased include pre-eclampsia [96] preterm pre-labour rupture of membranes [84] chorioamnionitis and postpartum hemorrhage [46,96].

With regards to neonatal complications, infants with mothers who tested positive closer to delivery were more likely to be admitted to the NICU than those with mothers who tested positive two or more weeks prior to delivery [53]. Stillbirths and neonatal death rates are not increased compared to the general population [53,96–98].

There is currently no robust evidence for vertical transmission of SARS-CoV-2. In a well-designed study Marin Gabriel at al [77] found no cases of vertical or horizontal transmission. Turan et al. in their meta- analysis reported that 2% of infants born to mothers with COVID-19 tested positive 16–24 h after birth by RT-PCR from nasopharyngeal and oropharyngeal swabs [53]. A similar positivity rate (1.1%) was reported in the PRIORITY study [91]. The findings of SARS-CoV-2 virions in syncytiotrophoblasts and microvilli of the placenta, suggest that transplacental transfer may be possible [97]. Furthermore, the finding of IgG and IgM antibodies against SARS-COV-2 in seronegative neonates of COVID-19 infected mothers [93,99–101] especially of IgM antibodies that cannot cross the placenta, suggest a fetal immune response against the virus in neonates born to infected mothers. SARS-CoV-2 has also been isolated

from maternal vaginal epithelium and stool samples, cord blood, placenta, and amniotic fluid [53].

Pregnancy is a hypercoagulability state with a 4–6 fold increased risk of venous thromboembolism. There is evidence that COVID-19 is associated with coagulation dysfunction predisposing those with severe illness to both venous and arterial thrombosis. Reported thromboembolism rates vary form 20–70% in those with severe disease. A systematic review by Malas et al. [102] of 42 studies enrolling 8271 patients (non-pregnant) reported a DVT rate of 20% (95%CI, 13–28%), pulmonary embolism rate of 13% (95%CI 11–16%) and an arterial thrombosis rate of 2% (95%CI 1–4%). In pregnancy, Jering et al [80] reported a doubled VTE rate in infected compared to uninfected women (0.2% versus 0.1%) giving an aOR of 3.43 (95CI 2.01–5.82) [80,103–104]. VTE is reported mainly in hospitalized patients with rates of 6% (95%CI, 2–11) in those with critical illness and 0.2% in those with mild-moderate illness and 0% in asymptomatic women [80]

Treatment of COVID-19

A variety of treatment options have been investigated for COVID-19 and although some have shown benefits, such as decreasing hospital length of stay or improving overall morbidity, there is currently no cure or optimal and agreed-upon comprehensive treatment. Current treatments shown to be beneficial in various trials include remdesivir, dexamethasone, tocilizumab (antibodies) and convalescent plasma [105–107]. Pregnant women were, however, excluded in most of the clinical trials. Remdesivir, an anti-viral agent found in the 'Adaptive COVID-19 Treatment Trial (ACTT-1) to reduce the duration of disease in patients requiring oxygen therapy is recommended by NIH COvid-19a Guidelines panel for hospitalised patients with SpO2 $\leq$ 94% on ambient air (at sea level) or those who require supplemental oxygen and those on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [108]. Though pregnant women were excluded, there are, however, no known teratogenic effects of remdesivir and it is therefore considered a treatment option in pregnancy [106–108]. The RECOVERY trial, which demonstrated that dexamethasone 6 mg daily decreased the risk of mortality in those requiring mechanical ventilation and also those requiring oxygen for COVID-19 included pregnant and breastfeeding women [109]. The dose of dexamethasone in this trial was not high enough to reach that shown in early pregnancy to be teratogenic. The SMFM and other bodies, on the basis of benefits (of mortality reduction) versus risks therefore, recommend that dexamethasone should be offered to pregnant patients with COVID-19 requiring oxygen or mechanical ventilation. It is recommended that where steroids for fetal lung maturity are also required, dexamethasone 6 mg IM every 12 h for 48 h (4 doses) should be enough followed by up to a total of 10 days of 6 mg dexamethasone PO/IV daily. However, where this is not indicated, 6 mg dexamethasone daily (PO/IV) for up to 10 days should be administered as in nonpregnant patients [105]. Monoclonal antibodies such as bamlanivimab and polyclonal "cocktails" of antibodies such as casirivimab and imdevimab have been given emergency approval [108] for the treatment of mild to moderate COVID-19 in adults who are at high risk for progressing to severe COVID-19 and/or hospitalization. Criteria for use include: high BMI greater than 35 kg/m^2, chronic kidney disease, diabetes, and immunosuppressive treatment. Those on supplemental oxygen are excluded. Pregnant women with these criteria are at an increased risk of progression to severe/critical disease and therefore consideration should be given to their use as long as the risks versus benefits are clearly discussed with the patients [105–106].

Other treatments that have been tried but not shown to be effective include chloroquine/hydroxychloroquine and as such

are not recommended for use in COVID-19 [105–108]. The use of antibiotics should be when there are bacteria coinfections for example pneumonia. For such infections, the antibiotic ceftriaxone combined with azithromycin or ceftriaxone (not contraindicated in pregnancy) alone commonly used to treat community-acquired pneumonia can be used.

Thromboprophylaxis with low-molecular weight heparin should be considered in those with additional risk factors [96], who are self-isolating or being managed at home and should be offered to all hospitalised pregnant patients with COVID-19 especially as pregnancy is a hypercoagulable state and the reported risk of VTE is doubled in these women [52,80,110].

Antenatal care management of pregnancy

This is best guided by the clinical stage of the disease. Fig. 2 shows our suggested antenatal care pathway. In planning and delivering antenatal care the welfare of the woman and that of her unborn child as well as that of healthcare providers should be taken into consideration. Delivery of antenatal care is best in settings with the necessary precautions to reduce person-to-person transmission – maintaining a distance of 2 m between patients waiting to be seen, wearing face mask and staff wearing appropriate personal protective equipment (PPE) [105–108]. Antenatal care should be planned and delivered for those (a) with suspected but yet to be confirmed COVID-19 including known contacts with infected individuals (b) who are asymptomatic or have mild confirmed COVID-19 and (c) with moderate, severe or critical COVID-19.

Pregnant women with unconfirmed SARS-CoV-2 infection (based on symptoms and or history of contact with a confirmed infected individual), are advised to self-isolate and be assessed and tested in the hospital. It should be recognised that other pathologies such as chorioamnionitis, pneumonia, URTI may manifest with symptoms of fever, cough, malaise and sore throat. Appropriate counselling about fetal movements and indications for presentation to hospital should be provided and those considered high risk (ethnic minorities, obese, hypertensive, diabetic) reviewed in-person or remotely at least twice a week to ensure no deterioration. Since most positive patients are less likely to be infectious 10 days after the onset of symptoms [30], these women should return to routine face-to-face antenatal care 14 days after the onset of symptoms or isolation. Those with confirmed SARS-CoV-2 infection but with mild symptoms should be self-isolated and managed as above. Those with moderate or severe symptoms and those with mild symptoms but with additional risk factors should be managed in hospitals by multidisciplinary care teams. Once recovered they should be back to routine antenatal care but follow-up serial growth ultrasound scans are recommended [105–108] starting from about 2 weeks after acute illness.

Management of labour and delivery

The timing of delivery should be individualized according to maternal clinical condition or obstetric factors, and not by the diagnosis of COVID-19 alone. Early delivery can be indicated to improve maternal ventilation in those with severe or critical disease [105–108]. This decision should be made by a multidisciplinary team of obstetricians, anaesthetists, neonatologists and microbiologist (infective disease specialists) [105–108].

The mode of delivery should not be influenced by the presence of COVID-19 i.e. vaginal delivery should be supported especially as there is no evidence of vertical transmission of SARS-CoV-2 [111]. Although COVID-19 is not an indication for caesarean section it
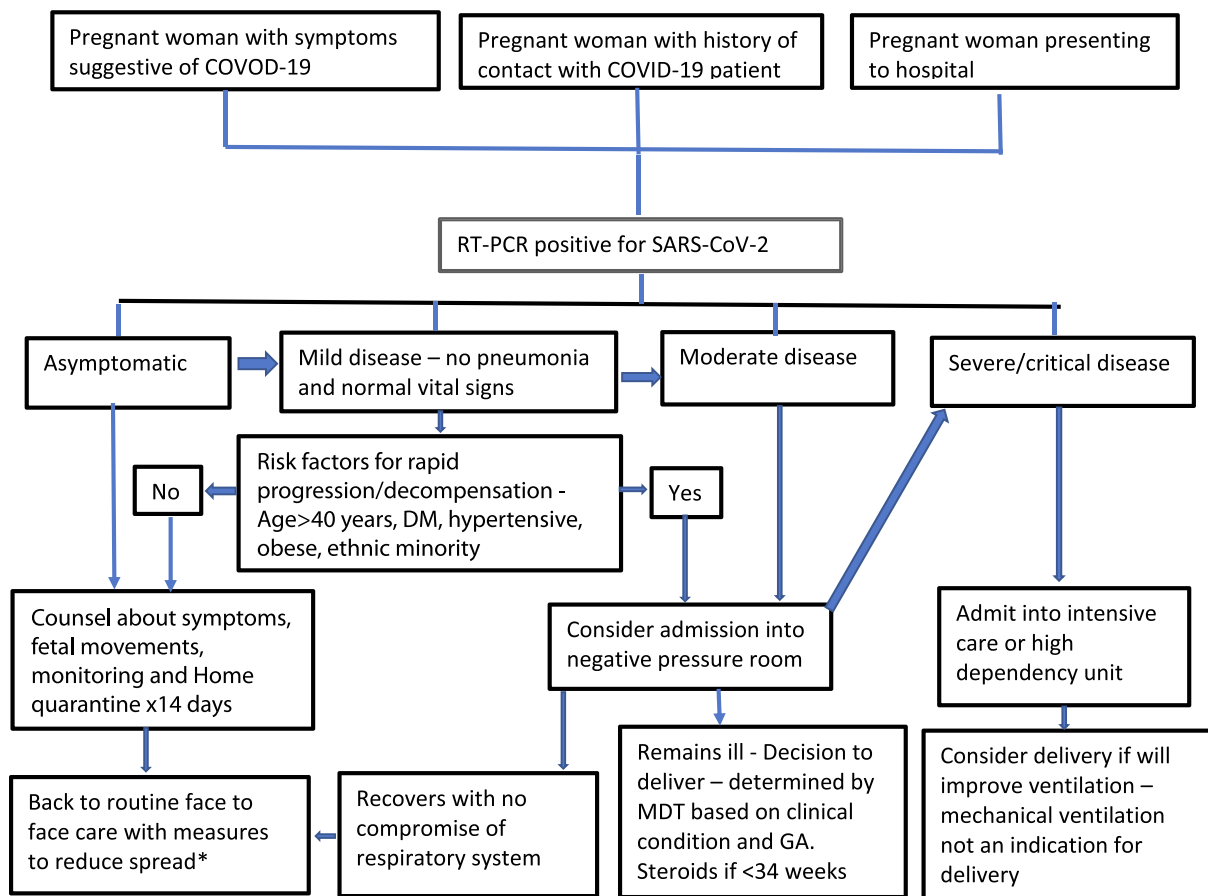
```
┌──────────────────────────┐  ┌──────────────────────────┐  ┌──────────────────────────┐
│ Pregnant woman with      │  │ Pregnant woman with      │  │ Pregnant woman presenting│
│ symptoms suggestive of   │  │ history of contact with  │  │ to hospital              │
│ COVOD-19                 │  │ COVID-19 patient         │  │                          │
└──────────────────────────┘  └──────────────────────────┘  └──────────────────────────┘
```

RT-PCR positive for SARS-CoV-2

| Asymptomatic | Mild disease – no pneumonia and normal vital signs | Moderate disease | Severe/critical disease |

Risk factors for rapid progression/decompensation - Age>40 years, DM, hypertensive, obese, ethnic minority — No / Yes

Counsel about symptoms, fetal movements, monitoring and Home quarantine x14 days

Consider admission into negative pressure room

Admit into intensive care or high dependency unit

Back to routine face to face care with measures to reduce spread*

Recovers with no compromise of respiratory system

Remains ill - Decision to deliver – determined by MDT based on clinical condition and GA. Steroids if <34 weeks

Consider delivery if will improve ventilation – mechanical ventilation not an indication for delivery

Fig. 2. Suggested algorithm for antenatal care of women with COVID-19. *Consider serial growth scans from about 2 weeks after acute illness.

should be considered where it would facilitate maternal respiratory support or resuscitation [105–108].

For COVID-19 patients undergoing elective delivery by induction of labour or CS within 10 days of diagnosis of SARS-COV-2, consideration should be given to delaying this if there are no major risks to either the mother or the fetus. This will allow the mother to recover and reduce the risk of transmission to staff during delivery and to the neonate [105,106].

Pain relief should be discussed and options include Entonox with a single patient microbiological filter [106] (there is no evidence its use is an aerosol-generating procedure) [106]. Epidurals should be encouraged in early labour as they reduce the spread of the virus by the relaxed mother and the need for GA if there is a need for emergency procedures. There is no evidence that either epidural or spinal analgesia or anaesthesia are contraindicated in the presence of SARS-CoV-2 infection [106].

There is no evidence that SARS-CoV-2 infection causes fetal distress in labour, hence continuous electronic fetal monitoring is not indicated in otherwise low risk asymptomatic or mildly symptomatic women for the sole reason of COVID-19 infection [105,106]. This also applies to those who go into labour more than 10 days from the onset of symptoms. Where there are options of home or water birth these are permitted in low risk women as long as staff take the necessary preventative precautions [105,106].

In those with moderate/severe/critical disease or mild disease with additional risk factors labour should be in the hospital with continuous electronic fetal monitoring due to the risk of fetal distress either from the disease or deterioration in the maternal condition [105–108]. Furthermore, in addition to the routine observations of BP, temperature and respiratory rate oxygen satu-

rations should be carried out hourly or more frequently as deemed appropriate [106]. Consideration should be given to shortening the second stage in symptomatic women who are hypoxic or have respiratory compromise [106].

Regional anaesthesia is the preferred mode of anaesthesia for CS. Airway management with tracheal intubation and extubation during general anaesthesia poses great risk of transmission of SARS-CoV-2 to the attending staff, hence it should be avoided if possible.

Additional precautions in labour include minimizing the number of staff members entering the labour room or operating theatre, all staff to wear PPE when entering the room and elective caesarian sections to be scheduled at the end of the operating list [106]. Fig. 3 shows a suggested algorithm for intrapartum care.

Neonatal care

Neonatal SARS-CoV-2 infection which is uncommon and mostly asymptomatic is not affected by mode of delivery but occurs primarily through respiratory droplets from infected asymptomatic/symptomatic individuals/mothers to whom the neonates are exposed in the postnatal period [105,106]. The rate of infection is not greater when the baby is breastfed or allowed contact with the mother [112]. The benefits of contact of the neonate with its mother and her ability to breast feed outweigh potential benefits of separation. Consequently, most guidelines advise skin-to-skin contact and breastfeeding if the mother with suspected or confirmed COVID-19 uses hand hygiene precautions and (ideally) wears a surgical face mask (fluid-resistant if available) [112] where
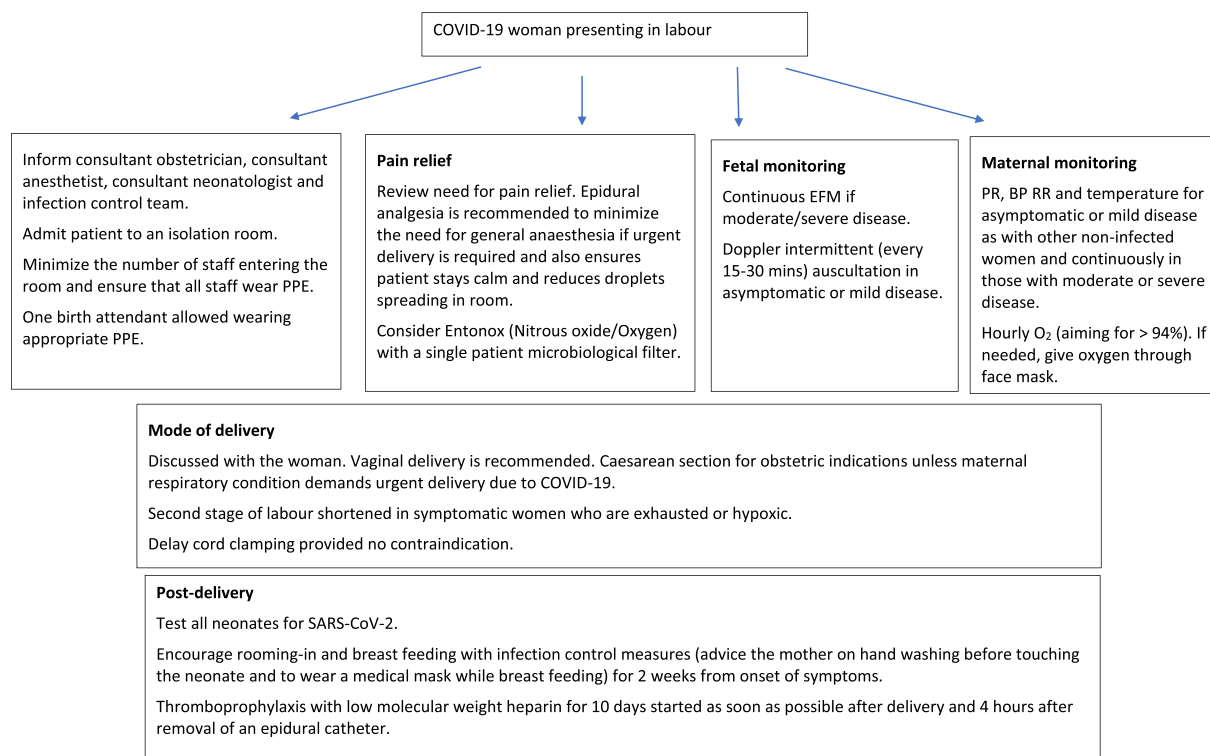
Fig. 3. Suggested Algorithm for intrapartum care of women with COVID-19.

the baby does not require neonatal unit care. Maintaining physical separation of more than two metres at other times is also recommended [112,113]. Rooming-in has many well-established benefits and data suggest that there is no difference in risk of SARS-CoV-2 infection to the neonate whether cared for in a separate room or in the mother's room [106,112]. All neonates born to mothers with suspected or confirmed COVID-19 regardless of their symptoms, should, however be tested [105,106,112].

COVID-19 vaccination in pregnancy

As of June 2021, at least seven different vaccines across three platforms have been approved in several countries. The most commonly offered ones are the Pfizer-BioNtech vaccine (mRNA) taken as 2 shots 3 weeks apart, Moderna vaccine (mRNA) taken as 2 shots 4 weeks apart, the Johnson & Johnson's Janssen Ad26.COV2.S vaccine (adenoviral vector) taken as a single shot, the AstraZeneca, University of Oxford and Serum Institute of India ChAsOx1 CoV-19 vaccine (Adenoviral vector-based) and the Russian Sputnik V (Gam-COVID-Vac) an adenovirus vector vaccine administered as 2 doses 3 weeks apart. These vaccines have been shown to be extremely effective (69–95%) in reducing risk for moderate to severe illness, hospitalization, and deaths from COVID-19 [114,115]. There are very limited data on their safety in pregnancy. The Centers for Disease Control and Prevention (CDC) is tracking more than 30,000 mRNA vaccine recipients who were pregnant at the time of vaccination. Nearly 1800 pregnant women were enrolled in a v-safe pregnancy registry. So far, pregnant women appear to have the same vaccine side effects as non-pregnant adults with no reported increase in miscarriages, stillbirths, preterm births or congenital malformations linked with the vaccines (Table 4) [116,117]. Overall, the risks of COVID-19 in pregnancy outweigh those of receiving the vaccine. Furthermore, a recent study by Collier et al [118] showed that not only was the mRNA vaccine immunogenic in pregnant women but that vaccine-elicited antibodies were pre-

Table 4
V-safe pregnancy registry outcomes in 275 COVID-19 vaccinated pregnant women from February 18, 2021 (102).

Pregnancy outcomes	V-safe pregnancy registry %	Background rate %
Miscarriage	15	26
Stillbirth	1	0.6
Gestational diabetes	10	7–14
Pre-eclampsia	15	10–15
Eclampsia	0	0.27
IUGR	1	3–7
Neonatal outcomes	**V-safe pregnancy registry %**	**Background rate %**
Preterm birth	10	10.10
Congenital anomalies	4	3
Small for gestational age	4	3–7
Neonatal death	0	0.38

sent in cord blood and infant milk hence potentially providing passive immunity to the neonate. The Centers for Disease Control and Prevention, the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG), FIGO and the Royal College of Obstetricians and Gynaecologists, on balance therefore recommend that COVID-19 vaccines should be offered to both pregnant and lactating mothers [105–108].

A prothrombotic syndrome known as either vaccine-induced thrombotic thrombocytopenia (VITT) or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) has been reported in a small number of recipients of the adenovirus vector vaccines (Johnson & Johnson and AstraZeneca, University of Oxford) [119]. This is thought to be caused by immunoglobin (Ig) antibodies that bind to platelet factor 4 (PF4) also known as CXCL4. Binding to PF4 activates platelets and stimulates the coagulation system with the ensuing clinically significant thromboembolic complications [120]. The thrombosis caused include venous (cerebral venous), splanchnic vein thrombosis (mesenteric vein, portal vein, splenic and

hepatic vein) adrenal vein thrombosis (which may present as adrenal failure), pulmonary embolism and arterial thrombosis (including ischaemic stroke and acute limb ischaemia [119,120]. While this is a very rare complication, it has been associated with mortality. Since pregnancy more than doubles the risk of VTE and severe SARS-CoV-2 doubles the risk of VTE in pregnant women with severe illness, it would be prudent to avoid the adenonovirus vaccines in those who are planning pregnancy or are pregnant. The mRNA vaccines appear to be safe and should be the choice vaccines for these women.

Conclusion

SARS-CoV-2 which causes COVID-19 poses significant risk to a small proportion of pregnant women including an increased risk for critical disease requiring ventilation support as well as complications such as preterm labour. Mortality from the infection is not much higher than in non-pregnant women. Most women (over 80%) are asymptomatic and management following diagnosis should be same as for non-pregnant adults. However, for those with additional risk factors such as hypertension, obesity, diabetes ethnic minority and diagnosis in the third trimester, consideration should be given to in-patient care irrespective of disease severity. There are currently no data demonstrating vertical transmission during pregnancy or intrapartum. COVID-19 hence it is not an indication for induction of labour or caesarean section. However, second stage should be assisted in those with severe or critical disease and CS maybe indicated to allow for improved ventilation support or resuscitation. Pregnancies should be managed as normal taking all the necessary precautions to minimize risk to healthcare workers and other patients. COVID-19 is not a contraindication to breast feeding. Vaccination has been shown to be highly effective in reducing the risk of severe disease and although data are limited there are no known adverse effects and is therefore recommended on balance to be given to pregnant and breastfeeding mothers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. World Health Organization (WHO) (Press release). 11 March 2020. Archived from the original on 11 March 2020. Retrieved 12 March 2020.

[2] https://coronavirus.jhu.edu/map.html. Assessed 24th March 2021.

[3] Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536–44.

[4] Machhi J, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. J Neuroimmune Pharmacol 2020;15:359–86.

[5] Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF (17 March 2020). Correspondence: The proximal origin of SARS-CoV-2. Nat Med. 26: 450–452.

[6] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.

[7] Mathad JS, Gupta A. Pulmonary infections in pregnancy. Semin Respir Crit Care Med. 2017;38(2):174–84.

[8] Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. Nat Rev 2019;17:181–92.

[9] Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Rev 2005;69:635–64.

[10] Hasoksuz M, Alekseev K, Vlasova A, Zhang X, Spiro D, Halpin R, et al. Biologic, antigenic, and full-length genomic characterization of a bovine-like coronavirus isolated from a giraffe. J Virol 2007;81:4981–90.

[11] Christian MD, Poutanen SM, Loutfy MR, Muller MP, Low DE. Severe acute respiratory syndrome. Clin Infect Dis 2004;38:1420–7.

[12] Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgraduate Med J 2020:1–9. https://doi.org/10.1136/postgradmedj-2020-138577.

[13] Yan R, Zhang Y, Li Y, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full length human ACE2. Science 2020;367:1444–8.

[14] Cevik M, Bamford CGG, Ho A. COVID-19 pandemic – a focused review for clinicians. Clin Microbiol Infect 2020;26:842–7.

[15] Montel V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infection in engineered human tissues using clinical-grade soluble human ACE2. Cell 2020;181:905–13.

[16] Albini A, Di Guardo G, Noonan DM, Lombardo M. The SARS-CoV-2 receptor, ACE-2, is expressed on many different cell types: implications for ACE-inhibitor- and angiotensin II receptor blocker-based cardiovascular therapies. Intern Emerg Med 2020;15:759–66.

[17] Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCOV. American Journal of Respiratory and Critical Care Medicine 202, pp. 756–759.

[18] Mason RJ. Pathogeensis of COVID-19 from a cell biology perspective Eur Respir J 2020;55:1-3. Https://doi.org/10.1183/13993003.00607-2020.

[19] Tang NL, Chan PK, Wong CK, TO kf, Wu AK, Sung YM, Hui DS et al. Early enhanced expression of interferon-inducible protein 10 (CXC-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. Clin Chem 2005;51:2333–2340.

[20] Sinha P, Mathay MA, Calfee CS. Is a "Cytokine Storm" relevant to COVID-19? JAMA Internal Med 2020;180(9):1152–4.

[21] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis and treatment of coronavirus disease 2019 (COVID-19). JAMA.2020;324(8):782–793.

[22] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China of novel coronavirus-infected pneumonia. N Eng J Med 2020;383:1199–207.

[23] Available https://www.who.int/news-room/commentarires/detail/modes-of-transmission-of-virus-causing-COVID-19-implications-for-ipc-precaution-recommendations (accessed 20 January 2021).

[24] Liu J, Liao X, Qian S, Yuan J, Wang F, Lui Y, et al. Community transmission of severe acute respiratory syndrome coronavirus-2, Shenzhen, China. Emerg Infect Dis 2020.

[25] European Centre for Disease Prevention and Control. Surveillance definitions for COVID-19. 2020. https://.ecdc.europa.eu/en/covid-19/surveillance/surveillance-definitions.

[26] Cevik M, Kuppali K, Kindrachuk J, Peiris M. Virology, transmission and pathogenesis of SARS-CoV-2 BMJ 2020;371:m3862|doi:10.1136/bmj.m3862.

[27] Cevik M, Marcus J, Buckee C, Smith T. SARS-COV-2 transmission dynamics should inform policy. Clin Infec Dis 2020. https://doi.org/10.1093/cid/ciaa1442.

[28] Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2 theoretical considerations and available evidence. JAMA 2020:3244:441–441.

[29] Center for Disease Control and Prevention: How COVID-19 spreads. 2020. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads/html.

[30] Center for Disease Control and Prevention. Scientific brief:SARS-CoV-2 and potential airborne transmission. 2020. https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sara.cov.2html.

[31] Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JHW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med 2004;350:1731–11719.

[32] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020 May 5;172(9):577–82.

[33] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L et al. China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019.

[34] Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS—CoV-2 SARS-CoV-1 and MERS-CoV viral dynamics, duration of viral shedding and infectiousness: a living systematic review and meta-analysis. Lancet Microbe 2020. https://doi.org/10.1016/S2666-5247 (20)30172-5.

[35] Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HT. Taiwan COVID-19 outbreak: Investigation Team. Contact tracing assessment of COvid-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med 2020;180:1156–63.

[36] Vintzileos WS, Muscat J, Hoffmann E, John NS, Vertichio R, Vintzileos AM. Screening all pregnant women admitted to labor and delivery for the virus responsible for coronavirus disease 2019. Am J Obstet Gynecol 2020 – August 2020.

[37] Diaz-Corvillon P, Monckeberg M, Barros A, Illanes SE, Soldati A, Nien J, Schepeler M, Caradeux J. Routine screening for SARS CoV-2 in unselected pregnant women at delivery Journal. Pone.o239887PloNe.

[38] Delahoy MJ, Whitaker M, O'Halloran A, Chai SJ, Kirley PD, Alden N, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-9-COVID-NET, 13 states, march 1-August 22 2020. Morb Mortal Wkly Rep 2020;69:1347–54.

[39] Maru S, Patil U, Carroll-Bennett R, Baum A, Bohn-Hemmerdinger T, Ditchik A, et al. Universal screening for SARS-CoV-2 infection among pregnant women

at Elmhurst Hospital Center, Queens, New York. PloSOne December 10 2929. https://doi.org/10.1371/journal.pone.0238409.

[40] Campbell KH, Tornatore JM, Lawrence KE, Illuzzi JL, Sussman S, Lipkind HS, et al. Prevalence of SARS-CoV-2 among patients admitted for childbirth in southern Connecticut. JAMA 2020;323(24):2520–2.

[41] Abeysuria S, Wasif S, Counihan C, Shah N, Iliodromiti S, Cutino-Moquel TC, Saeed F, Velauthat L. Universal screening for SARS-VoV-2 in pregnant women at term. Eu J Obstet Gynecol Reprod Biol 2020;252:444-446 [Newham hospital, London].

[42] Waghmare R, Gajbhiye R, Mahajan NN, Modi D, Mukherjee S, Mahale SD. Universal screening identifies asymptomatic carriers of SARS-CoV-2 among pregnancy women in India. Eu J Obstet Gynecol Reprod Biol 2021;256:503–5.

[43] Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. N Eng J Med 2020;382:2163 [Columbia Irving Medical Center, New York].

[44] Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire MD, Collins RJ, et al. Pregnancy outcomes among women with and without severe acute respiratory syndrome coronavirus 2 infection. JAMA Network Open 2020;3: e2029256.

[45] Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K. Ring L 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 May;2(2):100118.

[46] 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;370:m3320.

[47] Oran DP,AM, Topol, EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: a systematic Review Ann Intern Med. doi:10.7326/M20-6976 Annals of Internal Medicine. Ann Intern Med. 2021 Jan 22 : M20-6976.

[48] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.

[49] Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;19(368): m606.

[50] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan. Allergy 2020. https://doi.org/10.1111/all.14238.

[51] Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical Liu et al. 2020.

[52] Liu D, Li L, Wu X, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: a preliminary analysis. Am J Roentgenol. 2020;215(1):127–32. https://doi.org/10.2214/AJR.20.23072.

[53] Turan O, Hakim A, Dashraath P, Jeslyn WJL, Wright A, Abdul-Kadir R. Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 in- fection among hospitalized pregnant women: a systematic review. Int J Gynecol Obstet. 2020;151(1). https://doi.org/10.1002/ijgo.13329.

[54] Boushra MN, Koyfman A, Long B. COVID-19 in pregnancy and the puerperium: a review for emergency physicians. Am J Emerg Med 2020;40:193–8.

[55] Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory confirmed SARS-COV-2 infection by pregnancy status – United States, January 22-June 2 2020. Morb Mortal Wkly Rep 2020;69:769–75.

[56] What's new | COVID-19 Treatment Guidelines;2020 https://www.covid19treatmentguidelines.nih.gov/whats-new/(accessed January 2021).

[57] Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020;323:2249–51.

[58] Casto AM, Huang ML, Nalla A, Perchetti G, Sampoleo R, Shrestha L, Wei Y, Zhu H, Greninger AL, Jerome KR. Comparative performance of SARS-CoV-2 detection assays using seven different primers/probe sets and one assay kit. J Clin Microbiol 2020;JCM.00557-20.

[59] Wolfe R, Corman VW, Guggemos W, Seilmaier M, Zange S, Muller MA et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020. Published online April1. 2020. doi:101038/s41586-02-2196-x.

[60] CDC. Return-to-work criteria for healthcare workers. Update April 30.2020. Accessed May 3 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work/html.

[61] Butler-Laprorte G, Lawandi A, Schiller I, Yao M, Dendukuri N, McDonald EG, et al. Comparison of saliva and nasopharyngeal swan nuclei acid amplification testing for detection of SARS-CoV-2. A systematic review and meta-analysis. JAMA Int Med. 2021;181(3):353–60.

[62] To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020;20:565–74.

[63] Xiao AT, Gao C, Zhang S. Profile of specific antibodies to SARS-CoV-2: the first report. J Infect 2020(20):30138–9. S0163–4453.

[64] https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/covid-19 testing overview.html. Accessed 17/3/2021. Updated February 23rd 2021.

[65] https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html. Accessed 2/3/2021.

[66] Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis. 2020;ciaa310. Published online March 21, 2020. Doi:10.1093/cid/ciaa310.

[67] Jefferson T, Spencer EA, Brassey J, Heneghan C. Viral cultures for COVID-19 infectivity assessment – a systematic review. Clinical Infectious Dis 2020. https://doi.org/10.1093/cid/ciaa1764.

[68] https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html. SARS-CoV-2 Variant Classifications and Definitions. Updated June 1, 2021. Accessed June 2nd 2021.

[69] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al. for the China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019 N Engl J Med 2020; 382:727-733 DOI: 10.1056/NEJMoa2001017.

[70] Islam MR, Hoque MN, Rahman MS, Rubayet ASM, Akther M, Puspo JA et al. Genome-wide analysis of SARS-CoV-2 virus strains circulating worldwide implicates heterogeneity Nature Scientific Reports (2020) 10:14004 | https://doi.org/10.1038/s41598-020-70812-6.

[71] Abu-Raddad LJ, Chemaitelly H. Butt AA for the National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. N Eng J Med 2021. https://doi.org/10.1056/NEJMc2104974.

[72] Doherty AB, Harrison EM, Green CA, Hardwick H, Pius R, Norman L et al. Features of 16749 hospitalised UK patients with COVID-19 using the ISARIC WHO clinical characterisation protocol. medRxiv. doi: https://doi.org/10.1101/2020.04.23.20076042.

[73] Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team 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 2020 / 69(44);1641–1647.

[74] Cohen J, Vignaux O, Jacquemard F. Covid-19 in pregnant women: general data from a French national survey. Eur J Obstet Gynecol Reprod Biol 2020;251 (1):267–8. https://doi.org/10.1016/j.ejogrb.2020.06.002.

[75] Hirshberg A, Kern-Goldberger AR, Levine LD, Williams RP, Short WR, Parry S, et al. Care of critically ill pregnant patients with coronavirus disease 2019: a case series. Am J Obstet Gynecol 2020;223(2):286–90. https://doi.org/10.1016/j.ajog.2020.04.029.

[76] Yan J, Guo J, Fan C, Juan J, Yu X, Li J, Feng L et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020;223(1). https://doi.org/10.1016/j. ajog.2020.04.014 111.e1–111.e14.

[77] Marín Gabriel, Miguel A, Vergeli Mar Reyne, Carbonero Sonia Caserío, Laia Sole, Molina Tamara Carrizosa, et al. Maternal, perinatal, and neonatal outcomes with COVID-19: a multicenter study of 242 pregnancies and their 248 infant newborns during their first month of life. Pediatr Infect Dis J 2020. https://doi.org/10.1097/INF.0000000000002902. Still in print.

[78] San-Juan R, Barbero P, Fernández-Ruiz M, Lopez Medrano F, Lizasoain M, Hernandez-Jimenez P, et al. Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: a single-Centre cohort study from Spain. E Clin Med 2020;23:. https://doi.org/10.1016/j.eclinm.2020. 100407100407.

[79] Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med. 2020;144(7):799–805. https://doi.org/10.5858/arpa.2020-0901-SA.

[80] Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, et al. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. Jama Internal Medicine 2021;181:714–7.

[81] Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: a preliminary analysis. Am J Roentgenol. 2020;215(1):127–32. https://doi.org/10.2214/AJR.20.23072.

[82] Mathus B, Rentsch C, Morton CE, Schultz A, MacKenna B, Eggo RM, et al. Ethnic differences in SARS-CoV-2 infection and COVID-19 related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. Lancet 2021;397:1711–24.

[83] Morales DR, Ali SN. Covid-19 and disparities affecting ethnic minorities. Lancet 2021;397:1684–5.

[84] Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation 2020;141(20):1648–55. https://doi.org/10.1161/CIRCULATIONAHA.120. 046941.

[85] Thompson JL, Nguyen LM, Noble KN, Aronoff DM. COVID-19-related disease severity in pregnancy. Am J Reprod Immunol. November 2020;84(5):e13339. Doi: 10.111/aji.1339.

[86] Kuhrt K, McMicking J, Nanda S, Nelson-Piercy C, Shennan A. Placental abruption in a twin pregnancy at 32 weeks' gestation complicated by coronavirus disease 2019 without vertical transmission to the babies. Am J Obstetr Gynecol MFM. 2020;2(3):. https://doi.org/10.1016/j. ajogmf.2020.100135100135.

[87] Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, Pomar L. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA. 2020;323(21):2198–200. https://doi.org/10. 1001/jama.2020.7233.

[88] Freiesleben LCN, Egerup P, Hviid KVR, Severinsen ER, Kolte AM, Westergaard D, L et al. SARS-CoV-2 in first trimester pregnancy: a cohort study Hum Repro 2021 Jan 1;36(1):40-47. doi: 10.1093/humrep/deaa311.

[89] Cosma S, Carosso RA, Cusato J, Borella F, Carosso M, MBovetti M, Filippini C, D'Avolio A, Ghisetti V, Di Perri G, Benedetto C. Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients 2021 224:391.e1-391.e7.doi: 10.1016/j.ajog.2020.10.005

[90] Rotshenker-Olshinka K, Volodarsky-Perel A, Steiner N, Rubenfeld E, Dahan MH COVID-19 pandemic effect on early pregnancy: are miscarriage rates altered, in asymptomatic women? Archives of Gynecology and Obstetrics https://doi.org/10.1007/s00404-020-05848-0 Received: 31 August 2020 / Accepted: 14 October 2020.

[91] Flaherman VJ, Afshar Y, Boscardin J, Keller RL, Mardy AH, Prahl MK, et al. Infant outcomes following maternal infection with SARS-CoV-2: first report from the PRIORITY study. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa1411.

[92] Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. AnalysisofSARS-CoV-2verticaltransmissionduring pregnancy. Nat Commun 2020;11(1):5128. https://doi.org/10.1038/s41467-020-.

[93] Carosso A, Cosma S, Serafini P, Benedetto C, Mahmood T. How to reduce the potential risk of vertical transmission of SARS-CoV-2 during vaginal delivery? Eur J Obstet Gynecol Reprod Biol 2020;250:246–9. https://doi.org/10.1016/j.ejogrb.2020.04.065.

[94] Perlman S. Another decade, another coronavirus. N Engl J Med 2020;382 (8):760–2. https://doi.org/10.1056/NEJMe2001126.

[95] Knight M, Bunch, K,Vousden N, Vousden N, Morris E, Simpson N, Gale C et al. Characteristics and outcomes of pregnant women admitted to hospitals with confirmed SARS-CoV-2 infection in UK: national population-based cohort study. BMJ2020;369:m2017.

[96] Ahlberg M, Neovius M, Saltvedt S, SÖderling J, Pettersson K, Brandkvist C, Stephansson O. Association of SARS-CoV-2 test status and pregnancy outcome. JAMA 2020;324(17):1782–85.

[97] Handley SC, Mullin AM, Elovitz MA, Gerson KD, Montoya-Williams D, Lorch SA, Burris HH. Changes in preterm birth phenotypes and stillbirth at Philadelphia Hospitals during the SARS-CoV-2 pandemic, March-June 2020. JAMA. 2020;5:325(1):87–89.

[98] Stowe J, Smith H, Thurland K, Ramsay ME, Andrews N, Ladhani SN. Stillbirths during the COVID-19 pandemic in England, April-June 2020. JAMA 2021;325 (1):86–7.

[99] Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395 (10226):809–15.

[100] Baergen RN, Heller DS. Placental pathology in Covid-19 positive mothers: prelimi- nary findings. Pediatr Dev Pathol. 2020;23(3):177–80. https://doi.org/10.1177/1093526620925569.

[101] Chen S, Huang B, Luo DJ, Li X, Yang F, Zhao Y, Nei X, Huang BX. Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. Chinese journal of Pathology. 2020;49(0). https://doi.org/10. 3760/cma.j.cn112151-20200225-00138 E005.

[102] Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R. Clary B Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. EClinicalMedicin. 2020;29:10063. https://doi.org/10.1016/j.eclinm.2020.100639. Epub 2020 Nov 20.

[103] Metz TD, Clifton RG, Hughes BL, Sandoval G, Saade GR, Grobman WA, et al. for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Disease severity and perinatal outcomes of pregnant patients with Coronavirus Disease 2019 (COVID-19). Obstet Gynecol 2021;137 (137):571–80.

[104] Servante J, Swallo G, Thornton G, et al. Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis. BMC Pregnancy Childbirth 2021;21:108.

[105] Halscott T, Vaught J and the Society for Maternal-Fetal Medicine COVID-19 Task Force. Management Considerations for Pregnant Patients With COVID-19 Developed with guidance from 2.2.21 https://www.smfm.org/covid19. Accessed March 19th 2021

[106] Royal College of Obstetricians and Gynaecolgists, Royal College of Midwives, Royal College of Paediatrics and Child Health, Public Health England and Health Protection Scotland. Coronavirus (COVID-19) infection in pregnancy: information for Healthcare Professionals (version 11, July 34th 2020.

[107] Centers for Disease Control and Prevention (CDC). Considerations for Inpatient Obstetric Healthcare Settings https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html Updated Dec. 1, 2020 Accessed: February 18, 2021.

[108] National Institute of Health (NIH). Special Considerations in Pregnancy https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy/ Last Updated: August 27, 2020, Accessed March 19 2021

[109] The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 N Engl J Med 2021; 384:693-704. DOI: 10.1056/NEJMoa2021436.

[110] Royal College of Obstetricians and Gynaecologists, London. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top guideline No 37a, April 2015.

[111] Walker K F, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, Jim G Thornton JG Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: A systematic review and critical analysis BJOG. 2020 Oct;127(11):1324-1336. doi: 10.1111/1471-0528.16362. Epub 2020 Jul 22.

[112] Narvey M. Breastfeeding when mothers have suspected or proven COVID-19. Canadian Paediatric Society; 2020.

[113] Initiative UUBF. Statement on infant feeding on neonatal units during the coronavirus (COVID-19) outbreak 2020 [Available from: https://www.unicef.org.uk/babyfriendly/infant-feeding-on-neonatal-units- during-the-covid-19-outbreak/.

[114] Logunov DY, Dolzhikova IV, Tukhvatullin AI, Shcheblyakov DV. Safety and efficacy of the Russian covid-19 vaccine: more information needed—authors' reply. Lancet 2020;396:54–5. https://doi.org/10.1016/S0140-6736(20)31970-X.

[115] https://www.statnews.com/2021/02/02/comparing-the-covid-19-vaccines-developed-by-pfizer-moderna-and-johnson-johnson/ accessed 22March 2021.

[116] https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19 accessed 22nd March 2021.

[117] Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. for the CDC v-safe COVID-19 Pregnancy Registry Team Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. April 21, 2021. DOI: 10.1056/NEJM.

[118] Collier AY, McMahan K, Yu J, Tostanoski LH, Aguayo R, Ansel J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. JAMA 2021. https://doi.org/10.1001/jama.2021.7563.

[119] Warkentin TE, Cuker A. COVID-19: Vaccine-induced immune thrombotic thrombocytopenia (VITT). Update May 07 2021.

[120] Berghella V, Hughes B. COVID-19" pregnancy issues and antenatal care. Update May14, 2021.