# The Impact of COVID-19 on Pregnancy and Emerging Therapeutic Drug Development Options

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**Abstract**

Emerging data shows pregnant women with COVID-19 are at significantly higher risk of severe outcomes compared to non-pregnant women of similar age. This review discusses the invaluable insight revealed from vaccine clinical trials in women who were vaccinated and inadvertently became pregnant during the trial period. It further explores a number of clinical avenues in their management and proposes a drug development strategy in-line with clinical trials for vaccines and drug treatments for the drug development community. Little is known of the long-term effects of COVID-19 on the mother and the baby. We provide a rationale for our hypothesis that COVID-19 predisposes pregnant women to cardiovascular diseases later in life, in a similar way, to preeclampsia and may increase the risk of preeclampsia in their subsequent pregnancy. This is an ever-evolving landscape and early knowledge for healthcare providers and drug innovators is offered to ensure benefits outweigh the risks.

## Introduction

Coronavirus-19 disease (COVID-19) continues to spread across the world, creating an unprecedented global public health crisis. Protracted cardiovascular effects, especially in those with pre-existing disease, may occur in COVID-19 (1, 2). Cardiovascular disease is the most common co-morbidity associated with COVID-19. The mortality rate in COVID-19 patients with cardiovascular disease is higher compared to other comorbidities, such as diabetes, chronic kidney disease or cancer (3).

With 131 million women giving birth annually, governments have taken steps to safeguard this group, earmarking them as at risk (4). Emerging data from the United Kingdom and United States highlights an increased risk of pregnant women with COVID-19 requiring intensive care admission (5-7). A multicentre retrospective cohort study in Washington State showed the COVID-19 hospitalisation and case fatality rate in pregnant patients was 13.6-fold higher compared to similarly aged individuals (8). Regulators alongside medical societies now recommend clinicians should offer COVID-19 vaccines to pregnant women on a case-by-case basis. However, with limited data available, making an evidence-based decision is challenging. In addition, new and faster spreading severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants have added further urgency for the vaccine push, especially for priority groups (9). Here we explore how the drug development community should manage the need to keep pregnant women safe from COVID-19. The long-term sequalae of COVID-19 is evolving and many organ systems may be implicated. In this review, we hypothesise and provide a rationale why pregnant women with COVID-19 may also experience a higher risk of

cardiovascular disease, stroke and dementia in later life in a similar way to women with preeclampsia (10). Indeed, a recent US study showed that pregnant women with COVID-19 had higher incidence of myocardial infarction, venous thromboembolism and preeclampsia events (11). This data supports our hypothesis that pregnant women with moderate-severe COVID-19 are predisposed to increased long-term cardiovascular risk later in life and increased risk of preeclampsia in their subsequent pregnancy.

**Clinical manifestations of COVID-19 in pregnant women, the fetus and neonate**

Women of reproductive age are reported to comprise 21% of all COVID-19 cases. Nine per cent of whom were pregnant at the time of the test (12). Viral respiratory illnesses are associated with a higher risk of obstetric complications and adverse perinatal outcomes, including pneumonia, preterm labour and low birth weight (13-16). The previous coronavirus infections: severe acute respiratory syndrome and Middle East respiratory syndrome (SARS) demonstrated higher rates of maternal and fetal complications and mortality, warranting close attention to pregnant women in the current pandemic (17). Data from prospective cohort studies have suggested that maternal outcomes overall in COVID-19 were similar to non-pregnant women (18, 19). The incidence of hospitalisation of UK pregnant women with symptomatic SARS-CoV-2 has been estimated as 2.0 per 1000 maternities (March to August 31$^{st}$ 2020) (5). The clinical situation is, however, evolving and results from a large and regularly updated US dataset suggests pregnant women with COVID-19 are at significantly higher risk of severe outcomes compared with non-pregnant women, including intensive care treatment, invasive ventilation, extracorporeal membrane oxygenation and death (7). Although this retrospective study does have limitations,

such as substantial missing data and pregnancy status ascertained in 36% of women of reproductive age only, it flags risks that cannot be ignored, particularly in the light of more infectious strains of SARS-CoV-2. Data from the UK has also recently indicated the proportion of pregnant women admitted to intensive care is increasing, especially in comparison to the first wave of COVID-19 (6) possibly indicating the impact of the 'Kent' variant (B.1.1.7) that is widespread in the country.

As with non-pregnant individuals, advanced age, obesity, pre-existing hypertension and diabetes are significant risk factors and increase the chances of a more severe disease presentation and evolution (12, 20). Interestingly, a living systemic review identified pregnant women as less likely to present with fever and myalgia (20). This may be due to routine testing of all pregnant women and therefore the identification of asymptomatic sufferers.

SARS-CoV-2 infection may increase the risk of pre-term delivery to manage obstetric or medical complications, but rates of spontaneous pre-term labour do not appear to be elevated (20). The incidence of stillbirth and neonatal death do not seem to be higher than the background rate (5, 7, 20). Admission to neonatal units has been noted to be increased in studies (5). The rationale for this increase may include local policies on observation and quarantine of infants with exposure to SARS-CoV-2.

In utero vertical transmission has been reported in case studies and although rare, the SARS-CoV-2 genome has been found in umbilical cord blood, amniotic fluid, maternal vaginal mucosa and full-term placenta (21). Fortunately, infection of neonates and infants is uncommon (22). If neonates do become infected, most

cases are asymptomatic or mild and outcomes are favourable (23, 24). Most complications in neonates born to COVID-19 positive mothers are a result of prematurity rather than COVID-19 infection (25). Interestingly, both IgG and IgM antibodies against COVID-19 have been found in seronegative neonates born to COVID-19 infected mothers (26). As IgM antibodies cannot cross the placenta, the suggestion of a fetal immune response against the virus is possible (26).

SARS-CoV-2 appears to attack the cardiovascular system, causing numerous cardiovascular complications. Over 20%–30% of all adult patients hospitalised with COVID-19, have some evidence of myocardial involvement (1, 2, 27). The virus induces an overactive inflammatory response with increased production of tumour necrosis factor (TNF), interleukin-6 (IL-6), and IL-1β leading to increased risk of vascular hyperpermeability (28). Recent evidence also suggests SARS-CoV-2 may also directly attack the vascular endothelium and disrupt vascular barrier, leading to disseminated intravascular coagulation and inflammatory cell infiltration (29, 30). Cardiac blood marker analysis from patients recovered from COVID-19 infection showed ongoing myocardial inflammation in 60% of participants, independent of pre-existing conditions, severity and overall course of the acute illness (27). Chronic myocardial inflammation may lead to long-term consequences to cardiovascular system. In addition, myocarditis has been seen in previously healthy subjects including pregnant women with COVID-19 (31). Preeclampsia is associated with chronic immune activation that leads to an increased production of inflammatory cytokines by proinflammatory T cells (32, 33). The risk of developing chronic hypertension later in life increases by two to eight-fold in women with hypertensive pregnancy disorder compared to normotensive pregnancy (34-37). Women with a

history of preeclampsia have 3.7-fold risk of developing hypertension 14 years post pregnancy, twice the risk of developing ischemic heart failure after 11.7 years and twice the risk of getting stroke 10.4 years after their pregnancy (38). Just like preeclampsia, COVID-19 affects the lining of the blood vessels and SARS-CoV-2-mediated endothelial cell injury is an important effector of the virus causing multi-organ damage. We hypothesise, that these damages may cause higher risk of cardiovascular disease, stroke and dementia in later life in a similar way to women with preeclampsia.

**Therapeutic options and specifics of drug development in pregnancy**

Researchers around the world are working at record pace to progress treatment and prophylactic options for COVID-19. Any drug or vaccine candidate needs to be evaluated for risk/benefit in pregnant women plus potential effects on the fetus, newborn and breastfed infant. In this global emergency, methods to accelerate the understanding of risk/benefit profiles must ensure inclusion of special groups such as pregnant women, and include the conduct of developmental and reproductive toxicity (DART) studies and using already established pregnancy and post-marketing registries (39) (Figure 1).

**Vaccines**

The effectiveness of SARS-CoV-2 immunisation during pregnancy, depends upon the efficacy of the vaccine in inducing protective immune responses coupled with the timing of vaccine delivery. Drug developers seek to harmonise peak vaccine response with the time of greatest vulnerability in pregnancy. This needs to be offset by any impact on fetal programming and adverse outcomes. Phase II and phase III

trials have strict processes and checkpoints to ensure patient safety. These include internal development and safety physicians, independent Data Monitoring Committees (DMC) and regulatory compliant pharmacovigilance and safety reporting pathways (40, 41). During the pandemic, regulators have undertaken rolling review (42) of vaccine data and independent vaccine committees offer input. These platforms could be modified to have a pregnancy focus with a maternal-fetal expert on the DMC.

There are over 200 vaccines in development, with 63 vaccines in clinical stage evaluation (43). A handful of vaccines are rolling out in select countries following regulators' approval. These include Pfizer-BioNTech and Moderna, which use the instructions from the mRNA. In contrast, vaccines from Janssen and AstraZeneca-University of Oxford's viral vector utilises the double-stranded DNA for immunisation. The interim results from Janssen's phase III clinical trial, one dose DNA vaccine, are with the U.S. Food and Drug Administration (FDA). It could win emergency-use authorisation within two to three weeks. These mRNA and DNA vaccines are in fact example of 'gene therapy' delivered either using an replication-deficient adenoviral vector or lipid-based, biodegradable carriers (44). None of the compounds are live attenuated vaccines, so could be used in pregnancy but no data is available on the use of mRNA vaccines in pregnant or breastfeeding women. These and other currently recruiting large-scale vaccine studies have not actively recruited pregnant women (although Janssen do enrol breastfeeding women), leading to limitations in safety data in a group that is potentially at risk.

Inactivated virus technology is 'tried and tested' methodology for developing vaccines and historically have a good safety profile both in the short-term and long-term evaluation. This approach may be a safer for the pregnant women and for future generations of COVID-19 vaccines as the virus mutates. The use of ‘inactivated whole virus’ used by Sinovac from SinoPharma may offer greater protection than vaccines that only target ‘a single spike protein’. The SinoPharma vaccine has gone into the arms of over twelve million people around the world including multi-ethnic groups in United Arab Emirates, but the company has yet to publish their phase III clinical data.

Inclusion of pregnant women in vaccine trials, especially those looking to rapidly deliver results, is challenging but maternal immunisation is a highly successful tool and can, critically, provide dual protection. The influenza vaccine protects both the mother and infant and pertussis vaccines given in pregnancy afford passive protection to the infant (45). The prospect of passive immunity through IgG transfer from a vaccinated pregnant mother is an attractive additional benefit for COVID-19 vaccines (46).

Current vaccine studies include thousands of female subjects. Extrapolating data from women of childbearing age in clinical trials and those who inadvertently become pregnant offers invaluable insights. Women accounted for approximately 49.4% of Pfizer-BioNTech BNT162b2 phase III trial participants and as of the 14th November 2020 data cut, 23 participants reported intercurrent pregnancy (12 subjects in the vaccine group) (47). The Moderna mRNA-1273 trial reported 13 reports of inadvertent pregnancies (6 cases in the vaccine group as of December 2, 2020) (48).

The Oxford-AstraZeneca AZD1222 phase III trial has reported 21 pregnancies (12 in the vaccine group as of November 21, 2020). Of these pregnancies, five ended in spontaneous abortion, two in the AZD1222group (49). Outcomes of cases are actively being followed.

With a total of 57 inadvertent pregnancies and limited details on outcomes currently reported, additional strategies to help provide data are needed. DART studies can be conducted early in a clinical development plan, including during the preclinical phase and are recommended by regulators (39). Many structural and functional parallels exist between human and animal models, providing a valuable platform for evaluating safety and efficacy of potential drug candidates. Rodents, for example, have a haemochorial placenta, short gestation and large litters making them ideal for performing high throughput screening of candidate therapeutics (50). Animal models are important for identifying drug-related teratogenic effects and their timing during pregnancy. For example, rodent and rabbit models were instrumental in demonstrating drug-related teratogenic effects of artemisinin-based combination therapies for malaria were limited to the first trimester (51). Animal studies can provide the first insights into the optimum window to administer COVID-19 vaccines and if any teratogenic effects exist. DART studies with BNT162b2, Moderna and limited data from AstraZeneca have revealed no vaccine related effects on female fertility, pregnancy, or embryo-fetal development (47). Data from DART studies can be extrapolated to other compounds with similar mechanisms of action. Interim data from Janssen's Ad26.COV2.S has just been released. This programme offers a unique opportunity as it is a single dose strategy and there is already some working data on the effects in pregnancy. Ad26+ has had exposure in Ebola (1000 patients).

Pregnant women are excluded from the Phase III COVID-19 trial, but breastfeeding women are eligible. Janssen alongside other Sponsors should prioritise publishing available data on pregnant women, in juxtaposition, with the rest of their data. The early completion of DART studies is critical and could offer a catalytic step to earlier recruitment of pregnant women in vaccines and novel agent development plans.

The data from currently approved vaccines has not indicated any safety concerns, allowing the regulatory bodies like MHRA and FDA to recommend that clinicians undertake case-by-case assessments for the use of COVID-19 vaccines by pregnant women, particularly those with high-risk comorbidities (52). Unfortunately, with minimal available data, this is challenging. An example of this is with maternal hyperthermia, which particularly in the first trimester is associated with neural tube defects and other congenital abnormalities (53). All three licensed vaccines have reported pyrexia, a symptoms of vaccine reactogenicity, as very common (> 10%). Clinicians will need to infer conclusions, such as potentially avoiding immunisation in the first trimester until further data is available. Other open clinical questions include how long immune protection lasts and if a vaccine is given pre-conception, will it safeguard the whole pregnancy. To aid decision-making, DART studies should be published, alongside regular updates from inadvertent pregnancy outcomes and a rolling review of all post-marketing studies. Regulators have asked that sponsors commit to post-marketing safety and active surveillance studies and registries in pregnant women. Currently on-going and prospective studies are listed in Table 1.

In the US, vaccines are currently being prioritised in a phased approach, with healthcare workers participating in wave 1a. Approximately, 75% of the US

healthcare workers are women and it is estimate 330,00 women could be pregnant or postpartum during the first phase of vaccine implementation. This and other large-scale data from pregnancy-specific cohorts will further the understanding of whether pregnancy alters the effectiveness of treatments and if there is any impact on fetal development and breastfeeding. These women will all be followed up via pregnancy registries or post-marketing studies. Rare adverse drug reactions will, however, only be picked up once the vaccines enter general use, therefore, pregnancy registries specific to vaccines are essential. Obstetricians, general physicians and midwives should be made aware of safety reporting pathways in their individual countries to facilitate this process.

SARS-CoV-2 variants have arisen in several locations including the United Kingdom, South Africa and Brazil. Although the current crops of vaccines are likely be effective for the British and South African variants, the Brazilian variants have been identified with changes to the receptor-binding domain (54, 55). Future mutations may further increase transmission and also, worryingly for pregnant women, virulence. Drug developers from the 200 other vaccines in development should aim to evaluate safety markers in pregnancy and follow the successful precedent set by the approved vaccines to advance the inclusion of pregnant women in COVID-19 trials.

**Medical treatments**

Repurposing drugs with known safety profiles in pregnancy is an attractive approach with COVID-19. The RECOVERY trial is an open-label, platform study which is currently enrolling pregnant women into convalescent plasma, synthetic neutralising antibodies (Regeneron's REGN10933 and REGN10987), aspirin and tocilizumab

arms (56). The study design includes protocol-specific pregnancy documents prepared by a panel of maternal-fetal experts, and a pregnancy lead appointed to work with the Principal Investigator at each site. The study has shown a mortality benefit of low dose dexamethasone in patients with COVID-19 who required respiratory support, which is now a cornerstone for COVID-19 management (57). No pregnancy associated adverse outcomes have been reported.

Remdesivir has been shown to reduce time to recovery, particularly in those requiring supplemental oxygen (58). It was used to treat pregnant women during the Ebola and Marburg virus epidemics (59) and although the recent trial in COVID-19 did not include pregnant women, there were no significant safety concerns reported in women of childbearing potential (58). Its subsequent use by hospitalised pregnant women suffering with severe COVID-19 disease has occurred via expanded access programs (60). Evaluation of the first 86 pregnant women to use the drug from five countries has been favourable, demonstrating high recovery rates within 28 days and low rates of serious adverse events (60). The use of steroids and remdesivir are now included in national guidelines (61). Several trials and observational studies looking at convalescent plasma have included pregnant women (62). Results are conflicting but convalescent plasma may offer a benefit when given early in the course of the disease. The results from large studies including RECOVERY are expected shortly.

There are several trials looking at interferon (IFN) alpha and beta use in COVID-19, mostly in addition to antivirals. Results with injectable forms have been disappointing (63). An investigational inhaled nebulised IFN beta-1a (SNG001) has however,

shown some promise. When administered to hospitalised patients with COVID-19 in a phase IIb study, the likelihood of recovery by day 15 compared with placebo was increased (63). Several studies (mostly in multiple sclerosis) have shown no increase in congenital abnormalities with INF use (64), this coupled with the potentially to bypass the placenta makes nebulised IFN beta-1a an attractive option for pregnant women. DART studies should also be conducted with this investigational product to allow further insights to the risk/benefit in pregnant women. The use of other agents such as monoclonal antibody therapies have shown some promise in clinical trials and case-reports of use in pregnant women are growing (65, 66). Given the potential for higher risk in pregnant women, in the absence of absolute contraindications, it may be reasonable to include pregnant women in clinical trials of these therapeutic approaches.

The COVID-19 pandemic has fuelled innovation never previously seen. The collaborative links between industry, academic, regulatory and government bodies has allowed clinical development programmes, which usually take a decade to be delivered in less than a year. This momentum and lessons learned for efficient and patient centred drug development plans should now go beyond SARS-CoV-2 and to other infectious states, which severely impact pregnancy and neonates such as zika and respiratory syncytial virus.

**Conclusion**

Immunisation and treatment strategies for pregnant women during the COVID-19 pandemic should be tailored to optimise protection for the mother, the fetus and the infant. The race to find appropriate treatments and vaccines for COVID-19 is

progressing swiftly, but with the urgency of more transmissible variants and more intensive care admissions, strategies to enrol pregnant women earlier into clinical development plans should be utilised. To ensure safety of pregnant women and neonates, drug developers should prioritise early initiation of DART studies followed by systematic review of inadvertent pregnancies during clinical trials in the general population. Figure 2 summaries our recommendations for vaccine and drug development and accessibility for pregnant patients with COVID-19. This, coupled with industry supported pregnancy registries and close collaboration with regulators and government bodies, will allow pregnant women to have access to investigational clinical trials whilst mitigating potential risks.

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**CONFLICT OF INTEREST**

None.

## References


1. Bandyopadhyay D, Akhtar T, Hajra A, Gupta M, Das A, Chakraborty S, et al. COVID-19 Pandemic: Cardiovascular Complications and Future Implications. Am J Cardiovasc Drugs. 2020;20(4):311-24.
2. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. Heart Rhythm. 2020;17(11):1984-90.
3. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS One. 2020;15(8):e0238215.
4. Lerberghe WV, Manuel A, Matthews Z, Wolfheim C. World Health Report 2005 make every mother and child count.; 2005.
5. Vousden N, Bunch K, Morris E, Simpson N, Christopher, O'Brien P, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: a national cohort study using the UK Obstetric Surveillance System (UKOSS). MedRxiv. 2021.
6. ICNARC. Intensive care national audit & research centre report on COVID-19 536 in critical care: England, Wales and Northern Ireland.: Intensive care national audit & research centre 2021 8 January 2020.
7. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. Morbidity and Mortality Weekly Report. 2020;69(44):1641–7.
8. Lokken EM, Huebner EM, Taylor GG, Hendrickson S, Vanderhoeven J, Kachikis A, et al. Disease Severity, Pregnancy Outcomes and Maternal Deaths among Pregnant Patients with SARS-CoV-2 Infection in Washington State. American Journal of Obstetrics and Gynecology. 2021.
9. Organisation WH. SARS-CoV-2 Variants. Disease outbreak news: World Health Organisation; 31 December 2020 [Available from: https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/.
10. Ahmed A, Rezai H, Broadway-Stringer S. Evidence-Based Revised View of the Pathophysiology of Preeclampsia. Adv Exp Med Biol. 2017;956:355-74.
11. 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 Intern Med. 2021.
12. 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 7, 2020. Morbidity and Mortality Weekly Report. 2020;69(25):769–75.
13. Chen YH, Keller J, Wang IT, Lin CC, Lin HC. Pneumonia and pregnancy outcomes: a nationwide population-based study. Am J Obstet Gynecol. 2012;207(4):288 e1-7.
14. Ramsey PS, Ramin KD. Pneumonia in pregnancy. Obstet Gynecol Clin North Am. 2001;28(3):553-69.

15. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517-25.
16. Banhidy F, Acs N, Puho EH, Czeizel AE. Maternal acute respiratory infectious diseases during pregnancy and birth outcomes. Eur J Epidemiol. 2008;23(1):29-35.
17. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound Obstet Gynecol. 2020;55(5):586-92.
18. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RRJ, et al. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA Netw Open. 2020;3(11):e2029256.
19. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020;369:m2107.
20. 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.
21. Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. Nat Commun. 2020;11(1):5128.
22. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(2):100107.
23. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. JAMA Pediatr. 2020;174(7):722-5.
24. 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.
25. Flaherman VJ, Afshar Y, Boscardin J, Keller RL, Mardy A, Prahl MK, et al. Infant Outcomes Following Maternal Infection with SARS-CoV-2: First Report from the PRIORITY Study. Clin Infect Dis. 2020.
26. 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.
27. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(11):1265-73.
28. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020;8(6):e46-e7.
29. Greene R, Zapol WM, Snider MT, Reid L, Snow R, O'Connell RS, et al. Early bedside detection of pulmonary vascular occlusion during acute respiratory failure. Am Rev Respir Dis. 1981;124(5):593-601.

30. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-8.
31. Juusela A, Nazir M, Gimovsky M. Two cases of coronavirus 2019-related cardiomyopathy in pregnancy. Am J Obstet Gynecol MFM. 2020;2(2):100113.
32. Clark P, Boswell F, Greer IA. The neutrophil and preeclampsia. Semin Reprod Endocrinol. 1998;16(1):57-64.
33. Bennett WA, Lagoo-Deenadayalan S, Stopple JA, Barber WH, Hale E, Brackin MN, et al. Cytokine expression by first-trimester human chorionic villi. Am J Reprod Immunol. 1998;40(5):309-18.
34. Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, et al. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ. 2017;358:j3078.
35. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension. 2009;53(6):944-51.
36. Bokslag A, Teunissen PW, Franssen C, van Kesteren F, Kamp O, Ganzevoort W, et al. Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life. Am J Obstet Gynecol. 2017;216(5):523 e1- e7.
37. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, Vogelvang TE, Lely AT, Franx A, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. BJOG. 2018;125(13):1642-54.
38. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.
39. ICH. ICH guideline M3(R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals 2009 [Available from: https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf.
40. FDA. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. In: Services USDoHaH, editor. 2006.
41. EMEA. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95),ICH Topic E 6, Step 5, , Consolidated Guideline 1.5.1996. In: EMEA L, editor. 1996.
42. EMA. EMA starts first rolling review of a COVID-19 vaccine in the EU 2021 [Available from: https://www.ema.europa.eu/en/news/ema-starts-first-rolling-review-covid-19-vaccine-eu.
43. WHO. Draft landscape and tracker of COVID-19 candidate vaccines: World Health Organisation; 2021 [Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
44. Park KS, Sun X, Aikins ME, Moon JJ. Non-viral COVID-19 vaccine delivery systems. Adv Drug Deliv Rev. 2021;169:137-51.
45. Shakib JH, Korgenski K, Presson AP, Sheng X, Varner MW, Pavia AT, et al. Influenza in Infants Born to Women Vaccinated During Pregnancy. Pediatrics. 2016;137(6).
46. Flannery DD, Gouma S, Dhudasia MB, Mukhopadhyay S, Pfeifer MR, Woodford EC, et al. Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. JAMA Pediatr. 2021.

47. FDA. Vaccine and related biolofical products advisory committee: Pfizer-Biontech COVID-19 Vaccine (BNT162, PF-07302048) VRBPAC Briefing Document. 2020.
48. FDA. Vaccines and Related Biological Products Advisory Committee Meeting: Moderna COVID-19 Vaccine VRBPAC Briefing Document. 2020.
49. MHRA. Public Assessment Report Authorisation for Temporary Supply: COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S[recombinant]). In: (DHSC) DoHaSC, editor. 2020.
50. Grigsby PL. Animal Models to Study Placental Development and Function throughout Normal and Dysfunctional Human Pregnancy. Semin Reprod Med. 2016;34(1):11-6.
51. Clark RL. Embryotoxicity of the artemisinin antimalarials and potential consequences for use in women in the first trimester. Reprod Toxicol. 2009;28(3):285-96.
52. RCOG. Royal College of Obstetricians and Gynaecologists. Updated advice on COVID-19 vaccination in pregnancy and women who are breastfeeding 2020 [
53. Graham JM, Jr. Update on the gestational effects of maternal hyperthermia. Birth Defects Res. 2020;112(12):943-52.
54. Voloch CM, Jr RdSF, Almeida LGPd, Cardoso CC, Brustolini OJ, Gerber AL, et al. Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. MedRxiv. 2020.
55. Resende PC, Bezerra JF, Vasconcelos RHTd, Arantes I, Appolinario L, Mendonça AC, et al. Spike E484K mutation in the first SARS-CoV-2 reinfection case confirmed in Brazil, 2020: virological.org; 2021 [Available from: https://virological.org/t/spike-e484k-mutation-in-the-first-sars-cov-2-reinfection-case-confirmed-in-brazil-2020/584.
56. RecoveryTrial. RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY): recoverytrial.net; 2020 [Available from: https://www.recoverytrial.net/files/recovery-protocol-v12-1-2020-12-16.pdf.
57. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.
58. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-26.
59. Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019;381(24):2293-303.
60. McCoy JA, Short WR, Srinivas SK, Levine LD, Hirshberg A. Compassionate use of remdesivir for treatment of severe coronavirus disease 2019 in pregnant women at a United States academic center. Am J Obstet Gynecol MFM. 2020;2(3):100164.
61. RCOG. Royal College of Obstetricians and Gynaecologists. Coronavirus (COVID-19) infection in pregnancy. RCOG guideline: Royal College of Obstetricians and Gynaecologists; 2020 [Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/2020-10-14-coronavirus-covid-19-infection-in-pregnancy-v12.pdf.
62. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. The New England Journal of Medicine. 2021.

63. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020.
64. Hellwig K, Geissbuehler Y, Sabido M, Popescu C, Adamo A, Klinger J, et al. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. J Neurol. 2020;267(6):1715-23.
65. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. MedRxiv. 2021.
66. Naqvi M, Zakowski P, Glucksman L, Smithson S, Burwick RM. Tocilizumab and Remdesivir in a Pregnant Patient With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2020;136(5):1025-9.

## Figure Legend

**Figure 1.** Diagram to illustrate the recommendations for inclusion of pregnant women in COVID-19 vaccine and drug development trials. Vaccine and drug development during the COVID-19 pandemic has accelerated, with phases overlapping and at risk vaccine production during clinical trials. Developmental and Reproductive Studies should take place as early as possible in the clinical development programme, ideally during preclinical evaluation of diverse animal models. Inclusion of pregnant women in Phase III with rolling review by data monitoring and safety committees, as well as post-marketing studies will provide clinicians with data to make evidence-based decisions.

**Figure 2.** Recommendations for vaccine and drug development and accessibility for pregnant patients with COVID-19.