COVID-19 and the cardiovascular system in pregnancy

***Anna S. Herrey*[*], *Ayesha Osman*[#], *P Soma-Pillay*[†], *Karen Sliwa*[‡,∞] *and Ntobeko A.B. Ntusi*[‡,∞,ʃ]

[*]Barts Heart Centre, Barts NHS Trust and University College London, London, United Kingdom
[#]Department of Obstetrics and Gynaecology, Groote Schuur Hospital and University of Cape Town, Observatory, Cape Town, South Africa
[†]Department of Obstetrics and Gynaecology, Maternal and Fetal Medicine, Steve Biko Academic Hospital and University of Pretoria, Pretoria, South Africa
[‡]Hatter Institute for Cardiovascular Research in Africa, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, South Africa
[∞]Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Observatory, Cape Town, South Africa
[ʃ]Cape Universities Body Imaging Centre, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, South Africa

Address for correspondence:
Dr Anna S. Herrey
St Bartholomew's Hospital/Barts Heart Centre
West Smithfield
London
EC1A 7BE
United Kingdom

Email:
a.herrey@nhs.net

ABSTRACT

Pregnancy and coronavirus disease-2019 (COVID-19) share several common features which makes differentiation between the 2 difficult. Both are multisystem disorders, may present with breathlessness, are associated with hypercoagulability and frequently cause significant anxiety in both the patient and those around them. Pregnancy represents a state of partial immune suppression, with pregnant women more vulnerable to viral infections. However, these concerns have not been borne out in clinical practice and have not stood up to epidemiological scrutiny. From limited data available on COVID-19 in pregnancy, the outcomes are mostly favourable. While cardiac disease and hypertension are independent predictors of hospital admission with COVID-19 in pregnancy, the prevalence of cardiac disease in the pregnant COVID-19 population is low. Pregnant women are younger, and asymptomatic SARS-CoV-2 infection and favourable outcomes are reported in those below 55 years of age. Indeed, large numbers of asymptomatic cases have been reported in pregnancy, suggesting that pregnant patients with more severe disease courses may be over-represented in the current literature, particularly the early case reports and case series. Cardiovascular involvement in pregnancy includes new-onset hypertension, myocarditis, cardiomyopathy, pulmonary embolism and a pre-eclampsia-like syndrome. SAHeart 2020;17:288-295

INTRODUCTION

Pregnancy and coronavirus disease-2019 (COVID-19) share several common features: both are multisystem disorders, may present with breathlessness, are associated with hypercoagulability and frequently cause significant anxiety in both the patient and those around them – see Table I for abbreviations. Pregnancy represents a state of partial immune suppression, with pregnant women more vulnerable to viral infections, and morbidity and mortality higher even with seasonal influenza. In addition to influenza, infection with H1N1, Zika, Middle East respiratory syndrome (MERS) and severe acute respiratory distress syndrome (SARS) during pregnancy may have catastrophic effects on both mother and baby: pregnant women have worse outcomes, including higher mortality rates and higher risk of fetal loss, preterm birth and growth restriction. For MERS and SARS, case fatality rates are as high as 23% - 25%.[1,2] Zika virus infection, on the other hand, affects cerebral and ocular development in utero, while maternal outcomes are largely unaltered.[3] Given its aetiological agent, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a related virus and there has been concern that the COVID-19 epidemic may have serious consequences for pregnant women and their babies. However, these concerns have not been borne out in clinical practice and have not stood up to epidemiological scrutiny.

Interim guidance has been issued by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) on managing COVID-19, which include some recommendations specific to pregnant women, mostly drawn on experience from previous coronavirus outbreaks.[4,5]

TABLE I: Abbreviations.

ACOG	American College of Obstetricians and Gynecologists
AHA	American Heart Association
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease-2019
CVD	Cardiovascular disease
MERS	Middle East Respiratory Syndrome
SARS	Severe Acute Respiratory Distress Syndrome
SARS-CoV-2	Severe Acute Respiratory Distress Syndrome Coronavirus-2
UKOSS	United Kingdom Obstetric Surveillance System
WHO	World Health Organization

Chinese expert recommendations for the care of pregnant women with suspected and confirmed COVID-19 were developed and disseminated in China quite early following the outbreak in Wuhan,[6] and have been dynamic and evolving as more knowledge about epidemiology, pathogenesis, disease progression and clinical course among infected pregnant patients has been gathered. With thousands of pregnant women treated for COVID-19 and delivered in China, there have been no pregnancy-related deaths.[7,8] The Royal College of Obstetricians and Gynaecologists (RCOG), for example, classifies pregnant women as vulnerable, advising them to shield – incorporating guidance from the UK Maternal Cardiac Society – which states women with significant cardiovascular disease (CVD), congenital or acquired, should be treated as extremely vulnerable, based on expert consensus rather than evidence.[9] The South African National Department of Health has also promulgated guidance on COVID-19 and maternal care, which mandate that high risk women should be managed in a designated unit, but do not make specific reference to CVD.[10] While there have been many case reports and small case series, the scarcity of published data on pregnancy associated with COVID-19 has meant that guidance in many countries is based less on evidence and more on consensus opinion of experts and on data extrapolated from other respiratory viral infections.

At a time when health services were overwhelmed with COVID-19 cases globally, healthcare workers on the frontline experienced a new syndrome of covid-centricity, where breathlessness and hypoxia, including in pregnant women, is readily ascribed to COVID-19, risking cardiac decompensation in pregnancy from either pre-existing or new CVD being overlooked, with potentially life-threatening consequences for mother and unborn baby.[9]

POTENTIAL RISKS OF COVID-19 IN PREGNANCY

Hypertensive disorders of pregnancy, which include pre-eclampsia and eclampsia, are the most common direct cause of maternal mortality and account for 18% of all maternal deaths in South Africa.[11] Pre-eclampsia is diagnosed in women presenting with a blood pressure of >140/90mmHg accompanied by proteinuria or the evidence of organ dysfunction after the 20th week of pregnancy.[11] Typical presentations of pre-eclampsia and eclampsia include headaches, seizures, loss of consciousness, haemolysis, elevated liver enzymes, thrombocytopenia and renal dysfunction. Several disorders such as acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura and haemolytic uremic syndrome have previously proved to imitate pre-eclampsia, because they share similar clinical and laboratory findings of patients with pre-eclampsia. An accurate diagnosis is important when caring for such patients, as the management and prognosis of these conditions differ widely.

Although COVID-19 is primarily a respiratory infection, it has important systemic effects including hypertension, renal disease, thrombocytopenia and liver injury.[12] SARS-CoV-2 invades the host through cell entry via the receptor angiotensin-converting enzyme 2 (ACE2), resulting in dysfunction of the renin-angiotensin-aldosterone system.[13] By contrast, pre-eclampsia is the consequence of endothelial damage caused by placental oxidative stress and angiogenic imbalance. In a prospective observational study of 42 consecutive pregnancies, 12% developed features of pre-eclampsia – all with severe presentations. However, abnormal angiogenic biomarkers and uterine artery pulsatility could only be demonstrated in one case, suggesting that severe COVID-19 infection among pregnant women may induce a pre-eclampsia-like syndrome.[12] Furthermore, a retrospective case series of hospitalised patients with COVID-19 showed that 36% of patients had neurological symptoms including headache, seizures and loss of consciousness.[14] Low platelets and elevated liver enzymes have also been reported in patients with COVID-19, including those with acute cerebrovascular manifestations.[15] Women presenting with these overlapping clinical scenarios require an accurate diagnosis, because misdiagnosis and incorrect management have implications for pregnancy outcome and infection control practices.

Changes in the coagulation system during pregnancy produce a physiological hypercoagulable state, in preparation for haemostasis following delivery. Concentrations of clotting factors, particularly factors VIII, IX and X, are increased. Fibrinogen levels rise significantly by up to 50% and fibrinolytic activity is decreased. Concentrations of endogenous anticoagulants such as antithrombin and protein S decrease. Thus,

pregnancy alters the balance within the coagulation system in favour of clotting, predisposing the pregnant and postpartum woman to venous thrombosis. SARS-CoV-2 infection further increases the risk for thrombosis by causing the release of inflammatory cytokines that induce the production of tissue factor and activate thrombin and clot formation.[16] In non-pregnant patients admitted to the intensive care with COVID-19 pneumonia, the frequency of venous thrombo-embolic disorders was 25%,[17] but arterial and venous thrombo-embolism is described in 31% of those admitted with COVID-19 pneumonia.[18] Thrombotic complications such as ovarian vein thrombosis and pulmonary emboli have also been reported in pregnant women with COVID-19,[19,20] while the first COVID-19 maternal death reported in the United Kingdom was the result of pneumonia complicated by thrombosis.[21] The South African Framework and Guidelines for Maternal and Neonatal Care for COVID-19 recommend that low-molecular-weight heparin be considered for all women admitted to hospital with COVID-19.[10]

CURRENT STATE OF KNOWLEDGE ON COVID-19 AND PREGNANCY

Asymptomatic infection with SARS-CoV-2 appears to be common in pregnant women. After implementation of universal testing in 2 affiliated New York City hospitals, asymptomatic infection of a third of pregnant women presenting to their maternity services was noted.[22] Seventy-one percent developed symptoms during their pregnancy, but 86% of all COVID-19 pregnant women exhibited only mild symptoms (Table II depicts severity scores for COVID-19). Nine percent had severe presentations and 5% critical disease; these 14% required hospital admission. Seventeen percent reported symptoms of chest pain, but no cardiac biomarkers were recorded, and no CVD was reported. Importantly, there were no deaths, and no vertical transmission occurred. Mean age was 29 years and mean gestational age at diagnosis was 37 weeks. All caesarean sections were for obstetric reasons, none related to COVID-19 diagnosis. Neonatal outcomes were good.[22]

A small case series of 9 pregnant women (age range 26 - 40 years) infected with SARS-CoV-2 in Wuhan, China, demonstrated that the clinical characteristics of pregnant patients did not differ from non-pregnant patients.[7] All 9 had presented in the third trimester, had live births, and all women survived. The babies were delivered via caesarean section in good condition beyond 36 weeks' gestation. Cord blood, amniotic fluid and neonatal throat swabs were negative for the presence of the virus, and it was not detected in the breastmilk samples examined. In this small study, no vertical transmission was observed. None of the patients had pre-existing illnesses such as diabetes, hypertension or other CVD, and no cardiac symptoms or evidence of cardiovascular manifestations of COVID-19 were reported, although markers of cardiac injury such as serum troponin were not measured.[7] Similarly, Khan, et al. describe a series of 3 women (age range 27 - 33 years) with COVID-19 who delivered vaginally, 2 at term and 1 at 34 weeks' gestation. All patients and babies had good outcomes, and no in utero or vertical transmission occurred.[23]

TABLE II: Classification of COVID-19 disease severity.

US National Institutes of Health classification of disease severity[50]		Wu classification of disease severity[51]	
Asymptomatic or pre-symptomatic infection	Positive test for SARS-CoV-2, but no symptoms.	Mild	No or mild symptoms (fever, fatigue, cough, and/or less common features of COVID-19).
Mild illness	Any signs and symptoms (e.g. fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging.	Severe	Tachypnoea (respiratory rate >30 breaths per minute), hypoxia (oxygen saturation ≤93% on room air or PaO_2/FiO_2 <300 mmHg), or >50% lung involvement on imaging).
Moderate illness	Evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SaO_2) >93% on room air at sea level.	Critical	Respiratory failure, shock, or multiorgan dysfunction.
Severe illness	Respiratory frequency >30 breaths per minute, SaO_2 ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50%.		
Critical illness	Respiratory failure, septic shock, and/or multiple organ dysfunction.		

Recently, data on larger cohorts of pregnant patients with COVID-19 have become available. Pierce-Williams and colleagues have reported on 64 pregnant women hospitalised across 12 institutions with severe or critical SARS-CoV-2 infection.[24] Of these, 17% had pre-existing cardiac disease, but none died, and none developed cardiomyopathy. One woman survived a cardiac arrest. Mean gestational age at hospitalisation in this study was low (30 weeks), and 75% were non-Caucasian, including Hispanic ethnicity. Preterm birth occurred in approximately 60%, with deliveries <34 weeks' gestation more common in the critical disease cohort. The authors recommend iatrogenic preterm delivery in women with pre-existing disease to allow more aggressive treatment if the patient progresses to a critical disease stage and conclude that pregnancy itself should not be considered an independent predictor of a more severe disease course.[24]

The UK Obstetric Surveillance System (UKOSS) has published the largest cohort of COVID-19 patients who are pregnant and is the only population-based report. All 194 consultant-led maternity units in the UK participated, reporting on 427 pregnant women admitted with COVID-19 in a 6-week period between March and April 2020, against an estimated background of over 86 000 maternities in the same period, representing an incidence of 4.9 per 100 000 maternities.[25] Most admissions with COVID-19 occurred in the third trimester (mean gestational age 34 weeks), with risk factors mirroring those seen in the general population, including older age. More than half of the patients were from Black and other non-Caucasian ethnic groups, with Black and Asian women mostly affected. Thirty-four percent had pre-existing medical conditions, of which only 1% had cardiac disease and 3% were hypertensive. No cardiac events are reported in this cohort. Nine percent required intensive care and 4 women required extracorporeal membrane oxygenation. Five women died, giving a case fatality rate or 1.2% and a maternal mortality of 5.6 per 100 000 maternities. Ninety-two percent were discharged well, with a further 7% still in hospital at the time of writing. Pregnancy loss was twice as common in the COVID-19 cohort compared to a historic population. Seventy-four percent of women who gave birth during this time delivered at term, 59% via caesarean section, of which only 27% had sections for maternal reasons. Five percent of neonates tested positive for SARS-CoV-2, and 2% had evident presence of viral RNA within twelve hours of birth, suggesting that vertical transmission may be possible – although only rarely. Neonatal outcomes, however, were reassuring.[25]

There appears to be some risk of premature rupture of membranes, preterm delivery, fetal tachycardia and fetal distress when SARS-CoV-2 infection occurs in the third trimester of pregnancy (Figure 1).[26,27] However, there is no evidence suggesting transplacental transmission based on limited data, as the analysis of amniotic fluid, cord blood, neonatal throat swab, and breast milk samples have all been found to be negative for SARS-COV-2. Whether virus shedding occurs vaginally is also not known. Whether COVID-19 increases the risk of stillbirth is unknown, though there has been no major signal to suggest such. There is a single case report of a 17-year-old pregnant woman who had a second trimester miscarriage and the placenta was infected with SARS-CoV-2.[28] In general, there is a paucity of data on COVID-19 and the risk of miscarriage or congenital abnormalities associated with first and second trimester infections. COVID-19 is associated with a maternal pyrexia. This increase in core body temperature in the first and second trimester during the critical period of organogenesis raises the theoretical concern of congenital abnormalities, especially neural tube defects.[29] However, this theoretical concern has not been observed in clinical practice, and there is no definitive evidence of fetal transmission described in the literature to date. Allotey, et al. also describe fewer pregnant women presenting with fever compared to the general population infected with SARS-CoV2.[27] Concerns have been expressed about women undergoing termination of pregnancy for fear of congenital infection and teratogenicity, but to date, no adverse outcomes have been reported in babies born to mothers infected with SARS-CoV2. Therefore, termination of pregnancy for fetal reasons does not appear to be indicated.[30] Information on effects of COVID-19 on course and outcome of pregnancy in the first and second trimesters is not yet available.

COMPARISON OF CURRENT KNOWLEDGE ON COVID-19 AND PREGNANCY TO HISTORIC KNOWLEDGE ON MERS AND SARS-COV AND PREGNANCY

A study of 12 pregnant women infected with SARS-CoV from Hong Kong reported high incidences of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction, but no vertical transmission occurred.[31] No cardiac involvement was described. Unlike with SARS-CoV-2 infection, pregnant women with SARS-CoV had worse outcomes than a comparable non-pregnant cohort, with a maternal death rate of 50%.[31]

A meta-analysis of pregnancy outcomes for MERS, SARS and SARS-CoV-2, reports on 79 pregnancies (52% with SARS-CoV-2, 15% with MERS, 33% with SARS) and observed that intensive care admission, need for mechanical ventilation, and maternal death were significantly lower in COVID-19 compared to those infected with MERS and SARS.[32] In this meta-analysis, COVID-19 was associated with a higher rate of pre-eclampsia, preterm birth, preterm prelabour rupture of membranes, fetal

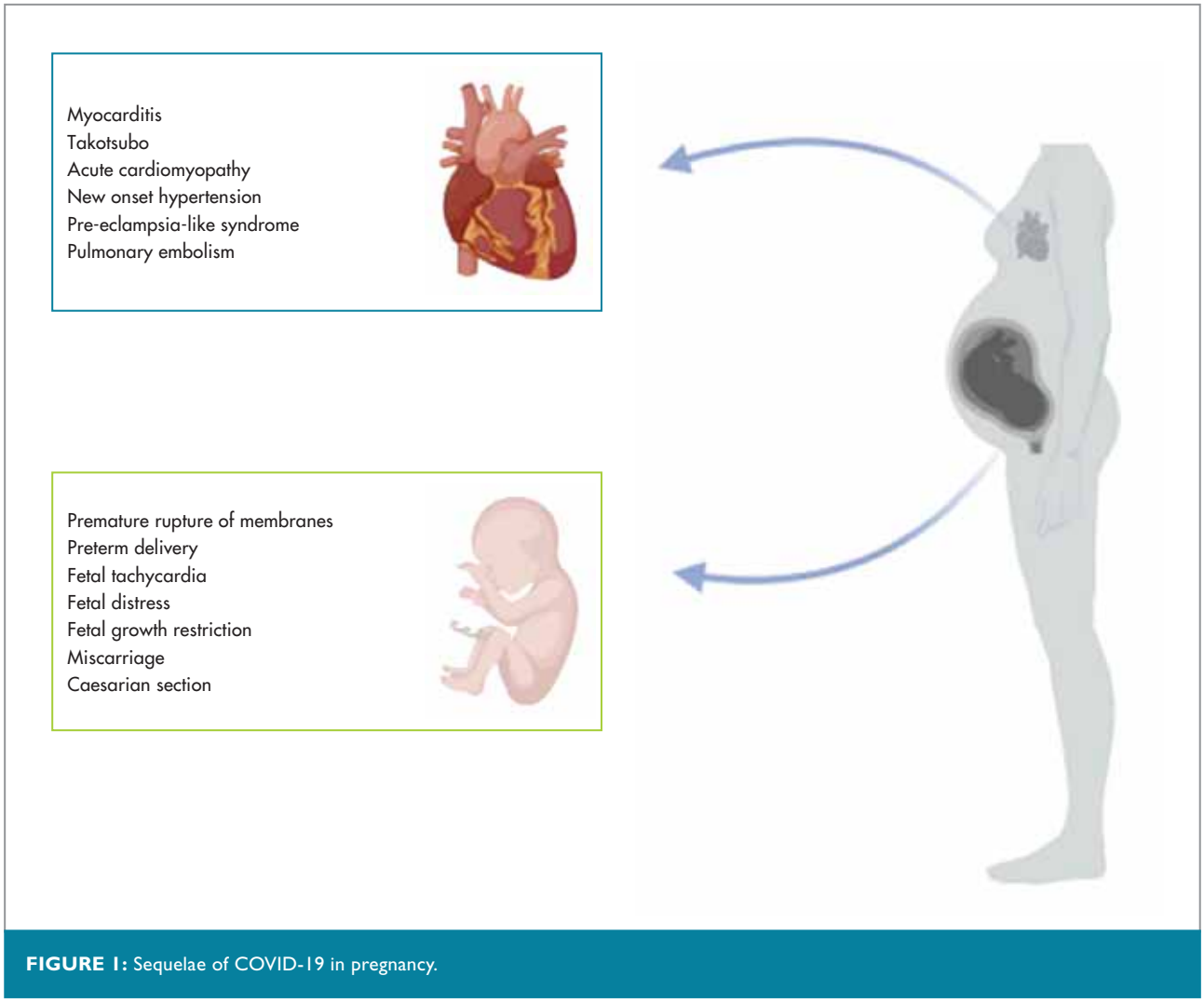

FIGURE 1: Sequelae of COVID-19 in pregnancy.

growth restriction, miscarriage and caesarean section. CVD is not mentioned in this study. They reported no vertical transmission for either coronavirus types.[32] Another meta-analysis of coronavirus infection in pregnancy included 32 COVID-19 cases, 2 of which required intensive care admission; however, SARS-CoV-2 was less lethal than other coronavirus infections (namely SARS and MERS).[33]

Placental pathology from 16 patients with SARS-CoV-2 infection was compared with controls, with evidence of increased rate of maternal vascular malperfusion, most specifically decidual arteriopathy as well as a significant increase in intervillous thrombi.[34] Prior to COVID-19, the major maternal risk factor associated with these placental findings was pre-eclampsia.[35] These findings suggest possible mechanisms for the observed adverse perinatal outcomes associated with COVID-19, and suggest that increased antenatal surveillance is indicated in pregnant women diagnosed with COVID-19.

CURRENT STATE OF KNOWLEDGE ON COVID-19 AND PREGNANCY-RELATED CARDIOVASCULAR DISEASE

Viral myocarditis and cardiomyopathy have been reported in non-pregnant COVID-19 patients.[36,37] A case series of non-pregnant COVID-19 patients demonstrated that 33% of those in intensive care developed cardiomyopathy.[36] A case series of the first 7 patients with COVID-19 in pregnancy in a US centre, showed that 2 of them developed a cardiomyopathy with moderately reduced left ventricular ejection fractions of 40% - 45% and global hypokinesis (Figure 1).[38]

In addition, there is increasing evidence that pulmonary embolism is a complication of COVID-19 in non-pregnant individuals.[18] A case of pulmonary embolism in an obese, pregnant woman with COVID-19 has been published.[20] Obese pregnant women with COVID-19 may have a particularly high risk of pulmonary embolism because of coexisting prothrom-

botic conditions and risk. Therefore, pregnant women with COVID-19 should be considered for tailored antithrombotic prophylaxis during pregnancy and in the puerperium (Table III).

MANAGEMENT OF THE PREGNANT WOMAN WITH COVID-19

The American College of Obstetricians and Gynecologists (ACOG),[39] the RCOG,[40] the Society for Maternal-Fetal Medicine,[41] the South African National Department of Health,[10] and others have promulgated guidelines on management of pregnancy during the COVID-19 pandemic. This guidance has focused on screening and testing, defining high-risk groups and tips for follow-up of the pregnant woman. Indications for and frequency of fetal testing are defined and include consideration of gestational age, stability of maternal vital signs, maternal oxygenation, and comorbidity. Implications for management of pregnant women with COVID-19 and CVD are summarised in Table III.

Most pregnant women with COVID-19 have mild disease and do not necessarily warrant hospital-level care during pregnancy. Acute respiratory distress syndrome (ARDS) and interstitial pneumonia are the causes of severe hypoxaemic respiratory failure critically ill patients. Complications of ARDS in COVID-19 include acute kidney, liver and cardiac injury. In pregnancy, maternal oxygen saturation should ideally be maintained at ≥95%.[42] While proning is important for recruitment and improving oxygenation in critically ill patients, the left lateral position is an alternative but may not be as effective in pregnant women. Padding above and below the gravid uterus after 24 weeks is desirable to avoid aortocaval compression. There are limited data on extracorporeal membrane oxygenation for treatment of ARDS in pregnancy, and it does not appear to be harmful to the foetus.[43]

To date there have been 2 reports describing the increased admission to ICU and need for a ventilator among pregnant women compared to the non-pregnant population.[44,45] More research is needed in this area is, to assess the effect of comorbidities such as hypertension, diabetes, CVD and obesity with respect to short and long term maternal and fetal outcomes.

Thromboembolic risk is increased in COVID-19,[46-48] therefore thromboprophylaxis should be initiated in all pregnant/postpartum women with COVID-19 admitted to the hospital. Studies are underway to assess treatment options for pregnant women with SARS-CoV-2 infection, but no results are available at the time of writing.

TABLE III: Implications for management of pregnant patients with Covid-19 and cardiovascular disease.

Prevalence of cardiovascular disease is low in the pregnant cohort published to date.
Outcomes of COVID-19 in pregnant patients are generally reassuring.
Cardiovascular complications of COVID-19 in pregnant women are not reported in the literature.
The current lack of data on pregnant COVID-19 patients with CVD needs to be addressed, ideally with an international registry – e.g. through existing international obstetric surveillance programmes such as INOSS.
Pregnancy itself should not be considered a risk factor for COVID-19 disease severity.
Cardiovascular care for pregnant women with COVID-19 and CVD is no different to that of non-infected patients.

TABLE IV: Key take-home messages on COVID-19 and the cardiovascular system in pregnancy.

COVID-19 and pregnancy share many common clinical features.
Pregnancy represents a state of partial immune suppression, with pregnant women more vulnerable to viral infections and with higher morbidity and mortality from SARS, Zika and MERS.
Concerns of increased maternal mortality and morbidity have not been borne out in clinical practice and have not stood up to epidemiological scrutiny. From limited data available on COVID-19 in pregnancy, the outcomes are mostly favourable.
There appears to be some risk of premature rupture of membranes, preterm delivery, fetal tachycardia and fetal distress when SARS-CoV-2 infection occurs in the third trimester of pregnancy.
Cardiovascular involvement in pregnancy includes new-onset hypertension, myocarditis, cardiomyopathy, pulmonary embolism, and a pre-eclampsia-like syndrome.
Pregnant women are younger, and asymptomatic SARS-CoV-2 infection and favourable outcomes are reported in those below 55 years of age.
To date, no proven treatment for SARS-CoV2 infection, specifically for pregnant women, is available.

CONCLUSION

COVID-19 and pregnancy share common features: both are multisystem disorders, may present with breathlessness, are associated with hypercoagulability and frequently cause significant anxiety in both the patient and those around them. From limited data available on COVID-19 in pregnancy, the outcomes are mostly favourable (Table IV). While cardiac disease and hypertension are independent predictors of hospital admission with COVID-19 in pregnancy, the prevalence of cardiac disease in the pregnant COVID-19 population is low. Pregnant women are younger, and asymptomatic SARS-CoV-2 infection and favourable outcomes are reported in those below 55 years of age. Indeed, large numbers of asymptomatic cases have been reported in pregnancy, suggesting that pregnant patients with more severe disease courses may be overrepresented in the current literature, particularly the early case reports and case series. Further, findings of the UKOSS suggest good pregnancy outcomes in COVID-19, even in symptomatic patients. To date, no proven treatment for SARS-CoV2 infection, specifically for pregnant women, is available.

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