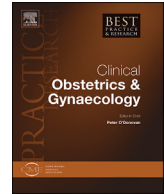




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Maternal medicine in the COVID era

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The coronavirus disease-19 (COVID-19) pandemic has directly and indirectly impacted pregnant women with co-morbidities or antenatal medical complications, through vulnerability to the severe effects of COVID-19 and service reconfiguration. Women with diabetes or hypertension in pregnancy are at higher risk of admission to intensive care, need for invasive ventilation and death from COVID-19. Suggested service modifications specific to maternal medicine services include home measurement of blood glucose or blood pressure, the use of risk calculators, adaptations to screening criteria for gestational diabetes and monitoring of obstetric cholestasis. Neither the added risk of COVID-19 on pregnant women with medical comorbidities nor the impact of maternal medicine service modifications has yet been established.

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Introduction

Maternal medicine, which focuses on the care of pregnant women with pre-existing co-morbidities or medical complications that arise during pregnancy, is critical during the coronavirus disease-2019 (COVID-19) pandemic. These women, who are at a high risk of complicated pregnancy, are affected by the pandemic both directly and indirectly. Pregnant women with pre-existing co-morbidities such as hypertension and diabetes are more likely to have severe COVID-19 than women at low risk; they are at increased risk of death, of being admitted to the intensive care unit and of needing invasive ventilation [1].

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The indirect effects of the pandemic on the maternal and perinatal health of high-risk pregnant women result from changes in the delivery of antenatal, intrapartum and postpartum care. Health services have been reconfigured in response to staffing crises caused by staff infected with or exposed to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or the redeployment of staff and resources and change in guidelines to minimise the risk of COVID-19 to pregnant women. Furthermore, access to care could also be compromised by countrywide policies, which involve 'stay at home' (lock-down) guidance and recommendations for those who are most vulnerable to SARS-CoV-2 infection to shield (not to leave home unless absolutely essential) [2,3].

In this review, we summarise the current evidence on the magnitude of COVID-19's impact on high-risk pregnant women and their babies and service modifications proposed by national guidelines for the care of such women during the pandemic (service modifications summarised in Table 1). Many of the service modifications have been pragmatic, given the urgency of the scenario. Reversion to pre-pandemic care is recommended as soon as safe.

Table 1

Summary of service modifications recommended for consideration in maternal medicine clinics during the COVID-19 pandemic.

Co-morbidity or antenatal medical complication	Suggested service modification
General advice	<ul style="list-style-type: none"> • Offer in-person appointments to coincide with appointments for other investigations, such as fetal ultrasound or blood tests [4]. • Where investigations and examinations are not necessary, offer consultation through virtual means [4]. • All women should have a venous thromboembolism risk assessment at the first antenatal appointment, and repeated throughout pregnancy, particularly when the woman's situation changes [5,6].
Hypertensive disorders in pregnancy	<ul style="list-style-type: none"> • Offer self-monitoring of blood pressure at home. Provide information on thresholds at which to seek a medical opinion. Clinician to review recorded measurements virtually [4]. • Where available, offer home urinalysis [4]. • Where pre-eclampsia is suspected, the initial assessment must be conducted in-person [4]. • Placental-growth factor-based testing should be offered to women with suspected pre-eclampsia where available to guide decisions on diagnosis, hospital admission, and time of birth [4]. • Consider the use of calculators to determine the risk of a woman developing pre-eclampsia complications [7,8].
Screening for gestational diabetes mellitus	<ul style="list-style-type: none"> • Consider offer of alternative screening pathways to reduce the risk of SARS-CoV-2 transmission. Alternative regimens available in the UK [4], Australia [9] and Canada [10]. • Consider screening based on risk prediction tool results [4].
Pre-existing and gestational diabetes mellitus	<ul style="list-style-type: none"> • Blood glucose measurements taken at home can be reviewed during a virtual consultation for the majority of women [4]. • Repeat prescriptions for medications of glucose monitoring equipment should be obtained in the community [4]. • Also offer home blood pressure monitoring for women with pre-existing diabetes, where equipment is available [4]. • Provide clear guidance on self-help and when to seek medical advice for high or low blood glucose measurements [4].
Cardiac disease	<ul style="list-style-type: none"> • Pregnant women with significant congenital or acquired heart disease are vulnerable to the severe effects of COVID-19; and therefore, efforts must be made to protect them from infection [2,3]. • Home monitoring of the international normalised ratio (INR) is possible, and where available should be prioritised amongst pregnant women to those with metallic heart valves [4].
Respiratory disease	<ul style="list-style-type: none"> • Individuals with asthma are advised to continue their regular medications including inhaled corticosteroids, in line with their personalised action plan [11,12]. • Individuals with cystic fibrosis and interstitial lung disease are vulnerable to the severe effects of COVID-19; and therefore, efforts must be made to protect them from infection [2,3].

Table 1 (continued)

Co-morbidity or antenatal medical complication	Suggested service modification
	<ul style="list-style-type: none"> • Women with cystic fibrosis and COVID-19 are encouraged to carry out airway clearance procedures whilst alone in a well-ventilated room, wherever possible, given that airway clearance procedures are likely to be aerosol generating [13]. • There is international disagreement on whether nebulisers are aerosol-generating and therefore whether healthcare workers administering them require the highest level of personal protective equipment (including filtering face piece masks) [11,14,15].
Disorders of haemoglobin and clotting	<ul style="list-style-type: none"> • Pregnant women with homozygous sickle cell disease (SCD) are vulnerable to the severe effects of COVID-19, therefore, efforts must be made to protect them from infection [2,3]. • Clinicians should have a low threshold to offer SARS-CoV-2 testing to women with SCD, who may present atypically. • For women using low molecular weight heparin, anti-factor Xa monitoring is essential only for those with antithrombin deficiency, or those with a metallic heart valve [4].
Renal disease	<ul style="list-style-type: none"> • Individuals with chronic kidney disease (CKD) are at a higher risk of becoming severely unwell with COVID-19, therefore, efforts must be made to protect them from infection [2,3]. • The frequency of monitoring for deteriorating renal function in adults with CKD or a renal transplant should be maintained for pregnant women during the pandemic.
Immunosuppressant use in pregnancy	<ul style="list-style-type: none"> • Individuals taking immunosuppressant medications are at increased risk of becoming severely unwell with COVID-19, therefore, efforts must be made to protect them from infection [2,3]. • Immunosuppressant medications should be continued as standard for pregnant women who do not have acute infection.
Obstetric cholestasis	<ul style="list-style-type: none"> • Monitoring bile acid levels can be limited to each in-person antenatal appointment at or after 34 weeks' gestation for pregnant women with persistent itch (where other causes have been excluded) [4]. • Women with bile acids <100 µmol/l may be offered elective birth at 39 weeks' gestation, but women with bile acids of 100 µmol/l of greater should be counselled re. The risks and benefits of elective birth at 35–36 weeks' gestation, or at the time of diagnosis if this occurs later [4].
Mental disorders	<ul style="list-style-type: none"> • Women with mild symptoms may be signposted to local or online sources for self-help [4]. • Pregnant women who express more worrying symptoms, such as suicidal ideation or hallucinations, should be referred immediately for psychiatric review [6].

Hypertensive disorders in pregnancy

Hypertension affects approximately 10% of pregnant women [16], including both chronic hypertensive diseases, which usually pre-date pregnancy and gestational disorders such as pre-eclampsia and gestational hypertension. Pregnant women with chronic hypertension are twice as likely to be affected by severe COVID-19 as non-pregnant reproductive aged women without chronic hypertension [1]. In non-pregnant adults, it is hypothesised that this association may be mediated through the upregulation of the angiotensin-converting enzyme (ACE)-2 in individuals taking renin-angiotensin-aldosterone inhibitors [17], but there is a lack of evidence to explain the association in pregnancy.

A few observational studies have suggested that COVID-19 disease either causes or can manifest itself as severe pre-eclampsia with the women's serum biochemistry findings similar to those seen in HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), but with a normal sFlt-1/PlGF ratio [18,19]. In the living systematic review on COVID-19 in pregnancy, an association was observed with pre-eclampsia diagnosis and severe COVID-19 [1], but the included studies were small with significant bias [20].

Antenatal guidelines on monitoring blood pressure for pregnant women with hypertensive disorders commonly recommend frequent in-person appointments, including twice weekly appointments for women in whom the blood pressure is not controlled (target <135/80 mmHg) [7,21]. Self-monitoring blood pressure at home can reduce the risk of SARS-CoV-2 transmission to both

pregnant women and healthcare staff during in-person clinic appointments [22]. A feasibility study found the intervention to be acceptable to women and well-adhered to, without adversely affecting mean systolic blood pressure [23]. There is an ongoing randomised trial on self-monitoring of blood pressure in pregnancy as compared to usual care in hospital [24]. Self-monitoring of blood pressure still requires clinicians to review blood pressure measurements (either in-person or remotely), arrange further foetal ultrasound assessment and maternal blood tests, to ensure timely recognition of maternal or foetal complications.

Both the sFlt-1/PIGF ratio and the PIGF test have been recommended for use during the pandemic, to aid discrimination between pre-eclampsia and the other hypertensive disorders of pregnancy, thereby guiding clinical care decisions and potentially supporting clinicians to avoid hospital admission, where it is not required [4,7]. Clinicians are also advised to use risk calculators, to determine the risk of complications [4,25]. The PREP-S risk calculator can be used to determine the risk of serious maternal complications or preterm birth prior to 34 weeks' gestation [8].

Pre-existing and gestational diabetes

Prevalence of diabetes in pregnancy is population-specific, because of differences in risk factors, such as obesity or Asian ethnicity. In the UK, up to 5% of pregnant women have diabetes (including gestational). Of these, approximately 12·5% (0.6% overall) have pre-existing type 1 or type 2 diabetes [26]. Diabetes is associated with an increased risk of severe COVID-19 in pregnancy [1,27]. This association is complex and likely contributed to by the associated characteristics (being overweight or obese or of Black or Asian ethnicity) and a pro-inflammatory and pro-thrombotic corporal environment [28].

COVID-19 might cause deterioration in diabetic control, through the binding of SARS-CoV-2 to ACE-2 receptors in pancreatic β -cells. Hyperglycaemia, at the time of hospital admission with COVID-19 has been found to be predictive of worse prognosis in non-pregnant individuals with diabetes [28].

Gestational diabetes mellitus (GDM) also appears to be an independent risk factor for severe COVID-19 [1]. Furthermore, individuals at risk of GDM have been affected internationally by modifications to GDM-screening criteria [4,9,10,29]. In usual practice, GDM screening is either offered universally or only to those women with risk factors, and centres around an offer of an oral glucose tolerance test (OGTT), with varying criteria for diagnosis [26,30]. These pre-pandemic screening strategies should continue to be adhered to when it is safe to do so during the pandemic, but it is acknowledged that an OGTT may require a prolonged hospital visit, where social distancing can be difficult in small waiting areas or staffing resources may be constrained.

Where the local prevalence of SARS-CoV-2 means that the risk of transmission to pregnant women is high, modified screening strategies allow the blood draw for GDM screening to be conducted at the same time as a draw for other antenatal bloods and include screening with both glycated haemoglobin A1c and fasting or random serum glucose [7,22–24]. Validated personalised risk calculators can be used to target individuals at highest risk and are most useful where universal screening is common practice [31]. Modified GDM screening strategies have been criticised because they result in the under-diagnosis of GDM when compared to classic screening strategies [32]. This was acknowledged at the time of recommendation by the authors of the modified UK Royal College of Obstetricians and Gynaecologists (RCOG) screening strategy, but it was also expected that the women with missed diagnosis were at the lowest risk of adverse perinatal outcomes [4]. The benefit to women in terms of the prevention of infection with SARS-CoV-2 is not known and cannot be easily measured.

For women with diabetes in pregnancy, ongoing management should focus on lifestyle advice, blood glucose surveillance and control, and monitoring and management of perinatal complications associated with diabetes [29]. Antenatal education sessions that target lifestyle interventions may be offered through virtual means, although consideration should be given to those who do not have access to video conferencing software or sufficient internet bandwidth, to prevent the inequity of provision. At present, published prediction models for the risk of complications are subject to bias and have not been externally validated; these are therefore not currently recommended for use outside of a research setting [33]. It is expected that monitoring for hyperglycaemia and medication titration can be offered to most women through virtual means (video or telephone call) [29], but in-person care is still

indicated in cases where remote communication is challenging, care is complex, or further investigations such as foetal growth surveillance are indicated. Clinicians are advised to arrange face-to-face care to coincide with other in-person appointments, to reduce the number of clinic visits to which each woman is invited [4].

Cardiac disease

Cardiac conditions in pregnancy (other than hypertension) are rare [34] but remain the most common cause of direct maternal death in developed countries [35]. COVID-19 is more severe in individuals with cardiovascular disease and may also cause myocardial injury in those without pre-existing disease [36]. Such myocardial injury has a varied phenotype (including those of acute coronary syndrome, arrhythmia, cardiogenic shock and myocarditis) and is associated with higher rates of death from COVID-19 [36,37]. Whether the risk of severe disease is also true for pregnant women remains unknown because co-existent cardiac disease and COVID-19 in pregnancy is rare and case numbers are too small to prove an association with severe disease. However, the UK Maternal Cardiology Society has published a list of cardiac conditions that are believed to put pregnancy women at highest risk [38]. These have been replicated in Box 1.

Box 1

Cardiac conditions identified by the UK Maternal Cardiology Society as putting women at highest risk from COVID-19.

Impaired left ventricular function (any cause)

A systemic right ventricle (e.g. from transposition of the great arteries) even if well-functioning.

Hypertrophic cardiomyopathy with abnormal systolic or diastolic function and/or outflow tract obstruction

Hypertensive heart disease with left ventricular hypertrophy

Fontan circulation

Pulmonary arterial hypertension (any cause)

Cyanotic conditions (those with blood oxygen saturation in air < 92%)

Moderate or severe valvar stenosis

Severe or moderate symptomatic valvar regurgitation

Symptomatic coronary artery disease

COVID-19 associated myocardial injury has been identified in pregnant women, following a finding of highly elevated cardiac-specific troponin, with or without elevated B-type natriuretic peptide (NT-proBNP). This is not always associated with dysfunction as demonstrated by cardiac echocardiography or clinical signs and symptoms [39,40]. The UK National Institute for Health and Care Excellence (NICE) has developed rapid guidance intended to assist non-cardiologist clinicians in the identification and management of COVID-19-associated myocardial injury. NICE recommends that myocardial injury should be suspected in patients with chest pain, palpitations, shortness of breath or severe fatigue, and that these patients should be investigated with an electrocardiogram (ECG) and serum cardiac markers (troponin I or T and NT-proBNP). In this context, elevated cardiac markers may represent a cardiac inflammatory response as opposed to acute cardiac syndrome. Further care should be arranged in conjunction with intensivists and cardiologists, should include an echocardiogram to assess cardiac function, and should occur in a setting where the pregnant woman can be intensively monitored and rapid deterioration quickly recognised [37].

Given that pregnant women with pre-existing cardiac disease are at a high risk of maternal complications during pregnancy, including mortality, antenatal care should be prioritised for this group of women and continue according to best practice, as far as possible.

Respiratory disease

Asthma is the most common respiratory disease affecting pregnant women. Despite early concerns that individuals with asthma were likely to be vulnerable to the severe effects of COVID-19 [2,3], this has not been proven in systematic reviews of observational literature for either the pregnant or non-pregnant population [1,41]. Individuals with asthma are advised to continue their regular medications, including inhaled corticosteroids, in line with their personalised action plan [11,12].

Individuals with cystic fibrosis and interstitial lung disease are at high risk of developing severe COVID-19, regardless of whether they are pregnant [2,3]. NICE have published rapid guidelines for the care of individuals with both of these respiratory conditions during the pandemic [13,42].

Women with cystic fibrosis and COVID-19 are encouraged to carry out airway clearance procedures whilst alone in a well-ventilated room, wherever possible, given that airway clearance procedures are likely to be aerosol generating. There is international disagreement as to whether nebulised medications represent aerosol-generating procedures, for which a higher level of personal protective equipment (PPE) is recommended for anyone present in the room at the time. UK guidelines suggest that nebulisers only release particles of medication and do not recommend high level PPE (including a filtering facepiece mask, visor and surgical gown) [11,14]. Guidelines from the USA suggest that nebulisers may release infectious aerosols although it is unknown whether it is this or close contact with the patient, which raises the risk of SARS-CoV-2 transmission [15].

All individuals with respiratory conditions who use equipment for their respiratory care (e.g. mouth pieces, spacers and peak flow meters) are encouraged to wash their hands before and after use, and to clean their equipment regularly with a detergent [11,13]. Routine respiratory investigations that are not urgently required to guide further management of the woman's condition, e.g. pulmonary function tests or bronchoscopy, should be reviewed and possibly deferred if they cannot be offered safely, particularly in areas affected by a high prevalence of COVID-19 or healthcare professional shortages [11,13,42].

Differentiating between acute presentations of respiratory disease deterioration and COVID-19 in individuals with respiratory co-morbidities can be difficult, particularly for individuals taking immunosuppressant medications, in whom COVID-19 may present atypically [11,42]. Where there is clinical uncertainty, infection control measures should be adhered to as if the individual has COVID-19, until virology investigations are conclusive to the contrary.

During flu season, there is international concern that the double threat of respiratory viruses may present further pressure on health services, although it is acknowledged that national infection control restrictions (e.g. 'lockdown', social distancing and wearing face coverings) may also reduce the transmission of influenza viruses [43]. Nevertheless, pregnant women are at an increased risk to become severely unwell from influenza [44], and vaccination is safe and effective [45]. It is, therefore, strongly recommended that all pregnant women are offered a flu virus vaccine during the local flu season.

Disorders of haemoglobin and clotting

Of the common haematological disorders affecting pregnant women, homozygous sickle cell disease (SCD) is the most important, in terms of increasing the risk of severe COVID-19 [46]. For this reason, women with SCD should be protected from the risk of transmission, with routine appointments carried out virtually if safe and possible to do so. Women should be advised to regularly check their temperature at home, and to speak to their haematologist if febrile [47]. Women with mild sickle pain should try to manage this at home with oral analgesia, but clinicians should have a low threshold to arrange for the woman to be seen by her haematologist and be offered SARS-CoV-2 testing. In those who do have COVID-19, a multidisciplinary team of clinicians (obstetricians, haematologists and intensivists where required) should be vigilant to the signs and symptoms of acute chest crisis

(thrombocytopenia, acute kidney injury, hepatic dysfunction and/or altered mental status), which can overlap with those of COVID-19. SCD increases the risk of developing thromboembolism in pregnancy as does COVID-19; therefore, a timely offer of thromboprophylaxis is essential [5].

It is acknowledged that COVID-19 is associated with a high rate of thrombotic complications (pulmonary microvascular thromboses and hospital-acquired venous thromboembolism [VTE]) [48], believed to be caused by a combination of inflammation, endothelial dysfunction, platelet activation, and stasis. Since pregnancy itself is pro-thrombotic, pregnant women are expected to be at equal or higher risk than the non-pregnant population [49]. In a UK review of COVID-19-associated maternal deaths during the first wave of the pandemic, the death of at least one of 11 women with COVID-19 was caused by VTE (it was also suspected as the cause of another death) [50]. All pregnant women should have a VTE risk assessment conducted in early pregnancy, and those at significant risk commenced on thromboprophylaxis according to local protocols [5]. Risk should be reassessed during pregnancy, particularly when the woman's situation changes, for example if she has reduced mobility during a period of self-isolation or a mild case of COVID-19. Thromboprophylaxis should also be offered at standard doses to all pregnant women hospitalised with COVID-19 and consideration should be given to increasing the dose for women receiving advanced respiratory support [4,51,52]. D-dimer levels are normally elevated in healthy pregnancy and more so with COVID-19; this acute elevation is not necessarily indicative of thromboembolism [53]. Therefore, pregnant women with suspected VTE should be primarily investigated with imaging as recommended by non-pandemic guidance [54].

Renal disease

Severe COVID-19 is associated with acute kidney injury (AKI) in at least a quarter of non-pregnant adults [55]. SARS-CoV-2 may directly injure the renal tubules or cause AKI through cytokine storm or fluid imbalance [56]. In pregnancy, the cause of AKI must be distinguished from other common causes, including obstructive nephropathy and pre-eclampsia. Medications that may contribute to AKI should be stopped and pregnant women admitted to hospital with COVID-19 should have their fluid balance monitored, taking into account insensible losses from fever and tachypnoea, and intravenous or oral fluids targeting euvolaemia administered [57].

Individuals with chronic kidney disease (CKD) are at a higher risk of becoming severely unwell with COVID-19 [2,3]. This association is not established in pregnancy; however, pregnant women with CKD should observe the same caution as non-pregnant adults. Whilst reducing the frequency of biochemical monitoring for non-pregnant individuals with CKD during the pandemic has been advised [58], such a strategy is not advisable in pregnancy, where physiological changes to the cardiovascular system may destabilise CKD. However, pregnant women with CKD may be able to self-monitor their blood pressure at home (as per section on hypertension), and this may reduce the frequency of appointments and hence, the risk of infection.

Women taking immunosuppressant medications

Pregnant women may take immunosuppressant medications for a variety of reasons, including inflammatory bowel disorders, rheumatological disorders or as recipients of solid organ transplants. Individuals taking immunosuppressant medications are at increased risk of becoming severely unwell with COVID-19 [2,3]. Immunosuppressant medications should be continued as standard for pregnant women who do not have acute infection. Where possible (when examination or investigations are not required or can safely be deferred), these women should be reviewed through remote consultation, to reduce the risk to become infected with SARS-CoV-2 during a clinic visit. Both women and clinicians should be aware that COVID-19 may present atypically in individuals on immunosuppression, including the absence of fever [59].

Pregnant women taking immunosuppressant medications who do become unwell with COVID-19 should be cared for by a multidisciplinary team, which includes a physician, intensivist (where admission to critical care is either considered or required), infectious disease specialist and an

1 obstetrician. Specialist advice should be sought before stopping immunosuppressant medications for
2 individuals with COVID-19.
3

4 **Obstetric cholestasis**

5
6 Prior to the COVID-19 pandemic, pregnant women with suspected or confirmed obstetric chole-
7 stasis (OC, intrahepatic cholestasis of pregnancy) were routinely invited for clinical assessment, which
8 includes the monitoring of liver enzymes and bile acids, weekly [60]. As neither ultrasound nor
9 electronic foetal monitoring have been found to prevent foetal death in women with OC, clinical visits
10 for foetal investigations are not helpful [60]. Every visit to the hospital increases the risk of a pregnant
11 woman being infected with SARS-CoV-2, particularly where local prevalence is high. A meta-analysis
12 published in 2019 found that the risk of stillbirth increased above background levels only for women
13 with bile acids of 100 $\mu\text{mol/l}$ or greater, and that there was a sudden increase in the risk after 36 weeks'
14 gestation [61]. For this reason, COVID-19 guidelines from the RCOG recommend that during the
15 pandemic, measurement of bile acid levels can be limited to each in-person antenatal appointment at
16 or after 34 weeks' gestation for pregnant women with a persistent itch (where other causes have been
17 excluded). Women with bile acids $<100 \mu\text{mol/l}$ may be offered elective birth at 39 weeks' gestation, but
18 women with bile acids of 100 $\mu\text{mol/l}$ or greater should be counselled with regard to the risks and
19 benefits of elective birth at 35–36 weeks' gestation or at the time of diagnosis if this occurs later [4].
20

21 **Mental well-being**

22
23 The COVID-19 pandemic has resulted in an increased level of anxiety and depressive symptoms for
24 the whole population, but for pregnant women to a greater extent [62]. Anxieties are caused by the fear
25 of being infected and the potential effect on mother and baby, social isolation and reduced support
26 from wider family and friends and the socioeconomic impacts of national lockdowns and major
27 changes in access to medical care [63]. The pandemic is expected to reduce options for access to mental
28 health services [64], meaning that deterioration in existing mental illness may go unnoticed, and
29 psychiatric care may be delayed. Pregnant women should therefore be asked about their mental well-
30 being during every contact with a healthcare professional. Women with mild symptoms may be
31 signposted to local or online sources for self-help. Pregnant women who express more worrying
32 symptoms, such as suicidal ideation or hallucinations, should be referred immediately for psychiatric
33 review [6].
34

35 **Summary**

36
37 Pregnant women with medical co-morbidities or complications of pregnancy have been both
38 directly and indirectly affected by the COVID-19 pandemic. Women with co-morbidities are at a higher
39 risk of the severe effects of COVID-19 in pregnancy, which include admission to intensive care units,
40 need for invasive ventilation and death. Pregnant women have also been affected by the reconfigu-
41 ration of maternal medicine services, including the increased offer of home monitoring, telemedicine
42 consultations, changes to diagnostic or intervention criteria and prioritisation of need.

43 Despite a large quantity of observational research being published during the pandemic, the
44 additional effect of COVID-19 on top of the existence of the high-risk status of pregnant women with
45 comorbidities and medical complications is yet to be established. Pregnant women, including those
46 who are at a high risk because of medical co-morbidity, have been excluded from most randomised
47 controlled trials assessing the effectiveness of medical treatments for severe COVID-19, leaving un-
48 certainty in how best to care for them. Robust studies that evaluate the effectiveness and safety of
49 medical treatments and vaccination for pregnant women, particularly those at highest risk because of
50 co-morbidity, and assess the impacts of service configuration on maternal and perinatal outcomes are
51 needed to inform ongoing and future pandemic planning.
52
53
54

Practice points

- Antenatal and postnatal care should continue to be provided during the pandemic according to best practice guidelines, where safe and feasible to do so.
- Pregnant women with significant co-morbidities should be cared for during pregnancy by a multidisciplinary team that includes an obstetrician with a specialist interest in maternal medicine and a physician with knowledge of the subject area.
- Clinicians should be aware of the list of medical co-morbidities for which there is an increased risk (or hypothetical risk) of the individual who becomes severely unwell with COVID-19.
- For women at the highest risk to become severely unwell with COVID-19, it may be possible to convert some clinic appointments to remote consultations, particularly where examination or investigation are not indicated, to reduce the risk of SARS-CoV-2 infection. Investigations that cannot be arranged at home should be scheduled together where possible, to avoid repeated hospital visits.
- Both COVID-19 and reduced mobility increase the risk of thromboembolic complications over and above the risk attributed to pregnancy and co-morbidities. Thromboprophylaxis should be offered to all pregnant women admitted to hospital with COVID-19.
- Pregnant women have an increased risk to develop symptoms of anxiety or depression during the pandemic and should be asked about their mental well-being at every contact with a healthcare professional.

Research agenda

- Large prospective studies are required to compare obstetric outcomes in high-risk pregnant women with and without COVID-19 to identify the added risk due to infection with SARS-CoV-2
- Randomised trials on various pharmacological treatments for COVID-19 will need to include high-risk pregnant women, who are most at risk of severe complications
- Robust studies are needed to determine the indirect impact of change in guidelines and practices for antenatal care of high-risk pregnant women due to the pandemic
- Interventions to facilitate remote care of high-risk pregnant women need to be co-developed with patient and public involvement groups to ensure that these are acceptable, feasible and equitable

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services in the evolving coronavirus (COVID-19) pandemic' and the lead of the PREGCOV project: Living Systematic Review on COVID-19 in pregnancy.

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