

ISSUES IN MEDICINE

Considerations for COVID-19 vaccination in pregnancy

J Zamparini,¹ MB ChB, FCP (SA), MMed (Int Med); **L Murray**,¹ MB ChB, FCP (SA), MMed (Int Med), DPhil (Oxon);
R T Sagers,² MB BCh, FC Paed (SA), MMed (Paed); **A J Wise**,^{3,4} MB BCh, FCOG (SA), MMed (O&G), Dip HIV Man (SA), Cert Maternal
and Fetal Medicine (SA); **H Lombaard**,^{3,4} MB ChB, FCOG (SA), MMed (O&G), Cert Maternal and Fetal Medicine (SA), PG Dip HSE

¹ *Division of Infectious Diseases, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

² *Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

³ *Department of Obstetrics and Gynaecology, Rahima Moosa Mother and Child Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

⁴ *Empilweni Services Research Unit, Rahima Moosa Mother and Child Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

Corresponding author: J Zamparini (jarrod.zamparini@wits.ac.za)

Pregnant women are at greater risk of severe COVID-19 than non-pregnant women. Despite limited safety data on use of COVID-19 vaccines in pregnancy, many international societies have recommended their use when pregnant women are at particularly high risk of acquiring COVID-19, or have suggested that vaccines should not be withheld from pregnant women where no other contraindications to COVID-19 vaccination exist. A number of vaccines, including those against influenza, tetanus and pertussis, have been shown to reduce both maternal and infant morbidity and mortality when used antenatally. We explore the role of COVID-19 vaccination in the setting of pregnancy, discuss the limited data available, and summarise current international guidelines.

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The South African (SA) government is undertaking a massive roll-out of COVID-19 vaccination, with the aim of vaccinating at least 67% of the population in order to achieve herd immunity. Initially frontline healthcare workers are being vaccinated, followed by essential workers, individuals aged >60 years and adults with comorbid disease. This phased roll-out is designed to vaccinate those most at risk of contracting COVID-19, followed by those most at risk of severe disease.^[1]

Pregnant women are at greater risk of severe COVID-19 than non-pregnant women, with increased rates of intensive care unit (ICU) admission, need for supplemental oxygen and invasive ventilation, and mortality.^[2-5] These findings are in keeping with other viral pneumonias, such as influenza, where pregnant women are disproportionately affected and have higher morbidity and mortality compared with non-pregnant women.^[6,7] Given the lack of safety data on vaccination in pregnancy, the SA government has recommended against vaccination in pregnant and breastfeeding women.^[8] This is in contrast to the recommendations of a number of international societies.

COVID-19 in pregnancy

The altered immune system in pregnancy, with a shift towards a T-helper 2 response and humoral immunity, as well as a decrease in natural killer cells and circulating plasmacytoid dendritic cells, predisposes pregnant women with viral infections to severe disease.^[9]

Despite early reports^[10] of pregnant and non-pregnant women with COVID-19 showing no difference in disease severity, it is now clear that pregnancy is an independent risk factor for severe COVID-19. A number of studies^[2-4] have shown that rates of ICU admission are higher in pregnant women with COVID-19 than in

their non-pregnant counterparts, with 10.5 v. 3.9 cases per 1 000 women, respectively, in a large report from the Centers for Disease Control and Prevention (CDC) in the USA.^[2] Similarly, the need for endotracheal intubation was significantly higher in pregnant women compared with non-pregnant women with COVID-19 (10.16% v. 1.67%, respectively),^[4] and the need for invasive ventilation increased in pregnant women with COVID-19.^[2,3]

Furthermore, the risk of mortality was shown to be 70% higher in pregnant women with COVID-19 compared with their non-pregnant counterparts (1.5 v. 1.2 per 1 000 cases; adjusted risk ratio 1.7, 95% confidence interval 1.2 - 2.4).^[2] It has also been shown that the risk of mortality is significantly higher in pregnant women with than without COVID-19 (141 v. 5 deaths per 100 000 women).^[5] Concerningly, data from both the USA and the UK have shown a disproportionate number of deaths in non-white women.^[2,11]

COVID-19 infection in pregnant women also increases the risk of adverse pregnancy outcomes. The risk of thromboembolic events, including myocardial infarction and venous thromboembolism, as well as pre-eclampsia, is higher in pregnant women with COVID-19 compared with those without.^[5] COVID-19 in pregnancy appears to be associated with an increased risk of preterm delivery, with 22% of neonates born prematurely, compared with the US national average of 10%, in a large review.^[12] Importantly, severity of disease seems to play a role, with preterm birth reported in 29% and 88% of pregnant women with severe disease and critical disease, respectively.^[13] Rates of miscarriage also increase in pregnancies affected by COVID-19.^[4,14]

COVID-19 in neonates

Intrauterine transmission of SARS-CoV-2 remains controversial. A number of cases supporting possible vertical transmission

have been reported,^[15-18] but none of these meet the criteria for confirmed vertical transmission proposed by Shah *et al.*^[19] Horizontal transmission of the virus is much more likely and can occur during vaginal delivery, via the faecal-oral route, or later through close contact with an infected mother during nursing.^[20] Despite this, the benefits of breastfeeding outweigh the risk of transmission of the virus through breastmilk, with some reporting that breastmilk may contain anti-SARS-CoV-2 antibodies.^[21]

A prospective population-based cohort study in the UK showed an incidence of confirmed COVID-19 in neonates of 5.6 per 100 000. The majority of neonates (68%) were diagnosed >7 days after birth, suggesting that horizontal transmission is more likely than vertical exposure.^[15] While neonates of mothers with COVID-19 rarely acquire the disease and hospital admission is uncommon, neonates who do become infected are at risk of severe disease. In the cohort study mentioned above, severe disease occurred in 42% of cases, 36% received ICU care and 33% required respiratory support.^[15] Furthermore, the long-term effects of COVID-19 acquired in the neonatal period are unknown, and ongoing research in this area is crucial.^[15,21]

Available COVID-19 vaccines

Various COVID-19 vaccines that utilise different vaccine platforms are available worldwide or are in advanced-stage clinical trials (Table 1).^[22] The SA government has committed to source vaccines from a combination of vaccine suppliers, but as of 15 March 2021, only the AstraZeneca/University of Oxford ChAdOx1 nCov-19 AZD1222 vaccine (AstraZeneca) had been granted authorisation for commercial use by the South African Health Products Regulatory Authority (SAHPRA). The Pfizer-BioNTech BNT-162b2 (Pfizer) and Johnson & Johnson/Janssen AD26.COVS.2 (J&J) vaccines are currently under review at SAHPRA, and the J&J vaccine is being rolled out to healthcare workers as part of the Sisonke open-label implementation trial.^[23] The Novavax NVX-CoV2373 vaccine (Novavax) has demonstrated efficacy in a recent phase 3 trial in SA and could potentially be available in the near future. Each of these vaccines utilises a different vaccine platform with unique considerations for use in pregnant women.

Viral vector vaccines

The AstraZeneca and J&J vaccines both use adenoviruses as the vector for delivery of SARS-CoV-2 viral proteins in order

to induce protective immune responses.^[22] The AstraZeneca vaccine uses a chimpanzee adenovirus vector and the J&J vaccine a recombinant human adenovirus serotype 26 (Ad26) vector. Both vaccine platforms have been used in vaccines against other viruses, including HIV, Ebola, Zika and respiratory syncytial virus (RSV).^[24,25] A frequently expressed concern regarding the use of adenovirus vectors in pregnant women is the theoretical potential for adenovirus vector infection of the fetus. This concern is unfounded, as both adenovirus vectors are attenuated viruses that are replication incompetent. This means that these vectors can infect human cells following inoculation but cannot replicate in those cells, thereby delivering SARS-CoV-2 viral proteins to the mother without transfer of the viral vector to the fetus. Studies in animal models using adenovirus vectors have shown no adverse effect in pregnancy, but clinical trials of these vaccines in humans so far have excluded pregnant women.^[26,27]

mRNA vaccines

The Pfizer and Moderna mRNA-1273 (Moderna) vaccines employ a novel vaccine technology based on mRNA.^[28,29] Both of these vaccines encode SARS-CoV-2 genetic information in the form of RNA packaged into lipid nanoparticles that, when injected, enter the cells of the vaccinated individual, causing SARS-CoV-2 antigens to be expressed on the cell surface.^[22] Host immune cells recognise these antigens and mount an immune response. Common misconceptions include that the mRNA can alter the DNA of the vaccinated individual and that the mRNA may be passed on to the fetus, with potential harmful consequences. However, the mRNA does not enter the nucleus of the cell and therefore cannot alter the cell's DNA.^[30] In addition, mRNA is degraded rapidly within the cell, making transmission of SARS-CoV-2 mRNA to the fetus very unlikely.^[30] While no mRNA vaccines have been purposefully used in pregnant women in trial settings, animal studies on the Moderna vaccine reported no effects on fetal development in rats given the vaccine prior to conception and during pregnancy.^[31] A common adverse effect associated with vaccination with both of the mRNA SARS-CoV-2 vaccines is a transient fever >38°C in up to 16% of vaccinees.^[28,29] Fever has been associated with adverse pregnancy outcomes, and use of antipyretics has therefore been suggested by the CDC as a means of managing this potential adverse effect in pregnancy.^[32]

Table 1. Overview of COVID-19 vaccines

Developer	Vaccine candidate	Platform	International approval status	South African approval status*
AstraZeneca and University of Oxford	ChAdOx1 nCov-19 (AZD1222/Covishield)	Viral vector	Granted EUA (or equivalent) in the EU, UK and India (among others)	Section 21 review finalised and EUA granted by SAHPRA on 22 January 2021
Johnson & Johnson (Janssen)	AD26.COVS.2	Viral vector	Rolling review application submitted to the UK Granted EUA in the EU and USA	Rolling review submission to SAHPRA – currently under review Rolled out as part of the Sisonke Vaccine Programme
Pfizer/BioNTech	BNT-162b2	mRNA	Granted EUA (or equivalent) in the UK and USA by the WHO and provisionally in the EU	Submitted to SAHPRA – currently under review
Moderna	mRNA-1273	mRNA	Granted EUA (or equivalent) in the UK, USA and EU	No submission to SAHPRA
Novavax	NVX-CoV2373	Recombinant protein	Rolling review submitted in the EU, USA, UK and Canada	No submission to SAHPRA

EUA = Emergency Use Authorisation; SAHPRA = South African Health Products Regulatory Authority; WHO = World Health Organization.
*As of 15 March 2021.

Protein vaccines

The Novavax vaccine is a recombinant nanoparticle protein vaccine based on the SARS-CoV-2 spike protein.^[33] Although pregnant women were also excluded from the clinical trials of this vaccine, Novavax have gathered safety data in previous trials for an RSV vaccine in pregnant women using a similar vaccine platform.^[34] In addition, protein-based vaccines have been used safely in pregnant women for immunisation against influenza and hepatitis B, and as a result there are fewer safety concerns regarding the use of these vaccines in pregnancy in comparison with other vaccine platforms.

Rationale for vaccinating pregnant women

Maternal vaccination decreases the risk of maternal illness and takes advantage of transplacental transfer of IgG to the fetus *in utero* and IgA transfer to the neonate in breastmilk.^[35,36] This antibody transfer protects the infant in the first few months of life when the immune system is immature and the infant is at risk of significant infection before the first scheduled vaccines are administered.

Evidence exists for benefits of influenza vaccination in pregnancy: vaccination reduces maternal mortality due to influenza, as well as preterm birth and intrauterine growth restriction. In addition, maternal vaccination confers protection against influenza in infants up to 6 months of age.^[37] Importantly, when given in pregnancy, influenza vaccination is safe.^[38] The influenza vaccine has been shown to provide partial protection in both HIV-negative and HIV-positive pregnant women and their infants in the SA setting and, along with tetanus toxoid, is offered to pregnant women during the antenatal period in SA during March and April in anticipation of the influenza season.^[39,40] Furthermore, and possibly owing to the reduction in viral pneumonia, the risk of pertussis pneumonia appears to be reduced by 50% following influenza vaccination.^[41]

Vaccines against tetanus and pertussis, among others, have also been shown to reduce infant morbidity and mortality when used antenatally.^[42] In a recent systematic review, the combined tetanus, diphtheria and pertussis vaccine was safe when given in the second or third trimester of pregnancy.^[43] Maternal pertussis vaccination is not yet included in SA guidelines, but maternal vaccination is more effective than cocooning strategies aimed at immunising all close contacts of the newborn.^[44]

Vaccinating pregnant women against COVID-19 may have a similar benefit in reducing maternal morbidity and mortality, although more trial and real-world data are needed. Clinical trials of current vaccine candidates have shown a significant effect in prevention of severe COVID-19 in non-pregnant women, and it is likely that this protection would extend to vaccinated pregnant women.^[24,28,29] Maternal vaccination may well also reduce neonatal morbidity and mortality through passive immunisation of the fetus. Supporting this hypothesis, a recent preprint has shown evidence of transfer of SARS-CoV-2-specific antibodies in cord blood following SARS-CoV-2 maternal vaccination.^[45]

Ethical considerations regarding the exclusion of pregnant women from COVID-19 vaccine trials

Despite early calls for vaccine manufacturers to include pregnant women in COVID-19 vaccine trials, they were excluded from the initial trials of the vaccines reported on here.^[46-49] The exclusion of women from clinical trials on the basis of pregnancy alone is contentious. While including pregnant women in the study of new vaccines could potentially cause harm, exclusion from such studies

may also have harmful consequences due to the lack of essential knowledge acquired concerning the use of such vaccines in pregnancy. Pregnant women and their fetuses deserve access to safe and effective evidence-based care. The autonomy of the pregnant woman and her ability to weigh up the risks and benefits of participation in clinical trials should be considered and respected. Pregnant women should be afforded the same opportunity to participate as non-pregnant individuals, always considering the wellbeing of the fetus and the potential for teratogenicity when making these decisions. Women should be given the opportunity to discuss concerns with their healthcare provider and the trial team and thereafter make an informed decision regarding participation.

Future studies are planned to investigate the use of COVID-19 vaccines in pregnant participants, but some limited data on their safety in pregnancy exist.^[50,51] A number of trials have reported outcomes on women who became pregnant during the trial period, although these women accounted for <0.1% of total trial participants.^[31,52-54] The Moderna and Pfizer vaccine trials reported 13 and 23 pregnancies, respectively, with a single miscarriage in the placebo group in both trials, while the AstraZeneca trial reported 21 pregnancies with 2 miscarriages in the vaccine group and 3 in the placebo group.^[31,52,53] J&J reported 8 pregnancies in their vaccine trial, with a single miscarriage in each group.^[54] Registries that include pregnant and breastfeeding women who have received COVID-19 vaccines, such as one established by the University of Washington, are important tools to monitor long-term outcomes in this patient group.^[55] The CDC's v-safe 'after-vaccination health checker' has had >16 000 pregnancies reported to it as of 16 February 2021.^[56]

Recommendations on vaccinating pregnant women

In contrast to guidance from the SA National Department of Health, the South African Society of Obstetricians and Gynaecologists has recommended that pregnant and breastfeeding women at high risk of contracting COVID-19 (e.g. healthcare workers) consider having COVID-19 vaccination.^[57] This guidance is in keeping with that offered by a number of international societies (Table 2), despite vaccine manufacturers advising against vaccination of pregnant women owing to the lack of clinical data.^[46-48,58,59] The WHO has suggested that pregnant women who are at high risk of exposure, such as healthcare workers, and those at risk of severe disease because of comorbidities may be vaccinated with the Moderna vaccine after consultation with their healthcare provider.^[60,61] The Health Services Executive in Ireland has recommended vaccination for all pregnant women between 14 and 33 weeks' gestation, whereas the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommends against routine vaccination of pregnant women in view of the low levels of community transmission in those countries.^[49]

Conclusions

It is becoming clear that pregnant women are at increased risk of severe COVID-19 resulting in increased maternal morbidity and mortality and poor pregnancy outcomes. Pregnant women have been excluded from trials investigating vaccines against COVID-19, and as such safety data on the use of these vaccines in pregnancy are lacking. While the theoretical benefit of maternal vaccination may outweigh the known risks associated with COVID-19 in pregnancy, pregnant and breastfeeding women have the right to autonomy and should be given the choice to vaccinate by making an informed decision in consultation with their healthcare provider, using the data available.

Table 2. Guidelines for vaccinating pregnant women

Country	Society/organisation	Date	Pregnancy recommendation	Breastfeeding recommendation
South Africa	National Department of Health ^[8]	30 January 2021	Not recommended	No information
	South African Society of Obstetricians and Gynaecologists ^[57]	28 January 2021	Recommends that pregnant and breastfeeding women at high risk of contracting COVID-19 (including HCWs, essential workers and those with comorbidities) should consider vaccination after discussion with their healthcare practitioner	
Australia and New Zealand	Royal Australian and New Zealand College of Obstetricians and Gynaecologists ^[49]	26 January 2021	Insufficient evidence to recommend routine use of COVID-19 vaccines in pregnancy	No recommendation
Brazil	FEBRASGO ^[62]	3 February 2021	Recommends that pregnant and breastfeeding women can be vaccinated after assessment of the risks and benefits between the woman and her physician	
Canada	Society of Obstetricians and Gynaecologists of Canada ^[8]	5 March 2021	Recommends that pregnant and breastfeeding women who are eligible due to exposure risk, medical status or other circumstances should be offered COVID-19 vaccination if no contraindications exist	
Ireland	Health Service Executive ^[63]	9 March 2021	Recommends COVID-19 vaccination for all pregnant women between 14 and 33 weeks' gestation	Recommends COVID-19 vaccination for all breastfeeding women
UK	Royal College of Obstetricians and Gynaecologists ^[48]	30 December 2020	Recommend that COVID-19 vaccination only be considered in pregnant women at high risk of unavoidable exposure or severe disease (i.e. HCWs or those with high-risk comorbidities) and that it be given through a maternity unit to allow for reporting to the UKOSS/UKTIS vaccine registry	Recommend that breastfeeding women be offered COVID-19 vaccination Women should be advised on the lack of safety data on COVID-19 vaccinations in pregnancy
	Macdonald Obstetric Medicine Society ^[48]		Benefits and risks of COVID-19 vaccination should be discussed on an individualised basis	
	UK Teratology Information Service ^[48]		Recommends that pregnant and breastfeeding women who are eligible be offered COVID-19 vaccination after engaging in shared decision-making with a healthcare professional	
USA	Society for Maternal-Fetal Medicine ^[46]	3 March 2021	Recommends that COVID-19 vaccination should not be withheld from pregnant women who meet criteria for vaccination as per ACIP priority groups	Recommends that COVID-19 vaccination be offered to breastfeeding women who meet criteria for vaccination as per ACIP priority groups
	American College of Obstetricians and Gynecologists ^[47]	4 March 2021	Recommends consultation with a healthcare provider but that this should not be required prior to vaccination	Recommends that women who are breastfeeding, and in a group eligible to receive the vaccine, may choose to receive the vaccine
Global	Centers for Disease Prevention and Control ^[64]	12 February 2021	Recommends that women who are pregnant, and in a group eligible to receive the vaccine, may choose to receive the vaccine	Recommends that women who are breastfeeding, and in a group eligible to receive the vaccine, may choose to receive the vaccine
	World Health Organization ^[60,61]	29 January 2021	Recommends a conversation between the woman and her healthcare provider, although this is not required prior to vaccination	Recommends that COVID-19 vaccination (with the Pfizer-BioNTech vaccine specifically) can be offered to breastfeeding women at high risk of exposure
			Recommends that pregnant women at high risk of exposure or with serious comorbidities may be vaccinated (with the Moderna vaccine specifically) in consultation with their healthcare provider	
			No recommendation for other vaccines	

HCWs = healthcare workers; FEBRASGO = Federação Brasileira das Associações de Ginecologia e Obstetrícia (Brazilian Federation of Gynecology and Obstetrics Associations); UKOSS = UK Obstetric Surveillance System; UKTIS = UK Teratology Information Service; ACIP = Advisory Committee on Immunization Practices.

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