An imperative to offer pregnant and lactating women access to the COVID-19 vaccination roll-out programme

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In view of the continuing worldwide spread of COVID-19 infection, the increased morbidity and mortality from the disease during pregnancy, and the current efficacy and safety of vaccines in non-pregnant individuals, vaccines should not be withheld from women simply because of pregnancy or lactation. All pregnant women, especially healthcare professionals, should be offered vaccination and counselled about its advantages and disadvantages by their maternity care providers. Complete eradication of COVID-19 infection will be possible if potential niduses of the infection, which may act as sources for future outbreaks, are protected against the pathogen. However, if a hypothetical medication is the only means yet proven of limiting severe compromise to maternal health, access to the medication should be at the pregnant woman's discretion. Shared decision-making requires physicians to actively engage with their patients and share their knowledge about the subject matter.

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COVID-19 is caused by a novel single-stranded RNA virus (SARS-CoV-2) that was initially identified in Wuhan, China, in December 2019.[1,2] The continuing global spread of the SARS-CoV-2 coronavirus is of particular concern for pregnant and lactating women, because they are at an increased risk of complications if they become infected by the virus. In pregnancy, the infection can result in complications such as stillbirths and preterm delivery, and increases in caesarean delivery rates (both iatrogenic and spontaneous), perinatal loss and even maternal death when compared with non-infected pregnant women.[3,4]

SARS-CoV-2 commonly spreads from person to person via respiratory droplets/nasal discharge. The current measures to prevent the spread of the COVID-19 pandemic are therefore use of public health guidelines such as physical distancing in public spaces, not congregating in large crowds, the wearing of facial coverings such as masks/shields, and the frequent washing of hands with soap and water. In the absence of the latter, the frequent use of alcohol-based sanitisers is recommended.[1,2] The global health crisis created by the pandemic necessitates a co-ordinated public health response that also includes effective and strategic roll-out of vaccinations to the population to gain control of viral spread and achieve herd/population immunity.[1-5]

The abovementioned public health measures have been reported to be effective in limiting the spread of the disease.[6] Although such measures are effective, they are dependent on individual and societal behaviour and may be difficult to maintain in all population groups over a long period of time.[6] This is crucial because the fear and anxiety created by the lockdown/restriction measures that restrict socioeconomic activities have led to a worldwide increase in mental health issues and gender-based violence, including in South Africa (SA).[7] Saccone *et al.*[8] reported that among pregnant women, more than half of the respondents rated the psychological impact of the COVID-19 outbreak as severe, and two-thirds reported higher-than-normal anxiety levels.

While there has been some success in addressing the pandemic through societal mechanisms, no pharmaceutical drugs have yet been proven effective for the prevention or treatment of mild to moderate COVID-19 disease. There are some agents, however, such as dexamethazone and remdesivir, an antiretroviral drug used for the management of Ebola, that have been used successfully,[9-11] notably in shortening the duration of hospital stay for patients who develop severe COVID-19 disease.[9,10] Currently, there is no drug generally accepted as preventive therapy for COVID-19 infection. Implementation of widespread vaccination programmes may result in herd/population immunity and prevent rapid spread of the disease and serious complications, including mortality.[12,13] It is therefore not surprising that numerous human clinical trials are being carried out to prevent SARS-CoV-2 infection.[12,13] However, no randomised COVID-19 clinical trials (RCTs) or vaccine trials to date have included pregnant women.[13] Vaccination of pregnant women has, however, been recommended to prevent seasonal influenza, pertussis and tetanus.[14] Clinical data on the safety and efficacy of influenza immunisation have been provided by an RCT involving 3 693 pregnant women in Nepal, in which immunisation was shown to decrease maternal influenza-like illness by 19% and infant influenza disease by 30%.[14] Given that COVID-19 is highly infectious and results in increased morbidity and mortality among pregnant women, we argue that pregnant and lactating individuals should be permitted and prioritised to receive the COVID-19 vaccine.[3,4,14]

Methods

A literature search was performed of all articles in the databases PubMed, Google Scholar and Clinical Keys using the keywords

COVID-19, COVID-19 vaccination, Pregnancy, and Maternal health. The information was accessed from 2020 to 2021, since roll-out of COVID-19 vaccination commenced in 2021 in SA.

COVID-19 vaccines

There are currently three types of COVID-19 vaccines, viz. mRNA vaccines, viral vector vaccines and protein subunit vaccines, which have been or are being developed and investigated in clinical trials worldwide.[5,12] None of these types of vaccines can cause COVID-19, because they produce antigens that stimulate the body's immune system, resulting in the production of T- and B-lymphocytes to guard against future infection.[5,12,13]

A considerable amount of data have been produced from some COVID-19 clinical trials (Pfizer BTN162b2, Moderna, AstraZeneca-Oxford and Sputnik vaccines).[5] The data include information on efficacy and safety. In general, these vaccines are all effective and well tolerated, with no serious safety concerns.[5] Owing to the results of studies on these vaccines, some of them have received emergency authorisation for vaccination programmes, and countries such as the UK and the USA have initiated immunisation programmes.

Considering the data available, it is surprising that pregnant and lactating women were excluded from the vaccine trials.[5,14,15] Presumably their exclusion is based on theoretical risks of harm to the fetus and transmission of the virus to the baby during lactation. Pharmaceutical companies are concerned about litigation post vaccination. However, the vaccine is of particular importance because current data on the impact of COVID-19 on pregnancy show an increase in stillbirths, preterm births, and even mortality compared with non-pregnant women.[3,4] Furthermore, the American College of Obstetricians and Gynaecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have advocated the inclusion of pregnant and breastfeeding women in vaccine trials.[16] There are also professional organisations that have indicated that healthcare workers, who are being considered as a priority group for vaccination, should be offered the vaccine if they are pregnant.[16,17] Furthermore, it is argued that in an active outbreak, pregnancy is associated with increased susceptibility to severe disease, and an effective approach to protecting the infant is through passive placental antibody transfer.[13]

Withholding globally approved vaccines from pregnant and breastfeeding women based on theoretical risks may be considered unethical, given the increased adverse events in pregnant women infected with SARS-CoV-2. Furthermore, vaccination of pregnant women against seasonal influenza, pertussis and tetanus is based on the increased risks that these infections pose to the pregnant woman and her fetus, and the well-established safety profiles for these inactivated vaccines.[13] Balancing the appropriateness of medical therapy and other treatments during pregnancy continues to be a challenging issue in ethics, especially when there appears to be a misalignment of maternal and fetal interests. However, most obstetric ethicists believe that it is the pregnant patient who is best placed to make choices regarding whether or not an intervention is appropriate for her. Maternal autonomy is of paramount importance, and it trumps the uncertainty presented by the paucity of safety data.[17,18]

Severity of COVID-19 infection in pregnancy

At present, there is controversy as to whether pregnant women should be included in vaccination programmes.[13-18] In SA, there is no clear indication that pregnant and lactating individuals would be included in the vaccination roll-out. We believe that a strong case can be made for inclusion of all pregnant women, or at least all pregnant health professionals regarded as being at increased risk of contracting COVID-19. International bodies such as the Royal College of Obstetricians and Gynaecologists recommend the vaccine for pregnant individuals who are at high risk of contracting the disease (e.g. healthcare workers) and those with comorbidities. The Food and Drug Administration and Centers for Disease Control and Prevention adopt a similar stance. Canada and Ireland argue that the risk/benefit ratio is in favour of vaccinating, and pregnant women should therefore benefit from the intervention.[2,16,19]

Current data, including a rapid appraisal of the impact of the first wave of COVID-19 on the use of maternal and reproductive health services and on perinatal deaths in SA, show an increase in maternal deaths since the lockdown started, compared with the same period in 2019.[20] These deaths may have been due to COVID-19 rather than indirect effects of COVID-19 exerting undue pressure on limited resources available for maternal health services, and/or pregnant women not attending healthcare services timeously. Furthermore, this increase in maternal deaths in SA should be analysed in terms of a decade in which the maternal mortality ratio has been declining yearly from the peak in 2010 - 2011.[21] In addition, there was an increase in stillbirths and preterm labours.[20] This scenario indicates that pregnant women are a vulnerable group, and recent US data evaluating pregnant and non-pregnant women with laboratory-confirmed SARS-CoV-2 also support this.[3,4] Physiological changes to the cardiorespiratory and immune systems in pregnancy increase maternal susceptibility to infection and hypoxia. One-fifth of healthy women in late pregnancy will suffer from gestational rhinitis caused by oestrogen-mediated hyperaemia of the nasopharynx, which may result in masking of the coryzal symptoms of COVID-19, allowing for unchecked transmission. Maternal pulmonary volumes are also decreased, and physiological dyspnoea needs to be distinguished from shortness of breath caused by COVID-19.[18]

Delahoy *et al.*[3] found that of 598 pregnant women found to be positive for COVID-19 when hospitalised for various reasons between March and August 2020, 326 (55%) did not have COVID symptoms at admission. Symptomatic women generally had severe disease, and 44 of the severe cases required treatment in an intensive care unit (ICU). There were two deaths among these 598 women (1%). The authors point out that ~5% of women of childbearing age (15 - 49 years) in the general population are pregnant; in their study, 26.5% of hospitalised women with COVID-19 in this age group were pregnant, indicating that pregnant women may be more susceptible to severe illness, although this figure could be confounded by the lower admission threshold that healthcare providers have when faced with pregnant women.[3,4]

The study by Delahoy *et al.*[3] also found that an overall 7.4% of all pregnant COVID-19-positive patients were admitted to an ICU, which is on par with the European statistic of 7.8%. However, in the symptomatic cohort of pregnant patients, this number jumped to 16.2%, implying that pregnant women with acute illness may have more severe outcomes.[3] Another study from the USA, published in November 2020, evaluated the characteristics of women of reproductive age who were symptomatic with laboratory-confirmed SARS-CoV-2 infection. It was found that among 400 000 women aged 15 - 44 years with symptoms of COVID-19, ICU admission, invasive ventilation, extracorporeal oxygenation and death were more likely in pregnant women than in non-pregnant women (10.5 v. 3.9 per 1 000 cases, adjusted relative risk 3.0).[4] Such data strongly suggest that pregnant women fall into the vulnerable group and are at increased risk of severe illness and death. They should therefore be counselled about the proven measures to prevent SARS-CoV-2 infection, and signs and symptoms for which to seek COVID-19 testing and treatment. There is consensus that receiving a recommendation for vaccination from a healthcare provider is the most important factor

in maternal decision-making, irrespective of geographical or social context. If an area of uncertainty exists, the final decision should be taken by the pregnant woman in consultation with healthcare providers who are knowledgeable about the risk/benefit ratio and the values and circumstances of the patient.[17]

COVID-19 vaccination in pregnancy and lactation

Now that SA is embarking on a COVID-19 vaccination programme, strong consideration should be given to vaccinating pregnant and lactating women and promoting their inclusion in future clinical vaccine studies, based on the following points:

- There is good evidence that pregnant women are among the vulnerable groups at increased risk of severe disease and that they are more likely to suffer increased COVID-19-related morbidity and mortality compared with non-pregnant women.
- Withholding globally approved vaccines from pregnant and breastfeeding women simply on the basis of theoretical risks may be considered unethical, given the increased adverse maternal and perinatal risks associated with COVID-19.
- It is standard practice to offer all pregnant women vaccination against seasonal influenza, pertussis and tetanus. Their use is based on the increased risk that these infections pose to the mother and the baby, and the well-established safety profiles for the inactivated vaccines. Vaccines are immunogenic, and individuals may experience body aches, fever and headaches for a few days. These side-effects are not life-threatening and must be recognised and discussed with the healthcare provider.
- Several professional organisations including the ACOG have consistently advocated for the inclusion of pregnant and lactating women in vaccine trials.
- The SMFM also strongly recommends that pregnant women should have access to COVID-19 vaccines. This recommendation includes pregnant healthcare professionals, who are considered a priority for vaccination. The South African Society of Obstetricians and Gynaecologists has released a 'poster' suggesting that all pregnant women at increased risk of COVID-19 (diabetics, and obese and hypertensive pregnant women) should be offered the vaccine.
- The fetal impact of COVID-19 vaccination is unknown, and the potential for fetal risk must be acknowledged. However, there have been animal studies that have shown no adverse effects on the embryo. Furthermore, during one vaccine trial, a small number of women were discovered to be pregnant; some of these pregnancies were ongoing at the time of writing this article, while there were no fetal/perinatal effects in those who had given birth.

Conclusions

Pregnant and lactating women should be considered in clinical trials during pandemics such as COVID-19. Several research investigations have shown that pregnant women are more susceptible to COVID-19 than non-pregnant women. Furthermore, studies have reported an increased rate of preterm births and stillbirths in COVID-19 pregnancies. We therefore highly recommend that pregnant women, especially those with comorbidities, are vaccinated, as COVID-19 poses a risk not only to maternal health but to fetal viability as well.

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