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Guidance on the use of the Janssen Ad26.COV2.S (COVID-19) vaccine in pregnant and lactating women

Background

Pregnant women are at higher risk of severe COVID-19 compared with women of childbearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth. This document offers some preliminary recommendations on the use of the Janssen Ad26.COV2.S (COVID-19) vaccine in pregnant or lactating women in the context of the Sisonke trial and in the future national rollout of the Janssen COVID-19 vaccine. These recommendations consider the safety of the vaccine including the recent reports of Vaccine induced Thrombotic Thrombocytopaenia (VITT).

Janssen Ad26.COV2.S (COVID-19) vaccine

The Ad26.COV2.S vaccine against COVID-19 is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein. This vaccine does not contain adjuvants, preservatives, materials of animal origin, or foetal tissue. A single dose of Ad26.COV2.S has an efficacy of 66.9% (95% confidence interval (CI): 59.0,73.4) against symptomatic SARS-CoV-2 infection, 76.7% (95% CI: 54.6, 89.1) against severe COVID-19 disease after 14 days, and 85.4% (95% CI: 54.2, 96.9) after day 28 . Vaccine efficacy against hospitalisations was 93.1% (95% CI: 72.7, 99.2). Vaccines that use the same viral vector have been given to pregnant people in all trimesters of pregnancy, including in a large-scale Ebola vaccination trial. No adverse pregnancy-related outcomes, including adverse outcomes that affected the infant, were associated with vaccination in these trials.

Clinical data on pregnant and lactating women

While caution about the inclusion of pregnant and lactating women in early clinical trials, evaluating new vaccines is common, there is a growing global realisation that pregnant and lactating women should be included in clinical trials at an early and safe point in product development so that they are not excluded from subsequent use of the product. In addition, other vaccines are specifically recommended during pregnancy because of the heightened risk of harm to mother and /or her infant. These include vaccines for influenza, pertussis and tetanus, with Group B Streptococcal vaccines and Respiratory Syncytial Virus vaccines in development.

The initial clinical trials of COVID-19 vaccines excluded women who are pregnant, and most studies excluded women who were lactating. In evaluating the use of COVID-19 vaccines in pregnant and lactating women consideration must be given to all relevant data including reproductive developmental toxicity studies, vaccine related adverse effects on female fertility, embryo-fetal or postnatal development and available clinical data.

The only direct evidence that can be accessed at this stage would come from inadvertent administration of COVID-19 vaccines to pregnant women who were inadvertently included in clinical trials protocols, and particularly from those women who were subsequently enrolled in pregnancy registries. Other data are emerging from routine rollouts across the globe and reporting to post-marketing surveillance pregnancy registries. One such set of data was reported in the NEJM by Shimabukuro *et al.*, 2021 drawing on the CDC v-safe COVID-19 Pregnancy Registry.

Janssen currently states the following in relation to the COVID-19 vaccine

Available data on Janssen COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. In a reproductive developmental toxicity study female rabbits were administered 1 mL of the Janssen COVID-19 Vaccine (a single human dose is 0.5 mL) by intramuscular injection 7 days prior to mating and on Gestation Days 6 and 20 (i.e., one vaccination during early and late gestation, respectively). No vaccine related adverse effects on female fertility, embryo-fetal or postnatal development up to Postnatal Day 28 were observed.
Data are not available to assess the effects of Janssen COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

Reports of adverse events following use of the Janssen COVID-19 Vaccine

According to Janssen, reports of adverse events following use of the Janssen COVID-19 vaccine under emergency use authorization in the United States suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal. The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia.

SAHPRA's review of the data generated to date from the Sisonke trial confirm that no cases of VITT have been identified but there have been some reported cases of thrombosis thought by the research team not to be associated with the use of the vaccine.

Current WHO recommendations

The available data on Ad26.COV2.S of pregnant women are insufficient to assess vaccine-associated risks in pregnancy. However, it should be noted that Ad26.COV2.S is a nonreplicating vaccine. No safety issues have been identified following vaccination of more than 1,600 pregnant women using the Ad26 vaccine platform for vaccines against other pathogens, such as the Ebola virus. Animal developmental and reproductive toxicity studies show no harm to the development of the foetus. Further studies are planned in pregnant women in the coming months, including a pregnancy sub-study and a pregnancy registry. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, pregnant women should receive Ad26.COV2.S only if the benefit of vaccination to the pregnant woman outweighs the potential vaccine risks, such as if the

woman is a health worker at high risk of exposure or has comorbidities that place them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety data on Ad26.COV2.S vaccine for pregnant women and the potential benefit of vaccination should be provided. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy because of vaccination. Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. It is unknown whether Ad26.COV2.S is excreted in human milk. As the Ad26.COV2.S vaccine is a non-replicating vaccine, it is unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, a lactating woman who is part of a group recommended for vaccination, e.g., health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination.

Two recent commentaries published in the SAMJ, by Moodley *et al.* and Zamparini *et al.* have accordingly called for a more enabling, individualised and patient-centred approach to the question. Their conclusions are, respectively:

- "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."
- "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."

in addition, the VMAC recommends the use COVID-19 vaccines in pregnant women, based on individual benefit -risk assessments, counselling and informed consent.

Conclusions/Recommendations

- It is not yet clear whether the Janssen COVID-19 vaccine is excreted in breast milk. Women who are breatstfeeding should be counselled on the absence of information in this regard and a benefit-risk assessment should be made by the enrolling clincian. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunization against COVID-19. It must be noted that the WHO does not recommend discontinuing breastfeeding after vaccination.
- Ensemble 1&2 study protocols using Janssen COVID-19 vaccine included participants who were lactating. The Ensemble study team/ Sisonke/J&J should submit data on lactating participants and should continue to collect this data as the Sisonke study continues.
- Pregnant women at high risk of exposure to SARS-CoV-2 (e.g., health workers) or who have comorbidities which add to their risk of severe COVID-19 disease may be vaccinated in consultation with their health care provider
- Vaccination data should be collected as part of the ongoing Sisonke Study and by national pregnancy exposure registries once the vaccine is being rolled out.