COVID-19 vaccination in pregnancy:

Symptomatic pregnant women with COVID-19 infection are at increased risk for more severe illness than their non-pregnant peers. Common obstetric comorbidities and complications such as obesity, hypertension, smoking, and diabetes further increase that risk. The CDC has included pregnancy as a risk factor increasing the risk for severe COVID-19 disease.

Although the absolute risks are low and most pregnant women with the corona virus do not become severely ill, symptomatic pregnant women with laboratory-confirmed COVID-19 are significantly higher risk for severe complications of COVID infection compared to their non-pregnant peers. According to a recent CDC evaluation of reproductive age women by pregnancy status (MMWR 2 Nov 2020), pregnant women are 3-fold more likely to be admitted to an ICU, 2.9 times more likely to require invasive ventilation, 2.4 times higher rate of ECMO, and 1.5 times more likely to die after adjusting for age, race/ethnicity, and medical comorbidities. Older pregnant women (ages 35-44) were at particularly high risk and were nearly four times more likely to require invasive ventilation and two-fold more likely to die than non-pregnant women.

The increased risk for severe outcome is likely related to changes in maternal physiology during pregnancy including increased oxygen consumption, decreased lung capacities (FRC), greater risk for thromboembolic events, and a shift away from cell-mediated immunity.

On 11 December 2020, the US FDA issued an emergency use authorization (EUA) for the Pfizer-BioNtech mRNA vaccine. The following day, the Advisory Committee on Immunization Practices recommended the vaccine in persons 16 and older for prevention of the COVID-19 illness. Both ACOG and SMFM recommend that vaccine should not be withheld from women based on pregnancy and breastfeeding who otherwise meet criteria for vaccination and should not change their priority for vaccination. Subsequently the Moderna and Johnson & Johnson vaccines were also approved. Currently, three vaccines to prevent moderate to severe disease from COVID-19 have received emergency use authorization from the US FDA. The two-dose Pfizer vaccine (people 16 and older), the two-dose Moderna vaccine (for people 18 and older), and the one-dose Johnson & Johnson vaccine (for people 18 and older).

The Pfizer vaccine received full FDA approval on 23 August 2021.

Because COVID-19 vaccines were anticipated to be given to large numbers of healthy people, the FDA set a higher standard for COVID vaccines than the usual EUA process

with evidence similar to the typical process for full FDA approval. The safety and efficacy data was reviewed at several levels (both within the FDA and by independent scientists) prior to authorization including the Data and Safety Monitoring Board (panel of independent scientists), FDA scientists, and finally review by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) which is an independent FDA advisory committee.

Patients should have the necessary information to make an informed decision about vaccination and its timing including occupational exposure level of risk, prevalence of the virus in the community, and maternal comorbidities which may increase the risk for maternal morbidity or mortality. Vaccination is not an alternative to public health risk-mitigation strategies already in place. The vaccines have not been tested prospectively in human pregnancy, and there is no evidence-based research on safety specific to human pregnancy. There is not data to indicate the vaccine is contraindicated and no safety signal generated during the DART studies for the Pfizer or Moderna vaccines.

The current vaccines are not live-virus vaccines. The mRNA vaccines are a new technology but are not derived from live virus, and the vaccine does not enter the nucleus or alter human DNA in recipients. Vaccines based on mRNA technology cannot alter the human genome or cause genetic damage. The theoretical risk from mRNA vaccines is very low as they induce humoral and cellular immunity through the use of viral mRNA. The vaccine is administered as an intramuscular injection. The vaccine acts locally at the site of injection and is rapidly degraded and removed by the patient's lymphatic system. The vaccine enters the cytoplasm of muscle cells in the patient's deltoid which results in manufacture of the spike protein which prompts an immune response and production of antibodies against COVID-19 spike protein. There is no virus in the vaccine, and the vaccine never enters the muscle cell's nucleus and thus does not interact with the host cell's DNA. The vaccine mRNA is degraded in the muscle cell's cytoplasm.

The Johnson & Johnson vaccine is based on older technology and is not an mRNA vaccine.

Pregnant women were not included in the original vaccine trials. Some participants did inadvertently become pregnant during the trial, and there have been no reports of adverse reproductive consequences or fetal anomalies. There is ongoing monitoring of these pregnancies. The CDC and others are tracking pregnant patients who received the COVID-19 vaccines. More than 30,000 pregnant women who were vaccinated have reported to the CDC, and no safety problems and no unexpected pregnancy or fetal complications have been reported. Women vaccinated during pregnancy have given

birth, and there are detectable levels of anti-COVID antibody in cord blood indicating that maternal immunity (IgG antibodies) cross the placenta (like any other antibody the mother has produced to prior vaccination or infection) and may protect the newborn through passive immunity. It is anticipated that vaccinated mothers will also produce IgA antibodies against COVID in breast milk which may provide some protection to newborns through respiratory and GI tract protection.

As more pregnant women have been vaccinated, data showing safety is now available. Women who have been vaccinated have no increase risk for miscarriage (https://jamanetwork.com/journals/jama/fullarticle/2784193). There is no increase in the risk for common pregnancy complications including miscarriage, IUFD, premature birth, IUGR, neonatal death, or congenital anomalies (https://www.nejm.org/doi/full/10.1056/nejmoa2104983). No relationship between receipt of vaccine and decreased fertility rates or subfertility has been demonstrated. (https://www.fertstertreports.org/article/S2666-3341(21)00068-4/fulltext).

Infection with COVID is associated with an increased risk for adverse pregnancy outcome. Recent observational data published by the NICHD MFMU (INTERCOVID trial) indicates that pregnancy complications are more common in women infected with COVID during pregnancy than a control group of women who were not infected with COVID. COVID-19 in pregnancy is strongly associated with preeclampsia, and the association is even stronger in nulliparous women. This association is independent of the severity of the COVID infection. Both preeclampsia and COVID are independently associated with an increased risk for preterm delivery, and the risk is at least additive. Women who are infected with COVID during pregnancy are 1.77 times more likely to develop preeclampsia, and nulliparous women are almost twice as likely to develop preeclampsia. Of all women who are infected with COVID and develop preeclampsia in pregnancy, preterm delivery is 4 times more common. Nulliparous women with a history of COVID during the pregnancy and a diagnosis of preeclampsia are more than 6 times more likely to deliver prematurely. (AJOG, 2021)

CDC, ACOG/SMFM, and the AAP strongly recommend that women planning pregnancy, who are currently pregnant, and postpartum women who are breastfeeding get vaccinated.

Pregnancy increases susceptibility and severity of disease, and the best way to protect the fetus/newborn is through passive immunity acquired transplacentally prior to vaccination. As with all medications in pregnancy, the patient should make a decision based on the best available information about safety and efficacy of the medication, potential risks of the medication, and the risk of the disease if the medication (in this

case vaccine) is not administered. Receipt of the vaccine should not alter personal and public health mitigation strategies including social distancing, mask wearing, and frequent, thorough hand hygiene.