COVID-19 vaccines provide protection against the COVID-19 virus, SARS-CoV-2, and are administered by injection. Several different COVID-19 vaccines have been developed.

Messenger ribonucleic acid (mRNA) vaccines use mRNA as the genetic vector to encode a spike protein of SARS-CoV-2, the protein found on the surface of the virus, to trigger an immune response. The mRNA does not enter the nucleus and therefore does not integrate into the DNA. The mRNA is degraded into the cell cytoplasm within hours to days after injection.

Magnitude of Teratogenic Risk to Child Born After Exposure During Gestation: UNLIKELY

Quality and Quantity of Data on Which Risk Estimate is Based: FAIR

Comments: RECEIVING A COVID-19 mRNA VACCINE IN THE FIRST TRIMESTER OF PREGNANCY IS UNLIKELY TO POSE A SUBSTANIAL TERATOGENIC RISK, BUT THE DATA ARE INSUFFICIENT TO STATE THAT THERE IS NO RISK.

Summary of Teratology Studies:

MAJOR CONGENITAL ANOMALIES

The rates of major malformations overall, and of congenital heart defects specifically, were no different among liveborn infants of 2134 mothers who were vaccinated with an mRNA COVID-19 vaccine in the first trimester of pregnancy and the infants of 3584 unvaccinated pregnant women in a large cohort study conducted in Israel (Goldshtein et al., 2022).

In a retrospective cohort study based on data from electronic medical records, the rate of major congenital anomalies identified on second-trimester ultrasonography among fetuses of 1149 women who received at least one dose of a COVID-19 vaccine anytime 30 days before conception through 14 weeks of gestation was similar to that seen in the fetuses of 2007 women who were unvaccinated or vaccinated outside the first trimester (adjusted odds ratio=1.01, 95% confidence interval 0.69-1.48) (Ruderman et al., 2022). No teratogenic effect was found when the window of exposure was narrowed down to two to ten weeks gestation. Although the authors of this study do not specify how many women actually received a COVID-19 mRNA vaccine, it can be safely presumed based on the location and timing of the study that the majority were immunized with a COVID -19 mRNA vaccine.

PREGNANCY AND NEONATAL OUTCOMES

Several systematic reviews and meta-analyses of epidemiological studies reporting on more than 117,552 vaccinated pregnancies--almost exclusively with mRNA vaccines--showed no significant differences in the overall frequency of adverse pregnancy and neonatal outcomes (spontaneous abortion, preterm birth, low birth weight, small for gestational age, NICU admission, and low Apgar scores) between vaccinated and unvaccinated pregnancies (Carbone et al., 2022; Ma et al., 2022; Prasad et al., 2022; Tormen et al., 2022; Watanabe et al., 2022). In fact, the incidence of some of these adverse outcomes, including stillbirth and preterm birth, were slightly reduced among vaccinated women compared to the rates seen in the unvaccinated group in some of these studies (Carbone et al., 2022; Prasad et al., 2022; Watanabe et al., 2022). Some of the studies included in those meta-analyses and reviews are discussed below.

The cumulative risk of spontaneous abortion (14.1%, 95% confidence interval 12.1-16.1) reported among 2456 pregnant women in the v-safe pregnancy registry who had received at least one dose of an mRNA COVID-19 vaccine either before conception or before 20 weeks of gestation was similar to that expected in the general population, and remained in the expected range in a secondary analysis using maternal age-standardization to the reference population (12.8%, 95% confidence interval 10.8-14.8) (Zauche et al., 2021). In two subsequent retrospective cohort studies, administration of an mRNA COVID-19 vaccine was not associated with a risk of early pregnancy loss among a total of 1149 vaccinated women compared to unvaccinated women (Aharon et al., 2022; Citu et al., 2022). No evidence of an increased rate of spontaneous abortion following first trimester COVID-19 mRNA vaccination was found in other reports (Magnus et al., 2021; Trostle et al., 2021). In a European pharmacovigilance study, the frequency of spontaneous abortion was lower among 2612 pregnant women who received an mRNA vaccine compared to 619 women who received a COVID-19 viral vector vaccine (odds ratio=0.80, 95% confidence interval 0.69-0.93) (Mascolo et al., 2022).
In another preliminary study of the v-safe pregnancy registry, no neonatal deaths were reported among 724 liveborn infants of mothers who received an mRNA COVID-19 vaccine in the third trimester of pregnancy, and rates for preterm birth (9.4%), small for gestational age (3.2%), and stillbirth (0.1%) were similar to background population rates (Shimabukuro et al., 2021). Similarly, no significant differences in early infant morbidity or mortality were detected among 16,689 liveborn infants who were prenatally exposed to an mRNA vaccine compared to liveborn infants born to 7591 unvaccinated pregnant women in a large cohort study in Israel (Goldstein et al., 2022). In other population-based studies conducted in Canada, Israel, Malaysia, Sweden, and Norway, vaccination against SARS-CoV-2 during pregnancy was not significantly associated with an increased risk of adverse pregnancy and neonatal outcomes, including stillbirth, small for gestational age, preterm delivery, low Apgar scores, or NICU admission, compared to the outcome of unvaccinated pregnant women (Arulappen et al., 2022; Fell et al., 2022; Kugelman et al., 2022; Magnus et al., 2022; Sadarangani et al., 2022). Most of the vaccinations in those studies were mRNA COVID-19 vaccines and were given during the second and third trimesters of pregnancy.

Pregnancy and neonatal outcomes of 127 women who received an mRNA vaccine were similar to those of a propensity score-matched cohort of 399 pregnant women who did not receive COVID-19 vaccines in pregnancy (Blakeway et al., 2022). Two cohort studies from Mexico and Australia reported on reduced incidences of stillbirth and preterm birth among a total of more than 44,157 vaccinated pregnant women with an mRNA vaccine compared to the outcome in unvaccinated women (Hui et al., 2022; Piekos et al., 2022).

**TRANSPLACENTAL PASSAGE OF SARS-CoV-2 ANTIBODIES**

Several studies reported SARS-CoV-2 IgG antibodies being detectable in the cord blood of infants whose mothers were vaccinated with an mRNA vaccine in the second half of pregnancy (Gray et al., 2021; Mithal et al., 2021; Rottenstreich et al., 2021; Kassis et al., 2022; Shook et al., 2022). Evidence of transplacental passage following vaccination in early pregnancy has also been demonstrated in some other reports (Atyeo et al., 2022; Rottenstreich et al., 2022; Sourouni et al., 2022).

**ANIMAL TERATOLOGY STUDIES**

No teratogenic or other adverse fetal effects were observed among the offspring of mice injected with mRNA-1273 vaccine during early pregnancy with over 50 times greater doses than those used in humans (Lu-Culligan et al., 2022). In the same study, pregnant dams vaccinated prior to placental establishment and fetal circulation conferred fetal transfer of antibodies up to the time of birth.

**Selected References:**

(Each paper is classified as a review [R], human case report [C], human epidemiological study [E], human clinical series [S], animal study [A], or other [O].)


COVID-19 VACCINE PREGNANCY REGISTRIES

Healthcare providers are encouraged to suggest their patients enroll in the following registries:

V-SAFE

A registry collecting health information from people who received COVID-19 vaccinations in the periconception period or during pregnancy is being maintained by the Centers for Disease Control and Prevention. The registry attempts to assist individuals and healthcare providers to make informed decisions about COVID-19 vaccination.

Pregnant vaccinated people who would like to participate must complete a registration in v-safe (a smartphone-based tool that uses text messaging and web surveys to provide personalized health check-ins after you receive a COVID-19 vaccine: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html). People who meet the conditions of the study will be contacted by the registry staff for additional details for enrollment in v-safe.
COVID-19 Vaccine Study

An observational pregnancy study by MotherToBaby has been established for women who received one or more doses of a COVID-19 vaccine during pregnancy or within one month prior to becoming pregnant. All study research will be performed via phone and office visits will not be required.

Additional information about the study can be found at MotherToBaby’s COVID-19 Vaccines (https://mothertobaby.org/ongoing-study/covid19-vaccines/). Healthcare providers are encouraged to enroll such patients at https://mothertobaby.org/join-a-study-form/.

C-VIPER (COVID-19 Vaccines International Pregnancy Exposure Registry)

A registry collecting information from pregnant women who were vaccinated against COVID-19 during pregnancy and is maintained by Pregistry in Los Angeles, Calif. This registry evaluates obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy to prevent COVID-19.

Healthcare providers may find additional information about this study at: https://www.clinicaltrials.gov/ct2/show/NCT04705116.

CANADIAN COVID-19 VACCINE REGISTRY FOR PREGNANT AND LACTATING INDIVIDUALS

A registry collecting information from women who are currently pregnant or breastfeeding regardless of vaccination status is maintained by the University of British Columbia in Vancouver, B.C., CANADA and in partnership with other Canadian vaccine surveillance networks. The registry is a longitudinal survey monitoring the safety, effectiveness, and opinions related to the COVID-19 vaccine.

Healthcare providers may find more information about this registry at: https://covered.med.ubc.ca/.