**Type of study: Review**

**Evaluation of safety concerns for COVID-19 immunization of pregnant women: A systematic review of emerging evidence**

**Running title: COVID-19 immunization of pregnant women**

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**Abstract:**

**Background:** There is an urgent need to review the status of COVID-19 vaccine immunization in pregnant women globally so that the adverse outcomes may be prevented.

**Objective:** To evaluate the probable outcome of COVID-19 vaccination in pregnant women.

**Search strategy:** An electronic search was conductedover the period of 3 months (June 15-August 15, 2021).

**Selection criteria:** The original studies evaluating safety concerns in pregnant women for COVID-19 vaccination were included.

**Data collection and analysis:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines were used for the collection of the data and reporting of the findings. The inclusion and exclusion criteria for the studies were determined based on ‘PICO principle’ (Population, Intervention, Comparator, and Outcome, Study design. Risk of bias assessment was done using National Institute of Health (NIH) tool for systematic reviews.

**Main results:** COVID-19 vaccination in pregnant women was not associated with increased adverse effects or complications to the mother as well as developing fetus or newborn compared to non-vaccinated pregnant women. Vaccinated pregnant women showed a robust immune response against COVID-19 infection.

**Conclusions:** COVID-19 vaccination during pregnancy causes no significant health risks for the mother or developing fetus or newborn.

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**Keywords:** COVID-19, Vaccine, Fetal outcome, Pregnancy, SARS CoV-2 Vaccine, Vertical transmission, Umbilical cord

**1 Introduction**

The subsequent waves of COVID-19, caused by new variants of SARS-CoV-2, have kept raging across the world. The vaccination for the COVID-19 is being ramped up globally in an attempt to stabilize the ongoing pandemic. Increasing number of studies established high efficacy of current COVID-19 vaccines in protection against infection and disease severity.  However, as most of the clinical trials for COVID-19 vaccines excluded pregnant women in their study there is not enough data about the vaccination safety and risks in this crucial population.

Teratogenic effect of many drugs as well as viral infections, which can cross the placental barrier to enter into fetal circulation, may influence the fetus development is a well-recognized (Fig 1).1 Particularly during the first trimester, the period of early embryogenesis, the risks of the teratogenicity are higher.1 Moreover, m-RNA and nano-particles based novel approaches in COVID-19 vaccines, has added to the apprehension of health policymakers, as their impacts on developing fetus are currently unknown. On the other hand, COVID-19 infection has some proven risks for pregnant women and their unborn babies. Pregnancy is an important risk factor for developing severe illness in COVID-19 infected women.2 Several researchers observed that hospitalization and maternal mortality in pregnant patients infected with COVID-19 were significantly higher in the comparison to women without COVID-19.3, 4 Besides this pregnant women with COVID-19 have an increased risk of premature and/or low-birth weight infants, preeclampsia or eclampsia, postpartum haemorrhage, ICU admission, intrauterine/foetal distress, premature rupture of membranes, prolonged admission after birth, and complications requiring emergency caesarean delivery.3, 5–13 The risk of neonatal adverse outcome, need for specialist neonatal care, and prolonged neonatal admission after birth were significantly higher in babies of mothers with SARS-CoV-2 infection.5 Intra-uterine fetal demises were more common in COVID-19 positive pregnant women in comparison to mother without COVID-19.7 Moreover, virus mediated inflammation and injury to placental tissue of infected mothers and vertical transmission of the COVID-19 infection from mother to fetus has been reported in multiple studies (both in utero, which is uncommon especially in third trimester, and peripartum.2, 14–16

The emerging evidence does not indicate any significant harm to the pregnant women taking vaccination when compared to the unvaccinated, however, a clear view on this issue is lacking till date. In this article, we present a systematic review of the existing evidence from the human studies regarding safety concerns of COVID-19 vaccination in pregnancy.

**2 Material and Methods**

**Objectives**

To evaluate the probable outcome of COVID-19 vaccination in pregnant women for the development of evidence-based policy for the vaccination.

**Information sources and search strategy**

The online literature sources including PubMed/Medline (EBSCO & Ovid), EMBASE, Google Scholar, Science Direct, Scopus, Bio Medical and Web of Science (WoS), and ClinicalTrials.gov were searched using multiple combination of MeSH (Medical Subject Headings) and free keywords representing the components of the objective of the study such as ("COVID -19 vaccine ") OR (“COVID vaccine”) OR (“SARS-COV-2 vaccine”) AND ("Pregnancy") OR ("Pregnant women") OR ("Pregnancy outcome") OR ("Newborn"), ("COVID -19 vaccine" AND “Umbilical cord”), etc. Additionally, publication citations in original studies and review/commentary papers we searched for the original studies. Apart from these, technical reports and other papers from government agencies or scientific groups or committees addressing COVID-19 vaccination in pregnant women were searched. The studies published up to 15 August, 2021 were considered eligible for this study.

**Protocol followed**

A systematic review of the original studies about effect of COVID-19 vaccination on health of mother and fetus was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [Fig. S 1]. The inclusion and exclusion criteria for the studies that met the objectives of this review were determined based on ‘PICO principle’ (Population, Intervention, Comparator, and Outcome, Study design) and are presented in Table S1.

**Data selection, extraction, risk of bias assessment, and qualitative synthesis**

Full articles reporting original clinical/epidemiological/case reports/ clinical trials/animal model studies were included in the study. A comprehensive literature search was performed to minimize the chances of publication bias. Assessments of the studies were performed in two steps. In first step, the titles and abstracts of citations were screened. The studies which did not meet the eligibility criteria were excluded at this step. Duplicates were also excluded. Studies that met the criteria at screening were included in second step and full text articles were assessed. Further the inclusion/exclusion eligibility criteria were applied to the full text articles and the studies only presenting relevant data were included for data extraction. No prioritization approach was adopted during search to prevent a selection bias.  Citation details and abstracts of all retrieved studies were downloaded into Zotero bibliography manager for the record. The articles with only abstract, case reports, review and meta-analyses, and newsletters, and non-English language articles were excluded from the study. The original studies not providing effects in controls or having test groups with no statistical significance were also excluded from the study, however, no quantitative data analysis or further statistical testing were performed. Any study report currently available in preprint was peer reviewed by the authors before considering for inclusion. Risk of bias assessment for each included study was done independently by two authors using National Institute of Health (NIH) tool for systematic reviews and meta-analyses [Table S2]. Two authors independently completed data collection while qualitative analysis was contributed and reviewed by all co-authors, and disagreements among the investigators were resolved by recheck for the errors (in the data collection and analysis process) and mutual discussions. Any study with odd results was discussed with all co-authors before its inclusion into the final analysis. The final inferences were made based on the qualitative synthesis from the collected data.

**3 Results**

Overall 2559 articles were identified using the relevant keywords and 6 articles from other sources. After exclusion of the duplicates, 1872 research articles were finalized for the screening, following which 1851 articles were excluded due to various reasons (contained no relevant data related to our study, or were perspective and commentary articles, etc.). Only 21 articles were found eligible for the final analysis based on the selection criteria (mentioned in the method section). Out of 21 studies, 19 studies were selected on the basis of availability of COVID-19 vaccine-related effect on mother and outcomes in newborn, antibody titers in mother and newborn related, and 2 studies were related to the effect of mRNA vaccination on implantation rates and embryological outcome during in-vitro fertilization. The findings of this review are being described below and key characteristics of the included studies have been provided in the tables [Tables 1-2].

**3.1 Local and systemic reactogenicity in pregnant women**

Pain (88.1-91.9%), soreness (57-88%), swelling (6.2- 11.9%), redness (3-5.4%), itching (1.5-5%), and rash (1-10.5%) at the injection site were the common local adverse reactions among vaccinated pregnant women after both vaccine doses, however, were more frequently reported after the second dose [Table 1 (k)].17–20 Fatigue (29.6-71.5%), headache (18.1-55.4%), myalgia (11.6-54.1%),arthralgia (0.1-5.5%),nausea (6.7-29%), chills (4.1-47%), fever or felt feverish (4.2-52%) ,uterine contraction (1.2-8.9%), muscle spasm (3%) and paraesthesia (2.3-4.6%), axillary lymphedema (0.3-2.1%), stomach-ache (<0.1%) etc., were the common systemic adverse effects, which were more frequent after the second dose of vaccination [Table 1 (k)].17–22 About 0.5-1.5% of the participants after dose 1 and 8.0-9.0 % after dose 2 of vaccination experienced temperature at or above 38°C [Table 1 (k)].17, 20 Only 0.76% of pregnant women had a fever of 39°C and above, following 2nd doseof vaccination[Table 1 (k)].20 Overall the adverse local and systemic effects in pregnant women were similar to the non-pregnant women after vaccination. No serious adverse events were reported in all included studies, except in one case, the participant developed seizure attack, however the subject was a diagnosed case of a seizure disorder under treatment [Table1 (k)].19

**3.2 Maternal and neonatal outcomes**

The pregnancy outcomes following vaccination were reported as live birth (77.1-100%) [Table 1 (c)], 17, 19, 21–24 abortion (0.0-20.8 %) [Table 1 (d)], 17, 21, 25–28 stillbirth (0.1-1.3%) [Table 1 (e)], 17, 21 premature rupture of membrane (PROM) (1.3-1.4%) [Table 1 (f)], 17, 20 preterm birth (0.0-9.4%) [Table 1 (g)], 17–21, 23, 24 intrauterine growth retardation/ small for age (IUGR/SGA) (0.5-7.9%)[Table 1 (h)], 17, 21, 23 congenital anomalies (0-2.2%) [Table 1 (i)], 17 and neonatal death (0-0.4%)[Table 1 (j)].17, 20 The mRNA COVID-19 vaccine preconception or during pregnancy was not associated with an increased risk of spontaneous abortion compared to recognized pregnancies.25 The incidences of pregnancy-related complications like a uterine contraction (1.2-8.9%) and vaginal bleeding (0.2-1.5%) were very low following vaccination [Table 1 (k)].17, 20 The adverse outcome index (AOI) (the number of patients with one or more identified adverse events, divided by the total number of deliveries) was not affected by vaccination and was also insignificant [Table 1 (l)].23 Further, the mode of delivery (caesarean section versus vaginal route) gestational age, thromboembolic events, and rates of gestational hypertensive disorders were similar in vaccinated and unvaccinated pregnant groups [Table 1 (l)].23 Furthermore, preeclampsia (0.0-1.8%), postpartum haemorrhage (PPH) (10.5%), polyhydramnios (3.5%), oligohydramnios (1.8%), placental abruption (3.5%), NICU hospitalization (0.7-4.3%), need of supplemental oxygen/CPAP (7.7%), Transient tachypnea of the newborn (TTN) (7.7%) occurred following vaccination [Table 1 (l)].18, 20, 23, 24 In overall, COVID-19 vaccination in pregnant women was not associated with any severe adverse effects or increased pregnancy or delivery related complications in comparison to unvaccinated pregnant women.

**3.3 Maternal immunogenic response (antibody) & placental antibody transfer**

Vaccination induced IgG, or IgM, or both antibodies were detected respectively in 71-100%, 30-56% and 16% of the pregnant mother, whereas 13% mother had neither IgG nor IgM [Table 2 (d)]. 29–31 Vaccinated pregnant women showed a robust immunological response in comparison to COVID-19 infection.32 IgG (subpopulation IgG1,IgG2, IgG3), IgM , IgA antibodies against spike protein (S1 and S2), receptor binding domain (RBD), pseudovirus neutralizing antibodies (NT50), FcR binding antibodies were found in the maternal serum following COVID-19 vaccination [Table 2 (d)].18, 22, 24, 30, 33 After 4 weeks of 1st dose, IgG antibodies were detected in blood of all the pregnant women and cord of newborns with rare exceptions.31 The earliest detection of antibodies after first dose of vaccination occurred in 5 days in the mothers and after 16 days in the cord blood of the newborns. Maternal IgG level were progressively increased, starting 2 weeks after 1st dose as well as 1-2 weeks after 2nd dose (p=0.05 & p=0.019 respectively [Table 2 (i)].31 IgG was detected in 89-99% and 44% of the tested cord blood samples of the newborns to the mothers who received two doses and single dose respectively, but none of them had detectable IgM [Table 2 (e)].31 IgG, IgG3 antibodies against spike protein, viral RBD, pseudovirus neutralizing antibodies (NT50), FcR binding antibodies were found frequently in the cord blood samples following maternal vaccination [Table 2 (e)].

Maternal to cord antibody transfer was noted in multiple studies [Table 2 (h)]. 29, 30, 34 Placental transfer ratio (cord: maternal) of antibodies correlated with number of weeks elapsed since maternal 2nd dose of vaccine [Table 2 (i)]. 29 An increased latency from vaccination to delivery (weeks) was associated with an increased transfer ratio and increased infant IgG levels. 29 Second vaccine dose before delivery was significantly correlated with increased infant IgG levels [Table 1 (i)].29, 34 SARS-CoV-2 anti-S and anti-RBD-specific IgG levels and IgG against all the analysed antigens except N antigens in maternal sera were positively correlated to their respective concentrations in cord blood. 24, 30, 34 SARS-CoV-2 anti-S and anti-RBD-specific IgG titers in cord blood were directly correlated with the total duration of time since the first mRNA vaccine dose [Table 2 (i)].29, 30, 34 Notably, in two studies the pregnant women had significantly lower SARS CoV-2 IgG levels and IgG subclass in maternal serum compared to the non-pregnant women.20, 33

**3.4 Placental changes in vaccinated group**

There were no increased incidences of decidual arteriopathy, fetal vascular malperfusion, chronic villitis, or histiocytic intervillositis in COVID-19 vaccinated group compared to unvaccinated control group. Incidence of high-grade chronic villitis was higher in the control group than in the vaccinated group.32

**3.5 Effect of COVID-19 vaccination on In-vitro Fertilization (IVF)**

The vaccinated individuals had similar implantation rates as the SARS-CoV-2 seropositive and seronegative pregnant women and the rates were consistent with pre-pandemic rates.35 Further, there were no differences in the vaccinated and control groups between the cycles in the length of ovarian stimulation (OS), total dose of gonadotropin used, peak estradiol and progesterone levels, number of oocytes and mature oocytes retrieved, and fertilization rate.36

**3.6 Vaccine effectiveness against COVID-19 infection**

Vaccine effectiveness (VE) of the BNT162b2 mRNA COVID-19 vaccine against COVID-19 infection in pregnant women was noted to be 67% in 14–20 days, 71% in 21 – 27 days following the first dose, and 96% in 7–56 days following the second dose of vaccination.37 The estimated VE for symptomatic infection was 66% in days 14–20 following the first dose, 76% in days 21 − 17 following the first dose, and 97% in 7–56 days following the second dose.VE for COVID-19 related hospitalization was 89% in 7–56 days following the second dose.37 28 days after vaccination, the incidences of COVID-19 infection were noted 0.13% in vaccinated and 0.61% in unvaccinated pregnant women, respectively.21 However, after 77 days post-vaccination, the incidences were significantly low (1.2-1.42%) in the vaccinated group in comparison to the unvaccinated (2.16-11.27%) [Table 1 (i), Table 2 (l)].23, 37 There was a statistically significant hazard reduction among vaccinated group during 11 to 28 days or more after vaccination[Table 1 (l)].21

**4 Discussion**

COVID 19 vaccination in pregnant women has come forth as a pertinent public health issue that required immediate resolution. Pregnancy is a condition of unique immunological and physiological tolerance that makes women more susceptible to viral infection.42 Despite the fact that pregnant women should be included in clinical studies, the rapid progress COVID-19 vaccinations and its unpredictability of fetal consequences reasoned to exclude pregnant women from the trials, As a result, currently, there is very little evidence available on the safety and efficacy of COVD-19 vaccines in pregnant women, However, several international agencies and scientific bodies have recently acknowledged the potential risks with keeping the pregnant women out of the vaccine trials.43 Of note, the previous experiences with the vaccination of pregnant women in other RNA -virus caused diseases have been largely uneventful. No prior use of mRNA based vaccines and lack of experience with corona virus vaccination draw scepticism for its administration during pregnancy. However, keeping the pregnant population unvaccinated has posed a serious public health risk as the emerging evidence indicated that non-vaccinated pregnant mothers not only have increased risk of developing severe COVID-19 but there is also a considerable risk to their in utero babies.21,23,24

Vaccines are generally advised for pregnant women when the possible benefit surpasses the potential risk by significant margin. Theoretically, the possible conceivable risk to the fetus comes from the live vaccines, however, all the licensed vaccines against SARS-CoV-2 are not live except one.44 The first COVID-19 vaccines to enter clinical trials were Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) and Moderna COVID-19 Vaccine (mRNA1273), both based on messenger RNA (mRNA).These mRNA vaccines have previously been studied for other viruses such as cytomegalovirus, influenza, and Zika viruses.45 The first Emergency Use Authorization (EUA) for Pfizer-mRNA BioNTech's COVID-19 vaccine was issued by the U.S. Food and Drug Administration (FDA). This permitted the vaccine to be distributed nationally to people over the age of 16 years based on the safety and efficacy data from their worldwide trial [U.S. Food and Drug Administration]. In India, based on the recommendations from National Technical Advisory Group on Immunization (NTAGI), Ministry of Health and Family welfare (MoHFW) has approved voluntary vaccination of pregnant women after being informed about the risks and benefits.46

Various pre-clinical as well as clinical studies showed no significant harms of COVID-19 vaccination in pregnancy, 17–21, 23, 27, 32, 47–49 however any systematic assessment of the impact of the COVID-19 vaccination in pregnant women is currently limited. In this systematic review we have assessed the emerging evidence in humans on adverse impacts of COVID-19 vaccination on the health of mother and in utero or newly born babies. Only a few vaccinations are currently accessible and being given to pregnant and nursing women, all of which have been manufactured by various manufacturers, details of which are in Table-3.

Our results bring forth multiple observations which may have significant impact on the deciding health policies regarding vaccination of the pregnant women. COVID-19 vaccination in pregnant women was not associated with any severe adverse effects and nor increased pregnancy or delivery related complications compared to non-vaccinated pregnant women, with a rare exception, where a participant developed seizure attack, however the subject was a diagnosed case of a seizure disorder and anticonvulsant level in blood was borderline low. 19 Vaccinated pregnant women showed a robust immunological in response of COVID-19 infection. IgG antibodies were detected in blood of the pregnant women and umbilical cord blood samples from newborns with rare exceptions.29, 31 A significantly lower levels of IgG antibodies following vaccination in the pregnant women in comparison to the non-pregnant noted in two studies20, 33 couldn’t be related to any adverse effects, however, needs further investigation through randomized clinical trials. There were no increased incidences of placental injuries in COVID-19 vaccinated group compared with unvaccinated control group. Furthermore, in cases of IVF, the vaccinated women had similar implantation rates as the SARS-CoV-2 seropositive and seronegative pregnant women and the rates were consistent with pre-pandemic rates. The vaccines were found equally effective in protecting against the severe COVID-19 in pregnant women compared to non-pregnant.

Risk of the teratogenicity on the developing fetus is a well-established fact with providing drugs to the pregnant woman, however, the known mechanism of action for the COVID-19 vaccines currently in practice, including m-RNA vaccines [Figs. 2-3], don’t warn for any potential risk [Figure 2]. Our review of the emerging evidence, which did not find a significant increase in risk in the vaccinated in comparison to the unvaccinated further confirms this [Tables 1-2].

**Limitations and strengths**

There are multiple limitations in this systematic review; first, the numbers of the original studies testing safety of the COVID-19 vaccines in pregnant women have been limited. Second, the sample sizes of most of the included studies were small. Third, the available studies did not precisely identify the safest period for the COVID-19 vaccination in pregnancy. Notably, most of the studies involved vaccination of the participants in the third trimester despite the fact that the first trimester of pregnancy is the most vulnerable period for the fetal injuries [1]. Fourth, for some studies matching of the controls for the demographic factors and health conditions were not adequately informed. Fifth and lastly, for the few studies method of assessment was survey based and hence the cases were not examined clinically, which may have missed some essential data. All these factors may have possible influence on the interpretation of the results included in the study.

Although, currently, original studies are limited, there has been a consensus across the studies that the COVID-19 vaccines have a protective role in the mother as well as baby against COVID-19 infection and developing severe disease, and no significant health risks are caused to the developing fetus. The evidence is continually emerging and results of the larger scale clinical trials in the pregnant women may further validate the safety of the COVID-19 vaccines, however, the indications from the currently available data are encouraging for the full-fledged vaccination in the pregnant women.

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**Table 1: Effect of COIV- 19 vaccine in pregnancy on maternal and neonatal outcomes.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors/Study** | **Type of**  **Study** | **Total**  **Pregnant**  **Participated**  **in study (a)**  **Gp1** | **Control (b)**  **Gp2** | **Live birth (c)** | **Abortion (d)** | **Stillbirth (e)** | **PROM (f)** | **Preterm**  **birth (g)** | **IUGR/SGA**  **(h)** | **Congenital**  **Anomalies**  **(i)** | **Neonatal**  **Death**  **(j)** | **Local & systemic adverse event in pregnant N (%) vs control N (%)**  **(k)** | **Other finding (l )**  **like preeclampsia/eclampsia, gestational hypertension, PPH** | **Reference** |
| Shimabukuro TT et al.  2021 | Surveillance based  Cohort study | 35,691 pregnant in V-safe Surveillance system who received mRNA vaccine (16982 pregnant=1st dose,  12273= 2nd dose)  3958 vaccinated pregnant enrolled for pregnancy & neonatal outcome  827 completed pregnancy]  Periconception=92 (2.3%)  1st trimester (<14 week) =1132(28.6%)  2nd trimester (≤14 to <28 week) =1714(43.3%)  3rd trimester (≥28 week) =1019(25.7%)  Missing data=1 (<0.1%) | Non pregnant Vaccinated  1st dose=10,09,602  2nd dose=6,23631 | 712  (86.1%) | 104/827  (12.6%) | 1/725  (0.1%)  # | NA | 60/636  (9.4%) & | 23/724  (3.2%)  $ | 16/724  (2.2%) | 0 | Pregnant 1st dose N=16982 & 2nd dose N=12273 vs non-pregnant 1st dose N=10,09,602 & 2nd dose N=6,23,631  Injection-site pain:  14962 (88.1%) & 11274 (91.9%) vs 8,38788 (83%) & 5,48,922 (88%) Injection site swelling:  1057(6.2%) & 1462 (11.9%) vs  1,30,439 (13%) & 1,27,354 (20.4%)  Injection-site redness:  508 (3%) & 660 (5.4%) vs NA  Injection-side itching:  260 (1.5%) vs 302 (2.5%) vs NA  Fatigue:  5022 (29.6%) & 8772 (71.5%) vs 3,23,121 (32%) & 4,42,846 (71%)  Headache:  3078 (18.1%) & 6800 (55.4%) vs  253231 (25%) &382607 (61%)  Myalgia:  1962 (11.6%) & 6638 (54.1%) vs  215795 (21%) & 392014 (62%)  Chills: 696 (4.1%) & 4502 (36.7%) vs  9,6632 (9.5%) & 2,88,645 (46%)  Fever or felt feverish:  709 (4.2%) & 4242 (34.6%) vs  97736 (9.6%) &283109 (45%)  Measured temperature ≥ 38°C:  92 (0.5%) & 979 (8%) vs NA  Measured temperature ≥ 39°C:  8 (<0.05%) & 67 (0.5%) vs  2226 (0.2%) &12,045 (1.9%)  Nausea: 1130 (6.7%) & 3265(26.6%) vs  75252 (7.4%) & 1,49,956 (24%)  Joint pain:  551 (3.2%) & 3,318 (25.6%) vs  85,592 (8.4%) & 2,25,852 (36%) | COVID -19 infection after vaccination-  I) ≤14 days after  first  dose of  vaccination in  10 pregnant (10/3958=0.3%)  II) >14 days after  first  dose of  vaccination in pregnant:  12 (12/3958=0.3%) | [17] |
| Shimabukuro TT et al.  2021@ | Surveillance based  Cohort study | 221 pregnant persons  First (0–13 weeks) = 81 (49.7%)  Second (14–27 weeks) 53 (32.5%) Third (28+ weeks) 29 (17.8%) | NA | 171  (77.3%) | 46  (20.8%) | 3  (1.3%) | 3  (1.3%) | 2  0.9%) | NA | 0  (0%) | 1 (0.4%) | Fatigue 44 (20%)  Headache 43 (20%)  Chills 30 (13.5%)  Pain in extremity 27 (12%)  Nausea 25 (11.3%)  Pain 21 (9.5%)  Fever 18 (8.1%)  Injection site pain 17 (7%)  Dizziness 17 (7%)  Injection site erythema 11 (4%) | Vaginal bleeding in 3 cases,  Fetal hydrops-2 cases  Each one case of calcified placenta, leakage of amniotic fluid, shortened cervix, gestational diabetes, pre-eclampsia, irregular/painful  contractions | [17] |
| Gray KJ et al., 2021 | Cohort  study | 84 pregnant  (13 deliverd during study)  GA at 1st dose =23.2 weeks (Mean) | 16 non-pregnant received vaccine | 13 | NA | NA | NA | 1 (7.7%) | 0 | NA | NA | First dose vaccine & Second dose (pregnant vs non-pregnant)  Injection-site soreness:  73 (88%) & 44 (57%)  vs 12 (75%) & 12 (75%)  Injection site reaction or rash:  1 (1%) &1 (1%) vs  0 (0%) & 0 (0%)  Headache: 7 (8%) &25 (32%) vs  5 (31%) & 6 (38%)  Muscle aches:  2 (2%) &37 (48%) vs  2 (12%) & 7 (44%)  Fatigue:  12 (14%) & 41(53%) vs  6 (38%) & 9 (56%)  Fever or chills:  1 (1%) & 25 (32%) vs  1 (6%) &8 (50%) | Preeclampsia- 0%  Supplemental oxygen/CPAP- 1(7.7%)  TTN-1 (7.7%)  Mode of delivery:  Vaginal 10 (77%)  Caesarean 3 (23%) | [18] |
| Kadali et al 2021 | Cross- sectional study | 38 pregnant received vaccine | 991 non-pregnant received vaccine | 38 | NA | NA | NA | NA | NA | NA | NA | Pregnant vs non-pregnant  Sore arm or pain: 37 (97%) vs 894 (90%)  Itching: 2 (5%) vs 98 (10%)  Muscle spasm: 1 (3%) vs 103 (10%)  Fatigue: 22 (58%) vs 643 (65%)  Headache: 19 (50%) vs 519 (52%)  Chills: 18 (47%) vs 424 (63%)  Myalgia: 13 (34%) vs 488 (49%)  Nausea: 11 (29%) vs 211 (21%)  Fever: 6 (16%) vs 279 (28%)  Rash: 4 (10.5%) vs 67 (6.7%)  Seizure: 1 (2.63%) vs 0 (0%) (p=0.0369), (history of seizure disorder & anticonvulsant level in blood was borderline low | NA | [19] |
| Goldshtein I et al 2021 | Retrospective Study | 7530 pregnant vaccinated  (1387 reached at end of pregnancy) | 7530 pregnant un vaccinated (1427 reached at end of pregnancy) | 1386 | 128 (1.7%) in Gp1 vs  118 (1.6%) in Gp2 | 1 (<0.1%) in Gp1 vs 2 (< 0.1%) in Gp2 | NA | 77/1387  (6.6%) Gp1vs  85/1427 (6%) in Gp2 | 36  ( 0.5%) in Gp1 vs  38 (0.5%)  In Gp2 | NA | NA | 68 women vaccinated during pregnancy reported post-vaccinated adverse events  Headache- 10 (0.1%)  General weakness- 8 (0.1%)  Stomachache- 5 (<0.1%)  Dizziness- 4 (<0.1%)  Rash -4 (<0.1%)  Nonspecified pain – 6 (<0.1%) | Preeclampsia- 20 (0.3%) in Gp1 vs 21 (0.3%) in Gp2  SARS-CoV-2 hospitalization 13 (0.2%) in Gp1 vs  23 (0.3%) in Gp2  A statistically significant hazard reduction was observed among vaccinated group during 11 to 28 days or more post vaccination.  In the initial 28 days  after vaccination, 10 and 46 infections were observed in  vaccinated and unvaccinated groups, respectively. | [21] |
| Bookstein Peretz S et al 2021 | Case- control Study | 390 vaccinated pregnant included in study  First dose vaccination  1st trimester=76  2nd trimester=193  3rd trimester=121 | 260 non-pregnant  vaccinated | 72  (57 had neonatal outcome data) | 0 | 0 | 3  (1.6%) | 0 | 3(5.3%) | NA | 0 | First dose & second dose (Pregnant vs non-pregnant)  Local pain/swelling:  358 (91.8%) & 360 (92.4%) vs  250(96.2%) & 235 (90.4 %)  Rash:  3 (0.8%) & 4 (1%) vs  2 (0.8%) &1 (0.4%)  Fever>38℃ :  6 (1.5%) & 35(9%) vs  1 (0.4%) & 26 (10%)  Fever>39℃ - 0 (0%) & 3 (0.76%) vs NA  Severe fatigue:  100 (25.6%) & 220 (56.4%) vs  72 (27.7%) & 154 (59.2%)  Arthralgia:  4 (0.1%) & 16 (5.5%) vs  10 (3.8%) & 56 (21.5%)  Myalgia:  23 (5.9%) & 94 (24.1%) vs  50 (19.2%) &128 (49.2%)  Paresthesia:  9 (2.3%) & 18 (4.6%) vs  4 (1.5%) & 3 (1.2%)  Headache:  18 (4.6%) & 40 (10.25%) vs  45 (17.3%) & 127 (48.8%)  Axillary lymphedema:  1 (0.3%) & 8(2.1%) vs  4 (1.5%) & 25 (9.6%)  Contraction: 5 1.2%) & 26 (8.9%) vs NA  Vaginal bleeding:  1 (0.2%) & 6 (1.5%) vs NA | Preeclampsia- 1 (1.8%)  PPH-6 (10.5%)  Polyhydraminos-2(3.5%)  OligohydraminoS 1 (1.8  Placental abruption 2 (3.5%)  Caesarean- 10 (17%)  NICU for respiratory support- 2(3.5%)  Neonatal invasive ventilation 2 (3.5%)  NICU hospitalization  2 (3.5%) | [20] |
| Theiler RN et al 2021 | Cohort | 140 pregnant received vaccine  GA at first  vaccine dose  (Median  (IQR))  32 (13.9-  40.6) days | 1650 unvaccinated uninfected pregnant  212 COVID 19 infection during pregnancy | 140  (2 twins) | NA | 0 | NA | Gp1 vs Gp2  (<24 week  to 36 & 6/7 week)  9.28 vs 8.5 | 11(7.9%)  {<2500g}  3 (2.1 %)  {,2500g} | NA | NA | NA | Maternal & pregnancy outcome (Vaccinated  Vs unvaccinated )  AOI- 7(5.0%) vs 91 (4.9%), p=0.9524  Hypoxic, Ischemic Encephalopathy- 0 (0.0%) vs 1  (0.1%), p-value-1.00  Uterine rupture, AOI: 0 (0%) vs 1 (0%); p= 1  Unplanned ICU Admission- 1 (0.7%) vs 2 (0.1%),  p= 0.195  Preeclampsia/eclampsia- 1 (0.7%) vs 23(1.2%), p=1.00  Gestational Hypertension 19 (13.6%) vs 225 (12.1%)  P=0.6038  NICU- 1 (0.7%) vs 11(0.6%), p=0.5821  5minute apgar<7- 3(2.1%) vs 38 (2%),p= 0.7617  Mode of delivery  Spontaneous Vaginal- 89(63.6%) vs 1238  (66.5%)  Operative Vaginal-7 (5%)vs 69 (3.7%)  Cesarean-44 (31.4%) vs 555 (29.8%)  p=0.6517  Gestational age delivery  37+- 127 (90.7%) vs 1703 (91.5%)  32-36 6/7-10 (7.1%) vs 134 (7.2%)  24-31 6/7- 2 (1.4%) vs 21 (1.1%)  <24- 1 (0.7%)vs 4 (0.2%)  p=0.7028  COVID 19 infection in vaccinated group significantly  low 2\*/140 (1.42%) Vs 210/1862 (11.27%)  [p=0.0004] | [23] |
| Collier AR et al 2021 | Cohort study | 30 vaccinated pregnant  (9 delivered during study)  GA at 1st dose:  <14 week =5 (17%)  14-28 week= 15 (50%)  ≥28 week=10 (33%) | 57 nonpregnant- (received vaccine)  22 infected unvaccinated pregnant | 9 | NA | NA | NA | NA | NA | NA | NA | Pregnant vs Non-pregnant  Fever after 1st dose;  0 (0%) vs 1 (2%)  Fever after 2nd dose:  4 (14%) vs 27 (52%) | NA | [22] |
| Beharier O et al 2021 | Cohort Study | 86 vaccinated pregnant  GA at first  vaccine dose  (Mean±SD)  34.5±7.5  weeks | 62 unvaccinated noninfected  65 pregnant infected | 86 | NA | NA | NA | 4  (<37 week) | NA | NA | NA | NA | NICU -4 (4.3%) | [24] |
| Zauche L et al, 2021 | Cohort study | 2456 pregnant  mRNA vaccine preconception or prior to 20 weeks’ gestation | NA | NA | Cumulative risk of SAB =14.1% (95% CI: 12.1, 16.1%)  Compared to the recognized pregnancies, mRNA COVID-19 vaccine preconception or during pregnancy was not associated with an increased risk. | NA | NA | NA | NA | NA | NA | NA | NA | [25] |
| During trial of Pfizer/BioNTech  COVID-19 vaccine | Vaccine Trial | 12 accidental pregnancy out of 18,860 participants  vaccinated | 11 accidental pregnancy in placebo out of 18846  unvaccinated | NA | 0 (0%) | NA | NA | NA | NA | NA | NA | NA | NA | [26] |
| During trial for  Moderna vaccine | Vaccine Trial | 6 accidental pregnancy out of  15181 participants vaccinated | 7 accidental pregnancy out of  15170 participants  unvaccinated | NA | 0 (0%) | NA | NA | NA | NA | NA | NA | NA | NA | [27] |
| During trial for AstraZeneca vaccine | Vaccine Trial | 12 accidental pregnancy out of  5807  Participant  vaccinated | 9 accidental pregnancy out of  5829  Participant  unvaccinated | NA | 2 (17%) | NA | NA | NA | NA | NA | NA | NA | NA | [28] |

Gp- Group

PROM- Prerupture of membrane

IUGR- Intra uterine growth retardation

SGA- Small for gestational age

NA- Not available any data in article

# The denominator consists of live born infants and stillbirth

& The denominator consists of only women vaccinated before 37 weeks of gestation

$ The denominator consists of 12 sets of twins

@ Adverse event finding on the VAERS (Vaccine Adverse Event Reporting System)

\*- 2 Infections occurred prior to first dose of vaccine

GA-Gestational age

PPH- postpartum hemorrhage

NICU- Neonatal intensive care unit

TTN- Transient tachypnea of the newborn

AOI -Adverse Outcomes Index

SAB- Spontaneous abortion (pregnancy loss occurring from 6 to < 20 weeks’ gestation

**Table 2. Effect of COVID- 19 vaccine in pregnancy on maternal antibody response and antibody transfer to neonates.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors/Study** | **Type of Study** | **Total**  **Pregnants**  **Participated**  **in study (a)** | **Control (b)** | **Live birth (c)** | **Ab in mother (d)** | **Ab in umbilical**  **Cord/Infants (e)** | **Ab in control (f)** | **Ab in milk (g)** | **Maternal to cord antibodyTransfer**  **(h)** | **Other findings (i)** | **Reference** |
| Mithal LB et al 2021 | Prospective Case Series | 27  (22 pregnant -2 doses of mRNA vaccine)  GA at first  vaccine dose  (Mean±SD)  33±2 weeks | 0 | 28  (1 twin) | 26 mother (96%)-  IgG  15 mother (56%)-IgM | 25 (89%) Infants  IgG^  0 infant- IgM | NA | NA | Average maternal to infant transfer ratio=1.0±0.6 | * An increased latency from vaccination to delivery associated with an increased transfer ratio   (β=0.2; 95% confidence interval [CI], 0.1-0.2).   * Second vaccine dose before delivery significantly associated with increased infant IgG levels (β=19.0; 95% CI, 7.1-30.8). * Latency from vaccination to delivery associated with   increased infant IgG levels (β=2.9; 95% CI, 0.7-5.1). | [29] |
| Rottenstreich A et al 2021 | Cohort Study | 20 pregnant  Vaccinated  Median time lapsed  1st vaccine to  delivery  interval  (Median  33(IQR  30-37  days)  2nd dose until delivery 11(IQR (9-15 days) | 0 | 20 | Anti-S IgG:  319 (IQR 211-1033) AU/mL  Anti-RBD-Specific IgG:  11,150 (IQR 6154-17,575)  AU/mL  IgG in 20 (100%)  IgM in 6 (30%) | Anti-S IgG (median : 193 (IQR 111-260) AU/mL  Anti-RBD-specific IgG (median : 3494 (IQR 1817-6163) AU/Ml  IgG in all,  No IgM in any infants | NA | NA | Placental transfer ratio  Anti-S IgG (median : 0.44 ((IQR 0.25-0.61)  Anti-RBD-specific IgG (median : 0.34 ((IQR 0.27-0.56) | * SARS-CoV-2 anti-S and anti-RBD-specific IgG levels in maternal sera positively correlated to that in cord blood; P<0.001 and; P <0.001, respectively). * SARS-CoV-2 anti-S and anti-RBD-specific IgG titers in cord blood directly correlated with increasing time since first dose of mRNA vaccine (P =0.001 and P=0.004, respectively). | [30] |
| Prabhu M et al 2021 | Cohort Study | 122  (67 -2 doses,  55-One dose of mRNA vaccine | 0 | 122 | 87(71%)- only IgG  19 (16%)- both IgG  +IgM  16- none £ | Received 2 doses 65/67 (99%) of cord –IgG antibody  Received one dose only 24/55 (44% ) -IgG antibody | NA | NA | NA | * After 4 weeks of 1st dose of vaccine, IgG antibodies detected in blood of all women and cord of newborns, except one. * The earliest detection of antibodies occurred after 5 days in women and after 16 days of first dose of vaccine in cord blood. * Maternal IgG and neonatal IgG correlation: (R: 0.89, p<2.2e -16). * Placental transfer ratio correlated with no of weeks elapsed since maternal 2nd dose of vaccine: (R: 0.8, p=2.6e -15). | [31] |
| Shanes et al 2021 | Cohort Study | 84 pregnant received vaccine  1st vaccine to  delivery  interval  (Mean±SD)  45.96±24.3  days | 116 not vaccinated | 84 | Vaccinated RBD IgG: 22.8±14.5 ,(P value<.001)  RBD IgM: 4.1±13.2,(P value=.001) in n=52 vaccine group | NA | Vaccinated RBD IgG: 0.04±0.05 ,(P value<.001)  RBD IgM: 0.19±0.12,(P value=.001) in n=116 control group | NA | NA | * Vaccinated women showed robust antibody response. * Placental changes in vaccinated group vs. control: no significant changes. * Incidence of decidual arteriopathy (10% in vaccinated vs 12% in control, p value=0.55 ,   fetal vascular malperfusion (6% vs 7%, p value=0.78) ,  low-grade chronic villitis (12%vs 8%, p value=0.33) ,   * high grade chronic villitis (5%vs 14%, p value=0.04) , chronic histiocytic intervillositis (0% vs 1.7%) | [32] |
| Atyeo C et al 2021 | Cohort Study | 84 vaccinated pregnant | 31 lactating,  16 non-pregnant  (Vaccinated) | NA | IgG antibodies IgG3, FcR binding antibody | IgG antibodies  IgG3, FcR binding antibody | IgG antibodies  FcR binding antibody | IgG antibodies  Boosting resultedin high FcR binding antibody  IgA & IgM | NA | * After 2-5.5 week following the 2nd dose of vaccine (V2), there were no significant differences in the vaccine response between pregnant/lactating and non-pregnant women. * Vaccine-specific titers found comparable, albeit slightly lower, between pregnant and lactating women, compared to non-pregnant controls. * Higher levels of antibodies found in maternal blood compared to cord blood. * Equivalent transfer of IgG1 spike (S)-specific antibody to the infant. * Low IgG3 and FcR binding antibodies transfer to the infant. | [33] |
| Zdanowski W et al 2021) | Retrospective Study | 16  GA at 1st dose 31.75 week (29-36 week)  GA at 2nd dose 35.13 week  (32-40 weeks) | 0 | 16 | Mean anti-S IgG antibody= 984.37 U/mL (±689.4) | Mean anti-S IgG antibody 1026.51 U/mL (±769.25) | NA | NA | Mean cord-maternal anti S antibody ratio=1.28±0.798 | * A significant positive correlation noted between number of weeks from first dose of vaccine to delivery and the anti-S antibody titer in cord blood serum (r =   0.63; p = 0.0092)   * A significantly positive correlation noted between the week of gestation at the time of vaccine doses and the cord-to-maternal ratio of antibody transfer (r = 0.48; p = 0.0029) for the first dose and (r = 0.39; p = 0.0102) for the second dose. | [34] |
| Gray KJ et al., 2021 | Cohort Study | 84 pregnant  (13 delivered during study)  GA at 1st dose =23.2 weeks (Mean) | 16 nonpregnant | 13 | IgM, IgA, IgG antibody response to S, RBD, S1 & S2 segment of S= significant rise from V0-V1, with further rise of Ig G from V1-V2.  Spike titers rose more rapidly than RBD. IgG response induced robustly after both dose in comparison to IgA & IgM which induced robustly after 1st dose | Anti-S, anti-RBD, IgG, Neutralizing antibody titer low in comparison to mother  Significant improvement of transfer of Anti- S specific 1Gg1 but not Anti-RBD into cord with time from V2. | Higher level of IgG after boost | IgG1 RBD increased significantly from V0-V2  But, Anti- RBD IgA& IgM  not significantly increased by either dose. | NA | NA | [18] |
| Bookstein Peretz S et al 2021 | Observational Case- control Study | 390 vaccinated pregnant included in study who returned digital questionnaire  (Out of 539 recruited pregnant) | 260 non-pregnant  vaccinated | 72  (57 completed second questionnaire | IgG = 27.03±10.72  (N=96 pregnant tested for IgG 2weeks to 2 month foolowing 2nd dose) | NA | IgG= 34.35±10.25  (n=96 non-pregnant) | NA | NA | * Pregnant women had significantly lower SARS CoV-2 IgG antibody level compared to non-pregnant women (27.03 vs 34.5 , p value<0.001) | [20] |
| Collier AR et al 2021 | Cohort Study | 30 vaccinated pregnant  (9 delivered during study)  GA at 1st dose:  <14 week =5 (17%)  14-28 week= 15 (50%)  ≥28 week=10 (33%) | 16 nonlactating  57 nonpregnant & nonlactating (received vaccine)  22 infected unvaccinated pregnant | 9 | RBD IgG antibodies titer in pregnant =27601AU Median pseudovirus Neutralizing antibodies titer (NT50)=910AU  after 2nd dose  RBD IgG antibodies titer in pregnant =14953AU Median pseudovirus Neutralizing antibodies titerNT50=1016AU  at delivery | RBD IgG antibodies titer=19873  Neutralizing antibodies titerNT50=324AU at delivery | RBD IgG antibodies titer in vaccinated nonpregnant=37839AU  In lactating=23497 AU  **Median NT50** in nonpregnant =901AU  Lactating=783AU  after 2nd dose | Breast milk RBD IgG=97 AU, NT50 =75AU and IgA binding antibodies=25 AU | NA | * CD4 & CD8 response were comparable in pregnant, lactating & nonpregnant. | [22] |
| Beharier O et al 2021 | Cohort Study | 86 vaccinated pregnant  GA at first  vaccine dose  (Mean±SD)  34.5±7.5  weeks | 62 unvaccinated noninfected  65 pregnant infected | 86 | After 1st dose –rapid IgG antibodies response to S1,S2, RBD but not N antigens  After 2nd dose further rise in IgG response. | IgG for S1,S2,AND RBD after 1stdose trailed after after the maternal  IgG showing a marked response already by day 15  Further increase after 2nd dose | In infected pregnant gradual rise in IgG response (anti-S1, -S2,  -RBD, and -N) during the first 45 days after infection | NA | Maternal to fetal IgG transfer ratio for S1, S2, RBD, and N  Significant differences  were found for S1, S2, and RBD, but not for N between the PCR-positive and  vaccinated anti-N–groups (*P <*0.0002) | * Serological response in cord blood correlated positively with maternal humoral response for IgG against all the analyzed antigens. * At the time of delivery, maternal IgG for S1 and RBD found significantly higher in vaccinated women (*P =* 0.0009, *P =* 0.0045, respectively). * IgG for S2 and N found significantly higher in PCR-positive women (*P =* 0.0016, *P <*0.0001, respectively). * Fetal IgG for S2 and N found significantly lower in cord blood samples of vaccinated women (*P <*0.0001, *P <*0.0001, respectively), however, fetal IgG for S1 and RBD did not differ from those of PCR-positive women (*P =* 0.7017, *P =* 0.6887, respectively). | [24] |
| Dagan Net al, 2021 | Cohort Study | 10861 pregnant vaccinated | 10861 not vaccinated | NA | NA | NA | NA | NA | NA | * Vaccine effectiveness (VE) against COVID-19 infection found to be 67%, 71% and 96% respectively in 14–20 days, in 21 – 27 days following the first dose and in 7–56 days following the second dose. * The estimated VE for symptomatic infection was 66% in days 14–20 following the first dose, 76% in days 21 − 17 following the first dose, and 97% in days 7–56 following the second dose. * VE for COVID-19 related hospitalization was 89% in days 7–56 following the second dose * During a median follow-up of 77d, 131(1.2%) infections documented in the vaccination group and 235 (2.16%) infections in the control. | [37] |

GA- Gestational age

^ 3 infants negative including twins whose mother receive 1st dose of vaccine 3 weeks before delivery

£ Mother receive 1 dose of vaccine 4 weeks before delivery

S- Spike

RBD- Receptor binding domain

V0- At the time of 1st vaccine dose /baseline

V1- At the time of 2nd dose/prime profile

V2- 2-6 week’s following 2nd dose / boost profile

ADCP - Antibody-dependent cellular phagocytosis

ADNP- Antibody-dependent neutrophil phagocytosis

NA- Not available data in study

AU- Arbitrary unit

VE- Vaccine effectiveness

**Table 3. Globally available COVID-19 vaccines, and their known outcomes in pregnant women.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Vaccine name** | **Vaccine developed by** | **Vaccine characteristics** | **No. of doses** | **Efficacy Based on Randomized Clinical Trial** | **Clinical trials and pregnancy** | **References** |
| mRNA BNT162b2 | Pfizer-BioNTech | Encodes a P2 mutant spike protein (PS 2) and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA | 2 | 95% | * Pregnant and lactating mothers, and those planning for pregnancy were excluded. * As of November 14, 2020, there had been 23 pregnant mothers accidentally exposed (12 vaccination and 11 placebo). | [38] |
| mRNA-1273 | Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID) in the USA. | LNP-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein | 2 | 94.5% | * Pregnant and lactating mothers, and those for pregnancy were excluded. * As of December 2, 2020, there had been 13 pregnant mothers accidentally exposed (6 vaccination and 7 placebo). | [39] |
| ChAdOx1-S [recombinant] vaccines | Oxford AstraZeneca AZD1222-Vaxzevria; Serum Institute India (SII) Covishield; and SK Bioscience | Adenovirus-vectored vaccine | 2 | 63.1% | * Pregnant, breastfeeding, and those attempting pregnancy excluded. No data on unintended vaccination in pregnancy available at this time. | [40] |
| Jansen Ad26.COV2.S. | Janssen Pharmaceuticals | Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein. | 1 | 66.9 | * Pregnant, lactating mothers and those planning for pregnancy were excluded from the study. At this point of time, there were no statistics available regarding inadvertent vaccination in pregnancy. | [41] |

**Figure legends:**

**Figure 1 Schematic illustration of SARS CoV-2 infection of human placenta**. The placenta uniquely contains maternal as well as fetal tissue components separated by an intricate septum known as ‘placental barrier’, which regulates maternal-fetal exchange of air, nutrients, and hormones. Multiple pathogens including some viruses circulating into the maternal blood are known to cross the tissue barrier and invade the fetal tissue. The SARS-CoV-2 entering into the blood vessels in the maternal component of the placenta (shown with larger arrow) can invade into the placental tissue—Trophoblasts , which is known to express viral host cell entry receptors, and further into the fetal tissue (shown with smaller arrow).

**Figure 2 Schematic diagram of SARS-CoV-2 showing its structural proteins as target antigens for various vaccines.** Most of the COVID-19 vaccines (1-8) are targeted to viral spike protein (S protein). The whole virion is used for the traditional inactivated vaccine, whereas various viral subunits are used for live attenuated vaccines.

**Figure 3** **Schematic diagram showing mechanism of action of an m-RNA vaccine on the human body.**