COVID-19 Vaccination During Gestation and Lactation: Leaps in Comprehension

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ABSTRACT

Introduction: A total of 7.3 billion vaccine doses of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been administered globally up to 19 November 2021. Yet, in the paucity of evidence regarding effectiveness and safety among special populations, the concern of undergoing vaccination during gestation and breastfeeding is a matter of considerable regional and global dilemma. However, herd immunity remains the only effective COVID-19 prevention strategy, which entails vaccinating gestational as well as breastfeeding females. Methods: We, therefore, present an up-to-date literature review of the most recent evidence and information using multiple research engines, including PubMed and Google Scholar, as well as ClinicalTrials.gov. Objectives: To retrieve concrete proof to aid in making an evidence-based approach towards maternal immunization. Results: The results showed growing evidence of benefit and insufficient proof of harm from several studies that enrolled gestational and lactating females. Studies also reported that gestational and breastfeeding participants mount a fairly similar initial serological response to that encountered in non-pregnant counterparts. Conclusion: It is strongly recommended to keep assessing clinical trials, observational studies, and all possible available findings to broaden our perception regarding vaccination in gestational and lactating females.

Keywords: COVID-19 vaccine; Gestation; Lactation.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 so-known as the coronavirus has persisted to wreak havoc worldwide, resulting in disastrous outcomes and lives lost. At the time of writing this article, nearly 255 million people had been infected, and over 5 million people had lost their lives worldwide. The alarming nature of the SARS-CoV-2 virus, as well as the race to alleviate the virus’s impacts on human health, constituted a necessity for more innovative approaches and vaccination studies. In January 2020, the SARS-CoV-2 genome was sequenced kicking off the emergence of several vaccine platforms, including, viral vector vaccines (Janssen/Johnson & Johnson and AstraZeneca), messenger RNA vaccines (Moderna and Pfizer), protein subunit vaccine (Novavax), as well as the inactivated vaccine, CoronaVac, which is being developed by Sinovac Biotech. While it takes about three years for vaccines to attain Phase III clinical trials, across the scenario of a pandemic, the Food and Drug Administration (FDA) of the United States (U.S) grants...
emergency use authorization (EUA) after assessing the safety data of Phase III trial. Table 1 illustrates the properties of the five most commonly used vaccines that have received EUA. As a prerequisite for granting EUA, the FDA required pharmaceutical companies to submit a phase III safety database of at least 3000 vaccine recipients with an average follow-up period of two months. As for the Sinopharm vaccine, analysis of phase III trial data demonstrated a 79% efficacy against symptomatic COVID-19 infection starting 14 days after the 2nd vaccine dose as well as against hospitalization with a median follow-up period of 112 days. However, the trial failed to demonstrate efficacy against severe disease in individuals with underlying comorbidities, pregnancy, or individuals over 60 years of age. Phase III trial in Brazil reported that the Sinovac-CoronaVac vaccine had a 51% efficacy against symptomatic COVID-19 infection, a 100% efficacy against severe SARS-CoV-2 infection, as well as a 100% efficacy against hospitalization starting 14 or more days after the 2nd dose.

In addition, the ChAdOx1 nCoV-19 (AstraZeneca-Oxford) phase III trial reported a vaccine efficacy of 79% in protecting against symptomatic SARS-CoV-2 infection and 100% efficacy of preventing severe disease and hospitalization. Remarkably, the vaccine was 80% effective among individuals 65 years of age and older. Moreover, data analysis of the BioNTech-Pfizer phase III trials revealed a vaccine efficacy of 95% among individuals without previous COVID-19 infection (first main objective) as well as in individuals with and without previous COVID-19 infection (second main objective), recorded seven days following the 2nd vaccine dose with a reported vaccine efficacy of more than 94% in participants 65 years or older.

Furthermore, phase III trial of the mRNA-1273 COVID-19 Vaccine reported an interim safety and initial efficacy results of 94.1% efficacy rate in preventing SARS-CoV-2 infection, including severe disease. Ad26.Cov2.S demonstrated a 66.9% efficacy against symptomatic moderate to severe COVID-19 infection as well as 93.1% efficacy against hospitalization, 28 days post administration. Lastly, Sputnik V interim analysis of the Sputnik V phase III clinical trial demonstrated a 91.6% efficacy against SARS-CoV-2 infection.

With nearly 7.3 billion vaccine doses of the SARS-CoV2 being administered worldwide (up until 19th of November, 2021) and as the vaccine industry has progressed over the years, it is pertinent to state the benefits and drawbacks when recommending novel vaccinations, particularly to special populations: especially, pregnant women.

There are currently no safety data for mRNA vaccine use in pregnant or breastfeeding mothers, and the potential adverse events to pregnant females and their fetuses remains questionable as they have been excluded from the initial trials. Also, there is no current timetable for when pregnant women will be included in vaccine recommendation guidelines. Historically, pregnant women have been exempted from clinical trials for a variety of reasons, including jurisdictional concerns, regulatory barriers, as well as ethical constraints about fetal exposure.

Recently published findings show that symptomatic pregnant patients infected with COVID-19 are at a heightened risk of more serious complications than nonpregnant patients, in particular those with comorbidities such as diabetes, hypertension, or cholestasis. The vascular, metabolic, as well as physiological shifts during normal and high-risk gestations, may aggravate these risks.

Although there is substantial uncertainty on whether COVID19 is associated with adverse events in gestation, several studies demonstrate a higher, intensive care unit (ICU) admission, extracorporeal membrane oxygenation, invasive ventilation, escalating preterm labor, stillbirth, and mortality rates. Thus, these findings demonstrate that the pregnant population is defenseless towards the deleterious effects of COVID-19 and, as with the general population, should carefully weigh the pros and cons of obtaining the vaccine.

**Material and Methods**

This literature review was conducted primarily using PubMed, Google Scholar databases along with ClinicalTrials.gov with a focus on the Pfizer-BioNTech and Moderna vaccines. Search terms included combinations of COVID-19 and lactation, mRNA vaccines in pregnancy, SARS-CoV-2 and pregnancy, messenger RNA, Moderna, Pfizer. A multiple-step scheme based on duplicate exclusion, title, and abstract sorting, article reading, and screening throughout the data-extraction process was used.

**Results**

On ClinicalTrials.gov, we found 10 trials: six by searching for ‘COVID-19 vaccine in pregnancy,’ four by ‘COVID-19 vaccination in pregnant women,’ and none by ‘COVID-19 vaccine in lactating women.’ Duplicates in the clinical trials were excluded, articles were reviewed from all databases previously stated, filtered via reading of the abstract and title. Six of the seven remaining trials on ClinicalTrials.gov were still recruiting, while one had been completed. The only completed trial, titled ‘COVID-19 Vaccine Confidence Among Pregnant Women and Mothers,’ aimed to evaluate the level of vaccine confidence among mothers and pregnant females using an online survey with no intervention.
Another case-control surveillance regarding COVID-19 vaccination during gestation and its relation with spontaneous abortion incorporated data from eight health systems in the U. S (December 2020 till June 2021) including 13160 spontaneous abortions and 92286 ongoing pregnancies among the 105446 pregnancies. During pregnancy and before twenty weeks of gestation, 0.5 % were administered the Ad26.COV.2.S vaccine, 6.0 % were administered the mRNA-1273 vaccine, and 7.8 % were administered the BNT162b2 vaccine. According to this study, participants with spontaneous abortions did not have an increased risk of being exposed to a vaccine in the previous 28 days when compared to ongoing pregnancies³¹.

A study comprised 122 pregnant females (January 2021- March 2021). All women had received one or both doses of an mRNA COVID-19 vaccine (37 received the mRNA-1273 vaccine, while 85 received the BNT162b2 vaccine). Fifty-five (45%) female participants were administered only the 1st dose of the vaccine while sixty-seven (55%) of the females were administered both vaccine doses by the time they gave birth. However, the study did not report any incidence of miscarriage among the 122 pregnant female participants³². A prospective case study enrolled a total of 27 pregnant females (January 2021-March 2021) who did receive a COVID-19 mRNA vaccination while pregnant. The average gestational age at the first vaccine dose was 33±2 weeks, with twenty-two females (74%) receiving both vaccine doses before delivery, with a mean latency of 6 ± 3 weeks. This study reported the delivery of 28 infants (1 twin pair) again with no reported incidence of miscarriage³³.

Another prospective cohort study (December to March 2021) enrolled a total of 131 female participants who were administered mRNA COVID-19 vaccination,

Table 1. List of SARS-CoV-2 vaccines having EUA grants (Until May 2021)⁴

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Type</th>
<th>No. of doses</th>
<th>Vaccine efficacy in phase III trials</th>
<th>Storage temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinopharm</td>
<td>Inactivated SARS-CoV-2</td>
<td>2</td>
<td>79</td>
<td>2–8</td>
</tr>
<tr>
<td>Sinovac</td>
<td>Inactivated SARS-CoV-2</td>
<td>2</td>
<td>51</td>
<td>2–8</td>
</tr>
<tr>
<td>AstraZeneca-Oxford</td>
<td>ChAdOx non-replicating chimpanzee adenoviral vector</td>
<td>2</td>
<td>79</td>
<td>2–8</td>
</tr>
<tr>
<td>BioNTech–Pfizer</td>
<td>mRNA vaccine</td>
<td>2</td>
<td>95</td>
<td>−70</td>
</tr>
<tr>
<td>Moderna</td>
<td>mRNA vaccine</td>
<td>2</td>
<td>94.1</td>
<td>2–8 up to 30 days/ –20 for long-term storage</td>
</tr>
<tr>
<td>Johnson &amp; Johnson-Janssen</td>
<td>Ad26 non-replicating human adenoviral vector</td>
<td>1</td>
<td>66.9</td>
<td>2–8 up to 3 months/ –4 for long-term storage</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>Ad5 and Ad26 non-replicating human adenoviral vector</td>
<td>2</td>
<td>91.6</td>
<td>2–8</td>
</tr>
</tbody>
</table>

SAFETY CONCERNS IN PREGNANCY

Issued preliminary data from 3 U. S vaccine safety surveillance systems regarding the safety of messenger RNA (mRNA) SARS-CoV2 vaccines in pregnant women (the v-safe pregnancy registry, "v-safe after vaccination health checker, and the Vaccine Adverse Event Reporting System (VAERS)). Those that received the vaccine during pregnancy or the preconception interval and are eighteen years or older are qualified eligible for registration. This retrospective study (December 2020 - February 2021) reported that 712 out of 827 completed pregnancies had a live birth (86.1 %), 104 had a spontaneous abortion (12.6 %), and 1 had an adverse event (induced abortion/ectopic pregnancy) (1.2 %). Out of 104 spontaneous abortions, 96 (92.3%) occurred before thirteen weeks of gestation, and 700 out of 712 live births (98.3%) occurred among individuals receiving their prime vaccine dose during the 3rd trimester. Based on the analysis of this data, and given that spontaneous abortion is a common presenting outcome affecting 11 to 22 % of recognized pregnancies²⁷,²⁸,²⁹, receiving an mRNA COVID-19 vaccine before or during pregnancy is not associated with an increased risk of spontaneous abortions. As for the neonatal outcomes, the adverse events throughout 724 live-born infants were preterm birth (60 of 636 among those vaccinated before 37 weeks), small size for gestational age (23 of 724), and major congenital anomalies (16 of 724) with no reports of newborn deaths. Interestingly, the vaccine was not administered in the 1st trimester or periconception interval to individuals with completed pregnancies who had congenital anomalies. However, no particular pattern of congenital anomalies was reported³⁰.
84 of them were pregnant with a mean gestational age at 1st dose of 23.2 weeks with 11 females receiving their 1st vaccine dose during their 1st trimester, 39 in 2nd trimester, and 34 in the 3rd trimester. The study reported one female participant with spontaneous preterm labor at 35 weeks of gestation with 17 days following vaccination.

Data from Norwegian registries were extracted and used in a case-control study (February 2021 - August 2021), pregnant females who had a miscarriage before 14 weeks of gestation (case-patients), and those with a confirmation of ongoing pregnancy in the 1st trimester (controls) were enrolled. This study aimed to estimate odds ratios for Covid-19 vaccination within 5-week and 3-week windows before a miscarriage or ongoing pregnancy. The median number of days between vaccination and miscarriage or confirmation of ongoing pregnancy was nineteen among 13,956 women with ongoing pregnancies (772=5.5% vaccinated) and 4521 women with miscarriages (231=5.1% vaccinated). Again, this investigation reported no evidence of an increased risk of miscarriage following Covid-19 vaccination, which adds to the findings of the previously cited studies that support Covid-19 vaccination during pregnancy.

Several case reports were retrieved including a case of A 34-year-old pregnant healthcare personnel receiving her 1st dose of the BNT162b2 mRNA vaccine at 32 weeks of gestation and her 2nd dose at 35 weeks. At term (38 weeks of gestation), an uncomplicated spontaneous vaginal delivery of a female neonate took place. In another case report, healthcare personnel (36 weeks gestation) was vaccinated with the mRNA-1273 COVID-19 vaccine. Three weeks after her first dose of the vaccine, a normal, vaginal delivery occurred. This 39-weeks’ gestation resulted in a full-term neonate with no reported health complications. The mother received her 2nd dose of the mRNA-1273 vaccine, following the standard 28-day vaccination protocol. On the other hand, four preterm deliveries and four neonatal intensive care unit (NICU) admissions were reported in the vaccinated group (N=92) of a cohort study, however, it was not stated in the study whether these preterm neonates themselves were admitted to the NICU.

MATERNAL IMPLICATION AND PLACENTAL ANTIBODY TRANSFER

Findings from a study revealed that immune responses due to COVID-19 mRNA vaccination were comparable in pregnant and breastfeeding women versus non-pregnant women. Titer were higher than those generated by SARS-CoV-2 infection while pregnant. All samples either from the umbilical cord blood as well as the breastmilk contained vaccine-induced immunoglobulins. SARS-CoV-2-IgG, but not IgA, rose in maternal blood and breastmilk following vaccination boost. This proves that maternal IgG can indeed cross the placenta and provide immunity to the newborn against SARS-CoV-2. Spike- and RBD-specific IgG were found in all umbilical cords following maternal COVID-19 mRNA vaccination. It’s worth mentioning that the cord with the least Spike- and RBD-specific IgG levels belonged to a female participant who gave birth between the 1st and 2nd vaccine doses that received her first vaccine dose seventeen days before delivery, implying that two doses may be required to maximize humoral immune transmission to the newborn. Interestingly, there was a substantial improvement in the transfer of S-specific IgG1 but not RBD-specific IgG1 into the umbilical cord with time from boost, implying that time from vaccination seems to be a significant aspect in the transfer rates of specific immunoglobulins subpopulations regarding immunization in pregnant women.

Transplacental transfer of vaccine-elicited binding and neutralizing antibodies was assessed in a descriptive cohort study using 9 paired maternal and infant cord blood samples from pregnant female participants following COVID-19 mRNA vaccination who delivered during the study period. The presence of binding and neutralizing antibodies in infant cord blood further affirms that maternal antibodies are efficiently transferred trans-placentally. A study reported that 43.6% (24/55) of neonates born to women that received only the prime vaccine dose had detectable IgG, while 98.5% (65/67) of neonates born to women that received both the prime and booster vaccine doses had detectable IgG. It also reported that placental transfer ratio was associated with the weeks that passed since the maternal 2nd dose of vaccine and with rising levels of maternal IgG as well as the escalating placental IgG transfer ratio by time, implies that the duration between vaccination and birth may be an essential aspect to consider in pregnancies vaccination protocols.

Another study revealed that three out of 28 newborns from 27 vaccinated pregnant participants (1 set of twins), had no positive IgG tests; these two mothers had received their 1st dose of vaccine less than three weeks before delivery. It was also observed that when a longer time elapsed between administering the vaccine and labor (in weeks) led to a higher transfer ratio. Correspondingly, having received the booster vaccine dose (2nd dose) before delivery was significantly associated with elevated infant IgG levels. The transplacental transfer was closely similar between participants infected with SARS-CoV-2 in the early phase of pregnancy (15-30 weeks) and those who received the BNT162b2 mRNA vaccine in the 3rd trimester, leading the researchers to speculate that anti-SARS-CoV-2 immunoglobulins developed by natural infection may require an increased time interval to transfers to cord blood.
VACCINE-INDUCED IMMUNITY IN BREASTMILK

Several studies were conducted to evaluate the patterns and dynamics of the breastmilk and serum immunological responses following mRNA vaccination. In prospective cohort study involving 84 volunteering lactating mothers who were administered the BNT162b2 (Pfizer-BioNTech) in two doses, 21 days apart revealed that SARS-CoV-2 specific IgA and IgG antibodies were secreted in mother’s milk for six weeks following vaccination. During the first three weeks, anti-SARS-CoV-2-specific IgG immunoglobulins were low in breast milk samples, but by weeks five and six, they had increased to 97% of positive breast milk samples collected. On the other hand, Anti–SARS-CoV-2-specific IgA immunoglobulins in breast milk rose dramatically two weeks following the first vaccination dose of the BNT162b2 (Pfizer-BioNTech), where 61.8% of samples tested positive. However, by the end of week six, 65.7% of the samples tested positive.

A cohort study enrolling 103 women of whom 30 were pregnant; 16 were lactating; and 57 were neither pregnant nor lactating (18 to 45 years) who received a COVID-19 mRNA vaccine (Fifty-six participants (54%) received BNT162b2; 47 (46%) received mRNA-1273) and 22 pregnant and 6 nonpregnant unvaccinated women with SARS-CoV-2 infection. The study revealed that Vaccination evoked binding and neutralizing antibodies in breast milk, but IgA responses were poor, apart from early breast milk from females who were administered the BNT162b2 vaccine during gestation.

Another cohort study which enrolled a total of 31 lactating females who received either the BNT162b2 or the mRNA-1273 vaccines a substantial production of anti-SARS-CoV-2-specific immunoglobulins (IgM, IgG, IgA) in breast milk samples following the 1st dose, with a sole increase in the IgG levels following the 2nd booster dose.

Vaccine-induced IgG and IgA titers in serum and breastmilk rose significantly seven days post administration of the BNT162b2COVID-19 vaccine, however, this fold-change increase stopped 14 days after the 2nd dose. Neutralizing ability was demonstrated by anti-spike IgA and IgG in all breastmilk samples. Notably, a current publication stated that only 62% of breastmilk samples (comprising immunoglobulins) from females who contracted COVID-19 had an in vitro neutralizing ability.

DISCUSSION

We present an insight into the current arguments regarding COVID-19 vaccination during gestation and lactation; however, there is a paucity of literature on this topic. In our fight against COVID-19, all efforts should be channeled toward broadening the vaccination panel to include populations that have been previously excluded from vaccination programs. Gestation involves complex immunological shifts, including immune system manipulation to endure the fetal allograft. These immunological adjustments, along with hormonal and physiological changes, result in a heightened susceptibility of pregnant women to morbidities from viral respiratory illnesses.

The majority of the data on the safety of inactivated vaccines during gestation and breastfeeding arises from observational studies since these populations were excluded from the primary vaccine trials. Live attenuated vaccines (LAV) are generally considered unsafe in gestation even though they are more immunogenic as they retain a replication capacity with a potential transplacental transfer. However, observational studies of females accidentally vaccinated with several LAVs during the early phase of gestation, however, have not found an increased incidence of adverse events (anomalies, premature labor, stillbirth, or miscarriage). On the other hand, some LAVs, in particular, smallpox (vaccinia virus) and anthrax (Bacillus anthracis) have been linked to a slight rise in birth defects. Table 2 summarizes a list of worldwide recommendations from nationwide vaccination technical advisory committees and a summit of clinical obstetric and gynecological institutions.

According to the findings of the studies implemented by Atyeo C et al., Prabh M et al. and Gray KJ et al. pregnant and breastfeeding individuals could indeed mount a serological response that is fairly similar to non-pregnant individuals in response to vaccination, with a comparable immunoglobulin response to the 2nd vaccine dose as controls. Interestingly, a prospective cohort study revealed a significant rise in immunoglobulin response post-COVID vaccine compared to natural infection during gestation. The lack of solid evidence of whether COVID-19 vaccination is related to pregnancy-related adverse events mainly spontaneous abortion/miscarriage contributes significantly to pregnant women’s reluctance to receive the vaccine. During the AstraZeneca, Pfizer/BioNTech, and Moderna vaccination clinical trials, a small proportion of pregnant females were unintentionally enrolled. The data revealed a single miscarriage in both the Pfizer/BioNTech and Moderna control groups and 0 in the vaccine group along with two miscarriages in the AstraZeneca vaccine group and three in the control group. Pfizer-BioNTech’s first phase, randomized clinical trial aimed to assess the safety, tolerability, and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in pregnant females aged 18 years or older began in February 2021 and is still recruiting (n=4000 volunteers). BNT162b2, mRNA-1273, and Ad26.COV2.S COVID-19 vaccines did not demonstrate any safety

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## Table 2. Summary of recommendations regarding COVID-19 vaccination for pregnant and lactating women

<table>
<thead>
<tr>
<th>Organization</th>
<th>Specific patient population</th>
<th>Pregnant</th>
<th>Lactating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention (CDC Nov. 19, 2021)(^55)</td>
<td>&quot;COVID-19 vaccination is recommended for people who are pregnant&quot; &quot;People who are pregnant may receive a COVID-19 vaccine booster shot&quot; &quot;data suggest that the benefits of receiving a COVID-19 vaccine outweigh any known or potential risks of vaccination during pregnancy&quot;</td>
<td>&quot;COVID-19 vaccination is recommended for people who are breastfeeding.&quot;</td>
<td></td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG Nov. 3, 2021)(^56)</td>
<td>&quot;ACOG recommends that all eligible persons, including pregnant and lactating individuals, receive a COVID-19 vaccine or vaccine series.&quot; &quot;ACOG recommends that pregnant and recently pregnant people up to 6 weeks postpartum receive a booster dose of COVID-19 vaccine&quot;</td>
<td></td>
<td>&quot;COVID-19 vaccines should be offered to lactating individuals similar to non-lactating individuals&quot; &quot;There is no need to avoid initiation or discontinue breastfeeding&quot;</td>
</tr>
<tr>
<td>European Society of Human Reproduction and Embryology (Jun. 8, 2021)(^57)</td>
<td>&quot;At this stage, there is no information on the safety of different vaccine types during assisted reproduction treatment or pregnancy, and no recommendation can be made on which type of vaccine is the safest for men and women aiming to attempt pregnancy&quot;</td>
<td></td>
<td>No data available</td>
</tr>
<tr>
<td>World Health Organization (WHO Jun. 2, 2021)(^58)</td>
<td>&quot;recommends vaccination in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks&quot; &quot;Not necessary to conduct pregnancy testing before vaccination. No need to delay or terminate a pregnancy because of vaccination&quot;</td>
<td></td>
<td>&quot;recommends vaccination in lactating women as in other adults &quot; &quot;does not recommend to discontinue breastfeeding because of vaccination&quot;</td>
</tr>
<tr>
<td>Royal College of Obstetricians and Gynecologists (RCOG Oct. 11, 2021)(^59)</td>
<td>&quot;COVID-19 vaccines are recommended in pregnancy&quot; &quot;Women trying to become pregnant do not need to avoid pregnancy after vaccination and there is no evidence to suggest that COVID-19 vaccines will affect fertility&quot;</td>
<td></td>
<td>&quot;COVID-19 vaccines are recommended to breastfeeding women&quot; &quot;You should therefore not stop breastfeeding to be vaccinated against COVID-19&quot;</td>
</tr>
<tr>
<td>Joint Committee on Vaccination and Immunization (JCVI Apr. 16, 2021)(^60)</td>
<td>&quot;advised that all pregnant women should be offered the coronavirus vaccine at the same time as people of the same age or risk group&quot; &quot;JCVI advises that it is preferable for the Pfizer-BioNTech or Moderna mRNA vaccines to be offered to pregnant women&quot;</td>
<td></td>
<td>&quot;no known risk associated with giving non-live vaccines whilst breastfeeding&quot; &quot;maybe offered any suitable COVID-19 vaccine&quot; &quot;should be informed about the absence of full safety data for the vaccine in breastfeeding&quot;</td>
</tr>
<tr>
<td>Society of Obstetricians and Gynecologists of Canada (SOCG Nov. 4, 2021)(^61)</td>
<td>&quot;COVID-19 vaccination is recommended during pregnancy in any trimester and while breastfeeding&quot; &quot;Given that pregnant people are at increased risk of morbidity from COVID-19 infection, all pregnant persons should be prioritized to receive a COVID-19 vaccination&quot;</td>
<td></td>
<td>&quot;COVID-19 vaccination is recommended during pregnancy in any trimester and while breastfeeding&quot;</td>
</tr>
</tbody>
</table>

issues, as well as no adverse impacts on female fertility, neonatal or postnatal progress. Despite limited data from the literature, there is no solid safety warns concerning pregnancy or neonatal outcomes associated with Covid-19 vaccination in the third trimester of pregnancy in all of the previously cited studies (Data are summarized in Table 3) along with the data extracted from the v-safe pregnancy registry where mRNA-based vaccines were mostly administered to pregnant female participants.

Vaccination of neonates has been shown to be less efficient in lowering infection-related deaths than that of the adult and pediatric sectors. The presumably tolerogenic character of the neonatal immune system, immature nature of newborn immune cells along dimmed immunity attributed to the pre-existing maternal immunoglobulins have all been linked to reduced vaccine-induced immunity in newborns. Pathogens addressed primarily by maternal immunization approaches include Bordetella pertussis and influenza viruses.

Growing evidence presented by the previously cited data regarding the presence of anti-SARS-CoV-2 IgG in umbilical cord blood post maternal vaccination, with immunoglobulins transfer fractions showing a direct association with maternal immunoglobulins titers, duration of the period since administering the vaccine, and if both doses were administered. This is consistent with previous research, which demonstrated that administering influenza and whooping cough vaccine in the late-term contributes to higher antibody titers in newborns than administering during the early gestational phase.

According to Johns Hopkins "COVID-19 Maternal Immunization Tracker" (June 28, 2021) a total of 91 countries administer COVID-19 vaccine to eligible gestational females, including Saudi Arabia. On the other side, 41 countries have advised against this.

Breastmilk is documented to contain protective maternal immunoglobulins that aid in the development of the infant's immune system. However, the duration of the passive protection offered by the breastmilk-derived immunoglobulins in neonates is not presumed to last a while longer than the duration of breastfeeding. According to the previously stated data, most of the blood samples from the umbilical cord s and all tested breastmilk samples were positive for anti-SARS-CoV-2 immunoglobulins post-vaccination, as was almost every maternal serum of women vaccinated during pregnancy.

Table 3. Safety concerns in pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Non pregnant participants</th>
<th>Miscarriage</th>
<th>NICU</th>
<th>Preterm delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca-Oxford ChAdOx1 nCoV-19</td>
<td>12</td>
<td>2 ¥</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BioNTech-Pfizer BNT162b2</td>
<td>11</td>
<td>0 €</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderna mRNA-1273</td>
<td>6</td>
<td>0 I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shimabukuro et al.</td>
<td>827</td>
<td>104*</td>
<td>60**</td>
<td>N/A</td>
</tr>
<tr>
<td>Beharier et al.</td>
<td>86</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Prabhu et al.</td>
<td>122</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gray et al.</td>
<td>84</td>
<td>0</td>
<td>2***</td>
<td>1</td>
</tr>
<tr>
<td>Mithal et al.</td>
<td>27</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Jill et al.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gilbert et al.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*96 of 104 spontaneous abortions happened before 13 weeks of gestation and 701 of 712 live birth occurred among participants who were administered their 1st dose in the 3rd trimester.
**60 of 636 of those vaccinated before 37 weeks of gestation.
***1 term delivery, as well as 1 preterm delivery, was admitted to NICU.
¥ A total of 3 miscarriages out of 9 pregnancies occurred in the control group.
€ A total of 1 miscarriage out of 12 pregnancies occurred in the control group.
I A total of 1 miscarriage out of 7 pregnancies occurred in the control group.

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CONCLUSION

Despite mounting evidence of benefit and insufficient evidence of harm, from the previously cited studies, along with clear recommendations from public health communities32, challenges in vaccination among pregnant and lactating populations prevail33,34. Although it is unclear whether vaccines can generate the same lengthy immunity in people when administered during gestation or breastfeeding, preliminary data mentioned in this article suggest that gestational and breastfeeding participants mount a fairly similar serological response to that encountered in non-gestational counterparts. Therefore, healthcare providers must communicate these outcomes, as well as conduct individual tailored discussions about each female's detailed risks and potential benefits prior to vaccination.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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69. Global policies on COVID-19 vaccination in pregnancy vary widely by country according to new online tracker [Hub https://hub.jhu.edu/2021/06/28/tracker-map-of-vaccine-policies-for-pregnant-women/ (accessed 2021-11-05).


