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SYSTEMATIC REVIEW



# COVID-19 vaccination in pregnant and lactating women: a systematic review

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**ABSTRACT**

**Introduction:** The concern of undergoing vaccination during pregnancy and lactation, in absence of data on safety and efficacy in these target populations, is subject of ongoing debate nationally and internationally. However, the only real prophylactic strategy against COVID-19 is still mass vaccination, which means to vaccinate infants and pregnant and lactating women.

**Areas covered:** This is a systematic review aiming to evaluate the safety and the efficacy of COVID-19 vaccines in pregnant and lactating women and their newborns. We did advanced research on PubMed and Google Scholar, and searched for any evidence also on ClinicalTrials.gov. Results refer to a timeline going until 12 June 2021.

**Expert opinion:** Our efforts must be directed to vaccine more and more population groups which have been preliminarily excluded from the vaccination campaign. Studies have not so far highlighted plausible adverse effects in vaccinated pregnant women or in their newborns. Reactogenicity across lactating and pregnant women does not seem to differ from general population. Likewise, abortion rate does not differ from non-vaccinated pregnant women studied before the COVID-19 pandemic. It also seems that a major amount of anti-SARS-CoV-2 immunoglobulins is transferred through the placenta and the breastmilk to the newborn, providing humoral immunity.

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Pregnancy; lactation; COVID-19; vaccines; breastfeeding

## 1. Introduction

Since SARS-CoV-2 has spread all over the world, the demand for effective therapies has been growing. The necessity for prevention strategies that could stop the spreading of the disease has become a priority. Vaccination seems to be the most promising. The development of a vaccine that can be administered across all ages and health conditions is a universal concern. There is currently a lack of evidence about the efficacy and safety of vaccine in different categories, such as individuals under 16 years old (age limit for mRNA-based vaccines, such as Pfizer and Moderna) [1,2] or 18 years old (age limit for viral vector-based vaccines, such as Astrazeneca and Johnson&Johnson) [3,4], and pregnant or lactating women. All the randomized clinical trials, that have been conducted for the study of the COVID-19 vaccines, have not included pregnant and lactating women for an evaluation of their safety and effectiveness in these special categories. On the other side, several types of vaccines being currently used include inactivated pathogens as advanced technology, including TDaP [5] and influenza [6], and all demonstrated to be safe during pregnancy. Currently, there are no specific recommendations or position statements from academic and scientific societies for COVID-19 vaccination in pregnancy. So, the aim of this systematic review is to understand if COVID-19 mRNA-based vaccines, which are the only ones tested in the reported and selected articles, have raised any health issue both on fetus during pregnancy and on infant during lactation. Moreover, one of the main purposes is to understand whether the efficacy occurred in the mother may be demonstrated in the child at birthtime.

## 2. Methods

We conducted a systematic review of literature related to SARS-CoV-2 vaccination in pregnant and lactating women, following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

### 2.1. Search strategy

We made three attempts of advanced research on PubMed and as many on ClinicalTrials.gov, using some phrases containing specific keywords, in order to extend our results. All the results refer to a timeline going until Saturday 12 June 2021. The three search attempts on PubMed were respectively: 'COVID-19 vaccine AND pregnancy,' 'Lactating women COVID-19 vaccination,' and 'SARS antibodies in pregnant women.' On ClicalTrials.gov, we searched for: 'COVID-19 vaccine in pregnancy' (first attempt), 'COVID-19 vaccination in pregnant women' (second attempt), and 'COVID-19 vaccine in lactating women' (third attempt). We also consulted Google Scholar until 18 April 2021, where we searched for

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**Article highlights**

- Nowadays there is a lack of evidences about efficacy and safety of vaccine in certain categories, such as individuals under 16 or 18 years old, and pregnant or lactating women. All the randomized clinical trials, that have been conducted for the study of the COVID-19 vaccines, have not included pregnant and lactating women for deep evaluation of their safety and effectiveness.
- All of the pregnant women tested in the selected studies received a mRNA-based vaccine. 95.2% of maternal blood samples and 85% of umbilical cord blood samples collected were positive to SARS-CoV-2 immunoglobulins dosage.
- Breastmilk samples from lactating women were collected and screened for antibodies. All the breastmilk samples collected from lactating women and tested were positive for SARS-CoV-2 antibodies as well as maternal sera.
- No adjunctive risk has been assessed both for the mother and the newborn, although this finding is partial and needs to be further evaluated. Reactogenicity across lactating and pregnant women does not seem to differ from general population. Among all the consulted studies, six newborns from vaccinated mothers were admitted to NICU. There were also 65 preterm deliveries and 104 miscarriages. Nevertheless, abortion rate does not differ from non-vaccinated pregnant women studied before the COVID-19 pandemic.
- Unexpected data about SARS-CoV-2 vaccination in pregnant people came from accidental pregnancies occurred in the PfizerBioNTech, Moderna, and Oxford/Astrazeneca clinical trials. A total of 29 pregnancies occurred in the vaccinated groups with only 2 miscarriages. To compare these data, there were 28 pregnancies in the control groups with a total of 5 miscarriages.
- Scientific societies' recommendations advocate for COVID-19 vaccination during pregnancy and lactation, in particular it is highly recommended to women who work on the healthcare front-line or who have comorbidities.

'COVID-19 vaccination in pregnant women' and restricted our findings to 2021-only results. We expected that we would have often found the same articles by searching separately the keywords 'pregnant' and 'lactating,' and so it was at the end.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria were any paper that included information about COVID-19 vaccination in pregnant and lactating women, any health outcome on newborns of vaccinated mothers, and the presence of antibodies in newborns and/or umbilical cord blood, and in breastmilk samples of vaccinated mothers. We excluded articles that did not relate to our clinical aspects of interest, that reported data exclusively about vaccination of adults, those inherent to vertical transmission of immunity after SARS-CoV-2 infection, duplicate publications of the same study, and reviews, viewpoints, statements, or expert opinions. Each article was searched in English language.

### 2.3. Study selection

A four-step procedure, based on elimination of duplicates, screening of title and abstract, reading of full-text articles, and screening during the data-extraction phase, was performed. Elimination of duplicates was performed by one researcher, then titles and abstracts from PubMed, Google Scholar and ClinicalTrials.gov searches were independently screened by two authors, who perfectly agreed on studies elimination at the final confrontation. Selected full-text articles were read by all the authors. Complete consensus was found about articles included in the study. Each researcher following the inclusion criteria unanimously decided in the pre-selection phase.

### 2.4. Risk of bias and quality assessment

All included studies were assessed using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies), a tool to determine the quality of primary diagnostic accuracy studies included in systematic reviews focused on risk of bias and applicability in the study. Any judgment regarding risk of bias is to be based on the predefined signaling questions with regard to the following four domains: patient selection, index test, reference standard, and flow-timing. Judgment regarding applicability is based on the extent of which bias in any domain is likely to affect the question in the review. The risk of bias and applicability concerns were rated as 'low,' 'high,' or 'unclear.' The results of quality assessment using QUADAS-2 tool are summarized in (Figure 1), and proportions of studies with risk of bias and applicability concerns are graphically displayed in (Figure 2). Generally, there is a low risk of bias regarding 'flow-timing' and 'patients selection.' Unfortunately, there is an intermediate risk for index test, reference standard on risk of bias and reference standards on applicability because there is no reference standard and so it is not possible to answer the questions of these domains. The same thing concerns the flow-timing of the risk of bias, but in this case, for 8 out of 10 works, we can answer positively to one of the 3 questions, considering that all patients enrolled were included in the analysis. For the applicability concerns, only two articles have a low risk [7,8]. Two out of 10 articles are case reports, therefore the risk of bias and applicability in patient selection is high [9,10]. We gave a high risk of applicability to those works which considered women during pregnancy [11] or during breastfeeding [12] vaccinated with only one kind of vaccine; while an unclear risk was given to works selecting only pregnant or lactating women, but evaluating the response to all existing vaccines [13–16]. Adjunctively, according to AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews 2) score, 'high quality review' evaluation was obtained for this work.

## 3. Results

We identified 253 articles on PubMed: 137 by searching for 'COVID-19 vaccine AND pregnancy,' 32 by 'Lactating women COVID-19 vaccination,' and 84 by 'SARS antibodies in pregnant women.' We also found 1.650 articles on Google Scholar by searching 'COVID-19 vaccination in pregnant women.' All these articles included all the studies primarily identified on PubMed. On ClinicalTrials.gov, we found six trials: three by searching for 'COVID-19 vaccine in pregnancy,' three by "COVID-19 vaccination in pregnant women, and no result by 'COVID-19 vaccine in lactating women.' Then, we eliminated 189 duplicate articles on PubMed and Google Scholar and 2 on ClinicalTrials.gov. On all

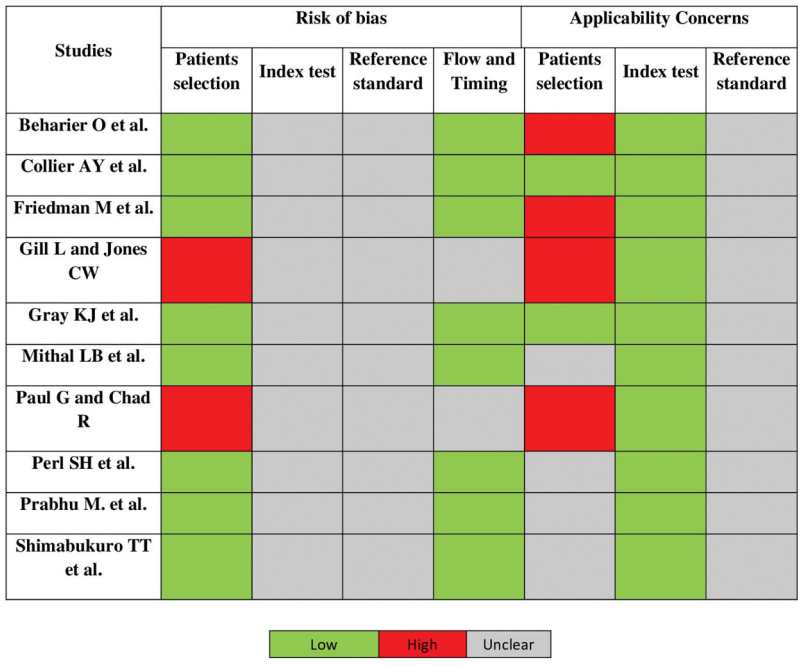


Figure 1. Quality assessment of included studies using QUADAS-2 tool.

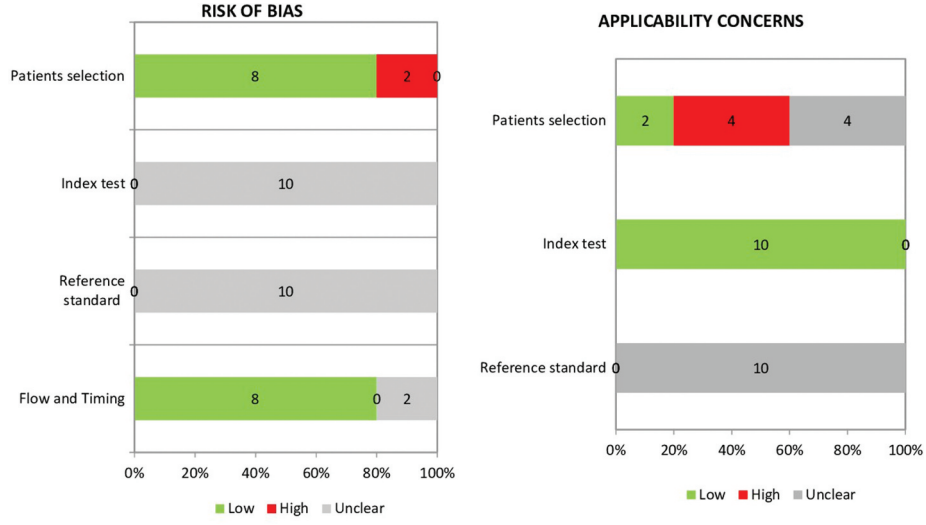


Figure 2. Percentage of the studies with risk of bias and applicability concerns in different domains of QUADAS-2 tool.

the consulted databases 1718 articles were screened and most of them were excluded via reading of the title and abstract, because they were not pertinent to our objective. Among the four remaining trials on ClinicalTrials.gov, two were not recruiting yet, one was still recruiting, and one was completed. Unfortunately, this last trial, named 'COVID-19 Vaccine Confidence Among Pregnant Women and Mothers,' was excluded because it was not pertinent to this review. Then, 16 full-text articles were evaluated for eligibility. Six of them did not report any adjunctive level of evidence for vaccination in pregnant and lactating women. Therefore, among these ones only a total of 10 articles were finally included, being effectively related to maternal-placental and breastmilk immunity (Figure 3). These are two case reports, two case series, one retrospective, and five cohort studies.

### 3.1. Efficacy outcomes in pregnant women

An illustrative self-report [9] was selected, including 34-year-old multi-gravid patient, working in healthcare, who was vaccinated at 32 6/7 weeks of gestation. She received her second dose of mRNA vaccine at 35 2/7 weeks. No adverse effects were present except for mild pain at an injection site. Unmedicated vaginal delivery without complication was carried out. Apgar scores were of 9 and 9 at 1 and 5 minutes respectively, and weight was adequate for gestational age. The presence of antibodies to SARS-COV-2 was found in both maternal blood and umbilical cord blood. Maternal blood was positive for immunoglobulin G at a titer of 1:25,600. The cord blood was also positive for anti-SARS-CoV-2–specific immunoglobulin G at the same titer of the mother (1:25,600). The second illustrative case report

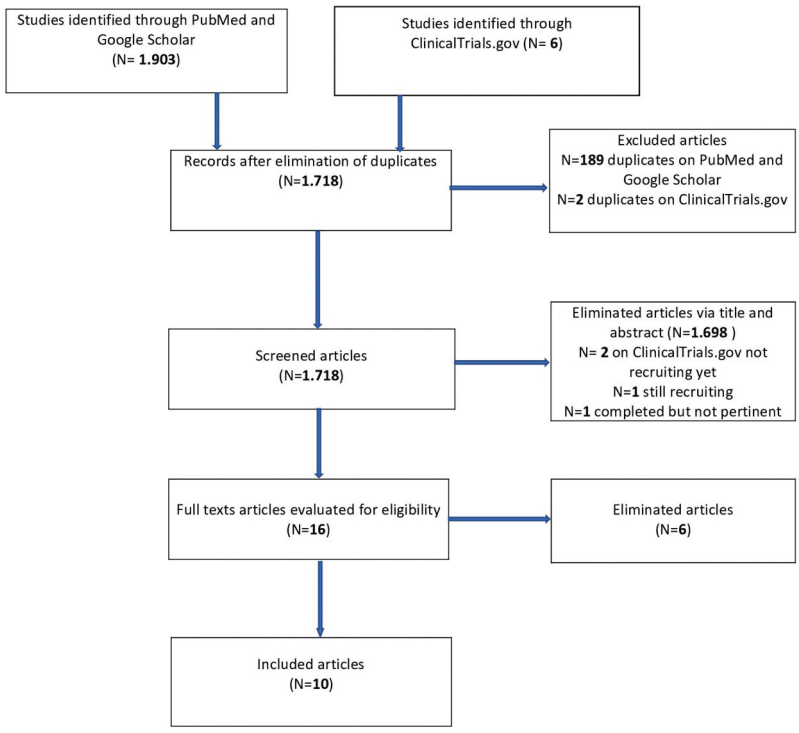


Figure 3. Search results following PRISMA methodology.

selected [10] suggests that maternal vaccination protects the fetus and reduces the infection from SARS-CoV-2. It was demonstrated through the case of a front-line healthcare worker vaccinated with mRNA COVID-19 vaccine at gestational age of 36 weeks and 3 days. She gave birth to the baby 3 weeks after vaccination. The most important evidence was that cord blood antibodies IgG for SARS-CoV-2 were detected at a level of 1.31 U/ml, even if duration of antibody protection remains actually unknown. Therefore, it could be useful effectuate serial total antibody measurements to determine how long protection is expected and this could help to understand when it's the best time to begin vaccination in newborns from vaccinated mothers. The third selected work was a cohort study [7] that enrolled 131 women, from 17 December to 2 March 2021, who received mRNA-based vaccine: 84 pregnant, 31 lactating and 16 non pregnant of reproductive age. Blood and breastmilk from lactating women were collected at: first vaccine dose/baseline, second/"prime" vaccine dose profile, 2–6 weeks following the 2nd vaccine dose/"boost" profile and at delivery. These groups were compared to 37 pregnant women infected with COVID-19 during pregnancy at 4–12 weeks after natural infection. Maternal comorbidities were: chronic hypertension, that was present in the measure of 6% in non-pregnant women, 4% in pregnant and 10% in lactating women; diabetes/gestational age was present in the measure of 0% in non-pregnant women, 4% in pregnant and 10% in lactating; BMI>30 was present in the measure of 12% in non-pregnant women, 12% in pregnant and 10% in lactating; asthma was present in 12% of non-pregnant, 19% of pregnant and 23% of lactating; immunosuppression/cancer was present in the measure of 0% in non-pregnant and lactating and 4% of pregnant. Regarding the timing of vaccine administration, 13% of pregnant women were vaccinated during the 1st trimester, 46% were vaccinated during the 2nd trimester and 40% during the 3rd trimester. Side effects between groups following vaccination were not so different. Headache, injection site soreness, fatigue were the most common side effects after each vaccine dose, while chills and fever were present after the 2nd dose. All vaccine-generated antibody titers in pregnant, lactating and non-pregnant women were significantly higher than those ones induced by SARS-CoV -2 infection during pregnancy ($p < 0.0001$), showing that the natural infection gives lower immunity than the vaccination. Vaccine-induced antibodies were present in all umbilical cord blood and breastmilk samples. Nevertheless, neutralizing antibody titers were lower in umbilical cord blood compared to maternal sera, but this finding did not achieve statistical significance (median [IQR] 104.7 [61.2–188.2] maternal sera, 52.3 [11.7–69.6] cord sera, $p = 0.05$). The boost dose increased SARS-CoV-2-specific IgG, but not IgA, in maternal blood and breastmilk. Differences about reactogenicity among the groups were not demonstrated. The fourth study selected [8] is a cohort study which enrolled 103 female participants aged 18 to 45 years old, of whom 30 pregnant women and 16 lactating. Samples were obtained a median of 21 days (IQR, 17–27 days) after the second vaccine dose from non-pregnant women, 21 days (IQR, 14–36 days) from pregnant women, and 26 days (IQR, 19–31 days) from lactating women. Nine women delivered and contributed newborn cord blood. Eleven pregnant participants (37%) received PfizerBioNTech vaccine and 19 (63%) received Moderna. SARS-CoV-2 infection was diagnosed in 4 (4%) of the vaccinated participants (1 non-pregnant, 2 pregnant and 1 lactating). Among pregnant participants, 5 (17%) received the first vaccine dose in the first trimester, 15 (50%) in the second, and 10 (33%) in the third. 22 pregnant and 6 non-

pregnant unvaccinated women with SARS-CoV-2 infection were included as comparators to the vaccine group. As far as reactogenicity is concerned, after the second dose fever was reported in 27 non-pregnant (52%, SD 7%) and 4 pregnant (14%, SD, 6%). No severe adverse events or pregnancy or neonatal complications were observed. Antibody as well as CD4 and CD8 T-cell responses were present in pregnant and non-pregnant women following vaccination. Maternal titers were higher after vaccination than natural infection. Binding and neutralizing antibodies were also observed in all infant cord blood. The fifth study consulted [13] is a case series which analyzed maternal sera and umbilical cord blood samples from 27 women who received the first vaccinal injection at 33 ± 2 weeks of gestational age. Each of them delivered and 1 delivered a twin set. All but 1 woman had positive SARS-CoV-2 IgG at the time of delivery. Only 3 cord blood samples were negative to IgG dosage, including the two twin newborns. These two women got their first vaccine dose less than 3 weeks before delivery. Twenty-two women (74%) received both vaccine doses prior to delivery with a mean latency of 6 ± 3 weeks. Prabhu et al. examined 122 pregnant women and their newborns at birthtime [14]. Fifty-five women received only one dose of the vaccine and 67 women received both doses of the vaccine prior giving birth. Eighty-five women received the PfizerBioNTech vaccine, while 37 women received the Moderna vaccine. All women tested negative for SARS-CoV-2 infection by use of PCR on nasopharyngeal swabs. Semi-quantitative testing for RBD antibodies was performed on sera of maternal peripheral blood and neonatal cord blood at the time of delivery to identify immunoglobulins. 106 pregnant women vaccinated with mRNA-based COVID-19 vaccines during pregnancy and tested at time of birth had detectable antibody response. Eighty-seven women tested at birth produced only an IgG response, and 19 women produced both an IgM and IgG response. 16 women tested at birth had no detectable antibody response, and they were all within four weeks after vaccination dose. All women and their newborns, except for one neonate, had detectable IgG antibodies by 4 weeks after maternal first dose of vaccination. 43.6% (24/55) of neonates born to women that received only one vaccine dose had detectable IgG, while 98.5% (65/67) of neonates born to women that received both vaccine doses had detectable IgG. Another cohort study performed in Israel [11] enrolled 1094 pregnant participants, whose matched maternal cord blood samples were collected in 86 vaccinated pregnant women, 65 SARS-CoV-2 infected during pregnancy and 62 unvaccinated non-infected pregnant controls. 66 non-infected unvaccinated participants were included as control group. First dose receipt occurred at 34.5 weeks of mean gestational age. Each participant delivered during the study work-up and each vaccinated woman received the PfizerBioNTech vaccine. The conclusion of this study is that the vaccine elicits strong maternal humoral IgG response (both anti-S and RBD) that crosses the placenta barrier. In fact, cord blood titers tested all positive to SARS-CoV-2 as well as maternal samples. Maternal to neonatal anti-COVID-19 antibodies ratio did not differ compared to controls.

Among 351 pregnant women vaccinated in the seven studies, a total of 260 infants were delivered (74.1%) and 62 of them (2 in the Gray et al.'s cohort study and 60 in the two-case series) delivered before receiving the second dose (23.8%). In the Gray et al.'s cohort study, umbilical cord blood samples were collected from 10 of 13 deliveries. Among the aforementioned studies where gestational age at first dose injection was reported, most of pregnant women received their first administration in the third trimester. Of all 351 pregnant women, 348 received a mRNA-based vaccine and 3 an unknown vaccine: 68.9% received the PfizerBioNTech one, 30.2% the Moderna one and the remaining ones a non-specified vaccine. 95.2% of maternal blood samples and 85% of umbilical cord blood samples collected and tested were positive to SARS-CoV-2 immunoglobulins dosage. All these data are summarized in (Table 1).

### 3.2. Safety outcomes in pregnant women

We found just one work, based on the V-safe Surveillance System and Pregnancy Registry and Vaccine Adverse Event Reporting System (VAERS), focusing on vaccination safety in pregnancy [15]. Among non-pregnant and pregnant women were observed similar patterns of reactogenicity. The registry enrolled 3958 participants, of whom 3719 (94.0%) worked as health-care personnel. Among the enrolled participants, most were 25–44 years of age (98.8%), non-Hispanic White (79.0%), and, at the time of interview, did not report a COVID-19 diagnosis during pregnancy (97.6%). Receipt of a first dose of vaccine was reported by 92 participants (2.3%) during the periconception period, by 1132 (28.6%) in the first trimester of pregnancy, by 1714 (43.3%) in the second trimester, and by 1019 (25.7%) in the third trimester. 54% of 3958 included participants received PfizerBioNTech and 46% Moderna. Among 1040 participants (91.9%) who received a vaccine in the first trimester and 1700 (99.2%) who received a vaccine in the second trimester, initial data had been collected and follow-up scheduled at designated time points approximately 10 to 12 weeks apart; limited follow-up calls had been made at the time of this analysis. Among 827 participants who had a complete pregnancy, this one resulted in a live birth in 712 (86.1%), in a spontaneous abortion in 104 (12.6%), in stillbirth in 1 (0.1%), and in other outcomes (induced abortion and ectopic pregnancy) in 10 (1.2%). A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation, and 700 of 712 pregnancies that resulted in a live birth (98.3%) were among persons who received their first eligible vaccine dose in the third trimester. Adverse outcomes among 724 live-born infants, including 12 sets of multiple gestation, were preterm birth (60 of 636 among those vaccinated before 37 weeks [9.4%]), small size for gestational age (23 of 724 [3.2%]), and major congenital anomalies (16 of 724 [2.2%]); no neonatal deaths were reported at the time of interview. Among the participants with completed pregnancies who reported congenital anomalies, none had received COVID-19 vaccine in the first trimester or periconception period, and no specific pattern of congenital anomalies was observed. Calculated proportions of pregnancy and neonatal outcomes appeared similar to incidences published in the peer-reviewed literature.

Behaier et al.'s Israelian cohort study identified four preterm deliveries and 4 NICU admissions. We do not know if

Table 1. Efficacy outcomes in pregnant women.

| Author (study type) | | Gilbert et al. (case report) | Jill et al. (case report) | Gray et al. (cohort study) | Collier et al. (cohort study) | Mithal et al. (case series | Prabhu et al. (case series) | Beharier et al. (cohort study) | Total |
|---|---|---|---|---|---|---|---|---|---|
| **No. pregnant vaccinated** | | 1 | 1 | 84 | 30 | 27 | 122 | 86 | 351 |
| **No. infants delivered** | | 1 | 1 | 13* | 9 | 28*** | 122 | 86 | 260 |
| **Gestational age at 1st dose** | 1st trimester | 0 | 0 | 11 | 5 | 0 | n/a | n/a | 16 |
| | 2nd trimester | 0 | 0 | 39 | 15 | 0 | n/a | n/a | 54 |
| | 3rd trimester | 1 | 1 | 34 | 10 | 27 | n/a | n/a | 73 |
| **Type of vaccine** | Pfizer | 0 | 1 | 41 | 11 | 18 | 85 | 86 | 242 |
| | Moderna | 1 | 0 | 43 | 19 | 6 | 37 | 0 | 106 |
| | Unknown | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 3 |
| **Positive maternal blood antibodies after vaccination** | | 1 | 1 | 84 | 30 | 26 | 106**** | 86 | 334 |
| **Positive umbilical cord blood antibodies after vaccination** | | 1 | 1 | 10** | 9 | 25 | 89 | 86 | 221 |

** Only 1 preterm delivery who presented transient tachypnea of the newborn (TTN) was submitted to supplemental oxygen by CPAP and was admitted to NICU; also 1 term delivery was admitted to NICU.*
*** Only 10 of 13 umbilical cord blood samples were collected after delivery; 2 women delivered before receiving the 2nd dose.*
**** Among 27 deliveries there was 1 twin set.*
***** 16 women had no detectable antibodies at birthtime; all of them delivered within 4 weeks after 1st dose administration.*

these preterm deliveries themselves were admitted to intensive care, as it is not specified in the study. However, we cannot absolutely correlate the role of the vaccination to these adverse neonatal outcomes.

Unfortunately, it is clear that safety outcomes in the newborns of vaccinated pregnant women have not been consistently reported in the literature. All the reported data in the remaining studies are referred to data extraction process, which may have generated some selection bias or accidentally omitted relevant ones. In these selected studies, it seems that no correlated adverse event occurred in newborns of vaccinated mothers. Most of first-dose administrations in the studies focusing on vaccine safety in pregnancy were done in the 2nd trimester. Among 4279 pregnancies in the selected studies and according to extracted data, there were 6 (0.14%) NICU admissions and 65 (1.52%) preterm deliveries. One-hundred-and-four miscarriages on 827 participants who had a complete pregnancy occurred only among the Shimabukuro's vaccinated pregnant participants. Nevertheless, abortion rate does not differ from non-vaccinated pregnant women studied before the COVID-19 pandemic. All the corresponding data are reported in (Table 2).

Table 2. Safety outcomes in pregnant women.

| Author (study type) | No. pregnancies | No. miscarriages | No. preterm deliveries | No. NICU admissions |
|---|---|---|---|---|
| Gilbert et al. (case report) | 1 | 0 | 0 | 0 |
| Jill et al. (case report) | 1 | 0 | 0 | 0 |
| Gray et al. (cohort study) | 84 | 0 | 1 | 2 |
| Mithal et al. (case series) | 27 | 0 | n/a | n/a |
| Prabhu et al. (case series) | 122 | 0 | n/a | n/a |
| Shimabukuro et al. (retrospective study) | 3958 | 104* | 60** | n/a |
| Behaier et al. (cohort study) | 86 | 0 | 4 | 4 |
| Total | 4279 | 104 | 65 | 6 |

** On 827 participants who had a complete pregnancy.*
*** On 636 pregnant women who were vaccinated before 37 weeks of gestational age.*

### 3.3. Outcomes in lactating women

In all the selected cohort studies, breastmilk samples from lactating women were collected and screened for antibodies. Of 31 lactating women of the aforementioned cohort study [7] the median months after delivery at 1st dose were 7.3. 51.6% of lactating women received the PfizerBioNTech vaccine and 48,4% the Moderna one. All the 31 collected breastmilk samples were positive for anti-SARS-CoV-2 antibodies as well as maternal sera. In the second consulted cohort study [16], 504 breastmilk samples from 84 women were collected before administration of the PfizerBioNTech vaccine and then once weekly for 6 weeks starting at week 2 after the first dose, and finally analyzed. Mean length of time in months at samples collection after delivery was 1.3. Anti–SARS-CoV-2-specific IgA antibodies in the breastmilk were positive in 86.1% of samples at week 4, that was 1 week after the second vaccine dose injection. Samples also tested positive for anti–SARS-CoV -2-specific IgG antibodies in 97% of cases at weeks 5 and 6. Because of the exclusive analysis of the immunoglobulins in the samples, we could not induct how many women had specific anti-SARS-CoV-2 antibodies in their breastmilk. In a third analyzed prospective study [12], 10 lactating women received two doses of the PfizerBioNTech mRNA-based vaccine (the first dose was administered at 5.1 months postpartum). The antibody response was rapid and highly synchronized between breastmilk and serum, reaching stabilization 14 days after the second dose. Control serum (n = 10) and lactoserum samples (n = 10) were obtained before the COVID-19 pandemic. All maternal blood samples as well breastmilk samples were positive for anti-SARS-CoV-2 antibodies. The predominant serum antibody was IgG. The response

Table 3. Outcomes in lactating women.

| Author (study type) | | Gray et al. (cohort study) | Perl et al. (cohort study) | Friedman et al. (cohort study) | Collier et al. (cohort study) | Total |
|---|---|---|---|---|---|---|
| **No. lactating vaccinated** | | 31 | 84 | 10 | 16 | 141 |
| **Birth months at 1st dose** | | 7.3 (median) | 10.3 (mean) | 5.1 (mean) | n/a | n/a |
| **Type of vaccine** | Pfizer | 16 | 84 | 10 | 11 | 121 |
| | Moderna | 15 | 0 | 0 | 5 | 20 |
| **Positive maternal blood antibodies after vaccination** | | 31 | n/a | 10 | 16 | 57 |
| **Positive breastmilk antibodies after vaccination** | | 31 | n/a | 10 | 16 | 57 |

in the breastmilk included both IgG and IgA with neutralizing capacity. Collier et al. [8] demonstrated the presence of antibody titers both in sera and breastmilk of all 16 examined lactating women. Among 16 lactating, 11 (69%) received PfizerBioNTech and 5 (31%) Moderna vaccine. Although eliciting a strong humoral immunity in breastmilk, the median IgA and IgG binding antibodies were lower in breastmilk samples after vaccination than natural infection.

Therefore, a total of 141 women in lactation were vaccinated and 85.8% of them received the Pfizer vaccine, whereas 14.2% the Moderna one. It was not possible to assess global efficacy in vaccinated women both in breastmilk and maternal sera because of lacking data in the study of Perl et al. However, 100% of tested samples were positive for anti-Spike and/or anti-RBD antibodies. Thus, relative data are schematized in (Table 3).

## 4. Discussion

We present an overview of the current evidence on COVID-19 vaccination during pregnancy and lactation. We specifically focused on the safety and efficacy outcomes in children, however, the literature on this topic is scarce. In the battle against COVID-19 our efforts must be directed to vaccine more and more categories which have been preliminarily excluded from the vaccination campaigns. In all the selected studies mRNA-based vaccines have been mostly administered and no evidence of concerns about COVID-19 emerged. We know that Anti-SARS-CoV-2 immunoglobulins (both IgG and IgA) are transferred through the placenta and the breastmilk to the newborn, providing humoral immunity. 85% of umbilical cord blood samples and all the tested breastmilk samples were positive to anti-SARS-CoV-2 antibodies after vaccination as well as 95.2% of maternal sera of women vaccinated during pregnancy. Only 1.52% of infants were born preterm. There was 1 preterm delivery after which the newborn presented transient tachypnea of the newborn (TTN), was submitted to CPAP and finally admitted to Neonatal Intensive Care Unit (NICU). In another case, a term newborn was admitted to NICU because of persistent hypoglycemia. Other 4 preterm deliveries and as many NICU admissions are reported in Behaier's et al's study, unfortunately without any mutual association. According to extracted data, one-hundred-and-four miscarriages on 827 participants who had a complete pregnancy occurred exclusively among the Shimabukuro's vaccinated pregnant participants. However, none of these cases seems to correlate with vaccination. Therefore, no adjunctive risk has been identified for the mother and the newborn, despite limited information and data from the literature. Reactogenicity across lactating and pregnant women does not seem to differ from general population. Unexpected data about SARS-CoV-2 vaccination in pregnant people came from accidental pregnancies occurred in the PfizerBioNTech, Moderna and Oxford/Astrazeneca clinical trials. Paradoxically, these trials, which had excluded pregnant women and asked participants to avoid to become pregnant, brought additional data to this topic. Incredibly a sort of balance between the number of pregnancies in the control group and the vaccinated one has been reached in all three aforementioned trials. A total of 29 pregnancies occurred in the vaccinated groups with only 2 miscarriages (all of them happened in the Astrazeneca trial). There were 28 pregnancies in the control groups with a total of 5 miscarriages (1 in Moderna, 1 in Pfizer and 3 in Astrazeneca). Further information is provided in (Table 4) [17–19]. Moreover, according to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing documents, reproductive and developmental toxicology studies were held in rodents only with the Moderna vaccine and no adverse effect was showed on female reproduction, embryonic development or postnatal development [20]. The first phase 2/3, randomized, placebo-controlled, observer-blind trial for vaccination in healthy pregnant women aged 18 and older, which is committed by PfizerBioNTech, started in February 2021 and is still recruiting. It will evaluate safety, tolerability and immunogenicity of BNT162b2 mRNA COVID-19 vaccine in 4000 estimated participants [21]. Another observational prospective study will assess efficacy on mother and child at delivery by collecting blood samples and measuring their antibodies titers. Participants will also be followed through 90 days postpartum to obtain obstetrical and neonatal outcomes [22]. Furthermore, COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) is going to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy to prevent

Table 4. Pregnancies and safety outcomes in RCT.

| Vaccine trial | Vaccinated group | | | Control group | | |
|---|---|---|---|---|---|---|
| | Participants | Pregnancies | Miscarriages (%) | Participants | Pregnancies | Miscarriages (%) |
| PfizerBioNTech | 18,860 | 11 | 0 | 18,846 | 12 | 1 (8) |
| Moderna | 15,181 | 6 | 0 | 15,170 | 7 | 1 (14) |
| Oxford/Astrazeneca | 5,807 | 12 | 2 (17) | 5,829 | 9 | 3 (33) |
| Total | 39,848 | 29 | 2 (6.9) | 39,845 | 28 | 5 (17.9) |

COVID-19 [23]. Unfortunately, none of these cited studies is complete yet. As said above, the scientific societies did not publish any explicit recommendation for COVID-19 vaccination in pregnancy. Societies, like the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM), continue to advocate for making COVID-19 vaccines available to pregnant and lactating women [24]. The World Health Organization (WHO) revised its statement on the 29 January 2021 and adopted a more permissive position, that 'pregnant women at high risk of exposure to SARS-CoV-2 (e.g. health workers) or who have comorbidities which add to their risk of severe disease, may be vaccinated in consultation with their health care provider [25].' Surely a great lack of data for the use of mRNA vaccines during lactation is reflected in recommendations of the Academy of Breastfeeding Medicine, which states: 'During lactation, it is unlikely that the vaccine lipid would enter the blood stream and reach breast tissue. If it does, it is even less likely that either the intact nanoparticle or mRNA transfer into milk. In the unlikely event that mRNA is present in milk, it would be expected to be digested by the child and would be unlikely to have any biological effects [26].' It is clear from the positions of the scientific societies that COVID-19 vaccine may be proposed to pregnant women if the benefits outweigh the potential risks, taking into consideration the absence of RCT that can give strength to vaccination of the aforementioned categories. Doubtless, it is to underline that all the actual recommendations apply to Pfizer and Moderna vaccines. The Centers for Disease Control and prevention (CDC) state that 'people who are pregnant and part of a group recommended to receive COVID-19 vaccination, such as health care personnel, may choose to be vaccinated.' Moreover, it is stated that there is no need for pregnancy testing before vaccination and it is not recommended to avoid pregnancy in people who are trying to become pregnant [27]. Not different is the position of the American College of Obstetricians and Gynecologists (ACOG), which 'recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.' The Society for Maternal-Fetal Medicine (SMFM) 'strongly recommends that pregnant people have access to COVID-19 vaccine.' According to SMFM, the risk of harm to fetus from RNA vaccines is thought to be low because of the expected degradation of the nucleic acids in the bloodstream. It seems to be more cautious the FDA, which says that 'available data on COVID-19 vaccine administered to pregnant individuals are insufficient to inform vaccine associated risks in pregnancy.' In conclusion, mRNA vaccines do not seem to be linked to any adverse outcomes in newborns, even if this represents an issue that has to be definitely proven in the trials in progress. According to the reported articles, vertical-transmitted immunity is demonstrated, and it seems that the sooner vaccination is performed more efficient it is. However, a more careful definition of its characteristic has to be given in order to identify a specific timeline for COVID-19 vaccination during pregnancy.

### 4.1. Limitations of the study

The main limitation of this systematic review is the low number of relevant articles identified due to the paucity of the available evidence in the literature. Nevertheless, the lack of evidence on safety of COVID-19 vaccination for pregnant and lactating women is a key point. Furthermore, the efficacy of the vaccination for newborns has been tested only on a small number of infants and needs further evaluation. At this time, we do not really know the duration of vertically transferred immunity in newborn. The optimal timing of the vaccine administration during gestation as well as in infancy needs to be further evaluated in future studies.

## 5. Expert opinion

In the battle against COVID-19, our efforts must be directed to vaccine more and more categories which have been preliminarily excluded from the vaccination campaigns. In all the selected studies, mRNA-based vaccines have been mostly administered and no evidence of concerns about their use emerged. We know that anti-SARS-CoV-2 immunoglobulins (both IgG and IgA) are transferred through the placenta and the breastmilk to the newborn, providing humoral immunity. According to included data, most of umbilical cord blood samples and all the tested breastmilk samples were positive to anti-SARS-CoV-2 antibodies after vaccination as well as almost every maternal serum of women vaccinated during pregnancy. No adjunctive risk has been assessed both for the mother and the newborn, although this finding is partial and needs to be further evaluated. Reactogenicity across lactating and pregnant women does not seem to differ from general population. Among all the consulted studies, six newborns from vaccinated mothers were admitted to NICU. There were also 65 preterm deliveries and 104 miscarriages. Nevertheless, abortion rate does not differ from non-vaccinated pregnant women studied before the COVID-19 pandemic. Therefore, no

adjunctive risk has been identified for the mother and the newborn, despite limited information and data from the literature. Unexpected data about SARS-CoV-2 vaccination in pregnant people came from accidental pregnancies occurred in the PfizerBioNTech, Moderna, and Oxford/Astrazeneca clinical trials. A total of 29 pregnancies occurred in the vaccinated groups with only 2 miscarriages (all of them happened in the Astrazeneca trial). There were 28 pregnancies in the control groups with a total of 5 miscarriages (1 in Moderna, 1 in Pfizer and 3 in Astrazeneca). Moreover, according to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing documents, reproductive and developmental toxicology studies were held in rodents only with the Moderna vaccine and no adverse effect was showed on female reproduction, embryonic development, or postnatal development. Scientific societies' recommendations advocate for COVID-19 vaccination during pregnancy and lactation, in particular it is highly recommended to women who work on the healthcare front-line or who have comorbidities. Therefore, it is clear that COVID-19 vaccine could be proposed to pregnant women if the benefits outweigh the potential risks, taking into consideration the absence of RCT that can give strength to vaccination of the aforementioned categories. As regards safety in lactating women, the Academy of Breastfeeding Medicine states as follows: 'During lactation, it is unlikely that the vaccine lipid would enter the blood stream and reach breast tissue. If it does, it is even less likely that either the intact nanoparticle or mRNA transfer into milk. In the unlikely event that mRNA is present in milk, it would be expected to be digested by the child and would be unlikely to have any biological effects.' In conclusion, mRNA vaccines do not seem to be linked to any adverse outcomes in newborns, even if this represents an issue that has to be definitely proven in the trials in progress. According to the reported articles, vertical-transmitted immunity is demonstrated, and it seems that the sooner vaccination is performed more efficient it is. However, a more careful definition of its characteristic has to be given in order to identify a specific timeline for COVID-19 vaccination during pregnancy.

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