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The association between coronavirus disease 2019 vaccination during pregnancy and neonatal health outcomes

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ABSTRACT

Importance: Pregnant women have a higher risk of severe illness or complications due to a severe acute respiratory syndrome coronavirus 2 infection. To reduce these risks, pregnant women are advised to coronavirus disease 2019 (COVID-19) vaccination. Continued monitoring of the safety of maternal COVID-19 vaccination remains important.

Objective: To evaluate the association between maternal COVID-19 vaccination and neonatal health.

Methods: Data from the Dutch Pregnancy Drug Register were used. In this prospective cohort study, pregnant women self-reported COVID-19 vaccination and neonatal health outcomes. We included women with a due date between January 15, 2021, and May 15, 2022, and a singleton live birth after at least 24 weeks gestation. Using log-binomial regression analysis we studied the association between COVID-19 vaccination during pregnancy and the health outcomes; small for gestational age (SGA), large for gestational age (LGA), and neonatal health problems. We corrected for potential confounders using inverse probability of treatment weighting.

Results: In total, 3655 participants were included (92.1% COVID-19 vaccinated during pregnancy). Of all participants, 8.9% reported SGA, 11.1% reported LGA, and 16.4% reported neonatal health problems. Maternal COVID-19 vaccination was not statistically significantly associated with SGA (adjusted prevalence ratio [aPR]: 0.90; 95% confidence interval [CI]: 0.59–1.36), LGA (aPR: 1.07; 95% CI: 0.70–1.63), or neonatal health problems (aPR: 0.84; 95% CI: 0.63–1.11).

Interpretation: This study indicates that COVID-19 vaccination during pregnancy is not associated with self-reported adverse neonatal health outcomes. These findings contribute to the growing body of evidence on the safety of COVID-19 vaccination during pregnancy.

KEYWORDS

COVID-19, Cohort, Large for gestational age, Pregnancy, Small for gestational age, Vaccination

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INTRODUCTION

Even though coronavirus disease 2019 (COVID-19) is no longer defined as a pandemic, still many infections take place worldwide.[1] The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend COVID-19 vaccination to protect those at the highest risk of severe illness or complications due to an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pregnant women belong to one of these high-risk groups.[2,3] Pregnant women have a higher risk of maternal mortality and morbidity, and neonatal morbidity after an infection with SARS-CoV-2.[4] These health risks can be reduced by COVID-19 vaccination.[5,6] So far, previous studies have not found safety concerns about COVID-19 vaccination during pregnancy with respect to reactogenicity and pregnancy and infant-related outcomes.[5,7–11] However, since the WHO and CDC recommend routinely COVID-19 vaccination during pregnancy,[2,3] continued vaccine safety evaluation remains imperative to ensure its safety and to retain confidence in maternal vaccination.[12,13]

In the Netherlands, we previously studied the safety of COVID-19 vaccination during pregnancy with respect to reactogenicity,[8] miscarriage,[9] preterm delivery,[10] and major congenital malformations in the offspring.[11] In these studies we supported the growing body of evidence regarding the safety of COVID-19 vaccination during pregnancy. However, the risk of adverse neonatal health outcomes after a COVID-19 vaccination during pregnancy has not been studied in the Dutch setting before. Since confidence in vaccine safety is an important predictor for vaccination intention during pregnancy, knowledge about the potential risks and safety after maternal COVID-19 vaccination regarding neonatal health, can help with informed decision-making.[14,15]

In the current paper, we studied the association between COVID-19 vaccination during pregnancy and neonatal health outcomes; small for gestational age (SGA) at birth, large for gestational age (LGA) at birth, and neonatal health problems, using data from the Dutch Pregnancy Drug Register.

METHODS

Ethical approval

The Medical Ethical Committee Brabant judged in 2022 that the Dutch Pregnancy Drug Register does not require specific ethical approval since it collects data by means of questionnaires only (protocol number NW2022-41). All procedures performed were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants digitally provided informed consent.

Study design

The Dutch Pregnancy Drug Register is an ongoing cohort study that monitors the safety of drug exposure during pregnancy and breastfeeding. Inclusion criteria are being pregnant, an age of at least 18 years, and proficiency in the Dutch language. Pregnant women can participate in the registry independent of medication use or vaccination. Participants self-report their data. They receive a maximum of six online questionnaires; two or three during pregnancy (depending on the gestational age at enrolment) and three postpartum. The questionnaires contain questions about general health, lifestyle, drug exposure, vaccination, course of pregnancy, childbirth, and child health. Details about the study design, including all topics questioned over the course of all questionnaires, have been described previously.[16]

Study population

For the current research question, we included participants with an estimated date of delivery (EDD) between January 15, 2021, and May 15, 2022, to ensure everybody had the same chance of delivery and to complete the first postpartum questionnaire by the end of August 2022, the moment of data extraction. In this way, we prevented disproportionate numbers of preterm births. We included pregnancies that ended in a singleton live birth after 24 weeks gestation. The EDD was used to calculate the start of pregnancy and gestational age. Participants with an unknown COVID-19 vaccination status, an unknown timing of vaccination, or missing outcome data were excluded.

Exposure definitions

A participant was considered exposed during pregnancy if she reported at least one COVID-19 vaccination (of any brand) between conception (gestational week 2^{+0}) and the end of pregnancy. The timing of vaccination could be reported as a date or as a gestational week. If a participant exclusively reported receiving COVID-19 vaccinations before conception or after delivery, or no COVID-19 vaccination at all, she was considered unexposed. The questions used to define the exposures are listed in Table S1.

Outcome definitions

We included the neonatal health outcomes; SGA at birth, LGA at birth, and neonatal health problems. All outcomes were self-reported by the participant in the first postpartum questionnaire. The questions used to define the outcomes are listed in Table S1.

SGA and LGA

Participants reported the date of birth, sex, and birth weight of their child. This information was used to define SGA and LGA at birth based on the Dutch reference norms,[17] taking into account gestational age in days and sex of the child. SGA was defined as a birthweight below the 10th percentile values and LGA was defined as a birthweight above the 90th percentile values.

Neonatal health problems

Participants were asked if their child had one or more predefined health problems shortly after birth. Due to power considerations, these health problems were constructed into a composite outcome of neonatal health problems. Neonates were classified as having neonatal health problems if at least one of the following problems occurring shortly after birth were reported by the participant: problems with breathing; problems with glucose levels; low muscle tone; high muscle tension; infant jaundice requiring phototherapy; and/or (possible) infection.

Covariables

We took into account the following a-priory selected potential confounders: maternal and paternal age at EDD, maternal and paternal education level, self-perceived maternal and paternal ethnicity (taken into account because ethnic background is associated with birthweight/SGA[18]), urbanicity (based on zip code[19]), maternal pre-pregnancy Body Mass Index (BMI), parity, obstetrical history of SGA, obstetrical history of LGA, obstetrical history of preeclampsia, maternal alcohol use, smoking, and illicit drug use in the three months before or during pregnancy, pregnancy duration, gestational diabetes, gestational hypertension, preeclampsia, COVID-19 risk-group (people with chronic respiratory conditions, chronic heart disease, kidney disease, diabetes, morbid obesity [pre-pregnancy BMI $\geq$ 40], and/or immune deficiencies),[20] and maternal COVID-19 vaccination in the year prior to pregnancy. All variables were self-reported. Age, pre-pregnancy BMI, and pregnancy duration were included as continuous variables, all other variables were categorized. Definitions are presented in Table 1.

Statistical analyses

We described the characteristics of the study population using the mean with standard deviation (SD) for continuous variables and using numbers with percentages for categorical variables. We handled missing values for covariables with multiple imputation (five imputation sets and 20 iterations) using the MICE R package.[21]

The prevalence of the neonatal health outcomes and Wilson score 95% confidence interval (CI) was calculated by COVID-19 vaccination status. To study the association between COVID-19 vaccination during pregnancy and the different outcomes measures, we used log-binomial regression analyses where we compared participants who were vaccinated against COVID-19 during pregnancy with the control group of participants who were not vaccinated against COVID-19 during pregnancy. Log-binomial regression was used to calculate the prevalence ratio (PR). First, we estimated the crude association of COVID-19 vaccination with each of the selected outcomes. Second, we corrected for potential confounding using inverse probability of treatment weighting (IPTW) based on propensity scores.[22] Propensity scores were calculated using logistic regression analyses with COVID-19 vaccination status during pregnancy as an outcome and the potential confounders described above as independent variables. Balance after IPTW was assessed using the standardized mean differences (SMD) with an adequate balance criteria of SMD < 0.1. All variables had adequate balance after IPTW (Table S2).

We performed multiple sensitivity analyses to study the robustness of our findings. In the first sensitivity analysis, we excluded preterm deliveries (<37 weeks gestational age) since this is associated with adverse neonatal health outcomes. In the second sensitivity analysis, we excluded participants who experienced a SARS-CoV-2 infection during pregnancy to overcome the potential impact of a SARS-CoV-2 infection on the outcome measures. In the third sensitivity analysis, we only included 3rd-trimester vaccinations in the exposed group to explore the possible impact of a COVID-19 vaccination on neonatal health outcomes when given more closely before birth. In the fourth sensitivity analysis, we only included the mRNA-based vaccines from BioNTech/Pfizer or Moderna, because of the guideline to administer an mRNA-based vaccine during pregnancy. In the fifth and last sensitivity analyses, we took into account a 2-week and a 4-week lag time in the exposure definition, since SGA and LGA do not develop in a few days. Meaning that a COVID-19 vaccination given within 2 or 4 weeks before delivery was defined as unexposed during pregnancy. For all sensitivity analyses, propensity scores and weights were recalculated and checked for balance using the SMD.

All analyses were performed in R version 4.1.3 (R Foundation for Statistical Computing, www.R-project.org) with a statistical significance level of $P < 0.05$.

RESULTS

Study population

There were 3844 participants in the Dutch Pregnancy Drug Register with an EDD between January 15, 2021, and May 15, 2022, and a singleton live birth after at least 24 weeks

gestation (Figure 1). We excluded four participants because of an unknown COVID-19 vaccination status, 98 participants because of an unknown timing of the COVID-19 vaccination, and 87 participants with missing outcome data, leaving 3655 participants eligible for the analyses. The vast majority of the participants reported to be vaccinated during pregnancy (n = 3365; 92.1%). Most participants received the vaccine Comirnaty from BioNTech/Pfizer (n = 2745, 81.6%), followed by Spikevax from Moderna (n = 523, 15.5%), Vaxzevria from AstraZeneca (n = 56, 1.7%), and Jcovden from Janssen (n = 8, 0.2%). For 33 participants (1.0%) the COVID-19 vaccine brand was unknown. Characteristics of the study population are presented in Table 1.

Neonatal health outcomes

Overall, 8.9% of the participants reported SGA at birth, 11.1% reported LGA at birth, and 16.4% reported neonatal health problems. The prevalence of the outcomes by COVID-19 vaccination status is presented in Figure 2. We did not observe a statistically significant association between COVID-19 vaccination during pregnancy and SGA at birth (adjusted PR [aPR]: 0.90; 95% CI: 0.59–1.36), LGA at birth (aPR: 1.07; 95% CI: 0.70–1.63), or neonatal health problems (aPR: 0.84; 95% CI: 0.63–1.11) (Table 2).

Sensitivity analyses

For the sensitivity analyses, we excluded 156 participants when excluding preterm deliveries, 417 when excluding participants with a SARS-CoV-2 infection during pregnancy, 2400 when only including 3rd-trimester vaccinations as exposed, and 97 when only including mRNA-based vaccines. In the sensitivity analyses using an exposure definition with a 2-week lag time, 3302 (90.3%) participants were defined as COVID-19 vaccinated. In the sensitivity analyses using an exposure definition with a 4-week lag time, 3203 (87.6%) participants were defined as COVID-19 vaccinated. The sensitivity analyses showed no statistically significant associations between COVID-19 vaccination and any of the outcome variables (Table 3). Compared to the main analyses, the aPR for SGA at birth was somewhat higher in the sensitivity analysis excluding preterm deliveries (aPR: 1.06; 95% CI: 0.70–1.61) and in the sensitivity analysis excluding participants with a SARS-CoV-2 infection during pregnancy (aPR: 1.03; 95% CI: 0.66–1.61). The results of the other sensitivity analyses were comparable to the main analyses.

DISCUSSION

This study shows that COVID-19 vaccination during pregnancy was not statistically significantly associated with self-reported health outcomes SGA at birth, LGA at birth, and neonatal health problems. Multiple sensitivity analyses (exclusion of preterm deliveries, excluding participants with a SARS-CoV-2 infection, only including 3rd-trimester vaccinations as exposed, only including mRNA-based vaccines, including a 2-week lag time in the exposure definition, and including a 4-week lag time in the exposure definition) did not change this result.

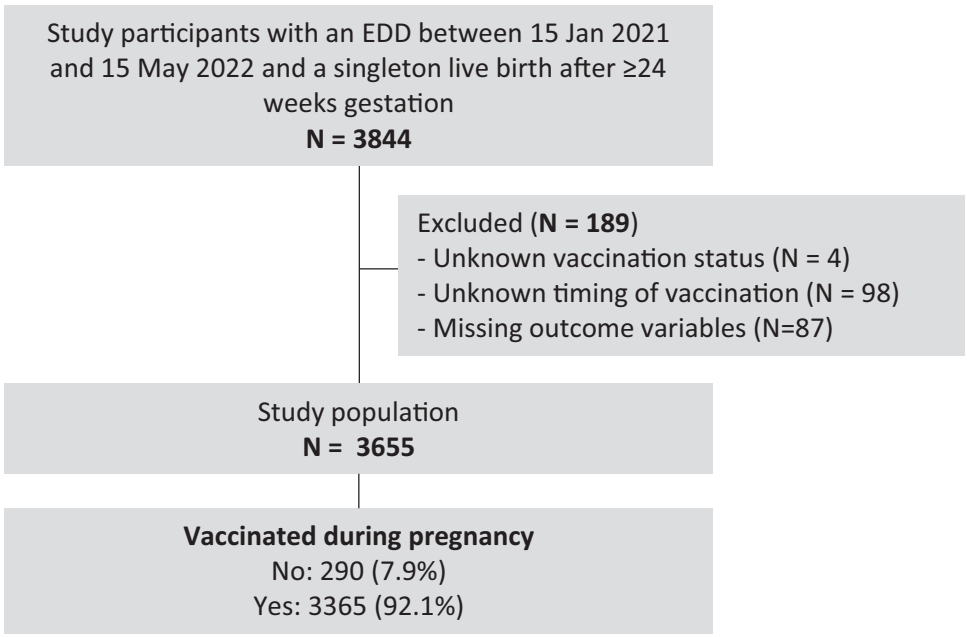

FIGURE 1 Flowchart of the study population. EDD, estimated date of delivery.

TABLE 1 Characteristics of the study population

Variables	Not vaccinated[a] ($n = 290$)	Vaccinated[a] ($n = 3365$)	*P*-value
Maternal age at EDD (years)	32.2 ± 3.9	33.2 ± 3.6	<0.01
Paternal age at EDD (years)	34.2 ± 5.0	35.4 ± 4.8	<0.01
Maternal education level[b]			<0.01
High/intermediate	227 (78.3)	2995 (89.0)	
Low	62 (21.4)	344 (10.2)	
Paternal education level			<0.01
High/intermediate	172 (59.3)	2564 (76.2)	
Low	108 (37.2)	680 (20.2)	
Maternal self-perceived ethnicity			0.71
Dutch	266 (91.7)	3048 (90.6)	
Non-Dutch	23 (7.9)	294 (8.7)	
Paternal self-perceived ethnicity			0.56
Dutch	251 (86.6)	2941 (87.4)	
Non-Dutch	32 (11.0)	328 (9.7)	
Urbanity[c]			<0.01
Very high	60 (20.7)	952 (28.3)	
High	63 (21.7)	876 (26.0)	
Moderately high	64 (22.1)	576 (17.1)	
Low	62 (21.4)	532 (15.8)	
Very low	40 (13.8)	393 (11.7)	
Maternal pre-pregnancy BMI (kg/m^2)	24.1 ± 5.0	24.1 ± 4.4	0.91
Parity			0.88
Nullipara	159 (54.8)	1805 (53.6)	
Multipara	131 (45.2)	1526 (45.3)	
History of SGA			0.10
Nullipara	159 (54.8)	1805 (53.6)	
No history of SGA	109 (37.6)	1363 (40.5)	
History of SGA	22 (7.6)	163 (4.8)	
History of LGA			0.92
Nullipara	159 (54.8)	1805 (53.6)	
No history of LGA	124 (42.8)	1455 (43.2)	
History of LGA	7 (2.4)	71 (2.1)	
History of preeclampsia			0.14
Nullipara	159 (54.8)	1805 (53.6)	
No	121 (41.7)	1477 (43.9)	
Yes	10 (3.4)	61 (1.8)	
Alcohol use			0.05
No alcohol in the 3m before pregnancy	85 (29.3)	773 (23.0)	
Stopped before conception	155 (53.4)	1978 (58.8)	
Stopped at a positive pregnancy test	35 (12.1)	469 (13.9)	
Continued alcohol during pregnancy	13 (4.5)	108 (3.2)	
Smoking behaviour			<0.01
No smoking in the 3 m before pregnancy	258 (89.0)	3110 (92.4)	

(Continues)

TABLE 1 (Continued)

Variables	Not vaccinated[a] ($n = 290$)	Vaccinated[a] ($n = 3365$)	*P*-value
Stopped before conception	20 (6.9)	140 (4.2)	
Stopped at a positive pregnancy test	4 (1.4)	54 (1.6)	
Continued smoking during pregnancy	7 (2.4)	28 (0.8)	
Any illicit drug use[d]			0.33
No	279 (96.2)	3248 (96.5)	
Yes	11 (3.8)	88 (2.6)	
Pregnancy duration (weeks)	39.2 ± 1.7	39.3 ± 1.5	0.17
Preterm delivery			0.12
No	272 (93.8)	3227 (95.9)	
Yes	18 (6.2)	138 (4.1)	
Mode of delivery			0.91
Vaginal delivery	242 (83.4)	2837 (84.3)	
Cesarean section	42 (14.5)	475 (14.1)	
Gestational diabetes			0.60
No	274 (94.5)	3126 (92.9)	
Yes	16 (5.5)	217 (6.4)	
Gestational hypertension			0.40
No	256 (88.3)	3009 (89.4)	
Yes	34 (11.7)	334 (9.9)	
Preeclampsia			0.60
No	284 (97.9)	3250 (96.6)	
Yes	6 (2.1)	93 (2.8)	
COVID-19 risk-group[e]			0.77
No	246 (84.8)	2808 (83.4)	
Yes	44 (15.2)	535 (15.9)	
≥1 COVID-19 vaccination in the year prior to pregnancy			0.46
No	241 (83.1)	2901 (86.2)	
Yes	44 (15.2)	459 (13.6)	
SARS-CoV-2 infection during pregnancy			<0.01
No	216 (74.5)	2710 (80.5)	
Yes	55 (19.0)	362 (10.8)	

The data were shown as mean ± standard deviation or *n* (%). Missing values: maternal age ($n = 22$, 0.6%), paternal age ($n = 141$, 3.9%), maternal education level ($n = 27$, 0.7%), paternal education level ($n = 131$, 3.6%), maternal self-perceived ethnicity ($n = 24$, 0.7%), paternal self-perceived ethnicity ($n = 103$, 2.8%), urbanicity ($n = 37$, 1.0%), maternal pre-pregnancy BMI ($n = 188$, 5.1%), parity ($n = 34$, 0.9%), history of SGA ($n = 34$, 0.9%), history of LGA ($n = 34$, 0.9%), history of preeclampsia ($n = 22$, 0.6%), alcohol use ($n = 49$, 1.1%), smoking behaviour ($n = 34$, 0.9%), any illicit drug use ($n = 28$, 0.8%), mode of delivery ($n = 59$, 1.6%), gestational diabetes ($n = 22$, 0.6%), gestational hypertension ($n = 22$, 0.6%), preeclampsia ($n = 22$, 0.6%), COVID-19 risk-group ($n = 22$, 0.6%), COVID-19 vaccination prior to pregnancy ($n = 10$, 0.3%), and SARS-CoV-2 infection during pregnancy ($n = 312$, 8.5%).

[a]COVID-19 vaccination during pregnancy (between gestational age 2^{+0} weeks and delivery).

[b]High/intermediate included secondary vocational education, school of higher general secondary education, pre-university education, university of applied sciences, and university. Low included all other levels of education.

[c]Based on ZIP code.

[d]In the 3 months before or during pregnancy.

[e]People with chronic respiratory conditions, chronic heart disease, kidney disease, diabetes mellitus, morbid obesity (pre-pregnancy BMI ≥40), or immune deficiencies.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; EDD, estimated date of delivery; LGA, large for gestational age; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age.

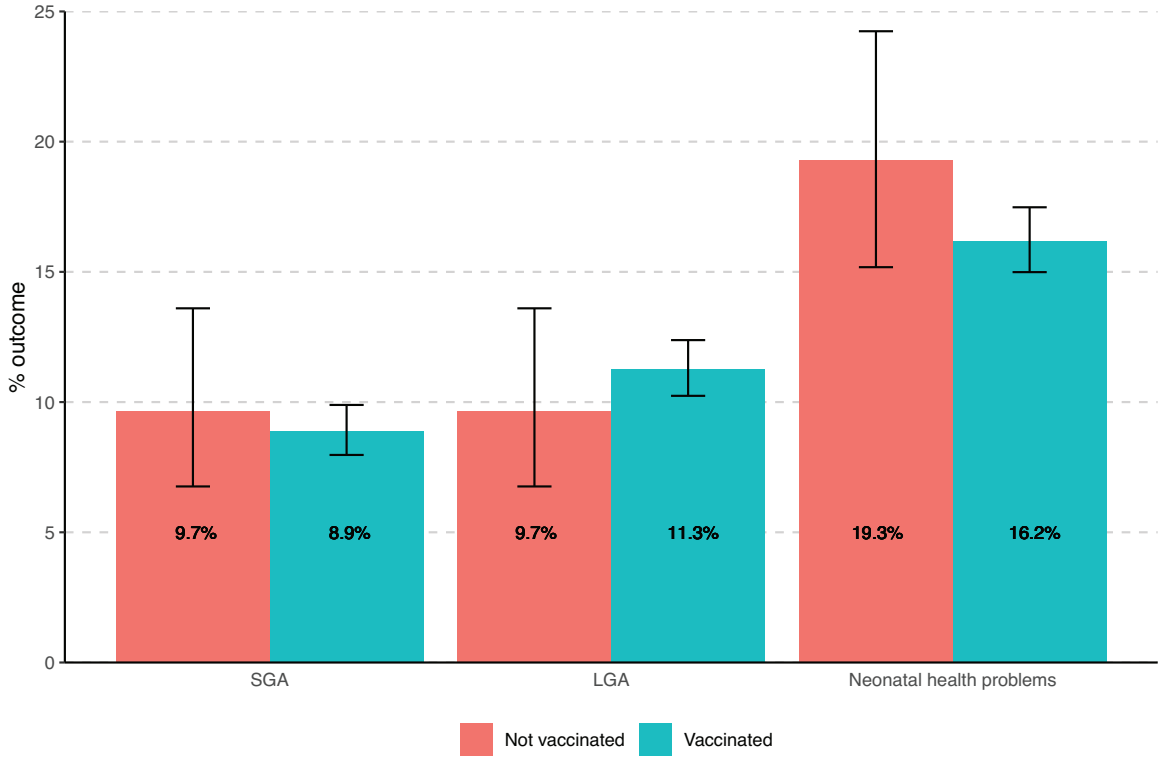

FIGURE 2 Prevalence of SGA at birth, LGA at birth, and neonatal health problems, by COVID-19 vaccination status during pregnancy. SGA: <10th percentile birthweights. LGA: >90th percentile birthweights. Neonatal health problems included: problems with breathing; problems with glucose levels; low muscle tone; high muscle tension; infant jaundice requiring phototherapy; and/or (possible) infection. COVID-19, coronavirus disease 2019; LGA, large for gestational age; SGA, small for gestational age.

TABLE 2 Results of the log-binomial regression analyses studying the association between COVID-19 vaccination during pregnancy and different neonatal health outcomes

			PR (95% CI)	
Outcome[a]	**Not vaccinated (n = 284)[b]**	**Vaccinated (n = 3311)[b]**	**Crude**	**Adjusted[c]**
SGA	28	298	0.91 (0.65–1.35)	0.90 (0.59–1.36)
LGA	28	369	1.13 (0.80–1.67)	1.07 (0.70–1.63)
Neonatal health problems	56	535	0.82 (0.65–1.06)	0.84 (0.63–1.11)

Participants with missing data for one of the confounders after multiple imputations were excluded from the analyses.
[a]SGA: <10th percentile birthweights. LGA: >90th percentile birthweights. Neonatal health problems included problems with breathing, problems with glucose levels, low muscle tone, high muscle tension, infant jaundice requiring phototherapy, and/or (possible) infection.
[b]COVID-19 vaccination during pregnancy (between gestational age 2^{+0} weeks and delivery).
[c]Variables that were taken into account in the IPTW were: maternal and paternal age at estimated date of delivery, maternal and paternal education level, self-perceived maternal and paternal ethnicity, urbanicity, maternal pre-pregnancy body mass index, parity, history of SGA, history of LGA, history of preeclampsia, alcohol use, smoking behavior, any illicit drug use, pregnancy duration, gestational diabetes, gestational hypertension, preeclampsia, COVID-19 risk-group, and COVID-19 vaccination in the year prior to pregnancy.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; LGA, large for gestational age; PR, prevalence ratio; SGA, small for gestational age.

We used a well-defined study population with both COVID-19 vaccinated and COVID-19 unvaccinated participants and various potential confounders to correct for. We performed multiple sensitivity analyses to assess the robustness of our findings. However, we do acknowledge some limitations. First, we used self-reported data for all variables which is prone to recall bias and might have led to misclassification. If women who were COVID-19 vaccinated during pregnancy were more likely to recall or report negative neonatal health outcomes, we could

TABLE 3 Results of the sensitivity analyses[a]

	Excluding preterm deliveries	Excluding participants with a SARS-CoV-2 infection	Only including 3rd-trimester vaccination	Only including mRNA-based vaccines	Including a lag time of 2 weeks	Including a lag time of 4 weeks
Outcome[b]	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)
SGA	1.06 (0.70–1.61)	1.03 (0.66–1.61)	0.87 (0.57–1.32)	0.90 (0.59–1.36)	0.89 (0.61–1.30)	0.91 (0.66–1.25)
LGA	1.05 (0.73–1.51)	1.05 (0.70–1.55)	1.07 (0.71–1.62)	1.05 (0.69–1.61)	1.12 (0.78–1.61)	1.07 (0.79–1.46)
Neonatal health problems	0.84 (0.63–1.12)	0.80 (0.61–1.05)	0.82 (0.62–1.09)	0.84 (0.63–1.11)	0.89 (0.69–1.14)	0.89 (0.71–1.11)

Participants with missing data for one of the confounders after multiple imputations were excluded from the analyses.
Exposure was defined as at least one COVID-19 vaccination during pregnancy (between gestational age 2^{+0} weeks and delivery).
[a]Analyses were adjusted for possible confounders using inverse probability of treatment weighting. Possible confounders that were taken into account were: maternal and paternal age at estimated date of delivery, maternal and paternal education level, self-perceived maternal and paternal ethnicity, urbanicity, maternal pre-pregnancy Body Mass Index, parity, history of SGA, history of LGA, history of preeclampsia, alcohol use, smoking behavior, any illicit drug use, pregnancy duration, gestational diabetes, gestational hypertension, preeclampsia, COVID-19 risk-group, COVID-19 vaccination in the year prior to pregnancy.
[b]SGA: <10th percentile birthweights. LGA: >90th percentile birthweights. Neonatal health problems included problems with breathing, problems with glucose levels, low muscle tone, high muscle tension, infant jaundice requiring phototherapy, and/or (possible) infection.
Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; LGA, large for gestational age; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age.

have overestimated the effect of COVID-19 vaccination. We expect limited misclassification for the outcomes SGA and LGA at birth, as these outcomes are based on birthweight which is not susceptible to interpretation. For the outcome of neonatal health problems, we did not take clinical importance into account and the problems were solely based on the interpretation of the participant. However, previous literature shows that perinatal outcomes reported by participants through online questionnaires are very comparable to obstetric records.[23] Second, the vast majority of our study population was COVID-19 vaccinated during pregnancy (92.1%), resulting in a small unvaccinated control group and impacting the power of our study. For many participants, the COVID-19 vaccination was the motivation to participate in our cohort, explaining the high vaccination coverage compared to the estimated ± 50% for the general Dutch pregnant population during the study period.[24] Last, the generalizability of our results is debatable since our study population is not representative of all pregnant women in the Netherlands. For example, our study population is more often highly educated and perceived their ethnicity as Dutch.[16] We corrected for various potential confounders to limit potential bias.

Our results are in line with previous research where maternal COVID-19 vaccination did not lead to an increased risk on the outcomes SGA at birth or birthweight.[5,25–27] However, most studies did not include a lag time in the exposure definition of COVID-19 vaccination, possibly leading to biased results since SGA does not develop acutely.[26–29] The analyses by Fell et al.[30,31] and the sensitivity analyses by Magnus et al.[32] did include a 2-week lag time. In these large population-based studies, no association was found between COVID-19 vaccination and SGA. There are only a few studies focusing on the outcome of LGA at birth. The study by Rottenstreich et al.[33] found no statistically significant difference in the LGA rate between COVID-19 vaccinated and unvaccinated individuals in univariable analyses. In the study by Norman et al.,[34] the percentage of LGA was more or less comparable between COVID-19 vaccinated and unvaccinated individuals, but this was not tested. Because mRNA-based COVID-19 vaccines do not seem to pass or affect the placenta,[35,36] an effect on fetal growth problems resulting in SGA or LGA is not expected. Altogether, the results strengthen the hypothesis that COVID-19 vaccination during pregnancy does not increase the risk of SGA and LGA at birth.

To define neonatal health problems we used a composite outcome, which makes a direct comparison to the literature difficult. A meta-analysis showed no association between COVID-19 vaccination during pregnancy and the adverse neonatal outcome of newborn respiratory complications.[25] Previous research also found no association between COVID-19 vaccination during pregnancy and other outcomes, like jaundice, the need for mechanical ventilation, or hypoglycemia.[33] In our main analyses we included COVID-19 vaccinations at any time during pregnancy, to explore all possible mechanisms of COVID-19

vaccination during pregnancy and the effect on the outcomes. For neonatal health problems, there might be a short-term effect of the COVID-19 vaccination, for example owing to the reactogenicity of the vaccination[37,38] If this is the case, this short-term effect might be masked when analyzing a COVID-19 vaccination at any time during pregnancy. Our sensitivity analysis including only 3rd-trimester vaccinations as exposed found no association between COVID-19 vaccination and neonatal health problems, indicating there is no short-term effect of the vaccination.

Adverse neonatal health outcomes are associated with increased morbidity and mortality and are risk factors for short-term as well as long-term health problems. For example, children born SGA or LGA have a higher chance of neonatal metabolic complications including hypoglycemia, and are more prone to develop cardiovascular disease, obesity, and diabetes mellitus later in life.[39–42] The absence of an association between maternal COVID-19 vaccination and adverse neonatal health outcomes is reassuring for vaccine safety. Our results could help in the informed decision-making regarding COVID-19 vaccination during pregnancy. Future studies should focus on the potential association between COVID-19 vaccination during pregnancy and possible long-term health outcomes for the children.

In conclusion, there was no association between COVID-19 vaccination during pregnancy and the self-reported neonatal health outcomes SGA at birth, LGA at birth, and neonatal health problems. The findings contribute to the growing body of evidence on the safety of the COVID-19 vaccination during pregnancy on neonatal health outcomes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. World Health Organization (WHO). WHO COVID-19 Dashboard. Accessed March 20, 2024. https://data.who.int/dashboards/covid19/cases
2. World Health Organization (WHO). COVID-19 Advice for the Public: Getting Vaccinated 2023. Accessed January 17, 2024. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice
3. Centers for Disease Control and Prevention (CDC). COVID-19 Vaccines While Pregnant or Breastfeeding 2023. Accessed January 17, 2024. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html
4. Smith ER, Oakley E, Grandner GW, Ferguson K, Farooq F, Afshar Y, et al. Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: an individual participant data meta-analysis. *BMJ Glob Health.* 2023;8:e009495. DOI: 10.1136/bmjgh-2022-009495
5. Prasad S, Kalafat E, Blakeway H, Townsend R, O'Brien P, Morris E, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. *Nat Commun.* 2022;13:2414. DOI: 10.1038/s41467-022-30052-w
6. Carlsen EØ, Magnus MC, Oakley L, Fell DB, Greve-Isdahl M, Kinge JM, et al. Association of COVID-19 vaccination during pregnancy with incidence of SARS-CoV-2 infection in infants. *JAMA Intern Med.* 2022;182:825-831. DOI: 10.1001/jamainternmed.2022.2442
7. Fleming-Dutra KE, Zauche LH, Roper LE, Ellington SR, Olson CK, Sharma AJ, et al. Safety and effectiveness of maternal COVID-19 vaccines among pregnant people and infants. *Obstet Gynecol Clin North Am.* 2023;50:279-297. DOI: 10.1016/j.ogc.2023.02.003
8. Woestenberg PJ, Litjens CHC, Vissers LCM, Kant A, Berrens M, Vorstenbosch S. Self-reported maternal adverse events of COVID-19 vaccination during pregnancy (in Dutch). *Ned Tijdschr Geneeskd.* 2022;166:D6831.
9. de Feijter M, van Gelder M, Vissers LCM, Kant AC, Woestenberg PJ. The risk of miscarriage after COVID-19 vaccination before and during pregnancy. *Pharmacoepidemiol Drug Saf.* 2024;33:e5724. DOI: 10.1002/pds.5724
10. de Feijter M, Vissers LCM, Davidson L, Kant AC, Woestenberg PJ. The risk of preterm labor after COVID-19 vaccination before and during pregnancy. *Front Drug Saf Regul.* 2023;3:1235051. DOI: 10.3389/fdsfr.2023.1235051
11. Woestenberg PJ, de Feijter M, Bergman JEH, Lutke LR, Passier A, Kant AC. Maternal first trimester COVID-19 vaccination and risk of major non-genetic congenital anomalies. *Birth Defects Res.* 2023;115:1746-1757. DOI: 10.1002/bdr2.2251
12. Razai MS, Mansour R, Goldsmith L, Freeman S, Mason-Apps C, Ravindran P, et al. Interventions to increase vaccination against COVID-19, influenza and pertussis during pregnancy: a systematic review and meta-analysis. *J Travel Med.* 2023;30:taad138. DOI: 10.1093/jtm/taad138
13. Etti M, Calvert A, Galiza E, Lim S, Khalil A, Le Doare K, et al. Maternal vaccination: a review of current evidence and recommendations. *Am J Obstet Gynecol.* 2022;226:459-474. DOI: 10.1016/j.ajog.2021.10.041
14. Sarantaki A, Kalogeropoulou VE, Taskou C, Nanou C, Lykeridou A. COVID-19 vaccination and related determinants of hesitancy among pregnant women: a systematic review and meta-analysis. *Vaccines (Basel).* 2022;10:2055. DOI: 10.3390/vaccines10122055
15. Lutz CS, Carr W, Cohn A, Rodriguez L. Understanding barriers and predictors of maternal immunization: identify-

ing gaps through an exploratory literature review. *Vaccine.* 2018;36:7445-7455. DOI: 10.1016/j.vaccine.2018.10.046
16. Vorstenbosch S, Te Winkel B, van Gelder MMHJ, Kant A, Roeleveld N, van Puijenbroek E. Aim and design of pREGnant, the Dutch Pregnancy Drug Register. *Drug Saf.* 2019;42:1-12. DOI: 10.1007/s40264-018-0722-7
17. Perined. Perined Hoftiezer geboortegewichtcurven. in: *Perined Hoftiezer Reference Birth Weights*. Accessed September 1, 2022. https://www.perined.nl/geboortegewichtcurven
18. McCowan L, Horgan RP. Risk factors for small for gestational age infants. *Best Pract Res Clin Obstet Gynaecol.* 2009;23:779-793. DOI: 10.1016/j.bpobgyn.2009.06.003
19. Centraal Bureau voor de Statistiek [Statistics Netherlands] (CBS). *Kerncijfers per Postcode*. 2021. Accessed September 1, 2022. https://www.cbs.nl/nl-nl/dossier/nederland-regionaal/geografische-data/gegevens-per-postcode
20. Nederlandse Vereniging voor Obstetrie & Gynaecologie (NVOG). Vaccination against COVID-19 regarding child with pregnancy and maternity 6 January 2022. Accessed September 1, 2022. https://www.nvog.nl/update-standpunt-vaccinatie-tegen-covid-19-rondom-zwangerschap-en-kraambed-2/
21. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Statis Software.* 2011;45:1-67. DOI: 10.18637/jss.v045.i03
22. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46:399-424. DOI: 10.1080/00273171.2011.568786
23. van Gelder M, Vorstenbosch S, Derks L, Te Winkel B, van Puijenbroek EP, Roeleveld N. Web-based questionnaires to assess perinatal outcome proved to be valid. *J Clin Epidemiol.* 2017;90:136-143. DOI: 10.1016/j.jclinepi.2017.07.004
24. Nederlandse vereniging obstetrie en gynaecologie (NVOG). Answers to 23 questions about pregnancy/fertility and corona vaccination. 2022. Accessed September 1, 2022. https://www.nvog.nl/vragen-en-antwoorden-van-de-livestream-over-zwangerschap-en-coronavaccinatie-12-01-2022/
25. Shafiee A, Kohandel Gargari O, Teymouri Athar MM, Fathi H, Ghaemi M, Mozhgani SH. COVID-19 vaccination during pregnancy: a systematic review and meta-analysis. *BMC Pregnancy Childbirth.* 2023;23:45. DOI: 10.1186/s12884-023-05374-2
26. Blakeway H, Prasad S, Kalafat E, Heath PT, Ladhani SN, Le Doare K, et al. COVID-19 vaccination during pregnancy: coverage and safety. *Am J Obstet Gynecol.* 2022;226:236.e1-236.e14. DOI: 10.1016/j.ajog.2021.08.007
27. Peretz-Machluf R, Hirsh-Yechezkel G, Zaslavsky-Paltiel I, Farhi A, Avisar N, Lerner-Geva L, et al. Obstetric and neonatal outcomes following COVID-19 vaccination in pregnancy. *J Clin Med.* 2022;11:2540. DOI: 10.3390/jcm11092540
28. Lipkind HS, Vazquez-Benitez G, DeSilva M, Vesco KK, Ackerman-Banks C, Zhu J, et al. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at Birth - eight integrated health care organizations, United States, December 15, 2020-July 22, 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71:26-30. DOI: 10.15585/mmwr.mm7101e1
29. Goldshtein I, Steinberg DM, Kuint J, Chodick G, Segal Y, Shapiro Ben David S, et al. Association of BNT162b2 COVID-19 vaccination during pregnancy with neonatal and early infant outcomes. *JAMA Pediatr.* 2022;176:470-477. DOI: 10.1001/jamapediatrics.2022.0001
30. Fell DB, Dimanlig-Cruz S, Regan AK, Håberg SE, Gravel CA, Oakley L, et al. Risk of preterm birth, small for gestational age at birth, and stillbirth after covid-19 vaccination during pregnancy: population based retrospective cohort study. *BMJ.* 2022;378:e071416. DOI: 10.1136/bmj-2022-071416
31. Fell DB, Dimanlig-Cruz S, Török E, Håberg SE, Regan AK, Kaufman JS, et al. Pregnancy, fetal, and neonatal outcomes after a first booster dose of covid-19 vaccine during pregnancy in Ontario, Canada: population based, retrospective cohort study. *BMJ Med.* 2023;2:e000632. DOI: 10.1136/bmjmed-2023-000632
32. Magnus MC, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, Oakley L, et al. Association of SARS-CoV-2 vaccination during pregnancy with pregnancy outcomes. *JAMA.* 2022;327:1469-1477. DOI: 10.1001/jama.2022.3271
33. Rottenstreich M, Sela HY, Rotem R, Kadish E, Wiener-Well Y, Grisaru-Granovsky S. COVID-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study. *BJOG.* 2022;129:248-255. DOI: 10.1111/1471-0528.16941
34. Norman M, Magnus MC, Söderling J, Juliusson PB, Navér L, Örtqvist AK, et al. Neonatal outcomes after COVID-19 vaccination in pregnancy. *JAMA.* 2024;331:396-407. DOI: 10.1001/jama.2023.26945
35. Prahl M, Golan Y, Cassidy AG, Matsui Y, Li L, Alvarenga B, et al. Evaluation of transplacental transfer of mRNA vaccine products and functional antibodies during pregnancy and infancy. *Nat Commun.* 2022;13:4422. DOI: 10.1038/s41467-022-32188-1
36. Gonzalez VJ, Li L, Buarpung S, Prahl M, Robinson JF, Gaw SL. Minimal mRNA uptake and inflammatory response to COVID-19 mRNA vaccine exposure in human placental explants. *iScience.* 2023;26:107549. DOI: 10.1016/j.isci.2023.107549
37. Rolfes L, Härmark L, Kant A, van Balveren L, Hilgersom W, van Hunsel F. COVID-19 vaccine reactogenicity - A cohort event monitoring study in the Netherlands using patient reported outcomes. *Vaccine.* 2022;40:970-976. DOI: 10.1016/j.vaccine.2022.01.013
38. DeSilva M, Haapala J, Vazquez-Benitez G, Vesco KK, Daley MF, Getahun D, et al. Evaluation of acute adverse events after COVID-19 vaccination during pregnancy. *N Engl J Med.* 2022;387:187-189. DOI: 10.1056/NEJMc2205276
39. Salam RA, Das JK, Bhutta ZA. Impact of intrauterine growth restriction on long-term health. *Curr Opin Clin Nutr Metab Care.* 2014;17:249-254. DOI: 10.1097/MCO.0000000000000051
40. Katz J, Wu LA, Mullany LC, Coles CL, Lee AC, Kozuki N, et al. Prevalence of small-for-gestational-age and its mortality risk varies by choice of birth-weight-for-gestation

reference population. *PLoS One.* 2014;9:e92074. DOI: 10.1371/journal.pone.0092074
41. Arcangeli T, Thilaganathan B, Hooper R, Khan KS, Bhide A. Neurodevelopmental delay in small babies at term: a systematic review. *Ultrasound Obstet Gynecol.* 2012;40:267-275. DOI: 10.1002/uog.11112
42. Scifres CM. Short- and long-term outcomes associated with large for gestational age birth weight. *Obstet Gynecol Clin North Am.* 2021;48:325-337. DOI: 10.1016/j.ogc.2021.02.005

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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