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Published in:
Birth Defects Research

DOI:
10.1002/bdr2.2251

Received: 12 July 2023 | Revised: 21 August 2023 | Accepted: 6 September 2023

DOI: 10.1002/bdr2.2251

Birth Defects Research | Society for Birth Defects Research & Prevention | WILEY

RESEARCH ARTICLE

Maternal first trimester COVID-19 vaccination and risk of major non-genetic congenital anomalies

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Abstract

Background: Information regarding the risk of early pregnancy COVID-19 vaccination on the development of major congenital anomalies in the offspring is still limited. Here, we study the association between any COVID-19 vaccination during the 1st trimester and at least one major non-genetic congenital anomaly in the offspring.

Methods: We used data from the Dutch Pregnancy Drug Register, an ongoing cohort study. We selected participants with a pregnancy that ended after at least 20 weeks gestation. Pregnant participants self-reported their COVID-19 vaccination status and the presence of congenital anomalies in the offspring. We used logistic regression analyses to study the association between 1st trimester COVID-19 vaccination (gestational week 2 + 0 to 12 + 6) and the risk of at least one major non-genetic congenital anomaly in the offspring. Clustering of anomalies on the ICD10 level by 1st trimester COVID-19 vaccination status was explored using Fisher exact tests.

Results: We included 3721 participants of whom 795 (21.4%) were COVID-19 vaccinated during the 1st trimester. The percentage of participants who gave birth to a child with at least one major non-genetic congenital anomaly was comparable between participants who were 1st trimester vaccinated (1.1%) and participants who were not (1.2%) (adjusted odd ratio 0.78 [95% confidence interval 0.35–1.71]). We found no clustering of major non-genetic congenital anomalies by 1st trimester COVID-19 vaccination status ($p > .05$).

Conclusions: There were no indications of an increased risk of major non-genetic congenital anomalies in the offspring after maternal 1st trimester COVID-19 vaccination. Our findings suggest COVID-19 vaccines are safe during early pregnancy.

KEYWORDS

birth defects, congenital malformations, immunization, pregnancy, prospective cohort, teratology, vaccination safety

1 | INTRODUCTION

An infection with Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) during pregnancy is associated with increased maternal mortality, maternal morbidity, and neonatal morbidity (Smith et al., 2023). These risks can be reduced by coronavirus disease 2019 (COVID-19) vaccination which has been shown to be effective against both maternal and neonatal (serious) SARS-CoV-2 infection (Beharier et al., 2021; Carlsen et al., 2022; Prasad et al., 2022).

The large scale of COVID-19 vaccination programs globally, including vaccination during pregnancy (Prabhu & Riley, 2023), underline the importance of monitoring the safety of maternal vaccination. Since pregnant individuals were generally excluded from randomized controlled trials, safety data on maternal COVID-19 vaccination is mainly based on observational studies (Smith et al., 2020). Previous research has shown no increased risk of miscarriage, preterm delivery, or other negative pregnancy outcomes (Prasad et al., 2022).

Information on a possible association between early maternal COVID-19 vaccination and the risk of major congenital anomalies is still limited (Calvert et al., 2023). The few studies that have been published, found no indications of an increased risk (Blakeway et al., 2022; Bleicher et al., 2021; Calvert et al., 2023; Favre et al., 2023; Goldshtein et al., 2022; Moro et al., 2022; Ruderman et al., 2022; Shimabukuro et al., 2021; Trostle et al., 2021). However, most previous studies had important methodological limitations. For example, these studies did not focus on 1st trimester exposure (the key risk period for most anomalies because of organ development; DeSilva et al., 2016), lacked an unvaccinated control group, or discarded relevant congenital anomalies diagnosed after birth or among terminated pregnancies (Blakeway et al., 2022; Bleicher et al., 2021; Favre et al., 2023; Goldshtein et al., 2022; Moro et al., 2022; Ruderman et al., 2022; Shimabukuro et al., 2021; Trostle et al., 2021). Because major congenital anomalies are associated with substantial burden (Hoffman, 2013; Sitkin & Farmer, 2016), it is important to ensure the safety of maternal COVID-19 vaccination on the development of anomalies in the offspring (Abu-Raya et al., 2021).

Here we study the association between maternal 1st trimester COVID-19 vaccination and the risk of a major non-genetic congenital anomaly in the offspring, using data from the Dutch Pregnancy Drug Register.

2 | METHODS

2.1 | Study design

The Dutch Pregnancy Drug Register is an ongoing cohort study with the main goal to study the safety of drug exposure during pregnancy and breastfeeding. The study design has been described in detail previously (Vorstenbosch et al., 2019). Briefly, the study started in 2014 and is still ongoing. Pregnant individuals of 18 years and older and living in the Netherlands can participate. In 5 or 6 online questionnaires (2 or 3 during pregnancy and 3 postpartum), self-reported information is gathered on general health, lifestyle, drug exposure, course of pregnancy, child birth, and child health. The study follows the principles of the 1975 Helsinki declaration and its later amendments. The Regional Committee on Research Involving Human Subjects, Arnhem-Nijmegen judged in 2013 that the Dutch Pregnancy Drug Register does not require specific ethical approval since it collects data by means of questionnaires only (protocol number 2013/259). In 2022, the Medical Ethical Committee Brabant judged this was still applicable (protocol number NW2022-41). All participants gave informed consent.

2.2 | Study population

For the current research question, we included participants with an estimated date of delivery (EDD) between 15-01-2021 and 15-05-2022 and with a pregnancy that ended after at least 20 weeks gestation (including elective terminations, fetal deaths, stillbirths, and live births). The selection of EDD was made to ensure everybody had been able to complete at least one questionnaire postpartum by the end of August 2022, which was the moment of data extraction. The EDD was based on ultrasound results and was used to calculate the start of pregnancy and gestational age at any moment in time. Exclusion criteria were: non-singleton pregnancy, unknown COVID-19 vaccination status, unknown timing of COVID-19 vaccination, use of teratogenic drugs during the drug sensitive risk period as presented in Supplement S1, missing information regarding congenital anomalies in the offspring, offspring with a genetic disorder.

2.3 | Exposure definition

We asked participants whether they were COVID-19 vaccinated during pregnancy and if yes, the timing of vaccination (as a date or gestational week). The question of receiving a COVID-19 vaccination was included in all questionnaires of The Dutch Pregnancy Drug Register. First trimester COVID-19 vaccination (exposure) was defined as at least one COVID-19 vaccination between gestational week 2 + 0 (conception) and 12 + 6, the key risk period for developing congenital anomalies (DeSilva et al., 2016). Participants who were not vaccinated during pregnancy or who received a COVID-19 vaccination

outside this risk period were defined as not vaccinated during the 1st trimester and were included as a control population.

2.4 | Outcome definition

The outcome was defined as presence of at least one major non-genetic congenital anomaly (a major congenital anomaly with no known genetic basis; hereafter "major anomaly") in the offspring. Self-reported information on congenital anomalies mentioned in the first questionnaire postpartum (within 3 months after given birth at most) were included. Reported anomalies were obtained as an answer to an open-ended question, then coded according to the International Classification of Diseases, Tenth Revision (ICD10) and, finally, classified as a major anomaly, a minor anomaly, or a genetic disorder according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) classification (European Commission, n.d.-a). If the self-reported information was ambiguous, a clinical geneticist from EUROCAT made the assessment. If afterwards it was still ambiguous whether the offspring had at least one major congenital anomaly or not, these participants were excluded. If children had a minor congenital anomaly (and no major congenital anomaly) this was defined as having no major anomaly.

2.5 | Covariables

Analyses were corrected for a-priory selected potential confounders. Variables that were taken into account were: age at EDD, age biological father at EDD, education level, education level biological father, level of urbanicity (based on zip code), congenital anomalies of either biological parents, parity, pre-pregnancy Body Mass Index (BMI), pre-pregnancy diabetes, any folic acid use in the 3 months before or during pregnancy, alcohol use in the 3 months before or during pregnancy, smoking behavior in the 3 months before or during pregnancy, any illicit drug use in the 3 months before or during pregnancy, COVID-19 vaccination in the year prior to pregnancy, pregnancy duration, and vaccination priority (people with chronic respiratory conditions, chronic heart disease, kidney disease, diabetes, morbid obesity, and immune deficiencies) (Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG), n.d.) who were strongly recommended to get vaccinated irrespective of pregnancy. All variables were self-reported and involve the pregnant participant unless stated otherwise. Age, pre-pregnancy BMI, and pregnancy duration were continuous, all other variables were categorized (Table 1).

2.6 | Data analyses

The demographics of our study population (in total and by 1st trimester COVID-19 vaccination status) were described using the mean with standard deviation (SD) for continuous variables and by numbers with percentage for categorical variables. Missing values for all confounders were handled using multiple imputation with 5 imputation sets and 20 iterations, using the MICE R package (van Buuren & Groothuis-Oudshoorn, 2011).

The percentage and Wilson score 95% confidence interval (CI) of participants who gave birth to a child with at least one major anomaly was calculated for participants vaccinated during the 1st trimester and for participants not vaccinated during the 1st trimester. We used logistic regression analyses to study the association between 1st trimester COVID-19 vaccination and the risk of at least one major anomaly in the offspring. To account for confounding, we used inverse probability of treatment weighting (IPTW) using propensity scores (Austin, 2011). Propensity scores were calculated using logistic regression analyses with 1st trimester COVID-19 vaccination status as an outcome and all potential confounders described above as independent variables. Balance after IPTW was assessed using the Standardized mean differences (SMD) with an adequate balance criteria of $SMD < 0.1$. The balance is presented in Supplement S2.

To estimate the robustness of our findings of the logistic regression analyses we performed multiple sensitivity analyses. In sensitivity analysis 1, we excluded participants who were not vaccinated during pregnancy and used only participants who were vaccinated during the 2nd or 3rd trimester in the reference group. This might be a better and more comparable control population than unvaccinated participants, since both populations opt-in for vaccination during pregnancy. In sensitivity analysis 2, we excluded participants who were vaccinated during the 2nd or 3rd trimester and used only participants who were not vaccinated during pregnancy as a reference group. In sensitivity analyses 3 and 4, we defined offspring where it was ambiguous if there was at least one major anomaly or not as no major anomaly (sensitivity analysis 3) or as major anomaly (sensitivity analysis 4). In sensitivity analysis 5 we excluded participants who reported a positive SARS-CoV-2 (self)test between gestational week $2+0$ to $19+6$ to overcome a potential impact of a SARS-CoV-2 infection on major anomalies during a broad risk period for congenital anomalies. Last, in sensitivity analyses 6, 7, and 8 we varied the definition of the exposure window. In sensitivity analysis 6, we used an exposure window of gestational week $0+0$ to $12+6$ to account for potential errors in assigning a date of conception. In sensitivity analysis 7, we used an exposure

window of gestational week 2 + 0 to 19 + 6, to include a lower, but still likely, risk period of congenital anomalies (DeSilva et al., 2016). In sensitivity analysis 8, we used a narrowed exposure window of gestational week 2 + 0 to 9 + 6, as this is the highest teratogenic risk window. For the sensitivity analyses, propensity scores and weights were recalculated and checked for balance using the SMD.

To explore if 1st trimester COVID-19 vaccination increases the risk of specific major anomalies, we studied potential clustering of major anomalies by 1st trimester COVID-19 vaccination status, by grouping ICD10 codes according to the ICD10 hierarchy. Clustering was tested with Fisher exact tests.

Last, we listed all reported major anomalies including the COVID-19 vaccination status. Because the risk period differs between specific major anomalies and a few major anomalies might have their origin by harmful exposure after the 1st trimester, we listed the gestational week of vaccine exposure for all COVID-19 vaccines given during pregnancy.

All analyses were performed in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org) with a statistical significance level of $p < .05$.

3 | RESULTS

3.1 | Study population

In total 3909 participants reported an EDD between 15-01-2021 and 15-05-2022 and a pregnancy that ended after at least 20 gestational weeks (Figure 1). Non-singleton pregnancies ($n = 49$), participants with an unknown COVID-19 vaccination status ($n = 4$), or an unknown timing of vaccination ($n = 99$) were excluded, leaving 3757 participants. Of these 3757 participants,

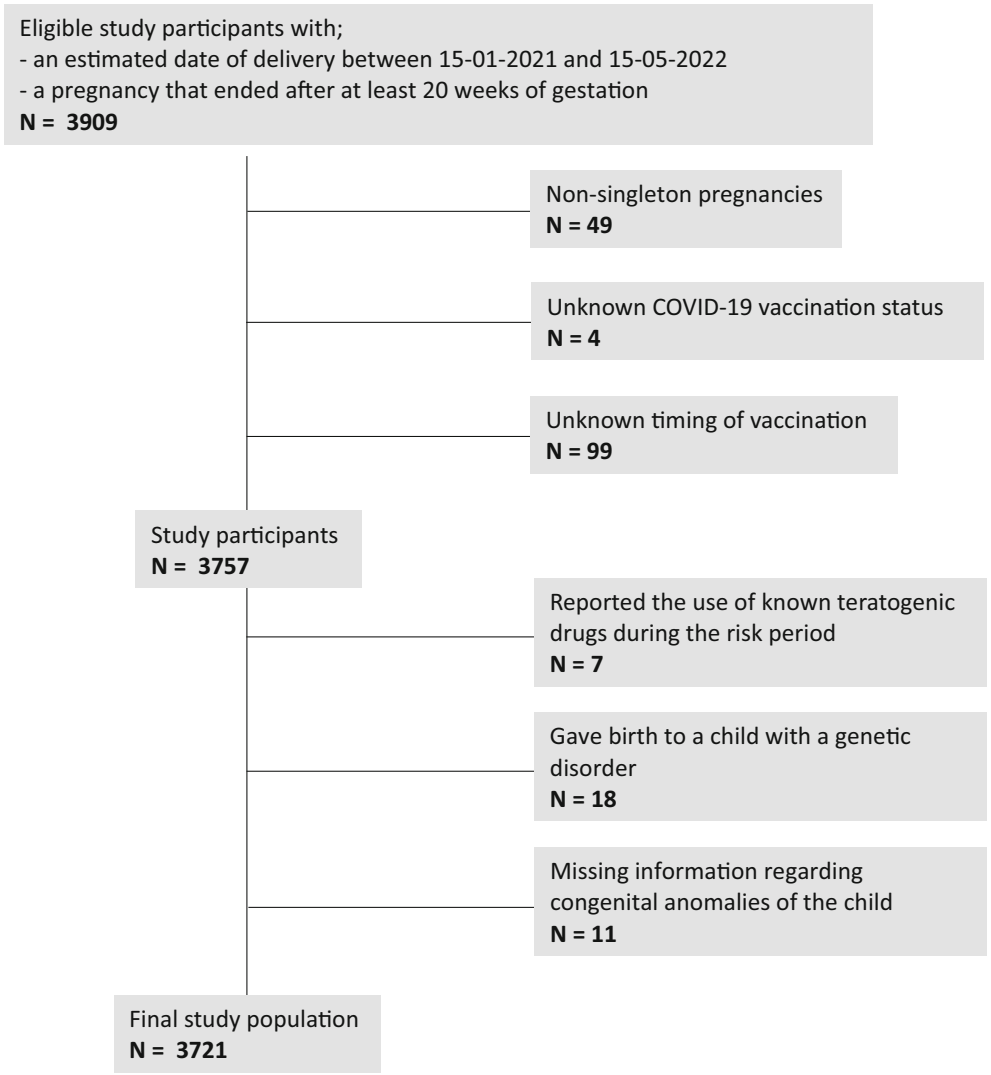

FIGURE 1 Flowchart of the included study participants.

TABLE 1 Baseline characteristics of the study population.

	Total population	Not vaccinated during 1st trimester[a]	Vaccinated during 1st trimester
	Mean/ count (SD/%)	Mean/count (SD/%)	Mean/count (SD/%)
N	3721	2926	795
Age at EDD	33.1 (3.7)	33.0 (3.7)	33.3 (3.7)
Age biological father at EDD	35.3 (4.8)	35.3 (4.8)	35.4 (4.7)
Education level			
High	3279 (88.1%)	2558 (87.4%)	721 (90.7%)
Low/middle	413 (11.1%)	344 (11.8%)	69 (8.7%)
Education level biological father			
High	2782 (74.8%)	2184 (74.6%)	598 (75.2%)
Low/middle	806 (21.7%)	638 (21.8%)	168 (21.1%)
Level of urbanicity[b]			
Very high	1021 (27.4%)	790 (27%)	231 (29.1%)
High	961 (25.8%)	770 (26.3%)	191 (24%)
Moderately high	654 (17.6%)	516 (17.6%)	138 (17.4%)
Low	606 (16.3%)	475 (16.2%)	131 (16.5%)
Very low	441 (11.9%)	346 (11.8%)	95 (11.9%)
Congenital anomalies biological parents			
No anomaly	3308 (88.9%)	2601 (88.9%)	707 (88.9%)
One or both parents with anomalies	286 (7.7%)	226 (7.7%)	60 (7.5%)
Parity			
Nullipara	2012 (54.1%)	1600 (54.7%)	412 (51.8%)
Multipara	1673 (45%)	1299 (44.4%)	374 (47%)
Pre-pregnancy BMI	24.1 (4.5)	24.1 (4.5)	24.2 (4.3)
Pre-pregnancy diabetes			
No	3678 (98.8%)	2892 (98.8%)	786 (98.9%)
Yes	20 (0.5%)	16 (0.5%)	4 (0.5%)
Any folic acid use[c]			
No	15 (0.4%)	11 (0.4%)	4 (0.5%)
Yes	3683 (99.0%)	2897 (99.0%)	786 (98.9%)
Alcohol use[c]			
No alcohol	866 (23.3%)	688 (23.5%)	178 (22.4%)
Stopped before conception	2181 (58.6%)	1773 (60.6%)	408 (51.3%)
Stopped at positive pregnancy test	513 (13.8%)	344 (11.8%)	169 (21.3%)
Continued alcohol during pregnancy	122 (3.3%)	92 (3.1%)	30 (3.8%)
Smoking behavior[c]			
No smoking	3422 (92.0%)	2691 (92.0%)	731 (91.9%)
Stopped before conception	168 (4.5%)	139 (4.8%)	29 (3.6%)
Stopped at positive pregnancy test	61 (1.6%)	42 (1.4%)	19 (2.4%)
Continued smoking during pregnancy	35 (0.9%)	26 (0.9%)	9 (1.1%)

TABLE 1 (Continued)

	Total population	Not vaccinated during 1st trimester[a]	Vaccinated during 1st trimester
	Mean/ count (SD/%)	Mean/count (SD/%)	Mean/count (SD/%)
Any illicit drug use[c]			
No	3591 (96.5%)	2827 (96.6%)	764 (96.1%)
Yes	100 (2.7%)	77 (2.6%)	23 (2.9%)
COVID-19 vaccination prior to pregnancy[d]			
No	3197 (85.9%)	2623 (89.6%)	574 (72.2%)
Yes	514 (13.8%)	294 (10%)	220 (27.7%)
Vaccination priority[e]			
No	3113 (83.7%)	2441 (83.4%)	672 (84.5%)
Yes	585 (15.7%)	467 (16%)	118 (14.8%)
Pregnancy duration	39.3 (1.7)	39.3 (1.7)	39.3 (1.5)

Note: Missing values: age at EDD ($n = 23$, 0.6%), age biological father at EDD ($n = 142$, 3.8%), education level ($n = 29$, 0.8%), education level biological father ($n = 133$, 3.6%), level of urbanicity ($n = 38$, 1.0%), congenital anomalies biological parents ($n = 127$, 3.4%), parity ($n = 36$, 1.0%), pre-pregnancy BMI ($n = 216$, 5.8%), pre-pregnancy diabetes ($n = 23$, 0.6%), any folic acid use ($n = 23$, 0.6%), alcohol use ($n = 39$, 1.0%), smoking behavior ($n = 35$, 0.9%), any illicit drug use ($n = 30$, 0.8%), COVID-19 vaccination prior to pregnancy ($n = 10$, 0.3%), COVID-19 vaccination priority ($n = 23$, 0.6%), pregnancy duration ($n = 0$, 0%). All characteristics involve the pregnant participant unless stated otherwise.

Abbreviations: BMI, Body Mass Index; EDD, estimated date of delivery; SD, standard deviation.

[a]COVID-19 vaccination during 1st trimester (gestational week 2 + 0 to 12 + 6).

[b]Based on ZIP code.

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

[d]COVID-19 vaccination in the year prior to pregnancy.

[e]People with chronic respiratory conditions, chronic heart disease, kidney disease, diabetes, morbid obesity, or immune deficiencies had COVID-19 vaccination priority.

7 (0.2%) participants reported the use of known teratogenic drugs during the risk period and were excluded from the analyses. Participants who gave birth to a child with a genetic disorder ($n = 18$) or with missing information regarding congenital anomalies of the child ($n = 11$) were also excluded. The final study population included 3721 participants.

Of the final study population, 795 (21.4%) participants were vaccinated during the 1st trimester ($n = 609$, 76.6% Comirnaty; $n = 144$, 18.1% Spikevax; $n = 27$, 3.4% Vaxzevria; $n = 6$, 0.8% Jcovden; $n = 9$, 1.1%, unknown vaccine brand). The majority of the population were not vaccinated during the 1st trimester ($n = 2926$, 78.6%). Characteristics of the study population are presented in Table 1.

3.2 | Major non-genetic congenital anomalies

Three women were excluded because it was ambiguous if the offspring had a major anomaly or not. In total 44 (1.2%) participants gave birth to a child with at least one major anomaly. The percentage of participants who gave birth to a child with at least one major anomaly was similar between participants who were 1st trimester COVID-19 vaccinated (1.1%, $n = 9$) and participants who were not 1st trimester COVID-19 vaccinated (1.2%, $n = 35$) (Figure 2).

Comparing participants who were 1st trimester COVID-19 vaccinated with participants who were not 1st trimester COVID-19 vaccinated, the adjusted OR of given birth to a child with at least one major anomaly was 0.78 (95% CI 0.35–1.71) (Table 2). Results of the sensitivity analyses are also presented in Table 2. For most sensitivity analyses the findings did not change substantially. However, after excluding participants who were vaccinated during the 2nd or 3rd trimester and only including participants who were not vaccinated during pregnancy as a reference group (sensitivity analysis 2), the adjusted OR was higher than 1 but with large confidence intervals not statistically significant (1.34 [95% CI 0.29–6.30]). With an exposure window of gestational week 2 + 0 to 9 + 6 (sensitivity analysis 8), the adjusted OR was (0.98 [95% CI 0.40–2.38]) and with an exposure window of gestational week 2 + 0 to 19 + 6 (sensitivity analysis 7), the adjusted OR was (0.60 [95% CI 0.32–1.15]). All sensitivity analyses were statistically not significant.

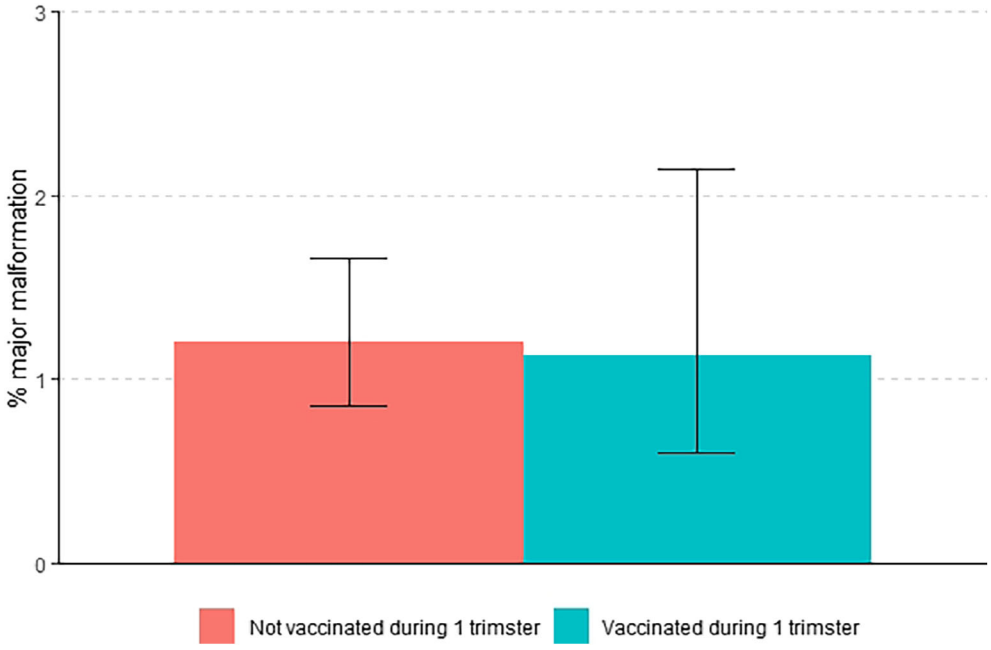

FIGURE 2 Percentage of children born with at least one major non-genetic congenital anomaly, by maternal 1st trimester COVID-19 vaccination status.

We found no statistically significant clustering of major anomalies by 1st trimester COVID-19 vaccination status (Table 3). However, of all major anomalies among offspring from 1st trimester vaccinated participants, 33.3% consisted of "congenital malformations of the urinary system" (ICD10 Q60-Q64) and 33.3% of "congenital malformations and deformations of the musculoskeletal system" (ICD10 Q65-Q79) compared to 11.6% and 20.9% respectively among participants not vaccinated in the 1st trimester.

All reported major anomalies are listed in Supplement S3, including the maternal COVID-19 vaccination status and the gestational week of exposure. "Congenital talipes equinovarus" (ICD10 Q66.0) might have the risk period after gestational week 20. There were four cases of this anomaly with a COVID-19 vaccination after gestational week 20. In three of these four cases the anomaly was already diagnosed during the ultrasound at gestational week 20, ruling out an potential impact of a late vaccination on the diagnoses (data not shown).

4 | DISCUSSION

We observed no association between 1st trimester COVID-19 vaccination and the risk of at least one major anomaly in the offspring. Also, with varying exposure windows and other sensitivity analyses we found no associations. There were also no indications of clustering of major anomalies by 1st trimester COVID-19 vaccination status.

Our study adds to the limited evidence regarding the risk of major anomalies after 1st trimester COVID-19 vaccination. Strengths of our study are that we used a cohort of both vaccinated and unvaccinated women with multiple potential confounders available, a well-defined exposure window, and information on anomalies independent of the outcome of the pregnancy. We do acknowledge some limitations. First, because we had limited numbers of major anomalies, the power of our study was relatively low and we were unable to study specific major anomalies separately. If 1st trimester COVID-19 vaccination increases the risk of specific major anomalies, this effect might be masked in the analyses studying at least one major anomaly. We did look at clustering of anomalies by 1st trimester COVID-19 vaccination status, but also for this analysis, the power was limited. In order to study specific major anomalies separately, large population-based studies are needed (Dolk et al., 2022). Second, there were relatively few participants who were not vaccinated during pregnancy, leading to large confidence intervals for the analyses only including participants who were not vaccinated during pregnancy in the reference group. Third, the prevalence of offspring with at least one major anomaly in our study (1.2%) was somewhat lower compared to the prevalence in European countries and the Netherlands specifically (about 2% and 2.2% respectively according to EUROCAT) (European Commission, n.d.-b). A possible explanation is that in our study major anomalies diagnosed after the first questionnaire postpartum (within 3 months at most) or which led to a termination of pregnancy due to a fetal anomaly prior to gestational week 20 were not taken into account. Moreover, individuals for whom the child was diagnosed with a serious anomaly during ultrasound might be more reluctant to participate in our study. In addition, we used

TABLE 2 Results of the logistic regression analyses studying the risk of at least one major non-genetic congenital anomaly after 1st trimester COVID-19 vaccination.

	Exposed	Non-exposed	Comparing COVID-19 vaccination exposed with non-exposed	
	n anomalies/*N*	*n* anomalies/*N*	OR (95% CI)	
			Crude	With IPTW[a]
Main analysis[b]	9/782	35/2874	0.94 (0.42–1.89)	0.78 (0.35–1.71)
Sensitivity analyses				
1: Excluding participants not vaccinated during pregnancy	9/782	33/2586	0.90 (0.40–1.81)	0.75 (0.34–1.66)
2: Excluding participants vaccinated during 2nd/3th trimester only	9/782	2/288	1.66 (0.43–10.96)	1.34 (0.29–6.30)
3: Ambiguous anomalies, included as not major	9/782	35/2877	0.95 (0.43–1.89)	0.78 (0.35–1.72)
4: Ambiguous anomalies, included as major	9/782	38/2877	0.87 (0.39–1.73)	0.70 (0.32–1.54)
5: Excluding participants with a SARS-CoV-2 infection[c]	9/776	33/2840	1.00 (0.45–2.01)	0.82 (0.37–1.82)
6: Exposure window: gestational week 0 + 0 to 12 + 6[d]	9/866	35/2794	0.83 (0.37–1.65)	0.70 (0.31–1.59)
7: Exposure window: gestational week 2 + 0 to 19 + 6	14/1582	30/2074	0.61 (0.31–1.13)	0.60 (0.32–1.15)
8: Exposure window: gestational week 2 + 0 to 9 + 6	8/568	36/3088	1.21 (0.52–2.49)	0.98 (0.4–2.38)

Note: Participants with missing data for one of the confounders after multiple imputation were excluded from the analyses.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; OR, odds ratio.

[a]Variables that were taken into account in the inverse probability of treatment weighting (IPTW) were: Age at estimated date of delivery, age biological father at estimated date of delivery, education level, education level biological father, level of urbanicity, congenital anomalies biological parents, parity, pre-pregnancy Body Mass Index, pre-pregnancy diabetes, any folic acid use, alcohol use, smoking behavior, any illicit drug use, COVID-19 vaccination in the year prior to pregnancy, vaccination priority, pregnancy duration.

[b]Using an exposure window of gestational weeks 2 + 0 and 12 + 6.

[c]A positive SARS-CoV-2 (self)test between gestational weeks 2 + 0 and 19 + 6.

[d]Compared to the main analyses, 4 more participants were included because of a COVID-19 vaccination between gestational weeks 0 + 0 and 1 + 6, but an unknown timing of the follow-up vaccination.

self-reported information regarding congenital anomalies, which may have led to underreporting. However, previous studies validating the use of web-based questionnaires among pregnant women show that the quality of this data is comparable with data collected from obstetric records (van Gelder et al., 2015; van Gelder et al., 2017). Last, our study is not representative for the total Dutch pregnant population. For example, our study population is more often highly educated (Vorstenbosch et al., 2019) and the COVID-19 vaccination coverage is higher than estimated for the general Dutch pregnant population (±50%) (Nederlandse vereniging obstetrie en gynaecologie (NVOG), n.d.). While we did correct for a number of potential confounders, we cannot rule out residual confounding.

Our results are in line with previous studies finding no associations between maternal COVID-19 vaccination and congenital anomalies in the offspring (Calvert et al., 2023; Favre et al., 2023; Goldshtein et al., 2022). Even though the type of data, study populations, methods, and definitions vary across these studies, the consistent finding of no increased risk is reassuring.

While we found no statistically significant clustering of major anomalies by 1st trimester COVID-19 vaccination status, urinary and musculoskeletal anomalies were somewhat more prevalent among 1st trimester vaccinated participants compared to participants not vaccinated during the 1st trimester. According to EUROCAT (European Commission, n.d.-b) these anomalies are relatively prevalent in general so a higher prevalence compared to other anomalies could be expected. In the study by Calvert et al. (Calvert et al., 2023) the distribution of different types of anomalies, including urinary, were similar between vaccinated and unvaccinated women, suggesting there is no need for concern. Because we had limited number of cases in our cohort, urinary and

TABLE 3 Clustering of major non-genetic congenital anomalies by 1st trimester COVID-19 vaccination.

	Not vaccinated during 1st trimester[a]	Vaccinated during 1st trimester[a]	
	N (%)	*N* (%)	Fisher's exact *p*-value
	n = 43	*n* = 9	
Major non-genetic congenital anomaly, ICD10 clustered			.56
Q04—Other congenital malformations of brain	0	1 (11.1)	
Q12—Congenital lens malformations	1 (2.3)	0	
Q16—Congenital malformations of ear causing impairment of hearing	1 (2.3)	0	
Q21—Congenital malformations of cardiac septa	10 (23.3)	1 (11.1)	
Q22—Congenital malformations of pulmonary and tricuspid valves	3 (7.0)	0	
Q23—Congenital malformations of aortic and mitral valves	1 (2.3)	0	
Q25—Congenital malformations of great arteries	2 (4.7)	0	
Q33—Congenital malformations of lung	1 (2.3)	0	
Q35—Cleft palate	3 (7.0)	1 (11.1)	
Q37—Cleft palate with cleft lip	1 (2.3)	0	
Q39—Congenital malformations of esophagus	1 (2.3)	0	
Q41—Congenital absence, atresia and stenosis of small intestine	1 (2.3)	0	
Q42—Congenital absence, atresia and stenosis of large intestine	1 (2.3)	0	
Q54—Hypospadias	2 (4.7)	0	
Q60—Renal agenesis and other reduction defects of kidney	2 (4.7)	2 (22.2)	
Q61—Cystic kidney disease	1 (2.3)	0	
Q62—Congenital obstructive defects of renal pelvis and congenital malformations of ureter	1 (2.3)	1 (11.1)	
Q63—Other congenital malformations of kidney	1 (2.3)	0	
Q66—Congenital deformities of feet	3 (7.0)	1 (11.1)	
Q69—Polydactyly	4 (9.3)	0	
Q70—Syndactyly	1 (2.3)	0	
Q71—Reduction defects of upper limb	1 (2.3)	1 (11.1)	
Q79—Congenital malformations of musculoskeletal system, not elsewhere classified	0	1 (11.1)	
Q87—Other specified congenital malformation syndromes affecting multiple systems (Pierre Robin sequence)	1 (2.3)	0	

TABLE 3 (Continued)

	Not vaccinated during 1st trimester[a]	Vaccinated during 1st trimester[a]	
	N (%)	*N* (%)	Fisher's exact *p*-value
	n = 43	*n* = 9	
Major non-genetic congenital anomaly, ICD10 clustered higher level			.31
Q00–Q07—Congenital malformations of the nervous system	0	1 (11.1)	
Q10–Q18—Congenital malformations of eye, ear, face and neck	2 (4.7)	0	
Q20–Q28—Congenital malformations of the circulatory system	16 (37.2)	1 (11.1)	
Q30–Q34—Congenital malformations of the respiratory system	1 (2.3)	0	
Q35–Q37—Cleft lip and cleft palate	4 (9.3)	1 (11.1)	
Q38–Q45—Other congenital malformations of the digestive system	3 (7.0)	0	
Q50–Q56—Congenital malformations of genital organs	2 (4.7)	0	
Q60–Q64—Congenital malformations of the urinary system	5 (11.6)	3 (33.3)	
Q65–Q79—Congenital malformations and deformations of the musculoskeletal system	9 (20.9)	3 (33.3)	
Q80–Q89—Other congenital malformations	1 (2.3)	0	

[a]Using an exposure window of gestational weeks 2 + 0 and 12 + 6.

musculoskeletal anomalies could be studied in more detail in future population-based cohort studies with larger sample sizes (Dolk et al., 2022).

Ideally, specific major anomalies are studied with an anomaly specific exposure window. In this study, we focused on COVID-19 vaccinations early in pregnancy in general, but we also provided a list of all reported major anomalies including all COVID-19 vaccinations given during pregnancy and the gestational week of exposure. This case-by-case approach did not lead to other insights regarding COVID-19 vaccination during pregnancy and the risk of major anomalies.

The COVID-19 vaccination coverage among pregnant individuals falls behind compared to non-pregnant individuals, leaving them at risk for SARS-CoV-2 related morbidity and mortality (Azami et al., 2022). Concerns about the vaccine safety during pregnancy are one of the main barriers affecting vaccine uptake (Galanis et al., 2022; Sarantaki et al., 2022). In our study, there were no indications for an association between 1st trimester COVID-19 vaccination and the risk of major non-genetic congenital anomalies in the offspring. Despite larger population based studies being needed to study specific anomalies in more detail, our finding suggests COVID-19 vaccines are safe during early pregnancy.

ACKNOWLEDGMENTS

We thank all participants of the Dutch Pregnancy Drug Register for their contribution and Judith Hendriks, Roos Zonneveld, Jennifer Groenewoud, Maaike Lamers, and Veronique Maas (Lareb) for their involvement in coding and classifying congenital anomalies. This work was supported by the Ministry of Health, Welfare and Sport, the Netherlands. The funders had no role in study design, data collection and analysis, interpretation of data, decision to publish, or preparations of the manuscript.

CONFLICT OF INTEREST STATEMENT

All authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Woestenberg, P. J., de Feijter, M., Bergman, J. E. H., Lutke, L. R., Passier, A. J. L. M., & Kant, A. C. (2023). Maternal first trimester COVID-19 vaccination and risk of major non-genetic congenital anomalies. *Birth Defects Research*, *115*(18), 1746–1757. https://doi.org/10.1002/bdr2.2251