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Impact of prenatal COVID-19 vaccination on delivery and neonatal outcomes: Results from a New York City cohort

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ABSTRACT

Research suggest prenatal vaccination against coronavirus disease-19 (COVID-19) is safe. However, previous studies utilized retrospectively collected data or examined late pregnancy vaccinations. We investigated the associations of COVID-19 vaccination throughout pregnancy with delivery and neonatal outcomes. We included 1,794 mother-neonate dyads enrolled in the Generation C Study with known prenatal COVID-19 vaccination status and complete covariate and outcome data. We used multivariable quantile regressions to estimate the effect of prenatal COVID-19 vaccination on birthweight, delivery gestational age, and blood loss at delivery; and Poisson generalized linear models for Caesarean delivery (CD) and Neonatal Intensive Care Unit (NICU) admission. Using the above methods, we estimated effects of trimester of vaccine initiation on these outcomes. In our sample, 13.7% (n = 250) received at least one prenatal dose of any COVID-19 vaccine. Vaccination was not associated with birthweight (β = 12.42 g [-90.5, 114.8]), gestational age (β = 0.2 days [-1.1, 1.5]), blood loss (β = -50.6 ml [-107.0, 5.8]), the risks of CD (RR = 0.8; [0.6, 1.1]) or NICU admission (RR = 0.9 [0.5, 1.7]). Trimester of vaccine initiation was also not associated with these outcomes. Our findings suggest that there is no associated risk between prenatal COVID-19 vaccination and adverse delivery and neonatal outcomes in a cohort sample from NYC.

1. Introduction

As of April 2022, there have been ~ 205,000 confirmed coronavirus disease-19 (COVID-19) cases in pregnant individuals in the U.S. [1], not including many likely asymptomatic and unconfirmed cases. Early observational studies showed that pregnant individuals with COVID-19 were more frequently admitted to intensive care units and required invasive ventilation compared to non-pregnant individuals of the same age [2]. Moreover, research has reported a myriad of adverse neonatal outcomes related to SARS-CoV-2 infection during pregnancy, including preterm birth and low birthweight [3–6].

Due to the increased risk of severe COVID-19 illness and adverse pregnancy outcomes, the Centers for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) encourage pregnant individuals to get vaccinated to protect themselves from COVID-19 [7,8]. By mid-February 2022, around 69% of the pregnant US population had received at least one dose of the COVID-19 vaccine [9].

To protect against infection, vaccines must elicit an immune response, which is usually brief and may range from mild to severe with fever and increased cytokine levels [10,11]. Evidence from

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animal [12,13] and epidemiological [14–16] research suggests that prenatal exposure to inflammation may lead to adverse pregnancy outcomes. So far, research from national registries and hospital data suggests that prenatal COVID-19 vaccination is effective, protecting against COVID-19 illness and maternal/neonatal hospitalization [17–20], and safe, i.e., not associated with adverse pregnancy outcomes (e.g., preterm birth, birthweight, Neonatal Intensive Care Unit (NICU) admissions, and postpartum hemorrhage) [21–29]. However, studies were restricted to studying the effect of COVID-19 vaccination in late pregnancy, registry-based retrospective cohorts, or compared outcomes to historical pregnancy data or non-pregnant persons [21,22,24,26–30]. Additionally, studies either: 1) restricted their samples to those with no history of SARS-CoV-2 infection [25–28], which has been associated with several adverse delivery outcomes such as preterm birth and low birthweight [3–6]; or 2) classified history of SARS-CoV-2 infection using questionnaires or polymerase chain reaction (PCR) tests from medical charts, which could exclude asymptomatic SARS-CoV-2 infections which were never captured by a PCR test [21,23,24,29,30]. Here, we examine the associations of prenatal COVID-19 vaccination in all trimesters with birthweight, gestational age at delivery, quantitative blood loss at delivery, mode of delivery, and NICU admission in a large prospective pregnancy cohort in New York City (NYC). These outcomes were selected due to their general indication of maternal and neonatal health. Given the considerable proportion of individuals already vaccinated during pregnancy, the significant number of pregnant individuals who are not yet vaccinated, and the potential necessity of future booster shots, understanding the impact of prenatal COVID-19 vaccination on delivery and neonatal outcomes is crucial.

2. Materials and methods

2.1. Study design and population

The Generation C Study (Generation C) is a prospective pregnancy cohort study within the Mount Sinai Health System (MSHS) in NYC, which delivers over 14,750 babies a year [31]. Generation C was designed to examine the impact of SARS-CoV-2 in pregnant individuals on pregnancy, fetal, and neonatal outcomes. A detailed cohort description can be found elsewhere [32]. Briefly, pregnant persons receiving obstetrical care within the MSHS were approached for study participation at a prenatal visit or on Labor and Delivery (L&D). Recruitment began in April 2020 and concluded in February 2022. As part of routine blood collections for prenatal lab testing, additional blood samples were obtained. Participants provided informed consent.

2.2. Measurements

Information on COVID-19 vaccination status was ascertained from the patients' electronic medical records (EMR). The EMR of the MSHS is linked the New York Citywide Immunization Registry (CIR), which consolidates all immunization information across NYC, including vaccination outside of the MSHS (e.g., immunization in pharmacies), into a centralized database. Reporting of all administered COVID-19 vaccine doses to the CIR is required within 24 h of administration. This information is accessible via the EMR of any NYC hospital system. Here, participants were considered 'vaccinated' if they received at least one dose of a viral-vector vaccine Janssen (Johnson & Johnson) (Ad26.COV2.S), or mRNA vaccines Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) at any point during pregnancy. None of the participants reported receiving a COVID-19 vaccine not authorized in the US. Timing (before, during, or after pregnancy) and trimester of each dose administration (if applicable) were calculated based on gestational age established using ultrasounds. Participants were categorized as 'fully vaccinated', defined as the completion of the two-dose series of the mRNA vaccines or one-dose of the viral-vector vaccine, or as 'partially vaccinated', defined as the completion of the first of two mRNA vaccine doses. Participants were considered 'unvaccinated' (i.e., not vaccinated during pregnancy) if they 1) were pregnant at a time when the COVID-19 vaccine was available but received the first dose of any COVID-19 vaccine after delivery or 2) delivered before the authorization of the vaccine in NYC (December 14, 2020). We excluded individuals who delivered after December 14, 2020, if their vaccination status was unknown (i.e., missing or incomplete EMR data on vaccination status), or if they were fully vaccinated before pregnancy (Fig. 1).

Information on SARS-CoV-2 infection history was obtained using several methods. First, an enzyme-linked immunosorbent assay (ELISA) was used to measure immunoglobulin G (IgG) titer levels to the SARS-CoV-2 spike protein in blood samples collected throughout pregnancy and at L&D. This ELISA has high sensitivity and specificity [33]. However, SARS-CoV-2 spike protein antibodies indicate prior exposure to either SARS-CoV-2 or the COVID-19 vaccine. Thus, for all participants with known vaccination status (as per the EMR) and with IgG positive samples collected after December 14, 2020 (when vaccination began in NYC), samples were further tested for the presence of SARS-CoV-2 nucleocapsid antibodies using the MILLIPLEX SARS-CoV-2 Antigen Panel 1 IgG from Millipore [34]. This assay allows distinction of antibodies produced in response to COVID-19 vaccination from antibodies produced in response to prior SARS-CoV-2 infection. Nucleocapsid antibodies are only found after prior infection, not after vaccination. Running the MILLIPLEX assay, thus, allowed us to establish prior infection history and confirm vaccination status based on the presence of nucleocapsid antibodies. We established which participants were 1) vaccinated but not infected, and which were 2) vaccinated and infected. Lastly, we used EMR data on SARS-CoV-2 polymerase chain reaction (PCR) tests to further identify SARS-CoV-2 infection history.

In our analysis, we included SARS-CoV-2 infection history prior to delivery as covariate. No data were available on symptomatology or infection severity of SARS-CoV-2 infection. Additionally, participants were considered "unknown" for SARS-CoV-2 infection history if they did not have adequate amounts of plasma (n = 38) or if their samples had not yet been analyzed (n = 3).

We examined the following delivery and neonatal outcomes: birthweight (grams), gestational age at delivery (days), quantitative blood loss at delivery (ml), mode of delivery (Caesarean vs vaginal delivery), and Neonatal Intensive Care Unit admission (NICU; yes, no). Due to low numbers, we excluded spontaneous abortions (pregnancy loss < 20 weeks gestation), intrauterine fetal demise, and induced abortions (i.e., elective abortions at any point during pregnancy) from the primary analysis; however, below we report the frequency of these outcomes by vaccination group. Outcome data were ascertained from the EMR.

2.3. Covariates

Covariates were chosen based on published literature [21,22,28] and include SARS-CoV-2 infection history (yes, no, unknown), race and ethnicity (non-Hispanic Asian, non-Hispanic Black, Hispanic, unknown, non-Hispanic White, or none of the above), maternal age at delivery (years; 18–34, 35–50), parity (nulliparous, multiparous), pre-pregnancy hypertension (yes, no), pre-pregnancy diabetes (yes, no), and pre-pregnancy body mass index (BMI, kg/m^2; underweight (<18.5), healthy weight (18.5–24.9), overweight (25–29.9), obesity (30 +)). We additionally controlled

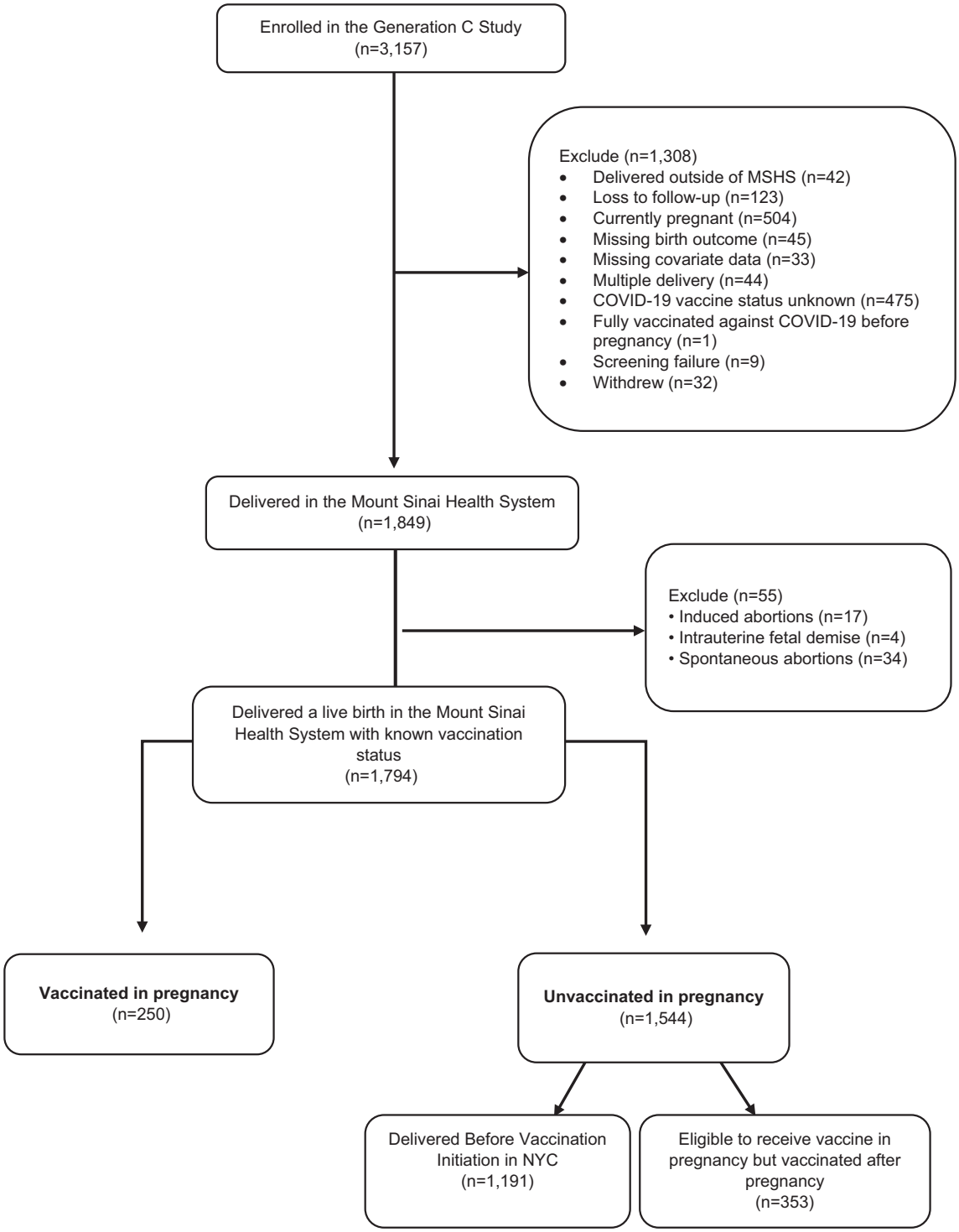

Fig. 1. Participant flow chart.

for study-specific variables: 1) enrollment center (prenatal appointment or L&D) to account for different recruitment strategies which may have influenced who was recruited, and 2) time between the first confirmed case of COVID-19 in NYC (March 1, 2020) and birth (months) to account for timing of the pandemic. Descriptive covariate data were ascertained through EMRs, with the addition of the above-mentioned ELISA and MILLIPLEX assays from blood samples to supplement SARS-CoV-2 infection history.

2.4. Statistical analysis

Pearson's chi-square, Fischer's exact test, and Wilcoxon Rank-Sum tests were used to compare demographic variables, where appropriate. For the primary analysis, quantile regression analysis was used to obtain the beta values and 95% confidence intervals (CIs) to estimate the effect of the COVID-19 vaccine on the continuous variables birthweight (grams), gestational age at delivery

(days), and quantitative blood loss at delivery (ml), as these outcomes are not normally distributed. Generalized linear mixed with Poisson distribution and log-link were used to obtain the risk ratios and 95% CIs to estimate the effect of the COVID-19 vaccine on the categorical variables delivery mode (Caesarean vs vaginal delivery) and NICU admission (yes, no). For the secondary analysis, we analyzed the effect of timing (trimester) of vaccine initiation (i.e., first dose) on our selected outcomes using the statistical methods outlined above. We compared individuals who initiated vaccination in the first, second or third trimester to unvaccinated individuals. Descriptive statistics for the selected outcomes per trimester are provided. We performed a sensitivity analysis restricting our analysis to participants who delivered after December 14, 2020 to investigate pregnancy outcomes of those who delayed vaccination until after delivery to those who chose to be vaccinated during pregnancy and control for timing of the pandemic and vaccine availability. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

2.5. Ethics approval

The institutional review board (IRB) at the Icahn School of Medicine at Mount Sinai reviewed and approved the study protocol (protocol IRB-20–00425, April 20, 2020).

3. Results

Generation C enrolled 3,157 participants from April 2020 to February 2022. Here, we include 1,794 individuals with a live delivery encounter within the MSHS, who had data on vaccination status and timing, as well as covariate and outcome data. In our sample, 13.9% (n = 250) received at least one dose of any COVID-19 vaccine during pregnancy and 86.1% (n = 1,544) were unvaccinated during pregnancy (n = 353 received the first dose after pregnancy despite being eligible for prenatal COVID-19 vaccination and n = 1,191 delivered before December 14, 2020) (Fig. 1). Supplemental table 1 summarizes the demographics and characteristics of the included (n = 1,794) and excluded (n = 1,322) participants. A visual timeline of when COVID-19 vaccination occurred in our sample is presented as Supplemental Fig. 1.

Sample characteristics of the vaccinated (n = 250) and unvaccinated (n = 1,544) participants are presented in Table 1. Compared to unvaccinated participants, vaccinated participants were more likely to 1) not have a history of SARS-CoV-2 infection, 2) identify as non-Hispanic White, 3) be nulliparous, 4) have a healthy pre-pregnancy BMI, and be enrolled 5) at a prenatal appointment rather than at L&D, 6) earlier in pregnancy, and 7) later in the pandemic. There were no differences in pre-pregnancy hypertension and pre-pregnancy diabetes (Table 1). Outcome data by group are presented in Table 2.

Overall, there were 55 non-live birth pregnancy outcomes out of 1,849 delivery encounters (3%). Of the 1,849 delivery encounters, 1,596 were unvaccinated and 253 were vaccinated. Among those unvaccinated (n = 1,596), 34 (2%) experienced spontaneous abortions, 3 (0.2%) experienced intrauterine fetal demise, and 15 (1%) had induced abortions. Of the vaccinated participants with a delivery encounter (n = 253), one experienced intrauterine fetal demise (0.4%) and two (0.8%) had an induced abortion. No sponta-

Table 1
Sample characteristics of vaccinated and unvaccinated participants enrolled in the Generation C study at the Mount Sinai Health System, April 2020 – November 2021 (N = 1,794).

Characteristic	Vaccinated n = 250	Unvaccinated n = 1,544	p-value*
Previous SARS-CoV-2 infection, n (%)			0.01
Yes	36 (14)	336 (22)	
No	211 (84)	1,171 (76)	
Unknown	3 (1)	37 (2)	
Race and Ethnicity, *n (%)*			<0.0001
Non-Hispanic Asian	33 (13)	160 (10)	
Non-Hispanic Black	18 (7)	235 (15)	
Hispanic	30 (12)	432 (28)	
Unknown	10 (4)	68 (4)	
Non-Hispanic White	135 (54)	633 (41)	
None of the above	24 (10)	16 (1)	
Pre-pregnancy hypertension, *n (%)*	9 (4)	43 (3)	0.48
Pre-pregnancy diabetes, *n (%)*	7 (3)	21 (1)	0.09
Enrollment center, *n (%)*			<0.0001
Prenatal appointment	213 (85)	879 (57)	
Labor and Delivery	37 (15)	665 (43)	
Parity, *n (%)*			0.004
Nulliparous	153 (61)	792 (51)	
Multiparous	97 (39)	752 (49)	
Age at delivery (years), *n (%)*			<0.0001
18 to 34	95 (38)	922 (60)	
35 to 50	155 (62)	622 (40)	
Pre-pregnancy BMI (kg/m^2), *n (%)*			0.0008
Underweight (Below 18.5)	4 (2)	39 (3)	
Healthy Weight (18.5 to 24.9)	133 (53)	648 (42)	
Overweight (25 to 29.9)	75 (30)	460 (30)	
Obesity (30 or higher)	38 (15)	397 (26)	
Gestational age at recruitment (weeks), *median (IQR)*	12 (9, 18)	36 (22, 39)	<0.0001
Pandemic timing (months), *median (IQR)***	15 (14, 17)	6 (4, 9)	<0.0001

IQR = Interquartile range.
*Pearson's chi-square or Fischer's exact test (where appropriate) test for categorical variables; Wilcoxon Two-Sample Test for continuous variables.
**Months between first confirmed case of COVID-19 in New York City to delivery.

Table 2
Summary statistics of delivery and neonatal outcomes of vaccinated and unvaccinated participants in the Generation C study at the Mount Sinai Health System, April 2020 – November 2021 (N = 1,794).

Outcome	Vaccinated n = 250	Unvaccinated n = 1,544	p-value*
Birthweight (grams), *median (IQR)*	3,224.9 (2,935.0, 3,549.9)	3,259.9 (2,935.0, 3,572.5)	0.32
Small for gestational age, *n (%)*	23 (9)	147 (9)	0.87
Delivery gestational age (weeks), *median (IQR)*	39.0 (38.0, 39.0)	39.0 (38.0, 39.0)	0.99
Preterm birth (<37 weeks), *n (%)*	16 (6)	139 (9)	0.17
Quantitative blood loss (ml), *median (IQR)*	327.0 (200.0, 582.0)	328.0 (200.0, 544.0)	0.58
>= 1,000 ml, *n (%)*	8 (3)	58 (4)	0.67
Caesarean delivery, *n (%)*	99 (40)	541 (35)	0.16
NICU admission, *n (%)*	25 (10)	152 (10)	0.94

NICU = Neonatal Intensive Care Unit; IQR = Interquartile range; Small for gestational age is defined as birthweight below 10th sex-specific percentile.
*Pearson's chi-square test for categorical variables; Wilcoxon Two-Sample Test for continuous variables.

neous abortions occurred in the vaccinated group. For the sample characteristics of the participants with non-live birth outcomes, who were excluded from the analyses, see Supplemental table 2.

Of the vaccinated participants included in our sample (n = 250), 87% (n = 217) received two doses of an mRNA vaccine in pregnancy or one dose of the viral-vector vaccine during pregnancy, 1% (n = 3) received one dose of an mRNA vaccine prior to pregnancy and the second during pregnancy, and 12% (n = 30) received one dose of an mRNA vaccine during pregnancy and the second after pregnancy. By trimester, 35 (14%) received their first dose during the first trimester, 105 (42%) received their first dose during the second trimester, 105 (42%) received their first dose during the third trimester, and 2 (1%) individuals had no date of vaccine initiation (but had received their second mRNA dose in pregnancy).The majority of vaccinated participants (97%) received an mRNA vaccine (n = 249), <1% received a viral-vector vaccine (n = 4), and < 1% did not have a vaccine brand specified (n = 3) (Supplemental table 3).

Table 3 presents the results from the primary analysis, unadjusted and adjusted quantile and log-Poisson regression models adjusted for history of COVID-19, race and ethnicity, age at delivery, parity, pre-pregnancy hypertension, pre-pregnancy diabetes, pre-pregnancy BMI, enrollment center, and time between the first confirmed case of COVID-19 in NYC (March 1, 2020) and birth. In both the unadjusted and the adjusted models, we did not find an association of prenatal COVID-19 vaccination with birthweight, delivery gestational age, quantitative blood loss at delivery, mode of delivery and NICU admission.

Results from the secondary analysis, which examined our selected delivery and neonatal outcomes by trimester of COVID-19 vaccine initiation, showed no trimester-specific effects of the COVID-19 vaccine on birthweight, delivery gestational age, quantitative blood loss at delivery, or mode of delivery (Table 4).

The sensitivity analysis, which was restricted to participants who delivered after December 14, 2020 (N = 603) to investigate pregnancy outcomes of those who delayed vaccination until after delivery to those who chose to be vaccinated during pregnancy and control for timing of the pandemic and vaccine availability, also found no effect of prenatal vaccination against COVID-19 on delivery or birth outcomes (Supplemental tables 4, 5, 6).

4. Discussion

We found that COVID-19 vaccination during pregnancy was not associated with birthweight, gestational age, blood loss at delivery, Caesarean birth, or NICU admission in our prospective pregnancy cohort. We further did not find trimester-specific effects of the COVID-19 vaccine on these delivery and birth outcomes. Additionally, these findings remained the same when the sample was restricted to those who delivered after December 14, 2020, when the COVID-19 vaccine was first available to all pregnant persons in NYC.

Vaccines are a key mitigation strategy for preventing and controlling the spread of COVID-19. Due to the increased risk of severe COVID-19 illness and adverse pregnancy outcomes affecting both the pregnant person and their child, vaccination during pregnancy is recommended by the CDC, ACOG, and SMFM [7,8]. However, concerns regarding the safety of the COVID-19 vaccine during pregnancy have arisen partly because of the speed with which the vaccines were developed and because pregnant individuals were not included in the phase III trials of the vaccines [35]. Moreover, the desired goal of vaccines is to trigger a cell-mediated immune response against a virus (i.e., the pro-inflammatory cytokines tumor necrosis factor (TNF)α, interleukin (IL)-1, IL-6, and Type I and II interferons (IFNs)) [36,37], in this case

Table 3
Unadjusted and adjusted† quantile and log-Poisson regression of vaccination in pregnancy with delivery and neonatal outcomes, Mount Sinai Health System, April 2020 – November 2021 (N = 1,794).

Outcome	Unadjusted Estimate (95% CI)	Adjusted† Estimate (95% CI)
Birthweight (grams)*	−34.9 (-114.2, 44.5)	12.2 (-90.5, 114.8)
Delivery gestational age (days)*	0.0 (-0.8, 0.8)	0.2 (-1.1, 1.5)
Quantitative blood loss at delivery (ml)*	0.02 (-45.5, 45.5)	−50.6 (-107.0, 5.8)
Caesarean delivery**	1.1 (0.9, 1.4)	0.8 (0.6, 1.1)
NICU admission**	1.0 (0.7, 1.6)	0.9 (0.5, 1.7)

†Adjusted for: SARS-CoV-2 infection history, race and ethnicity, maternal age at delivery, parity, pre-pregnancy hypertension, diabetes, pre-pregnancy BMI, enrollment center, and time between first case of COVID-19 in New York City and birth (months); NICU = Neonatal Intensive Care Unit.
*Quantile regression at the median performed, beta (95% CI) presented.
**Log-Poisson regression performed, risk ratio (95% CI) presented.

Table 4
Adjusted quantile regression and log-Poisson regression results by trimester of first dose of the COVID-19 vaccine in those who delivered after December 14, 2020, with delivery and neonatal outcomes (n = 1,789)†.

		Birthweight (grams)*	Delivery gestational age (days)*	Quantitative blood loss at delivery (ml)*	Caesarean delivery**	NICU admission**
Trimester of vaccine initiation	**First (n = 35)**	3,270 (3,020, 3,560)	275 (269, 278)	300 (157, 550)	14 (40)	5 (14)
	Second (n = 105)	3,210 (2,910, 3,560)	274 (268, 278)	359 (211, 604)	46 (44)	11 (10)
	Third (n = 105)	3,220 (2,965, 3,470)	274 (268, 279)	310 (200, 546)	37 (35)	9 (9)
Adj. estimate: trimester of initiation vs unvaccinated	**First**	−22.3 (-227.3, 182.7)	−1.5 (-4.1, 1.1)	83.1 (−32.5, 198.6)	0.7 (0.4, 1.4)	1.3 (0.5, 3.7)
	Second	−12.3 (-148.1, 123.5)	0.4 (-2.1, 1.4)	36.5 (-40.1, 113.1)	0.9 (0.6, 1.3)	1.0 (0.5, 2.2)
	Third	−9.7 (-133.0, 113.6)	0.1 (-1.4, 1.7)	63.1 (-6.4, 132.6)	0.8 (0.5, 1.1)	0.8 (0.4, 1.8)

Adjusted for: SARS-CoV-2 infection history, race and ethnicity, maternal age at delivery, parity, pre-pregnancy hypertension, diabetes, BMI, enrollment center, and time between first case of COVID-19 in New York City and birth; NICU = Neonatal Intensive Care Unit; IQR = Interquartile range.
†Excluding n = 3 with pre-pregnancy vaccine and n = 2 with unknown date of vaccine initiation.
*Median (IQR) presented. Quantile regression at the median performed, beta (95% CI) presented.
**N (%) presented. Log-Poisson regression performed, risk ratio (95% CI) presented.

SARS-CoV-2. This immune response has been associated with adverse pregnancy outcomes in animal models [36,37]. In human and mice studies, maternal immune activation has further been linked to an increased risk for preterm birth [38,39] lower birthweight [40], and adverse offspring neurobehavioral outcomes [12,41,42]. Yet, our and several large prospective and registry-based retrospective cohort studies provide reassurance regarding the safety of the COVID-19 vaccine during pregnancy. Namely, we found no increased risk of adverse pregnancy outcomes associated with vaccination against COVID-19 and no trimester-specific effects. In line with previous findings, our research shows that vaccinated and unvaccinated pregnant individuals do not differ with regard to birthweight, gestational age at delivery, postpartum hemorrhage, and mode of delivery [21–23,25–27]. While previous studies investigated the effects COVID-19 vaccination in the second and/or third trimesters, employed retrospective designs or compared pregnancy outcomes of vaccinated individuals to historical pregnancy data or non-pregnant persons, we examined the impact of COVID-19 vaccinations in all three trimesters in a large prospective pregnancy cohort [21–30]. By including participants who were vaccinated at any point during pregnancy, we were able to elucidate trimester-specific effects of COVID-19 vaccination. Our prospective pregnancy cohort, which was established in NYC early in the COVID-19 pandemic, further allowed us to compare vaccinated and unvaccinated individuals who were pregnant during the pandemic. Thus, the current study substantially expands on available data that suggest no increased risk of adverse pregnancy outcomes among individuals vaccinated against COVID-19 during pregnancy.

Our results suggest no increased risk of lower birthweight, preterm birth, increased blood loss at delivery, Caesarian birth or NICU admission and, therefore, provide support for the vaccination recommendations by the CDC, ACOG, and SMFM. A likely added benefit of receiving the COVID-19 vaccine during pregnancy, established in other studies, is that antibodies are transferred to the fetus [19,43–45], offering the infant protection against the virus during the first months of life. This is particularly important since infants less than 6 months of age are not eligible for vaccination at the time of this analysis. Evidence regarding the efficacy and safety of COVID-19 vaccination during pregnancy is still emerging as vaccination and booster campaigns are ongoing worldwide. Consequently, more individuals vaccinated against COVID-19 during pregnancy will give birth in the future, allowing us to expand our sample sizes, as well as to investigate vaccine- and trimester-specific effects in more detail. Furthermore, future studies are needed to understand the longer-term effects of prenatal exposure to the COVID-19 vaccines on children's immunity to COVID-19, as well as on their developmental milestones and neurobehavioral health.

The strengths of our study include the use of 1) prospective data from a large diverse sample; 2) EMR data on COVID-19 vaccination to determine timing, and minimize exposure misclassification and researcher bias; 3) highly sensitive assays to distinguish between SARS-CoV-2 infection and COVID-19 vaccination, allowing us to control for SARS-CoV-2 infection history and potential sequalae; and 4) trimester-specific vaccination data allowing us to investigate the effects of vaccination timing on delivery and neonatal outcomes.

The limitations of our study include potential sampling bias; our included and excluded participants differed on various characteristics and limited power to investigate the effects by race and ethnicity. Thus, our findings may not be generalizable to other populations. Second, we cannot preclude a healthy vaccination effect. Namely, it is conceivable that those who received a prenatal COVID-19 vaccine may be healthier and less prone to adverse delivery and/or neonatal outcomes. The healthy vaccination effect may be reflected in the smaller numbers of non-live births in the vaccinated group. Yet, in our analysis, we controlled for a range of covariates such as SARS-CoV-2 infection history, maternal age at delivery, pre-pregnancy hypertension, diabetes and pre-pregnancy BMI to account for maternal health. Due to the small number of events, non-live births were not included in the analyses and thus should be interpreted with caution. Additionally, exposure misclassification may result from our use of the New York Citywide Immunization Registry as the primary source of vaccination information. Individuals who were excluded due to unknown vaccination status may have received the COVID-19 vaccine outside of NYC or declined vaccination. However, those excluded from the analysis due to missing vaccination information (n = 475) did not differ from those included in the analytical sample (n = 1,796) with regard to zip code and NYC residency (supplemental table 7). Third, most of the unvaccinated individuals delivered prior to vaccine distribution in NYC (67%), in April-December 2020. Individuals who delivered in the earlier phases of the pandemic may have experienced various economic, social, and medical impacts of early public health measures introduced to mitigate the pandemic [45]. To address this issue, we included the time between the first confirmed case of COVID-19 in NYC (March 1, 2020) and birth and conducted a sensitivity analysis restricting our sample to those who delivered after the vaccine became available. Results of the main analysis and the sensitivity analysis were identical. Fourth, the sample sizes of certain subanalyses are relatively small (e.g., first-trimester vaccination). Thus, these analyses may be underpowered. Future research with larger samples is required to confirm our findings. Fifth, we were unable to control for the severity of COVID-19 in these analyses as these data were unavailable. Yet, we did include SARS-CoV-2 infection history in our model. Unlike previous research [21,23–30], we classified history of SARS-CoV-2 infection based on both SARS-CoV-2 PCR test data from the EMR and blood samples collected throughout pregnancy measuring SARS-CoV-2 anti-S IgG antibodies. The use of SARS-CoV-2 antibodies is a strength of this study as it detects asymptomatic cases as well as those who never underwent testing. Sixth, there were small numbers of pre-pregnancy SARS-CoV-2 infections in (7/36 SARS-CoV-2 positive and vaccinated; 12/336 SARS-CoV-2 positive and unvaccinated). We hope to assess how pre-pregnancy and trimester-specific SARS-CoV-2 infection and vaccination timing impacts delivery and neonatal outcomes in the future. Lastly, we are unable to assess the impact of the different types of vaccines due to the small number of participants who received the viral vector vaccine (n = 4).

5. Conclusion

COVID-19 vaccination during pregnancy was not adversely associated with birthweight, gestational age at delivery, blood loss at delivery, mode of delivery, and NICU admission in a prospective cohort sample from New York City. Our study adds to the growing literature on the safety of COVID-19 vaccination in pregnancy and supports the continued recommendation of vaccination of pregnant individuals against SARS-CoV-2. Thus, it may help providers counsel pregnant patients on the safety and benefits of COVID-19 vaccination during pregnancy, which is particularly important considering the higher risk of severe COVID-19 during pregnancy.

6. Author contributions

Conceptualization, Erona Ibroci, Veerle Bergink and Anna-Sophie Rommel; Data curation, Erona Ibroci and Elianna Kaplowitz; Formal analysis, Erona Ibroci; Funding acquisition, Elizabeth Howell, Siobhan Dolan, Joanne Stone and Veerle Bergink;

Investigation, Erona Ibroci, Veerle Bergink and Anna-Sophie Rommel; Methodology, Erona Ibroci, Xiaoqin Liu, Veerle Bergink and Anna-Sophie Rommel; Project administration, Elizabeth Howell, Siobhan Dolan, Joanne Stone and Veerle Bergink; Resources, Erona Ibroci, Frederieke Gigase, Kyle Chung, Mara Graziani, Sophie Ohrn, Jezelle Lynch, Juliana Castro, Christina Marshall, Rushna Tubassum, Farida Mutawakil and Elianna Kaplowitz; Software, Erona Ibroci; Supervision, Veerle Bergink and Anna-Sophie Rommel; Validation, Erona Ibroci; Visualization, Erona Ibroci and Anna-Sophie Rommel; Writing – original draft, Erona Ibroci, Veerle Bergink and Anna-Sophie Rommel; Writing – review & editing, Erona Ibroci, Xiaoqin Liu, Whitney Lieb, Rebecca Jessel, Frederieke Gigase, Kyle Chung, Mara Graziani, Molly Lieber, Sophie Ohrn, Jezelle Lynch, Juliana Castro, Christina Marshall, Rushna Tubassum, Farida Mutawakil, Elianna Kaplowitz, Sascha Ellington, Nina Molenaar, Rhoda Sperling, Elizabeth Howell, Teresa Janevic, Siobhan Dolan, Joanne Stone, Lotje De Witte, Veerle Bergink and Anna-Sophie Rommel. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the Icahn School of Medicine (protocol IRB-20–00425, April 20, 2020).

Informed Consent Statement.

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement.

Not applicable.

Data availability

The data that has been used is confidential.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

The following supporting information can be downloaded at https://www.mdpi.com/xxx/s1, Table S1: Sample characteristics of participants included and excluded from analysis, Mount Sinai Health System, April 2020 – February 2022 (N = 3,116); Table S2: Summary demographics of participants with non-live birth outcomes with known vaccination status, Mount Sinai Health System, April 2020 – February 2022 (n = 55); Table S3: Detailed COVID-19 vaccination information of vaccinated participants with delivery and neonatal outcomes, Mount Sinai Health System, April 2020 – February 2022 (N = 250); Table S4: Sensitivity analysis sample characteristics restricted to participants who delivered after introduction of COVID-19 in New York City, Mount Sinai Health System, December 14, 2020 – February 2022 (N = 603); Table S5: Summary statistics for the sensitivity analysis restricted to participants who delivered after introduction of COVID-19 in New York City, Mount Sinai Health System, December 14, 2020 – February 2022 (N = 603); Table S6: Unadjusted and adjusted† quantile and log-Poisson regression of vaccination in pregnancy with delivery and neonatal outcomes, restricted to participants who delivered after introduction of COVID-19 in New York City, Mount Sinai Health System, December 14, 2020 – February 2022 (N = 603). Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.09.095.

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