The effect of SARS-CoV-2 infection and COVID-19 vaccination during pregnancy on neonatal outcomes

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Abstract

This study explored the effect of SARS-CoV-2 infection and COVID-19 vaccination during pregnancy on neonatal outcomes among women from the general Dutch population. VASCO is an ongoing prospective cohort study aimed to assess vaccine effectiveness of COVID-19 vaccination. Pregnancy status was reported at baseline and through regular follow-up questionnaires. As extension to the main study, all female participants who reported to have been pregnant between enrollment (May-December 2021) and January 2023 were requested to complete an additional questionnaire on neonatal outcomes. Multivariable linear and logistic regression analyses were used to determine the associations between self-reported SARS-CoV-2 infection or COVID-19 vaccination during pregnancy and neonatal outcomes, adjusted for age, educational level and presence of a medical risk condition. Infection analyses were additionally adjusted for COVID-19 vaccination before and during pregnancy, and vaccination analyses for SARS-CoV-2 infection before and during pregnancy. Of 312 eligible participants, 232 (74%) completed the questionnaire. In total, 196 COVID-19 vaccinations and 115 SARS-CoV-2 infections during pregnancy were reported. Infections were mostly first infections (86; 75%), caused by the Omicron variant (95; 83%), in women who had received ≥1 vaccination prior to infection (101; 88%). SARS-CoV-2 infection during pregnancy was not significantly associated with gestational age (β=1.7; 95%CI: -1.6-5.0), birth weight (β=82; -59-223), Apgar-score<9 (odds ratio (OR):1.3; 0.6-2.9), postpartum hospital stay (OR:1.0; 0.6-1.8) or neonatal intensive care unit (NICU) admission (OR:0.8; 0.2-3.2). COVID-19 vaccination during pregnancy was not significantly associated with gestational age (β=-0.4; -4.0-3.2), birth weight (β=88; -64-240), Apgar-score<9 (OR:0.9; 0.4-2.3), postpartum hospital stay (OR:0.9; 0.5-1.7) or NICU admission (OR:1.6; 0.4-8.6). In conclusion, this study did not find an effect of SARS-CoV-2 infection or COVID-19 vaccination during pregnancy on any of the studied neonatal outcomes among a general Dutch, largely vaccinated, population. Together with data from other studies, this supports safety of COVID-19 vaccination during pregnancy.

Introduction

The first cases of the coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus were identified in December 2019. Since then, COVID-19 has globally spread and caused many deaths worldwide. The world health organization (WHO) declared COVID-19 to be a pandemic in March 2020 [1]. Within a year after SARS-CoV-2 emerged, the first vaccines were developed and approved. In the Netherlands, the COVID-19 vaccination campaign started in January 2021. Vaccines were first available for prioritized groups of people (i.e., healthcare employees in direct COVID-19 care, residents and staff of long-term care facilities, and adults living in an institution). The subsequent vaccine roll-out in the non-institutionalized adult population followed an age-specific approach, starting with the elderly. From May 2021 all adults were eligible for COVID-19 vaccination [2].

Pregnant women are at higher risk of severe COVID-19 illness compared to the general population, and infection involves both the mother as well as the neonate [3-5]. Studies have reported that pregnant women with SARS-CoV-2 infection have an increased risk for composite morbidity, admission to an intensive care unit (ICU), ventilatory support, preeclampsia and preterm birth, compared to pregnant women without SARS-CoV-2 infection [6,7]. Furthermore, SARS-CoV-2 infection during pregnancy is reported to increase the risk of fetal distress, neonatal respiratory distress and admission of the neonate to the neonatal intensive care unit (NICU) [8,9].

COVID-19 vaccination protects pregnant women against severe COVID-19 illness. Despite their higher risk of severe COVID-19, pregnant and postpartum women were initially not prioritized in the Dutch COVID-19 vaccination campaign due to insufficient vaccine safety data [10]. COVID-19 vaccination became available for Dutch pregnant women from May 2021 onwards [2]. Several studies have now shown that the vaccines that were available in the Netherlands during the COVID-19 pandemic can be used safely during pregnancy [11,12]. Also, COVID-19 vaccination has been shown to reduce the incidence of COVID-19-related adverse pregnancy and neonatal health outcomes. Several systematic reviews showed that vaccinated mothers with a SARS-CoV-2 infection compared to unvaccinated mothers with an infection had a decreased risk of still or preterm birth, newborn death, NICU admissions and small for gestational age (SGA) [13-15].

Previously conducted studies were often based on surveillance data that lacked sufficient metadata on possible confounders. Furthermore, they often focused on hospitalized pregnant women with severe or critical COVID-19. This study aimed to explore the effect of SARS-CoV-2 infection and COVID-19 vaccination during pregnancy on neonatal outcomes in relatively healthy women from the general population while controlling for potential confounding.

Methods

Study population and design
VASCO is an ongoing observational population-based prospective cohort study in the Netherlands. The design and methods of this study have been described elsewhere [16]. Briefly, between May and December 2021 over 45,000 community-dwelling persons aged 18-85 years were included in the study. The main aim of VASCO is to assess vaccine effectiveness against SARS-CoV-2 infection of COVID-19 vaccines authorized in the Netherlands. Pregnancy status of participants was reported at

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baseline and through regular follow-up questionnaires. The current study was an extension to the main study. In January 2023 we invited all female VASCO participants aged <50 years who, since the start of VASCO, had reported to have given birth or to be pregnant for more than 28 weeks and whose due date had passed. All VASCO participants provided written informed consent. The study adheres to the Declaration of Helsinki's principles, and its protocol was approved by the non-profit independent medical ethics committee at the Stichting Beoordeling Ethiek Biomedisch Onderzoek in Assen, the Netherlands.

Data collection
All invited participants were asked to complete an additional one-time questionnaire on pregnancy and neonatal outcomes. These self-reported outcomes were gestational age, single or multiple birth, birth weight, Apgar-score, postpartum hospital stay including reason for stay (child's health, mother's health or both), hospital admission in the first week after delivery including reason for this admission, and NICU admissions.

Studied exposures were self-reported SARS-CoV-2 infections and COVID-19 vaccinations. During study follow-up, participants were asked about SARS-CoV-2 positive tests, either polymerase chain reaction (PCR) or (self-administered) antigen test, and COVID-19 vaccinations in the regular online questionnaires. Furthermore, participants were able to notify positive SARS-CoV-2 tests and COVID-19 vaccinations through the study website or app real-time. SARS-CoV-2 antigen lateral flow tests are provided to participants to facilitate self-testing in case of COVID-19-like symptoms. Fingerprick blood samples were collected every six months during follow-up. Whether a reported positive SARS-CoV-2 test during pregnancy was a first or recurring infection was based on self-reported positive SARS-CoV-2 tests and presence of antibodies against SARS-CoV-2 nucleocapsid protein (N-antibodies) in fingerprick blood samples before this infection [16]. Infections that occurred from 10 January 2022, when >90% of the infections in the Netherlands were caused by the Omicron variant [17], were considered to be Omicron infections. Infections were classified as symptomatic if symptoms were reported either in the questionnaire in which the infection was reported, or in the follow-up questionnaire which was received by all participants one month after their reported infection. In this latter questionnaire participants were also asked whether they had contact with their general practitioner or were hospitalized because of their symptoms. Infections were classified as asymptomatic if participants did not report symptoms in either questionnaire and reported to experience no symptoms in at least one of them. Data on self-reported vaccinations were cross-referenced with the COVID-19 vaccination records in the Dutch national vaccination information and monitoring system (CIMS)[16]. COVID-19 vaccines included those used in the Netherlands until the end of 2022.

Possible confounding factors, including age, educational level and presence of a medical risk condition were available from the VASCO baseline and regular follow-up questionnaires. Educational level was defined as low (no or primary education), intermediate (secondary school or vocational training), or high (bachelor's degree, university). Vaccination status was categorized as unvaccinated (no vaccination received), partly vaccinated (one dose of Vaxzevria, Comirnaty or Spikevax 7+ days ago), primary vaccination series received (one dose of Jcovden 28+ days ago, or two doses of Vaxzevria, Comirnaty or Spikevax 14+ days ago), or primary vaccination series and one booster received (primary vaccination series + one additional dose 7+ days ago). A medical risk condition was

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considered to be present if a participant reported having one or more of the following health conditions: diabetes mellitus, lung disease or asthma, asplenia, cardiovascular disease, immune deficiency, cancer, liver disease, neurological disease, renal disease, or having undergone organ or bone marrow transplantation.

Statistical analysis

Statistical analyses were performed using the statistical package R version 4.3.0. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR) when not-normally distributed. Categorical variables were presented as frequencies and percentages. Multivariable linear regression analysis was used to determine the association between SARS-CoV-2 infection or COVID-19 vaccination during pregnancy (any vs. none) and gestational age and birth weight (both continuous variables). Multivariable logistic regression analysis was used to determine the association between SARS-CoV-2 infection or COVID-19 vaccination during pregnancy (any vs. none) and Apgar score <9 (vs. 9 or 10), postpartum hospital stay (yes/no) and NICU admission (yes/no). Crude analyses were performed first, followed by analyses adjusted for age (continuous), educational level (categorized as described above), and presence of a medical risk condition (yes/no). Furthermore, the models with SARS-CoV-2 infection during pregnancy as the main exposure were additionally adjusted for COVID-19 vaccination status before pregnancy (categorized as described above) and COVID-19 vaccination during pregnancy. Similarly, the models with COVID-19 vaccination during pregnancy as the main exposure were additionally adjusted for SARS-CoV-2 infection before pregnancy and SARS-CoV-2 infection during pregnancy. Crude and adjusted regression coefficients and odds ratios (ORs) were presented with 95% confidence intervals (CI). P-values <0.05 were considered statistically significant.

Results

Study population

Of the 312 VASCO participants who were invited to complete the additional questionnaire on pregnancy and neonatal outcomes 232 responded (74%; **Table 1**). Half of the participants was already pregnant (106) or recently gave birth (9) at inclusion, while the other half became pregnant later during follow-up (117, 50%). Characteristics between responders and non-responders were comparable. Mean age of the responders was 32.6 (SD 3.9) and ranged between 22 and 44. Thirty seven women reported a medical risk condition (16%), with lung disease and asthma being most frequently reported (27; 73%). The majority of the women was of Dutch origin (85%) and had a high educational level (84%). Three women reported to have given birth to twins. The absolute number of reported childbirths reported by the participants was higher in 2022 compared with 2021, most likely the result of a larger number of study participants in this period (**Supplementary Figure S1**).

Of the 232 included women, 80 (34%) reported not to have been vaccinated before the start of their pregnancy. Others were vaccinated before pregnancy and either did not complete their primary series yet (16, 7%), completed their primary series (98, 42%) or already received a booster dose (38, 16%). 167 women (72%) reported to have been vaccinated during pregnancy. A total of 196 vaccinations, of which 62 (32%) were first doses, were reported during the first (75, 38%), second

(59, 30%) and third trimester (62, 32%) (**Figure 1A**). SARS-CoV-2 incidence among the sub-study sample of pregnant women (**Figure 1B**) corresponded well with the incidence in the entire VASCO study population [16] and the general Dutch population [18] during the same time period. The Omicron variant became dominant in January 2022, causing a large peak in incidence. In total, 109 women reported 115 infections during pregnancy. The majority of the infections concerned a first infection (86; 75%), were considered to be caused by the Omicron variant (95; 83%) and occurred after vaccination, referred to as breakthrough infections (101; 88%). Infections were reported to be symptomatic (n=97, 84%), asymptomatic (n=9, 8%) or symptom status was unknown (n=9, 8%). In total, 6 (5%) pregnant women reported a consult with their general practitioner and 2 (2%) a hospitalization because of the infection. Infections occurred more or less evenly in all trimesters of pregnancy, with 33 (29%), 45 (39%), 37 (32%) infections in the first, second, and third trimester, respectively.

Effect of SARS-CoV-2 infection during pregnancy on neonatal outcomes

None or only small non-significant differences were observed in gestational age, birth weight, Apgar-score, postpartum hospital stay, reasons for this stay and NICU admission between women with and without an infection during pregnancy (**Table 2**). In **Supplementary Table S1-S3** outcome descriptives are reported stratified by trimester in which infection occurred, by first and repeat infections, and by infection before and after vaccination. No deviances from the main results were observed here. Results of crude and adjusted models were comparable. Multivariable analyses, with adjustment for age, educational level, medical risk condition, COVID-19 vaccination status before pregnancy and COVID-19 vaccination during pregnancy showed that experiencing a SARS-CoV-2 infection during pregnancy was not statistically significantly associated with gestational age (β=1.7, 95%CI: -1.6-5.0) or birth weight (β=82, 95%CI: -59-223)(**Table 2**). Infection during pregnancy was not statistically significantly associated with Apgar score <9 (OR: 1.3, 95%CI: 0.6-2.9), postpartum hospital stay (OR: 1.0, 95%CI: 0.6-1.8) or NICU admission (OR: 0.8, 95%CI: 0.2-3.2) either.

Effect of COVID-19 vaccination during pregnancy on neonatal outcomes
None or only small non-significant differences were observed in gestational age, birth weight, Apgar-score, postpartum hospital stay, reasons for this stay and NICU admissions between women with and without COVID-19 vaccination during pregnancy (**Table 3**). In **Supplementary Table S4** outcome descriptives are reported stratified by trimester in which vaccination occurred. Univariable and multivariable analyses, with adjustment for age, educational level, medical risk condition, and SARS-CoV-2 infection during pregnancy, showed that there were no statistically significant associations between COVID-19 vaccination during pregnancy and gestational age (β= -0.4, 95%CI: -4.0-3.2), birth weight (β=88, 95%CI: -64-241)(**Table 3**). Vaccination during pregnancy was not statistically significantly associated with Apgar score <9 (OR: 0.9, 95%CI: 0.4-2.3), postpartum hospital stay (OR: 0.9, 95%CI: 0.5-1.7) or NICU admission (OR: 1.6, 95%CI: 0.4-8.6) either.

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Discussion

This study evaluated the effect of SARS-CoV-2 infection and COVID-19 vaccination during pregnancy on neonatal outcomes in a period when Omicron subtypes were prevalent and a high percentage of women was already vaccinated. Multivariable analyses showed that experiencing a SARS-CoV-2 infection or receiving COVID-19 vaccination during pregnancy was not significantly associated with gestational age, birth weight, Apgar-score, post-partum hospital stay or NICU admission.

Several systematic reviews and meta-analyses have been published on the effect of SARS-CoV-2 infection and/or COVID-19 vaccination during pregnancy on neonatal outcomes. Several studies reported that experiencing a SARS-CoV-2 infection during pregnancy was associated with preterm birth [19,20], lower birth weight or SGA [19-22], a 5-minute Apgar score <7 [21], NICU admission [20-23], but not with neonatal death [21]. We did not find these associations in our study. This might possibly be explained by the small sample size of this study. Also, studies included in the systematic reviews often included pregnant women who had been hospitalized because of COVID-19 whereas our participants mostly experienced mild SARS-CoV-2 infections. Indeed, several studies have suggested an association between severity of COVID-19 infection during pregnancy and adverse neonatal outcomes [24,25]. Furthermore, in our study a large percentage of the infections experienced during pregnancy were breakthrough infections (88%) and considered to be caused by the Omicron variant (95%), which could have mitigated the impact of infection on neonatal outcomes [7].

Studies have thus far not reported any evidence for an increased risk of earlier gestation or preterm birth [13,26,27], low or very low birth weight [13-15,26-28], Apgar score <7 [13-15], or NICU admission [13-15,26] after COVID-19 vaccination during pregnancy. Some studies even suggest a lower risk. This scientific evidence aligns with the results of this study. We observed a somewhat higher rate of blood sugar problems in newborns as reason for post-partum hospital stay among women who were vaccinated during pregnancy (9 of 39, 23%) compared to women who were not vaccinated during pregnancy (1 of 26, 4%). Numbers were small and differences were non-significant (p=0.125).

Strengths and limitations

This study has several strengths. Where most studies focus on pregnant women who were hospitalized because of COVID-19, we were able to assess the effects of infection and vaccination in relatively healthy women in the general population. The observed proportions of hospital births (77%), gestational age <37 weeks (5%) and Apgar score <7 (2%) were comparable to proportions in the Dutch population (73%, 7% and 2%, respectively)[29]. Also, estimates could be adjusted for confounders, including age, educational level and medical risk condition, using extensive data from regular questionnaires.

Some limitations need to be taken into account when interpreting the results of this study. As a result of a relatively small sample size we were only able to detect possible large effects, and not able to detect the effects of SARS-CoV-2 infection and COVID-19 vaccination on rare outcomes, including neonatal death. Our results could contribute to meta-analyses. Also, although the response rate was relatively high, some selection bias could have been present. For example, women who

experienced more severe adverse (neonatal) outcomes may have felt uncomfortable to complete the questionnaire. On the contrary, they may have been more motivated to contribute to research on the subject. In the study we relied on self-reported data for both exposure and outcome which might have resulted in misclassification. Based on serologic data [16] of the pregnant study population without reporting of a positive SARS-CoV-2 test, we suspect to have missed about 10% of the infections during pregnancy. Self-reported vaccination data was confirmed by linkage to vaccination registry data, limiting exposure misclassification.

Conclusion

In the current study, we did not find evidence of an association between SARS-CoV-2 infection or COVID-19 vaccination during pregnancy and gestational age, birth weight, Apgar-score, postpartum hospital stay and NICU admission. Our results add to the increasing evidence supporting safety of COVID-19 vaccination during pregnancy, specifically among the general pregnant population.

Conflicts of interest

None.

Data availability statement

Anonymized data reported from this study can be obtained from the corresponding author upon request. The dataset may include individual data and a data dictionary will be provided. Data requests should include a proposal for the planned analyses. Data transfer will require a signed data sharing agreement.

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Tables

Table 1. Baseline characteristics participants and non-respondents

	Sub-study participants (n=232)	Non-responders (n=80)
Age, mean (SD)*	32.6 (3.9)	32.5 (4.3)
Medical risk condition[1] 'yes', n (%)	37 (15.9)	11 (13.8)
Migrant status[2], n (%)		
Dutch origin	198 (85.3)	72 (90.0)
Migrant	15 (6.5)	5 (6.2)
Child of migrant(s)	19 (8.2)	3 (3.8)
Educational level[3], n (%)		
High	195 (84.1)	67 (83.8)
Intermediate	35 (15.1)	13 (16.2)
Low	2 (0.9)	0 (0)
COVID-19 vaccination status before pregnancy[4], n (%)		
Unvaccinated	80 (34.5)	11 (19.3)
Partly vaccinated (primary series not completed)	16 (6.9)	4 (7.0)
Primary series completed	98 (42.2)	32 (56.1)
At least one booster received	38 (16.4)	10 (17.5)
At least one COVID-19 vaccination during pregnancy[4], n (%)	165 (71.1)	30 (52.6)
At least one SARS-CoV-2 infection before pregnancy[4], n (%)	50 (21.6)	18 (31.6)
At least one SARS-CoV-2 infection during pregnancy[4], n (%)	109 (47.0)	32 (56.1)

SD – Standard deviation. *Age was missing for one person.

[1] Medical risk condition was present if one or more of the following health conditions was present: diabetes mellitus, lung disease or asthma, asplenia, cardiovascular disease, immune deficiency, cancer , liver disease, neurological disease, renal disease, or having undergone organ or bone marrow transplantation. [2] Migrant status was defined as Dutch origin (born in the Netherlands, as well as both parents), migrant (born outside of the Netherlands), child of migrant(s) (born in the Netherlands and one or both parents born abroad). [3] Educational level was defined as low (no or primary education), intermediate (secondary school or vocational

training), or high (bachelor's degree, university).[4] For non-responders this was based on due date, which was

known for 57 (71%) non-responders.

Table 2. Birth outcome descriptives stratified for SARS-CoV-2 infection during pregnancy

	No infection (n=126)	Infection (n=109)	Crude outcome measure (95%CI)	Adjusted[1] outcome measure (95%CI)	Adjusted[2] outcome measure (95%CI)
Gestational age in weeks, mean (SD)	39.7 (2.0)	39.8 (1.4)	1.0 (-2.2 - 4.2)[3]	0.9 (-2.3 - 4.1)[3]	1.7 (-1.6 - 5.0)[3]
Birth weight in grams, mean (SD)	3571 (572)	3605 (467)	34 (-102 - 169)[3]	41 (-94 - 175)[3]	82 (-59 - 223)[3]
Apgar score* <9, n (%)	15 (11.9)	17 (15.6)	1.3 (1.6 - 2.9)[4]	1.4 (0.7 - 3.1)[4]	1.3 (0.6 - 2.9)[4]
Gave birth in hospital, n (%)	93 (73.8)	89 (81.7)			
Stayed night in hospital, n (%)	50 (53.8)	48 (53.9)	1.2 (0.7 – 2.0)[4]	1.3 (0.7 - 2.2)[4]	1.0 (0.6 - 1.8)[4]
Due to child's health	20 (40.0)	13 (27.1)			
Due to mother's health	17 (34.0)	16 (33.3)			
Due to mother and child's health	13 (26.0)	19 (39.6)			
Reason when due to child's health, n (%)					
Jaundice	1 (3.0)	1 (3.1)			
Blood sugar problems	5 (15.2)	5 (15.6)			
Breathing disorder	1 (3.0)	3 (9.4)			
Infection	2 (6.1)	1 (3.1)			
Other	24 (72.3)	22 (68.8)			
NICU admission, n (%)	6 (4.8)	4 (3.7)	0.8 (0.2 - 2.7)[4]	0.8 (0.2 - 2.9)[4]	0.8 (0.2 - 3.2)[4]
Neonatal death, n (%)	0 (0)	0 (0)			

SD – Standard deviation, IQR – Interquartile range, CI - Confidence interval, NICU – Neonatal intensive care unit. * Apgar score was missing for 32 newborns.

[1]Adjusted for age, educational level (low, intermediate, high) and medical risk condition, reference groups was women without infection during pregnancy. [2]Additionally adjusted for vaccination status before pregnancy and COVID-19 vaccination during pregnancy. [3]Presented as regression coefficient. [4]Presented as odds ratio.

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Table 3. Birth outcome descriptives stratified for COVID-19 vaccination during pregnancy

	No vaccination (n=68)	Vaccination (n=167)	Crude outcome measure (95%CI)	Adjusted[1] outcome measure (95%CI)	Adjusted[2] outcome measure (95%CI)
Gestational age in weeks, mean (SD)	39.7 (2.4)	39.8 (1.5)	0.2 (-3.3 - 3.8)[3]	-0.6 (-4.1 - 3.0)[3]	-0.4 (-4.0 - 3.2)[3]
Birth weight in grams, mean (SD)	3511 (606)	3618 (486)	108 (-41 - 256)[3]	79 (-71 - 230)[3]	88 (-64 - 241)[3]
Apgar score* <9, n (%)	10 (14.7)	22 (13.2)	0.8 (0.3 - 1.8)[4]	0.9 (0.4 - 2.1)[4]	0.9 (0.4 - 2.3)[4]
Gave birth in hospital, n (%)	56 (82.4)	126 (75.4)			
Stayed night in hospital, n (%)	31 (55.3)	67 (53.2)	0.8 (0.5 - 1.4)[4]	0.9 (0.5 - 1.6)[4]	0.9 (0.5 - 1.7)[4]
Due to child's health	16 (51.6)	17 (25.4)			
Due to mother's health	5 (16.1)	28 (41.8)			
Due to mother and child's health	10 (32.3)	22 (32.8)			
Reason when due to child's health, n (%)					
Jaundice	2 (7.7)	0 (0)			
Blood sugar problems	1 (3.8)	9 (23.1)			
Breathing disorder	2 (7.7)	2 (5.1)			
Infection	1 (3.8)	2 (5.1)			
Other	20 (76.9)	26 (66.7)			
NICU admission, n (%)	3 (4.4)	7 (4.2)	0.9 (0.3 - 4.5)[4]	1.6 (0.4 - 8.6)[4]	1.6 (0.4 - 8.6)[4]
Neonatal death, n (%)	0 (0)	0 (0)			

SD – Standard deviation, IQR – Interquartile range, CI - Confidence interval, NICU – Neonatal intensive care unit. * Apgar score was missing for 32 newborns.

[1]Adjusted for age, educational level (low, intermediate, high) and medical risk condition, reference group was women without infection during pregnancy. [2]Additionally adjusted for SARS-CoV-2 infection before pregnancy and SARS-CoV-2 infection during pregnancy. [3]Presented as regression coefficient. [4]Presented as odds ratio.

Figures

Figure 1. Total number of COVID-19 vaccinations (A) and SARS-CoV-2 infections (B) per month, by trimester