Clinical Microbiology and Infection 31 (2025) 266–273

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Neurodevelopmental outcomes of infants after *in utero* exposure to SARS-CoV-2 or mRNA-COVID-19 vaccine compared with unexposed infants: a COVI-PREG prospective cohort study

Guillaume Favre [1], Rebecca L. Bromley [2], Matthew Bluett-Duncan [2], Emeline Maisonneuve [1,3,11], Léo Pomar [1,4], Charlotte Daire [1], Anda-Petronela Radan [5], Luigi Raio [5], Daniel Surbek [5], Carolin Blume [6], Stylianos Kalimeris [6], Yoann Madec [7], Juliane Schneider [8], Myriam Bickle Graz [8], Ursula Winterfeld [9], Alice Panchaud [3,10,†], David Baud [1,*,†]

[1] *Materno-Fetal and Obstetrics Research Unit, Woman-Mother-Child Department, Centre Hospitalier Universitaire Vaudois (CHUV), University Hospital, Lausanne, Switzerland*
[2] *Division of Neuroscience, School of Biological Sciences, Faculty of Medicine, Biology and Health, University of Manchester, Manchester, United Kingdom*
[3] *Institute of Primary Health Care Berner Institut für Hausarztmedizin (BIHAM), University of Bern, Bern, Switzerland*
[4] *School of Health Sciences Haute Ecole de Santé Vaud (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland*
[5] *Department of Obstetrics and Fetal-Maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland*
[6] *Kantonsspital Graubünden, Frauenklinik Fontana, Chur, Switzerland*
[7] *Emerging Diseases Epidemiology Unit, Institut Pasteur, Paris, France*
[8] *Clinic of Neonatology and Developmental Unit, Woman-Mother-Child Department, University Hospital Center and University of Lausanne, Lausanne, Switzerland*
[9] *Swiss Teratogen Information Service, Clinical Pharmacology Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*
[10] *Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*
[11] *Graduate School for Health Sciences (GHS), University of Bern, Bern, Switzerland*

ARTICLE INFO

Article history:
Received 10 August 2024
Received in revised form
15 October 2024
Accepted 20 October 2024
Available online 23 October 2024

Editor: L. Leibovici

Keywords:
ASQ
Child
COVI-PREG
COVID-19
Infant
mRNA
Neurodevelopment
Neurologic
SARS-CoV-2
Vaccine

ABSTRACT

Objectives: Data are lacking regarding the long-term consequences of SARS-CoV-2 and COVID-19 mRNA vaccine on infants exposed *in utero*. We aimed to evaluate the neurodevelopment of infants exposed prenatally to SARS-CoV-2 or mRNA-COVID-19 vaccine during pregnancy at 12 months after birth.
Methods: Infants born to mothers exposed to SARS-CoV-2 or mRNA-COVID-19 vaccine during pregnancy, or unexposed to either the virus or the vaccine were enrolled from 2021 to 2023. Infants with prenatal exposure to the virus or vaccine were compared with infants without prenatal exposure to the virus and/or vaccine. Parents received a neurodevelopmental questionnaire (ages and stages questionnaire third edition) at 12 months after birth assessing five subdomains: communication, gross motor, fine motor, problem-solving, and personal social development. A low score was defined as <2 standard deviations below the normative mean in at least one of the subdomains.
Results: A total of 330 infants were included (76 in the SARS-CoV-2 group, 153 in the mRNA-COVID-19 vaccine group, and 101 in the reference group). *In utero* exposure to the SARS-CoV-2 or mRNA-COVID-19 vaccine was not associated with an increased risk of a low score for at least one subdomain compared with the reference group. The crude ORs were 1.16 (95% CI, 0.59–2.28) and 1.04 (95% CI, 0.58–1.86), respectively. Results remained consistent in the multivariate analysis, showing no increased risk of a low score for at least one subdomain for infants exposed to the SARS-CoV-2 or mRNA-COVID-19 vaccine, compared with the reference group. The adjusted ORs were 1.74 (95% CI, 0.76–3.99) and 0.76 (95% CI, 0.39–1.49), respectively.

DOI of original article: https://doi.org/10.1016/j.cmi.2024.12.027.
* Corresponding author. David Baud, Materno-Fetal and Obstetrics Research Unit, Woman-Mother-Child Department, Centre Hospitalier Universitaire Vaudois (CHUV), University Hospital, Bureau Maternité CI/04-209, Avenue Pierre-Decker 2, CH-1011 Lausanne, Switzerland.
E-mail address: david.baud@chuv.ch (D. Baud).
† The last two authors contributed equally to the work.

https://doi.org/10.1016/j.cmi.2024.10.019

Discussion: In utero exposure to SARS-CoV-2 or mRNA-COVID-19 vaccine was not associated with an increased risk of a low score for at least one ages and stages questionnaire third edition subdomain at 12 months after birth. Additional studies are needed to confirm our results, especially longer-term evaluation of infant development. **Guillaume Favre, Clin Microbiol Infect 2025;31:266**

Introduction

Women who tested positive for SARS-CoV-2 during pregnancy have been reported to be at high risk for a severe form of the disease, including increased risk for admission to the intensive care unit, advanced oxygen requirements, and death [1,2]. They also have an increased risk of preterm delivery, often medically induced for maternal indication [1]. The risk of stillbirth seemed to be higher during the pandemic period, which may partially be attributed to placental deterioration caused by the virus itself [3,4]. A few cases were published reporting fetal hypoxia shortly after confirmed mild to moderate maternal COVID-19, leading to emergency delivery and critical neonatal situations. The placentas of these women showed critical intervillitis, resulting in acute placental insufficiency that may have been responsible for stillbirth if not detected on time [5]. Additionally, a positive test for SARS-CoV-2 during pregnancy has been associated with a higher incidence of low placental weight at birth [6]. The long-term consequences of exposure to SARS-CoV-2 during pregnancy still remain unclear [7]. Drawing an analogy with HIV-exposed uninfected infants, it is conceivable that infants exposed to SARS-CoV-2 during pregnancy might experience worse neurodevelopmental and infectious outcomes [8,9].

Since the advent of the COVID-19 vaccine, recommendations have progressively emerged to promote vaccination during pregnancy. Despite the exclusion of pregnant women from most clinical trials, evidence from observational studies showed that vaccines against SARS-CoV-2 are safe and effective to protect against severe COVID-19, for both the mother and her offspring due to the transplacental transfer of antibodies [10–13]. However, the long-term consequences of COVID-19 vaccine exposure during pregnancy on infant health are unknown [14].

A study by Shuffrey et al. [15] suggested that infants exposed *in utero* to SARS-CoV-2 did not report lower neurodevelopmental scores as measured by a standardized screen. However, the *in utero* exposure was associated with lower scores compared with a historical cohort of infants evaluated before the pandemic, especially in the gross motor, fine motor, and personal social subdomains of the test. Similarly, another study conducted by Edlow et al. [16] suggested that SARS-CoV-2 *in utero* exposure ($n = 222$) was associated with neurodevelopmental disorders at 1 year of life, however, they used only diagnostic codes for conditions, which are more often diagnosed outside of the included age range.

The neurodevelopmental impact of SARS-CoV-2 on infants exposed *in utero* continues to require better clarification. To the best of our knowledge, only one study has been published regarding the impact of COVID-19 vaccine exposure during pregnancy, which suggested no impact on infant neurodevelopment [17].

We thus aimed to investigate the neurodevelopment of infants born to mothers exposed to SARS-CoV-2 infection or COVID-19 vaccine during pregnancy compared with infants born to uninfected/unvaccinated mothers, at 12 months of life, using a standardized parent-based questionnaire.

Methods

Settings

Infants were enrolled in this study from September 2021 to April 2023 through the prospective COVI-PREG registry [1], which aims to assess the impact of SARS-CoV-2 infection in pregnant women and their newborns. Three Swiss hospitals participated in this study: Lausanne University Hospital, Bern University Hospital, and Chur Hospital. The Swiss Ethical Board (CER-VD-2020-00548) approved the study.

Participants

Liveborn infants were eligible for the study. Infants included were born to mothers within the subsample of the COVI-PREG registry from Lausanne University Hospital, Bern University Hospital, and Chur Hospital, as previously described in references [1,11,18]. Infants from multiple pregnancies and those with pathology known to induce a neurodevelopmental impairment (e.g. Down syndrome) were excluded. Infants born to mothers who were under the legal age of 18 years and/or who were not able to consent were also excluded. Written consent was obtained from both the mother and her partner, when applicable.

Data collection

Infants were eligible for inclusion if their mother was exposed to either SARS-CoV-2 or mRNA-COVID-19 vaccine during pregnancy. Pregnant women who tested positive for SARS-CoV-2 or received an mRNA-COVID-19 vaccine injection during pregnancy were initially included in the COVI-PREG registry [19] at the time of the positive test or vaccine injection, to investigate the impact of exposure on maternal, pregnancy, and neonatal outcomes. Investigators completed a form at inclusion and a follow-up form at the end of the pregnancy.

A comparison group, defined as the reference group, was selected by identifying infants born immediately after each included infant in the exposure group using data from the local delivery registries of the maternity unit.

Parents of eligible infants were contacted at 12 months after birth and invited to participate. If they accepted, parents received a consent form and a questionnaire with questions related to the exposure (virus/vaccine) during pregnancy and the age-dependent ages and stages questionnaire third edition (ASQ-3) [20]. Data were collected individually from medical records and stored as de-identified data using the Research Electronic Data Capture online database.

SARS-CoV-2/COVID-19 vaccine exposure and reference groups

Infants were allocated to the SARS-CoV-2 group if their mother tested positive for SARS-CoV-2 during pregnancy. Infants were allocated to the vaccine group if their mother was vaccinated with

at least one injection of COVID-19 mRNA vaccine between conception and the end of pregnancy and never tested positive for SARS-CoV-2 during pregnancy. Infants were allocated to the reference group if their mother was neither vaccinated nor tested positive for SARS-CoV-2 during pregnancy. No information was available about SARS-CoV-2 infection or vaccine exposure before the pregnancy.

If infants initially allocated to the reference group were exposed to the SARS-CoV-2 or COVID-19 vaccine during pregnancy, based on their answers to the questionnaire, they were reallocated to the corresponding groups. Infants whose mothers were exposed to both SARS-CoV-2 during pregnancy and COVID-19 vaccine during pregnancy were excluded.

Infant neurodevelopment follow-up

Infant neurodevelopment was assessed using the ASQ-3. This questionnaire was sent to the parents of the infant at 12 months after birth. The questionnaire was answered by parents at home. It assessed five subdomains of the neurodevelopment of the infant: communication, gross motor, fine motor, problem-solving, and personal social activities, individually scored on a total of 60. Premature infants were assessed using the adjusted age [20].

Neurodevelopment scores

A low neurodevelopmental score was defined as a score below the age-dependent 'referral' cut-off of the ASQ-3 subdomain [corresponding to <2 standard deviations (SDs) of the validated cohort] [20].

An intermediate neurodevelopmental score was defined as a score below the age-dependent 'monitoring' cut-off of the ASQ-3 subdomain (corresponding to <1 SD of the validated cohort) [20].

Composite low score subdomains outcome

We defined a composite low score subdomain outcome as an infant having at least one of the five subdomains with a score <2 SDs ('≥1 low score subdomain').

Covariates

Infant demographic characteristics included maternal characteristics, pregnancy, and neonatal outcomes as listed in Supplementary data.

Statistical analysis

We conducted descriptive statistics using absolute numbers (n), proportions (%), and 95% confidence intervals (CIs) for baseline characteristics, ASQ-3 scores, and the number of neurodevelopmental subdomains with low scores. Means and interquartile intervals were used for cord blood arterial pH. Means, SDs, and interquartile intervals were used for ASQ-3 scores. The association between SARS-CoV-2 or COVID-19 vaccine exposure during pregnancy and the presence of at least one neurodevelopmental subdomain with a low score was compared with the reference group. A multivariate analysis was performed using a logistic regression, adjusting for all potential confounding factors that were unbalanced between groups, defined as a standardized difference >10% between groups. Statistical analyses were performed with Stata (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Sensitivity analysis

The ASQ-3 questionnaire is, by definition, adjusted for prematurity with the use of corrected age based on gestational age at birth. However, because SARS-CoV-2 infection has been associated with birth below 37 weeks of gestation [22,23] and prematurity could also impact infant neurodevelopment, we conducted a sensitivity analysis excluding preterm infants [24].

Results

Altogether, 659 participants were approached for the study, including 88 who never answered, 5 who declined to participate, and 566 who accepted to participate at our phone call. Out of 566 who accepted by phone, 330 participants completed and returned the questionnaire. A total of 330 infants were included, with 76 in the SARS-CoV-2 group, 153 in the vaccine group, and 101 in the reference group. Baseline characteristics of patients are presented in Table 1.

Among infants in the SARS-CoV-2 group, prenatal exposure to the virus occurred during the first, second, and third trimesters, in 42.1% ($n = 32/76$), 21.1% ($n = 16/76$), and 35.5% ($n = 27/76$) of cases, respectively. The period of exposure was unknown in 1.3% ($n = 1/76$). Among mothers of infants prenatally exposed to SARS-CoV-2, 6.6% ($n = 5/76$) were asymptomatic, 86.8% (66/76) had mild to moderate symptoms, and were not hospitalized, 2.6% ($n = 2/76$) were hospitalized without oxygen requirements, and 3.9% ($n = 3/76$) required mechanical ventilation. Among infants in the vaccine group, prenatal exposure to the vaccine occurred during the first, second, and third trimesters in 9.8% ($n = 15/153$), 46.4% ($n = 71/153$), and 30.1% ($n = 46/153$) of cases, respectively. The period of exposure was unknown in 13.7% ($n = 21/153$) of cases. Mode of delivery was similar between groups, with vaginal delivery ranging from 79.7% to 84.2% of cases. Preterm deliveries accounted for 2.6% ($n = 2/76$), 7.2% ($n = 11/153$), and none in the SARS-CoV-2, COVID-19 vaccine, and reference groups, respectively. Apgar scores of <7 accounted for 1.3% ($n = 1/76$), 0.7% ($n = 1/156$), and 1.0% ($n = 1/101$) in the SARS-CoV-2, COVID-19 vaccine, and reference groups, respectively. Neonatal intensive care unit admission was higher in the SARS-CoV-2 group, accounting for 9.2% (7/76) compared with the COVID-19 vaccine and reference groups, with 3.3% ($n = 5/153$) and 3.0% ($n = 3/101$), respectively. Standardized differences between groups are reported in Table S1.

Neurodevelopmental scores

ASQ-3 mean scores and subdomain categories are presented in Table S2 and Table 2. A total of 76, 153, and 101 ASQ-3 questionnaires were completed at 12 months after birth in the SARS-CoV-2, COVID-19 vaccine, and reference groups, respectively.

SARS-CoV-2 group

The subdomains with the highest proportion of low scores at 12 months were gross motor skills ($n = 12/76$, 15.8%; 95% CI, 8.4–26.0), and problem-solving (8/76, 10.5%; 95% CI, 4.7–19.7).

Vaccine group

The subdomain with the highest proportion of low scores at 12 months was gross motor skills ($n = 33/153$, 21.6%; 95% CI, 15.3–28.9).

Reference group

The subdomain with the highest proportion of low scores at 12 months was gross motor skills ($n = 21/101$, 20.8%; 95% CI, 13.4–30.0).

Table 1
Baseline maternal, obstetrical, and neonatal characteristics of infants exposed to SARS-CoV-2 or COVID-19 vaccine during pregnancy compared with the reference group.

	SARS-CoV-2			COVID-19 vaccine			Reference		
	***n* = 76**			***n* = 153**			***n* = 101**		
	n	**%**		**n**	**%**		**n**	**%**	
Maternal age in years-*n* %									
≤25	4	5.3	%	1	0.7	%	2	2.0	%
26–30	20	26.3	%	22	14.4	%	31	30.7	%
31–35	34	44.7	%	71	46.4	%	40	39.6	%
36–40	14	18.4	%	48	31.4	%	26	25.7	%
>40	4	5.3	%	11	7.2	%	2	2.0	%
Maternal marital status-*n* %									
Married or domestic partnership	57	75.0	%	124	81.0	%	76	75.2	
Single never married	18	23.7	%	24	15.7	%	21	20.8	%
Divorced or separated	1	1.3	%	4	2.6	%	3	3.0	%
Widowed	0	0.0	%	0	0.0	%	0	0.0	%
Unknown	0	0.0	%	1	0.7	%	1	1.0	%
Maternal ethnicity-*n* %									
White	66	86.8	%	129	84.3	%	69	68.3	%
Hispanic or Latino	4	5.3	%	7	4.6	%	5	5.0	%
Black or African American	2	2.6	%	1	0.7	%	3	3.0	%
Asian or Pacific Islander	1	1.3	%	1	0.7	%	4	4.0	%
Other	2	2.6	%	4	2.6	%	6	5.9	%
Unknown	1	1.3	%	11	7.2	%	14	13.9	%
Mother education level-*n* %									
Higher education	59	77.6	%	135	88.2	%	73	72.3	%
Secondary school completed	10	13.2	%	14	9.2	%	22	21.8	%
Primary school or less	3	3.9	%	1	0.7	%	2	2.0	%
Unknown	4	5.3	%	3	2.0	%	4	4.0	%
Partner education level-*n* %									
Higher education	53	69.7	%	115	75.2	%	64	63.4	%
Secondary school completed	16	21.1	%	21	13.7	%	21	20.8	%
Primary school or less	1	1.3	%	1	0.7	%	4	4.0	%
Unknown	6	7.9	%	16	10.5	%	12	11.9	%
Maternal BMI-*n* %									
BMI >35	3	3.9	%	1	0.7	%	2	2.0	%
Maternal addiction									
Drug	0	0.0	%	1	0.7	%	2	2.0	%
Tobacco	7	9.2	%	6	3.9	%	13	12.9	%
Alcohol	1	1.3	%	3	2.0	%	1	1.0	%
Total	7	9.2	%	8	5.3	%	15	15.5	%
Maternal obstetrical history									
Nulliparous	30	39.5	%	87	56.9	%	56	55.4	%
Maternal medical history									
Pulmonary	2	2.6	%	19	12.4	%	4	4.0	%
Cardiac	0	0.0	%	3	2.0	%	2	2.0	%
Hypertensive	1	1.3	%	0	0.0	%	0	0.0	%
Diabetes	1	1.3	%	0	0.0	%	0	0.0	%
Immunosuppression	0	0.0	%	3	2.0	%	0	0.0	%
Neurological	1	1.3	%	0	0.0	%	1	1.0	%
Digestive	1	1.3	%	3	2.0	%	1	1.0	%
Renal	0	0.0	%	0	0.0	%	1	1.0	%
Urological	0	0.0	%	2	1.3	%	0	0.0	%
Oncological	0	0.0	%	0	0.0	%	0	0.0	%
Thyroid imbalance	4	5.3	%	15	9.8	%	5	5.0	%
Pregnancy complications									
Preeclampsia	2	2.6	%	4	2.6	%	2	2.0	%
Gestational diabetes	3	3.9	%	8	5.2	%	9	8.9	%
Intrauterine growth restriction	1	1.3	%	19	12.4	%	12	11.9	%
Abnormal fetal Doppler	0	0.0	%	0	0.0	%	0	0.0	%
Macrosomia	1	1.3	%	1	0.7	%	2	2.0	%
Threatened preterm labour	2	2.6	%	2	1.3	%	0	0.0	%
PPROM	0	0.0	%	4	2.6	%	0	0.0	%
Postpartum haemorrhage	1	1.3	%	22	14.4	%	14	13.9	%
SARS-CoV-2 exposure-Trimester of infection									
Trimester 1	32	42.1	%	—			—		
Trimester 2	16	21.1	%	—			—		
Trimester 3	27	35.5	%	—			—		
Unknown	1	1.3	%	—			—		
Vaccine exposure-trimester of injection									
Trimester 1	—			15	9.8	%	—		
Trimester 2	—			71	46.4	%	—		
Trimester 3	—			46	30.1	%	—		
Unknown	—			21	13.7	%	—		
Delivery									
Vaginal delivery	64	84.2	%	122	79.7	%	85	84.2	%
Caesarean delivery	12	15.8	%	31	20.3	%	16	15.8	%

(*continued on next page*)

Table 1 (*continued*)

	SARS-CoV-2			COVID-19 vaccine			Reference		
	***n* = 76**			***n* = 153**			***n* = 101**		
	n	**%**		**n**	**%**		**n**	**%**	
Gestational age at birth									
≥37 + 0 weeks	74	97.4	%	142	92.8	%	101	100.0	%
Preterm 32+0–36 + 6 wk	2	2.6	%	11	7.2	%	0	0.0	%
Preterm 28+0–31 + 6 wk	0	0.0	%	0	0.0	%	0	0.0	%
Preterm 24+0–27 + 6 wk	0	0.0	%	0	0.0	%	0	0.0	%
Neonatal details									
Female	45	59.2	%	87	56.9	%	57	56.4	%
Apgar <7 at 5 min	1	1.3		1	0.7	%	1	1.0	%
Weight at birth < p10[a]	3	3.9	%	7	4.6	%	8	7.9	%
Weight at birth < p3[a]	1	1.3	%	2	1.3	%	3	3.0	%
NICU admission	7	9.2	%	5	3.3	%	3	3.0	%

BMI, body mass index; NICU, neonatal intensive care unit; O_2, oxygen; pHa, arterial pH; PPROM, preterm premature rupture of membranes.
[a] <p10, <p3: birth weight <10th and 3rd percentile according to INTERGROWTH-21st charts [21].

Table 2
Description of ASQ-3 categories (normal, intermediate, and low) in infants, at 12 months after birth, after *in utero* exposure to SARS-CoV-2 infection or COVID-19 vaccine compared with the reference group.

	SARS-CoV-2																	
	Normal						Intermediate						Low					
	n	**%**		95% CI			*n*	**%**		95% CI			*n*	**%**		95% CI		
Follow-up at 12 months	*n* = 76																	
Communication	74	97.4	%	90.8	-	99.7	2	2.6	%	0.3	-	9.2	0	0.0	%	0.0	-	4.7
Gross motor	52	68.4	%	56.7	-	78.6	12	15.8	%	8.4	-	26.0	12	15.8	%	8.4	-	26.0
Fine motor	68	89.5	%	80.3	-	95.3	6	7.9	%	3.0	-	16.4	2	2.6	%	0.3	-	9.2
Problem-solving	64	84.2	%	74.0	-	91.6	4	5.3	%	1.5	-	12.9	8	10.5	%	4.7	-	19.7
Personal social	61	80.3	%	69.5	-	88.5	11	14.5	%	7.5	-	24.4	4	5.3	%	1.5	-	12.9
	COVID-19 vaccine																	
	Normal						**Intermediate**						**Low**					
	n	**%**		95% CI			*n*	**%**		95% CI			*n*	**%**		95% CI		
Follow-up at 12 months	*n* = 153																	
Communication	139	90.8	%	85.1	–	94.9	9	5.9	%	2.7	–	10.9	5	3.3	%	1.1	–	7.5
Gross motor	92	60.1	%	51.9	–	67.9	28	18.3	%	12.5	–	25.4	33	21.6	%	15.3	–	28.9
Fine motor	137	89.5	%	83.6	–	93.9	12	7.8	%	4.1	–	13.3	4	2.6	%	0.7	–	6.6
Problem-solving	133	86.9	%	80.5	–	91.8	15	9.8	%	5.6	–	15.7	5	3.3	%	1.1	–	7.5
Personal social	130	85.0	%	78.3	–	90.2	17	11.1	%	6.6	–	17.2	6	3.9	%	1.5	–	8.3
	Reference																	
	Normal						**Intermediate**						**Low**					
	n	**%**		95% CI			*n*	**%**		95% CI			*n*	**%**		95% CI		
Follow-up at 12 months	*n* = 101																	
Communication	95	94.1	%	87.5	–	97.8	2	2.0	%	0.2	–	7.0	4	4.0	%	1.1	–	9.8
Gross motor	68	67.3	%	57.3	–	76.3	12	11.9	%	6.3	–	19.8	21	20.8	%	13.4	–	30.0
Fine motor	90	89.1	%	81.3	–	94.4	8	7.9	%	3.5	–	15.0	3	3.0	%	0.6	–	8.4
Problem-solving	91	90.1	%	82.5	–	95.1	7	6.9	%	2.8	–	13.8	3	3.0	%	0.6	–	8.4
Personal social	90	89.1	%	81.3	–	94.4	8	7.9	%	3.5	–	15.0	3	3.0	%	0.6	–	8.4

Normal: score >1 standard deviation (SD). Intermediate: score >2SD and <1SD. Low: score <2SD. ASQ-3, ages and stages questionnaire third edition.

Composite low score subdomain outcome

Regarding our composite outcome, 27.6% (95% CI, 18.0–39.1; *n* = 21/76), 25.5% (95% CI, 18.8–33.2; *n* = 39/153) and 24.8% (95% CI, 16.7–34.3; *n* = 24/101) of infants had at least one subdomain with a low score in the SARS-CoV-2, vaccine, and reference groups, respectively (Table 3).

SARS-CoV-2 exposure *in utero* was not associated with an increased risk of having at least one subdomain with a low score at 12 months, compared with the reference group, with a crude OR of 1.16 (95% CI, 0.59–2.28) and an adjusted OR of 1.74 (95% CI, 0.76–3.99) (Table 4). Similarly, COVID-19 vaccine exposure *in utero* was not associated with an increased risk of having at least one subdomain with a low score in infants, compared with the reference group, with a crude OR of 1.04 (95% CI, 0.58–1.86) and an adjusted OR of 0.76 (95% CI, 0.39–1.49) (Table 4).

Sensitivity analysis

Two neonates were born preterm in the SARS-CoV-2 group, 11 in the COVID-19 vaccine group, and none in the reference group. After the exclusion of these preterm neonates, the SARS-CoV-2, COVID-19 vaccine, and reference groups were composed of 74, 142, and 101 infants, respectively (Table S3). ASQ-3 scores are presented in Tables S4 and S5. The proportion of infants with at least one subdomain with a low score is presented in Table S6. After excluding preterm births, results were unchanged with an adjusted OR of 1.58

Table 3
Numbers of ASQ-3 with low score domains in infants, at 12 months after birth, after *in utero* exposure to SARS-CoV-2 infection or COVID-19 vaccine compared with the reference group.

	SARS-CoV-2						COVID-19 vaccine						Reference					
	n	%		95% CI			*n*	%		95% CI			*n*	%		95% CI		
Follow-up at 12 months	***n* = 76**						***n* = 153**						***n* = 101**					
≥1 low score domain	21	27.6	%	18.0	–	39.1	39	25.5	%	18.8	–	33.2	25	24.8	%	16.7	–	34.3
No low score domain	55	72.4	%	60.9	–	82.0	114	74.5	%	66.8	–	81.2	76	75.2	%	65.7	–	83.3
1 low score domain	18	23.7	%	14.7	–	34.8	30	19.6	%	13.6	–	26.8	20	19.8	%	12.5	–	28.9
2 low score domain	1	1.3	%	0.0	–	7.1	6	3.9	%	1.5	–	8.3	3	3.0	%	0.6	–	8.4
3 low score domain	2	2.6	%	0.3	–	9.2	2	1.3	%	0.2	–	4.6	1	1.0	%	0.0	–	5.4
4 low score domain	0	—					0	—					0	—				
5 low score domain	0	—					1	0.7	%	0.0	–	3.6	1	1.0	%	0.0	–	5.4

Low: score <2SD. ASQ-3, ages and stages questionnaire third edition; SD, standard deviation.

Table 4
Association between the proportion of low neurodevelopment domain score and *in utero* exposure to SARS-CoV-2 infection or COVID-19 vaccine compared with controls among infants evaluated at 12 months after birth.

		Univariate analysis					Multivariate analysis				
		OR	95% CI			p	adj. OR	95% CI			p
12 months follow-up											
≥1 low score domain	SARS-CoV-2 vs. reference group	1.16	0.59	—	2.28	0.666	1.74[a]	0.76	—	3.99	0.188
	COVID-19 vaccine vs. reference group	1.04	0.58	—	1.86	0.895	0.76[b]	0.39	—	1.49	0.427

Adjustment with all potential confounding factors unbalanced between groups is defined as a standardized difference of >10%. Adj. OR, adjusted OR; BMI, body mass index.
[a] Maternal age, marital status, maternal ethnicity, maternal and partner education level, maternal BMI >35, maternal addiction, maternal nulliparous status, pregnancy complications, neonatal birth weight < p10, and admission to the neonatal intensive care unit.
[b] Maternal age, marital status, maternal ethnicity, maternal and partner education level, maternal addiction, maternal medical history, pregnancy complications, mode of delivery, prematurity, and neonatal birth weight < p10.

(95% CI, 0.69–3.66) and 0.83 (95% CI, 0.43–1.64), for SARS-CoV-2 and COVID-19 vaccine exposure *in utero*, respectively (Table S6).

Discussion

To the best of our knowledge, this is the first study investigating the neurodevelopmental impact in infants after COVID-19 vaccination exposure *in utero*. Infants exposed to the SARS-CoV-2 or COVID-19 vaccine *in utero* had neurodevelopmental ASQ-3 mean scores within the normal expected range in all five subdomains assessed. SARS-CoV-2 and COVID-19 vaccine exposure *in utero* does not appear to be associated with a significant increased risk of altered developmental trajectories at 12 months of life, when compared with an unexposed reference group, within the limits of the small sample size of this study.

These results are consistent with a recent study that assessed ASQ-3 scores at 6 months after birth in infants born to mothers exposed to COVID-19 during pregnancy. The authors did not find any association with neurodevelopmental changes in the five subdomains compared with infants born to mothers not exposed to the virus. However, they found that infants born during the pandemic, regardless of the maternal SARS-CoV-2 status, had lower scores than a historical cohort of infants assessed before the pandemic, highlighting the potential impact of the pandemic environment itself [15]. Similar results have been published in an update by this group, where again they found no difference between infants born to mothers with asymptomatic to mild SARS-CoV-2 infection during pregnancy compared with unexposed infants [25]. Our cohort extends this by including a contemporaneously recruited reference group of children not exposed to SARS-CoV-2 or a COVID-19 vaccine, and found no difference in the developmental trajectories in Swiss children with *in utero* exposure to either SARS-CoV-2 infection or COVID-19 vaccination.

Our findings contrast with those from the Edlow et al. [16] study, however, which used data from a population database including 222 patients who tested positive for SARS-CoV-2 during pregnancy. That study reported that SARS-CoV-2 exposure during pregnancy was more frequently associated with a neurodevelopmental disorder diagnosis in the exposed infants, with an OR of 2.17 (95% CI, 1.24–3.79; p 0.006) and an adjusted OR of 1.86 (95% CI, 1.03–3.36; p 0.04), compared with unexposed infants. This study did not distinguish between neurodevelopmental disorders, and the primary outcome definition was based on the International Classification of Disease 10th Revision for neurodevelopmental disorders, which may lack sensitivity. Additionally, follow-up was limited to 1 year of age, which is lower than the average age of diagnosis for most of the included neurodevelopmental disorder outcomes [16].

This study adds to the evidence that the COVID-19 vaccine during pregnancy appears to be safe for infant neurodevelopment. A study by Jaswa et al. [17] reported that COVID-19 vaccination was safe during pregnancy from the perspective of infant neurodevelopment up to 18 months of age. These findings align with previous studies that assessed the developmental and health outcomes of infants after exposure to influenza or pertussis vaccines during pregnancy [26–28].

Strengths and limitations

The strength of our research lies in the prospective inclusion of infants and the relatively large number of parents who responded to the questionnaires across all three groups. The patients were enrolled in Switzerland, mitigating potential confounders related to inter-cultural and socio-economic factors often present in international studies. The inclusion of a contemporary reference group is of major importance as the pandemic environment itself may represent a potential confounder, as previously described in reference [15].

Several limitations need to be addressed. First, the identification of SARS-CoV-2 exposure *in utero* was influenced by evolving testing policies, which changed over time and across hospitals. This may

have introduced a misclassification bias, a concern previously highlighted in our research. Second, the ASQ-3 is a parent-reported questionnaire and therefore open to a degree of bias. However, parents are well placed to understand their child's everyday development and the ASQ-3 has been demonstrated to be a sensitive and reliable predictor of clinical outcomes [29]. However, it will be important for future research to further investigate neurodevelopmental outcomes following SARS-CoV-2 and COVID-19 vaccine exposure using standardized and blinded research-administered direct assessments of development. Third, the size of the samples does not allow us to conclude on the significance of subtle differences. It is also important to mention that half of the solicited potential participants did not return the questionnaire, introducing a selection bias. Finally, symptoms caused by vaccination were not collected from the questionnaire sent to participants and could represent potential factors that have an influence on the outcome, such as fever during pregnancy.

Future research should focus on longer-term neurodevelopmental assessment of both *in utero* SARS-CoV-2 and COVID-19 vaccine exposure at and beyond 2 years of life. Neurodevelopment typically becomes more stable at this point and a better predictor of later developmental outcomes [30].

In conclusion, our findings indicate that both SARS-CoV-2 and COVID-19 vaccine exposure *in utero* were not associated with an increased risk of neurodevelopmental low scores of at least one of the five subdomains, as assessed by the ASQ-3, among infants compared with the reference group at 12 months after birth. However, these results remain limited and future studies should focus on larger sample sizes and explore neurodevelopmental outcomes beyond 2 years of age.

Author contributions

G.F., R.L.B., C.D., A.P., and D.B. conceived and designed the study. G.F., A.P., and D.B. were responsible for funding acquisition and project administration. G.F., E.M., L.P., C.D., and A.P. analysed and interpreted the data. G.F., E.M., and C.D. drafted the manuscript. A.P. and D.B. provided supervision and contributed equally to this work. All authors contributed to data collection, reviewed and edited the manuscript, made a significant contribution to manuscript drafting and revision, and accept accountability for the overall work. All authors approved the final version of the report.

Transparency declaration

Potential conflict of interest

A.P. received grants from the Swiss Federal Office of Public Health and the CHUV Foundation; also received grants from Vifor, the European Medicine Agency (EMA/2017/09/PE and EMA/2017/09/PE/11), the Fonds Paritaire RBP IV, and a H2020 grant (ConcePTION WP 3-4), outside the submitted work. The other authors declare that they have no conflicts of interest.

Financial report

This research was funded by a grant from the Swiss Federal Office of Public Health, and the CHUV Foundation. The research was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network which is a public academic partnership coordinated by the Utrecht University, The Netherlands. The project named CONSIGN has received support from the European Medicines Agency under the Framework service contract no. EMA/2018/28/PE. The content of this paper expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Data availability

Data are available through joint research agreements from the corresponding authors.

Acknowledgements

The authors would like to thank the parents for their participation in the study. The ages and stages questionnaire was used on licence from Brookes Publishing for the COVI-PREG study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.10.019.

References

[1] Vouga M, Favre G, Martinez-Perez O, Pomar L, Acebal LF, Abascal-Saiz A, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. Sci Rep 2021;11:13898. https://doi.org/10.1038/s41598-021-92357-y.
[2] Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID Multinational Cohort Study. JAMA Pediatr 2021;175:817–26. https://doi.org/10.1001/jamapediatrics.2021.1050.
[3] Schwartz DA. Stillbirth after COVID-19 in unvaccinated mothers can result from SARS-CoV-2 placentitis, placental insufficiency, and hypoxic ischemic fetal demise, not direct fetal infection: potential role of maternal vaccination in pregnancy. Viruses 2022;14:458. https://doi.org/10.3390/v14030458.
[4] DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization — United States, March 2020-September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1640–5. https://doi.org/10.15585/mmwrmm7047e1.
[5] Favre G, Mazzetti S, Gengler C, Bertelli C, Schneider J, Laubscher B, et al. Decreased fetal movements: a sign of placental SARS-CoV-2 infection with perinatal brain injury. Viruses 2021;13:2517. https://doi.org/10.3390/v13122517.
[6] Radan A-P, Baud D, Favre G, Papadia A, Surbek D, Baumann M, et al. Low placental weight and altered metabolic scaling after severe acute respiratory syndrome coronavirus type 2 infection during pregnancy: a prospective multicentric study. Clin Microbiol Infect 2022;28:718–22. https://doi.org/10.1016/j.cmi.2022.02.003.
[7] Abbas-Hanif A, Modi N, Majeed A. Long term implications of covid-19 in pregnancy. BMJ 2022;377:e071296. https://doi.org/10.1136/bmj-2022-071296.
[8] Kerr SJ, Puthanakit T, Vibol U, Aurpibul L, Vonthanak S, Kosalaraksa P, et al. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. AIDS Care 2014;26:1327–35. https://doi.org/10.1080/09540121.2014.920949.
[9] Wedderburn CJ, Weldon E, Bertran-Cobo C, Rehman AM, Stein DJ, Gibb DM, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health 2022;6:393–408. https://doi.org/10.1016/S2352-4642(22)00071-2.
[10] Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. Lancet 2020;396:e22. https://doi.org/10.1016/S0140-6736(20)31822-5.
[11] Favre G, Maisonneuve E, Pomar L, Winterfeld U, Daire C, de Tejada BM, et al. COVID-19 mRNA vaccine in pregnancy: results of the Swiss COVI-PREG registry, an observational prospective cohort study. Lancet Reg Health Eur 2022;18:100410. https://doi.org/10.1016/j.lanepe.2022.100410.
[12] Villar J, Conti CPS, Gunier RB, Ariff S, Craik R, Cavoretto PI, et al. Pregnancy outcomes and vaccine effectiveness during the period of omicron as the variant of concern, INTERCOVID-2022: a multinational, observational study. Lancet 2023;401:447–57. https://doi.org/10.1016/S0140-6736(22)02467-9.
[13] Favre G, Maisonneuve E, Pomar L, Daire C, Monod C, Martinez de Tejada BM, et al. Risk of congenital malformation following first trimester mRNA COVID-19 vaccine exposure in pregnancy: the COVI-PREG prospective cohort. Clin Microbiol Infect 2023;29:1306–12. https://doi.org/10.1016/j.cmi.2023.06.015.
[14] Karrow NA, Shandilya UK, Pelech S, Wagter-Lesperance L, McLeod D, Bridle B, et al. Maternal COVID-19 vaccination and its potential impact on fetal and neonatal development. Vaccines (Basel). 2021;9:1351. https://doi.org/10.3390/vaccines9111351.

[15] Shuffrey LC, Firestein MR, Kyle MH, Fields A, Alcántara C, Amso D, et al. Association of birth during the COVID-19 pandemic with neurodevelopmental status at 6 months in infants with and without *in utero* exposure to maternal SARS-CoV-2 infection. JAMA Pediatr 2022;176:e215563. https://doi.org/10.1001/jamapediatrics.2021.5563.

[16] Edlow AG, Castro VM, Shook LL, Kaimal AJ, Perlis RH. Neurodevelopmental outcomes at 1 year in infants of mothers who tested positive for SARS-CoV-2 during pregnancy. JAMA Netw Open 2022;5:e2215787. https://doi.org/10.1001/jamanetworkopen.2022.15787.

[17] Jaswa EG, Cedars MI, Lindquist KJ, Bishop SL, Kim Y-S, Kaing A, et al. *In utero* exposure to maternal COVID-19 vaccination and offspring neurodevelopment at 12 and 18 months. JAMA Pediatr 2024;178:258–65. https://doi.org/10.1001/jamapediatrics.2023.5743.

[18] Favre G, Maisonneuve E, Pomar L, Daire C, Poncelet C, Quibel T, et al. Maternal and perinatal outcomes following pre-Delta, Delta, and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry. Lancet Reg Health Eur 2023;26:100569. https://doi.org/10.1016/j.lanepe.2022.100569.

[19] Panchaud A, Favre G, Pomar L, Vouga M, Aebi-Popp K, Baud D. An international registry for emergent pathogens and pregnancy. Lancet 2020;395:1483–4. https://doi.org/10.1016/S0140-6736(20)30981-8.

[20] Squire J, Twombly E, Bricker D, Potter L. ASQ-3:User's guide. BaltimoreBrookes Publishing: Ages & Stages Questionnaires®; 2009. Third Edition (ASQ-3TM).

[21] Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, et al. Postnatal growth standards for preterm infants: the preterm postnatal follow-up study of the INTERGROWTH-21st project. Lancet Glob Health 2015;3:e681–91. https://doi.org/10.1016/S2214-109X(15)00163-1.

[22] Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy – SET-NET, 16 jurisdictions, March 29-October 14, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1635–40. https://doi.org/10.15585/mmwr.mm6944e2.

[23] Karasek D, Baer RJ, McLemore MR, Bell AJ, Blebu BE, Casey JA, et al. The association of COVID-19 infection in pregnancy with preterm birth: a retrospective cohort study in California. Lancet Reg Health Am 2021;2:100027. https://doi.org/10.1016/j.lana.2021.100027.

[24] Chen Z, Xiong C, Liu H, Duan J, Kang C, Yao C, et al. Impact of early term and late preterm birth on infants' neurodevelopment: evidence from a cohort study in Wuhan, China. BMC Pediatr 2022;22:251. https://doi.org/10.1186/s12887-022-03312-3.

[25] Firestein MR, Shuffrey LC, Hu Y, Kyle M, Hussain M, Bianco C, et al. Assessment of neurodevelopment in infants with and without exposure to asymptomatic or mild maternal SARS-CoV-2 infection during pregnancy. JAMA Netw Open 2023;6:e237396. https://doi.org/10.1001/jamanetworkopen.2023.7396.

[26] Foo DYP, Sarna M, Pereira G, Moore HC, Fell DB, Regan AK. Early childhood health outcomes following *in utero* exposure to influenza vaccines: a systematic review. Pediatrics 2020;146:e20200375. https://doi.org/10.1542/peds.2020-0375.

[27] Foo D, Sarna M, Pereira G, Moore HC, Regan AK. Association between maternal influenza vaccination and neurodevelopmental disorders in childhood: a longitudinal, population-based linked cohort study. Arch Dis Child 2023;108:647–53. https://doi.org/10.1136/archdischild-2022-324269.

[28] Laverty M, Crowcroft N, Bolotin S, Hawken S, Wilson K, Amirthalingam G, et al. Health outcomes in young children following pertussis vaccination during pregnancy. Pediatrics 2021;147:e2020042507. https://doi.org/10.1542/peds.2020-042507.

[29] Bluett-Duncan M, Bullen P, Campbell E, Clayton-Smith J, Craig J, García-Fiñana M, et al. The use of parent-completed questionnaires to investigate developmental outcomes in large populations of children exposed to antiseizure medications in pregnancy. Epilepsia 2024;65:2017–29. https://doi.org/10.1111/epi.18001.

[30] Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389:77–90. https://doi.org/10.1016/S0140-6736(16)31389-7.