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In Utero Exposure to Maternal COVID-19 Vaccination and Offspring Neurodevelopment at 12 and 18 Months

Eleni G. Jaswa, MD, MSc; Marcelle I. Cedars, MD; Karla J. Lindquist, PhD; Somer L. Bishop, PhD; Young-Shin Kim, MD, MS, MPH, PhD; Amy Kaing, MD; Mary Prahl, MD; Stephanie L. Gaw, MD, PhD; Jamie Corley, BS; Elena Hoskin, MS; Yoon Jae Cho, MD; Elizabeth Rogers, MD; Heather G. Huddleston, MD

IMPORTANCE Uptake of COVID-19 vaccines among pregnant individuals was hampered by safety concerns around potential risks to unborn children. Data clarifying early neurodevelopmental outcomes of offspring exposed to COVID-19 vaccination in utero are lacking.

OBJECTIVE To determine whether in utero exposure to maternal COVID-19 vaccination was associated with differences in scores on the Ages and Stages Questionnaire, third edition (ASQ-3), at 12 and 18 months of age.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study, Assessing the Safety of Pregnancy During the Coronavirus Pandemic (ASPIRE), enrolled pregnant participants from May 2020 to August 2021; follow-up of children from these pregnancies is ongoing. Participants, which included pregnant individuals and their offspring from all 50 states, self-enrolled online. Study activities were performed remotely.

EXPOSURE In utero exposure of the fetus to maternal COVID-19 vaccination during pregnancy was compared with those unexposed.

MAIN OUTCOMES AND MEASURES Neurodevelopmental scores on validated ASQ-3, completed by birth mothers at 12 and 18 months. A score below the established cutoff in any of 5 subdomains (communication, gross motor, fine motor, problem solving, social skills) constituted an abnormal screen for developmental delay.

RESULTS A total of 2487 pregnant individuals (mean [SD] age, 33.3 [4.2] years) enrolled at less than 10 weeks' gestation and completed research activities, yielding a total of 2261 and 1940 infants aged 12 and 18 months, respectively, with neurodevelopmental assessments. In crude analyses, 471 of 1541 exposed infants (30.6%) screened abnormally for developmental delay at 12 months vs 203 of 720 unexposed infants (28.2%; $\chi^2 = 1.32$; $P = .25$); the corresponding prevalences at 18 months were 262 of 1301 (20.1%) vs 148 of 639 (23.2%), respectively ($\chi^2 = 2.35$; $P = .13$). In multivariable mixed-effects logistic regression models adjusting for maternal age, race, ethnicity, education, income, maternal depression, and anxiety, no difference in risk for abnormal ASQ-3 screens was observed at either time point (12 months: adjusted risk ratio [aRR], 1.14; 95% CI, 0.97-1.33; 18 months: aRR, 0.88; 95% CI, 0.72-1.07). Further adjustment for preterm birth and infant sex did not affect results (12 months: aRR, 1.16; 95% CI, 0.98-1.36; 18 months: aRR, 0.87; 95% CI, 0.71-1.07).

CONCLUSIONS AND RELEVANCE Results of this cohort study suggest that COVID-19 vaccination was safe during pregnancy from the perspective of infant neurodevelopment to 18 months of age. Additional longer-term research should be conducted to corroborate these findings and buttress clinical guidance with a strong evidence base.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Eleni G. Jaswa, MD, MSc, Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Reproductive Endocrinology and Infertility, University of California, San Francisco, 499 Illinois St, San Francisco, CA 94158-2519 (eleni.jaswa@ucsf.edu).

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In the COVID-19 pandemic, a virus never before seen by the human species spread globally taking a death toll of nearly 7 million.[1] The daily lives of billions were fundamentally altered as populations improvised countermeasures, first via public health interventions and ultimately via novel vaccinations and medications. As societies emerge from this acute phase, there is a need to better understand the longer-term sequelae of both the virus and the interventions directed against it.

One group facing many unanswered questions includes individuals who were pregnant during the pandemic and their offspring. Although pregnancy was identified as a high-risk condition early in the pandemic in light of an increased risk of severe disease and death,[2,3] considerations surrounding the impact of exposures to the offspring, in the form of infectious agents or countermeasures, remain poorly understood.

Problematically, pregnant individuals were excluded from the initial large-scale randomized clinical trials of COVID-19 vaccines. Despite subsequent demonstrations of COVID-19 vaccine safety and efficacy in pregnant individuals[4-7] and guidance from professional organizations recommending vaccination of this population,[8] vaccine hesitancy obstructed universal vaccine uptake. As of May 2022, the majority of those planning pregnancy or currently pregnant expressed doubt if pregnant people should get the COVID-19 vaccine in a Kaiser Family Foundation study.[9] Indeed, early safety data focused on vaccine adverse effects and short-term perinatal outcomes such as miscarriage and preterm birth,[6] but longer-term offspring developmental outcomes could not yet be assessed when real-time guidance was issued.

Sources of vaccine hesitancy include unknown risks to the fetus. Although a popular concern linking childhood vaccination and risk of autism spectrum disorder has been debunked,[10-12] misinformation persists.[13]

Neurodevelopmental disorders comprise a heterogeneous group of behaviorally defined conditions characterized by early abnormalities in cognitive, motor, language, and/or social development; autism spectrum disorder falls within the umbrella of neurodevelopmental disorders.[14] A range of genetic and environmental factors may underlie neurodevelopmental disorders, and fetal exposure to maternal inflammation represents a potential source of risk[15] that has found increasing support from converging lines of epidemiologic[16-20] and animal model evidence.[21-24] For example, in utero exposures to other infections including influenza and rubella have been linked to subsequent increases in lifelong neurodevelopmental and psychiatric impairments including autism spectrum disorder, intellectual disability, schizophrenia, anxiety, and depression.[16-20]

COVID-19 disease is characterized in some cases by profound immune activation, and, indeed, vaccines against COVID-19 also prompt a systemic immune response. Early studies have examined the association of maternal COVID-19 infection and early childhood neurodevelopment with mixed results.[25-29] However, no publication, to the authors' knowledge, has yet examined the association between maternal COVID-19 vaccination and offspring neurodevelopment. The purpose of this study was to begin to fill this critical knowledge gap.

Key Points

Question Is previous exposure to maternal COVID-19 vaccination in utero associated with increased risk for neurodevelopmental impairment in 12- and 18-month-old infants?

Findings In this cohort study including 2261 and 1940 infants aged 12 and 18 months, respectively, in utero exposure to COVID-19 vaccination was not associated with abnormal neurodevelopmental scores on the Ages and Stages Questionnaire, third edition, at 12 or 18 months of life.

Meaning Results suggest that maternal vaccination against COVID-19 during pregnancy was safe from the perspective of offspring neurodevelopment up to age 18 months.

Methods

Study Design and Participants

This was a prospective cohort study launched in April 2020 to better understand the implications of COVID-19 for pregnancy. Pregnant individuals aged 18 years and older at 10 weeks' or less gestation were eligible to self-enroll via a secure REDCap platform (Vanderbilt University). Participants provided written informed consent and self-identified with the following race and ethnicity categories: Asian, Black, Hispanic, multiracial/other (which included all races and ethnicities not covered by the aforementioned self-identified groupings), and White. Race and ethnicity information was included to characterize and investigate sociodemographic determinants of health. The study was approved by the University of California San Francisco institutional review board and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[30]

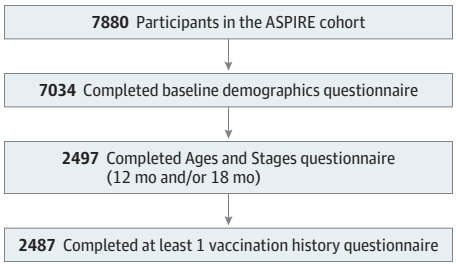
Participant recruitment occurred between May 2020 and August 2021 and leveraged partnerships with 2 organizations: the Society for Assisted Reproductive Technology, a centralized reporting organization for American reproductive health clinics, and BabyCenter, an online platform reaching 32 million expecting parents globally each month, including 90% of first-time expecting parents in the US. Recruitment materials highlighted the opportunity to participate in a study on pregnant individuals and their babies during the pandemic. Participants were followed up through pregnancy and for up to 2 years post partum, completing study activities remotely.

Eligibility for inclusion required the following: (1) completion of the baseline demographics questionnaire, (2) completion of Ages and Stages Questionnaire, third edition (ASQ-3) at 12 and/or 18 months postpartum, and 3) completion of vaccination history questionnaire, distributed monthly.

Outcome

The primary outcome was an abnormal screen on the ASQ-3,[31] indicating risk for developmental delay. An abnormal screen was defined as falling below the established threshold score (<2 SDs below the normative data average) on any of 5 subdomains: communication, gross motor, fine motor, problem solving, and social skills.

Figure 1. Study Inclusion/Exclusion Criteria and Sample Sizes



ASPIRE indicates Assessing the Safety of Pregnancy During the Coronavirus Pandemic.

Birth mothers completed the age-appropriate versions of the ASQ-3 at 12 and 18 months. The 30-item questionnaire asks parents to indicate the frequency with which their child performs expected milestones. Scores range from 0 (worst) to 60 (best) in each domain. The screener is valid, reliable, and ubiquitous in clinical and research settings, with sensitivity of 86%, specificity 85%,[32] and positive and negative predictive values of 54% and 78%, respectively.[33]

Exposure and Covariates

The primary exposure was COVID-19 vaccination during pregnancy. This was indicated by self-report and confirmed by investigators using dates of vaccination compared against estimated dates of conception and delivery. Any dose of a vaccine series during pregnancy qualified as exposure. Although all formulations were considered, the vast majority were messenger RNA (mRNA) vaccines. The unexposed cohort included participants not receiving COVID-19 vaccination during pregnancy, including individuals vaccinated before conception, after delivery, and never vaccinated. Covariates were selected a priori based on subject matter knowledge of relevant confounders: maternal age, race, ethnicity, education, and household income, maternal depression symptoms at baseline (Patient Health Questionnaire 9, score >4[34]), and generalized anxiety symptoms at baseline (Generalized Anxiety Disorder 7, score >4[35]). Additional potential mediator or effect modifier variables (preterm birth, infant sex, and COVID-19 infection during pregnancy) were added in subsequent iterations to isolate independent associations of the primary exposure with the outcome.

Statistical Analysis

Mixed-effects logistic regression models investigated associations between the primary exposure (COVID-19 vaccination during pregnancy) and outcome (abnormal developmental delay screen) at 12 and 18 months. To optimize power and ensure the same participants in all analyses, a single model was used. The primary exposure, timing of outcome measurement (12 or 18 months), an interaction term between exposure and timing of outcome measurement, and all covariates were modeled as fixed-effects terms. Random intercepts were used to account for the repeated measures correlation within participants. Risk ratios (RRs) were calculated for both time points using marginal predicted probabilities. Robust SEs and an unstructured correlation matrix for random effects were used.

An unadjusted base model was first analyzed (model 1). Next, we adjusted for confounders including maternal age, race, ethnicity, education, household income, maternal depression, and maternal anxiety (model 2). We subsequently added preterm birth (<37 weeks' gestation) and offspring sex as potential mediators or outcome modifiers to isolate the independent associations with the primary exposure (model 3).

Given established differences in the prevalence of neurodevelopmental disorders between male and female children and the widely held belief that sex-specific differences in vulnerability to in utero exposures may contribute to these differences,[36,37] we asked whether offspring sex modulated the association between COVID-19 vaccination and abnormal ASQ screen. Using marginal probabilities from models containing an interaction between infant sex, primary exposure (vaccination status), and age of outcome (12 or 18 months), we generated estimates for adjusted RRs (aRRs) for male and female offspring separately. We incorporated covariates progressively in 3 models analogous to the primary analyses.

Given the dynamic nature of embryonic and fetal development and the potential for critical windows of exposure, we asked whether trimester of vaccination affected the association between exposure and outcome, again generating estimates via marginal probabilities. We also asked whether COVID-19 infection during pregnancy (by self-report) was associated with our findings by adding this as a covariate (model 3), performing a likelihood ratio (LR) test to assess fit.

Lastly, we examined the sensitivity of our findings to missing data by (1) comparing rates of missing outcome data at 12 and 18 months between outcome groups (delay vs no delay), (2) examining the risk of delay among those with complete (12- and 18-month ASQ-3) vs incomplete data, and (3) assessing whether addition of an indicator of missing data contributed to overall model fit via LR testing. Analyses were conducted with R, version 4.2.3 (R Foundation for Statistical Computing)[38] and Stata/BE, version 18.0 (StataCorp)[39] software. All P values were 2-sided, and $P < .05$ was considered statistically significant.

Results

Ultimately, 7880 individuals from all 50 states and Puerto Rico initiated study activities, 7034 completed the baseline demographics questionnaire, 2497 completed the ASQ-3, and 2487 participants (mean [SD] age, 33.3 [4.2] years) completed at least 1 vaccination history questionnaire, yielding a total of 2261 and 1940 infants aged 12 and 18 months, respectively, with neurodevelopmental assessments (**Figure 1**). Characteristics of study participants overall and by exposure group are listed in **Table 1**. Participants self-identified with the following race and ethnicity categories: 113 Asian (4.6%), 52 Black (2.1%), 205 Hispanic (8.5%), 95 multiracial/other (3.9%), and 2178 White (89.3%). Overall, 68.0% of participants (1692 of 2487) reported vaccination during pregnancy. Among the vaccinated, a total of 1290 participants (76.2%) reported use of an

mRNA vaccine, and 59 participants (3.5%) reported a viral-vector vaccine. The remaining 343 individuals (20.3%) were uncertain of the type of vaccine used.

The prevalence of abnormal screens for developmental delay (ASQ-3 scores below established cutoff on at least 1 domain) at 12 months was 30.6% (471 of 1541) among exposed vs 28.2% (203 of 720) among unexposed (χ^2= 1.32; P = .25); at 18 months, the prevalence was 20.1% (262 of 1301) among exposed vs 23.2% (148 of 639) among unexposed (χ^2= 2.35; P = .13). The unadjusted model revealed no difference in developmental delay risk based on exposure at either time point in model 1 (12 months: RR, 1.08; 95% CI, 0.94-1.23; 18 months: RR, 0.86; 95% CI, 0.72-1.02) (**Table 2**).

After adjusting for baseline maternal age, race, ethnicity, education, household income, anxiety, and depression, no differences were observed in risk of an abnormal screen on the ASQ-3 after in utero exposure to COVID-19 vaccination at either 12 or 18 months in model 2 (12 months: aRR, 1.14; 95% CI, 0.97-1.33; 18 months: aRR, 0.88; 95% CI, 0.72-1.07) (Table 2). Subsequent addition of preterm birth and infant sex to the model did not affect results in model 3 (12 months: aRR, 1.16; 95% CI, 0.98-1.36; 18 months: aRR, 0.87; 95% CI, 0.71-1.07) (Table 2). A visual summary is captured in **Figure 2**.

We observed more abnormal screens for developmental delay among male vs female infants at 12 and 18 months of age overall, without regard to exposure status (12 months: 325 of 980 [33.2%] vs 278 of 984 [28.3%]; χ^2 = 5.57; P = .02; 18 months: 210 of 872 [24.1%] vs 161 of 836 [19.3%]; χ^2 = 5.84; P = .02). On calculating stratified estimates by sex from a model including interactions between sex, exposure, and age, at 12 months of age, we observed an increased risk of delay among exposed male infants in the unadjusted and adjusted analyses in model 3 (aRR, 1.29; 95% CI, 1.04-1.62) (**Table 3**)—a difference that was not sustained at 18 months (aRR, 1.06; 95% CI, 0.80-1.41) (Table 3). Meanwhile, a divergent pattern was observed for female infants. At age 12 months, there was no difference in risk of abnormal ASQ-3 screen among exposed vs unexposed (model 3 aRR, 1.02; 95% CI, 0.81-1.30) (Table 3); however, a reduction in risk was observed among exposed female infants at age 18 months (model 3 aRR, 0.69; 95% CI, 0.51-0.93) (Table 3).

Supplemental analyses exploring trimester of vaccine were conducted. Among individuals vaccinated during, 574 of 1674 (34.3%) were vaccinated in the first trimester, 751 of 1674 (44.7%) in the second, and 349 of 1674 (20.9%) in the third. There was no difference in prevalence of abnormal screen for developmental delay based on trimester of exposure at either 12 or 18 months. Abnormal 12-month screen for first, second, or third trimester vaccination exposure was 32.5% (170 of 523), 30.7% (212 of 690), and 26.1% (82 of 314), respectively (χ^2 = 3.86; P = .15). The corresponding figures at 18 months were 20.7% (92 of 444), 21.2% (120 of 567), and 17.5% (48 of 274), respectively (χ^2 = 1.62; P = .45). Null findings were sustained in all models (eTable in Supplement 1), with an exception of a signal for reduced developmental delay risk at 18 months after third trimester vaccination in the partially adjusted but not fully adjusted models (aRR, 0.72; 95% CI, 0.52-1.00 and aRR, 0.78; 95% CI, 0.56-1.09, respectively) (eTable in Supplement 1).

Table 1. Participant Characteristics, by In Utero COVID-19 Vaccination Exposure

Characteristic	Overall cohort (N = 2487)	Never vaccinated/ not during pregnancy (n = 795)	Vaccinated during pregnancy (n = 1692)
Measured at baseline			
Maternal age, mean (SD), y	33.3 (4.2)	32.9 (4.4)	33.4 (4.0)
Race, No. (%)			
Asian	113 (4.6)	31 (4.0)	82 (4.9%)
Black	52 (2.1)	28 (3.6)	24 (1.4)
Multiracial/other[a]	95 (3.9)	32 (4.1)	63 (3.8)
White	2178 (89.3)	682 (88.2)	1496 (89.8)
Hispanic ethnicity, No. (%)			
No	2214 (91.5)	705 (91.0)	1509 (91.8)
Yes	205 (8.5)	70 (9.0)	135 (8.2)
Education, No. (%)			
Less than bachelor's degree	301 (12.2)	140 (17.7)	161 (9.6)
Bachelor's degree	819 (33.1)	276 (34.9)	543 (32.3)
Graduate degree	1351 (54.7)	374 (47.3)	977 (58.1)
Household income, No. (%)			
<$50 000	186 (7.5)	87 (11.0)	99 (5.9)
$50 000-$99 000	635 (25.7)	257 (32.5)	378 (22.5)
$100 000-$250 000	1296 (52.4)	353 (44.7)	943 (56.0)
>$250 000	356 (14.4)	93 (11.8)	263 (15.6)
General anxiety (GAD-7), No. (%)			
Minimal	1612 (66.0)	517 (66.7)	1095 (65.6)
Mild-severe	832 (34.0)	258 (33.3)	574 (34.4)
Depression (PHQ-9), No. (%)			
Minimal	1316 (54.2)	428 (55.6)	888 (53.6)
Mild-severe	1110 (45.8)	342 (44.4)	768 (46.4)
Measured after baseline			
Infant sex, No. (%)			
Female	1049 (49.2)	272 (51.2)	710 (48.6)
Male	1066 (50.0)	254 (47.8)	742 (50.8)
Female and male	15 (0.7)	5 (0.9)	10 (0.7)
Premature (<37-wk gestation), No. (%)			
No	2312 (96.1)	724 (95.6)	1588 (96.4)
Yes	93 (3.9)	33 (4.4)	60 (3.6)
COVID-19 infection, No. (%)			
Never/not during pregnancy	2372 (95.4)	736 (92.6)	1636 (96.7)
During pregnancy	115 (4.6)	59 (7.4)	56 (3.3)

Abbreviations: GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire 9.

[a] Other included all other races not comprised in Asian, Black, and White categories.

To explore a potential mediation effect by COVID-19 infection, we included a history of infection during pregnancy in the fully adjusted model and found no association with delay (aRR, 1.15; 95% CI, 0.59-2.23) and no improvement in overall model fit (LR test, P = .69).

Finally, a sensitivity analysis for missing data was performed. Although 1714 of 2487 participants (68.9%) submitted complete ASQ-3 questionnaires at both 12 and 18 months,

Table 2. Risk of Child's Abnormal Developmental Screen at 12 and 18 Months, by In Utero COVID-19 Vaccination Exposure

Covariate	Model 1, RR (95% CI)[a]	aRR (95% CI) Model 2[b]	aRR (95% CI) Model 3[c]
Vaccinated during pregnancy (ref: never/not vaccinated during pregnancy): 12 mo[d]	1.08 (0.94-1.23)	1.14 (0.97-1.33)	1.16 (0.98-1.36)
Vaccinated during pregnancy (ref: never/not vaccinated during pregnancy): 18 mo[d]	0.86 (0.72-1.02)	0.88 (0.72-1.07)	0.87 (0.71-1.07)
Maternal age (per year)	NA	1.08 (1.05-1.12)[e]	1.09 (1.05-1.13)[e]
Maternal race Asian (ref: White)	NA	1.27 (0.65-2.45)	1.48 (0.73-3.01)
Maternal race Black (ref: White)	NA	2.09 (0.84-5.19)	1.56 (0.60-4.08)
Maternal race mixed/other (ref: White)	NA	0.73 (0.35-1.51)	0.77 (0.35-1.70)
Maternal ethnicity Hispanic (ref: not Hispanic)	NA	1.10 (0.67-1.83)	1.26 (0.73-2.17)
College degree (ref: no college degree)	NA	0.76 (0.47-1.22)	0.91 (0.55-1.52)
Graduate degree (ref: no college degree)	NA	0.80 (0.50-1.30)	0.96 (0.57-1.59)
Household income $50 000-99 000/y (ref:<$50 000)	NA	0.98 (0.54-1.78)	0.80 (0.43-1.48)
Household income $100 000-250 000/y (ref:<$50 000)	NA	0.76 (0.42-1.37)	0.64 (0.35-1.18)
Household income>$250 000/y (ref:<$50 000)	NA	0.59 (0.30-1.16)	0.56 (0.27-1.14)
General anxiety mild-severe (GAD-7, ref: minimal)	NA	1.24 (0.91-1.69)	1.16 (0.83-1.61)
Depression mild-severe (PHQ-9, ref: minimal)	NA	0.96 (0.71-1.29)	1.01 (0.73-1.39)
Infant sex female (ref: male)	NA	NA	0.64 (0.48-0.85)[e]
Premature (<37 wk) (ref: not premature)	NA	NA	2.77 (1.37-5.60)[e]

Abbreviations: aRR, adjusted risk ratio; GAD-7, Generalized Anxiety Disorder 7; NA, not applicable; PHQ-9, Patient Health Questionnaire 9; ref, reference; RR, risk ratio.

[a] Model 1: unadjusted mixed-effects model including only the month of Ages and Stages Questionnaire, third edition, measurement, vaccination status, a month-by-vaccination interaction term, and random intercepts for participants.

[b] Model 2: adjusted for covariates measured at baseline (chosen a priori, as shown in Table 1): maternal age, race, ethnicity, education, household income, mild-severe general anxiety by GAD-7, and mild-severe depression by PHQ-9.

[c] Model 3: adjusted for covariates measured at baseline plus infant sex and preterm birth (delivered <37 weeks of gestation).

[d] Estimates are generated using marginal probabilities from models containing an interaction between month and vaccination status.

[e] Indicates significant *P* value < .05.

226 of 2487 (9.1%) did not complete the 12-month questionnaire, and 547 of 2487 (22.0%) did not complete the 18-month questionnaire. However, we found that missing data were not associated with delay in the fully adjusted model (aRR, 1.11; 95% CI, 0.78-1.58), and addition of an indicator for missing data did not improve overall model fit (LR test, *P* = .57).

Discussion

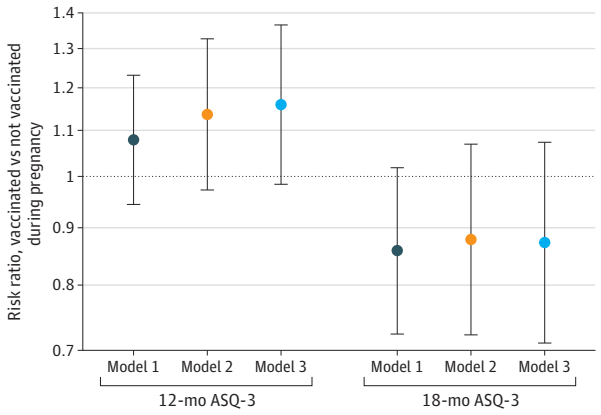
Although the acute phase of the COVID-19 pandemic may be over, the health ramifications of the global crisis endure. One group of future-facing people for whom such effects may be particularly relevant are pregnant individuals and their offspring. Indeed, decisions faced by pregnant individuals during the pandemic were particularly complex, with a need to balance benefits and risks of novel vaccine formulations, which may have differentially impacted mother and fetus.

In this prospective cohort study, we observed no difference in risk of developmental delay at 12 and 18 months for infants exposed to maternal COVID-19 vaccination vs those unexposed. To our knowledge, this represents the first meaningful evidence regarding the safety of maternal COVID-19 vaccination from the standpoint of early offspring neurodevelopment.

Understandably, there has been concern voiced regarding the potential impact of maternal COVID-19 vaccination on offspring. The theory of maternal immune activation hypothesizes that gestational provocations to the maternal inflammatory response may perturb neonatal neurodevelopment,[15] possibly due to direct effects of proinflammatory cytokines on the placenta and developing fetal brain.[40] Animal models implicate a number of cytokine pathways including interleukin 6 (IL-6),[41] interferon (IFN) I,[42] IL-17α,[43] and IL-1[44] as potential disruptors of neurodevelopment. Early evidence has begun to characterize vaccine-induced immune profiles among pregnant individuals,[45,46] with 1 small study[47] finding no difference in cord blood IL-6 levels between individuals with COVID-19 infection, recent COVID-19 vaccination, or controls. Another study[48] of 53 maternal-infant dyads comparing those having received the COVID-19 vaccine vs unvaccinated controls examined cytokine profiles at delivery and found decreased infant IL-1β but higher IFN-λ1 in the vaccinated group. However, current data are limited, and the impact of vaccination on cytokine profiles and the inflammatory response remain to be elucidated.

Until mechanistic clarity is achieved, early clinical data provide an indication of possible associations or lack thereof. The ASQ-3 is a screening tool to identify children at risk for neurodevelopmental disorders. Several investigations have assessed the related question of whether gestational COVID-19 infection is associated with lower ASQ-3 scores, yielding mixed results. Three of 4 observational studies with contemporaneous controls did not observe a difference in ASQ-3 scores among offspring exposed to COVID-19 infection in utero,[29,49,50] whereas the fourth small (n = 9

Figure 2. Risk of Abnormal Developmental Screen at 12 and 18 Months of Age, by In Utero COVID-19 Vaccination Exposure



Model 1: unadjusted mixed-effects model including only the month of Ages and Stages Questionnaire, third edition (ASQ-3), measurement, vaccination status, a month-by-vaccination interaction term, and random intercepts for participants. Model 2: adjusted for covariates measured at baseline (chosen a priori, as shown in Table 1): maternal age, race, ethnicity, education, household income, mild-severe general anxiety by Generalized Anxiety Disorder 7, and mild-severe depression by Patient Health Questionnaire 9. Model 3: adjusted for covariates measured at baseline plus infant sex and preterm birth (delivered <37 weeks of gestation). Bars indicate 95% CI ranges.

Table 3. Comparative Risks of Abnormal Developmental Screen at 12 and 18 Months for Female and Male Children, by In Utero COVID-19 Vaccination Exposure

Covariate	Model 1, RR (95% CI)[a]	aRR (95% CI)	
		Model 2[b]	Model 3[c]
Vaccinated during pregnancy (ref: never/not vaccinated during pregnancy): 12 mo[d]			
Female	0.97 (0.79-1.19)	1.01 (0.80-1.28)	1.02 (0.81-1.30)
Male	1.22 (1.01-1.49)[e]	1.29 (1.03-1.61)[e]	1.29 (1.04-1.62)[e]
Vaccinated during pregnancy (ref: never/not vaccinated during pregnancy): 18 mo[d]			
Female	0.70 (0.53-0.91)[e]	0.65 (0.48-0.88)[e]	0.69 (0.51-0.93)[e]
Male	0.95 (0.75-1.21)	1.06 (0.80-1.41)	1.06 (0.80-1.41)

Abbreviations: aRR, adjusted risk ratio; GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire 9; ref, reference; RR, risk ratio.

[a] Model 1: unadjusted mixed-effects model including only the month of Ages and Stages Questionnaire, third edition, measurement, vaccination status, a month-by-vaccination interaction term, and random intercepts for participants.

[b] Model 2: adjusted for covariates measured at baseline (chosen a priori, as shown in Table 1): maternal age, race, ethnicity, education, household income, mild-severe general anxiety by GAD-7, and mild-severe depression by PHQ-9.

[c] Model 3: adjusted for covariates measured at baseline plus preterm birth (delivered <37 weeks of gestation).

[d] Estimates are generated using marginal probabilities from models containing an interaction between month, vaccination status, and infant sex. Fifteen sets of mixed-sex multiple births were excluded from this analysis.

[e] Indicates significant *P* value < .05.

exposed) study observed an unadjusted reduction in fine motor skills among exposed offspring at 8 to 10 months of age.[26] Further, a systematic review and meta-analysis identified no associated increased risk of abnormal ASQ-3 scores among infants after in utero exposure to COVID-19 infection. However, a possible detriment in neurodevelopment of pandemic offspring vs historical controls has been identified, primarily in the communication subdomain.[51] Notably, none of the analyses included data regarding COVID-19 vaccination.

In our cohort, we observed reduced RRs of abnormal ASQ-3 screens at 18 months vs 12 months among all groups. Whether this reflects a higher level of noise in the measurement tool at younger ages vs a temporal effect of loosening pandemic restrictions relevant to child development, such as masking and social isolation, is subject to speculation.

We observed differential outcomes of exposure on neurodevelopmental delay by sex. Maternal COVID-19 vaccination was associated with increased risk of abnormal ASQ-3 screen at 12 months in male infants but not at 18 months. Interestingly, an electronic heath record study from 2 prominent Massachusetts health systems examining *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, billing codes for neurodevelopmental disorders identified an increased risk for neurodevelopmental disorders at 12 months among male but not female infants after in utero exposure to COVID-19 infection; this association was similarly not sustained at 18 months.[27] It is unclear whether these findings, in conjunction with those of our study, are spurious or associated with a true but transient phenomenon linking inflammatory exposures to developmental trajectories.

On the other hand, we observed an associated reduction in risk for abnormal ASQ-3 screen among female infants exposed to COVID-19 vaccination in utero at 18 months, a result unchanged by the addition of maternal COVID-19 infection to the model. In the absence of biological plausibility for how exposure to vaccination may promote female neurodevelopment, we are left to consider the possibility of residual confounding.

Strengths and Limitations

Strengths of our study include its large scale and geographically diverse base. We recruited at a uniquely early gestational age, allowing prospective assessment of first trimester exposures, which are notoriously challenging to study, yet may impact critical developmental windows. Our use of the widely used and validated ASQ-3 allows comparison between studies and has established predictive value clinically. Finally, our inclusion of both 12- and 18-month measures enhances power and accuracy.

Our study has several limitations. Given the digital recruitment strategy, volunteer bias may have impacted the distribution of participant characteristics, limiting extrapolation. Imperfect retention may have posed another source of selection bias, together restricting sociodemographic diversity. To address this, we performed several sensitivity analyses focusing on missing outcome data, with no observed impact on results. Although we followed up

children to 18 months of age, the longest follow-up on the topic to date, to our knowledge, it remains possible that disturbances in development may manifest later; prolonged follow-up is required to evaluate this possibility. The ASQ-3 is a screening tool reliant on parental assessment, which may be subject to outcome misclassification and requires diagnostic follow-up. Larger studies will be required to explore the sex-specific findings; caution is warranted in interpreting these results. Finally, as with all observational data, we cannot exclude the possibility of residual confounding. However, by grouping individuals vaccinated before and after pregnancy with individuals never vaccinated at all, anticipated demographic differences between vaccinated and unvaccinated populations should be muted.

Conclusions

In this cohort study, these data suggest that maternal vaccination against COVID-19 during pregnancy was safe from the perspective of offspring neurodevelopment through 18 months of age. Our findings more generally underscore the importance of ongoing prospective investigations in large, diverse cohorts of children across development, to provide an evidence basis for real-time clinical guidance in the setting of novel exposures to mothers and infants. As our basic science colleagues tease out the dynamic mechanistic underpinnings of in utero exposures, together we can transform these early data into knowledge to promote the health and well-being of our communities.

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Author Affiliations: Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Reproductive Endocrinology and Infertility, University of California, San Francisco, San Francisco (Jaswa, Cedars, Kaing, Corley, Hoskin, Huddleston); Department of Epidemiology & Biostatistics, University of California, San Francisco, San Francisco (Lindquist); Department of Psychiatry, University of California, San Francisco, San Francisco (Bishop, Kim, Cho); Department of Pediatrics, Division of Pediatric Infectious Disease and Global Health, University of California, San Francisco, San Francisco (Prahl); Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Maternal Fetal Medicine, University of California, San Francisco, San Francisco (Gaw); Department of Pediatrics, Division of Neonatology, University of California, San Francisco, San Francisco (Rogers).

Author Contributions: Dr Jaswa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jaswa, Lindquist, Kim, Kaing, Gaw, Corley, Hoskin, Rogers, Huddleston.
Acquisition, analysis, or interpretation of data: Jaswa, Lindquist, Kim, Kaing, Prahl, Gaw, Hoskin, Rogers, Huddleston.
Drafting of the manuscript: Jaswa.
Critical review of the manuscript for important intellectual content: Jaswa, Lindquist, Kim, Kaing, Prahl, Gaw, Corley, Hoskin, Rogers, Huddleston.
Statistical analysis: Lindquist, Kim.
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Supervision: Jaswa, Prahl, Hoskin, Rogers.

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