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Neurodevelopmental Outcomes at 1 Year in Infants of Mothers Who Tested Positive for SARS-CoV-2 During Pregnancy

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Abstract

IMPORTANCE Epidemiologic studies suggest maternal immune activation during pregnancy may be associated with neurodevelopmental effects in offspring.

OBJECTIVE To evaluate whether in utero exposure to SARS-CoV-2 is associated with risk for neurodevelopmental disorders in the first 12 months after birth.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study examined live offspring of all mothers who delivered between March and September 2020 at any of 6 Massachusetts hospitals across 2 health systems. Statistical analysis was performed from October to December 2021.

EXPOSURES Maternal SARS-CoV-2 infection confirmed by a polymerase chain reaction test during pregnancy.

MAIN OUTCOMES AND MEASURES Neurodevelopmental disorders determined from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnostic codes over the first 12 months of life; sociodemographic and clinical features of mothers and offspring; all drawn from the electronic health record.

RESULTS The cohort included 7772 live births (7466 pregnancies, 96% singleton, 222 births to SARS-CoV-2 positive mothers), with mean (SD) maternal age of 32.9 (5.0) years; offspring were 9.9% Asian (772), 8.4% Black (656), and 69.0% White (5363); 15.1% (1134) were of Hispanic ethnicity. Preterm delivery was more likely among exposed mothers: 14.4% (32) vs 8.7% (654) (P = .003). Maternal SARS-CoV-2 positivity during pregnancy was associated with greater rate of neurodevelopmental diagnoses in unadjusted models (odds ratio [OR], 2.17 [95% CI, 1.24-3.79]; P = .006) as well as those adjusted for race, ethnicity, insurance status, offspring sex, maternal age, and preterm status (adjusted OR, 1.86 [95% CI, 1.03-3.36]; P = .04). Third-trimester infection was associated with effects of larger magnitude (adjusted OR, 2.34 [95% CI, 1.23-4.44]; P = .01).

CONCLUSIONS AND RELEVANCE This cohort study of SARS-CoV-2 exposure in utero found preliminary evidence that maternal SARS-CoV-2 may be associated with neurodevelopmental sequelae in some offspring. Prospective studies with longer follow-up duration will be required to exclude confounding and confirm these associations.

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Key Points

Question Is COVID-19 exposure in utero associated with increased risk for neurodevelopmental disorders in the first year of life?

Findings In this cohort study of 7772 infants delivered during the COVID-19 pandemic, those born to the 222 mothers with a positive SARS-CoV-2 polymerase chain reaction test during pregnancy were more likely to receive a neurodevelopmental diagnosis in the first 12 months after delivery, even after accounting for preterm delivery.

Meaning These preliminary findings suggest that COVID-19 exposure may be associated with neurodevelopmental changes and highlight the need for prospective investigation of outcomes in children exposed to COVID-19 in utero.

+ Invited Commentary

+ Supplemental content

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Introduction

The potential relationship of maternal COVID-19 infection with offspring neurodevelopment, if any, is not yet understood. However, the profound immune activation observed in a subset of infected individuals suggests that the developing fetal brain may be influenced by maternal and placental inflammation and altered cytokine expression during key developmental windows.[1-5] (For a review of how these mechanisms might apply to COVID-19, see Shook et al.[1]) Regardless of mechanism, epidemiologic studies demonstrate that maternal infection in pregnancy, including other viral infections such as influenza, is associated with adverse neurodevelopmental outcomes in offspring, including autism spectrum disorders, schizophrenia, cerebral palsy, cognitive dysfunction, bipolar disorder, and anxiety and depression.[6-9] Although the magnitude of these effects and strength of association varies, the consistency of such associations is difficult to ignore.

As some of these disorders may not manifest until adolescence or adulthood, the true risks of maternal immune activation may not become apparent for decades. In both adults[10-13] and children,[14] a subset of individuals manifest neuropsychiatric symptoms after COVID-19 that can persist up to a year after acute illness. A recent large neuroimaging study in adults found region-specific morphologic changes following illness as well.[15] Moreover, an emerging body of evidence suggests that COVID-19 may be associated with preterm delivery and potentially other birth complications, with a recent report indicating greater severity of infection was associated with greater preterm risk.[16] Thus, converging lines of evidence indicate the potential for COVID-19 to exert persistent brain effects in children and adults, but less is known about the impact of maternal COVID-19 on the developing fetal brain. To begin to understand the potential for maternal SARS-CoV-2 infection to associate with neurodevelopmental changes in particular, we examined electronic health records (EHR) to provide preliminary estimates of risk for neurodevelopmental effects, comparing offspring of mothers with SARS-CoV-2 infection to offspring of those without, accounting for other potential confounding features.

Methods

Study Design and Data Set Generation

We extracted data from the EHR of 2 academic medical centers and 6 community hospitals: Massachusetts General Hospital, Brigham and Women's Hospital, Newton-Wellesley Hospital, North Shore Medical Center, Martha's Vineyard Hospital, Nantucket Cottage Hospital, Cooley Dickinson Hospital, and Wentworth Douglass Hospital to identify all live births occurring between March and September 2020. Offspring were linked to maternal health records using data from the Electronic Data Warehouse (EDW) based on date and time of birth, medical record number, and offspring sex. For mothers, we queried *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* billing codes, problem lists, medications, and laboratory studies occurring from date of estimated last menstrual period up to the discharge date of the delivery admission, as well as sociodemographic features (maternal age, self-reported gender, insurance type, and self-reported race and ethnicity based on US Census categories). Race and ethnicity were characterized to allow better control of confounding, recognizing that COVID-19 has differentially impacted these groups. For offspring, we also queried *ICD-10* billing codes and problem lists. Data were managed with i2b2 server software (i2b2 version 1.6.04). The Mass General-Brigham institutional review board approved all aspects of this study, with a waiver of informed consent as no patient contact was required, the study was considered to be minimal risk, and consent could not feasibly be obtained. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Outcome Definition

The primary outcome of interest was diagnosis of a neurodevelopmental disorder, based on presence of at least 1 *ICD-10* code included in the Healthcare Cost and Utilization Project (HCUP) level 2 developmental category (code 654), including F8x (pervasive and specific developmental disorders: developmental disorders of speech and language [F80]; specific developmental disorders of scholastic skills [F81]; specific developmental disorder of motor function [F82]; pervasive developmental disorders [F84]; other/unspecific disorder of psychological development [F88/89]) and F7x (intellectual disabilities). Although some of these codes (eg, regarding scholastic skills) are not relevant in the first 12 months of life, we sought to define a broad category that would remain constant for future analyses as this cohort ages. Charts for all positive cases among exposed offspring were reviewed independently by 2 physicians (R.P. and A.E.) to confirm documentation of corresponding diagnosis. Controls were defined as the absence of any of these codes. To further explore potential for confounding, we secondarily examined HCUP level 2 categories not reflecting delivery complications or congenital anomalies with prevalence of at least 2% in exposed or unexposed pregnancies.

Exposure Definition

Maternal SARS-CoV-2 positivity was defined on the basis of laboratory polymerase chain reaction (PCR) result at any point during pregnancy at any of the hospital network laboratories or tests at outside laboratories imported into the EHR. Exploratory analysis examined trimester of exposure. Exposure trimester was estimated based on the established gestational age in the EHR: first trimester (0-12 weeks' gestation), second trimester (12-26 weeks) and third trimester (26 weeks to delivery). Those individuals with no documented positive PCR results were considered to be negative.

Statistical Analysis

We fit logistic regression models associating maternal SARS-CoV-2 status with the neurodevelopmental outcome, then added maternal age in years, race and ethnicity, insurance type (public vs private), as well as offspring sex and preterm status, to yield unadjusted and adjusted estimates of effect and 95% CIs. To account for multiple births, they were considered to be clustered within deliveries; we used glm.cluster in the R miceadds package (v3.11-6) to generate robust standard errors. Sensitivity analyses restricting the cohort to full-term deliveries, or estimating effects limited to exposure in third trimester (excluding offspring with exposures in the other trimesters), used the same analytic approach. Additional sensitivity analyses to detect confounding examining other 12-month outcomes likewise applied crude and adjusted models with the same covariates; these analyses were not corrected for multiple comparisons as the aim was to show that confounding or collider bias did not uniformly inflate estimates of risk.

All analyses were performed using R version 4.0.3 (R Project for Statistical Computing) from October to December 2021. Statistical significance for the primary outcome was defined as uncorrected 2-tailed $P < .05$; results for exploratory analyses applied the same threshold. No observations for the covariates or outcome variables were missing. E-value[17]—the magnitude of association between a confounder and the exposure, and the confounder and outcome, required to yield the observed association if the true association is 1—was calculated using Evalue 4.1.3 in R (R Project for Statistical Computing).[18]

Results

Characteristics of the mother-offspring pairs exposed to SARS-CoV-2, as well as the unexposed pairs, are summarized in **Table 1**. The study cohort included 7772 live births (7466 pregnancies, 96% singleton), with mean (SD) maternal age of 32.9 [5.0] years; offspring included were 772 Asian infants (9.9%), 656 Black infants (8.4%), and 5363 White infants; 1134 infants (15.1%) were of Hispanic ethnicity. The overall rate of SARS-CoV-2 positivity in pregnancy was 2.9% (222 of 7772).

Zero exposed and 1 unexposed offspring were deceased before 12 months and were excluded from analysis. Exposed mothers were significantly less likely to be of Asian race (SARS-CoV-2 negative: 765 [10.1%] vs positive: 7 [3.2%]) or White race (SARS-CoV-2 negative: 5281 [69.9%] vs positive: 82 [36.9%]), more likely to be of Hispanic ethnicity (SARS-CoV-2 negative: 1019 [13.5%] vs positive: 115 [51.8%]), and more likely to have public vs private insurance (SARS-CoV-2 negative: 1297 [17.2%] with

Table 1. Sociodemographic and Clinical Characteristics of Maternal and Offspring Study Groups

Characteristic	Pregnancy SARS-Cov-2, No. (%)		*P* value[a]
	Negative (n = 7550)	Positive (n = 222)	
Maternal age, median (IQR), y	33.0 (30.0-36.0)	31.0 (26.2-35.0)	<.001
Maternal race			
Asian	765 (10.1)	7 (3.2)	<.001
Black or African American	617 (8.2)	39 (17.6)	
White	5281 (70)	82 (37)	
Other[b]	657 (8.7)	76 (34.2)	
Unknown	230 (3.0)	18 (8.1)	
Maternal ethnicity			
Hispanic	1019 (13)	115 (52)	<.001
Not Hispanic	6283 (83)	95 (43)	
Unavailable	248 (3.3)	12 (5.4)	
Maternal public insurance	1297 (17)	134 (60)	<.001
Trimester of maternal SARS-CoV-2 infection			
First	NA	1 (0.5)	NA
Second	NA	61 (27)	
Third	NA	160 (72)	
Unknown	7550 (100)	0	
Maternal gestational diabetes	1025 (14)	38 (17)	.13
Maternal preeclampsia	1398 (19)	43 (19)	.75
Maternal hemorrhage	1512 (20)	41 (18)	.57
Delivery hospital type			
Academic medical center	4383 (58)	165 (74)	<.001
Community hospital	3167 (42)	57 (26)	
Delivery method			
Cesarean	2423 (32)	70 (32)	.86
Vaginal	5127 (68)	152 (68)	
Multiple births	292 (3.9)	14 (6.3)	.07
Delivery admission length of stay, median (IQR), d	3.00 (2.00-3.00)	3.00 (2.00-3.00)	.85
Preterm birth			
Preterm	654 (8.7)	32 (14.4)	.003
Term	6896 (91)	190 (86)	
Offspring gender			
Female	3714 (49)	105 (47)	.58
Male	3836 (51)	117 (53)	
Offspring gestational age, median (IQR), wk	39.29 (38.43-40.14)	39.14 (37.71-40.11)	.01
Unknown	2	0	NA
Offspring birth weight, median (IQR), g	3345 (3015-3655)	3257 (2895-3544)	.001
Unknown	55	4	NA
Term offspring birth weight, median (IQR), g	3395 (3098-3688)	3317 (3010-3621)	.009
Unknown/excluded	677	32	NA
Offspring birth length, median (IQR), in	20.00 (19.00-20.50)	19.50 (19.00-20.08)	.02
Unknown	244	15	NA
APGAR score, median (IQR)			
Offspring 1-min	8.00 (8.00-9.00)	8.00 (8.00-8.00)	.052
Offspring 5-min	9.00 (9.00-9.00)	9.00 (9.00-9.00)	.85

Abbreviations: APGAR, appearance, pulse, grimace response, activity, and respiration; NA, not applicable.

[a] Wilcoxon rank sum test; Pearson χ^2 test; Fisher exact test.

[b] Other race includes American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

public insurance vs positive: 134 [60.4%] with public insurance). Rates of diabetes and hypertension were similar between the 2 groups. Preterm delivery was significantly more likely among exposed mothers: 14.4% (32) vs 8.7% (654) (P = .003).

In all, 14 of 222 exposed offspring (6.3%), and 227 of 7550 unexposed offspring (3.0%) received a neurodevelopmental diagnosis within 12 months (crude OR, 2.17 [95% CI, 1.24-3.79]; P = .006]. **Table 2** lists the most commonly observed neurodevelopmental diagnoses by case or control status, including specific developmental disorder of motor function (F82), expressive language disorder (F80.1), and developmental disorder of speech and language, unspecified (F80.9). Median (IQR) time to diagnosis was earlier among exposed (214 [183-316] days) compared with unexposed offspring (275 [253-346] days).

In fully adjusted regression models, accounting for nonsingleton deliveries as clustered within-delivery, OR for any neurodevelopmental diagnosis among COVID-exposed offspring was 1.86 (95% CI, 1.03-3.36; P = .04) (**Figure**). In sensitivity analysis, we examined the contribution of preterm delivery to observed risk. Without adjusting for preterm delivery, but with all other covariates included, adjusted OR was 1.97 (95% CI, 1.10-3.50; P = .02). When analysis was limited to full-term pregnancies (6896 unexposed offspring; 190 exposed offspring) fully adjusted OR was 1.68 (95% CI, 0.81-3.45; P = .16) (eFigure 1 in the Supplement). Incorporating length of hospital stay in these models yielded a fully adjusted OR of 1.57 (95% CI, 0.95-2.60; P = .08) (eFigure 2 in the Supplement). We also compared offspring of mothers infected in the third trimester alone with those of uninfected mothers, with exclusion of offspring of mothers infected in the first or second trimester, yielding an adjusted OR of 2.34 (95% CI, 1.23-4.44; P = .01) (eFigure 3 in the Supplement).

In addition to these sensitivity analyses, we sought to quantify the possibility that results reflected confounding by other aspects of maternal sociodemographic status or comorbidity not captured in our regression models. First, we calculated the E-value for the observed association,[17,19] yielding 3.12 (95% CI, 1.21 to not estimable), indicating that an undetected confounder would need to be 3.12 times more common among the exposed and cause a 3.12-fold increase in risk to yield the observed effect if true OR was 1. We also examined rates of nonneurodevelopmental diagnostic categories with frequency of at least 2% in either the exposed or unexposed groups, again using unadjusted and then adjusted multiple logistic regression models (eTable in the Supplement), anticipating that associations would be inflated by an unmeasured confounder. In adjusted models, among 27 diagnostic categories, only viral infection (of any type, which could include SARS-CoV-2) was significantly more common among exposed offspring (crude OR, 2.59 [95% CI, 1.76-3.81]; adjusted OR, 1.81 [95% CI, 1.20-2.72]).

Table 2. Frequency of Individual Developmental Disorder *ICD-10-CM* Codes in Cases and Controls

		Pregnancy SARS-Cov-2, No.[a]	
ICD-10-CM code	*ICD-10-CM* description	Negative (n = 7550)	Positive (n = 222)
F82	Specific developmental disorder of motor function	99	6
F80.1	Expressive language disorder	53	<5[b]
F80.9	Developmental disorder of speech and language, unspecified	48	7
F89	Unspecified disorder of psychological development	39	0
F88	Other disorders of psychological development	8	<5[b]
F80.2	Mixed receptive-expressive language disorder	<5[b]	0
F81.9	Developmental disorder of scholastic skills, unspecified	<5[b]	0
F80.0	Phonological disorder	<5[b]	0
F80.4	Speech and language development delay due to hearing loss	<5[b]	0

Abbreviation: *ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification*.

[a] Column totals exceed number of affected offspring because an individual may have more than 1 diagnosis.

[b] Cell counts less than 5 are replaced with <5 to minimize risk of reidentifiability, per institutional protocol.

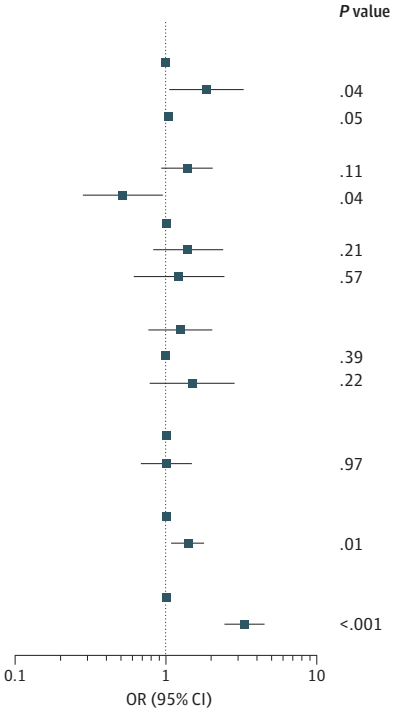
Discussion

In this analysis of 222 offspring of mothers infected with SARS-CoV-2, compared with the offspring of 7550 mothers in the control group (not infected) delivered during the same period, we observed neurodevelopmental diagnoses to be significantly more common among exposed offspring, particularly those exposed to third-trimester maternal infection. The majority of these diagnoses reflected developmental disorders of motor function or speech and language. Notably, although we identified greater risk of preterm delivery among SARS-CoV-2 positive mothers as in prior studies[20-22], adjustment for preterm birth did not account for all of the observed increased risk of incurring a neurodevelopmental diagnosis (ie, the fully adjusted regression model including preterm delivery still indicates significantly elevated risk, with adjusted OR of 1.86 for any neurodevelopmental diagnosis among offspring with SARS-CoV-2 exposure). Moreover, the magnitude of this association was only modestly diminished among infants delivered at 37 weeks or later, with an adjusted OR of 1.68, although the 95% CI in this secondary analysis crossed 1. Of note, given the known association between severe COVID-19 in pregnancy and increased risk for preterm birth,[16] those excluded in this sensitivity analysis are theoretically the individuals most at risk for adverse neurodevelopmental effects based on the proposed mechanism. The finding that the directionality and magnitude of effect is maintained among term deliveries provides further evidence that this association requires follow-up in larger studies adequately powered for such an analysis.

Whether a definitive connection exists between prenatal SARS-CoV-2 exposure and adverse neurodevelopment in offspring is not yet known, in part because children born to women infected in the first wave of the pandemic are younger than 2 years of age. A longitudinal cohort study of 57 infants with prenatal exposure to SARS-CoV-2 in China identified deficits in social-emotional domain of neurodevelopmental testing at 3 months of age, although the study design did not permit controlling for important confounders such as mother-baby separation nor did it include a noninfected comparator group.[22] In a recent study in which 272 mothers of infants born during the pandemic (both exposed and nonexposed to SARS-CoV-2 during pregnancy) completed a

Figure. Forest Plot of Adjusted Model for Risk of Offspring Developmental Disorder

Variable	Patients, No.	OR (95% CI)	*P* value
Pregnancy SARS-CoV-2 status			
SARS-CoV-2 negative	7550	1 [Reference]	
SARS-CoV-2 positive	222	1.86 (1.03-3.36)	.04
Maternal age, y	7772	1.03 (1.00-1.06)	.05
Maternal race			
Asian	772	1.38 (0.92-2.07)	.11
Black or African American	656	0.51 (0.27-0.96)	.04
White	5363	1 [Reference]	
Other	733	1.40 (0.82-2.40)	.21
Unknown	248	1.22 (0.61-2.48)	.57
Maternal ethnicity			
Hispanic	1134	1.25 (0.76-2.06)	
Non-Hispanic	6378	1 [Reference]	.39
Unavailable	260	1.51 (0.78-2.92)	.22
Maternal public insurance			
No	6341	1 [Reference]	
Yes	1431	1.01 (0.68-1.50)	.97
Offspring sex			
Female	3819	1 [Reference]	
Male	3953	1.39 (1.07-1.81)	.01
Preterm birth			
No	7086	1 [Reference]	
Yes	686	3.39 (2.49-4.62)	<.001



Other race includes American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

questionnaire at 6 months, the authors argue that observed neurodevelopmental deficits in both groups may be the product of pregnancy during the pandemic itself, rather than SARS-CoV-2 exposure per se.[23] The biological basis or mechanism by which maternal pandemic-associated stress would be a more dominant driver of offspring neurodevelopment than maternal viral illness in pregnancy remains unclear, and this putative association also requires validation in larger and longer-term studies. Our findings identifying an association between prenatal SARS-CoV-2 exposure and neurodevelopmental diagnoses at 12 months are consistent with a large body of literature including human and animal studies linking maternal viral infection and maternal immune activation with offspring neurodevelopmental disorders later in life,[6-9] some of which can be foreshadowed as early as the first year of life.[24]

Limitations

This study has some limitations. Our results must be recognized as preliminary given the limited duration of follow-up. In particular, we cannot exclude the possibility that additional neurodevelopmental effects will become apparent later in life; indeed, the offspring analyzed here are younger than the age at which neurodevelopmental disorders such as autism are typically diagnosed. Conversely, there may be a form of ascertainment bias arising from greater concern for offspring of mothers who were ill during pregnancy—that is, parents may be more inclined to seek evaluation, or clinicians more inclined to diagnose or refer for evaluation. Although the inclusion of both academic and community hospitals and their networks helps mitigate this form of collider bias, we cannot exclude other potential colliders, which have been shown to be a particular vulnerability in ascertainment for COVID-19 studies.[25] Our retrospective study design and reliance on *ICD-10* diagnosis codes also lacks the sensitivity of a prospective cohort study that incorporates detailed neurocognitive phenotyping; such studies will be important to better define the associations, if any, of maternal SARS-CoV-2 infection. As an open health system, we cannot exclude the possibility of misclassification, as mothers classified as SARS-CoV-2 negative may have received a positive test result or care for SARS-CoV-2 illness outside of our system, and offspring may receive follow-up in another health system. Such misclassification should occur completely at random (ie, there is no clear reason that SARS-CoV-2-exposed offspring delivered in a specific health system would be less likely to receive ongoing care in that system). In general, these effects of misclassified exposure or outcome would tend to bias our results toward the null hypothesis. We also note that our overall rate of SARS-CoV-2 positivity in pregnancy is lower than has been reported elsewhere,[26] likely reflecting the inclusion of smaller and community hospitals together with urban academic medical centers in our cohort. Finally, relatively small sample size precludes analysis of maternal infection severity, recently shown to be associated with risk for preterm delivery.[16]

Conclusions

These preliminary findings suggest greater risk for adverse neurodevelopmental outcomes at 1 year among offspring exposed to SARS-CoV-2, and highlight the urgency of follow-up studies in large and representative cohorts. More broadly, our analysis indicates the feasibility of leveraging EHR data for a retrospective cohort study that may enable detection of risk signals before such large-scale, prospective follow-up studies are available. The approach described here, using coded clinical data extracted from the EHR, is amenable to scaling across multiple health systems in the US and internationally. Such follow-up studies will be critical in confirming the associations we identify, and more precisely estimating the risk for, and potential nature of, neurodevelopmental sequelae of in utero exposure to SARS-CoV-2.

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Author Contributions: Dr Perlis 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: Castro, Kaimal, Perlis.

Acquisition, analysis, or interpretation of data: Edlow, Castro, Shook, Perlis.

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Supervision: Perlis.

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SUPPLEMENT.

eFigure 1. Forest Plot of Adjusted Model for Risk of Offspring Developmental Disorder Excluding Preterm Deliveries

eFigure 2. Forest Plot of Adjusted Model for Risk of Offspring Developmental Disorder With Addition of Hospital Length of Stay During Delivery Admission

eFigure 3. Forest Plot of Adjusted Model for Risk of Offspring Developmental Disorder Excluding Mothers Infected in the First or Second Trimester (62 Mothers Excluded)
eTable. Unadjusted and Adjusted Models for Pregnancy SARS-COV-2 Infection Risk of Offspring Diagnosis (Restricted to CCS Diagnosis With Greater Than 3% in Both Cases and Control Group)