BMC Medicine

RESEARCH

Open Access

COVID-19 infection history as a risk factor for early pregnancy loss: results from the electronic health record-based Southeast Texas COVID and Pregnancy Cohort Study

Micaela N. Sandoval[1*], Michelle R. Klawans[1†], MacKinsey A. Bach[1†], Jennifer Mikhail[2], Edward A. Graviss[3], Tru Cao[4], Jacqueline G. Parchem[5], Junaid Husain[2] and Eric Boerwinkle[1]

Abstract

Background The effects of SARS-CoV-2 infection before or during pregnancy on pregnancy outcomes are still largely unknown. We hypothesized that COVID-19 in early pregnancy is a risk factor for adverse pregnancy outcomes, particularly miscarriage.

Methods We examined the relationship between COVID-19 and adverse pregnancy outcomes, including spontaneous abortion, ectopic pregnancy, and preterm delivery in a large, retrospective, electronic health record (EHR)-based cohort, from 2019 to 2023. Generalized estimating equation modeling was performed to identify risk factors for adverse pregnancy outcomes. Study exposures included COVID-19 before pregnancy, COVID-19 during pregnancy, age, race/ethnicity, comorbidity burden, and neighborhood-level social vulnerability.

Results In the Southeast Texas Pregnancy and COVID Cohort (26,783 pregnancy episodes), the risk of miscarriage among pregnancy episodes with a miscarriage, livebirth, or delivery outcome was 6.3% (1514/ 24,119). In multivariable modeling, history of both mild and moderate to severe COVID-19 before pregnancy were associated with miscarriage (adjusted odds ratio (aOR) 2.48, confidence interval (CI) 2.21–2.78 and aOR 2.81, CI 1.8–4.38, respectively). Additionally, in the same model, both mild and moderate to severe COVID-19 in the first trimester were associated with miscarriage (aOR 2.31, CI 1.96–2.72 and aOR 2.45, CI 1.12–5.35, respectively).

Conclusions COVID-19 both prior to and during pregnancy was identified as a risk factor for spontaneous abortion in this study sample. These findings highlight the importance of COVID-19 vaccination and post-COVID management for pregnant people and those planning a pregnancy.

Keywords COVID-19, Pregnancy, Miscarriage, Infectious disease, Epidemiology, Electronic health records

†Michelle R. Klawans and MacKinsey A. Bach contributed equally to this work.

*Correspondence:
Micaela N. Sandoval
Micaela.N.Sandoval@uth.tmc.edu
Full list of author information is available at the end of the article

Background

The effects of SARS-CoV-2 infection before or during pregnancy on pregnancy outcomes are still largely unknown. In the first waves of the pandemic (pre-Delta), COVID-19 in late pregnancy or the peripartum period was linked to increased rates of complications, including hypertensive disorders of pregnancy, preterm birth, and maternal mortality [1–5]. The risk of severe COVID-19 in pregnant women, as in the general population, has fluctuated as novel variants arise and vaccinations have become available [6, 7]. Additionally, as the pandemic evolved, post-acute COVID-19 syndromes, including long COVID, have emerged among COVID-19 survivors [8–10]; the Centers for Disease Control and Prevention estimates that, by 2023, more than 8% of adults in the USA had experienced a post–COVID condition (PCC) [11].

The physiological relationship between SARS-CoV-2 infection at different stages of a pregnancy, or even infection preceding pregnancy, and maternal and neonatal outcomes is likely complex. Other viral infections, including human cytomegalovirus, rubella virus, and Zika virus, have been linked to miscarriage, birth defects, and adverse pregnancy outcomes, even in asymptomatic maternal infections [12–14]. In early pregnancy and the periconception period, SARS-CoV-2 infection may disrupt the complex immunology of pregnancy which shifts between the temporary immunosuppression necessary for implantation and fetal tolerance and the proinflammatory response which helps to prevent infections in mid-pregnancy [15–18]. Severe COVID-19 presenting with acute respiratory distress syndrome, coagulopathies, and other serious manifestations can cause acute obstetric emergencies or produce longer-term maternal health changes that may ultimately lead to complications, preterm delivery, or pregnancy loss [19–22]. The pathophysiology of PCCs is additionally complex and may vary widely between individuals [23, 24]. Current research suggests viral persistence, immune dysregulation, vascular changes, and organ damage from the initial infection can create significant, chronic disease months to years after the original COVID-19 episode [25–28]; there is emerging evidence of ongoing impacts of post-acute COVID-19 on pregnancy outcomes [29–31].

To examine the relationship between COVID-19 and miscarriage, we created a customized electronic health record (EHR)-based cohort of COVID-19 patients with at least one pregnancy episode between 2019 and 2023. We utilized a regional health information exchange (HIE) to overcome the challenges in ascertaining pregnancy episodes, outcomes, and gestational age through EHR data [32]. The HIE platform allowed us to collect clinical, demographic, and neighborhood-level social determinants of health for a very large, representative population of pregnant patients across Southeast Texas, one of the most diverse regions in the USA [33]. By marshalling these diverse information streams, we investigated COVID-19 before and during pregnancy as a risk factor for adverse pregnancy outcomes.

Methods

Southeast Texas Pregnancy and COVID Cohort

The Southeast Texas COVID cohort is a collaboration between The University of Texas Health Science Center at Houston School of Public Health and Healthconnect Texas (HTX), the regional HIE for Southeast Texas, and is described in detail elsewhere [34]. Briefly, the Southeast Texas COVID cohort includes all patients with a COVID-19 diagnosis, positive PCR or antigen laboratory result, and/or local health department case report captured between February 1, 2020, and June 1, 2023, in the HTX dataset. Patients residing outside of Texas based on the address on file on June 1, 2023, were excluded from these analyses.

The Southeast Texas Pregnancy and COVID cohort includes of all eligible Southeast Texas COVID Cohort patients with at least one defined pregnancy episode beginning between August 1, 2018, and June 1, 2022, and ending between June 1, 2019, and June 1, 2023 (Figs. 1 and 2). Women between the ages of 18 and 55 at the date of data capture (June 1, 2023) were eligible for inclusion. All eligible patients' diagnosis, laboratory test, and procedure code records from the period August 1, 2018, to June 1, 2023, were extracted and evaluated for the presence of pregnancy, birth, or obstetric-related indicators and outcomes.

The set of pregnancy-related indicators was based on the pregnancy-related Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) concepts curated by Matcho et al. [35]. Because this HIE-based dataset incorporates EHR data from disparate health systems which utilize a variety of coding standards, we first mapped all eligible patient codes to the OMOP-CDM concepts using the National Library of Medicine's I-MAGIC tool [36] and the Athena OHDSI Vocabularies Repositories [37]. To determine the date range and outcome of each potential pregnancy episode, we utilized the outcome classification system developed by Matcho et al. [35] as well as the algorithm developed by Jones et al. [32]. Episode identification and cleaning was performed in R 4.3.1 and Python 3.9.18.

Analytic cohort

To test our hypothesis that COVID-19 in early pregnancy would be a risk factor for adverse pregnancy outcomes, we created an analytic sub-cohort from the Southeast

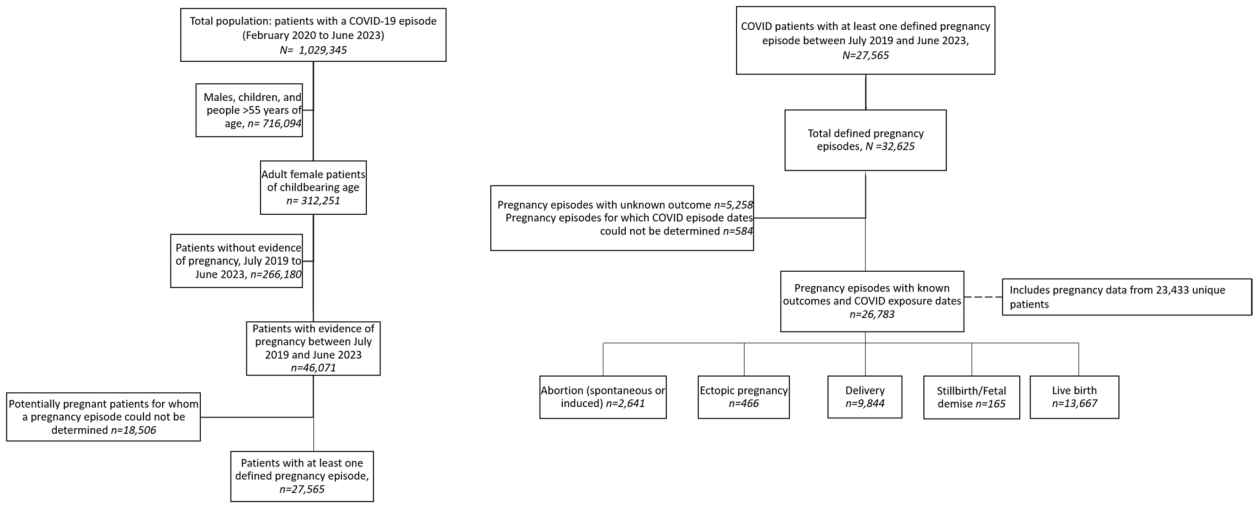

Fig. 1 Study flow

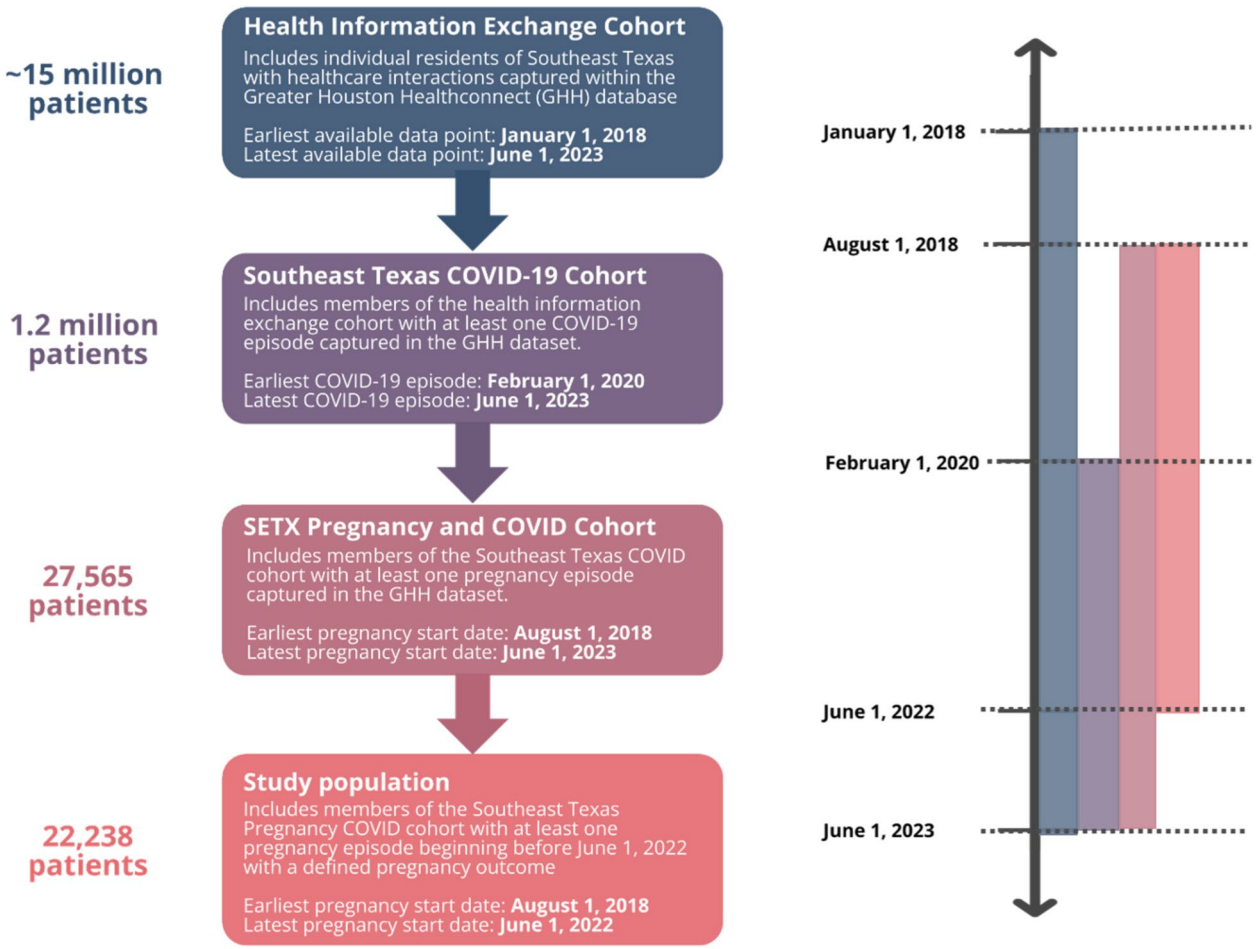

Fig. 2 Study population with inclusion criteria

Texas Pregnancy and COVID cohort. This study-specific subset consists of only pregnancy episodes for which a defined pregnancy outcome and at least one COVID-19 episode could be ascertained. To standardize observation times across pregnancy episodes and to mitigate the selection bias from the declining capture of COVID cases after the spring of 2022, we excluded pregnancy episodes beginning on or after June 1, 2022.

Study exposures

We defined a COVID-19 episode as 30 days from the index COVID-19 report. For all patients, the start date of each COVID-19 episode was compared to the start and end dates of each pregnancy episode, and COVID-19 episodes were classified as occurring before pregnancy, during pregnancy, or after pregnancy (Fig. 2). Each COVID-19 episode was classified using diagnosis and problem data into asymptomatic, mild, moderate, or severe categories according to the NIH/CDC definition of COVID-19 severity [38]. COVID-19 severity by time window categories represents the most severe episode within the risk time window. Pregnancy episodes that ended before any recorded COVID-19 episodes were considered non-exposed.

Patient demographics, including age at beginning and end of each pregnancy episode, race, and ethnicity, were extracted directly from the EHR. The Charlson Comorbidity Index (CCI) was calculated as a measure of overall comorbidity burden [39, 40]; individual CCI components were extracted by searching ICD-10-CM [41] and SNOMED CT [42] diagnosis codes associated with any encounter recorded from January 1, 2018, to the start date of each pregnancy episode. CCI scores were calculated and categorized into three comorbidity burden grades: mild, having CCI scores of 1–2; moderate, having CCI scores of 3–4; and severe, having CCI scores ≥ 5 [43].

Ecological measures of socioeconomic disadvantage, including the Area Deprivation Index (ADI), which measures relative deprivation between all census block groups by state [44, 45], and the Social Vulnerability Index (SVI), which measures relative vulnerability to external stresses to human health among all census tracts in the state [46], were calculated from the geocoded patient-provided home addresses collated and analyzed in June 2023. All geospatial analyses were performed on ArcGIS Pro version 3.1.1 (ESRI, Redlands, CA).

Outcomes

The primary outcome for this investigation was miscarriage, defined as spontaneous abortions before 20 weeks gestation among pregnancy episodes with known outcomes (ectopic pregnancies, abortions of unclear etiology [induced vs spontaneous], and induced abortions were excluded from this analysis). Pregnancy outcomes were initially classified into abortion (includes spontaneous and induced), ectopic pregnancy, stillbirth, livebirth, and delivery. Miscarriage was further separated from the abortion outcome based on diagnosis and procedure codes indicating spontaneous abortion, miscarriage, or intrauterine fetal death. Stillbirth was defined as intrauterine fetal death occurring at or after 20 weeks. Pregnancy endpoints were classified as delivery if there was a birth event recorded, but the vital status of the fetus could not be determined. Gestational age was calculated by comparing gestational age markers (e.g., Z3 A.38 [ICD-10 Code for 38 weeks gestation of pregnancy]) to date of delivery. Ectopic pregnancy and preterm delivery were additionally examined in independent, exploratory analyses. Singleton pregnancy episodes were classified as preterm if delivery occurred after 20 weeks and before 37 weeks. Multiple gestation episodes were excluded from term classifications.

Sensitivity analyses

To examine potential selection biases in the construction of the cohort, clinical and demographic characteristics were compared by pregnancy outcome and by pregnancy start date (before vs. after June 1, 2022) (Additional File 1: Tables 1 and 2); deliveries were additionally compared to American Community Survey fertility estimates (Additional File 2: Table 1). We were unable to include COVID-19 vaccination status in predictive models due to poor capture; we therefore conducted a sub-analysis within the population with a COVID-19 vaccination recorded before their pregnancy start dates (Additional File 3: Tables 1–3). Since not all abortions could be classified as induced vs. spontaneous, we conducted an additional supplementary analysis considering total abortions, including miscarriages (spontaneous abortions), abortions of unclear etiology, and induced abortions (Additional File 3: Table 4). The proportion of elective abortions in Texas is low and dependent upon recent policy changes; 53,949 induced terminations of pregnancy (includes medical and elective terminations) were reported in the state of Texas in 2020 [47], while only 17,514 were reported in 2022 [48]. As is typical in EHR-based analyses, some pregnancy endpoints could not be conclusively calculated as livebirth, as the vital status of the baby was not captured; these outcomes were classified as "delivery." A comparison of "delivery" vs. "livebirth" pregnancies is presented in Additional File 3: Table 5.

Statistical analyses

Demographic and clinical data were reported as frequencies and proportions for categorical variables.

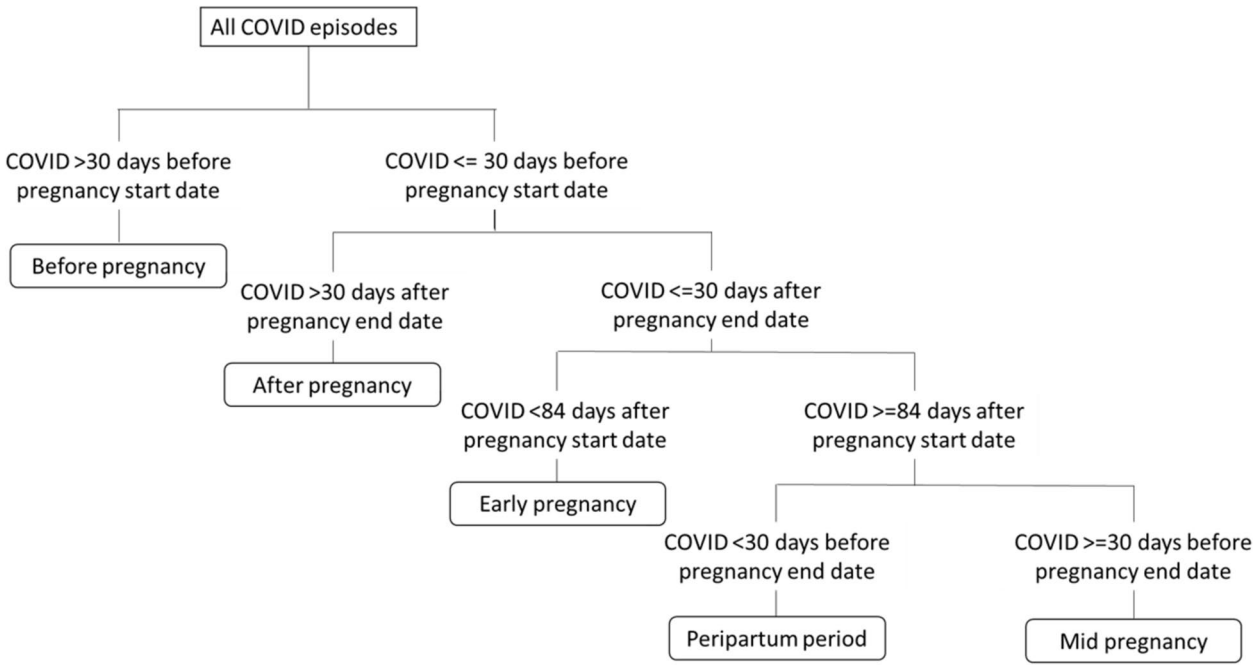

Fig. 3 COVID-19 and pregnancy episode temporal categorization

Generalized estimating equation modeling was performed to identify risk factors for miscarriage, ectopic pregnancy, and preterm delivery. Clustered error estimations were used to compensate for correlation within patients contributing multiple pregnancy episodes. Model results were presented as crude and adjusted odds ratios and 95% confidence intervals. Variable selection for the multivariable models was based on a priori clinical importance. All statistical analyses were performed on Stata MP version 17.0 (StataCorp LLC, College Station, TX). A p-value of <0.05 was considered statistically significant. Heat maps were created from kernel density estimates utilizing individual, de-duplicated patients' residential addresses; low-density values (< 15 th quantile) were truncated to preserve patient privacy. All geospatial analyses were performed on ArcGIS Pro version 3.1.1 (ESRI, Redlands, CA).

Ethics statement

This retrospective registry-based study was approved by the WGC Institutional Review Board as a quality improvement study and granted a waiver of informed consent (#20240775).

Results

Study population

Within the Southeast Texas COVID cohort (N= 1,029,345), we identified 27,565 patients with at least one defined pregnancy episode within the study period (Fig. 1). From these patients, we identified 32,625 pregnancy episodes, of which 26,783 (82%) had known outcomes and dates (Fig. 3, and Tables 1 and 2). The temporal relationship between COVID-19 infection episodes and pregnancy episodes is illustrated in Fig. 4. Kernel density estimates for patients' residential addresses are illustrated in Additional File 2: Fig. 1. For this analysis, 1725 pregnancy episodes beginning on or after June 1, 2022, were excluded; 25,058 total pregnancy episodes were included in statistical models.

Within this cohort of 25,058 pregnancy episodes, 2082 (8.3%) ended in abortion (spontaneous or induced), of which 1514 (6.0%) were further classified as miscarriages, 371 (1.5%) were ectopic, 12,950 (51.7%) were livebirths, 155 were stillbirths (0.6%), and 9500 (37.9%) were classified as deliveries. Among the 22,610 singleton pregnancies with gestational age at delivery greater than or equal to 20 weeks, 17,331 (76.7%) were able to be classified according to term status: 2896 (16.7%) of these deliveries were preterm, occurring before 37 weeks gestational age. Risk of adverse outcomes over time is illustrated in Fig. 5. We identified 17 patients who expired during the study period; of these, five were determined by expert review to be maternal mortality, defined according to the CDC as "maternal death within 1 year of any pregnancy endpoint due to condition caused or exacerbated by pregnancy or delivery" [49]. Of these, two patients died due to

Table 1 Characteristics of Southeast Texas COVID Cohort patients with a pregnancy episode, June 2019 to June 2023

Characteristics	Total *N*=23,433
Demographics	***n (%)***
Age at end of first captured pregnancy episode (years)	
Under 18	193 (0.8%)
18–24	5959 (25.4%)
25–34	12,838 (54.8%)
35–44	4334 (18.5%)
45+	109 (0.5%)
Race/Ethnicity	
Non-Hispanic White	6974 (29.8%)
Non-Hispanic Black or African American	4033 (17.2%)
Non-Hispanic Asian	1093 (4.7%)
Non-Hispanic Native American/Alaskan	78 (0.3%)
Non-Hispanic Native Hawaiian/Pacific Islander	33 (0.1%)
Non-Hispanic Other Race	1650 (7.0%)
Hispanic or Latino	9421 (40.2%)
Race/Ethnicity Unknown	151 (0.6%)
Social vulnerability index	
Quintile 1 (Least Vulnerable)	3158 (13.5%)
Quintile 2	3884 (16.6%)
Quintile 3	4328 (18.5%)
Quintile 4	5484 (23.4%)
Quintile 5 (Most Vulnerable)	6458 (27.6%)
Missing	121 (0.5%)
Area deprivation index	
Quintile 1 (Least Disadvantaged)	4135 (17.6%)
Quintile 2	4486 (19.1%)
Quintile 3	5907 (25.2%)
Quintile 4	5258 (22.4%)
Quintile 5 (Most Disadvantaged)	3399 (14.5%)
Missing	248 (1.1%)
Number of reported pregnancy episodes	
1	20,343 (86.8%)
2	2846 (12.1%)
3	227 (1.0%)
4	15 (0.1%)
5	2 (0.0%)

Values are represented as number (percent) for categorical and binary variables

"Number of reported pregnancies" includes pregnancy episodes captured within the Southeast Texas COVID and Pregnancy Cohort with defined start and end dates and known outcomes

Codes from the following standards/ontologies were utilized to flag potential pregnancies: International Classification of Diseases, Tenth Revision (ICD-10); International Classification of Diseases, Ninth Revision (ICD-9); International Classification of Diseases Tenth Revision, Clinical Modification (ICD-10-CM), International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM); The International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS); The International Classification of Diseases, 9th Revision, Procedure Coding System (ICD-9-PCS); Current Procedural Terminology (CPT®)/Healthcare Common Procedure Coding System (HCPCS); Logical Observation Identifiers Names and Codes (LOINC®); and SNOMED Clinical Terms (SNOMED CT)

complications of severe COVID-19 infection around the time of delivery.

Miscarriage

In the Southeast Texas Pregnancy and COVID Cohort, the risk of miscarriage among pregnancy episodes with a miscarriage, livebirth, or delivery outcome was 6.3% (1514/24,119). Due to the threat of multicollinearity, related variables such as binary history of COVID-19 infection, history of COVID-19 by severity category, and history of COVID-19 by temporal proximity to the pregnancy episode were examined in univariable analyses but could not be combined in multivariable models; univariate and multivariable models are presented in Fig. 6 and Additional File 4: Table 1. All multivariable models were adjusted for age, race/ethnicity, social vulnerability index, and comorbidity burden. In univariate generalized estimating equation models, history of COVID-19 infection was a significant risk factor for miscarriage, and COVID-19 infection 31 to 180 days, 181 to 365 days, and more than 365 days before pregnancy start date, had similar effect sizes compared to no COVID-19 before pregnancy (crude odds ratio (cOR) 2.33, 95% confidence interval (CI) 1.99–2.71; cOR 2.32 CI 1.95–2.75; and cOR 2.75, CI 2.32–3.26, respectively).

In the multivariable model (area under the receiver operator curve (AUC) 0.7169), mild and moderate to severe COVID-19 before pregnancy were associated with miscarriage compared to no history of COVID-19 (adjusted odds ratio (aOR) 2.48, CI 2.21–2.78 and aOR 2.81, CI 1.8–4.38, respectively). Additionally, in the same model, both mild COVID-19 and moderate to severe COVID-19 in early pregnancy were again associated with increasing odds of miscarriage (aOR 2.31, CI 1.96–2.72 and aOR 2.45, CI 1.12–5.35, respectively).

Exploratory analyses

The detailed results of these exploratory analyses are presented in Additional File 4: Tables 2 and 3 and Additional File 4: Figs. 1 and 2.

Ectopic pregnancy

Among all pregnancies, the risk of ectopic pregnancy was 1.5% (371/25,058). Based on the univariable results, the binary measure of COVID-19 history was used in the multivariable model (AUC 0.6327). COVID-19 infection prior to pregnancy was not significant in multivariable analyses (aOR 1.26, CI 0.99–1.6).

Preterm delivery

The risk of preterm delivery among singleton pregnancy episodes >20 weeks duration was 16.7% (2896/17,331). In the multivariable analysis (AUC 0.5788), history of

Table 2 Characteristics of pregnancy episodes identified within Southeast Texas COVID Cohort, June 2019 to June 2023

Characteristics	**Total** ***N* = 26,783**
Clinical characteristics	***n (%)***
Charlson Comorbidity Index calculated at pregnancy start date	
No comorbidity	25,871 (96.6%)
Mild comorbidity	815 (3.0%)
Moderate comorbidity	86 (0.3%)
Severe comorbidity	11 (0.0%)
Charlson Comorbidity Index components calculated at pregnancy start date	
Chronic pulmonary disease	415 (1.5%)
Cerebrovascular disease	19 (0.1%)
Dementia	0 (0.0%)
Diabetes without complications	288 (1.1%)
Diabetes with complications	26 (0.1%)
Congestive heart failure	15 (0.1%)
Hemiplegia	4 (0.0%)
Myocardial infarction history	1 (0.0%)
Mild liver disease	111 (0.4%)
Moderate to severe liver disease	41 (0.2%)
Mild to moderate renal disease	16 (0.1%)
Severe renal disease	10 (0.0%)
Peptic ulcer disease	8 (0.0%)
Peripheral vascular disease	13 (0.0%)
Rheumatic disease	61 (0.2%)
HIV infection	22 (0.1%)
HIV infection with complications	0 (0.0%)
Malignant neoplasm	30 (0.1%)
Solid tumor	6 (0.0%)
Pregnancy Start Date	
8/1/18–7/31/19	2605 (9.7%)
8/1/19–7/31/20	6387 (23.8%)
8/1/20–7/31/21	9710 (36.3%)
8/1/21–7/31/22	7221 (27.0%)
8/1/22–4/13/23	860 (3.2%)
COVID infection before pregnancy episode	
No COVID before pregnancy	20,045 (74.8%)
Mild COVID before pregnancy	6738 (25.2%)
Moderate or severe COVID before pregnancy	6738 (25.2%)
COVID infection during early pregnancy	
No COVID during early pregnancy	24,664 (92.1%)
Mild COVID during early pregnancy	2061 (7.7%)
Moderate or severe COVID during early pregnancy	58 (0.2%)
COVID infection during peripartum period	
No COVID during peripartum period	21,796 (81.4%)
Mild COVID during peripartum	4832 (18.0%)
Moderate or severe COVID during peripartum	155 (0.6%)
Pregnancy outcome	
Abortion (total)[a]	2641 (9.9%)
Miscarriage	2035 (7.6%)
Delivery	9844 (36.8%)

Table 2 (continued)

Characteristics	Total *N* = 26,783
Clinical characteristics	***n (%)***
Ectopic pregnancy	466 (1.7%)
Live birth	13,667 (51.0%)
Stillbirth	165 (0.6%)
Preterm birth	
Term birth	15,038 (56.1%)
Preterm birth	3136 (11.7%)
Not assessed	8609 (32.1%)
Multiple pregnancies	
Singleton	23,236 (86.8%)
Twin	383 (1.4%)
Triplet	5 (0.0%)
Not assessed	3159 (11.8%)
Maternal mortality	
No maternal mortality	26,778 (100.0%)
Non-COVID maternal mortality	3 (0.0%)
COVID-associated maternal mortality	2 (0.0%)

Values are represented as number (percent) for categorical and binary variables

[a] Total abortions includes miscarriages (spontaneous abortions), abortions of unclear etiology (induced vs spontaneous), and induced abortions

Includes pregnancy episodes captured within the Southeast Texas COVID and Pregnancy Cohort with defined start and end dates and known outcomes

Maternal/neonate matching: Taking advantage of the large HIE dataset, the HTX team attempted to match neonates to pregnant patients using the delivery encounter data, dates of delivery, date of birth, and residential address. To strengthen the specificity of the matching algorithm, we excluded addresses linked to group living quarters, including prisons, shelters, etc. Of the 16,437 pregnancy episodes originally classified as "deliveries," 7719 were successfully matched to neonates and subsequently reclassified as "livebirths." Of the 2814 pregnancy episodes originally classified as "livebirths," 1456 were matched to neonates. To validate these results, a random sample of 100 matched dyads were manually reviewed and confirmed to be true matches. All cases in which a single pregnancy episode was matched to multiple neonates ($n = 283$) were manually reviewed for accuracy

COVID severity by time window categories represents the most severe episode within the time window, i.e., if a patient had one mild and one severe COVID episode before their pregnancy episode, they would be classified as severe COVID before pregnancy

Maternal mortality defined as maternal death within 1 year of any pregnancy endpoint due to condition caused or exacerbated by pregnancy or delivery

prior mild COVID-19 infection was a risk factor, though moderate to severe infection history did not achieve significance (aOR 1.23, CI 1.11–1.36 and aOR 1.28, CI 0.8–2.05, respectively). Infection in early pregnancy was not a risk factor for preterm delivery (aOR 1.04, CI 0.89–1.21). While mild COVID-19 infection in the peripartum period was not significant (aOR 0.99, CI 0.9, 1.1), moderate to severe peripartum COVID-19 infection was a risk factor for preterm delivery, compared to no infection in the peripartum period (aOR 2.81; CI 1.86, 4.25).

Discussion

This study represents a large, regionally representative, HIE-based investigation of COVID-19 and adverse pregnancy outcomes. By examining COVID-19 and pregnancy episodes within variable windows of exposure, we revealed not only infection during pregnancy but also COVID-19 before pregnancy to be potential risk factors for miscarriage. In additional exploratory analyses, COVID-19 before pregnancy not significant as a risk factor for ectopic pregnancy in multivariable modeling. Similarly, while COVID-19 in early pregnancy was not predictive of preterm delivery in exploratory analyses, moderate or severe COVID-19 in the peripartum period was significant in multivariable analyses.

Consistent with existing literature [50, 51], we found increasing age, Black or Hispanic ethnicity, and higher comorbidity burden to be independently associated with miscarriage in multivariable models; notably, neighborhood level social vulnerability was not significant in the primary analysis. The literature around adverse pregnancy outcomes and COVID-19 is varied: rates of miscarriage reported in the early pandemic were not significantly higher than baseline [52–54], but there is evidence that infection with Delta or Omicron variants during pregnancy may increase risk of adverse pregnancy outcomes [55–58]. We found that miscarriage risk increased over the pandemic period, rising from around 5% in early 2020 to around 10% in late 2021. In a recent meta-analysis of 46 studies, among pregnant women with

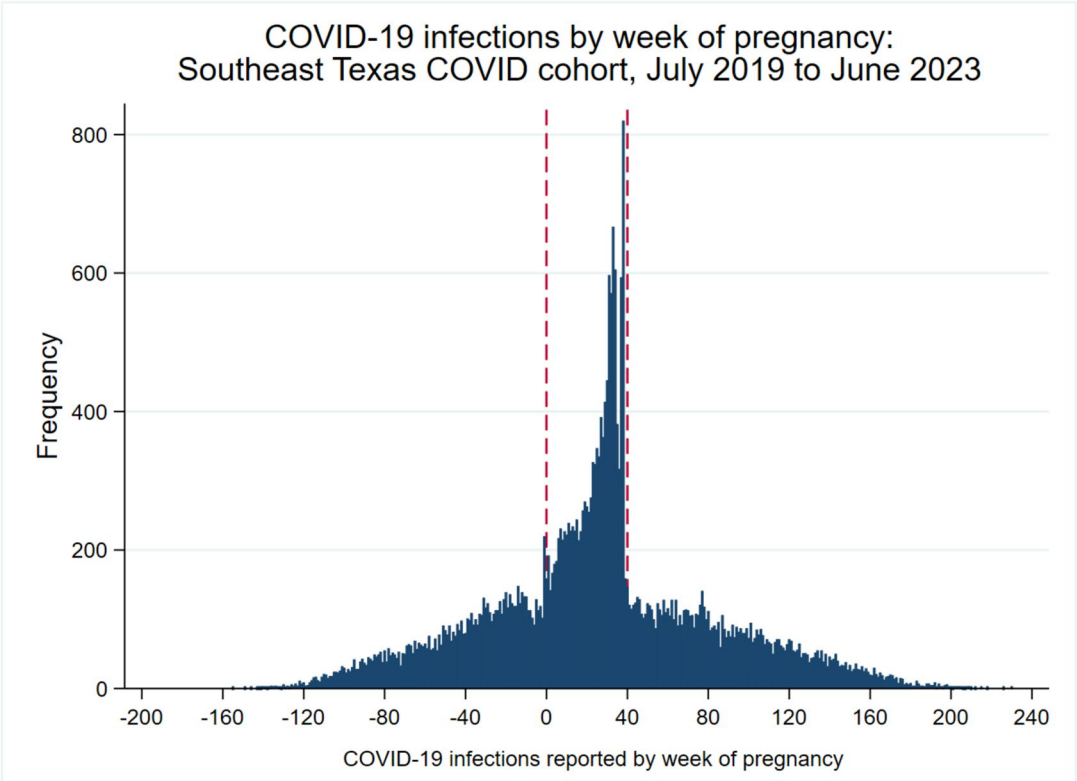

Fig. 4 COVID-19 infections relative to pregnancy. COVID infection episodes are defined as 30 days from the date of the index COVID-19 report (captured from diagnoses/public health registry report/lab tests). Any COVID report dated within this 30-day period was discarded, and any COVID report dated after this 30-day period became the index date of a new COVID episode. In this figure, the start date of each COVID episode was compared to the start dates of each pregnancy episode

SARS-CoV-2 infection, the prevalence of first trimester miscarriage increased from 7% in studies published in 2020 to between 11 and 13% in studies published in 2021 or 2022, though heterogeneity between studies was substantial [58]. Notably, because this cohort was predicated on COVID-19 case status, patients were more likely to have a pregnancy with a prior or concurrent COVID-19 exposure as time progressed, which created the potential for selection bias. In sensitivity analyses (Additional File 3: Table 6), pregnant patients with a prior recorded COVID episode were marginally older and more likely to be non-Hispanic Black than those without any COVID episode before pregnancy.

Proposed mechanisms of action for miscarriage secondary to acute COVID-19 include maternal hyperimmune response, microvascular changes, endothelial tissue damage, and transplacental viral transmission [59–62]. Furthermore, pregnancy-related upregulation of the angiotensin-converting enzyme 2 receptor, which SARS-CoV-2 binds, may contribute to higher risks of vascular injury and placental dysfunction [63–66]. While estimates vary, recent studies have found that 10–30% of women who were diagnosed with COVID-19 while pregnant went on to experience post COVID conditions (PCCs), with higher rates among those diagnosed in the pre-vaccination era and those with more severe COVID-19 episodes [29–31]. Though little is currently known about the effects of PCCs on subsequent pregnancies, associated pathologies such as pulmonary or cardiovascular disorders, dysautonomia, or metabolic disease can present significant comorbidity burden in previously healthy women [22, 23, 67]. Additionally, the chronic inflammatory response and reactivation of other viruses that has emerged as a feature of PCCs may affect first-trimester immune regulation in subsequent pregnancies [24–26].

The relationship between SARS-CoV-2 infection and preterm delivery is complex. Investigators have documented higher rates of risk factors for preterm delivery such as gestational diabetes, preeclampsia, and poor fetal growth within the pandemic period [68, 69]. This suggests COVID-19 history may be a mediator or moderator in the relationship between these known risk factors and preterm delivery. While we explored preterm delivery as a secondary outcome, additional research is needed to untangle the specific causal pathways between prior or

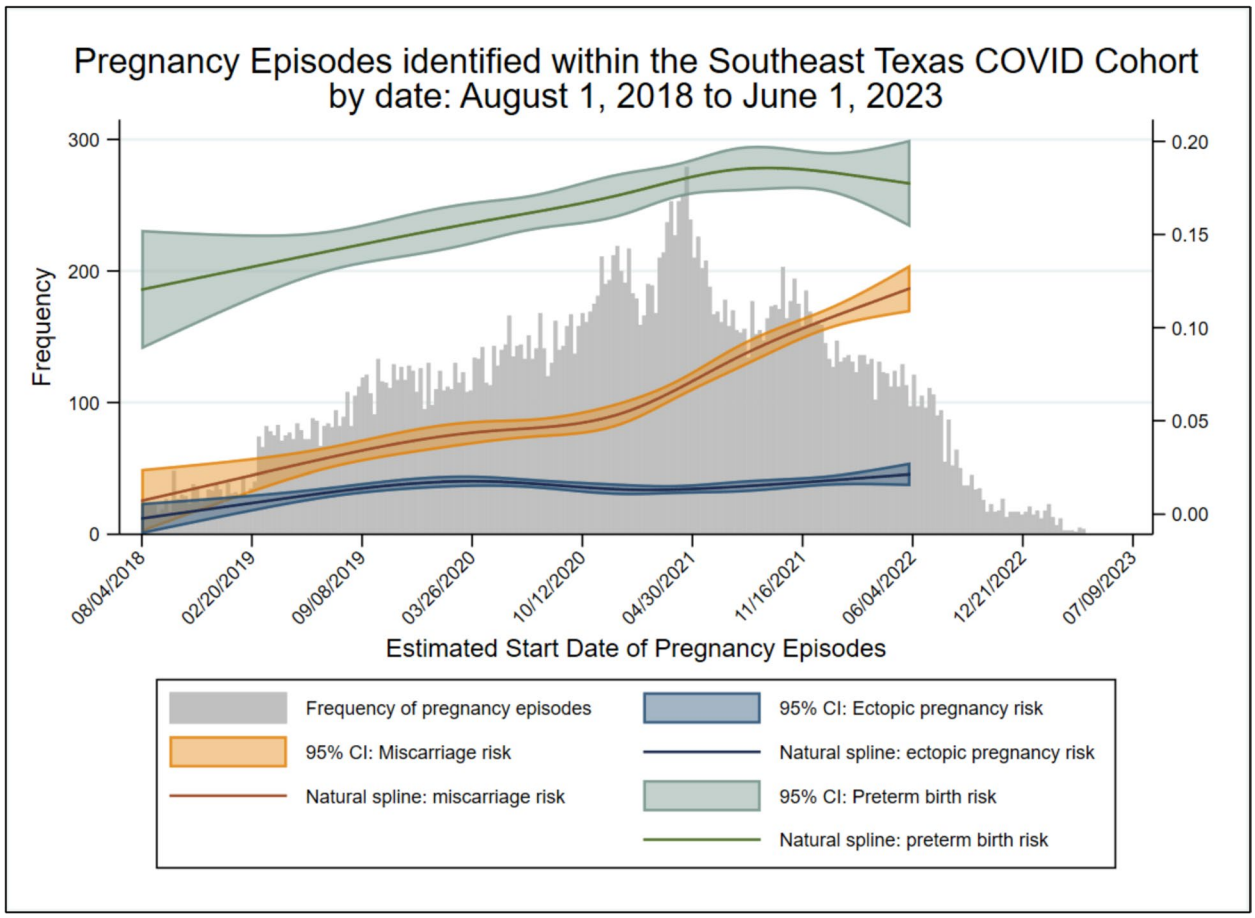

Fig. 5 Pregnancy episodes identified within the Southeast Texas COVID Cohort by date with adverse pregnancy outcomes. CI: Confidence interval. Miscarriage risk calculated as the proportion of miscarriage among Miscarriage models include spontaneous abortions among pregnancy episodes with known outcomes; ectopic pregnancies, abortions of unclear etiology (induced vs spontaneous), and induced abortions are excluded from this analysis (1514 events/ 24,119 episodes). Ectopic risk calculated as the proportion of ectopic pregnancy among all pregnancy episodes (371 events/25,058 episodes). Preterm birth risk calculated as the proportion of deliveries occurring between 20 and 36 weeks gestation among singleton pregnancy episodes of >20 weeks gestation with gestational age at delivery available (2896/17,331)

concurrent COVID-19 and established risk factors for spontaneous and induced preterm delivery. Likewise, additional research is needed to explore the potential relationship between COVID-19 and ectopic pregnancy.

A major strength of this investigation was the size (N= 25,058 pregnancy episodes contributed by 22,238 patients), diversity, and the study period, which spanned the pre-pandemic period (2018–2019) up to spring 2023. By utilizing an HIE with extensive coverage in Southeast Texas [34], we captured patients' movements between healthcare providers. In any EHR-based research, events occurring outside of a healthcare encounter, including very early or undetected miscarriage, and asymptomatic or mild COVID-19, are challenging to capture, and misclassification or selection bias could have affected our analyses. However, our population was representative of delivering patients in the Greater Houston region (Additional File 2: Table 1). Another strength was our ability to capture COVID-19 episodes independent of obstetric screenings, enabling us to examine COVID-19 prior to pregnancy as an independent predictor of adverse pregnancy outcomes. We further mitigated the selection bias from the declining capture of COVID-19 cases by limiting this analysis to pregnancy episodes beginning before June 2022. We were unable to include vaccination status in the primary models due to high missingness; in sensitivity analyses of a limited population with at least one SARS-CoV-2 vaccination recorded prior to pregnancy, COVID-19 in early pregnancy was not a significant risk factor for miscarriage (Additional File 3: Table 5). Vaccination status at the time of each COVID-19 episode before or during pregnancy may alter the risk for severe acute infection or serious sequelae, and future

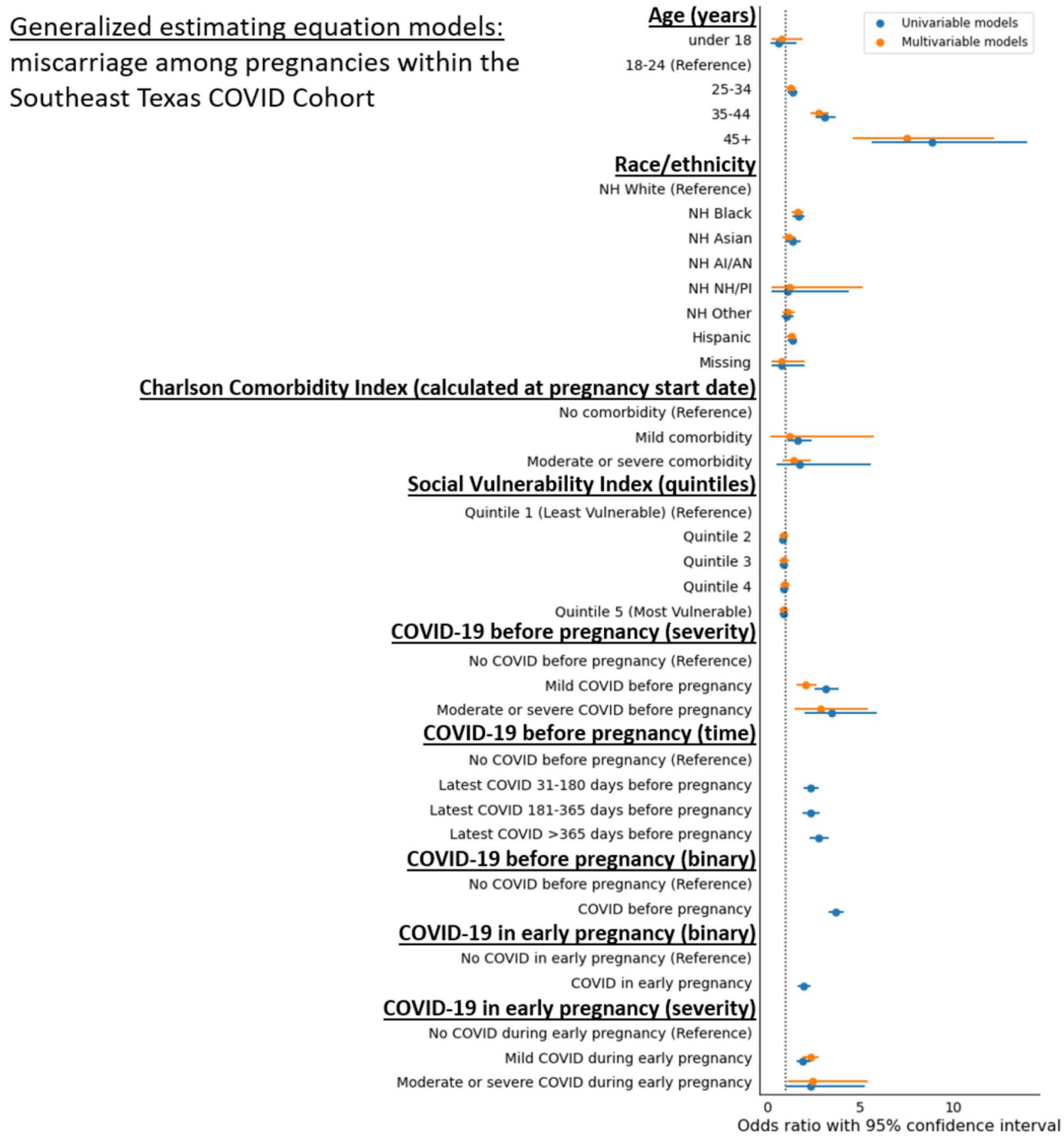

Fig. 6 Forest plot: Univariable and multivariable generalized estimating equation models for miscarriage. Results of univariable models reported as crude odds ratios [95% confidence intervals] and multivariable models reported as adjusted odds ratios [95% confidence intervals]. Miscarriage models examine spontaneous abortions among pregnancy episodes with known outcomes. Ectopic pregnancies, abortions of unclear etiology (induced vs spontaneous), and induced abortions are excluded from this analysis

investigations should incorporate vaccination level in the later pandemic years. Despite the limitations, this investigation represents one of the most comprehensive views of COVID-19 and pregnancy outcomes within a single study population to date.

Conclusions

COVID-19 both prior to and during pregnancy was identified as a risk factor for spontaneous abortion in this study sample. These findings highlight the importance of COVID prevention for pregnant people and

those planning a pregnancy. While exploratory analyses revealed potential increased risk of both ectopic pregnancy and preterm birth in women with a documented COVID-19 episode prior to pregnancy, further research is needed to elucidate this relationship.

Abbreviations

EHR	Electronic health record
aOR	Adjusted odds ratio
cOR	Crude odds ratio
OR	Odds ratio
CI	Confidence interval
PCC	Post–COVID condition
EHR	Electronic health record
HIE	Regional health information exchange
HTX	Healthconnect Texas
OMOP	Observational Medical Outcomes Partnership
CDM	Common Data Model
CCI	Charlson Comorbidity Index
ADI	Area Deprivation Index
SVI	Social Vulnerability Index
AUC	Area under the curve
SETX	Southeast Texas

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04094-y.

Additional file 1: Population characteristics: Southeast Texas Pregnancy and COVID Cohort. Table 1. Characteristics of pregnancy episodes by pregnancy outcome. Table 2. Characteristics of pregnancy episodes by date cutoff.

Additional file 2: Demographics of patients in the Southeast Texas COVID and Pregnancy Cohort with a delivery or live birth compared to the American Community Survey fertility estimates for Greater Houston by year. Table B.1. Maternal demographics of delivering mothers, GHH COVID and Pregnancy Cohort vs. ACS 1-year fertility estimates for Greater Houston Area by year. Figure B.1. Map: Relative density of patients in the Southeast Texas COVID and Pregnancy Cohort. Legend: The Southeast Texas COVID Cohort was created by UTHealth Houston School of Public Health in partnership with Greater Houston Healthconnect (GHH). Cohort patients with at least one pregnancy episode between July 1, 2019 and June 1, 2023 were included. Patient residential addresses are presented as kernel density estimates. Kernel density estimates should be interpreted as relative measures and are not population-based.

Additional file 3: Sensitivity analyses. 1. Characteristics of pregnancy episodes by date cutoff. 2. Characteristics of pregnancy episodes by pregnancy outcome (delivery vs livebirth). 3. Characteristics of pregnancy episodes by COVID vaccination record availability. 4. Characteristics of Southeast Texas COVID Cohort patients with a COVID episode before pregnancy episode, June 2019 to June 2023. 5. Generalized estimating equation models: miscarriage among pregnancies within the Southeast Texas COVID Cohort with at least one COVID vaccination recorded before pregnancy start date: August 1, 2018 to June 1, 2022 (*N*=1,923 pregnancy episodes). 6. Generalized estimating equation models: abortion (includes spontaneous and induced) among pregnancies within the Southeast Texas COVID Cohort: August 1, 2018 to June 1, 2022 (*N*=24,532 pregnancy episodes).

Additional file 4: Results of univariable and multivariable generalized estimating equation models. Table 1. Generalized estimating equation models: miscarriage among pregnancies within the Southeast Texas COVID Cohort: August 1, 2018 to June 1, 2022 (*N*=24,119 pregnancy episodes). Table 2. Generalized estimating equation models: ectopic pregnancy among pregnancies within the Southeast Texas COVID Cohort (*N*=25,058 pregnancy episodes). Table 3. Generalized estimating equation models: preterm birth among singleton pregnancies greater than 20 weeks gestation within the Southeast Texas COVID Cohort (*N*=17,331 pregnancy episodes). Figure 1. Forest plot: univariable and multivariable generalized estimating equation models: ectopic pregnancy among pregnancies within the Southeast Texas COVID Cohort. Legend: Results of univariable models reported as crude odds ratios [95% confidence intervals] and multivariable models reported as adjusted odds ratios [95% confidence intervals]. Ectopic models examine ectopic pregnancies among all pregnancy episodes. Figure 2. Forest plot: univariable and multivariable generalized estimating equation models: preterm birth among singleton pregnancies greater than 20 weeks gestation within the Southeast Texas COVID Cohort. Legend: Results of univariable models reported as crude odds ratios [95% confidence intervals] and multivariable models reported as adjusted odds ratios [95% confidence intervals]. Preterm models examine preterm delivery among singleton pregnancy episodes with known gestational age greater than 20 weeks at delivery.

Acknowledgements
The authors would like to thank the Cullen Foundation, Cullen Trust for Health Care, Elkins Foundation, and John P. McGovern Foundation for their generous support of the Southeast Texas COVID cohort. We would also like to thank the healthcare institutions of Southeast Texas for their support of treatment, payment and operations-related research.

Authors' contributions
MNS designed the study, conducted formal analysis, and wrote the manuscript; MAB contributed to study design, data cleaning and processing, and drafting and editing the manuscript; MK contributed to study design, and drafting and editing the manuscript; JM contributed to data collection, cleaning, and processing and drafting and editing the manuscript; EAG contributed to study design and drafting and editing the manuscript; TC contributed to formal analysis and data cleaning and processing, and drafting and editing the manuscript; JGP contributed to drafting and editing the manuscript; JH contributed to data collection and drafting and editing the manuscript; EB supervised and contributed to study design and drafting and editing the manuscript. All authors read and approved the final manuscript.

Funding
The authors declare that financial support was received for the research, authorship, and/or publication of this article. The Southeast Texas COVID cohort was supported by the Cullen Foundation, Cullen Trust for Health Care, Elkins Foundation and John P. McGovern Foundation. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data availability
Clinical data cannot be shared publicly because of patient confidentiality concerns as imposed by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects. Requests to access de-identified data can be made to cphs@uth.tmc.edu which will be evaluated on a case by case basis in line with institutional policies.

Declarations

Ethics approval and consent to participate
This retrospective registry-based study was approved by the WGC Institutional Review Board as a quality improvement study and granted a waiver of informed consent (#20240775).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Epidemiology, University of Texas Health Science Center at Houston School of Public Health, 1200 Pressler Street, Houston, TX 77006, USA. [2]Healthconnect Texas, Houston, TX, USA. [3]Houston Methodist Research Institute, Houston, TX, USA. [4]Department of Biostatistics and Data Science, University of Texas Health Science Center at Houston School of Public Health, Houston, TX, USA. [5]Department of Obstetrics, Gynecology & Reproductive Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA.

Received: 5 September 2024 Accepted: 24 April 2025
Published online: 09 May 2025

References

1. Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, Feng L, Xiong G, Sun G, Wang H, Zhao Y, Qiao J. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. N Engl J Med. 2020;382(25):e100.
2. Grechukhina O, Greenberg V, Lundsberg LS, Deshmukh U, Cate J, Lipkind HS, Campbell KH, Pettker CM, Kohari KS, Reddy UM. Coronavirus disease 2019 pregnancy outcomes in a racially and ethnically diverse population. Am J Obstet Gynecol MFM. 2020;2(4):100246.
3. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Brocklehurst P, Kurinczuk JJ; UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020;369:m2107.
4. Mattar CN, Kalimuddin S, Sadarangani SP, Tagore S, Thain S, Thoon KC, Hong EY, Kanneganti A, Ku CW, Chan GM, Lee KZ, Yap JJ, Tan SS, Yan B, Young BE, Lye DC, Anderson DE, Yang L, Su LL, Somani J, Tan LK, Choolani MA, Chan JK. Pregnancy outcomes in COVID-19: a prospective cohort study in Singapore. Ann Acad Med Singap. 2020;49(11):857–69.
5. Zhang L, Jiang Y, Wei M, Cheng BH, Zhou XC, Li J, Tian JH, Dong L, Hu RH. Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province. Zhonghua Fu Chan Ke Za Zhi. 2020;55(3):166–71 (Chinese).
6. Rimmer MP, Teh JJ, Mackenzie SC, Al Wattar BH. The risk of miscarriage following COVID-19 vaccination: a systematic review and meta-analysis. Hum Reprod. 20231;38(5):840–52.
7. Balachandren N, Davies MC, Hall JA, Stephenson JM, David AL, Barrett G, O'Neill HC, Ploubidis GB, Yasmin E, Mavrelos D. SARS-CoV-2 infection in the first trimester and the risk of early miscarriage: a UK population-based prospective cohort study of 3041 pregnancies conceived during the pandemic. Hum Reprod. 2022;37(6):1126–33.
8. Nalbandian A, Desai AD, Wan EY. Post-COVID-19 condition. Annu Rev Med. 2023;74:55–64.
9. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long covid: a meta-analysis and systematic review. J Infect Dis. 2022;226(9):1593–607.
10. Franco JVA, Garegnani LI, Metzendorf MI, Heldt K, Mumm R, Scheidt-Nave C. Post-covid-19 conditions in adults: systematic review and meta-analysis of health outcomes in controlled studies. BMJ Med. 2024;3(1):e000723.
11. Vahratian A, Saydah S, Bertolli J, Unger ER, Gregory CO. Prevalence of post-COVID-19 condition and activity-limiting post-COVID-19 condition among adults. JAMA Netw Open. 2024;7(12):e2451151.
12. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SE, Horne AW. The role of infection in miscarriage. Hum Reprod Update. 2016;22(1):116–33.
13. Racicot K, Mor G. Risks associated with viral infections during pregnancy. J Clin Invest. 2017;127(5):1591–9.
14. Wang R, Yan W, Du M, Tao L, Liu J. The effect of influenza virus infection on pregnancy outcomes: a systematic review and meta-analysis of cohort studies. Int J Infect Dis. 2021;105:567–78.
15. Cavalcante MB, de Melo Bezerra Cavalcante CT, Cavalcante ANM, Sarno M, Barini R, Kwak-Kim J. COVID-19 and miscarriage: From immunopathological mechanisms to actual clinical evidence. J Reprod Immunol. 2021;148:103382.
16. Kwak-Kim J, Bao S, Lee SK, Kim JW, Gilman-Sachs A. Immunological modes of pregnancy loss: inflammation, immune effectors, and stress. Am J Reprod Immunol. 2014;72(2):129–40.
17. Kumar D, Verma S, Mysorekar IU. COVID-19 and pregnancy: clinical outcomes; mechanisms, and vaccine efficacy. Transl Res. 2023;251:84–95.
18. Vesce F, Battisti C, Crudo M. The inflammatory cytokine imbalance for miscarriage, pregnancy loss and COVID-19 pneumonia. Front Immunol. 2022;13:861245.
19. Celewicz A, Celewicz M, Michalczyk M, Woźniakowska-Gondek P, Krejczy K, Misiek M, Rzepka R. Pregnancy as a risk factor of severe COVID-19. J Clin Med. 2021;10(22):5458.
20. Engjom HM, Ramakrishnan R, Vousden N, Bunch K, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Brocklehurst P, Kurinczuk JJ, Knight M. Perinatal outcomes after admission with COVID-19 in pregnancy: a UK national cohort study. Nat Commun. 2024;15(1):3234.
21. Zhou SM, Ahmadi H, Huo L, Lix LM, Maslin K, Latour JM, Shawe J. COVID-19 and pregnancy: a comprehensive study of comorbidities and outcomes. BMC Public Health. 2024;24(1):3157.
22. de Montalvão França AP, Paixão JT, de Souza Fonseca RR, Laurentino RV, de Montalvão Leite LG, Veras AS, Ribeiro FJ, das Neves PF, Falcão LF, de Montalvão Serrão AC, Oliveira-Filho AB. Clinical characteristics of pregnant women with COVID-19 and infection outcomes in one of the largest cities in the Brazilian Amazon. BMC Infect Dis. 2024;24(1):1–9.
23. Skevaki C, Moschopoulos CD, Fragkou PC, Grote K, Schieffer E, Schieffer B. Long-COVID-pathophysiology, current concepts and future directions. J Allergy Clin Immunol. 2025;155(4):1059–70.
24. Gusev E, Sarapultsev A. Exploring the pathophysiology of long COVID: the central role of low-grade inflammation and multisystem involvement. Int J Mol Sci. 2024;25(12):6389.
25. Diar Bakerly N, Smith N, Darbyshire JL, Kwon J, Bullock E, Baley S, Sivan M, Delaney B. Pathophysiological mechanisms in long COVID: a mixed method systematic review. Int J Environ Res Public Health. 2024;21(4):473.
26. Bohmwald K, Diethelm-Varela B, Rodríguez-Guilarte L, Rivera T, Riedel CA, González PA, Kalergis AM. Pathophysiological, immunological, and inflammatory features of long COVID. Front Immunol. 2024;15:1341600.
27. Tran VT, Porcher R, Pane I, Ravaud P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun. 2022;13(1):1812.
28. Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, Gokhale KM, Taverner T, Chandan JS, Brown K, Simms-Williams N, Shah AD, Singh M, Kidy F, Okoth K, Hotham R, Bashir N, Cockburn N, Lee SI, Turner GM, Gkoutos GV, Aiyegbusi OL, McMullan C, Denniston AK, Sapey E, Lord JM, Wraith DC, Leggett E, Iles C, Marshall T, Price MJ, Marwaha S, Davies EH, Jackson LJ, Matthews KL, Camaradou J, Calvert M, Haroon S. Symptoms and risk factors for long COVID in non-hospitalized adults. Nat Med. 2022;28(8):1706–14.
29. Yao Y, Sun L, Luo J, Qi W, Zuo X, Yang Z. The effect of long-term COVID-19 infection on maternal and fetal complications: a retrospective cohort study conducted at a single center in China. Sci Rep. 2024;14(1):17273.
30. Maisonneuve E, Favre G, Boucoiran I, Dashraath P, Panchaud A, Baud D. Post-COVID-19 condition: recommendations for pregnant individuals. Lancet Reg Health Eur. 2024;40:100916.
31. Georgakopoulou VE, Taskou C, Spandidos DA, Sarantaki A. Long COVID-19 and pregnancy: a systematic review. Biomed Rep. 2024;22(1):15.
32. Jones SE, Bradwell KR, Chan LE, McMurry JA, Olson-Chen C, Tarleton J, Wilkins KJ, Ly V, Ljazouli S, Qin Q. Who is pregnant? Defining real-world data-based pregnancy episodes in the National COVID cohort collaborative (N3C). JAMIA Open. 2023;6(3):ooad067.
33. Capps R, Fix M, Nwosu C. A Profile of Immigrants in Houston, the Nation's Most Diverse Metropolitan Area [Internet]. Mittelstadt M, editor. MPI. Washington DC: Migration Policy Institute; 2015 Mar [cited 2024 Jul 9] p. 4–10. Available from: https://www.migrationpolicy.org/research/profile-immigrants-houston-nations-most-diverse-metropolitan-area.
34. Sandoval MN, Mikhail JL, Fink MK, Tortolero GA, Cao T, Ramphul R, Husain J, Boerwinkle E. Social determinants of health predict readmission following COVID-19 hospitalization: a health information exchange-based retrospective cohort study. Front Public Health. 2024;12:1352240.
35. Matcho A, Ryan P, Fife D, Gifkins D, Knoll C, Friedman A. Inferring pregnancy episodes and outcomes within a network of observational databases. PLoS One. 2018;13(2):e0192033.

36. National Library of Medicine. I-MAGIC Browser. 2023. https://imagic.nlm.nih.gov/imagic . Cited 2023.
37. Collaborative OHDSI. ATHENA-OHDSI Vocabularies Repository 2023. Available from: https://athena.ohdsi.org.
38. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 9 July 2024.
39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
40. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of clinimetric properties. Psychother Psychosom. 2022;91(1):8–35.
41. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel J-M, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. American J Epidemiol. 2011;173(6):676–82.
42. Fortin SP, Reps J, Ryan P. Adaptation and validation of a coding algorithm for the Charlson Comorbidity Index in administrative claims data using the SNOMED CT standardized vocabulary. BMC Med Inform Decis Mak. 2022 Oct 7;22(1):261. Erratum in: BMC Med Inform Decis Mak. 2023;23(1):109.
43. Huang Y-q, Gou R, Diao Y-s, Yin Q-h, Fan W-x, Liang Y-p, Chen Y, Wu M, Zang L, Li L. Charlson comorbidity index helps predict the risk of mortality for patients with type 2 diabetic nephropathy. Journal Zhejiang Univ Sci B. 2014;15:58–66.
44. Kind AJ, Jencks S, Brock J, Yu M, Bartels C, Ehlenbach W, Greenberg C, Smith M. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. Ann Intern Med. 2014;161(11):765–74.
45. Area Deprivation Index, Texas. University of Wisconsin School of Medicine and Public Health. 2020 Area Deprivation Index. Downloaded from-https://www.neighborhoodatlas.medicine.wisc.edu/. Accessed 9 July 2023.
46. Flanagan BE, Gregory EW, Hallisey EJ, Heitgerd JL, Lewis B. A social vulnerability index for disaster management. J Homel Secur Emerg Manage. 2011;8(1):000010220215477355 1792.
47. Texas Department of State Health Services. 2020 Induced Terminations of Pregnancy for Texas Residents. 2021
48. Texas Department of State Health Services. 2022 Induced Terminations of Pregnancy for Texas Residents. 2023
49. Centers for Disease Control and Prevention. Maternal Mortality. In: Division of Reproductive Health National Center for Chronic Disease Prevention and Health Promotion. 2023. Mukherjee S, Velez Edwards DR, Baird DD, Savitz DA, Hartmann KE. Risk of miscarriage among black women and white women in a US prospective cohort study. Am J Epidemiol. 2013;177(11):1271–8.
50. de La Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod. 2002;17(6):1649–56.
51. Canfield M, Annegers J, Brender J, Cooper S, Greenberg F. Hispanic origin and neural tube defects in Houston/Harris County, Texas: II. Risk factors Am J Epidemiol. 1996;143(1):12–24.
52. Cosma S, Carosso AR, Cusato J, Borella F, Carosso M, Bovetti M, Filippini C, D'Avolio A, Ghisetti V, Di Perri G. Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. Am J Obstet Gynecol. 2021;224(4):391. e1-. e7.
53. Subramaniyam B, Farheen R, Rani PG, Reddy LJ. COVID-19 impact in early pregnancy losses: a retrospective study. Int J Clin Obstet Gynaecol. 2023.
54. Du M, Yang J, Han N, Liu M, Liu J. Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study. BMJ Open. 2021;11(2):e047900.
55. Morris C, Doshi H, Liu WF. Impact of COVID-19 in pregnancy on maternal and perinatal outcomes during the Delta variant period: a comparison of the Delta and pre-delta time periods, 2020–2021. Matern Health Neonatol Perinatol. 2024;10(1):20.
56. Günther J, Ziert Y, Andresen K, Pecks U, von Versen-Höynck F, Network CR. Variability in COVID-19 symptom presentation during pregnancy and its impact on maternal and infant outcomes across the pandemic. Int J Infect Dis. 2024;146:107157.
57. Mensah AA, Stowe J, Brown K, LopezBernal J, Ladhani S, Andrews N, Campbell H. COVID-19 reinfection in pregnancy: Assessment of severity and pregnancy outcomes in England. J Infect. 2025;90(2):106392.
58. van Baar JA, Kostova EB, Allotey J, Thangaratinam S, Zamora JR, Bonet M, Kim CR, Mofenson LM, Kunst H, Khalil A, van Leeuwen E. COVID-19 in pregnant women: a systematic review and meta-analysis on the risk and prevalence of pregnancy loss. Hum Reprod Update. 2024;30(2):133–52.
59. Heydarifard Z, Zadheidar S, Yavarian J, Shatizadeh Malekshahi S, Kalantari S, Mokhtari-Azad T, Shafiei-Jandaghi NZ. Potential role of viral infections in miscarriage and insights into the underlying molecular mechanisms. Congenit Anom. 2022;62(2):54–67.
60. Hanidziar D, Bittner EA. Hypotension, Systemic Inflammatory Response Syndrome, and COVID-19: A Clinical Conundrum. Anesth Analg. 2020;131(3):e175–6.
61. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation. 2020;141(23):1903–14.
62. Alcover N, Regiroli G, Benachi A, Vauloup-Fellous C, Vivanti AJ, De Luca D. Systematic review and synthesis of stillbirths and late miscarriages following SARS-CoV-2 infections. Am J Obstet Gynecol. 2023;229(2):118–28.
63. Bloise E, Zhang J, Nakpu J, Hamada H, Dunk CE, Li S, Imperio GE, Nadeem L, Kibschull M, Lye P. Expression of severe acute respiratory syndrome coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and transmembrane protease serine 2, in the placenta across gestation and at the maternal-fetal interface in pregnancies complicated by preterm birth or preeclampsia. Am J Obstet Gynecol. 2021;224(3):298. e1-. e8.
64. Sharps MC, Hayes DJ, Lee S, Zou Z, Brady CA, Almoghrabi Y, Kerby A, Tamber KK, Jones CJ, Waldorf KMA. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. Placenta. 2020;101:13–29.
65. Shende P, Gaikwad P, Gandhewar M, Ukey P, Bhide A, Patel V, Bhagat S, Bhor V, Mahale S, Gajbhiye R. Persistence of SARS-CoV-2 in the first trimester placenta leading to transplacental transmission and fetal demise from an asymptomatic mother. Hum Reprod. 2021;36(4):899–906.
66. Narang K, Enninga EAL, Gunaratne MD, Ibirogba ER, Trad ATA, Elrefaei A, Theiler RN, Ruano R, Szymanski LM, Chakraborty R, editors. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. Mayo Clin Proc; 2020. 95(8):1750–1765.
67. Assiri AM, Alamaa T, Elenezi F, Alsagheir A, Alzubaidi L, Tleyjeh I, Alhomod AS, Gaffas EM, Amer SA. Unveiling the Clinical Spectrum of Post-COVID-19 Conditions: Assessment and Recommended Strategies. Cureus. 2024;16(1):e52827.
68. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ. 2021;193(16):E540–8.
69. Liu S, Dzakpasu S, Nelson C, Wei SQ, Little J, Scott H, Joseph K. Pregnancy outcomes during the COVID-19 pandemic in Canada, March to August 2020. J Obstet Gynaecol Can. 2021;43(12):1406–15.

Publisher's Note