Second and Third Trimester Fetal Death in the Setting of COVID-19: A California 2020 Case Series

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Abstract
Maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the second and third trimesters of pregnancy may impact fetal development via vertical transmission, complications of coronavirus disease 2019 (COVID-19), or placental injury. However, potential associations between prenatal SARS-CoV-2 infection and fetal loss are not well understood. This case series of thirteen second and third trimester fetal losses reported by local public health departments to California’s state public health surveillance included maternal clinical and demographic characteristics as well as placental pathology, fetal autopsy reports, and coroner report. There was no evidence that maternal COVID-19 disease severity, placental injury, or SARS-CoV-2 vertical transmission contributed to pregnancy loss. However, this case series is a limited sample; more research is needed to identify factors of prenatal SARS-CoV-2 that may contribute to fetal death in the second and third trimesters.

Keywords: COVID-19; Fetal death; Prenatal infection; Stillbirth

Introduction
The impact of prenatal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on fetal survival is not well understood. Vertical transmission is rare but possible. SARS-CoV-2 may affect placental health, with reports noting villitis and intervillitis consistent with acute inflammation alongside histologic reports of localized dense macrophage infiltrate at the materno-fetal interface. While incidental maternal SARS-CoV-2 diagnosis upon labor and delivery admission is not associated with stillbirth, hospitalization for coronavirus disease 2019 (COVID-19) during pregnancy increases risk of fetal demise when compared to cases not needing hospitalization.

This case series uses public health surveillance, placental pathology, fetal autopsy, and a coroner report to characterize second- and third-trimester fetal deaths (FDs) in the setting of prenatal COVID-19.

Materials and methods
This case series concerns FDs diagnosed in the setting of confirmed prenatal COVID-19 from March 1st through December 31st, 2020 in California. FDs identified by local health jurisdictions across all of California via direct clinician reporting and public health interviews of pregnant COVID-19 cases were reported to the California Department of Public Health (CDPH), per CDPH statewide instructions. Medical records, pathology, autopsy, and coroner report abstracted by CDPH and the Los Angeles County Department of Public Health were used to determine the cause of death. Reported FDs were excluded if alive at delivery (heartbeat or breathing documented), or if FD occurred in the first trimester. This project used privacy-protected public health surveillance data and was conducted in accordance with the Declaration of Helsinki. This study was reviewed and determined not to be experimental human subject research by the California Health and Human Services Agency’s Committee for the Protection of Human Subjects. Written consent was waived because of the anonymity of the data.

Results
Sixteen FDs were identified, and three were excluded (two alive at delivery, one first trimester FD). Of 13 included, one occurred 17 weeks after maternal recovery per symptom resolution, with a negative SARS-CoV-2 polymerase chain reaction test at the time of delivery; others occurred concomitantly with maternal infection. Median maternal age was 31 years (range 21–39 years). Most mothers were Hispanic/Latina (10/13, 77%), had prior pregnancies (12/13, 92%), and at least one living child (9/13, 69%). Twelve (92%) received prenatal care; (9/13) 69% had at least one non-COVID-19 pregnancy complication diagnosed before FD. Regarding maternal COVID-19, most (12/13, 92%) were diagnosed upon admission to labor and delivery and were asymptomatic.
| Case | Maternal age (years) | Race/ethnicity | Gravida | para | Pre-natal care | Pregnancy complications* (GA †) | COVID-19 co-morbidity | COVID-19 symptom severity‡ | GA at COVID-19 diagnosis | GA at fetal death | Cause of fetal death |
|------|----------------------|----------------|---------|------|----------------|---------------------------------|----------------------|--------------------------|------------------------|------------------|---------------------|
| 1    | 21                   | Other/Non-Hispanic | G1P0    | Yes  | Yes            | Thrombocytopenia at time of fetal demise, CMV IgM serology, and placental swab suggestive of recent infection | None                | Yes, mild                | 32w 2d                 | 32w 2d          | CMV infection       |
| 2    | 26                   | White/Hispanic    | G3P2    | Yes  | Abnormal uterine bleeding (19w 2d) | None                | Yes, mild                | 21w 4d                 | 27w 4d          | Wolf-Hirschhorn Syndrome with large atrial-ventricular heart defect |
| 3    | 34                   | White/Non-Hispanic | G4P0    | Yes  | Cervical shortening with tunneling (20w 3d) | None                | Yes, mild                | 21w 5d                 | 21w 6d          | Umbilical cord abnormality: hypercoiled with strictures |
| 4    | 31                   | White/Hispanic    | G3P1    | Yes  | Placenta previa with hemorrhage (17w 3d) | Asthma, Morbid obesity | None                | 17w 4d                 | 17w 4d          | Placental previa with abortion and spontaneous abortion |
| 5    | 22                   | Other/Hispanic    | G3P1    | Yes  | Cervical shortening, preterm labor, PPROM (25w 3d) | None                | None                | 25w 6d                 | 27w 0d          | PPROM with chorioamnionitis |
| 6    | 39                   | White/Hispanic    | G2P0    | Yes  | Deep vein thrombosis (6w 2d), PPROM (22w 4d) | None                | None                | 23w 1d                 | 23w 0d          | PPROM with chorioamnionitis |
| 7    | 28                   | Unknown/Hispanic  | G5P3    | Yes  | DKA† | Diabetes               | Yes, severe                | 35w 3d                 | 36w 1d          | Complication from DKA in pregnancy |
| 8    | 35                   | White/Hispanic    | G5P3    | Yes  | PPROM (20w 4d) | None                | Yes, mild                | 21w 1d                 | 21w 3d          | PPROM with Chorioamnionitis |
| 9    | 36                   | White/Non-Hispanic | G7P6    | Yes  | None | CMV Ig G positive, IgM negative | None                | Yes, mildi| 7w 0d            | 24w 2d          | Tight nuchal cord |
| 10   | 30                   | White/Hispanic    | G4P2    | Yes  | Gestational diabetes, maternal blood cultures for E. Coli positive (36w 3d) | None                | None                | 28w 0d                 | 28w 0d          | Placental abruption |
| 11   | 26                   | White/Hispanic    | G2P0    | Yes  | None | None            | None                | Yes, mild                | 36w 3d                 | 36w 3d          | Chorioamnionitis |
| 12   | 38                   | Other/Hispanic    | G5P2    | Yes  | None | Gestational diabetes, gestational hypertension, pre-eclampsia | None                | Yes, mild                | 18w 3d                 | 18w 3d          | Chorioamnionitis with severe features |
| 13   | 34                   | White/Hispanic    | G7P3    | No   | Gestational diabetes, gestational hypertension, pre-eclampsia | None                | Yes, mild                | 27w 3d                 | 27w 3d          | Pre-eclampsia with severe features |

CMV: Cytomegalovirus; COVID-19: Coronavirus disease 2019; DKA: Diabetic ketoacidosis; GA: Gestational age; IgG: Immunoglobulin G; IgM: Immunoglobulin M; PPROM: Preterm premature rupture of the membranes.

* Defined as health problems that occurred in pregnancy.
† Gestational age in weeks (w) and days (d) at time of complication onset, if known. If GA is not listed, event occurred at the time of fetal death (see GA at diagnosis).
‡ Mild symptoms: no indication for prescription medication, procedure, or hospitalization; Severe symptoms: hospitalization with mechanical ventilation required.
†† Secondary to self-discontinuation of medication for diabetes during COVID-19 infection.
‡‡ Symptoms resolved before delivery.
(6/13, 46%) or reported mild symptoms (6/13, 46%). While (3/13) 23% had a co-morbidity predisposing to severe COVID-19 disease, only one (with severe COVID-19 symptoms) was hospitalized, requiring medication and mechanical ventilation for <1 day. The average gestational age at FD diagnosis was 26 weeks 2 days (range 17 weeks 4 days, 36 weeks 3 days). Associated pregnancy complications included chorioamnionitis (3/13, 38%) - (3/5) 60% of which were precipitated by preterm premature rupture of membranes- and placental abruption (2/13, 15%). In addition, umbilical cord abnormality, nuchal cord injury, primary cytomegalovirus infection, diabetic ketoacidosis, genetic syndrome, and pre-eclampsia with severe features accounted for the remaining cases (1/13, 8% each) (Table 1).

Twelve placental pathology, six autopsy, and one coroner report were available. Findings for all were consistent with associated pregnancy complications. Both placental abruption events (cases 4 and 10 in Table 1) were noted to have placental hematomas only. Among four FDs due to chorioamnionitis, with (cases 5, 6, and 8) or without (cases 11 and 12) preceding preterm premature rupture of membranes, placental pathology showed non-specific characteristic findings that were not mutually exclusive: maternal placental inflammatory response (n = 2), fetal placental inflammatory response (n = 2), funisitis (n = 3), deciduitis (n = 1), and phlebitis (n = 1). Finally, of the five remaining cases for which placental pathology was available (cases 1, 2, 3, 9, and 13), the following were noted: Case 1 showed polymerase chain reaction-proven placent al cytomegalovirus infection with an acute villous infarct and chronic decidu itis. Case 2, in which the fetus had genome-proven Wolf-Hirschhorn syndrome, showed mild chronic chorionitis and decidu itis, as well as hypovascular villi with mild fibrosis. Case 3, attributed to umbilical cord abnormality, showed a placenta normal for gestational age with mild patchy acute subchorio nitis (noted to be a maternal reaction that likely began following FD); the main pathology involved the umbilical cord having 1 twist per centimeter (cm) over a 15 cm span and was the presumptive cause for demise. Case 9, due to a tight nuchal cord, showed a second trimester placenta with focal infarctions and umbilical cord with increased twisting. Among four cases with SARS-CoV-2 testing of placental (case 5) or fetal tissues (cases 3, 6, and 11), none were positive. Finally, case 13, due to pre-eclampsia with severe features, showed multiple infarcts in an otherwise normal placenta.

Discussion
In this case series of second- and third-trimester FDs associated with prenatal SARS-CoV-2, there was no evidence that maternal COVID-19 disease severity or vertical transmission contributed to pregnancy loss. Affected pregnancies were born disproportionately to Hispanic/Latina mothers – 77% compared to 46.6% of all live births born to Hispanic/Latina mothers from 2017 to 2019, reflecting known statewide disproportions of COVID-19, where more than 70% of pregnant COVID-19 cases were Hispanic/Latina at the time these cases were reported. Underlying mechanisms were heterogeneous, largely resulting from pregnancy complications neither attributed to nor exacerbated by SARS-CoV-2 infection, which was diagnosed incidentally for almost all cases. While SARS-CoV-2 might have multiple pathways that could contribute to FD, these findings lack evidence to support that COVID-19 affected fetus or placenta in a consistent fashion, if at all. This case series is a limited sample. More research is needed to understand risk of FD posed by prenatal SARS-CoV-2.

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Author Contributions
REP: research design, data analysis, writing. SS: research design, data collection. VE: research design, writing. EB: data collection, writing. VN: data collection, writing. LS: research design, data collection. UAH: research design, data analysis, writing.

Conflicts of Interest
None.

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