Journal of Medical Toxicology (2023) 19:381–388
https://doi.org/10.1007/s13181-023-00961-3

ORIGINAL ARTICLE

# Adverse Events in Pregnant Patients Treated with Coronavirus Disease 2019 Therapeutics

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Received: 21 June 2023 / Revised: 31 July 2023 / Accepted: 2 August 2023 / Published online: 15 August 2023


## Abstract

**Background** Pregnant patients are at high risk of maternal and fetal complications from Coronavirus Disease 2019 (COVID-19) infections. The COVID-19 pandemic prompted a surge in the development and repurposing of therapies for the SARS-CoV-2 virus. Evidence is sparse on the efficacy and safety of these therapies in pregnant patients. Our objective was to describe adverse events (AEs) to COVID-19 therapeutics in pregnant patients.

**Methods** This was a case series of AEs reported to the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project between November 23, 2020, and June 28, 2022. FACT is an ongoing toxicosurveillance project at 17 sites to proactively identify and report AEs associated with COVID-19 therapeutics. Abstracted information includes demographics, case narratives, exposure details, clinical information, pregnancy details, treatments, and outcomes.

**Results** Forty-six COVID-19-positive pregnant patients who developed AEs following COVID-19 therapeutics were reported to the FACT Pharmacovigilance Project over 19 months. The most reported medications were remdesivir in 22 patients (47.8%) and casirivimab/imdevimab in 8 patients (17.4%). Four patients (8.7%) had life-threatening clinical manifestation, and 16 patients (34.8%) required intervention to prevent permanent damage. The most common maternal and fetal events were elevated serum alanine aminotransferase (26.1%) and non-reassuring fetal heart patterns (20.0%), respectively.

**Conclusions** This case series reports AEs of elevated serum alanine aminotransferase, maternal bradycardia, maternal hypothermia, non-reassuring fetal heart patterns, and emergent or unplanned cesarean sections following administration of several COVID-19 therapeutics. This study was not designed to definitely identify causation, and further study is needed to evaluate the causal role of these therapeutics in AEs affecting pregnant COVID-19 patients.

**Keywords** COVID-19 · Pregnancy · Adverse events · Therapeutics

Supervising Editor: Jeanmarie Perrone, MD

Data in this manuscript were previously presented at the North American Congress of Clinical Toxicology (NACCT) meeting, San Francisco, CA, September 2022.

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## Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic prompted a surge in the development and repurposing of therapies for the SARS-CoV-2 virus. These therapies now include an array of pharmaceuticals that are either approved or unapproved for use in COVID-19 treatment by the US Food and Drug Administration (FDA). Many unapproved pharmaceuticals have been administered through off-label use, FDA Expanded Access to investigational treatments, or FDA Emergency Use Authorizations [1, 2]. In clinical trials examining the safety and efficacy of these therapies, pregnant patients have generally been excluded out of concern for potential fetal risk.

Despite the paucity of safety and efficacy data, many pregnant patients are treated with COVID-19 therapeutics due to the increased risk of morbidity and mortality from COVID-19 infection in pregnancy. Pregnant patients are at an increased risk of death, acute respiratory distress syndrome, and acute renal failure from COVID-19 infection and are more likely to require invasive mechanical ventilation and intensive care unit admission than non-pregnant patients [3–8]. Furthermore, studies have found that pregnant patients with COVID-19 infection are more likely to have fetal adverse events (AEs) such as preterm birth, intrauterine fetal demise, and other markers of severe neonatal morbidity [9, 10].

There is a significant need for data to support the selection of safe and effective COVID-19 therapies in pregnancy. In response to the COVID-19 pandemic, the Toxicology Investigators Consortium (ToxIC), a multi-center research group managed by the American College of Medical Toxicology (ACMT), collaborated with the FDA to assemble the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project. The aim of the FACT Pharmacovigilance Project is to proactively identify and report AEs associated with COVID-19 therapeutics in all patients [11]. The objective of this study was to describe the AEs associated with COVID-19 therapeutics in pregnant patients reported to the FACT Pharmacovigilance Project.

## Methods

This study was an observational case series of AEs reported to the FACT Pharmacovigilance Project. The FACT Pharmacovigilance Project is a toxicosurveillance project that is active at 17 medical centers across the USA. This project was deemed to be non-human subjects research by the Western Institutional Review Board (IRB)-Copernicus Group and was reviewed and allowed by each participating institution's IRB. This study included cases submitted from each site between November 23, 2020, and June 28, 2022. The inclusion criteria in this subset analysis were pregnant patients with a suspected AE associated with a COVID-19 therapeutic.

In the FACT Pharmacovigilance Project, sites identify cases of interest through a variety of site-specific mechanisms. These methods include medical toxicology consultation, chart review, electronic medical record data query, and notification by healthcare teams. Case data were abstracted by trained research assistants and principal investigators at each site and entered into a de-identified standardized central database using the Research Electronic Data Capture (REDCap) platform through the *FACT Data Collection Form.* Abstracted information includes demographics, case narratives, exposure details, clinical signs/symptoms, treatments, and outcomes. For pregnant patients, a detailed supplemental form, the *FACT Pregnancy and Fetal Supplemental Data Collection Form*, was created to capture pregnancy-related information.

The details of each case were reviewed by the site principal investigator, who was a fellowship-trained medical toxicologist, and the strength of causality between the AE and the COVID-19 therapeutic was assessed. The determination categories included "Definitive (by re-challenge)," "Probable," "Possible," and "Doubtful." These determinations were based on expert opinion by the discretion and clinical judgement of the ToxIC principal investigators using the totality of assessments, diagnostic data, and concomitant medications. If needed, requests for clarification were sent to the site. In cases where the ToxIC principal investigators had concerns about a particular case's causality, the final determination was made by consensus. AE terms are aligned with the Maternal and Fetal AE Terminology (version 1.0), and grading was not performed [12]. Data were summarized with descriptive statistics. The median and interquartile range were calculated for non-normally distributed continuous variables and frequencies for nominal variables.

The *FACT Pregnancy and Fetal Supplemental Data Collection Form* used the term "fetal distress." However, to remain consistent with the *Neonatal Encephalopathy and Neurologic Outcome* guidelines from the American College of Obstetricians and Gynecologists, the case descriptions provided by the ToxIC principle investigators were reviewed for terms consistent with non-reassuring fetal heart patterns. Non-reassuring fetal status is a term that is recommended to replace "fetal distress," as the term "fetal distress" is non-specific, and fetal heart rate monitoring is only an indirect marker of the clinical status of the fetus [13, 14].

## Results

Of the 1072 cases recorded in the FACT registry during the study period, 46 (4.3%) cases were suspected AEs in pregnant patients. Table 1 displays the demographic data of the cases. The median age was 31.5 years (interquartile range 26–34 years, range 16–42 years). Fewer patients were known to be vaccinated for COVID-19 (28.3%) than unvaccinated (41.3%). The vaccination status was unknown in 30.4%. All 46 (100%) cases had a known, laboratory-confirmed COVID-19 infection. No cases involved medications taken prophylactically. Table 2 displays data

**Table 1** Characteristics of pregnant patients experiencing AEs after treatment with COVID-19 therapeutics.

| Characteristics | | Patients ($N=46$) |
|---|---|---|
| Age (years) | Median | 31.5 |
| | Interquartile range | 26–34 |
| | Range | 16–42 |
| Sex | Female | 46 (100%) |
| Race | American Indian or Alaska Native | 1 (2.2%) |
| | Asian or Asian-American | 2 (4.3%) |
| | Black or African-American | 11 (23.9%) |
| | Caucasian | 30 (65.2%) |
| | Unknown | 2 (4.3%) |
| Hispanic/Latinx | Yes | 14 (30.4%) |
| | No | 32 (69.6%) |
| Prior COVID-19 vaccination (complete or partial) | Yes | 13 (28.3%) |
| | No | 19 (41.3%) |
| | Unknown | 14 (30.4%) |

**Table 2** Details of the COVID-19 therapeutic implicated in the adverse event, time to onset of the adverse event, and clinical outcome.

| | | Patients ($N=46$) |
|---|---|---|
| COVID-19 therapeutic | Acetaminophen | 1 (2.2%) |
| | Bamlanivimab + etesevimab | 1 (2.2%) |
| | Baricitinib | 1 (2.2%) |
| | Bebtelovimab | 5 (10.9%) |
| | Casirivimab + imdevimab | 8 (17.4%) |
| | Nirmatrelvir + ritonavir | 1 (2.2%) |
| | Remdesivir | 22 (47.8%) |
| | Remdesivir + tocilizumab | 2 (4.3%) |
| | Sotrovimab | 5 (10.9%) |
| Time to symptom onset (hours) | < 12 | 22 (47.8%) |
| | 13–24 | 6 (13.0%) |
| | 25–48 | 6 (13.0%) |
| | 49–72 | 3 (6.5%) |
| | > 72 | 8 (17.4%) |
| | Unknown | 1 (2.2%) |
| Outcome | Death | 0 (0%) |
| | Permanent disability | 0 (0%) |
| | Life-threatening reaction | 4 (8.7%) |
| | Required intervention to prevent permanent damage | 16 (34.8%) |
| | Presented to Emergency Department | 18 (39.1%) |
| | New hospital admissions (28 patients already hospitalized) | 5 (10.9%) |
| | Transferred to different hospital | 2 (4.3%) |
| | Transferred to Intensive Care Unit | 2 (4.3%) |

on the implicated therapeutic exposure and outcome. All but 1 (2.2%) of the AEs were in patients treated with antiviral or monoclonal antibody therapies. In 22 (47.8%) cases, the onset of the AE was within 12 h of the implicated medication. Eighteen (39.1%) patients presented to an emergency department, and 5 (10.9%) required new hospital admission. Twenty-eight (60.9%) patients were already admitted to the hospital at the time of their AE. There were no deaths or cases of permanent disability attributed to an AE. However, 4 (8.7%) had life-threatening reactions, and 16 (34.8%) required intervention to prevent permanent damage. The life-threatening reactions that were documented were 1 case of maternal and fetal bradycardia and 3 cases of fetal bradycardia. Patients with interventions to prevent permanent damage included 9 (20.0%) patients with hypersensitivity reactions requiring rescue medication administration, 2 (4.4%) patients with ALT elevations to prevent further hepatic injury, and 1 (2.2%) patient with each of the following: concern for Hemolysis, Elevated Liver enzymes, Low Platelet (HELLP) syndrome requiring cesarian section, N-acetylcysteine administration and cesarian section, atrial fibrillation with rapid ventricular response, hypothermia requiring rewarming, and new hypoxic respiratory failure. The strength of causality of the COVID-19 therapeutic on the AE was assessed as "Definitive (by re-challenge)" in 2 (4.3%) cases, "Probable" in 25 (54.3%) cases, "Possible" in 11 (23.9%) cases, and "Unknown" in 8 (17.4%) cases.

Patients developed a wide range of clinical effects, as shown in Table 3. The most common organ systems affected were cardiovascular, gastrointestinal, and hepatic. There was a single case of maternal bradycardia in a patient who received remdesivir. The most common AE reported was an elevation in serum alanine aminotransferase (ALT). Eleven (24.9%) patients developed a new ALT elevation to 100–1000 IU/L. Ten of these patients received remdesivir, 3 completed the 5-day course, and 7 had remdesivir discontinued before completing the course. All 11 patients had a documented decrease in ALT after discontinuation of the COVID-19 therapeutic and required no further treatment. One (2.2%) patient developed an ALT greater than 1000 IU/L after non-prescribed supra-therapeutic acetaminophen use to treat COVID-19 symptoms. No patients developed liver failure. Aspartate aminotransferase was not tracked in the registry. Two (4.4%) patients developed mild hypothermia, with temperature nadirs of

**Table 3** Adverse events reported in the mother.

| System | Adverse event | Patients ($N=46$) |
|---|---|---|
| Cardiovascular | Chest pain/tightness | 4 (8.7%) |
| | Maternal tachycardia | 4 (8.7%) |
| | Hypotension | 2 (4.3%) |
| | Atrial fibrillation with rapid ventricular response | 1 (2.2%) |
| | Maternal bradycardia | 1 (2.2%) |
| Dermatologic | Flushing | 5 (10.9%) |
| Gastrointestinal | Nausea | 5 (10.9%) |
| | Vomiting | 3 (6.5%) |
| | Abdominal cramping | 2 (4.3%) |
| | Acute pancreatitis | 1 (2.2%) |
| Hematologic | Thrombocytopenia (platelets < 100,000/μL) | 1 (2.2%) |
| Hepatic | ALT 100–1000 IU/L | 11 (23.9%) |
| | ALT > 1000 IU/L | 1 (2.2%) |
| Immunologic | Intraoral/perioral swelling | 2 (4.3%) |
| | Hypothermia (≤ 35 °C) | 2 (4.3%) |
| | Rigors | 1 (2.2%) |
| Musculoskeletal | Back pain | 2 (4.3%) |
| Neurologic | Headache | 2 (4.3%) |
| | Anxiety | 1 (2.2%) |
| | Lightheadedness | 1 (2.2%) |
| | Muscle spasms | 1 (2.2%) |
| | Neuropathic pain | 1 (2.2%) |
| | Numbness/paresthesias | 1 (2.2%) |
| Pulmonary | Shortness of breath | 6 (13.0%) |
| | Increased oxygen requirement | 2 (4.3%) |
| Renal | Acute kidney injury (creatinine > 2.0 mg/dL) | 1 (2.2%) |

34.1 °C and 35 °C, and underwent external rewarming after receiving remdesivir.

In 45 (98%) cases, the reporter filled out the *FACT Pregnancy and Fetal Supplemental Data Collection Form*, presented in Table 4. The only case without the supplemental form completed was the case of supra-therapeutic acetaminophen use. Most patients (62.2%) were in the third trimester at the time of the AE.

The most common fetal AEs were non-reassuring fetal heart patterns. These were reported in 9 (20%) cases, and 2 cases displayed multiple non-reassuring fetal heart patterns. This included 6 (66.7%) cases of recurrent late decelerations (1 case associated with maternal bradycardia), 4 (44.4%) cases of prolonged fetal bradycardia, and 1 (11.1%) case of prolonged fetal tachycardia. Of these cases, 5 (55.6%) patients underwent emergency or unplanned cesarean sections, and 4 (44.4%) patients recovered spontaneously. Of these cases, 6 patients were administered remdesivir and 3 were administered casirivimab/imdevimab. Overall, 7 (15.6%) patients underwent emergency or unplanned cesarean section after the suspected AE; 5 of which were due to non-reassuring fetal status and 2 were due to worsening respiratory status suspected to be due to COVID-19 infection. Three (6.7%) patients developed pre-eclampsia, of whom 2 had received remdesivir and 1 had received casirivimab/imdevimab. Two (4.4%) patients had preterm premature rupture of membranes (PPROM), of whom 1 had received remdesivir and 1 had received nirmatrelvir/ritonavir. One (2.2%) patient who received remdesivir and dexamethasone during a COVID-19 infection in the first trimester delivered a child with multiple congenital anomalies consistent with Goldenhar syndrome.

## Discussion

Pregnant maternal–fetal dyads represent a medically vulnerable and underserved population given regular exclusion from COVID-19 therapeutic trials, changes in maternal physiology, and potential for fetal complications. The lack of inclusion of maternal–fetal dyads in premarket clinical studies precludes adequate recognition and description of AEs in the population which may negatively affect safe use. Without such information, a secondary way of collecting safety information in this population naturally falls to the analysis of postmarket safety data.

Over the first 19 months since its inception, the FACT Pharmacovigilance Project identified 1072 total cases of AEs potentially related to therapies utilized for the prophylaxis and treatment of COVID-19. This included 46 (2.2%) cases in pregnant patients. The AEs observed in this study varied in severity and nature. While there were no deaths or permanent disabilities, there were multiple potentially life-threatening events that required intervention to prevent permanent damage, medically necessitated procedures such as cesarian sections, and one congenital anomaly.

The most common AE was an elevation in serum ALT, nearly all of which were in patients on remdesivir. Elevations

**Table 4** Obstetric history of the mother and perinatal (maternal and fetal) adverse events from *FACT Pregnancy and Fetal Supplemental Data Collection Form.*

| Obstetric history and perinatal adverse events | | Patients ($N=45$) |
|---|---|---|
| Prior pregnancy | Yes | 30 (66.7%) |
| | No | 13 (28.9%) |
| | Unknown | 2 (4.4%) |
| Prior obstetric complications | Pregnancy loss (including miscarriage, stillbirth, or neonatal death) | 11 (24.4%) |
| | Premature birth (prior to 37 weeks) | 4 (8.9%) |
| | Ectopic pregnancy | 1 (2.2%) |
| Gestational age at time of adverse event | First trimester | 5 (11.1%) |
| | Second trimester | 10 (22.2%) |
| | Third trimester | 28 (62.2%) |
| | Unknown | 2 (4.4%) |
| Perinatal (maternal and fetal) adverse events | Non-reassuring fetal heart patterns (late decelerations, prolonged fetal bradycardia or tachycardia) | 9 (20.0%) |
| | Emergency or unplanned cesarean section | 7 (15.6%) |
| | Preterm premature rupture of membranes | 2 (4.4%) |
| | Pre-eclampsia | 3 (6.7%) |
| | Abnormal fetal growth | 1 (2.2%) |
| | Fetal structural abnormalities | 1 (2.2%) |
| | Hemorrhage in pregnancy: maternal | 1 (2.2%) |

in aminotransferases in COVID-19 patients who received remdesivir have been reported previously [15]. While there are reports that this could be through remdesivir's weak inhibition of human mitochondrial RNA polymerase [16], an in vitro study on human-derived liver cells concluded that this was not likely the primary mechanism [17]. The reports of elevated ALTs in this study did not require intervention, although some patients had the drug discontinued. All patients had ALT improvement. COVID-19 has been associated with transaminase elevations [18]. In addition, multiple conditions in pregnancy may cause elevations of aminotransferases, such as preeclampsia, HELLP syndrome, intrahepatic cholestasis of pregnancy, and acute fatty liver of pregnancy. There is an ongoing trial of remdesivir and its metabolite, GS-441524, in pregnant and non-pregnant patients of childbearing potential for the treatment of COVID-19 called IMPAACT 2032 [19].

This study identified one case of maternal bradycardia in the setting of remdesivir treatment for COVID-19. Multiple recent studies have reported severe and even fatal bradycardia in patients treated who received remdesivir for COVID-19 [20–22]. The case identified in this study was of a 26-year-old female who was G4P2012 at 37 weeks gestation with a history of asthma/COPD and obesity who was started on remdesivir and dexamethasone for COVID-19. Two days into treatment, the patient developed bradycardia between 50 to 60 beats per min, with a baseline heart rate of 90 beats per min during the admission. The patient experienced no bradycardia-related symptoms, but had a non-reassuring non-stress test due to persistent fetal bradycardia and underwent an emergency cesarean section. Only one previous case report has described maternal bradycardia in the setting of remdesivir treatment for a pregnant patient with COVID-19, and that patient had no fetal complications [23]. One retrospective study of 31 pregnant or immediately post-partum patients with severe or critical illness from COVID-19 infection found that 32% of patients in this population developed bradycardia, even without antiviral therapy [24]. Further study is needed to determine if remdesivir is associated with bradycardia in pregnant patients, despite the relatively increased heart rate associated with pregnancy. Additionally, further studies are needed to evaluate the impact on fetal perfusion and outcomes. It is unlikely in this case that this effect was caused by dexamethasone. Dexamethasone is regularly used in the third trimester for enhancing fetal lung maturity and is recommended by the United States National Institutes of Health COVID-19 Treatment Guidelines Panel for hospitalized pregnant patients with COVID-19 who require supplemental oxygen or are mechanically ventilated [25, 26].

This study reports two cases of pregnant patients with mild hypothermia in the setting of COVID-19 with remdesivir administration. Both patients presented to the hospital with known COVID-19 with shortness of breath but no reported fever or chills. Both patients had new onset hypothermia several hours after the first dose of remdesivir. The nadirs of the patient's temperatures were 34.1 and 35 °C, respectively. The route of temperature measurement was not reported. Both patients received only external rewarming, and the hypothermia lasted approximately 24 h and did not re-occur on successive doses of remdesivir. A literature review does not reveal any reports of remdesivir-associated hypothermia.

There were multiple instances of fetal AEs. The most common finding was non-reassuring fetal monitoring seen in 9 (20%) patients after receiving either remdesivir or casirivimab/imdevimab. There is a dearth of literature on the relationship between most COVID-19 therapeutics and fetal assessment. One case series describes two patients who had non-reassuring fetal status in the setting of COVID-19 treatment with casirivimab/imdevimab [27]. One patient had decelerations that spontaneously resolved, while the other had fetal bradycardia and was switched to remdesivir but required a cesarean section for non-reassuring fetal heart tracings. A different cohort study followed pregnant patients hospitalized with COVID-19 including numerous on remdesivir; however, the rate of non-reassuring fetal status of those on remdesivir was not measured [28]. Further study is needed to determine the consequences of COVID-19 therapeutics on fetal outcomes and the rate of non-reassuring fetal monitoring in untreated pregnant patients with COVID-19. Pregnant patients often do not receive fetal monitoring during the administration of COVID-19 therapeutics which limits the detection of non-reassuring fetal monitoring. Additionally, further study is also needed to assess the role of confounding factors for these findings, such as maternal status secondary to COVID-19 infection.

Two patients had PPROM after the use of a COVID-19 therapeutic. Of these cases, 1 (2.2%) patient was G5P1122 and had received remdesivir and 1 (2.2%) patient was G1P1000 and had received nirmatrelvir/ritonavir. Links between PPROM and remdesivir or nirmatrelvir are not established in the literature. Studies on ritonavir as part of maternal HIV antiretroviral therapy have suggested a possible association with preterm birth [29, 30]. Additionally, the increased risk of preterm labor in the setting of COVID-19 has been documented [3, 10, 31]. Further investigation is needed to determine if COVID-19 itself is the cause of this finding or a confounding variable in a sicker patient population. There has been little study into the subset of premature birth due to PPROM. A meta-analysis in 2021 found an increased rate of PPROM in patients with COVID-19 [32]. Multiple factors could have contributed to PPROM in this case.

While this study focused on maternal health, there was one case of significant fetal abnormalities reported. This patient

was a 34-year-old female who was G5P1122, not vaccinated for COVID-19, with a history of diabetes, who presented to a hospital at 9 weeks gestation with COVID-19 symptoms. During that visit, the patient was treated with 4 doses of remdesivir and dexamethasone and discharged home. The patient re-presented at 34 weeks gestation with PPROM and delivered a child with congenital anomalies consistent with Goldenhar syndrome. Newborn genetic testing identified two variants of uncertain significance in the NEK1 and YWHAZ genes; however, there is insufficient evidence to suggest that haploinsufficiency in these genes would lead to these findings. Maternal genetic testing was not reported. A literature review did not reveal any cases of Goldenhar syndrome associated with these medications; however, there are no epidemiological studies of congenital anomalies among infants whose mothers were treated with remdesivir during pregnancy.

While the landscape of the COVID-19 pandemic is changing, antiviral and monoclonal antibody therapies are often repurposed for emerging diseases or new indications for existing diseases. For example, remdesivir was originally evaluated in clinical trials for the Ebola Outbreak in 2014 but was repurposed for inhibiting viral replication of the SARS-CoV-2 virus [33]. Therefore, continued study on AEs in this population is imperative for COVID-19 or other disease treatment.

There are limitations to this study. This was an observational toxicosurveillance study intended to generate hypotheses, display possible associations between therapies that have limited prior study in pregnancy, and provide cases for the FDA to further evaluate. This study was not designed to definitively identify causation, which should not be implied from this data. Furthermore, this study relied on the recognition of a possible AE by the patient's care team or by investigators at participating sites. If an AE was not recognized as potentially associated with a COVID-19 therapeutic, it would not have been captured by this study. Additionally, the determination of causality for each case was made by ToxIC principal investigators' expert opinion. These determinations were made based on the totality of information presented, and only a minority of cases underwent re-challenging due to considerations over the patient's wellbeing. Finally, physiologic changes that occur during pregnancy or COVID-19 infection may confound the clinical and laboratory manifestations found in this study. There is no comparative cohort for the cases presented. Therefore, the underlying event rates in untreated pregnant patients are unavailable.

## Conclusions

Pregnant patients represent a high-risk group for morbidity and mortality from COVID-19 infection. There is limited safety and efficacy data on COVID-19 therapeutics for pregnant patients, and this population is at risk for unique drug-related or drug-disease-related AEs. This study reports and discusses pregnant patients who had AE associated with COVID-19 therapeutics and were observed to have elevated serum ALT, maternal bradycardia, maternal hypothermia, non-reassuring fetal monitoring, and a congenital malformation. Further study and analysis are needed to evaluate the maternal and fetal responses to COVID-19 infections and the administered COVID-19 therapeutics.

**Acknowledgements** To the FACT (Food and Drug Administration [FDA] and American College of Medical Toxicology [ACMT] Coronavirus Disease 2019 [COVID-19] Toxicology Investigators Consortium [ToxIC]) Pharmacovigilance Project Study Group: Maryann Amirshahi, Katie Boyle, Jennifer Carey, Michael Chary, Jason Devgun, Kennon Heard, Robert Hendrickson, Ziad Kazzi, Eric Lavonas, Michael Levine, Michael Brett Marlin, Travis Olives, Anthony Pizon, Tony Rianprakaisang, Kapil Sharma, Sophia Sheikh, Meghan Spyres, Timothy Wiegand.

**Funding** This study was supported by the U.S. Food and Drug Administration (FDA), contract 75F40119D10031/7540120F19003. The content is solely the responsibility of the authors and does not necessarily represent the official views of the FDA.

## Declarations

**Competing Interests** The authors declare no competing interests.

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