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Association Between Mode of Delivery Among Pregnant Women With COVID-19 and Maternal and Neonatal Outcomes in Spain

Data from China found severe complications in 8% of pregnant women with coronavirus disease 2019 (COVID-19).1 However, the high rate of cesarean deliveries (>90%) in Chinese reports is concerning,2 and whether mode of delivery is associated with maternal complications or neonatal transmission is unknown.3 We assessed births to women with COVID-19 by mode of delivery.

Methods | Women with singleton pregnancies and a positive reverse transcriptase–polymerase chain reaction (RT-PCR) test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between March 12 and April 6, 2020, and who delivered within the next 14 days at 96 level 2 or level 3 maternity hospitals throughout Spain were included.

The study was approved by the national ethics committee. Oral informed consent was obtained.

Pregnant women were tested if they presented with symptoms compatible with COVID-19 or a history of potential exposure; additionally, universal screening was started in some hospitals in April. Newborns had a nasopharyngeal swab obtained for RT-PCR within 6 hours of life.

Mothers were stratified by symptom severity at admission as asymptomatic, mild, or severe (need for advanced oxygen support: high-flow nasal cannula, noninvasive ventilation, or mechanical ventilation).

Maternal outcomes were defined as severe if mothers required advanced oxygen support or admission to the intensive care unit (ICU) or had signs of sepsis with hypoperfusion/organ dysfunction. Clinical deterioration was defined by an increased need for oxygen supplementation after delivery.

Neonatal outcomes considered were neonatal ICU (NICU) admission and rates of SARS-CoV-2 perinatal transmission.

Multivariable logistic regression was performed assessing the association between mode of delivery and maternal and neonatal outcomes among patients with mild symptoms, adjusting for maternal age, body mass index, comorbidities, need for oxygen supplementation at admission, abnormal chest x-ray findings at admission, nulliparity, smoking, and prematurity. Stata version 14 (StataCorp) was used. A 2-tailed $P < .05$ defined statistical significance.

Results | Of 82 pregnant patients included, 4 presented with severe COVID-19 symptoms, including 1 with concomitant preclampsia; all 4 underwent cesarean delivery and required ICU admission.

Seventy-eight patients presented with no or mild COVID-19 symptoms, including 11 patients requiring oxygen supplementation. Forty-one (53%) delivered vaginally and 37 (47%) by cesarean delivery, 29 for obstetrical indications and 8 for COVID-19 symptoms without other obstetrical indications. Women with cesarean deliveries were more likely to be multiparous, be obese, require oxygen at admission, and have abnormal chest x-ray findings than those delivering vaginally (Table 1). No patients with a vaginal delivery developed severe adverse outcomes, while 5 (13.5%) with cesarean delivery required ICU admission. Two patients (4.9%) with a vaginal delivery had clinical deterioration after birth vs 8 (21.6%) with cesarean delivery. After adjustment for potential confounding factors, cesarean birth was significantly associated with clinical deterioration (adjusted odds ratio, 13.4; 95% CI, 1.5-121.9; $P = .02$) (Table 2).

Eight newborns (19.5%) delivered vaginally and 11 (29.7%) born by cesarean delivery were admitted to the NICU. After adjustment for confounding factors, cesarean birth was not significantly associated with an increased risk of NICU admission (adjusted odds ratio, 1.2; 95% CI, 0.3-4.5; $P = .76$).
Three (4.2%) of 72 newborns tested within 6 hours after birth had a positive SARS-CoV-2 RT-PCR result. Repeat testing at 48 hours was negative. None developed COVID-19 symptoms within 10 days.

Two other newborns, both cesarean deliveries at term, developed COVID-19 symptoms within 10 days. Though initial testing at birth was negative, repeat testing was positive. Both newborns were in contact with their parents immediately after birth. Symptoms resolved within 48 hours.

**Discussion** | In this cohort of pregnant women in Spain, severe adverse maternal outcomes occurred in 11% (9/82), 4 of whom presented with severe and 5 with mild COVID-19 symptoms.
Among patients with mild symptoms at presentation, all patients with a vaginal birth had excellent outcomes. In contrast, 13.5% of women undergoing cesarean delivery had severe maternal outcomes and 21.6% had clinical deterioration. Women undergoing cesarean delivery may have been at higher risk of adverse outcomes, but after adjusting for confounding factors, cesarean birth remained independently associated with an increased risk of clinical deterioration. The physiological stress induced by surgery is known to increase postpartum maternal complications.4,5

Limitations include a lack of sufficient information on newborns to determine vertical transmission. The lack of association between cesarean delivery and risk of NICU admission may have been related to the lack of statistical power. Also, the 95% CIs around the odds ratios for cesarean birth and clinical deterioration were wide and the estimates fragile.

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Use of Risk Evaluation and Mitigation Strategies by the US Food and Drug Administration, 2008-2019

The US Food and Drug Administration (FDA) Amendments Act of 2007 gave the FDA authority to require a Risk Evaluation and Mitigation Strategy (REMS) to “ensure the benefits of the medication outweigh its risks.” At its inception, the REMS program could require (1) that pharmacies distribute medication guides; (2) that manufacturers design communication plans about specific safety issues; and/or (3) that manufacturers provide “elements to assure safe use” (ETASUs) such as prescriber training, prescriber/dispenser certifications, or patient registries.

Despite several important changes to the REMS program, including the 2011 decision to release (or remove) all medications that required a medication guide alone from the program, few comprehensive characterizations of the program have been performed.

Methods | In April 2019, we used FDA.gov to extract information on each medication (ie, unique chemical entity or combination, approved via various pathways) included in the REMS program, including those that may no longer be subject to a REMS and thus have been released from the program.

Results | A total of 222 medications had a REMS designation since the program’s inception. Of these, all 83 drugs that had a medication guide alone were released from the program, most between 2011 and 2012. The Figure depicts trends in the remaining 139 medications that required a communication plan or ETASU. The number of medications with an active REMS designation that required these strategies increased from 11 in 2008 to 60 in 2010. Since 2010, the number of medications that required a communication plan declined and those that required ETASUs increased. As of 2019, 80 medications that required these strategies remained in the program; 45 medications were added and 59 were released between 2010 and 2019.

Of the 57 medications that required a communication plan alone, 87.7% were released since the program’s inception, compared with 11.0% of the 82 medications that required ETASUs (alone [n = 63] or in combination [n = 19]) (Table). As of 2019, 51.3% of medications that required ETASUs used prescriber (38.8%) or dispenser (37.5%) certification or patient registries (28.8%); 13.6% of medications released had any of these requirements. Released medications also differed from those with an active REMS designation in terms of drug classes and risks the program was designed to mitigate. For example, 38.8% of medications with an active REMS designation were opioid analgesics associated with addiction and overdose, whereas half of released medications consisted of biologics (31.7%) and antidiabetics (16.7%), for which a REMS was primarily intended to reduce the risk of life-threatening infections and cardiovascular events, respectively.

Discussion | The REMS program has evolved, with the less restrictive strategies either released from the program (medication guides) or used less often (communication plans) and the...