



Center for Fatality Review & Prevention

COVID-19 and Pregnancy: **A LOOK AT ADVERSE MATERNAL AND NEONATAL OUTCOMES**

Telling Each Story to Save Lives Nationally





KEY FUNDING PARTNER

FEDERAL ACKNOWLEDGEMENT

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HOUSEKEEPING

Before we get started

- This webinar is being recorded and will be available on the National Center's webpage (URL: www.ncfrp.org).
- Participants are muted. Please use the question-and-answer box to ask questions.
- Due to the large number of participants, the speakers may be unable to answer all questions. Unanswered questions will be answered and posted with the recording.
- Contact the National Center (email: info@ncfrp.org) for any tech problems.





EVALUATION

<https://www.surveymonkey.com/r/32BRMMX>



HRSA'S VISION FOR THE NATIONAL CENTER

IMPROVING SYSTEMS OF CARE AND OUTCOMES FOR MOTHERS, INFANTS, CHILDREN, AND FAMILIES

Assist state and community programs in:

- Understanding how CDR and FIMR reviews can be used to address issues related to adverse maternal, infant, child, and adolescent outcomes
- Improving the quality and effectiveness of CDR/FIMR processes
- Increasing the availability and use of data to inform prevention efforts and for national dissemination



Learn how the SARS-CoV-2 virus (COVID-19) has contributed to poor neonatal outcomes



Review information on the prevalence and risk factors for pregnant persons with COVID-19



Learn current guidelines for medical and obstetric care and prevention strategies for pregnant patients with COVID-19



Identify opportunities to strengthen data collection on deaths directly and indirectly impacted by COVID-19



PRESENTATION GOALS



Keynote Speaker

Regan N. Theiler, M.D., Ph.D.

Chair, Division of OB/GYN, Mayo Clinic

Covid-19 in Pregnancy: Maternal, Fetal and Neonatal Outcomes

Regan Theiler, MD, PhD

Division Chair, Obstetrics



Epidemiology

Pregnancy-specific viral epidemiology and outcomes



Treatments

Safety and efficacy in pregnancy



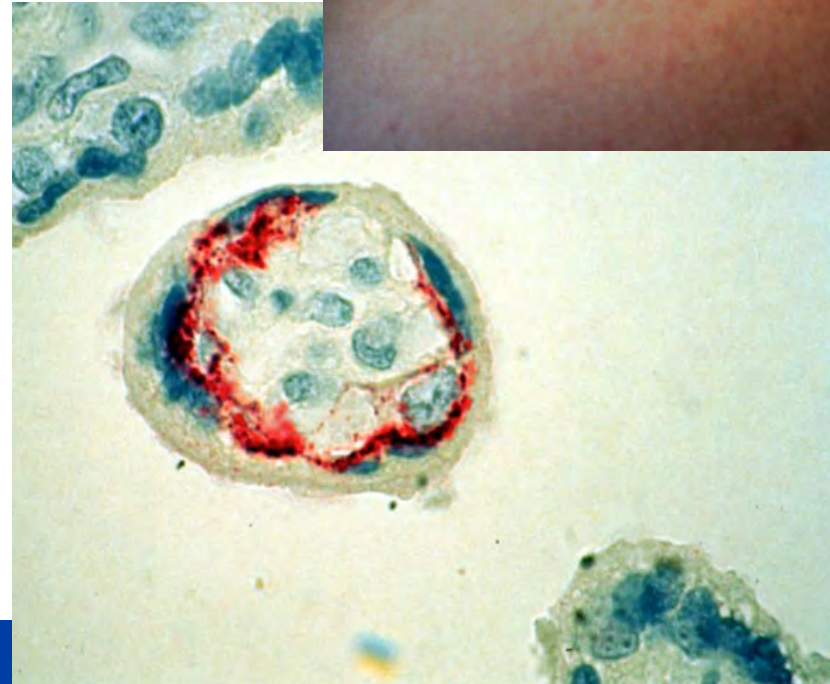
Vaccination

Vaccine uptake, safety, and efficacy

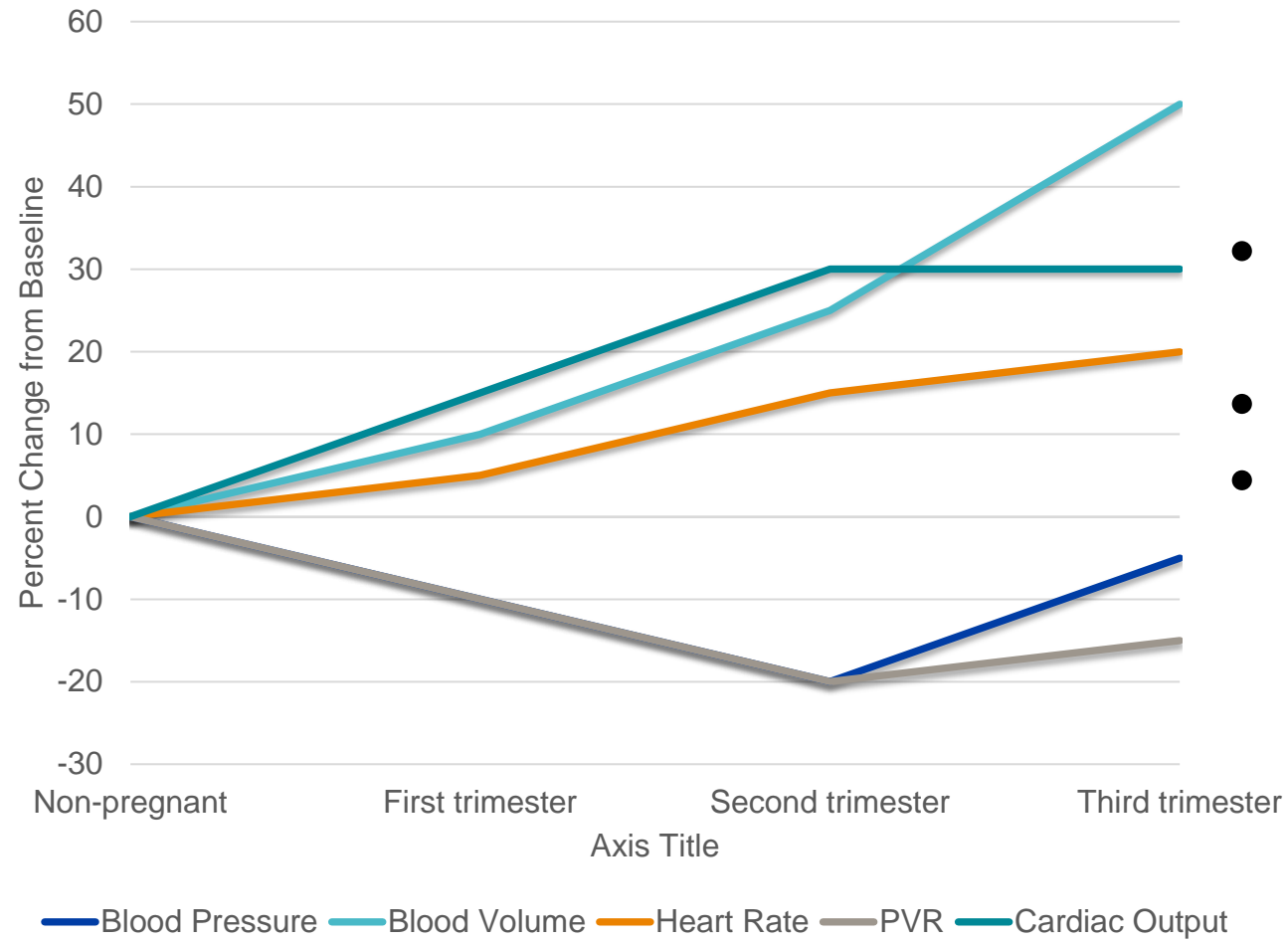
RESPIRATORY VIRUSES IN PREGNANCY

Increased severity

- Influenza (swine flu)
- Varicella Zoster Virus
- SARS
- Lassa fever



Pregnancy Physiology: Cardiovascular



- 2L/min increase in cardiac output at term
- Varies with supine position
- Autotransfusion at delivery with further increased CO

PREGNANCY PHYSIOLOGY:

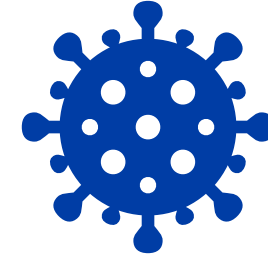
Respiratory

	Non-pregnant	First trimester	Second trimester	Third trimester
VO₂	0	+10%	+20%	+20-30%
PAO₂	93	105	105	105
PaCO₂	37	28	28	28
HCO₃	23	18	18	17
pH	7.4	7.42	7.43	7.43

- Increased tidal volume, decreased total lung capacity
- Decreased inspiratory/expiratory reserve
- Chronic respiratory alkalosis=> Dyspnea of pregnancy
- Chronic nasal congestion/edema



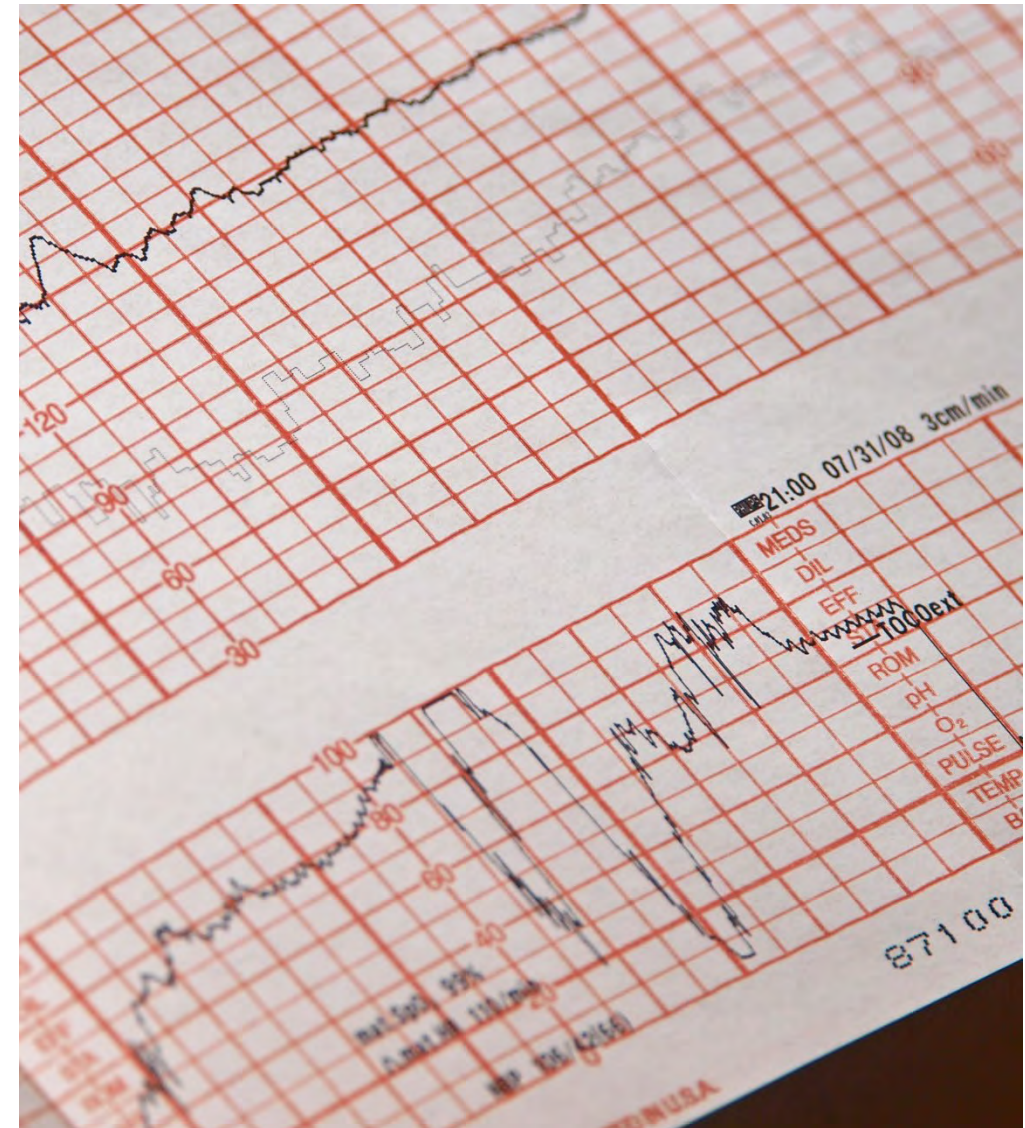
Pregnancy Immunology



- Pregnancy is immune altered state
- Placenta: Tolerogenic
 - 50% maternal and 50% paternal antigens
 - Inhibits immune recognition and rejection of trophoblasts
 - Transport of IgG and IgA to fetus
 - Intact and robust innate immunity
- Barrier, susceptible to intracellular pathogens

PREGNANCY PHYSIOLOGY: Fetal perfusion

- Placental perfusion= Fetal perfusion
 - Maternal cardiac output
 - Maternal oxygenation
 - Placental permeability and transport
- Fetal oxygenation and pH:
Cardiotocography
- Fetal growth reflects placental health



- 26 y.o. G2P1001, 23 0/7 weeks gestation
- New onset vaginal bleeding this morning, red with wiping
- Cold-like symptoms for one week, being treated for sinusitis. Living with COVID+ father.
- Unvaccinated
- Positive home COVID test 10 days ago
 - PMH: migraine, depression
 - POB HX: SVD, 37 weeks
 - PSH: Appendectomy

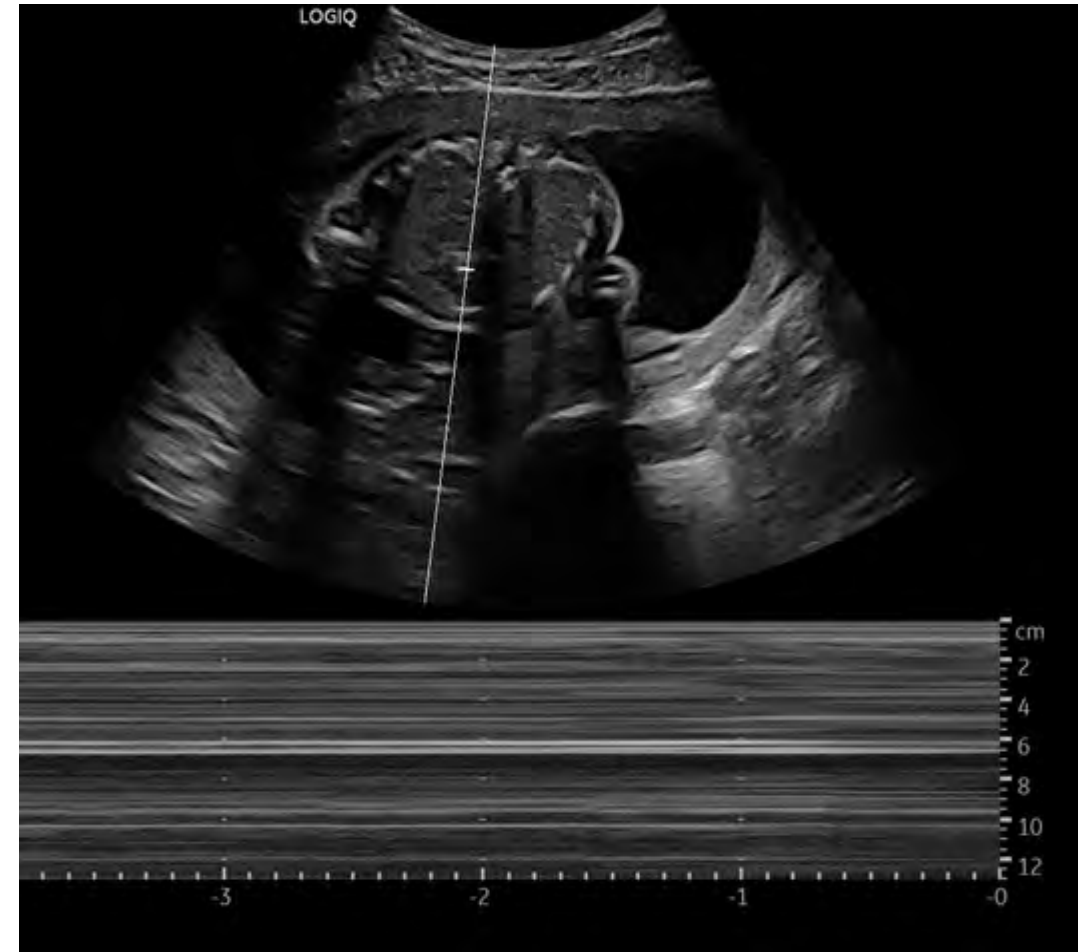


Ultrasound

Age by current ultrasound measurements: 22 weeks 4 days

Estimated fetal weight: 511 g. EFW %: 21.9 percentile

Fetal heart rate: Not detected



Laboratory Evaluation

SARS-CoV-2 rtPCR= Detected

Hb 15, Plt 78, WBC 4.8 (lymphs 0.71)

Fibrinogen 55 (critical)

APTT 39 (^)

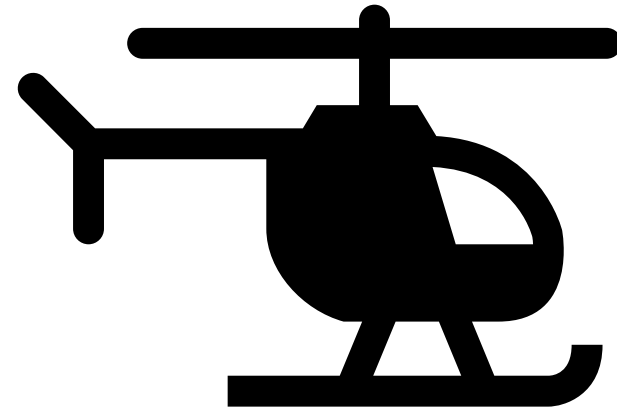
INR 1.0

D-Dimer >42000

AST 64

CRP 10.8

Blood Bank: Adequate cryo, RBCs, FFP
Single unit of platelets



Clinical Course

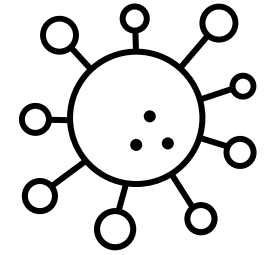
2U Cryoprecipitate administered

400 mcg misoprostol with subsequent SVD

Home PPD #1 with normalization of labs

On follow-up 6 weeks PP, still not interested in vaccine

Autopsy Findings



- 511g Macerated male fetus, consistent with 23 weeks gestational age
- No congenital abnormalities identified at autopsy or upon neuropathology consultation
- Postmortem chromosomal microarray and genetic screen normal

PLACENTAL PATHOLOGY

SARS-CoV-2 placentitis:

Positive postmortem SARS-CoV-2

Massive perivillous fibrin deposition

Acute and chronic histiocytic intervillitis

Villous trophoblast necrosis



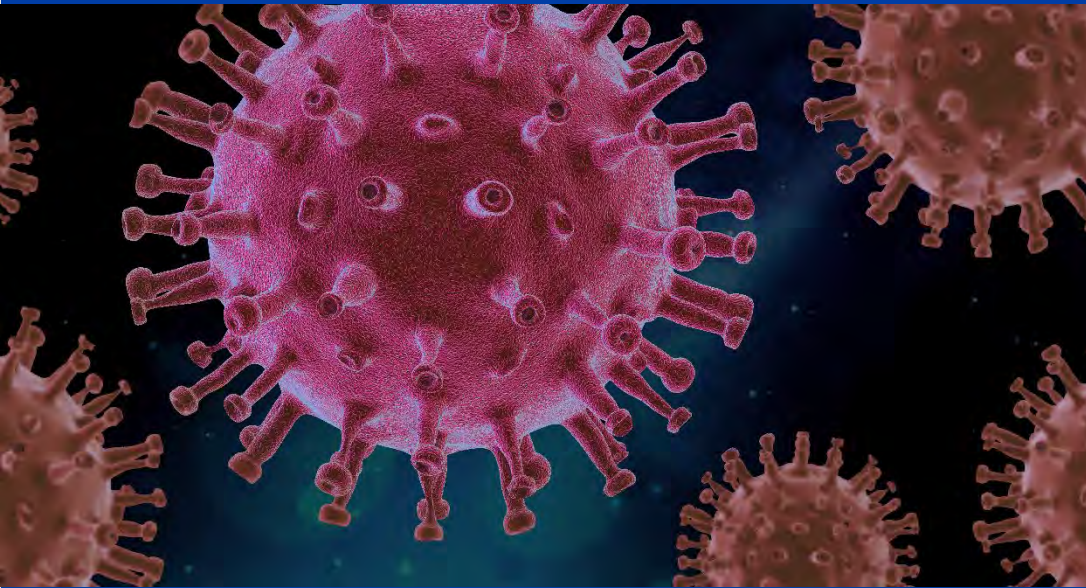


Causation

“In combining review of the medical record, autopsy findings, postmortem cytogenetic/molecular testing, and placental evaluation, ***it is our opinion that the cause of the stillbirth is SARS-CoV-2 placentitis.***”



Natural History of COVID-19 in Pregnancy



1

INCIDENCE

Pregnancy LIKELEY does not influence incidence of COVID-19

2

SEVERITY

COVID-19 causes more severe infection during pregnancy

3

NEONATAL OUTCOMES

Vertical transmission is rare,
Preterm birth sequelae increased

DATA LIMITATIONS

EPIDEMIOLOGY

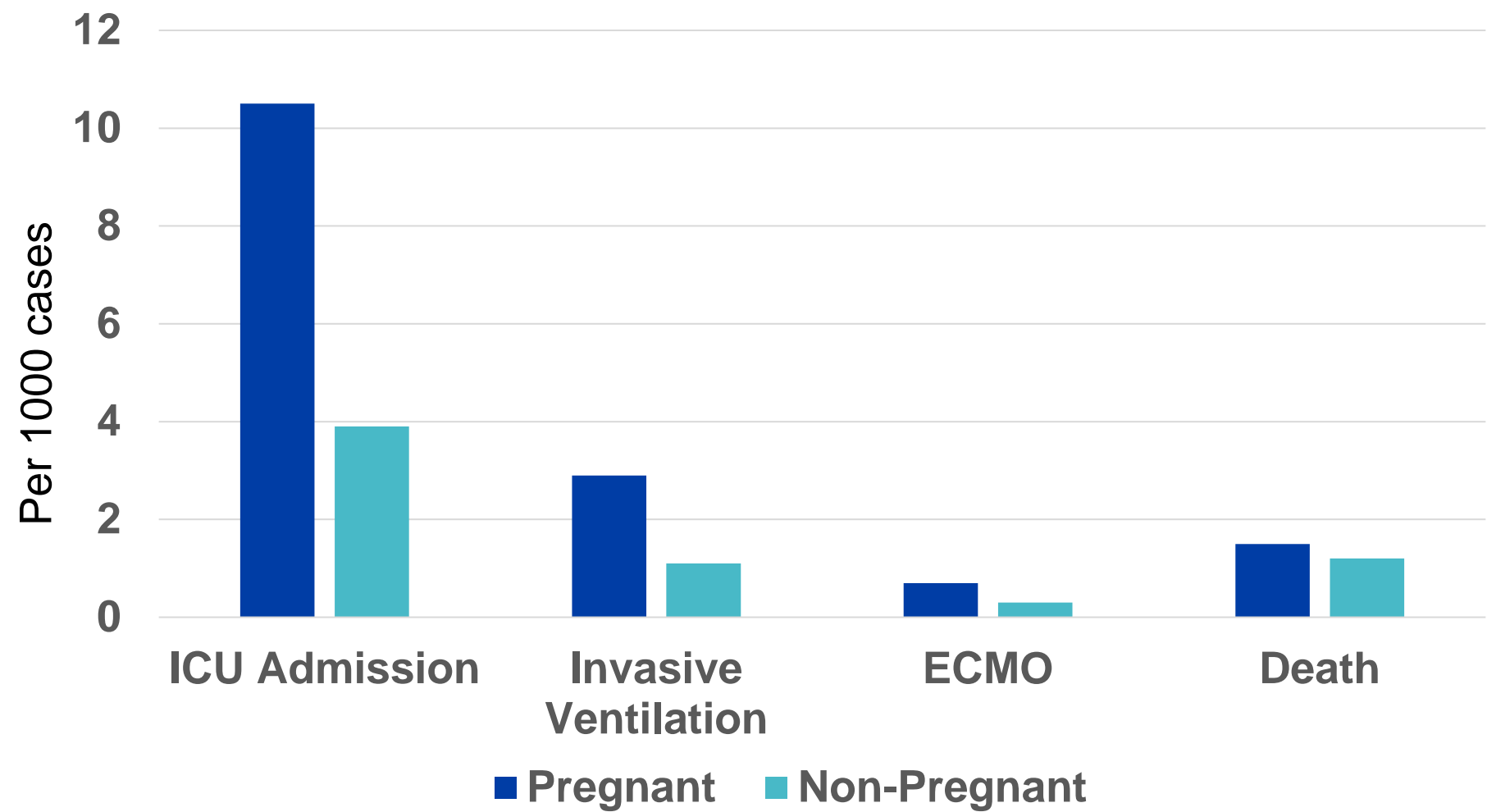
- Selection bias/reporting bias
- Testing bias (delivery hospitalization)
- Limited surveillance infrastructure

TREATMENTS and VACCINES

- No RCTs with pregnant patients
- No pregnant patients in FDA approval studies
- Access to therapeutics= Geography and severity, SES



COVID-19 SEVERITY IN PREGNANT VS. NON-PREGNANT



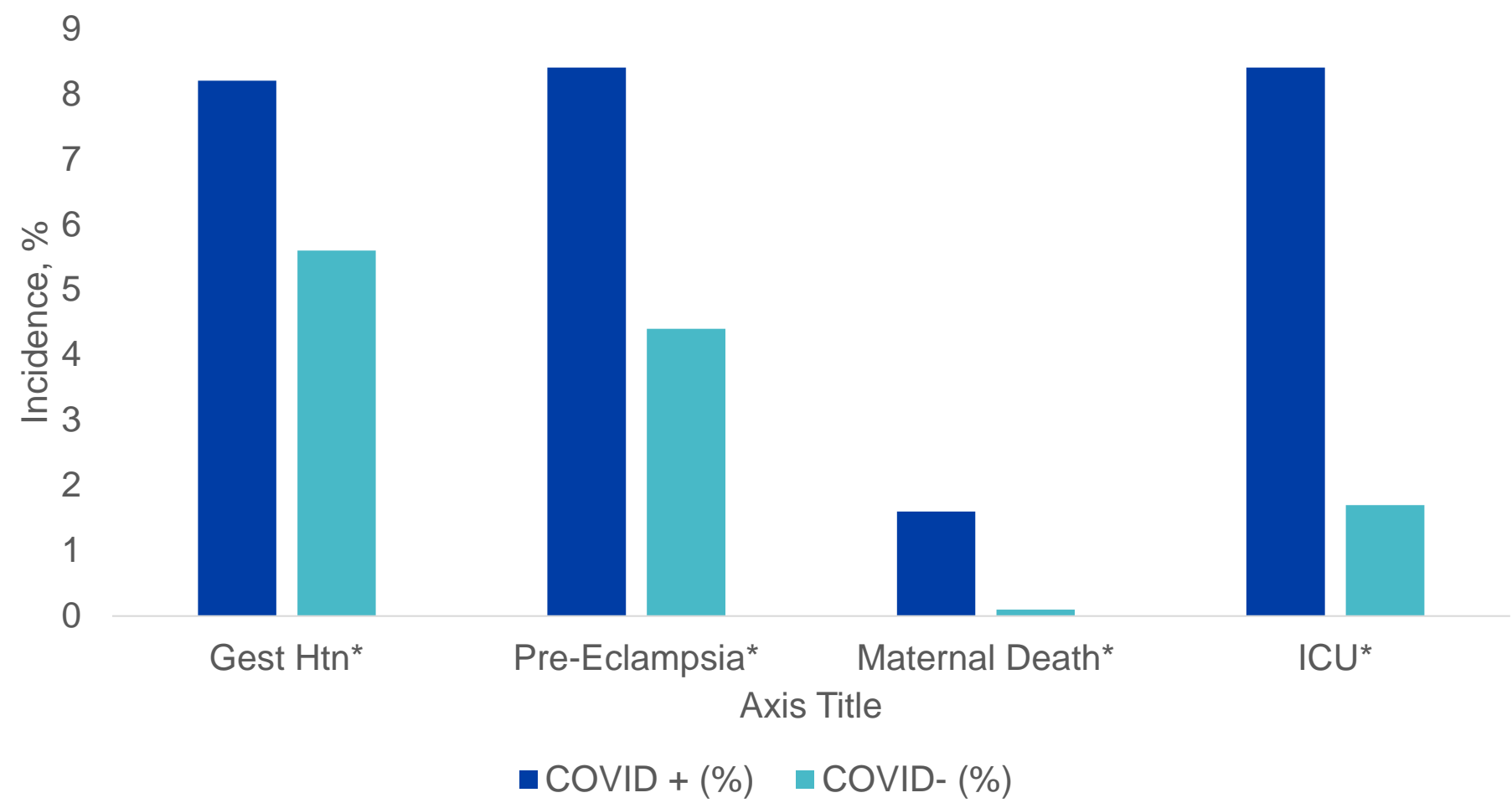
ICU Admission

	No. (per 1,000 cases) of symptomatic women		Risk ratio (95% CI)	
	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Crude†	Adjusted†,§
ICU admission				
All	245 (10.5)	1,492 (3.9)	2.7 (2.4–3.1)	3.0 (2.6–3.4)
Age group, yrs				
15–24	49 (7.6)	244 (1.8)	4.1 (3.0–5.6)	3.9 (2.8–5.3)
25–34	118 (9.1)	467 (3.5)	2.6 (2.1–3.1)	2.4 (2.0–3.0)
35–44	78 (19.4)	781 (6.4)	3.0 (2.4–3.8)	3.2 (2.5–4.0)

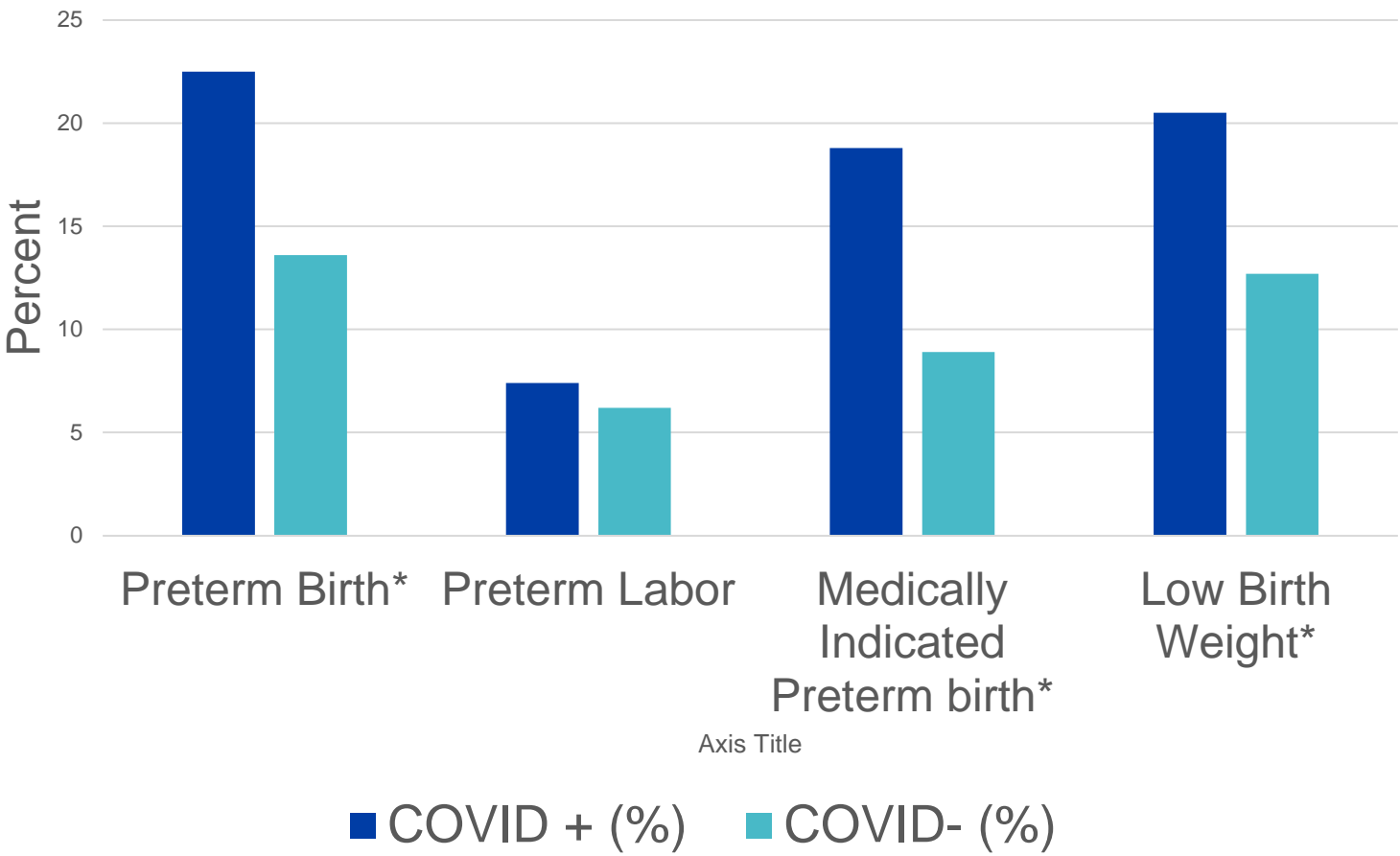
Death

	No. (per 1,000 cases) of symptomatic women		Risk ratio (95% CI)	
	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Crude†	Adjusted†,§
Death^{\$\$\$}				
All	34 (1.5)	447 (1.2)	1.3 (0.9–1.8)	1.7 (1.2–2.4)
Age group, yrs				
15–24	2 (0.3)	40 (0.3)	NA	NA
25–34	15 (1.2)	125 (0.9)	1.2 (0.7–2.1)	1.2 (0.7–2.1)
35–44	17 (4.2)	282 (2.3)	1.8 (1.1–3.0)	2.0 (1.2–3.2)

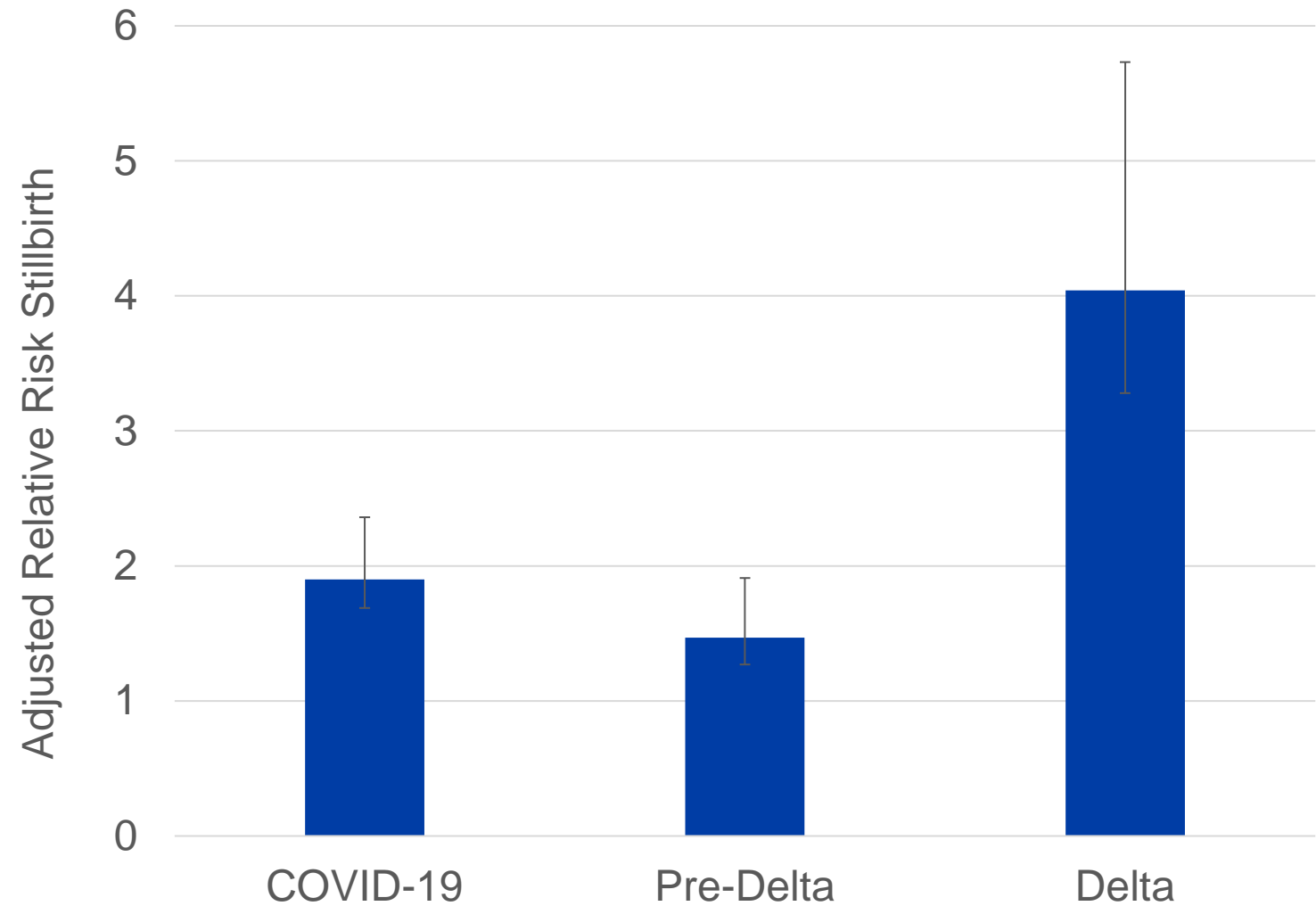
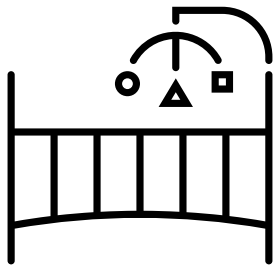
PREGNANCY OUTCOMES WITH AND WITHOUT MATERNAL COVID-19 INFECTION: INTERCOVID STUDY



NEONATAL OUTCOMES, INTERCOVID STUDY



STILLBIRTH



Stillbirths

Average 30 wks EGA at fetal death

Maternal Risk Factors

- Hypertension
- Diabetes
- Obesity
- Maternal ICU admission

NEONATAL OUTCOMES

- Transplacental transmission is rare
- No evidence for intrapartum transmission
- No evidence for lactation transmission
- Sequelae of prematurity common
- Perinatal death increased

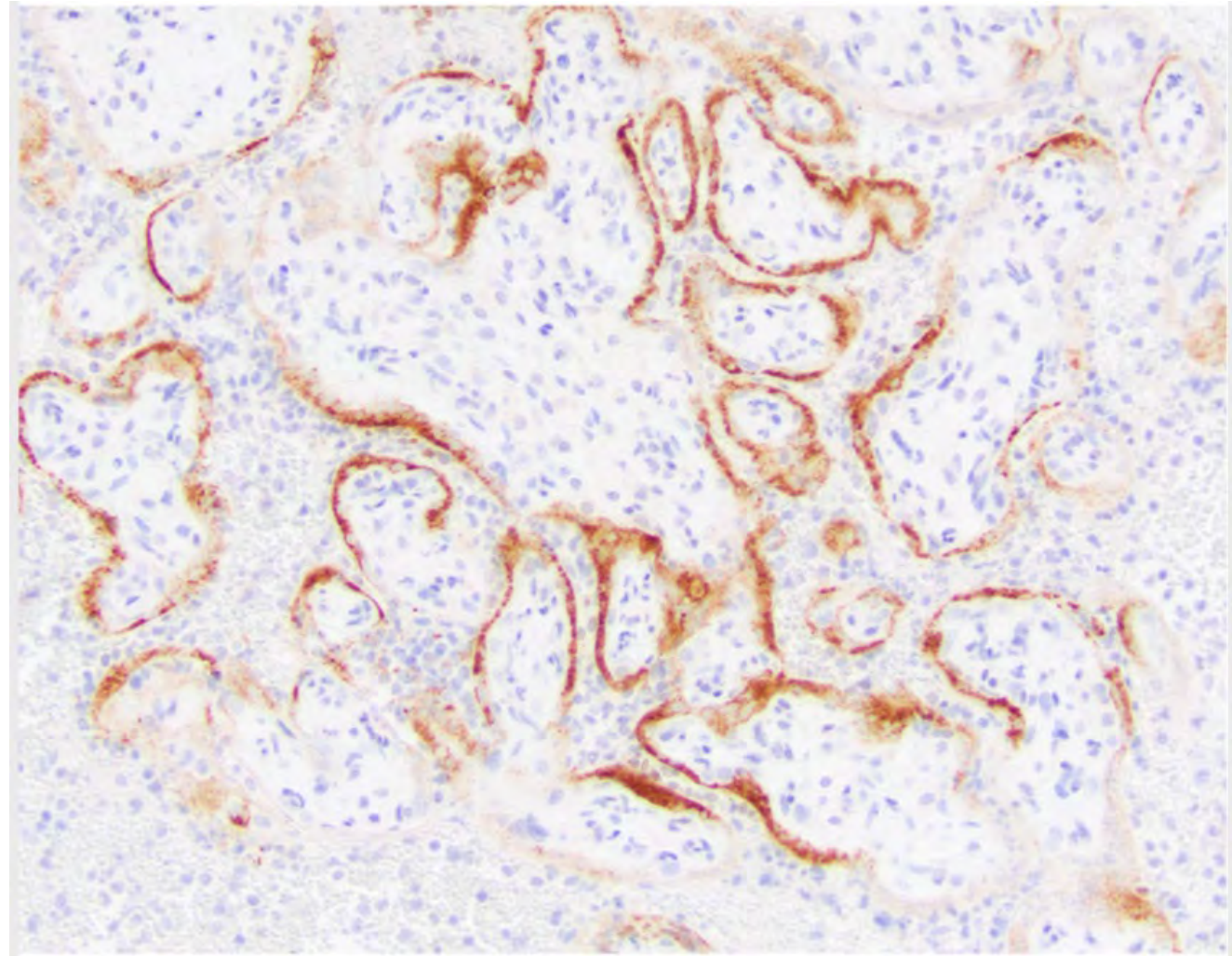


Mechanisms of Perinatal Death

- Cohort of 64 stillborn, 4 neonatal deaths
 - Maternal COVID-19,
 - Placental SARS-CoV-2 (+)
- All 68 placentas with
 - increased placental **fibrin deposition**
 - villous **trophoblast necrosis**
 - Average of 77% tissue involvement
- 19/30 fetal autopsies showed findings consistent with asphyxia
- 16/28 with SARS-CoV-2 detected in fetal tissue or NP swab

Placental Findings

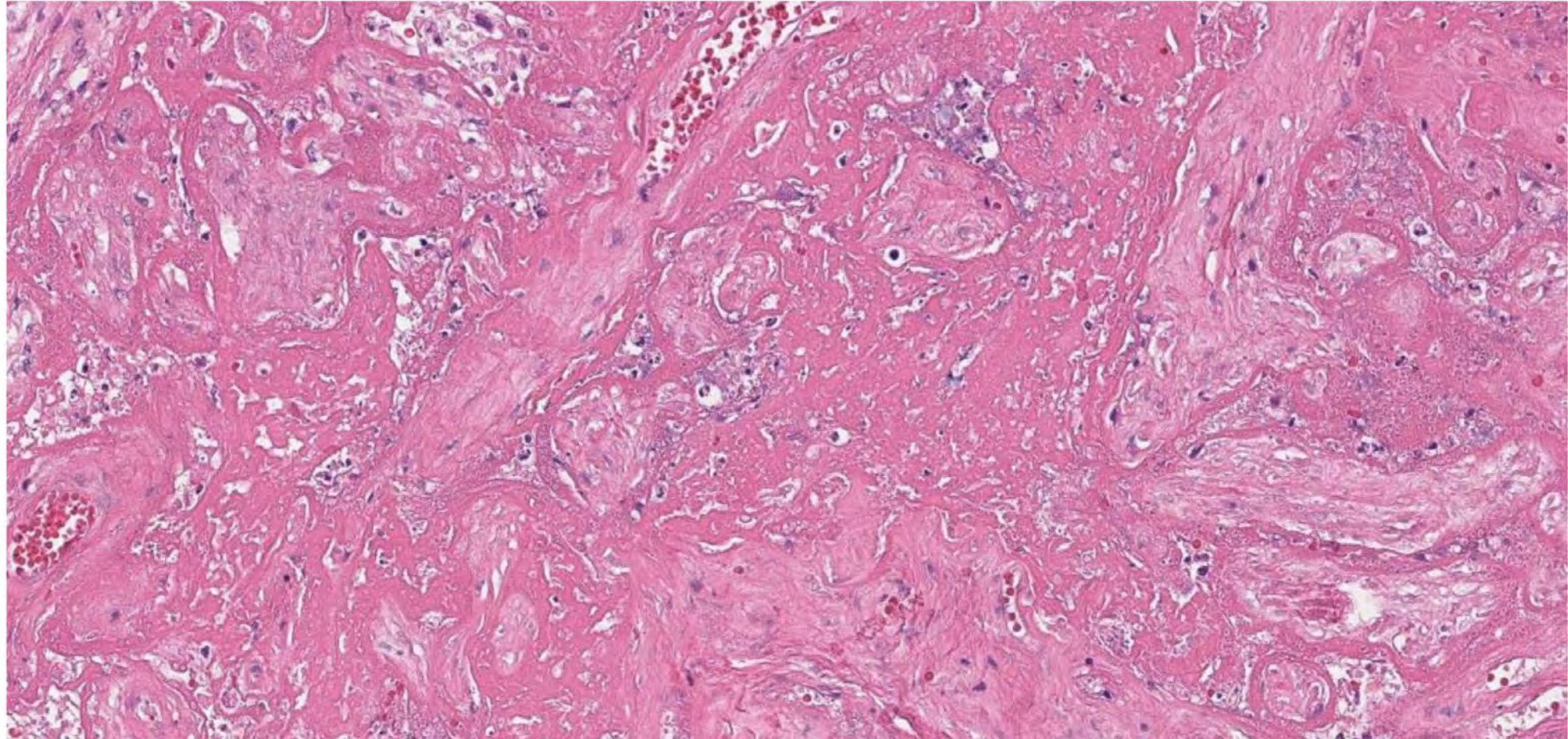
Placenta from a stillbirth demonstrating positive staining for SARS-CoV-2 in the syncytiotrophoblast using RNA in situ hybridization. X20.



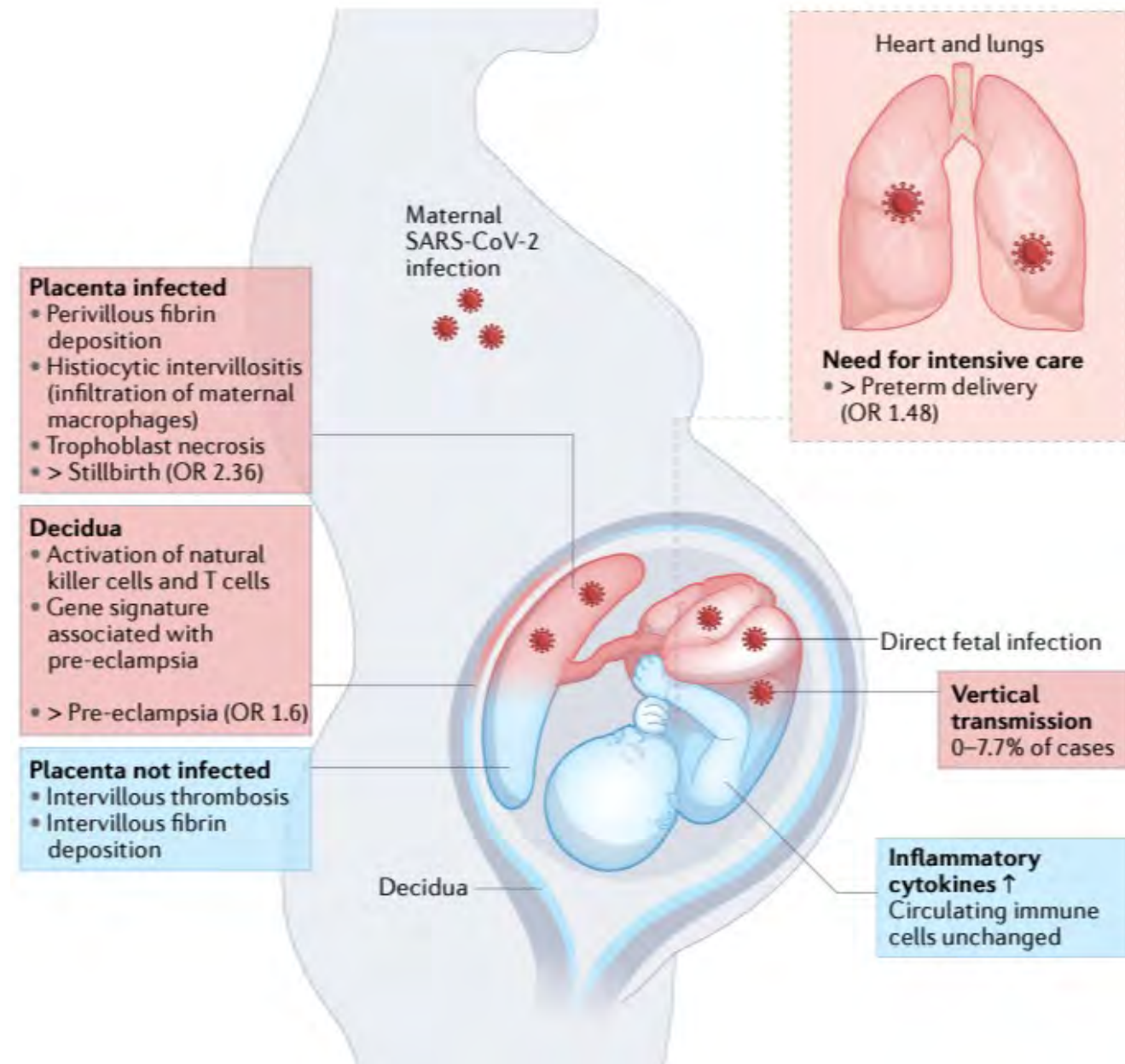
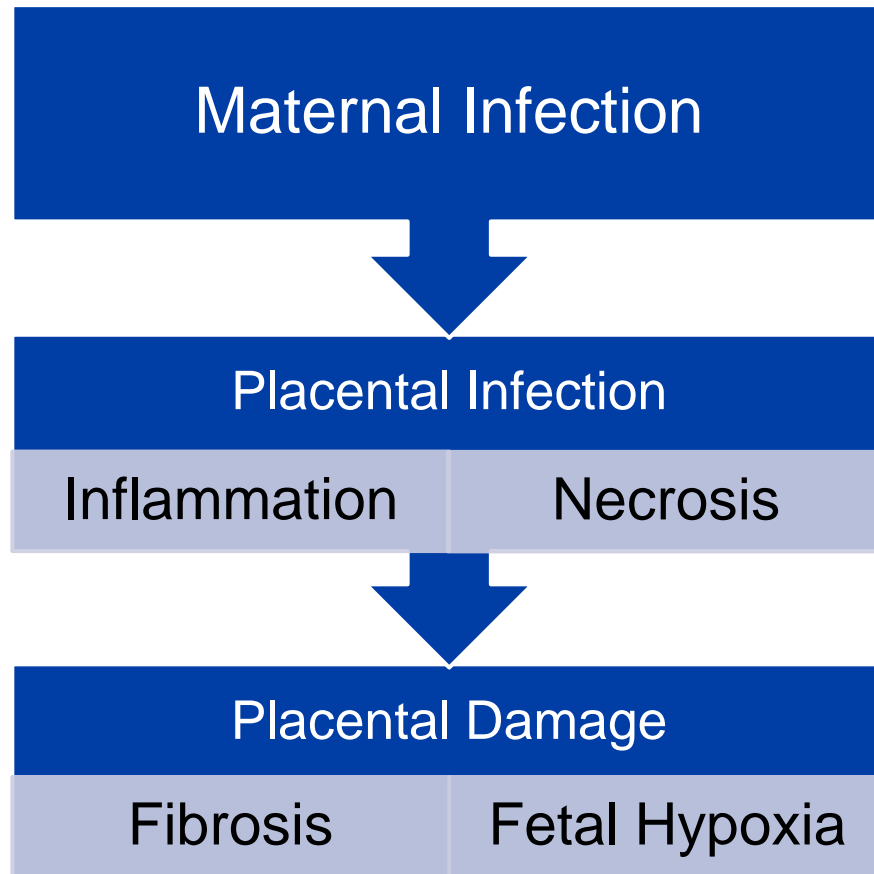
Arch Pathol Lab Med (2022)

<https://doi.org/10.5858/arpa.2022-0029-SA>

63 placentas: massive perivillous fibrin deposition



Current Model



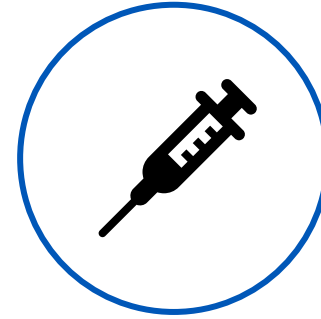
VACCINATION

Strongly recommended during pregnancy
(WHO, FDA, CDC, ACOG, SMFM)

mRNA vaccines preferred

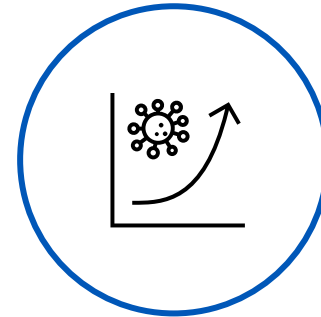
No need test for pregnancy

<https://www.smfm.org/covidclinical>



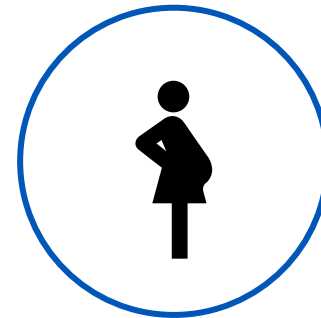
HESITANCY

Pregnant patients are the most hesitant demographic, estimated 30% uptake



EFFICACY

Similar to general population, limited studies



PREGNANCY SAFETY

No adverse safety signals

FERTILITY

- Theoretical infertility mechanism has been disproven—anti-spike antibodies do not bind to syncytin
- No vaccine or infection-related decrease in ovulation or implantation
- No known adverse pregnancy outcomes with pre-pregnancy vaccination
- No increased miscarriage rates with vaccination during pregnancy



VACCINATION IN PREGNANCY

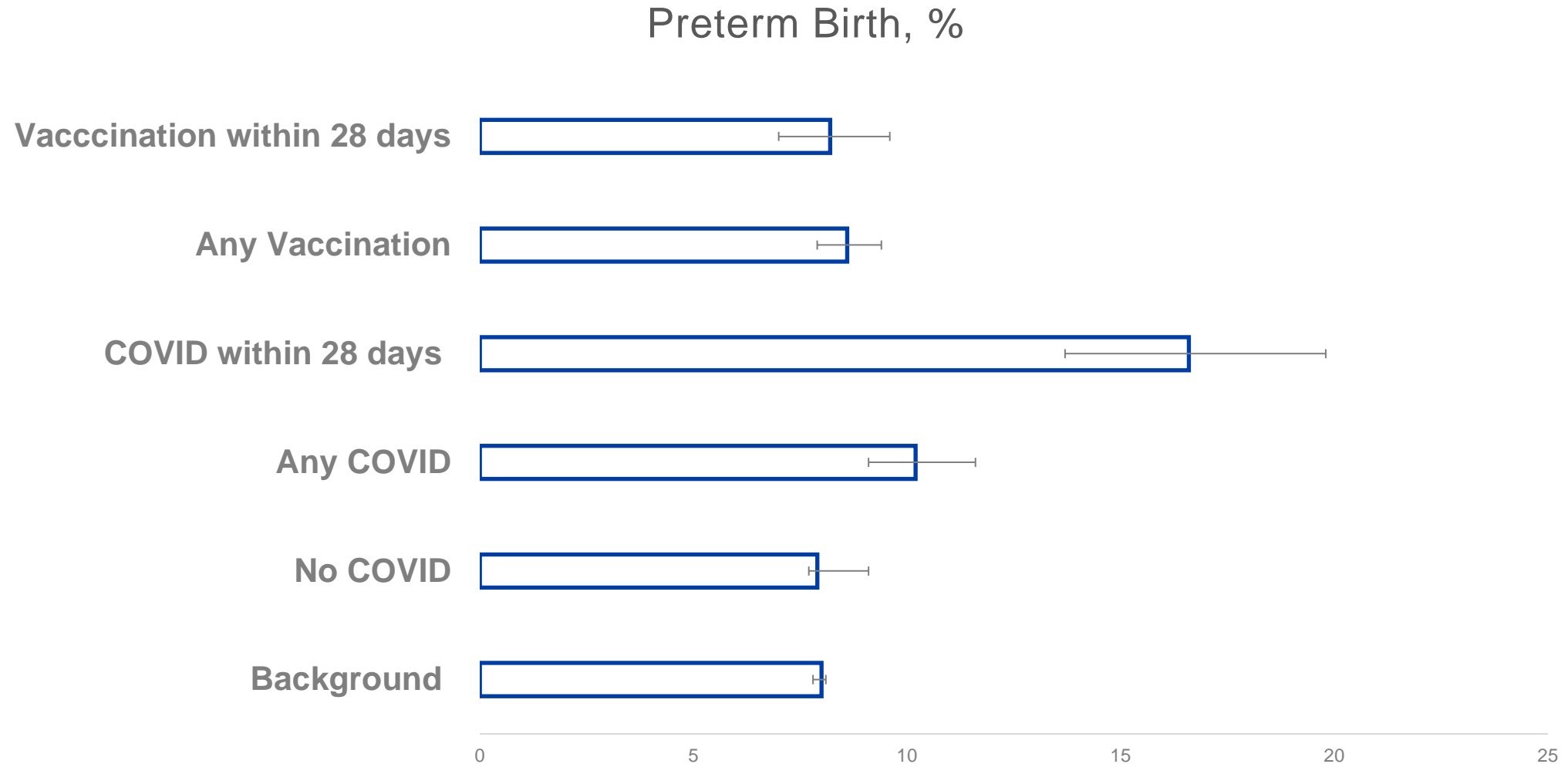
V-SAFE

- CDC data from 180k patients, no pattern of adverse events is obvious
- Patient-reported, short term AE
- Long-term data pending on 8,749 pregnancy registry patients

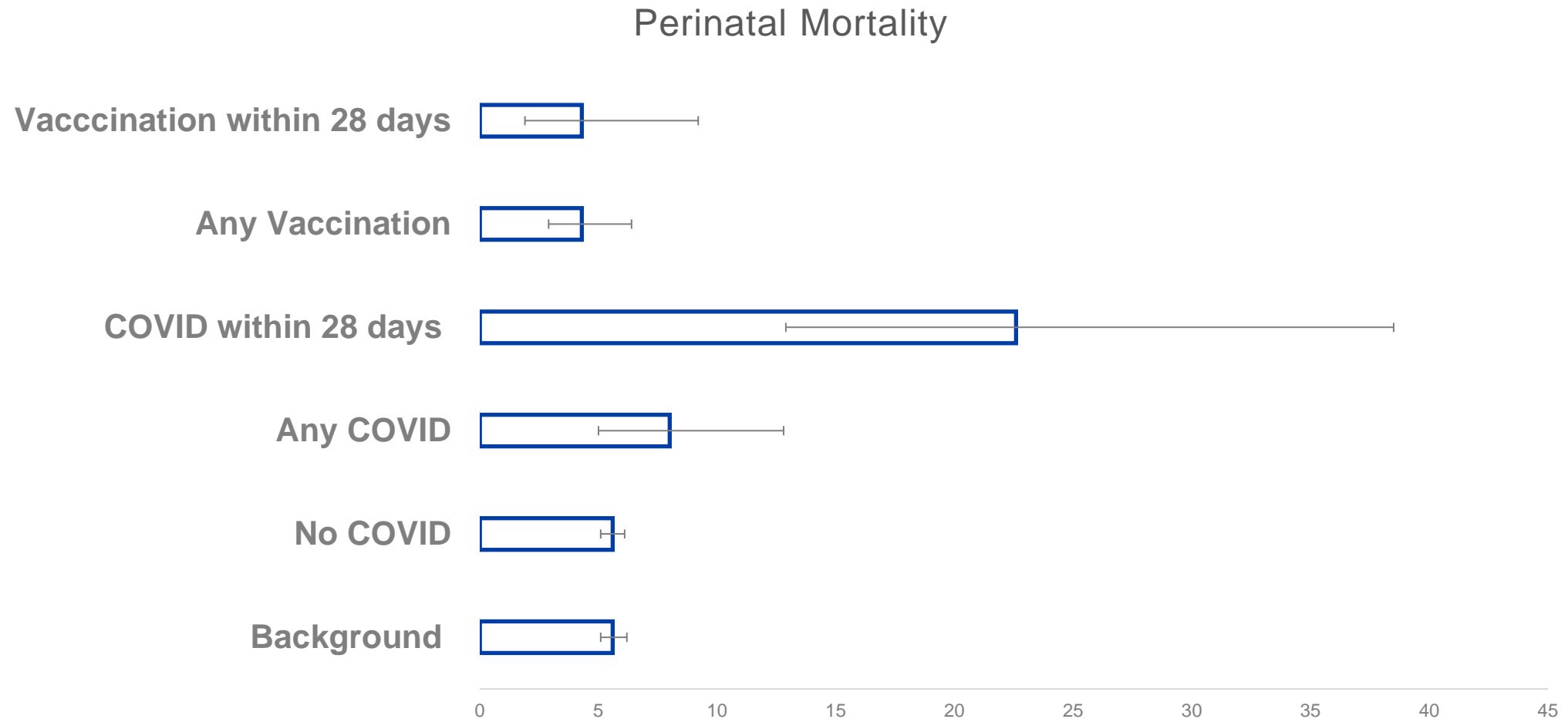
RETROSPECTIVE COHORTS

- IgG, CD4 and CD8 T cell responses documented
- 10,861 vaccinated (BNT162b2) with **96% efficacy**
- 141 patients vaccinated vs. 1800 controls- no adverse pregnancy outcomes
- 140 vaccinated vs 1188 controls , no adverse pregnancy outcomes

Preterm birth after maternal vaccination



Perinatal Mortality After Maternal Vaccination





PASSIVE IMMUNITY

- Within two weeks of maternal infection neutralizing anti-SARS-CoV-2 antibodies found in fetal blood
- Neutralizing antibodies found in breast milk
- Post-vaccination, high titer anti-spike protein neutralizing IgG transferred to fetus

Maternal Vaccination and Neonatal Hospitalization

Timing of maternal vaccination during pregnancy†	No. vaccinated¶/Total (%)		Vaccine effectiveness,* % (95% CI)
	Case-infants	Control-infants	
Any time	28/176 (15.9)	65/203 (32.0)	61 (31 to 78)
Early (first 20 weeks)	17/165 (10.3)	26/164 (15.9)	32 (–43 to 68)
Late (21 weeks' gestation through 14 days before delivery)	9/157 (5.7)	38/176 (21.6)	80 (55 to 91)

COVID-19 TREATMENT DURING PREGNANCY



1

MONOCLONAL ANTIBODIES

High-priority group

2

CORTICOSTEROIDS

Indicated for fetal lung maturation, COVID pneumonia

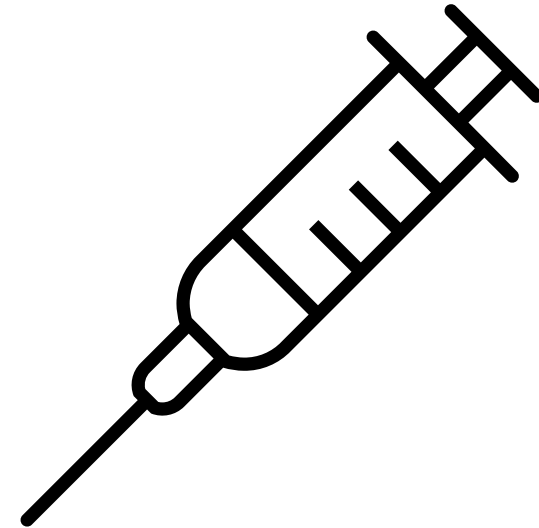
3

ANTIVIRALS

Mixed data

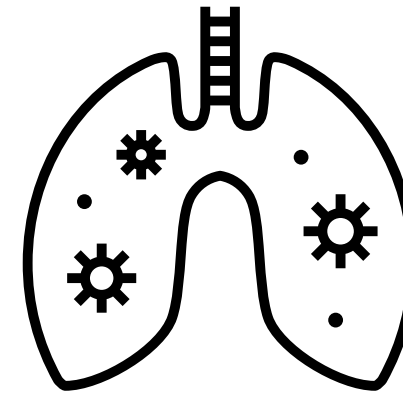
MONOCLONAL ANTIBODIES

- No RCTs in pregnancy
- Anti-TNF α and IL-6 mAbs generally safe for use (retrospective data)
- Series of 51 mild to moderate cases treated with anti-spike mAbs without adverse maternal or fetal effects



ANTIVIRAL DRUGS: Remdesivir

- Remdesivir
 - Single report of 86 critically ill patients
 - 69% had comorbid conditions
 - Median 28 weeks gestation
 - Low rates of drug-related AE
 - 7 discontinued drug (5 transaminitis)
 - 15% had creatinine elevations
 - 90% mothers survived to discharge
 - 69% extremely preterm birth 24-32 weeks



ANTIVIRAL DRUGS: Paxlovid

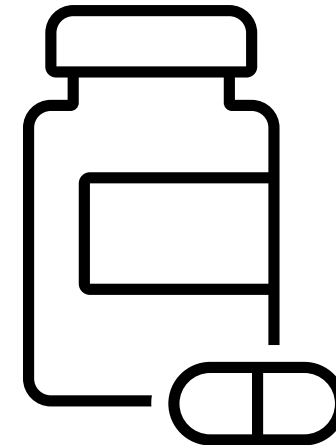
“SMFM supports the use of **Paxlovid** in pregnant patients with COVID-19”

Safety—

- Ritonavir established safety
- Nirmatrelvir---animal pregnancy data reassuring, possible risk of low birthweight

Decreased drug clearance (CYP 3A)

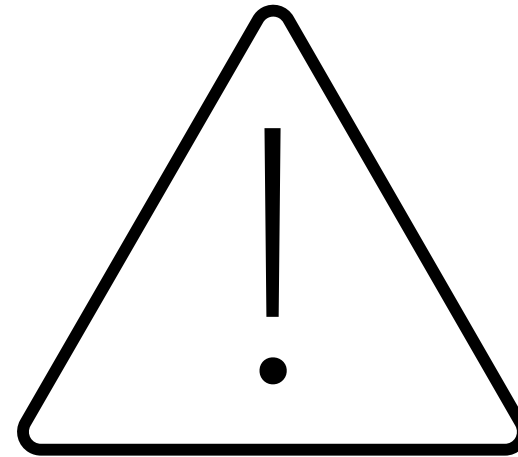
- ergot alkaloid metabolism—*methergine* contraindicated
- *Nifedipine*- decrease dose



<https://www.fda.gov/media/155050/download>

ANTIVIRAL DRUGS: Molnupravir

- **Mutagenic**- nucleoside analog, contraindicated in pregnancy
- Lactation- 4 day delay recommended
- Animal studies: embryoletal, teratogenic, delayed ossification
- Use effective contraception, *consider pregnancy testing* for women of reproductive age
- Pregnancy surveillance program: *[pregnancyreporting.msd.com](https://www.pregnancyreporting.msd.com)*



<https://www.fda.gov/media/155054/download>

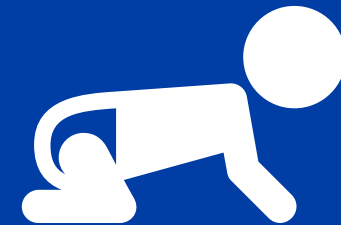
Healthy Mom

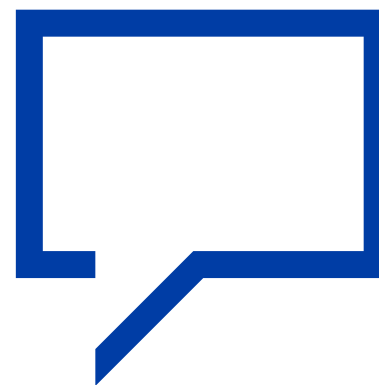


Healthy Placenta



Healthy Baby





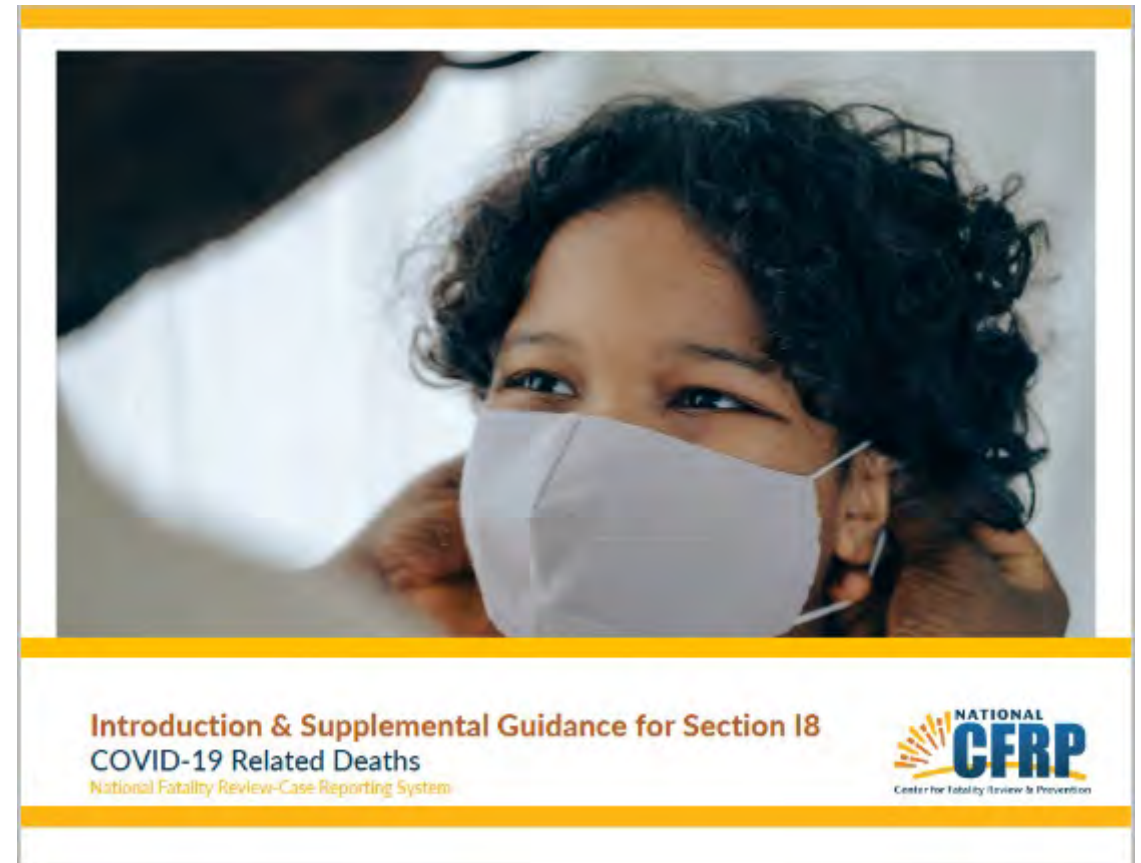
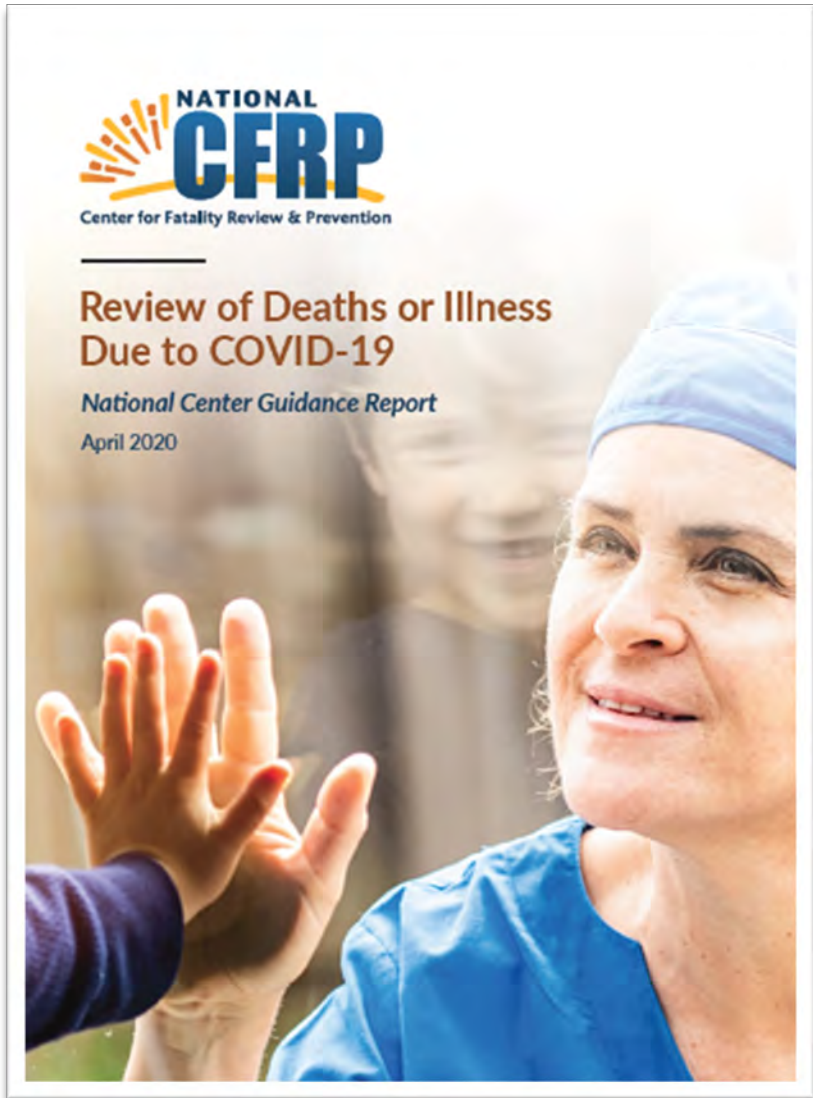
Questions & Discussion

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- 11. ZAMBRANO LD, ELLINGTON S, STRID P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1641-47.
- 12. HEGEWALD MJ, CRAPO RO. Respiratory physiology in pregnancy. Clin Chest Med 2011;32:1-13.
- 13. SANGHAVI M, RUTHERFORD JD. Cardiovascular physiology of pregnancy. Circulation 2014;130:1003-8.

Resources for Reviewing COVID-19 Deaths

www.ncfrp.org



COVID-19 During Pregnancy

Exploring Birth and Infant Outcomes
through Fatality Review

Coming Soon!



April 2022



**COVID-19 During Pregnancy:
Exploring Birth and Infant
Outcomes through Fatality Review**

National Center Guidance Report

QUESTIONS

WHAT ADDITIONAL INFORMATION WOULD BE HELPFUL?



USE THE QUESTION-AND-ANSWER BOX

The box is located at the bottom of the screen



UNANSWERED QUESTIONS

All unanswered questions will be answered and posted on the National Center's website (URL: www.ncfrp.org).

NFR-CRS Version 6.0 Release

Tuesday, May 24, 2022: 1:00 p.m. – 2:00 p.m. ET

Join staff from the National Center to discuss the release of the National Fatality Review-Case Reporting System (NFR-CRS) Version 6.0. Key changes will include:

- Revised cause of death sections
 - Revised COVID-19 section
 - Expanded life stressors section
 - Improved data entry for stillbirths
 - Incorporation of non-gendered language
 - Two factor authentication for all users
-
- **To Register:** <https://bit.ly/3vdGdU1>





EVALUATION

<https://www.surveymonkey.com/r/32BRMMX>



CONTACT INFORMATION



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www.ncfrp.org

A dark silhouette of a person with long, flowing hair, positioned in the center of the frame. The person appears to be looking away from the camera, with their hair blowing in the wind. This silhouette serves as a background for the text and the button.

THANK YOU FOR YOUR TIME!

www.ncfrp.com