COVID-19 and Pregnancy: A public health, evidence-based approach

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Pregnancy can be affected by medical comorbidities. It is known that pregnant individuals are susceptible to severe illness due to some viral infections, as evident in the H1N1 pandemic, with potential explanations such as the physiological changes of reduced lung volume from displacement by the uterus, and a dysregulated inflammatory cascade, characterized by "silencing" of Th1 pro-inflammatory response and strengthening of Th2 response to fend against miscarriage.[1] As the world continues to fight against the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 pandemic, the resurgence in hospitalizations and deaths worldwide, makes it imperative to place in context the risks this virus poses during and after pregnancy. More than 3,500 reports are in the literature, but what is missing are high quality longitudinal data on COVID-19 and pregnancy-related outcomes, adverse effects to the fetus, and the health of the infant to inform policy and practice. This commentary aims to identify the gaps in research that would inform and enable timely, prospective collection and dissemination of data to drive shared decision making with pregnant individuals in the era of COVID-19.

SARS-CO-V2 IN PREGNANCY: EMERGING DATA AND QUESTIONS

A search in PubMed of COVID-19 and pregnancy as of September 21, 2021 revealed 3579 articles. Early information from Wuhan, China, at the beginning of this pandemic on the severity of disease during pregnancy suggested a mild course in 109 of 118 women, with severe disease in nine (8%) and mechanical ventilation required by one woman.[2] Subsequently, many reports, and some meta-analyses or systematic reviews of the data from these reports, have described symptoms and adverse outcomes in pregnancies affected by COVID-19. Many of these reports are retrospective, do not compare pregnant to non-pregnant individuals, and lack data on maternal and neonatal outcomes. Pre-term births have been frequent but reported to be similar to the rate in the general pregnant population. Additionally, it is still not known whether COVID-19 during pregnancy harms the fetus or newborn, and evidence for vertical (mother to child) transmission of SARS-CoV-2 is sparse.

The U.S. Center for Disease Control (CDC) did report January to October 2020 surveillance data representing 30,415 pregnant adolescents and women (ages 15-44) with COVID-19 and 434,410 non-pregnant adolescents and women with COVID-19. This study suggested that pregnancy is associated with a higher risk of severe disease with higher rates of admission to the intensive care unit (adjusted RR 3.0; 95% CI 2.6–3.4), mechanical ventilation (adjusted RR 2.9; 95% CI 2.2–3.8) and increased mortality (adjusted RR = 1.7 (95% CI, 1.2–2.4).[3] However, as noted by the authors, the missing information on pregnancy status in 64.5% of 1,300,938 women of reproductive age with positive tests for the SARS-CoV-2 virus, is a limitation of this study, as are missing data on race, comorbidities and outcomes. In addition, due to incomplete information, the question of whether hospitalization in the sample studied was related to COVID-19 infection or pregnancy-related conditions, could not be answered.

In another report, data from pregnant women in 13 states collected and analyzed by the U.S. COVID-19 Associated Hospital Surveillance Network (COVID-NET) show that in 598 pregnant women with COVID-19 who were hospitalized, those who were symptomatic, compared to asymptomatic, were less likely to have live births (30% vs 70%) and more likely to be admitted to the intensive care unit, require mechanical ventilation and un-

dergo treatment with steroids and vasopressors.[4] Limitations of the COVID-NET report include the use of a convenience sample of 29% of hospitalized women-those who had been discharged and had a chart review—and the missing data on birth outcomes from pregnancies completed after hospital discharge. The amount of missing data underscores the need for improving surveillance and studies of COVID-19 in pregnancy. In both the CDC and COVID NET studies, Hispanic and non-Hispanic Black pregnant women appeared to be disproportionately affected by SARS-CoV-2 infection, but due to incomplete information on race and ethnicity, a definitive conclusion cannot be reached.

IMPORTANCE OF DISAGGREGATED DATA

A large body of literature points to excess morbidity and mortality in racial and ethnic minorities who have contracted COVID-19. Whether COVID-19 causes more serious complications in Black and Hispanic (Latinx) individuals who are pregnant is not yet clear. In both CDC and COVID NET studies, Hispanic and non-Hispanic Black pregnant women appeared to be disproportionately affected by SARS-CoV-2 infection, but firm conclusions cannot be made due to incomplete information on race and ethnicity. Clearly, more demographic data are needed, as well as information on comorbidities, such as obesity which affects 38% of the U.S. population. Superimposed on this analysis must be the analysis of pre-existing disparate racial pregnancy-related outcomes with the national figures showing Black women are 3-4 times more likely to suffer maternal mortality, and severe maternal morbidity, and have higher rates of low birthweight infants and the accompanying high infant mortality rates. The reasons for disparate maternal mortality have been examined by a number of researchers and published data point to inequities in the quality of care driven by a number of factors including implicit bias and health care systems dysfunctions.[5]

PUBLIC HEALTH MESSAGES

Based upon the information we have it is more than reasonable to limit exposure to COVID-19 by the rigorous use of appropriate social isolation and PPE for all pregnant individuals, but priority should also be placed on providing information through targeted public messaging that allows them to make informed choices. It should not be assumed that the public is not sophisticated enough to absorb complex health data -the effort should be to continuously engage and inform so that families are better equipped to understand test results and make tough decisions. For example, SARS COV1D-19 test inaccuracies, false negatives and positive rates as demonstrated in Table 1 [6–9] point to the urgent need for adherence to authorized instructions for use of a test, follow-up reflex testing with molecular assay when appropriate, and interpretation of test results within a clinical context. In the absence of symptoms current data do not support antigen or antibody testing. Test performance and varying disease prevalence have limited ability to inform clinical decision making. [10] False positive and negative test rates have been reported to be as high as 40 and 50 percent, respectively. [6,11] Tests can be divided into direct, indirect, and complementary tests. In the direct test, reverse transcriptase polymerase chain reaction (RT-PCR) assays are the molecular tests of choice for the diagnosis of COVID-19. Indirect testing, antigen-antibody-based techniques, are recommended for surveillance for the disease. Clinical context, timing of tests, adherence to manufacturer's recommendations all play a role in the accuracy of these tests, as well as the importance of knowing the population specific prevalence of the disease.

These test inaccuracies point to the urgent need for adherence to preventive measures even when an individual's SARS CoV-2 test results are known. Furthermore, more research is needed on the diagnostic accuracy of RT-PCR for SARS-CoV-2, including assessment of viral load in the respiratory samples of patients with varying severity of infection and points in time of disease. The confirmation of SARS-CoV-2 infection relies on detection of virus RNA in various body fluids. Currently, nucleic acid amplification tests (NAATs) provide the earliest and most sensitive detection of SARS-CoV-2 (Table 1). As a result, these molecular tests have become the primary means and as determined by the CDC, the "gold" standard for clinical diagnosis or identification of acute infections caused by SARS-CoV-2".[6]

Public awareness of current vaccine status adjoined by clear unambiguous messages are also needed. Clarity does not negate complexity and needs to be explicit in addressing the information regarding pregnancy. As of September 26, 2021, three vaccines are approved, or authorized for emergency use, in the United States (Table 2).[12–15] However, the absence of data on immunization during pregnancy makes recommendations difficult and dependent upon the perceived risk-benefit ratio – and this could be stated in public messaging. On December 21, 2020 the American College of Obstetrics and Gynecology (ACOG) recommended offering vaccination with the Pfizer-BioNtech mRNA vaccine (BNT162b2) or the Moderna-1273 COVID-19 vaccine to women during pregnancy and while breastfeeding, ages $\geq$ 16 and $\geq$18, respectively, and providing them with available safety and

Table 1. COVID-19 Test Accuracy with varying Disease Prevalence.

TESTING	SPECIMEN	TEST TIME	SENSITIVITY**	SPECIFICITY**	50% PREVALENCE PPV/ CLINICAL ACCURACY	0.9% PREVALENCE PPV/ CLINICAL ACCURACY	50% PREVALENCE NPV/ CLINICAL ACCURACY	0.9% PREVALAENCE NPV/ CLINICAL ACCURACY
MOLECULAR								
VIRAL -RT-PCR TO DETECT VIRAL RNA	Nasal, saliva pharyngeal, bronchoalveolar	One to seven days	94% (95%CI 81.5%-99.3%[1,2]	68% (95% CI 83% to 98.8%	82% to 98% 2% to 18% False Negative	32% to 83% 17% to 68% False Negative	81% to 99% 1% to 19% False Positive	97% to 99% 1% to 3% False Positive
VIRAL-ANTIGEN TO DETECT VIRAL SURFACE ANTIGEN	nasal, pharyngeal	15 minutes	56.2% (95%0CI 29.5-79.8%[3]	99.5% (95%CI 98.1% to 99.9%)	available data Insufficient to calculate clinical accuracy	available data Insufficient to calculate clinical accuracy	available data insufficient to calculate clinical accuracy	available data insufficient to calculate clinical accuracy
ANTIBODY Measuring IgG/ IgM	Blood or fingerstick sample	1 to 3days Or 15 to 30 minutes for point of care	18.4% to-96.1%[4]	96.6% (CI 94.3% to 98.2%)	data Insufficient To calculate	data Insufficient To calculate	data Insufficient To calculate	data Insufficient To calculate

Legend: *Table 1 summarizes the sensitivity, specificity, predictive value positive (PPV) and predictive value negatives (PPN) for the three classes of tests: molecular (RT-PCR) testing; antigen testing; and antibody COVID-19 testing. PPV varies with disease prevalence when interpreting results from diagnostic tests. PPV is the proportion of positive test results that are true positives. As disease prevalence decreases, the proportion of test results that are false positives increases.*

[1] *Yang Y, Yang M, Shen C, Wang F, et al, Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections, medRxiv, Published February 17, 2020, Direct Link: https://www.medrxiv.org/ content/10.1101/2020.02.11.20021493v2.full.pdf, DOI: https://doi.org/10.1101/2020.02.11.20021493*

[2] *Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W, Detection of SARS-CoV-2 in Different Types of Clinical Specimens, JAMA. 2020 May 12; 323(18): 1843–1844, Published online 2020 Mar 11. Direct Link:, DOI: http://doi.org/10.1001/jama.2020.3786, PMID: 32159775*

[3] *Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ru&ano L, Harris IM, Price MJ, Taylor-Phillips S, Hoo- L, Leeflang MMG, Spijker R, Van den Bruel A. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD013705. doi:10.1002/14651858.CD013705. www.cochranelibrary*

[4] *Lisboa Bastos M, Tavaziva G, Abidi SK, Campbell JR, Haraoui LP, Johnston JC, Lan Z, Law S, MacLean E, Trajman A, Menzies D, Benedetti A, Ahmad Khan F. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. BMJ. 2020 Jul 1;370:m2516. doi:10.1136/bmj.m2516. PMID: 32611558; PMCID: PMC7327913.*

efficacy data, noting the lack of clinical trial data during pregnancy. ACOG also recommends vaccination while trying to conceive, and enrolling individuals who become pregnant within 30 days of vaccination in the CDC V-SAFE program, which uses a smart phone app to track health after vaccination. [16] The CDC explains on their website that mRNA vaccines are unlikely to cause a risk during pregnancy and cannot either transmit COVID 19 or alter genetic material. In a report published in June 2021, analysis of data from surveillance systems of pregnant individuals and the v-safe pregnancy registry showed no safety signals, but the investigators recommended continued data collection to assess maternal, pregnancy, neonatal and childhood outcomes. [17] In a communication on the CDC website, dated August 11, 2021, the CDC encouraged vaccination of all pregnant people, people planning a pregnancy or breastfeeding, because they are reported to

be at high risk for developing severe COVID-19 related illness. [18] However, the CDC September 27, 2021, guidance document does not specifically include pregnant individuals as an eligible group to receive COVID-19 vaccine Booster. [18,19] The CDC December 6, 2021 update states that pregnant women may receive a COVID-19 booster shot.

Recommendations to improve pregnancy related outcomes

1. To drive public health practice, high quality local and national data are essential. While current studies have limitations, the development of a national, evidence-based public health strategy to address the care of all adults, always including pregnant individuals and children, is an urgent need. Standard queries for symptoms and serious adverse outcomes must be developed.

Table 2. Vaccines in the United States for Prevention of COVID-19: Approved, or with Emergency Use Authorization (EUA).

Vaccine Name/ Manufacturer	MOA	EUA or Approval Administratio	Age (Yr)	Efficacy, Clinical Trials*	Efficacy Analysis Population		
					N, (Male/ Female)	Race	Ethnicity
BNT162b2 Pfizer Inc and Bio-NTech	mRNA of spike protein	Full approval for age ≥ 16 yr; EUA for age 5-15 yr 2 doses 21 days apart; Booster for selected populations six mo after last dose	≥ 5	95% at ≥ seven days after second dose	40,277 (51%/ 49%)	82% W 10% B/AA 4% A 3% Other 0.2% NH, or PI 0.6% AI or AN	26% Hispanic or Latino, 73% Not Hispanic or Latino 0.6% NR
mRNA-1273 ModernaTX, Inc	mRNA of spike protein	EUA 2 doses 28 days apart; Booster for selected populations 6 months after second dose	≥ 18	94% ≥ 14 days after second dose	27,817 (53%/ 47%)	79% W 10% AA 5% A 0.8% AI, or AN 0.2% NH or PI 2% Other	20% Hispanic or Latino 79% not Hispanic or Latino
JNJ-78436735 J&J/Janssen	Adeno-virus non-replicating	EUA One primary dose and one booster 8 weeks after the primary dose	≥ 18	66.9% after two weeks. 66% after four weeks,	39,321 (55.5%/ 44.5%)	62% W 17% B/AA 8% AI, AN 3.5% A 0.3% NH or PI 5% Multiple 3% NK	45% Hispanic or Latino, 52% not Hispanic or Latino 2.5% NK

*MOA mechanism of action; EUA Emergency Use Authorization; * Efficacy refers to prevention of COVID-19 (positive COVID test) in the study population seven or more days after second dose Pfizer vaccine, 14 or more days after second dose Moderna vaccine, and prevention of moderate to severe COVID-19, two and four weeks after Janssen vaccine. W White, AA African American, A Asian, B/AA Black or African American, AI American Indian, AN Alaskan Native, NH Native Hawaiian, PI Pacific Islander including native Hawaiian, NR not reported, NK not known*

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FDA Briefing Document. Pfizer-BioNTech COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting, December 10, 2020; FDA Briefing Document. Moderna COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting, December 17, 2020; FDA Briefing Document. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. Vaccines and Related Biological Products Advisory Committee Meeting, February 26, 2021

Table 2 shows important information for each vaccine available in the United States, including status of FDA approval, lower limit for age, effectiveness, and demographics of the efficacy analysis clinical trial population by sex, race, and ethnicity. Table 2 was amended Dec 27, 2021.

2. A population perspective must involve methodological approaches to the assessment of the epidemiology in the subpopulations of pregnant individuals at highest risk. Collection of prospective longitudinal data, whether from routine surveillance or clinical studies, disaggregated by race, ethnicity, maternal age, trimester, socioeconomic status, and comorbidities, is essential if we wish to truly understand the effects of SARS-CoV-2 during pregnancy and develop effective evidence based interventions– including op-

timal advice for personal protection, equitable vaccination dissemination strategies, and pharmacologic treatments– that will protect the health of pregnant individuals and their newborns. With disaggregated data, targeted interventions for pregnant individuals including those in underserved subgroups, could be developed prospectively to protect both the birthing person and the child, and public health messaging could accurately report timely information so strategies that might mitigate and prevent the worst outcomes.

3. Evidence-based antenatal public health intervention should include influenza vaccination to decrease influenza associated pneumonia and use of intensive care resources. [20] For both of these viral respiratory diseases, influenza and COVID-19, the need to prioritize vulnerable populations is clear.

DECLARATIONS OF COMPETING INTEREST

None.

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