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COVID-19, pregnancy, and breastfeeding: What is the current medical consensus on how COVID-19 may affect pregnant individuals who contract the virus? Likewise, what is the current medical consensus on COVID-19 and breastfeeding?

1. Background

Coronavirus disease 2019 (COVID-19) is a respiratory viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has rapidly spread throughout the world. SARS-CoV-2 virus belongs to the same family as MERS-CoV and SARS-CoV, both of which were involved in prior respiratory illness epidemics [1]. COVID-19 is thought to have originated in Wuhan, China with the first cases reported in December 2019 [2]. As of September 23, 2020, the total number of cases in the U.S. has been reported at 6,874,982 and the total number of deaths has been 200,275 [3]. COVID-19 is thought to primarily spread through respiratory droplets, such as when a person coughs, sneezes, or speaks [4]. Transmission and spread are still under investigation, but the average number of people infected by one person with COVID-19 is currently estimated to be 2.5 people [5]. Clinical severity varies from selflimiting, mild cold-like symptoms to critical cases with multi-organ failure necessitating intensive care unit (ICU) admission and even death. Based on data from similar outbreaks of MERS and SARS in the past, pregnant women are thought to be at higher risk for a more complicated clinical course [6]. Given normal immunologic and physiologic changes during pregnancy, pregnant women are considered to be high risk and extensive precautions have been recommended to ensure proper hygiene and social distancing with potential exposures [7]. With a constant stream of new information, medical bodies such as the Center for Disease Control (CDC), American College of Obstetricians and Gynecologists (ACOG), Royal College of Obstetricians and Gynecologists (RCOG), and American Academy of Pediatrics (AAP) continue to update their recommendations regarding pregnancy and breastfeeding in the COVID-19 era.

2. COVID-19 and Pregnancy

a. Disease course and severity

Although early data suggested that pregnant women were not at increased risk of COVID-19 [8,9,10,11], a study released by the CDC in June 2020 highlighted data that pregnant women may be a particularly vulnerable population [12]. The CDC compiled and analyzed data from 8,207 pregnant women with COVID-19 between January 22–June 17 that showed increased hospitalization rates (31.5% vs 5.8%), increased ICU admission rates (1.5% vs 0.9%),

and increased mechanical ventilation rates (0.5% vs 0.27%) compared to non-pregnant women [12]. After adjusting for confounding factors, the study concluded that pregnant women are 5.4 times more likely to be hospitalized and 1.5 times more likely to be admitted to the ICU. However, death rates between pregnant and non-pregnant women appeared similar. In light of this study, the CDC released a statement warning that pregnant people may be at an increased risk for severe illness from COVID-19 [13]. ACOG also released a statement in light of this new data and are currently considering modification to clinical guidelines [14]. ACOG also highlighted the importance of including pregnant and lactating patients safely in clinical trials for vaccines. Overall, this new data suggests pregnant women with COVID-19 should be followed closely for worsening disease. Since the release of these statements, further systematic reviews have continued to show greater disease severity in pregnant women. A recent systemic review of 1316 pregnant women showed an ICU admission rate of 31.3% and an increased mortality rate of 2.7% [15].

Physiologic changes in pregnancy, including cardiorespiratory, immunologic, and respiratory, tend to increase a woman's susceptibility to severe infection. Such changes include increased maternal oxygen demands related to increased metabolism, gestational anemia, and fetal oxygen consumption; such changes commonly result in physiologic shortness of breath in pregnancy and must be distinguished from pathologic shortness of breath related to COVID-19 [7]. Additional pulmonary changes in pregnancy predispose these women to hypoxemic respiratory failure due to the rapidly progressive COVID-19 pneumonia. These changes may account for the greater disease severity observed in pregnant women.

b. Complications during pregnancy and risk to neonates

The most commonly diagnosed clinical symptom of COVID-19 in pregnant women is pneumonia, present in up to 90% of cases [6,15]. A recent systematic review by Khalil et al. showed that the most common symptoms in this population are cough (71%), fever (63%), and dyspnea (34%), with 14.5% being asymptomatic at the time of presentation [16]. The most common complication was pretern birth before 37 weeks of gestation (21.8%), usually medically indicated based on COVID-19 effects such as severe maternal pneumonia or fear of sudden maternal decompensation. Half of patients delivered via cesarean section, which has increased risks in and of itself. Additional studies have also suggested a higher risk of miscarriage, preeclampsia, preterm premature rupture of membranes, and fetal growth restriction [6,15]. Despite higher complication rates, Khalil et al. showed rare perinatal and maternal mortality (<1%), which contrasts with other coronavirus outbreaks such as SARS and MERS that have mortality rates of 18% and 25%, respectively [16]. Overall, there appears to be no indication that COVID-19 infection in the mother leads to increased risk of neonatal morbidity or mortality. However, a number of case series of maternal deaths due to severe COVID-19 have been reported and emphasized the potential for maternal death and warn professional societies against providing unproven reassurance [17,18]. The CDC and ACOG both acknowledge the increased frequency of preterm birth and similar complications but have maintained that it is unclear if COVID-19 is the cause of this observation [13,19].

A major point of concern is the risk of vertical transmission to the neonate, which has been seen in select case reports. A Paris case study demonstrated transplacental transmission of COVID-19 in a neonate born to a mother infected in her last trimester of pregnancy [20]. Additionally, reports of IgM antibodies in neonatal blood at birth suggest possible intrauterine infection of SARS-CoV-2 [21,22,23]. Despite these findings, thus far there has been inconclusive evidence of vertical transmission during pregnancy [11,15]. In a small case series of 9 women who underwent cesarean delivery after diagnosis of COVID-19, testing of the amniotic fluid, cord blood and breastmilk were negative for viral load, suggesting no vertical transmission [21]. Due to the limited data regarding vertical transmission, vaginal deliveries are not contraindicated at this time. Despite this, a large majority of patients have electively decided to undergo cesarean section [22]. Additionally, increased rates of cesarean sections have been largely preformed electively due to belief that prompt delivery would improve respiratory disease. While the CDC and ACOG state that intrauterine transmission is uncommon, both indicate the need for more data [13,19]. With emerging evidence of possible vertical transmission, RCOG states that vertical transmission is possible [24].

While COVID-19 is not an indication to alter route of delivery, a study in Spain which compared vaginal delivery and cesarean section in COVID-19 patients, higher rates of clinical deterioration were seen in pregnant women who delivered via cesarean section (Adjusted OR, 13.4; 95% CI, 1.5-121.9; P = .02) [25]. In this study clinical deterioration was defined as the need for oxygen supplementation after delivery. These results have not altered clinical guidelines in regard to route of delivery, but they certainly raise concerns of potential adverse outcomes in COVID-19 mothers who undergo cesarean section. Although vertical transmission in utero does not seem to pose a significant risk to the fetus, a potential risk early in pregnancy is hyperthermia associated with COVID-19. Studies have shown that fever during the first trimester is associated with increased rates of congenital anomalies, neural tube defects, and miscarriage [26]. Unfortunately, limited data currently exists on the effects of COVID-19 infection and early pregnancy.

c. Hypercoagulability

Despite presenting as a predominantly respiratory illness, mounting evidence has shown an increased risk of hypercoagulability and subsequent thromboembolic events in patients with COVID-19 [27]. Prophylactic and therapeutic anticoagulation is currently the primary form of management for this hypercoagulable state, as treatment for COVID-19 itself is still being investigated. This observed hypercoagulability from COVID-19 is a particular issue of interest in pregnant woman as normal physiologic changes during pregnancy lead to a baseline hypercoagulable state, thus compounding the effects of COVID-19 [28]. Preferred anticoagulants during pregnancy with or without COVID-19 are heparin compounds, with low molecular weight heparin recommended [29]. Both the NIH and RCOG recommend use of low molecular weight heparin for prophylaxis in all pregnant women admitted to the hospital with confirmed or suspected COVID-19 [24,29]. Furthermore, the NIH approves use of unfractionated heparin, low molecular weight heparin, and warfarin in breastfeeding women with COVID-19, as they do not accumulate in breast milk and therefore do not lead to anticoagulant effects in the newborn [29].

d. Steroid use in pregnancy

Use of corticosteroids is a standard of care for women delivering prematurely, prior to 37 weeks of gestation, in order to help induce fetal lung maturity and thereby improve neonatal outcomes. However, corticosteroids have been associated with worse outcomes in patients with COVID-19, including ICU admission, invasive ventilation, secondary infection, and death [30]. Although the steroid dosages are significantly less for prematurity than that initially used in the ICU setting for COVID-19 cases, it is important to reassess the use of corticosteroids and to weight the risks and benefits in COVID-19 positive pregnant women [30]. The World Health Organization (WHO) generally recommends avoidance of steroids but emphasizes the need for situation-specific decision making for pregnant women in pretern labor prior to 34 weeks of gestation [31]. ACOG initially recommended offering antenatal corticosteroids in women with suspected or confirmed COVID-19 prior to 34 weeks of gestation, but not offering corticosteroids between 34 and 37 weeks of gestation due to potential maternal harm [32]. However, ACOG has updated their recommendations based on more recent safety data and now recommend offering antenatal corticosteroids for all women at risk for preterm delivery prior to 37 weeks of gestation [32].

3. COVID-19 and Breastfeeding

Both ACOG and the CDC have maintained that maternal COVID-19 is not a contraindication to breastfeeding, as it is still unknown whether SARS-CoV-2 is transmitted through breastmilk [13,19]. The AAP also strongly supports breastfeeding in mothers with COVID-19 [33]. There have been a few reported cases of detectable SARS-CoV-2 RNA in nursing mothers known to be positive for COVID-19 [34,35]. However, further studies have shown that detection of viral RNA does not equate with infectivity as the presence of SARS-CoV-2 RNA does not represent replication-competent virus [36]. Although there is insufficient data to demonstrate viral transmission through breast milk, shared decision making is recommended as there is still risk of transmission through respiratory droplet when feeding. As a result, the CDC, ACOG, and AAP recommend appropriate preventive precautions including the use of a facemask and proper hand and breast hygiene while breastfeeding [13,19,33]. If a mother decides to use a breast pump, the baby should ideally be fed by a healthy individual and proper cleaning of all parts of the pump is recommended after each use [13,19]. Additionally, current data suggests no difference in risk of SARS-CoV-2 infection to the neonate when cared for in a separate room or in the mother's room, allowing for uninterrupted breastfeeding in the first few days of life [19,37]. Overall, the infant and maternal benefits of breastfeeding outweigh the risks of potential airborne exposure from the mother.

Breast milk is a source of passive immunity for infants, by transferring antibodies from mother to infant, which currently has limited data for COVID-19 immunity. A recent case report of a woman known to be positive for SARS-CoV-2 by throat swab was found to have IgG and

IgA antibodies to SARS-CoV-2 detect in breast milk, with no detection of viral RNA in breast milk [38]. This data points to potential immune protection against COVID-19 for infants. Although limited data exists regarding the presence of COVID-19 antibodies and potential for transferring immunity, some understanding can be gained based on data from previous coronavirus outbreaks. A systematic review by Huang et al. showed that the presence of antiviral antibodies depends on the timing of maternal infection, with median time to detection of IgG of 12 days for SARS-CoV-1, 11 days for SARS-CoV-2, and 16 days for MERS-CoV [39]. Additionally, levels of IgG were detectable for at least a year and provided possible protection from reinfection, although waning over time. Although not specific to breast milk, if antibodies are found to be present in breast milk, these results imply that protection against SARS-CoV-2 infection is possible, although likely transient.

4. Racial Disparities

As the pandemic has progressed, increasing information has revealed how the COVID-19 pandemic has disproportionately affected racial and ethnic minorities, with higher mortality rates in African American, Native American, and Latinx groups [40]. Minority pregnant women have further been affected by COVID-19, with one systematic review showing 50.8% of the women infected with SARS-CoV-2 in pregnancy to be from Black, Asian, or other minority ethnic groups [16]. Even prior to the COVID-19 pandemic, maternal mortality had disproportionately affected minorities, especially Black women [41]. The COVID-19 crisis has attracted national attention and brought these racial disparities, including maternal morbidity and mortality, to the forefront. The disproportionate impact on minorities can in part be traced to a foundation of structural racism and other societal factors [42]. Thus, essential structural and societal changes are required to allow for health equity that should be explored well beyond this paper.

4. Conclusion

Overall, our understanding of COVID-19 and pregnancy is limited by the amount of data currently available in the medical literature. As a result, medical recommendations are rapidly evolving as new data emerges. The statements and recommendations by CDC, ACOG, RCOG, and AAP as they relate to the effects of COVID-19 and pregnancy are outlined in Table 1. With recent data, the medical community, particularly the CDC and ACOG, have released statements warning that pregnant women represent a vulnerable population and may develop more severe disease compared to the general healthy counterparts. Clinical course in most cases manifests with cold-like symptoms, fevers and pneumonia. However long-term effects of COVID-19 on pregnancy have yet to be elucidated. Furthermore, most studies to date have described cases of pregnant women in the 3rd trimester or presenting in labor. Therefore, further studies would be needed to understand the effect of COVID-19 on pregnancy in the earlier stages of gestation. The most common fetal complications are mainly limited to preterm birth and cesarean sections and further studies will be needed to understand long term effects. The CDC, ACOG, and AAP are all in consensus that there is inconclusive data to suggest viral transmission through either transplacental exchange or breastmilk. As a result, vaginal delivery, unless contraindicated for other medical reasons, and breastfeeding are both encouraged.

The consensus is that COVID-19 does not affect the general management of pregnancy/labor and proper precautions similar to the non-pregnant population should be maintained. In light of the potential risk related to COVID-19 illness, ACOG recommends that clinicians counsel patients and emphasize the importance of preventative measures for pregnant women and families [19]. A better understanding of the effects of COVID-19 on pregnancy, birth and post-partum care will require more data including a larger set of patients across the all stages of pregnancy. Further investigations should also be targeted at racial disparities and socioeconomic factors in regard to COVID-19 and pregnancy.

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	Infection risk /	Risk to Baby	Anticoagulation	Breastfeeding
an a1	disease severity			** 111 1 1 1
CDC ¹	Potentially increased risk for more severe	Increased risk for preterm birth	May be at increased risk for thrombosis	Unlikely to be spread through breast milk
	illness	XX 1		
		Vertical	No specific	Encourage safety
		unlikely	regarding treatment	hands, wear a mask)
ACOG ^{2,3}	Potentially increased	Vertical	May be at increased	Unlikely to be spread
	risk for severe	transmission	risk for thrombosis	through breast milk,
	illness (ICU	appears to be	Desservela to	no contraindication to
	admissions,	uncommon,	Reasonable to	breastieeding
	ventilation	reported cases	anticongulation	Infants at risk of
	ventilation)	reported cases	anticoaguiation	transmission through
	No increased risk of			respiratory droplet
	maternal mortality			encourage safety
	maternar mortanty			measures
RCOG ⁴	Similar severity to	Vertical	Likely increased risk	No evidence of
	non-pregnant adults;	transmission may	for thrombosis	transmission through
	most cases are	be possible;		breast milk,
	mild/moderate	requires further	Hospitalized	recommend
		investigation	pregnant women	breastfeeding
	Some reported cases		with suspected or	
	of maternal death,		confirmed COVID-	Encourage safety
	although more data		19 should receive	precautions
	need		heparin prophylaxis	
AAP ⁵	-	-	-	No evidence of
				transmission through
				breast milk, strongly
				support breastfeeding
				Recommend strict
				preventive precautions
				(e.g., mask, breast &
				hand hygiene)

Table 1. CDC, ACOG, RCOG, and AAP Recommendations on COVID-19 and Pregnancy

- "If You Are Pregnant, Breastfeeding, or Caring for Young Children." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention; 2020. Available at: <u>www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnancybreastfeeding.html</u>. Retrieved 14 September 2020.F
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