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Practical considerations for pregnant women with diabetes and severe acute respiratory syndrome coronavirus 2 infection

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Epidemiologic data available so far suggest that individuals with diabetes, especially when not well controlled, are at a greater risk than the general population for severe acute respiratory syndrome coronavirus 2 morbidity such as acute respiratory distress syndrome, multiorgan failure, and mortality. Given the significant correlation between severity of coronavirus disease 2019 and diabetes mellitus and the lack of pregnancy-specific recommendations, we aim to provide some guidance and practical recommendations for the management of diabetes in pregnant women during the pandemic, especially for general obstetricians-gynecologists and non-obstetricians taking care of these patients.

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in Wuhan Province, China, in December 2019 and thereafter rapidly spread across the globe. The World Health Organization declared the outbreak a global pandemic on March 11, 2020, and at the time of writing (May 2020), there were more than 1.7 million confirmed cases and 100,000 deaths in the United States alone.[1] The coronavirus disease 2019 (COVID-19) pandemic has created unprecedented challenges for healthcare providers, including obstetrical services.

Pregnant women undergo immunologic and physiological changes rendering them susceptible to severe disease from viral infection, as has been observed with influenza, varicella, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS).[2] Early data from case series did not suggest markedly worse maternal and fetal outcomes with COVID-19, although severe illness did occur. For example, a systematic review (n=51) from Italy reported 1 fetal death, 1 neonatal death, and no maternal deaths.[3] A case series (n=116) from China reported a 6.9% rate of severe pneumonia and 1 neonatal death and no maternal deaths,[4]

and another series (n=43) from New York reported a 14% rate of severe to critical disease with no maternal deaths.[5] Finally, data from the largest UK cohort of pregnant women hospitalized with COVID-19 (n=427) estimated a hospitalization rate of 4.9 (95% confidence interval [CI], 4.5–5.4) per 1000 pregnancies. Among those admitted to the hospital, there was a 9% rate of need for respiratory support, 5% neonatal infection rate, and 1 maternal death.[6] Although original reports suggest that maternal outcomes are comparable with those of the general population with similar ages and comorbidities, a Morbidity and Mortality Weekly Report from the Centers for Disease Control and Prevention reports that among women with COVID-19, pregnant women were more likely to be hospitalized (31.5% vs 5.8%), admitted to the intensive care unit (adjusted rate ratio [aRR], 1.5; 95% CI, 1.2–1.8), or receive mechanical ventilation (aRR, 1.7; 95% CI, 1.2–2.4), compared with nonpregnant women. However, only 16 (0.2%) COVID-19–related deaths were reported among pregnant women.[7] Although data are constantly evolving, we must remember that, historically, pregnant women have had disproportionately severe outcomes during times of pandemic.[8]

COVID-19 has relevance within the context of another ongoing epidemic: maternal obesity and diabetes. Pregestational diabetes is estimated to affect approximately 2% of all pregnancies in the United States,[9] whereas gestational diabetes has an estimated incidence of at least 6%.[10] Academic and referral centers naturally report higher prevalence among their patient populations. Rates vary between groups by race, ethnicity, and presence of obesity or other components of metabolic syndrome and are continuing to increase amidst the obesity epidemic.[11] The consequences of maternal diabetes are far-reaching; diabetes increases the risk for preeclampsia, cesarean delivery, uteroplacental insufficiency, stillbirth, intrauterine growth restriction and fetal macrosomia, and other adverse obstetrical and neonatal outcomes. As the pandemic unfolds, appropriately managing diabetes and diabetic complications in pregnant women with COVID-19 will be necessary to optimize maternal and fetal outcomes.

Diabetes appears to be an important risk factor for severe disease or death from COVID-19 in nonpregnant patients. Outcomes specific to pregnant women with diabetes are not yet known. A report issued by the Chinese Center for Disease Control and Prevention including >72,000 patients showed increased rates of severe disease and mortality in patients with diabetes.[12] Studies from Italy (n=1382) and the United States (n=1122) have also reported higher mortality in those with diabetes or uncontrolled hyperglycemia.[13,14] Findings are consistent with those from SARS and MERS in which patients with diabetes experienced more frequent severe disease or death from those illnesses.[15,16] Possible mechanisms for this association include coronavirus-mediated dysregulation of the angiotensin-converting enzyme 2 receptor or the dipeptidyl peptidase-4 enzyme, both of which play roles in glucose metabolism and inflammation.[17]

These circumstances place pregnant patients with diabetes in an especially vulnerable position. We offer the following comments and recommendations on the basis of current available evidence and our own experience:

Pregnant Women with Diabetes, Especially Type 1, and Coronavirus Disease 2019 must be Evaluated for Severe Hyperglycemia or Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a life-threatening complication that affects between 0.5% and 3% of pregnancies of women with diabetes. Fetal mortality rates up to 9% to 36% have been reported, making this an obstetrical emergency.[18] DKA can be difficult to recognize during pregnancy, as it may present at significantly lower glucose concentrations and with unimpressive symptoms.[19] Acute viral infection is a common precipitant for DKA—not surprisingly, there are reports of COVID-19–associated hyperglycemic episodes in patients with diabetes.[20,21] Moreover, there is also evidence that the illness may induce ketosis in those without diabetes.[21] Considering COVID-19 may affect metabolic pathways favoring hyperglycemia and ketosis, there should be an extremely low threshold to evaluate for DKA in pregnant women with infection, especially those with type 1 diabetes mellitus. This is especially pertinent to nonobstetricians who may be unfamiliar with atypical presentations of DKA during pregnancy.

In women with diabetes with asymptomatic or mild COVID-19 and without DKA or severe hyperglycemia, we would not consider COVID-19 alone as a criterion for inpatient glucose management. This decision should be individualized, considering factors such as the patient's current glycemic control, reliability to monitor blood sugar at home, and ability to return for worsening symptoms.

Oral Diabetes Medications Should be Discontinued in Pregnant Patients Who are Admitted with Moderate to Severe Coronavirus Disease 2019

Metformin is often continued in pregnancy in women with pregestational type 2 diabetes or used as a primary therapy in the third trimester for gestational diabetes. Glyburide may also be used. Although not approved by the US Food and Drug Administration (FDA) for pregnancy, these agents are commonly used and are regarded as safe and provide an alternative or supplement to insulin.[22] However, in women with COVID-19, acute illness and dehydration along with metformin use may increase the risk of lactic acidosis; therefore, this medication should be discontinued.[17] Oral agents in general should likely be discontinued in hospitalized patients, especially among those with moderate to severe disease, with insulin being the preferred agent for maintenance of glycemic control.[23] The use of infusion pump insulin therapy is recommended to achieve glycemic targets until the patient's clinical condition is improved.[24]

Continuous Glucose Monitoring Offers Practical Advantages and Should be Considered in the Setting of Coronavirus Disease 2019

In randomized controlled trials (RCTs), continuous glucose monitoring (CGM) has shown benefit in glycemic control of nonpregnant and pregnant adults with diabetes.[25,26] It is used most often, but not exclusively in patients with type 1 diabetes. As discussed earlier, there seem to be associations between poor glycemic control and worse outcomes in patients with COVID-19. CGM may be useful in this setting to facilitate glucose control. For patients not located on antepartum floors, CGM could alleviate burden on nurses who may be unfamiliar with pregnancy-specific monitoring protocols or have unusually high workloads because of the pandemic. Finally, CGM allows remote monitoring of glucose levels, which limits exposure of healthcare workers to the virus and may help preserve personal protective equipment. The FDA recently issued guidance to help expand access to inpatient remote monitoring, including CGM.[27]

Administration of Antenatal Corticosteroids Should be Highly Individualized

Antenatal corticosteroid (ACS) administration for mothers at risk of preterm delivery has well-established neonatal benefits. However, corticosteroids are known to cause transient maternal hyperglycemia and lead patients to require higher doses of insulin for short periods of time. The decision of whether to administer corticosteroids to a patient at risk of preterm delivery must balance potential neonatal benefits with both (1) the indeterminate effect of corticosteroids on the COVID-19 disease process[28] and (2) potential maternal complications, such as hyperglycemia or even DKA. There are no studies specifically reporting outcomes of pregnant patients with COVID-19 who received ACSs. It is imperative that providers exercise extreme caution in pregnant women with diabetes and make the decision for ACSs with inputs from maternal fetal medicine, neonatologists, and infectious disease specialists.[29] We contend that it is logical to avoid antenatal late preterm steroid (ALPS) use altogether in patients with diabetes with COVID-19 given the less compelling neonatal benefits associated with ALPS use.[30,31]

Moreover, there are emerging data that dexamethasone administration may improve mortality and other outcomes in

hospitalized patients with COVID-19. In an open-label RCT (the Randomised Evaluation of COVID-19 Therapy [RE-COVERY] trial), patients hospitalized with COVID-19 were randomly assigned to receive oral or intravenous dexamethasone or usual care. In a preliminary report, patients who required oxygen supplementation or invasive mechanical ventilation and received dexamethasone had reduced 28-day mortality. This survival benefit was not seen, and dexamethasone was possibly associated with harm among those with milder disease not requiring respiratory support.[32] Although the RECOVERY trial was notable for including pregnant and breastfeeding women (n=6), participants received dexamethasone at different dosing intervals (6 mg daily for up to 10 days) than what is recommended to promote fetal lung maturity.[33] In addition, participants were older (mean age of >60 years) than pregnant women, and more than half had medical comorbidities.[32] On the basis of the above findings, in pregnant women hospitalized with COVID-19 who meet the eligibility criteria of the RECOVERY trial and require respiratory support, it would be reasonable to offer dexamethasone in accordance with the trial's protocol. However, a careful discussion between the patient and maternal fetal medicine and critical care physicians is recommended to address risks and benefits, given the possible maternal risks of corticosteroids discussed above and the potential nongeneralizability of evidence to this specific patient population.

Antenatal Testing in Women with Diabetes Who Have Coronavirus Disease 2019 Should Follow Standard Practice

A recent systematic review, albeit limited by inclusion of studies with small sample sizes, concluded that pregnancies complicated by COVID-19 may be at a higher risk for adverse perinatal outcomes such as preterm birth, fetal distress, or perinatal death, but not intrauterine growth restriction.[34] Antenatal surveillance for diabetes generally consists of serial fetal growth ultrasounds and antenatal testing,[11,22] with specific frequencies varying by institution. Although there may be a role for antenatal surveillance in pregnancies affected by COVID-19, until more robust evidence is available, we do not recommend performing more frequent antenatal testing than what is already indicated for pregestational or gestational diabetes. There is no evidence that oversurveillance is beneficial, and, in fact, it may lead to iatrogenic complications. In addition, many facilities may not have separate COVID-19 units capable of extra antenatal testing. Recommendations on antenatal surveillance in the general pregnant population with COVID-19 is beyond the scope of this commentary.

Institutional Algorithms for Diabetes Management in Coronavirus Disease may be Beneficial

Hospitalized pregnant women are typically managed on antepartum services. During the COVID-19 pandemic, many women are being managed primarily by internists and infectious diseases or critical care specialists. Clear communication between medical teams is essential. This is particularly important for women with diabetes, as glycemic goals are more stringent during pregnancy. In addition, guidelines should aim to standardize management to avoid hyperglycemia, which could worsen COVID-19, and hypoglycemia, which can be life-threatening especially for pregnant women with other comorbidities.[23] Our institution has published guidelines for the management of hyperglycemia and DKA in nonpregnant adults with COVID-19.[35] Similar algorithms specific to pregnant women may be useful to improve coordination of care.

Conclusion

COVID-19 poses significant challenges to providing care for pregnant women, including those with diabetes mellitus. We discussed some practical applications to improve and adapt the care of these patients, despite the lack of data. We urge the scientific communities and professional societies to continue to advocate for the inclusion of pregnant women with diabetes and COVID-19 in research studies to provide evidence-based information to guide clinical care. ∎

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