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COVID-19 Pandemic and Pregnancy in Kidney Disease

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a rapidly spreading pandemic. Owing to changes in the immune system and respiratory physiology, pregnant women are vulnerable to severe viral pneumonia. We review the clinical course, pregnancy outcomes, and management of women with COVID-19 in pregnancy with a focus on those with kidney involvement. Current evidence does not show an increased risk of acquiring SARS-CoV-2 during pregnancy and the maternal course appears to be similar to nonpregnant patients. However, severe maternal disease can lead to complex management challenges and has shown to be associated with higher incidence of preterm and caesarean births. The risk of congenital infection with SARS-CoV-2 is not known. All neonates must be considered as high-risk contacts and should be screened at birth and isolated. Pregnant women should follow all measures to prevent SARS-CoV-2 exposure and this fear should not compromise antenatal care. Use of telemedicine, videoconferencing, and noninvasive fetal and maternal home monitoring devices should be encouraged. High-risk pregnant patients with comorbidities and COVID-19 require hospitalization and close monitoring. Pregnant women with COVID-19 and kidney disease are a high-risk group and should be managed by a multidisciplinary team approach including a nephrologist and neonatologist.

Key Words: COVID-19, Pregnancy, Acute kidney injury, Chronic kidney disease, Kidney transplant

As of June 17, 2020, the coronavirus disease 2019 (COVID-19) has affected 8,184,331 individuals from 213 countries and resulted in 443,959 deaths (https://coronavirus.jhu.edu/). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes COVID-19. It belongs to the same family as previous SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) which causes significant morbidity and mortality in pregnant women.[1] Here we discuss the practical aspects of COVID-19 in pregnancy, on the premise that evidence in this field is rapidly evolving and that currently available is limited mostly to retrospective case series.

ARE PREGNANT WOMEN MORE SUSCEPTIBLE TO COVID-19?

Changes in the immune system and the respiratory physiology make pregnant women vulnerable to severe viral infections. To "tolerate" the developing fetus, there is an attenuation of cellular immunity (T helper cell 1 to T helper cell 2 shift). This, along with alteration in the hormonal milieu (prostaglandins and progesterone) is known to worsen the risk of influenza in pregnancy.[2] Pregnancy is also associated with a decrease in lung volume and hampered capability to clear airway secretions, predisposing the woman to severe hypoxia in cases of pneumonia. Pregnant women who acquire respiratory infections in the third trimester are more likely to have a severe disease course.[3] Physiological rhinitis, shortness of breath, and dry cough related to laryngeal acid reflux are common in pregnancy and can lead to delay in diagnosis of COVID-19. To enter the cell, SARS-C0V-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors via its spike-like protein.[4] In pregnancy, there is a significant increase in the ACE2 mRNA in the kidney, placenta, and uterus which can impact the vulnerability of the pregnant woman for COVID-19.[5]

Experts agree that social distancing decreases the chances of acquiring COVID-19.[4] However, pregnancy mandates several health center visits for examination, ultrasonography, fetal viability tests such as nonstress test, and biophysical profile, which might increase their exposure. Thus, pregnant women face a double whammy of increased exposure and susceptibility due to physiological changes as discussed previously. As per the available evidence, pregnancy has not shown to increase the risk of acquiring COVID-19.[1,6-8] Nonetheless, we need more evidence from the prospective cohort studies to ascertain the true susceptibility of pregnant women to COVID-19.

DOES PREGNANCY AFFECT THE COURSE OF COVID-19 IN THE MOTHER?

At the beginning of the pandemic, it was hypothesized that a relatively younger age of this population may favor milder disease. In addition, increased anti-inflammatory cytokines (interleukin-4 and interleukin-10) associated with pregnancy might attenuate the cytokine release syndrome which is associated with severe disease.[9] Comorbidities (hypertension, diabetes, severe heart or lung disease, severe obesity, and immunocompromised state) increase the risk of severe disease as in the nonpregnant

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population. Early reports suggested that the course of COVID-19 in pregnant women is not worse than in nonpregnant population.[10-13] However, a recent report of 91,412 pregnant women from the Centers for Disease Control noted that pregnant women were more likely to receive intensive care (1.5% vs 0.9%) and mechanical ventilation (0.5% vs 0.3%) as compared with the nonpregnant patients even after adjusting for age, comorbidities, and ethnicity.[14] This is in contrast with previously published literature from across the globe. In a cohort of 147 pregnant women in the WHO-China Joint Mission Report with COVID-19, 8% of women had severe disease, and 1% of the study cohort was critical.[15] In a systematic review including 538 pregnancies with COVID-19, 15% had severe disease and 1.4% were critical.[16] In comparison, 80% of the nonpregnant population with COVID-19 from China had mild disease, 15% had severe disease, and 5% were critical.[17] In a study from New York where all obstetric admissions were screened for SARS-CoV-2 infection, 14 of 43 (32.6%) women were found to be asymptomatic at presentation, of which, 10 (71%) women developed symptoms during delivery admission or postpartum (8 women developed mild disease and 2 women developed severe/critical disease).[18] As of 11 June 2020, published literature has 13 maternal deaths.[19-21] It is important to note that most of these women did not have any comorbidities. They were diagnosed to have COVID-19 late in pregnancy which might have contributed to the adverse outcome. There are additional deaths reported in media which were also in premorbid healthy women diagnosed to have COVID-19 late in pregnancy.[22-24] As the evidence in evolving on the maternal course in COVID-19, it is imperative that pregnant women must be considered a high-risk group and should be closely monitored for the worsening of the disease.

CLINICAL SUMMARY

- Social distancing, hand hygiene, and delivery of antenatal care via telemedicine can help in reducing the exposure to SARS-CoV-2 in pregnant women.
- Clinical manifestations of COVID-19 in pregnant women are similar to nonpregnant patients; however, they should be closely monitored for worsening of the disease.
- Symptomatic women with COVID-19 have an increased frequency of preterm births and caesarean section.
- Pregnant women with COVID-19 are at risk of developing acute kidney injury which needs to be differentiated from other causes of pregnancy-related acute kidney injury.
- Pregnant women with COVID-19 and underlying chronic kidney disease and kidney transplant are at a higher risk for maternal and fetal complications and warrant close monitoring.

DOES COVID-19 AFFECT PREGNANCY OUTCOMES?

In 2 systematic reviews[16,25] of 252 and 538 pregnant women each with COVID-19, 15% - 20% had preterm births, and 70% - 85% were caesarean deliveries. It is important to note that these studies predominantly report symptomatic women (up to 75%). Various factors can contribute to increased preterm and caesarean births in women with COVID-19 including fever, hypoxia, shock, and deteriorating maternal condition. In a study from France reporting 21 deliveries of women with COVID-19, 5 were preterm births and they were medically indicated for a severe maternal condition related to COVID-19.[26] In addition, 7 of 9 caesarean sections were performed due to COVID-19. Thus, severe COVID-19 in late pregnancy can indirectly affect pregnancy outcomes by increasing the chances of elective preterm deliveries. Labored breathing during vaginal delivery along with the difficulty to wear a face mask might increase the chances of aerosolization. However, there is no conclusive evidence to date to alter the route of delivery due to COVID-19 and it should be guided by standard obstetric indications. Although reports from first trimester infections are scarce, miscarriages are seen in only 2% of patients.[15] Maternal hyperthermia during organogenesis increases the risk of congenital anomalies[27] such as neural tube defects and childhood inattention disorders.[28] These have not been reported yet in COVID-19.

WHAT ARE THE CHANCES OF VERTICAL TRANSMISSION OF SARS-CoV-2?

ACE2 receptors, which function as the "doorway" for SARS-CoV-2 to enter the cell, are widely expressed in the placenta. Nonetheless, the maternal viremia rate is low making placental seeding less likely.[29] In 2 systematic reviews of 538 and 51 pregnancies each, there was no evidence of vertical transmission.[16,30] However, few reports have documented positive early nasopharyngeal swabs[31,32] from the neonates and/or presence of neonatal IgM antibodies.[33,34] None of these cases were positive for amniotic fluid, placenta, or fetal blood. As IgM antibodies do not normally cross the placenta, their presence can either be due to injured placenta allowing passage or production by neonate if the virus crosses the placenta. False positive tests and cross-reactivity can occur. To date, the virus has not been detected in the cord blood and amniotic fluid specimens. Positive vaginal swab has been reported in 1 patient.[35] This neonate was delivered at 35 weeks and 5 days by planned caesarean section, had no contact with vaginal fluid, membranes were intact before birth and there was no skin-to-skin contact with the mother after birth. Neonatal nasopharyngeal swabs were positive at birth, on day 2 and day 7. Placenta showed multiple areas of inflammation and infarction, suggestive of primary SARS-CoV-2 infection. There was no respiratory involvement in the neonate.[35] As of June 10, 2020, the risk of congenital infection with SARS-CoV-2 is not clearly known. However, the neonate is at a definite risk of acquiring the infection postnatally; hence she/he should be considered a high-risk contact and managed accordingly (see below).

WHAT PRECAUTIONS SHOULD BE TAKEN DURING ANTENATAL CARE OF THE PREGNANT WOMAN?

Adequate antenatal care is associated with improved maternal and fetal outcomes, and it should not be compromised for the fear of contracting COVID-19. It should be emphasized that pregnant women should follow all the recommendations for the nonpregnant population for avoiding exposure (for example, hand hygiene, surface decontamination, and social distancing). Women with an exposure to a patient with COVID-19 should self-isolate and monitor for symptoms. The testing of contacts and screening of asymptomatic pregnant women before delivery is dictated by the local policies and availability of the test. For women who are low risk (singleton pregnancy, no previous bad obstetric history, normotensive, nondiabetic, and no heart disease), the antenatal visits can be reduced by grouping the tests and utilizing teleconferencing. When in the hospital, the time spent should be minimized, all patients and health care workers should be wearing at least a surgical mask and no visitors should be allowed. Pregnant health care workers should avoid face-to-face contact with patients positive or suspected COVID-19. The International Society of Infectious Disease in Obstetrics and Gynaecology recommends that pregnant health care workers should be transferred to low-risk exposure settings, after 24 weeks of gestation.[36]

MANAGEMENT OF PREGNANT WOMEN WITH COVID-19

The American College of Obstetricians and Gynaecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists have issued guidelines for the management of pregnant women with COVID-19.[37,38] Most women with COVID-19 are either asymptomatic or have mild disease (upper respiratory tract symptoms but no shortness of breath). In the absence of any obstetric complication, they can be managed conservatively at home. Care is similar to nonpregnant patients (cough etiquettes, hand hygiene, and self-isolation). When at home, women should be educated to self-monitor the symptoms related to COVID-19. They must notify any worsening of clinical symptoms immediately to the health care provider via teleconferencing. Adequate hydration must be ensured as fever can lead to significant insensible fluid loss. Frequent repositioning and ambulation should be encouraged. If possible, they should attempt prone or semiprone positioning (cautiously in the third trimester). Women in the third trimester should monitor fetal movements (daily fetal kick count). The US Food and Drug Administration has approved the use of noninvasive fetal and maternal monitoring devices at home for stable patients.[39] These can be used to measure fetal heart rate, maternal heart rate, and maternal uterine activities which can be readily shared with the health care provider. These are to be used under the direction of the health care provider via prescription.

Pregnant patients with comorbidities, moderate to severe disease, or those with obstetric indications should be hospitalized and managed by a multidisciplinary team. The ACOG recommends the use of an algorithm for triaging patients with COVID-19.[40] In patients with acute respiratory distress syndrome, maternal peripheral oxygen saturation (SpO_2) should be maintained at ≥95% and partial pressure of oxygen should be ≥ 70 mmHg. This is to maintain an oxygen diffusion gradient from the mother to the fetal side of the placenta. As prone positioning will be difficult later in pregnancy, a semiprone position can be tried to improve oxygenation. Chest radiograph and computed tomography can be performed if clinically indicated with an abdominal shield as they carry a low fetal radiation dose. Admission D-dimer levels > 1 μg/mL are known to predict increased mortality in COVID-19,[41] but these levels are normally elevated in pregnancy hence difficult to interpret.[42] The ACOG recommends the administration of antenatal betamethasone to women at higher risk of preterm birth between 24 weeks to 34 weeks of gestation.[43] Beyond 34 weeks, the benefits of steroids are more modest and the decision should be individualized on a case to case basis. Drugs such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs should be avoided in pregnancy. Optimum fetal monitoring should be facilitated based on gestational age and maternal vital signs. An external fetal monitor that can transmit the fetal heart rate tracings wirelessly to the obstetrician can be used. An abnormal tracing will guide escalating maternal oxygen therapy and might aid the timing of emergency caesarean delivery for the obstetric provider. All patients with COVID-19 should be closely monitored for preterm labor. During the management of labor, all attempts must be made to minimize the exposure of health care workers and the neonate.[43]

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Emerging evidence suggests that hypercoagulability adversely impacts prognosis in COVID-19[44] and routine pharmacologic prophylaxis is recommended in hospitalized patients with COVID-19 unless contraindicated.[45] Pregnancy itself is a hypercoagulable state and is associated with an increased risk of venous thromboembolism.[46] Low molecular weight heparin should be given to hospitalized pregnant patients with COIVD-19. They can be later transitioned to unfractionated heparin in the peripartum period.

PREGNANCY CONSIDERATIONS OF DRUGS USED FOR THE TREATMENT OF COVID-19

Several drugs are currently being evaluated for the treatment of COVID-19. Remdesivir is a nucleotide analog that has activity against SARS-CoV-2 in vitro. It has been safely used in pregnant women with Ebola and Marburg disease.[47] Currently, it is being used on a compassionate-use basis in pregnant patients with COVID-19, but most of the randomized trials have excluded pregnant women. Chloroquine and its metabolites have also been used safely in pregnancy in the past; however, owing to a large volume of distribution, higher doses will be needed in pregnancy (1000 mg/day).[48] Hydroxychloroquine with or without azithromycin can cause arrythmias due to QT prolongation and should be used cautiously with cardiac

monitoring.[49] Protease inhibitor, lopinavir-ritonavir, is known to be safe in pregnancy. Although they cross the placenta, no adverse effect is seen on the fetus. Baricitinib, a Janus kinase inhibitor, is a potential drug for COVID-19; however, it has shown embryotoxicity in animal studies[50] and is thus to be avoided in pregnancy. Tocilizumab, a humanized monoclonal antibody against interleukin-6, crosses the placenta and is secreted in breast milk. Caution should be exercised with its use in pregnancy. Steroids have been evaluated for patients with severe COVID-19 including acute respiratory distress syndrome and shock. Both dexamethasone and methylprednisolone cross the placenta. There is some association with their use in the first trimester and increased abortions and birth defects such as oral clefts.[51,52] However, the evidence is not conclusive and the risk depends on the dose and duration of use. The use of antenatal steroids for the standard obstetric indication is discussed previously.

CARE OF NEONATE BORN TO A MOTHER WITH COVID-19

Babies born to positive mothers are to be considered as high-risk contacts. They should be tested within 24 hours with nasopharyngeal/throat swabs and also for the presence of IgG and IgM antibodies. Irrespective of the result of this testing, they should be kept in isolation from other healthy infants and should be cared for with all the precautions used for positive patients. According to the Centers for Disease Control and Prevention, the decision on whether to separate the positive mother and her baby should be individualized based on the clinical condition of the mother and the baby, the mother's desire to breast-feed, facilities, and additional caregivers available for separation at the hospital and home. It should be a shared decision of the mother, the caregivers, and the clinician. If separation is indicated but could not be implemented, physical distancing (≥6 feet) from the mother can be practiced. The mother can wear a face mask and practice hand hygiene when in close contact.

There are minimal data on the transmission of SARS-CoV-2 through breast milk. Of 29 samples tested in 2 studies, 1 tested positive for SARS-CoV-2 by nucleic acid testing.[25,53] Close contact while breast-feeding can lead to droplet infection. Nonetheless, the benefits of breast-feeding to the baby and the mother outweigh the risk known up till now. If the mother chooses to breast-feed, she should wear a mask and clean her hands and breasts before each feeding. Breast milk can also be expressed using all personal hygiene precautions and can be fed to the baby by an uninfected caregiver.

THE PSYCHOLOGICAL IMPACT OF COVID-19 ON PREGNANT WOMEN

During pregnancy, the mother can experience several psychological changes and is vulnerable to develop anxiety and depression.[54] The socioeconomic effects of COVID-19 can adversely affect the mental health of expectant mothers. With social and travel restrictions, women may feel secluded; in addition, if COVID-19 positive, they may experience further feelings of alienation. Financial hardships with unemployment or underemployment may provide more stress to mothers and their families. In the quarantine, there is a potential for increased rates of domestic violence and gender-based discrimination.[55,56] In a population-based study from China, more than half of the respondents experienced moderate to severe psychological impact.[57] Given the current concern of acquiring COVID-19, there may be a decrease in seeking preventive health care for both mother and the baby. Telehealth and group video sessions can be useful tools to provide women with quality care and support during this time. Whether women attend visits in-person or virtually, all pregnant women should be screened for mood and anxiety disorders.

SPECIAL CONSIDERATIONS FROM THE NEPHROLOGIST'S PERSPECTIVE

Acute Kidney Injury in a Pregnant Woman With COVID-19

About 25% to 29% of nonpregnant patients who are critically ill with COVID-19 can develop acute kidney injury (AKI).[58,59] Pregnancy-related hemodynamic changes involving the kidney makes the woman vulnerable to develop AKI.[60] In healthy pregnant women, increased kidney blood flow and glomerular hyperfiltration result in lower estimated glomerular filtration rate (eGFR). Thus, creatinine values considered normal in the nonpregnant state will be high in pregnancy.[61] Hence cutoff for eGFR defining AKI is lower than the nonpregnant population (>0.8 mg/dl or >70.72 μmol/L).[62,63] AKI in a patient with COVID-19 can be attributed to multiple etiologies. SARS-CoV-2 can cause direct damage to the tubular injury or can indirectly lead to AKI secondary to cytokine storm.[64] Fever and tachypnea may contribute to volume depletion with the need for judicious fluid resuscitation to prevent hypervolemia. Intrarenal etiologies such as preeclampsia, thrombotic microangiopathies, peripartum sepsis, acute cortical necrosis, acute pyelonephritis, flare from underlying glomerulonephritis such as lupus nephritis or progression of chronic kidney disease should also be included in the differential diagnosis for kidney dysfunction in patients with COVID-19. Evaluation for obstructive etiologies for AKI should also be considered. Diuretics should be used judiciously to prevent volume depletion. Extra caution to be exercised during kidney replacement therapies such as continuous kidney replacement therapy or hemodialysis to avoid the risk of intradialytic hypotension which may compromise fetal circulation.

Pregnant Women With Chronic Kidney Disease and COVID-19

Pregnant women with underlying kidney disease are at a higher risk of developing maternal and fetal complications.[65,66] Maternal complications include worsening of kidney disease and secondary preeclampsia. Adverse fetal outcomes associated with pregnancy in women with kidney disease include preterm birth, fetal growth restriction, stillbirth, and neonatal death.[66,67] Thus, women with

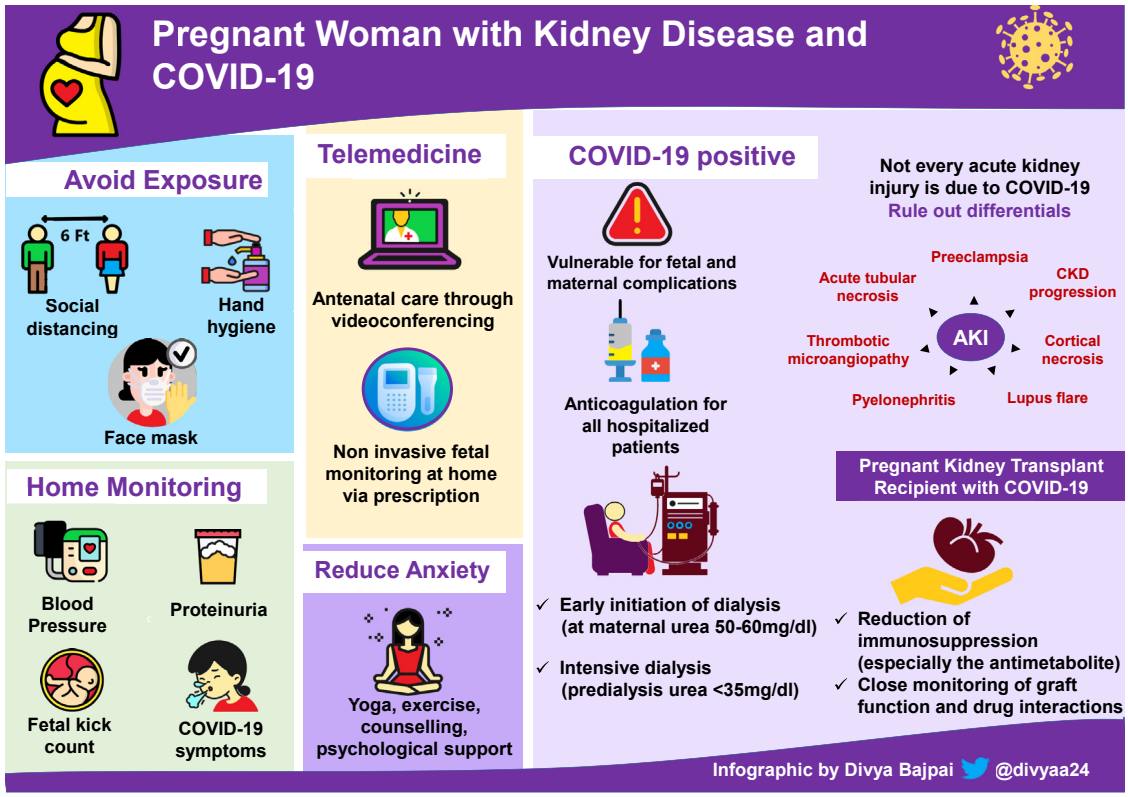

Figure 1. Pregnant women with kidney disease and coronavirus disease 2019 (COVID-19).

kidney disease should be monitored more closely throughout the pregnancy. During the COVID-19 pandemic, visits can be done via video conferencing, and patients should be taught to monitor blood pressure at home. They should also be trained to monitor symptoms of worsening kidney disease and preeclampsia so that they can promptly notify the clinical team. Low-dose aspirin is not contraindicated in patients with COVID-19 and might mitigate the risk of preeclampsia in this population. In pregnant women with chronic kidney disease, once the eGFR declines < 20 mL/min/1.73 m^2 or the blood urea nitrogen increases >50 - 60 mg/dL, it is preferable to initiate dialysis as untreated uremia is associated with poor fetal outcomes.[68,69] Guidelines recommend intensive dialysis in these patients based on their residual kidney function (up to 36 hours per week to keep the predialysis urea < 35 mg/dL).[70,71] During the COVID-19 pandemic, there can be limited availability of dialysis, especially in low resource settings. Close monitoring of the eGFR and pre-emptive planning for dialysis initiation may be required should the need arise.

COVID-19 in a Pregnant Kidney Transplant Recipient

Kidney transplant offers the best hope to women with end-stage kidney disease who wish to conceive. However, transplant recipients are also at a higher risk of fetal and maternal complications during their pregnancy than the general population.[72] Transplant recipients are also at higher risk of severe COVID-19 due to immunosuppressed state and higher prevalence of comorbidities.[73] Early reports of COVID-19 in transplant recipients are reassuring with most patients showing recovery.[74-76] However, there have been no reported cases of pregnant kidney transplant recipients with COVID-19 to date. Discontinuation or reduction in immunosuppression (especially the antimetabolite) is likely needed but should be individualized based on the severity of illness and the net level of immunosuppression. Diarrhea which is a common symptom of COVID-19 can cause increased tacrolimus trough levels. Thus, close monitoring of calcineurin inhibitors trough levels, kidney function, and fetal parameters is needed. Figure 1 shows various strategies for the prevention and management of pregnant women with COVID-19 and kidney disease.

CONCLUSION

In conclusion, pregnant patients constitute a vulnerable population that requires multidisciplinary care during the COVID-19 pandemic. We are still unaware of the exact risk and the long-term consequences of COVID-19 to the mother and the baby. There is an urgent need for large prospective studies with international collaboration. The surveillance data collected during antenatal and delivery visits can also be extrapolated to asymptomatic nonpregnant populations strengthening the knowledge base. Finally, patients with chronic kidney disease who conceive during the COVID-19 pandemic require dedicated specialized care for a successful pregnancy course.

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