

# COVID-19 in Pregnancy: Update on the Disease and its Management

N Moran<sup>1</sup>, S Gebhardt<sup>2</sup>, A Wise<sup>3</sup>, T Hlongwane<sup>4</sup>

<sup>1</sup> Head of Clinical Department: Obstetrics and Gynaecology, KwaZulu-Natal Department of Health, South Africa

<sup>2</sup> Head of Clinical Department, Stellenbosch University, Stellenbosch, South Africa

<sup>3</sup> Rahima Moosa Mother and Child Hospital, University of the Witwatersrand, Johannesburg, South Africa

<sup>4</sup> South African Medical Research Council, University of Pretoria Maternal and Infant Health Care Strategies Unit, Department of Obstetrics and Gynaecology, Pretoria, South Africa

## Introduction

At the time of writing (24<sup>th</sup> August 2020), it has been over 5 months since the first case of COVID-19 was diagnosed in South Africa. Since then over 600,000 cases have been diagnosed in South Africa, of which over 13,000 have unfortunately resulted in death. The previous edition of the O+G Forum, three months ago (issue 2, 2020), included an editorial about South Africa's initial response to the COVID-19 pandemic, as well as an overview of management of obstetric patients with COVID-19. Since then the course of the pandemic has evolved and the scientific literature has been dominated by publications relating to various aspects of the pandemic and its management.

When the COVID-19 pandemic first arrived in South Africa in March 2020, a few hospitals in each province were identified as the COVID hospitals to which all confirmed cases would be referred. Once the scale of pandemic was better appreciated, it became clear that these few hospitals would not be able to cope with managing all the COVID patients. We now have a situation where all designated birthing (delivery) sites must be able to identify potential COVID-19 cases, test for COVID-19, identify patients with severe COVID-19 and be able to manage intrapartum care for COVID-19 patients with mild disease. Cases with severe disease must selectively be referred to designated hospitals with the appropriate resources including high-care and ICU facilities and a multi-disciplinary specialist team.

This article serves as an update to the COVID-19 articles in the previous edition of the O+G forum, taking into account advances in scientific knowledge about the disease and its management, as well as drawing on local and international experiences in managing the disease and coping with the pandemic. The article draws heavily on COVID-19 Maternal and Newborn Care Guidelines, Version 2 (updated 8 July 2020)<sup>1</sup>, collated by the South African Medical Research Council /University of Pretoria's Maternal and Infant Health Care Strategies Unit, and contributed to by the authors of this article. Detail about obstetric anaesthesia and resuscitation for COVID-19 patients is covered in a separate article in this edition.

## Transmission of SARS-CoV-2 between adults

The early public health messages about the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus

which causes COVID-19, suggested that the virus is mainly spread through respiratory droplets by infected people coughing and sneezing on others within a one metre distance of them. It was also suggested that when infected people cough and sneeze on surfaces or objects, these surfaces or objects can act as fomites, from which others can pick up the virus with their hands and transfer it to their eyes, nose or mouth, leading to infection. It is now clear that this is a simplistic view of SARS-CoV-2 transmission, as there is evidence that transmission from asymptomatic people does occur. The WHO has acknowledged that the infection can be transmitted through talking and singing<sup>2</sup>, not just coughing and sneezing. In some circumstances, an infected person can generate virus-containing aerosols, which could lead to airborne transmission over greater distances than droplet transmission. A Scientific Brief issued by the WHO on 9<sup>th</sup> July 2020 stated: "there is still a lot we do not understand about different possible modes of transmission. As research continues, we expect to gain a better understanding about the relative importance of different transmission routes, including through droplets, physical contact and fomites; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required for transmission to occur, the characteristics of people and situations that facilitate superspreading events such as those observed in various closed settings, the proportion of infected people who remain asymptomatic throughout the course of their infection; the proportion of truly asymptomatic persons who transmit the virus to others; the specific factors that drive asymptomatic and pre-symptomatic transmission; and the proportion of all infections that are transmitted from asymptomatic and pre-symptomatic individuals".<sup>2</sup> What does seem clear is that the virus is predominantly transmitted from the respiratory tract of infected people and is highly contagious, particularly when there is close contact with infected individuals in poorly ventilated environments.

There is justified concern about the risk for staff who are working in labour ward, as they need to be in close contact with individual patients over several hours, and a woman in labour will inevitably be exhaling forcefully, particularly in the second stage of labour, which may increase the likelihood of aerosol generation. Universal screening on admission in labour at two hospitals in New York in March/April 2020 (at a time when there was high COVID-19 prevalence) found that 13.7% of asymptomatic women tested positive for COVID-19.<sup>3</sup> This indicates that at the height of the pandemic, any woman who presents in labour could be infected with COVID-19 and therefore that infection prevention and control measures must be applied to all. Whereas health workers

## Correspondence

Dr N Moran

email: neil.moran@kznhealth.gov.za

tend to be very aware of the risk of infection posed by patients, they sometimes overlook the risk posed by colleagues. Where there have been outbreaks of COVID-19 amongst staff at health facilities, it is clear that many of the cases have resulted from transmission between staff members.

#### Practical tips

- During the time of the COVID-19 pandemic, even asymptomatic people should wear some type of face mask/covering (covering nose and mouth) when leaving home for activities that will necessitate close interaction with others. This is to prevent transmission from asymptomatic infected people to others. This applies to all staff working at health facilities, and all patients, including women in labour.
- Health workers at work during the pandemic must consciously avoid unnecessary close contact with colleagues at work, such as greeting with handshakes, hugs and kisses. Any essential meetings, that cannot be conducted remotely, must be held in a well-ventilated venue, ensuring that participants maintain a 1.5 metre distance between each other. All participants must wear face masks, especially when speaking.
- Special attention must be paid to parts of the health facility designated for social interaction between staff members, such as staff tea lounges. Strict rules must be applied to limit the number of staff who can be in the room at one time, so that social distancing can be maintained at all times.

#### Infectious period

Recent evidence suggests that those infected continue to emit viable virus for up to 8 or 9 days after the onset of symptoms in mild disease or after the stabilisation of symptoms in severe disease. Accordingly, the national guidelines have recently been amended, reducing the required isolation period for those who have been diagnosed with COVID-19 from the previously recommended 14 days as follows:<sup>4</sup>

- 1) Confirmed case: isolation until 10 days after the onset of symptoms (mild disease) or 10 days after stabilisation (no longer needing oxygen therapy) (severe disease)
- 2) Confirmed case remaining asymptomatic: isolation until 10 days after the date when the first positive test was taken
- 3) Person under investigation for COVID-19 (PUI): isolation until COVID-19 is excluded, or if COVID-19 is confirmed, then until 10 days after onset of symptoms (mild disease) or 10 days after stabilisation of the condition (severe disease)

Repeat COVID-19 testing after the 10-day isolation period is not necessary or recommended to confirm that the patient is no longer infectious, as the test may still come back positive for a number of days due to persistent traces of viral RNA, even though there is no longer emission of viable virus.

#### Practical tip

- Women with COVID-19 who are at home, but require essential pregnancy or reproductive health services such as contraception, termination of pregnancy, antenatal care and post-natal care, can have their visits re-scheduled a minimum of 10 days after the onset of the COVID-19 symptoms, unless there is a current emergency that needs immediate attention. They should remain in self-isolation meanwhile.

#### Effects of maternal COVID-19 on the pregnant woman and her baby

There have been a number of case series describing the effects of COVID-19 on the pregnant woman and her baby. Probably the best information so far available about the effects of COVID-19 on pregnant women comes from the UK Obstetric Surveillance System (UKOSS)<sup>5</sup>, which is a research platform that collects national population-based information about specific severe

complications of pregnancy from all 194 hospitals in the UK with a consultant-led maternity unit. This system was activated to collect data on all pregnant women admitted with confirmed COVID-19. An initial report analysed data from 1<sup>st</sup> March to 14<sup>th</sup> April 2020 on 427 pregnant women with COVID-19 admitted across the country.

Based on the available evidence, pregnant women with COVID-19 appear to present with similar clinical manifestations to non-pregnant adults. Pregnancy in itself does not seem to be a risk factor for severe disease. The most important risk factor for severe COVID-19 is advanced age, and as pregnant women are under 50 years old, they are all in a relatively low-risk group. In the UK, 10% of pregnant women admitted with COVID-19 required critical care (respiratory support), and 1% of pregnant women admitted with COVID-19 died, which is not higher than the rate in non-pregnant women of reproductive age admitted with COVID-19.

A high incidence of venous thrombosis and thromboembolic disease has been documented in non-pregnant patients with severe COVID-19 in the ICU setting (patients over 50 years old), including cases of pulmonary embolism<sup>6</sup>. An association between COVID-19 and venous thromboembolism has not been reported so far in pregnant women. However, as pregnancy is itself a hypercoagulable state, it is reasonable to speculate that pregnant women with severe COVID-19 will be at high risk of this complication.

There is currently no data suggesting an increased risk of miscarriage or early pregnancy loss in relation to COVID-19. There is also no evidence of any specific syndrome (e.g. congenital defects) that could be attributed to congenital COVID-19 infection in early pregnancy. However, it should be noted that because the disease only emerged a few months ago, there are still relatively few women infected in early pregnancy who have given birth.

Multiple reports suggest an association between preterm birth and COVID-19 in pregnancy (in the UK 25% of births in pregnant women with COVID-19 were preterm)<sup>5</sup>. This does not imply that COVID-19 causes preterm labour, as the majority of these preterm births were due to iatrogenic preterm delivery for example for maternal indications related to the infection. Although a few reports have suggested a high rate of fetal compromise in pregnant women with COVID-19, there is inadequate evidence to confirm such an association. In the UK, of 262 women with COVID-19 who gave birth, there were 3 stillbirths and 2 neonatal deaths, none of them clearly a consequence of the maternal COVID-19.

Neonatal infection with SARS-CoV-2 has been described (The prevalence in the UK was 5% of neonates born to mothers with COVID-19 in pregnancy)<sup>5</sup>. However, vertical transmission (in-utero or intrapartum transmission) seems to be very rare. There is at least one REVIEW demonstrating that transplacental infection of the fetus in the third trimester of pregnancy can occur<sup>7</sup>, but this seems to be the exception. In this case, the baby was born at 35 weeks' gestation by caesarean section to a mother with symptomatic COVID-19 at the time of delivery. The virus was isolated from the amniotic fluid before rupture of the membranes, and subsequently from the placenta and from a neonatal blood sample taken immediately after birth, as well as from the neonatal respiratory tract. Interestingly this baby developed neurological symptoms including irritability, hypertonia, and opisthotonus, which resolved gradually over a few days. SARS-CoV-2 was not found in the CSF, but the clinical presentation was attributed to acute neonatal COVID-19. Transmission to the neonate seems more likely to occur after delivery, through close contact with the mother or other infected people.

The virus has been detected in the breastmilk of one mother who developed symptoms of COVID-19 a few days after giving birth and tested positive for the virus.<sup>8</sup> The virus was detected in the breastmilk over a four-day period while the mother was symptomatic, and then became undetectable in the breastmilk. The baby also tested positive for SARS-CoV-2 during the same period, but it is not clear whether transmission to the baby was through breastfeeding or whether it was through close contact with the symptomatic mother. It is therefore not yet clear whether

breastfeeding is a route of transmission. Recent evidence provides reassurance about safety of breastfeeding with COVID-19<sup>9,10</sup>, suggesting that the risk of transmission to the neonate is very small as long as the mother takes precautions to wash hands before breastfeeding and wears a mask. WHO strongly recommends breastfeeding, irrespective of the mother's COVID-19 status.<sup>11</sup>

In South Africa, there is anecdotal evidence of a number of maternal deaths that have occurred in 2020 due to direct complications of COVID-19 in pregnancy. There is also concern that the general disruption of health services caused by the pandemic and the associated lockdown (including reduced access to or quality of contraception services, antenatal care, intrapartum care and post-partum care) may have resulted in an increase in adverse maternal and perinatal outcomes not directly related to COVID-19.

#### Practical tip

- During the COVID-19 pandemic other important conditions and complications in pregnancy must not be neglected. For example, all pregnant women must be screened for TB, and where appropriate, must be tested for TB. There is overlap between the symptoms of COVID-19 and the symptoms of TB. It would be inappropriate for patients with possible symptoms of TB to be tested for COVID-19 only and to be sent home without testing for TB.

#### Therapeutic agents

There are many ongoing studies and trials evaluating various different drugs as therapy for or prophylaxis against COVID-19. The National Essential Medicines List Sub-Committee on COVID-19 has been conducting rapid reviews of evidence available for treatment options for COVID-19.<sup>12</sup> These are regularly updated and provide a useful summary of the evidence with recommendations for clinical practice. So far, only the following drugs are recommended in South Africa for treating COVID-19:

- corticosteroids (only for patients with COVID-19 severe enough to require oxygen therapy), based on results from the Recovery trial (see clinical note 13 below)
- heparin thromboprophylaxis for patients with COVID-19 severe enough to warrant hospital admission (see clinical note 11 below). This recommendation is not based on new COVID-specific trial evidence, but follows established practice for critically ill patients admitted to high care and ICU settings, and takes into account the evidence that thromboembolic disease is often part of the pathology of severe COVID-19

There is some evidence that the anti-viral agent remdesivir may shorten the time to recovery in patients with severe COVID-19 and may reduce the risk of disease progression to the stage of requiring ventilation. However, no impact on mortality has been demonstrated so far. The drug has not been registered by the South African Health Products Regulatory Agency (SAHPRA), which complicates access to the drug. Furthermore, the high price of the drug means that its widespread use would not be justifiable unless more substantial benefits are demonstrated. At present, National guidelines do not recommend its use in COVID-19.

There is no evidence at present for the use of any drug as prophylaxis against acquiring COVID-19.

#### Notes on Clinical Management

1. Diagnosis of COVID-19 tends to be made on the basis of a positive PCR test for SARS-CoV-2 RNA. This is problematic because although the test is very specific (false positive tests are unlikely), it is not very sensitive, meaning that false negative tests are common. Furthermore, due to the large demand for SARS-CoV-2 testing, there have in many facilities been long delays, often of several days, in getting the test result. Unless

a positive test result is obtained promptly, a provisional diagnosis must be made based on clinical assessment, and other available investigations. There must be no delay in initiating appropriate resuscitative management, including ventilatory support if clinically indicated, even if COVID test results are still pending.

2. In cases with significant respiratory compromise, radiographic investigations should be performed to aid diagnosis, as COVID-19 infection results in characteristic changes on chest X-ray and CT of the chest. Pregnancy is not a contraindication to these investigations (reasonable efforts to protect the fetus from radioactive exposure should be made, as per usual protocol).
3. Health worker fears about contracting COVID-19 have unfortunately led to situations where patients suspected of having COVID-19 (PUIs) are not thoroughly assessed clinically, at least until a negative test COVID-19 test result is obtained. Isolation of the patient is prioritised over assessing and treating the patient's condition. Doctors, nurses, radiographers and all other relevant health workers should have access to appropriate personal protective equipment (PPE), and have a responsibility to assess any patient with respiratory compromise thoroughly and urgently. There are many causes of respiratory distress in pregnant women other than COVID-19, and diagnosis of these other conditions must not be delayed because of fear of examining the patient.
4. Where there are inadequate numbers of solitary isolation rooms to accommodate all the in-patients with COVID-19 or suspected COVID-19 (PUIs), then "cohort isolation" of multiple patients in a designated room or ward will be necessary. Cohort isolation is suitable for patients with confirmed COVID-19, as there is no concern regarding COVID-19 spreading from one patient to another. The main infection prevention focus will be on health workers protecting themselves from infection when working in the ward, and on preventing spread to other parts of the hospital when they leave the ward. On the other hand, cohort isolation of in-patient PUIs (awaiting COVID-19 test results) in the same room or ward is not recommended, as this will result in a high risk of COVID-19 spreading from those who really have COVID-19 to those who are in fact COVID-19 negative. Therefore, solitary isolation rooms should be allocated as a priority to PUIs, rather than to COVID-19 confirmed cases. This principle applies to hospitals as well as to quarantine/isolation facilities.
5. COVID-19 infection is not an indication for delivery, unless delivery is required as part of maternal resuscitation to improve maternal oxygenation, or to restore haemodynamic stability.
6. COVID-19 infection is not an indication for caesarean delivery. Women with COVID-19 infection should be allowed to deliver vaginally, unless there are clear obstetric indications for caesarean section.
7. Shortening the second stage by assisted vaginal delivery can be considered if the woman is exhausted or has respiratory distress.
8. For suspected and confirmed cases of COVID-19 infection, intrapartum care, delivery and immediate postnatal care should be conducted in an appropriate isolation room. There must be dedicated midwives allocated to care for the woman and her newborn. These midwives must not be involved with managing other women in labour on the same shift. Appropriate personal protective equipment (PPE) must be worn by the midwives caring for the COVID-19 patient.
9. Induction of labour (IOL) is not routinely indicated for women with COVID-19, but should be performed for

appropriate obstetric indications. The decision for IOL should involve an experienced obstetric doctor, to ensure that the IOL is definitely indicated. Where possible, it would be better to avoid labour and delivery until the woman has recovered from the COVID-19, and is past the infectious period. For PUIs, where possible IOL should be delayed until the COVID test result is known.

10. Women scheduled for elective caesarean sections, who have contracted COVID-19 should if possible, have the caesarean section postponed until 10 days after the onset of COVID-19 symptoms. PUIs should wait for the test result before a decision is made on the timing of the caesarean section. The postponing of elective caesarean sections should be overseen by an experienced obstetric doctor, to ensure that it is safe to do so, and to determine an appropriate monitoring/review schedule for the mother while awaiting the new date.
11. All pregnant women with COVID-19 or suspected COVID-19, who require admission because of the severity of their infection, should receive heparin thromboprophylaxis unless birth is expected within 12 hours, or there is a contraindication to heparin (e.g. antepartum haemorrhage). Either unfractionated heparin or low-molecular weight heparin can be used as per National Department of Health's Essential Medicines' List Clinical Guide. Some have suggested therapeutic doses of heparin, rather than prophylactic, should be used for thromboprophylaxis with COVID-19<sup>12</sup>. However, there is no trial evidence to support this, and the risk of bleeding complications would increase. Therefore, the decision for and appropriate dosing regimen of the heparin thromboprophylaxis should ideally be discussed by a multi-disciplinary team that includes a specialist obstetrician, specialist physician, and specialist anaesthetist/intensivist, taking into account haemorrhage risks, likely need for and mode of delivery, as well as thrombosis risk. Following delivery, once bleeding risk is no longer a concern, the heparin can be started/restarted, and continued until fit for discharge.
12. There is no evidence at present to support the use of heparin thromboprophylaxis in pregnant women with asymptomatic or mild COVID-19, not requiring admission.
13. Pregnant women who are admitted with severe COVID-19, requiring respiratory support in the form of oxygen therapy or ventilation, should be given a course of steroids for 10 days or until discharged from hospital if that is sooner. The recommendation is based on the results of the dexamethasone arm of the Recovery trial<sup>13</sup>, which showed a lower mortality in patients with severe COVID-19 who received steroids compared with those who received placebo. Pregnant women in the trial received either 40mg oral prednisolone per day or 80mg intravenous hydrocortisone twice a day, rather than dexamethasone<sup>14</sup>. This is because there were concerns about the possible adverse effects on the fetus of a ten-day course of dexamethasone, which is readily transferred across the placenta to the fetus. Prednisolone and hydrocortisone are not readily transferred to the fetus; they are also considered safe to use for breastfeeding mothers. It is therefore recommended that pregnant or breastfeeding women with severe COVID-19 requiring respiratory support be given a 10-day course of oral prednisolone, or intravenous hydrocortisone if unable to take orally.
14. For symptomatic relief of fever or headache, paracetamol is recommended. There are some concerns (not proven) that non-steroidal anti-inflammatory drugs, specifically ibuprofen, may worsen the course of COVID-19, and

they should therefore not be used as first-line treatment for symptomatic relief. Use of NSAIDs during pregnancy is not recommended anyway due to the risk of premature closure of the ductus arteriosus.

15. Where preterm delivery is anticipated in a pregnant woman with COVID-19, antenatal steroids for promoting fetal lung maturity may be administered according to the standard protocols used in non COVID-19 pregnant women.
16. When a woman with COVID-19 presents with spontaneous preterm labour, suppression of labour should not be done, however the antenatal corticosteroids can still be administered – time permitting.
17. The frequency and need for fetal heart rate monitoring should be considered on an individual basis, taking into consideration the gestational age of the fetus and the maternal condition. In general, fetal monitoring should be performed as per standard guidelines according to the non-COVID-19 obstetric risk factors. However, avoid monitoring fetal condition in a woman with severe COVID-19, until she is stabilised. The presence of the fetal heart beat can be checked intermittently in such cases.
18. Delayed cord clamping is still recommended following birth, provided there are no other contraindications. The baby can be cleaned and dried as normal, while the cord is still intact.
19. Mothers with suspected or confirmed COVID-19 should routinely be kept together with their newborn for bonding and breastfeeding, while applying necessary infection prevention precautions (the mother should wear a mask and wash or sanitize her hands frequently). The mother/baby pair must remain in a designated isolation area.
20. Routine neonatal criteria for admission to the neonatal nursery/NICU apply. Expressed breast milk would be ideal for the baby in this situation, if the mother is not able to enter the neonatal nursery due to infection concerns.
21. If the mother is unable to breastfeed the baby because she is critically ill, sourcing donor breast milk for the baby should be attempted.
22. When mother with COVID-19 and baby are both fit for discharge, they can be discharged home as long as home circumstances will allow self-isolation of the mother/baby pair. If this is not possible, referral to an alternative isolation/quarantine unit may be necessary.
23. For PUIs, every attempt must be made to obtain a COVID-19 test result before discharge to clarify isolation requirements post-discharge.
24. The postnatal visit schedule must be arranged before discharge. Discharge must be authorized by a senior team member. On discharge, the mother with COVID-19 must be provided with contact details of the relevant postnatal/neonatal care team member to call if she has any concerns before her next scheduled visit. The postnatal/neonatal team should also obtain contact numbers for the mother, so that telephonic follow-up can be conducted if required.

### Conclusion

The strict lockdown imposed on South Africans at the start of the pandemic has certainly limited the scale of the pandemic in South Africa compared to some other countries, where lockdown was less strict. There has been widespread messaging about how to minimize transmission through measures such as hand hygiene, social distancing and mask wearing, and the South African population has adjusted its behaviour accordingly. Much has been learnt about this new disease, and health workers have incorporated the new knowledge and are continuously adapting their practice to better combat the pandemic. As lockdown regulations are gradually

relaxed, South Africans need to take responsibility to maintain the new safe behaviour they have learnt in order to prevent a resurgence of COVID-19 cases. The pandemic is far from over, and we need to keep rigorously monitoring and auditing maternal and perinatal outcomes in these times to understand the impact of the pandemic and respond appropriately.

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