



## **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) implications on pregnancy outcomes. What obstetrician should know?**

**Mahmoud Mansour<sup>1</sup>; Mohamed Taman<sup>2</sup>, Ashraf Shoma<sup>3</sup>**

<sup>1</sup> Final Year Medical Student, Mansoura Manchester Medical Programme, Faculty of Medicine, Mansoura University.

<sup>2</sup> Department of Obstetrics and Gynecology, Mansoura University Hospital, Mansoura Faculty of Medicine, Mansoura.

<sup>3</sup> Professor of General Surgery, Mansoura University Hospital, Mansoura,

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### **Abstract**

In less than a year, more than 60 million cases of COVID-19 were reported worldwide. Most of the data available still unclear. It affects vulnerable populations as those with lowered immunity, chronic diseases and pregnant females. Many questions have to be answered as during pregnancy care should be given to mother, fetus and neonate. Also, the obstetricians should follow the evidence-based recommendations during their routine antenatal care and during labor. We reviewed the recent and available online published researches since the outbreak of COVID-19 to know what we know about the impact of the recent pandemic on the pregnancy and pregnant women. Till now it is reported that being pregnant does not make women at more risk compared to general population, however the use of prophylactic doses of LMWH is essential to prevent venous thromboembolism. COVID-19 might lead to fetal growth restriction or miscarriage, but the evidence to date remains uncertain. Vertical transmission of the virus is a possibility, but it is not excreted in breast milk. With the evolution of many vaccines and many immunological therapies, it is mandatory to assess their safety during pregnancy and lactation.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that novel virus, started spreading from Wuhan, China in December 2019 and led to a pandemic that affected the whole world not only on the health side but in most of life's activities (1).

Considering spreading through respiratory droplet so r secretions from infected patients and as asymptomatic persons infected with SARS-CoV-2 carry high viral loads in their nasal secretions, they can silently and efficiently spread the virus. Most of the countries considered lockdown, quarantine, and social distancing for varying periods in 2020 to limit the spread of the disease (2).

COVID-19 affects people in different degrees from mild symptoms reaching to severe health impact requiring hospitalization and even ICU admission. SARS-CoV-2 is known to have more impact on immunocompromised patients who are vulnerable and have increased risk of ICU admission, need for invasive ventilation, and death. Due to lower body immunity, patients with known comorbidities like pregnancy, coronary diseases, cancers, renal diseases, and diabetes are at more risk for a severe form of the disease (3).

Being a novel virus, we haven't dealt with it before and we don't have a treatment or a vaccine, the data we know about COVID-19 is limited and studies are being run around the world to help us understand its nature and update guidelines for health care providers on how to deal with patients with COVID-19. At the moment, there is a large amount of research being done to discover suitable treatments. Great

governmental efforts have been made on the development of potential efficacious vaccines (4). We accessed the data published on Pub Med, web of science and Scopus in the last year to answer many questions regarding disease impact on mother, fetus and neonate. Also, to know the evidence-based plan of management during pregnancy, labor and lactation.

### Epidemiology of the disease

By November 27<sup>th</sup>, 2020, the world health organization (WHO) reported more than 60,000,000 confirmed cases of COVID-19, including 1.4 million deaths (5). The Egyptian ministry of health reported more than 114,000 confirmed cases and more than 6,000 deaths were recorded by November 2020 (6).

In their weekly updated COVID-19 pregnancy data, Centers for Disease Control and Prevention (CDC) estimated the number of pregnant women with COVID-19 in the United States between January 22 and September 1, 2020, to be 20,216 including 44 deaths (7).

### Effect of COVID-19 on pregnant women

#### I. Immunology and pregnancy

During pregnancy a change of cell-mediated immunity normally occurs, this includes weakness of the Th1 type action with strengthening of the Th2 type (8). The function of Th1-type cells is anti-microbial and pro-inflammatory, and include IFN- $\gamma$ , IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, and IL-12; on the other hand, the function of Th2 type is anti-inflammatory as IL-4, IL-10, IL-13, and TGF- $\beta$  (9).

This alternation toward an anti-inflammatory state occurs mainly during the second trimester which is considered essential to allow fetal growth (10).

This shift aims to provide an immunologically

tolerated state toward the placenta and the fetus by inhibition of the body rejection to unknown objects in it. This makes women more vulnerable to pathogens like viruses and increase their susceptibility to a severe form of the diseases than non-pregnant (11).

Th1 type response is high and lasts for long time when looking to the cytokine analysis of people having severe acute respiratory syndrome-related coronavirus (SARS-CoV), which has an 80% genetic similarity to SARS-CoV-2, this leads to elevated levels of pro-inflammatory cytokines for more than fourteen days from the start of the disease (12). This causes an increased risk of maternal massive lung damage, intrauterine fetal death or premature delivery (13). Fortunately, in COVID-19, The detected duration and levels of both Th1 and Th2 type responses are similar, with elevated levels of IFN- $\gamma$  and IL-1 $\beta$  in circulation (pro-inflammatory cytokines) as well as of IL-4 and IL-10 (anti-inflammatory cytokines). The mortality of patients having SARS-CoV-2 infection is related to increased circulating levels of IL-6 which is considered the needle of the scale (14).

As the inflammatory behavior plays a pivotal role in coronavirus course of infection, the cytokine profile and response recorded during SARS CoV-

2 infection makes us to expect less severe outcomes than SARS-CoV (15).

A study published by clinicians in New York suggested that being pregnant doesn't add more risk than the general population. Based on 43 females who were pregnant and tested positive for SARS CoV-2 and the severity of their diseases was similar to that of the non-pregnant patients: 86% mild, 9% severe, and 5% critical, but pregnant women's number described in the study was not enough to get a final conclusion and they had not been compared to individuals with similar age, gender or co-morbidities (16).

## II. Clinical presentation

Evidence shows that there are infected populations who are asymptomatic or have very little symptoms and they are considered virus carriers and they are spreading the disease in silence, but they have unknown prevalence. A prospective study based on 675 females who were pregnant and admitted to 3 different hospitals at New York City for labor, all of them were tested for COVID-19, found 70 women (10%) were positive for SARS-CoV-2; 55 (79%) of those infected were asymptomatic. Maternal presentation at admission is shown in **Table 1** (17).

**Table 1:** Maternal presentation of COVID-19, stratified by being COVID-19 positive or negative depending on RT-PCR result and the status of their symptoms (17)

Maternal presentation at admission	COVID-19 Positive cases		COVID-19 Negative cases	P-value
	Symptomatic n = 15	Asymptomatic n = 55	n = 605	
Temperature (°C), mean (SD)	37.0 (0.7)	36.8 (0.3)	--	0.17
HR (beats /minute), mean(SD)	91.8 (11.1)	88.4 (17.3)	--	0.47
RR (breaths /minute), mean (SD)	19.5 (5.5)	18.0 (2.0)	--	0.11
SpO2 (%), median (IQR)	99.0 (97.0–100.0)	99.0 (98.0–100.0)	--	0.60
WBC count, mean (SD)	8.8 (2.4)	9.0 (3.1)	--	0.78
Platelet count, mean (SD)	231.8 (101.5)	207.9 (72.4)	--	0.30

RT-PCR: reverse transcription-polymerase chain reaction.

HR: heart rate

RR: respiratory rate

SpO2: oxygen saturation

WBC: white blood cells

Being asymptomatic, enough attention should be dedicated to limit and contain the spread of the virus among workers in the health sector, also among admitted women who are, or about to be, pregnant and among their newborns as well. This will be achieved by active protective measures for COVID-19 and by directing attention towards the management of pregnant women in different hospital departments specifically obstetrics and gynecology wards(15).

Fortunately, only mild or moderate flu-like symptoms will affect the majority of pregnant women. While shortness of breath, anosmia, cough, fever and headache are considered as possible symptoms (18).

The most common symptoms reported by pregnant women in order are fever, coughing and breathlessness. This is based on an interim report from the largest available cohort of pregnant women admitted to hospital with SARS-CoV-2 infection to date which was published on 08 June 2020 by United Kingdom Obstetric Surveillance System (UKOSS)(19).

Those who are immunosuppressed, elderly, or those with chronic diseases like cancer, diabetes or chronic lung conditions are expected to have marked hypoxia and more severe symptoms suggesting pneumonia (20). Early and rapid assessment, identification and supportive treatment are necessary in pregnant women as they are expected to have infection with severe symptoms(21).

### **III. Venous thromboembolism prevention**

Pregnancy is widely recognized as a hypercoagulable state(22). Emerging evidence shows the ability of COVID-19 as well to make hypercoagulability

among infected patients admitted to hospitals (23). The risk of maternal venous thromboembolism (VTE) is likely to be increased due to SARS-CoV-2 infection. Many factors are to be considered to increase the risk of VTE including quarantines and isolation, at hospital admission or at home, resulting in decreased motility and other maternal or obstetric morbidity(21).

The recently updated guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) version 11 advises that pregnant women should stay well hydrated and mobile, VTE risk assessment performed during their pregnancy. COVID-19 infection should be recognized as a transient risk factor. Low molecular weight heparin (LMWH) should be prescribed to all pregnant ladies admitted to hospitals with suspected or confirmed SARS-CoV-2 infection, unless they are expecting within 12 hours. After hospital discharge and for 10 days, LMWH should be prescribed to all pregnant women with confirmed COVID-19

as a thromboprophylaxis. And it should be prescribed for a longer duration if the woman has a persistent morbidity(21).

### **Effect of COVID-19 on the fetus**

Till now, available data does not suggest the risk of miscarriage to be increased by COVID-19. There is no established relationship between infection and risk of second trimester loss or miscarriage according to studies and case reports on pregnant women with SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV)(24).

At the moment, evidence does not suggest that COVID-19 can cause fetal growth restriction

(FGR); however, FGR is considered possible with SARS as it affected two-thirds of pregnancies (25).

### Vertical transmission of COVID-19

There is a controversy between available researches on whether Coronavirus disease 2019 could be transmitted from the mother to her infant through the placenta antenatally or intrapartum.

While a meta-

analysis published on July 17<sup>th</sup>, 2020 on 432 newborns whose mother tested positive for SARS-CoV-2 infection before labor showed that there was a total of 10 out of 432 (2.3%) neonates tested positive for COVID-19 (26).

Inclusion and exclusion criteria for this study were restricted to ensure that if a newborn tested positive it would be due to intra uterine transmission not due to after delivery contact with the mother, doctors, or the environment. This was achieved by testing newborns for COVID-19 shortly after their birth and they were given a certain care by health care providers, such as wearing masks by the health care team and the mother, using negative pressure wards, and isolation.

The main clinical features and preventive measures used of the neonates with early COVID-19 in included studies are shown in **Table 2** (26).

Samples to test for SARS-CoV-2 in these studies were collected from the throat, serum, urine, feces, amniotic fluid, umbilical cord blood, placenta, breast milk, bronchoalveolar secretion, cervical and vaginal secretions from the mother.

Another 6 neonates tested positive but were excluded from the study due to being false positive ( $n = 1$ ), being infected 36 hours after delivery without being able to be sure if

enough protective measures were applied ( $n = 3$ ), being caused by not wearing masks while breastfeeding due to the late diagnosis of the mother in the postpartum period ( $n = 2$ ) (26).

In another established larger systematic review published June 12<sup>th</sup>, 2020 based on 666 newborns described as being born to infected women with SARS-CoV-2, it concluded that 28 newborns out of 666 (4%) had confirmed SARS-CoV-2 infection after delivery (34).

On the other hand, a meta-

analysis published in August 2020, which included 236 pregnant women with COVID-19, concluded that there is currently no evidence that SARS-CoV-2 can be vertically transmitted. As their included studies were not significant with the P value was greater than 0.05 which is not conclusive regarding vertical transmission. Without intrauterine tissue samples being tested, they were not able to confirm whether the SARS-CoV-2 infection in neonates was a result of intrauterine transmission (35).

### Mode of delivery

Delivery methods was questionable since the beginning of the outbreak. RCOG declared that at the moment evidence is not enough to indicate cesarean section in pregnant females who are positive for COVID-19 (21).

In the UKOSS study, 265 infants whose mothers were infected with COVID-19 were tested, 253 of them were negative for SARS-CoV-2 infection. 12 (5%) of them tested positive for SARS-CoV-2; 6 in the first 12 hours (4 were born by cesarean section and 2 by unassisted vaginal birth) and 6 after 12 hours (4 born by cesarean section and 2 vaginally) **Table 3** (19).

When the baby is born by vaginal delivery, the rate of ne-

onatal COVID-19 infection is the same. Therefore, evidence is not enough to choose single method of

delivery over the other in delivering women with SARS-CoV-2 (34).

**Table 2: Main clinical features and preventive measures used of the neonates with early COVID-19 in included studies (26)**

Included studies	Country	Age, Weight and Mode of delivery	Method of diagnosis	Preventive measures and outcomes
Nie et al. (27)	China n = 1	- C-section	RT-PCR: Cord blood + throat swab + placenta	N95 mask was used by the mother during delivery. Immediate isolation of the newborn after birth. No Treatment was given; discharged on the 16 <sup>th</sup> day.
Alzamora et al. (28)	Peru n = 1	33 weeks 2,97 Kg C-section	RT-PCR: Serology + throat swab	Immediate separation and intubation of the baby as the mother was sedated. Skin-to-skin care and cord clamping was delayed, and breastfeeding was not done.
Khan et al. (29)	China n = 2	- 3,36 kg/3,57 Kg Cesarean	RT-PCR: throat swab	Babies were tested within the first day after the delivery and was positive in two of them.
Zeng et al. (30)	China n = 3	40/40/31 weeks 3,25 Kg/3,36 Kg /1,58 Kg C-section	RT-PCR: anal and throat swab	During labors, infection control measures were strictly applied.
Dong et al. (31)	China n = 1	- 3,12 Kg C-section	RT-PCR: Serology, throat swab + vaginal secretions of mother	An isolation room with negative pressure was used during delivery. Newborn showed no clinical symptoms and was quarantined directly. And discharged on the 26 <sup>th</sup> day.
Hantoushzadeh et al. (32)	Iran n = 1	30 weeks 2,1 Kg C-section	RT-PCR: throat swab	In the beginning, the test for the premature newborn was negative. On the 7 <sup>th</sup> day, the neonate tested positive during intubation.
Hu et al. (33)	China n = 1	40 weeks 3,25 Kg C-section	RT-PCR: blood, throat, feces and urine	Normal Chest X-ray reports on the 1 <sup>st</sup> day of life. And the neonate showed no symptoms.

**Table 3: Neonatal outcomes among liveborn infants of pregnant women with confirmed COVID-19 infection (19).**

Neonatal outcomes	No. of liveborn babies of women with COVID-19 (n=265)
Negative SARS-CoV-2 test	253 (158 by Cesarean birth, 95 by vaginal birth)
Positive SARS-CoV-2 test	12 (5%)
Positive test <12 hours of age	6 (4 by Cesarean birth, 2 by vaginal birth)
Positive test ≥12 hours of age	6 (4 by Cesarean birth, 2 by vaginal birth)

### Breastfeeding and postnatal care

There has been a debate between guidelines on whether separation of a newborn after delivery

who is born to a COVID-19 positive mother is necessary. Or whether breastfeeding is a safe practice. Each health system has its own guidance



on this issue as data are limited on neonatal care for newborns who are born for women who tested positive for COVID-19 in the 3<sup>rd</sup> trimester (36).

Any possible hazard to the baby from contracting the virus through breast milk is to be outweighed by the well-known long-term benefits of breastfeeding (37).

It is reassuring that a recent study based on 24 lactating females who were COVID-19 positive, found that PCR for their breast milk tested negative for SARS-CoV-2. **Table 4**; however, this evidence should be followed by caution as the number of cases were small. The route of infection during breastfeeding will be the direct contact between the mother and her baby through infective respiratory droplets (38).

**In the light of this evidence, the recently updated RCOG guidance version 11 gives a list of advices for practitioners (21).**

- Encourage close contact between mother and her baby if she is not in need of ICU care.
- Encourage skin to skin contact if the baby is not in need of special medical care.
- Encourage mother to breastfeed their babies with wearing face mask during lactation.
- Frequent advices and support should be given to all lactating mother.

**Royal College of Pediatrics and Child Health (RCPCH) precautions during feeding of the baby should be followed to limit viral spread (46).**

- If the mother is critically ill, another healthy person should take care of the baby.
- Hand washing is mandatory before dealing with baby towels or supplies.
- Wearing fluid-resistant mask or a face covering during lactation is recommended.
- Don't use any face mask for babies to avoid

suffocation.

- Adequate sterilization of baby feeding-bottles before their use.

### Conclusion

COVID-19 has affected a large number of individuals worldwide with a mortality rate of 3.3%. Being a novel virus, the data we have on it is limited so researches should continue to improve our knowledge and help us take better management plans and update our guidelines.

Most of the infected pregnant women will be asymptomatic or have only flu-like symptoms. A few percentages will get severe symptoms, but being pregnant does not make them at more risk than the general population.

Pregnancy and COVID-19 are both a hypercoagulable state, so prophylactic doses of LMWH should be prescribed to suspected or confirmed pregnant women with COVID-19.

Evidence of miscarriage or FGR as a complication of COVID-19 is not available. Depending on data related to SARS-CoV-2, there should be no risk of miscarriage but FGR is an established complication.

Vertical transmission of COVID-19 is a possibility, but we need more focused researches on larger numbers of newborns who are tested just after delivery, the sample to be taken from the umbilical blood and/or the placenta, and the baby to be born with isolation and prevention measures.

No available evidence to support one mode of delivery over the other in COVID-19 patients. So vaginal delivery will be the standard unless there are other indications for cesarean section.

Mothers and their newborns should not be separated after delivery. As SARS-CoV-2 is not excreted in breast milk, women with COVID-19 should be encouraged to breastfeed their babies while considering the necessary precautions.

More national researches on the topic are needed which will be more suitable for our community,

hospitals, and health care system.

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