

## REVIEW ARTICLE

## Generation COVID-19 – Should the foetus be worried?

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**Abstract**

**Aim:** The aim of this narrative review was to evaluate the risks, both direct and indirect, to the foetus from the COVID-19 pandemic.

**Methods:** Direct and indirect risks were defined as (a) vertical infection (congenital or intrapartum), (b) maternal infection and its sequelae, and (c) sources of maternal stress during lockdown, including social isolation and altered healthcare provision.

**Results:** Early studies suggest that vertical viral transmission is low; however, there may be an important effect of maternal infection on foetal growth and development. The impact of various degrees of lockdown on prospective mothers' health, habits and healthcare provision is of concern. In particular, increased maternal stress has been shown to have a significant effect on foetal brain development increasing the risk of mental health, and cognitive and behavioural disorders in later life.

**Conclusion:** From the evidence available to date, direct risks to the foetus from the SARS-CoV-2 virus are low. Indirect effects of the pandemic, particularly resulting from the effect of maternal stress on the developing brain, can have lifelong detrimental impacts for this generation of children.

**KEYWORDS**

COVID-19, foetus, lockdown, neurodevelopment, SARS-CoV-2

**1 | INTRODUCTION**

The emergence of a novel coronavirus (SARS-CoV-2) has sent a shockwave around the world. On 11 March, the World Health Organization declared it a pandemic, and to date, over 30 million cases have been reported with 950 000 deaths in 188 countries.<sup>1</sup> As the world grapples to understand this new disease, it has become clear that not everyone faces the same risk, with men, individuals with predisposing medical conditions and those over 75 years of age being the most vulnerable.<sup>2</sup> However, the disease has only come

into international existence over the past eight months, and for one group of patients, the effect of the coronavirus pandemic still remains unclear: the unborn child.

Pregnant women and their foetuses have been amongst those with the poorest outcomes in previous epidemics such as Ebola, Zika, SARS and MERS.<sup>3</sup> Initial reports suggest that perinatal infection with SARS-CoV-2 is reassuringly rare.<sup>4</sup> However, the complex socio-economic, domestic and broader maternal lifestyle factors, which can influence a child's lifelong well-being, have been modulated during the experience of this pandemic (Figure 1). In this

**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DOHaD, Development Origins of Health and Disease; FA, functional anisotropy; IUGR, intrauterine growth restriction; SAGE, Scientific Advisory Group for Emergencies; UKOSS, UK Obstetric Surveillance System.

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article, we consider the potential impact of this pandemic from the viewpoint of the foetus and ask should the foetus be worried?

## 2 | FOETAL INFECTION

Given the lack of previous maternal exposure and immunity against the novel SARS-CoV-2 virus, the most obvious risk for the foetus is vertical transmission (congenital or intrapartum). Congenital viral infections have a range of adverse outcomes from intrauterine growth restriction (IUGR), congenital birth defects, particularly with adverse neurological sequelae, preterm delivery, spontaneous abortion or stillbirth.<sup>5</sup>



**FIGURE 1** The various interacting effects of the COVID-19 pandemic on the foetus. Risk of congenital or intrapartum foetal infection (A), the outcomes of maternal infection and its sequelae (B), impact of lockdown on individual mothers' lifestyles (C), contact with and behaviour of those surrounding pregnant women (D) and the changes brought about in the delivery of and access to health care (E). These factors can influence maternal stress (F) which in turn affects foetal brain development

The first cases of SARS-CoV-2-positive pregnant women reported some newborn infants were infected early in life.<sup>3</sup> However, it was not possible to determine whether these were true vertically transmitted infections or horizontally in the immediate postnatal period.<sup>6</sup> Chen et al, in February 2020, tested the amniotic fluid, cord blood and breastmilk of six infected women, as well as taking neonatal throat swabs; all samples were negative for the virus.<sup>7</sup> The first confirmed case of intrauterine transmission, as defined by the criteria set out by Shah et al, was a French study on 14 July 2020.<sup>8,9</sup> The UK Obstetric Surveillance System (UKOSS), which recorded 427 pregnancies of women who were SARS-CoV-2-positive, concluded that while transmission to the foetus is possible it is uncommon as only two per cent of infants born returned a positive sample for viral

### Key Notes

- Vertical transmission of SARS-CoV-2 is rare, but the impact of lockdown has had a disproportionate effect on pregnant women.
- Lockdown has altered personal, social and healthcare factors known to affect pregnancy outcomes and contributed to increased maternal stress.
- Maternal stress is known to alter foetal brain development putting the infant at lifelong risk of cognitive, behavioural and affective disorders.

RNA within 12 hours of birth and this was again without controlling for the possibility of post-delivery transmission.<sup>10</sup> More recently, a systematic review of neonatal SARS-CoV-2 infections reported that of 176 published cases, 30% were likely due to vertical transmission although only 5.7% were confirmed congenital infections.<sup>11</sup>

Despite the evidence thus far suggesting vertical transmission to be rare, there is good reason to remain cautious. We still know very little about the basic pathophysiology of SARS-CoV-2 in pregnancy and the factors, which determine this virus' ability to infect a foetus. Generally, pathogens are less likely to be able to cross the placenta earlier in pregnancy, but when they do, the consequences are usually more severe.<sup>12</sup> To date, no first-trimester effect has been reported as many of these infants have yet to be born.<sup>3</sup> In the 2014-2016 Brazilian outbreak of Zika virus, the spike in infants born with microcephaly coincided with those who had been conceived or were in their first trimester during the height of the epidemic nine months prior.<sup>13</sup> Moreover, consequences of foetal viral infection may not even be apparent at birth; hearing loss due to asymptomatic cytomegalovirus infection manifests after two years of age,<sup>14</sup> and postnatal persistence of congenital rubella infection can lead to a progressive panencephalitis, the onset of which is typically in the teenage years of life.<sup>15</sup> This emphasises the importance of long-term surveillance of infants who are SARS-CoV-2-positive at birth.

## 3 | MATERNAL INFECTION

Even in the absence of vertical transmission of the virus, maternal infection may have a significant adverse effect on the foetus by compromising maternal health or the placenta. While there was little evidence for intrauterine transmission of SARS and MERS, an increased risk of miscarriage was noted.<sup>16</sup> In influenza, while vertical transmission is rare, maternal infection is associated with preterm birth, spontaneous abortion, central nervous system defects, neural tube defects and congenital heart defects.<sup>17</sup>

The placenta itself can be infected, without necessarily resulting in transplacental transmission, and this can affect its structure and function. Placental infection can elicit an inflammatory response in the foetus, risking downstream effects on organ development.<sup>18</sup> By

altering placental invasion, infection can be linked to pre-eclampsia, hypoxia and IUGR.<sup>17,19</sup> Viral infection may alter the normal response of placental tissue to bacterial products resulting in a pro-inflammatory cytokine storm and preterm birth or compromise the ability of the placenta to protect the foetus from other pathogens.<sup>18,19</sup> A recent case-control study from Sweden showed a significant increase in pre-eclampsia in mothers who were SARS-CoV-2-positive.<sup>20</sup>

Data from UKOSS between 1 March and 14 April (the peak of the first wave of the pandemic in the UK) reported 427 pregnant women admitted to hospital with confirmed SARS-CoV-2 infection with 262 giving birth in this period.<sup>10</sup> Five infants died; while three deaths were unrelated to SARS-CoV-2 infection, it is unclear what role it played in two stillbirths. Sixty-six (25%) were born preterm with 32 (48%) delivered due to maternal COVID-19 infection, representing a not insignificant morbidity to the infant from maternal infection.

#### 4 | EFFECTS OF LIVING IN A PANDEMIC

The COVID-19 pandemic has led to unprecedented circumstances as countries have adopted various models of 'lockdown' in attempts to contain the disease. The consequences are far-reaching and have transformed life for most people, modifying societal and lifestyle factors which are already known to influence pregnancy and may have increased maternal stress experienced by some groups of women (Figure 1).<sup>21</sup> This time of domestic and social upheaval has been accompanied by the loss of normal personal and professional support structures and changes in the delivery of health care (Figure 1).

#### 5 | SOURCES OF MATERNAL STRESS IN LOCKDOWN

As with many countries, in the UK, pregnant women were defined as being at 'moderate risk' from coronavirus as a precautionary measure and were asked to remain in their homes as far as possible.<sup>22</sup> The consequences of lockdown upon these women are twofold, causing both material hardship and psychological distress.

One major concern is the financial difficulties that lockdown has brought about and, for the least well off in society, exacerbated. The UK Institute for Fiscal Studies reporting a sharp decrease in employment and incomes with the poorest fifth of households saw a 15% reduction in median earnings.<sup>23</sup> Finances in turn influence broader lifestyle factors such as diet and sleep, and there is evidence of this in the general UK population: 62% of those facing financial consequences as a result of lockdown report disturbed sleep and food insecurity has quadrupled for the UK adults in the past few months with more people depending on food banks, eating food past the best before date and relying on cheaper diets made up of processed, carbohydrate-rich foods.<sup>24-26</sup> Trends seen in the general population are especially worrying for the foetus. Broader determinants of health such as poverty, stress, housing conditions and poor nutrition can affect younger women of childbearing age and pregnant women

particularly and impact upon the outcomes of their pregnancy and their child's development.<sup>27-30</sup>

Lockdown has also caused significant psychological distress within households. In an initial report, 2240 participants surveyed linked poorer mental health with greater financial hardship, losing contact with friends and family, less sense of community in the neighbourhood and increased conflict with household members.<sup>31</sup> These findings point to a feeling of lack of social support, which is an important determinant of a pregnant woman's quality of life, symptoms of depression, her health behaviours and a protective factor for her foetus.<sup>32</sup>

Lack of wider social support and domestic conflict may be part of the reason; there has been a sharp increase in the incidence of domestic abuse in the UK since lockdown began; calls to the National Domestic Abuse Helpline increased 49% and 16 women were killed within the first three weeks of lockdown alone - triple the number in the same period last year.<sup>33</sup> Pregnancy is known to be a risk factor for domestic violence, and those who have experienced intimate partner violence are five times more likely to have a preterm birth or a baby of low birthweight.<sup>34,35</sup>

Major stressful events in the community have been linked to preterm delivery and low birthweight, both acutely following a disaster, and several months after the event. Following the 9/11 attacks on New York and Washington, there was a shift in the population distribution of birthweights, with neonates more likely to be born with lower birthweight.<sup>36</sup> This phenomenon continued for several months to include pregnancies that would have been in their first or second trimester at the time of 9/11.<sup>36</sup>

Interestingly, a number of countries have reported that during the height of the pandemic in April there was a reduction in the admission of preterm infants to neonatal units.<sup>37</sup> While it is too early to fully understand this observation, it has been suggested that the focus on hygiene and less social contact may have reduced the usual risk of maternal infection leading to preterm birth. For some, lockdown resulted in reduced stress during pregnancy as individuals no longer had to commute to work or work in stressful environments.<sup>37</sup> Ongoing surveillance in the months ahead will be important to ascertain the effect of the COVID-19 pandemic on preterm delivery and low birthweight in different groups of women.

#### 6 | HEALTH CARE IN THE TIME OF COVID-19

The provision of antenatal health care by hospitals, primary care practices, community midwives and social services has changed dramatically during the pandemic. Even away from the frontline services, there has been impact on healthcare provision due to significant loss of staff through illness, self-isolation and shielding.<sup>38</sup> It would not be unreasonable to expect that this will impact on the quality of care received by women during their pregnancy.

It has also been widely reported that patients are reluctant to attend hospital for fear of being exposed to the virus.<sup>39</sup> A paper from

the Scientific Advisory Group for Emergencies (SAGE) estimates that it is possible that changes to emergency care in response to COVID-19 may account for 6000 excess deaths in March and April 2020.<sup>40</sup> One trust reported that presentations of obstetric related conditions to the emergency department were among those to fall most rapidly compared with the same time last year.<sup>41</sup> Expectant mothers' reluctance to attend and delay in seeking treatment may result in more complex presentations and potentially poorer outcomes.

Despite the best intentions of healthcare providers, the Board of Human Rights in Childbirth reported the undermining of women's basic human rights in a number of different countries, including women being denied the right to a companion during labour and birth, women being subjected to forced inductions and caesarean sections without medical indications, and mothers being separated from their infants and discouraged from breastfeeding.<sup>42</sup> In the UK, home births have been cancelled and there is restricted visitation to postnatal wards and neonatal units.<sup>43</sup>

The measures put in place to allow the National Health Service to cope with the added pressure of responding to a global health emergency have not come without a cost for non-COVID-19 patients, the impact on routine care before, during and after pregnancy upon the foetus remains to be seen.

## 7 | MATERNAL STRESS AND FOETAL BRAIN DEVELOPMENT

The theory of the Developmental Origins of Health and Disease (DOHaD) suggests that the foetus can respond to cues from its environment *in utero* to alter the trajectory of its development.<sup>44</sup> While this 'programming' may convey benefit to the foetus in future life, altering the development and thus structure and function of the foetus' organs has also been shown to increase the risk of non-communicable diseases in a variety of organ systems, including in the brain.<sup>44</sup>

Maternal stress is considered one of the important 'programming cues' which affects foetal brain development, with studies consistently linking prenatal stress to changes in cognition, behaviour and psychosocial outcomes becoming apparent in infants, children and adults.<sup>45</sup> One study showed *in utero* exposure to maternal bereavement was associated with an increased likelihood of an individual taking medication for attention-deficit/hyperactivity disorder (ADHD) in childhood (25%) and taking medication to treat anxiety (13%) or depression (8%) in adulthood.<sup>46</sup> Suffering the loss of their father *in utero* compared to within the first year of life puts an individual at increased risk of developing schizophrenia as an adult.<sup>47</sup>

The effect of maternal stress is thought to be mediated, at least in part, by increased antenatal exposure to glucocorticoids, altering the structure and function of the foetal brain.<sup>45</sup> Animal studies using various models of prenatal stress have found structural changes in various regions of the brain. In both rodents and non-human primates, exposing pregnant dams to stressors or mimicking the effect of a stressor by injecting dexamethasone leads to decrease in gross

hippocampal volume.<sup>45</sup> The hippocampus is thought to be involved in memory and learning, and decreased volume is an important risk factor for psychopathology.<sup>48</sup> Even on a subcellular level, rat studies have shown decreased dendritic arborisation and synaptic loss in the CA1 area of offspring which speaks to the pervasive effect maternal stress has on foetal brain development.<sup>49</sup>

In humans, it is challenging to conduct prospective studies, but it is becoming clear that prenatal stress alters the development of the brain causing structural differences to be seen even in childhood. Children, aged between six and nine years, whose mothers had suffered pregnancy anxiety earlier rather than later in gestation had decreased regional grey matter density in various areas including the prefrontal cortex, medial temporal lobe and fusiform gyrus, areas responsible for social behaviour, decision-making and cognitive processing.<sup>50</sup> Neurobehavioral disorders such as ADHD and autism spectrum disorder (ASD) have been linked to differences in the connectome, that is the pattern of connectivity or 'wiring' that exists within and between regions of the brain.<sup>51</sup> Functional anisotropy (FA) is a measure of more organised, strongly myelinated tracts and was found to be relatively decreased in areas responsible for sensory processing, cognition and socio-emotional function in neonates who had been exposed to prenatal stress.<sup>51</sup>

## 8 | CONCLUSION

History has taught us that viral infections can have unique and harmful impacts on the unborn baby. With the rapid emergence of a new pathogen, SARS-CoV-2, intense research is underway to study the acute effect of the virus on health. From the evidence available to date, direct risks to the foetus from congenital or intrapartum infection are low. However, it is clear that maternal stress resulting from the pandemic and in particular of lockdown can adversely affect the developing brain. It is therefore important that healthcare workers and policymakers are aware of this and that long-term surveillance of infants conceived and born during the pandemic is put in place to mitigate against any detrimental impact for this generation of children.

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### CONFLICT OF INTEREST

The author has no conflicts of interest relevant to this article to disclose.

### ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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