Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Viral pulmonary infection in pregnancy – Including COVID-19, SARS, influenza A, and varicella

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A B S T R A C T

The COVID-19 pandemic has been at the forefront of medicine over the last few years. Pregnant women are often exposed to infectious agents that can be harmful not only to the mother but also to the foetus. Moreover, changes during pregnancy means that pregnant women have increased vulnerability to viral infections, especially pulmonary infections. Epidemiological studies have shown a link between maternal viral infections and miscarriage, preterm birth as well as congenital defects. With potential poor outcomes for both women and their newborns, having a good understanding of the presentation and management of these viral pulmonary infections is essential. The increased risk of adverse outcomes has been highlighted during the COVID-19, SARS and H1N1 influenza pandemics.

Physiological and immunological adaptations in pregnancy

Both physiological and immunological changes during pregnancy contribute to the increased risk of infection and poor maternal and perinatal outcomes. Distinguishing between expected adaptations and pathological changes is vital in the management of pulmonary infection in pregnant women.

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Table 1
Normal physiological changes in the respiratory system during pregnancy.

Parameters	Changes
Tidal volume	↑
Functional residual capacity	↓
Expiratory reserve volume	↓
Inspiratory reserve volume	↓ in first trimester ↑ in third trimester
Total lung capacity	↓
FEV_1	↔
FVC	↔
Vital capacity	↔
Minute ventilation	↑

FEV1 Forced expiratory volume, FVC Forced vital capacity

Anatomically, as the foetus develops and grows, the uterus expands, leading to displacement of the diaphragm cranially. Concurrent compensatory increase in the chest diameter allows the vital capacity to remain unchanged. However, there is a 5% reduction in total lung capacity and 20% decrease in functional residual capacity and expiratory reserve volume (Table 1) [1]. There are also cardiovascular changes such as reduced pulmonary vascular resistance. Endocrinologically, rising progesterone levels lead to a 30–50% increase in minute ventilation and raised partial pressure of oxygen, which accommodates the increase in maternal oxygen consumption during pregnancy [1]. Comparatively, raised oestrogen levels can result in oedema and subsequent upper airway obstruction due to the hypersecretion from respiratory epithelial cells [2].

Immunological adaptations also occur, though the exact mechanisms remain unclear. The placenta likely plays a pivotal role as a potent immune-regulatory interface to create a tolerogenic environment [3–5]. However, in the context of viral pulmonary infections, we explore the dynamic changes occurring in the maternal immune system during normal pregnancy [2]. Within the innate immunological system, there is increased complement activity. This is balanced by simultaneously rising levels of regulatory proteins [6]. Maintaining this balance is essential as increased complement activation has been linked to pre-eclampsia and preterm birth [6,7]. While there is a gradual increase in both neutrophils and monocytes from the first trimester onwards, eosinophil and basophil levels remain unchanged. Similarly, in the adaptive immune system, the overall lymphocyte count remains stable. However, there is a shift away from cell-mediated immunity towards humoral immunity [8]. Although both the total number of T-cells and B-cells are reduced, the latter is much more prominent. Pregnancy is largely viewed as an enhanced Th2 and suppressed Th1 states, supported by studies showing a worsening of Th2-mediated autoimmune diseases and an improved Th1 autoimmune conditions. These changes have been linked with rising levels of oestrogen during pregnancy. They indicate a dynamically modulated immune state rather than a broadly suppressed immune system; one which results in differential responses depending on both the microorganisms and stages of the pregnancy [3].

Improving our understanding of these adaptations is essential as pregnancy represents a period of heightened vulnerability not only for the developing foetus but also for the mother. Indirect sepsis, from non-pregnancy-related infections such as influenza, pneumonia and others, has been shown to account for 5% of maternal mortalities between 2017 and 2019 in the UK [9]. Moreover, the knowledge of these changes not only shapes management approaches but also aids in the optimisation of prevention strategies such as vaccination schedules, which have been under the spotlight during the COVID-19 pandemic.

COVID-19 pandemic

The COVID-19 pandemic, first identified in 2019 in Wuhan City, China, is caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Over the last few years, COVID-19 has caused

an unprecedented impact on societies and health systems globally [10]. The COVID-19 pandemic has led to significant changes in healthcare delivery and clinical management of pregnant women and their newborns as we strive to improve our understanding of this disease, respond to fluctuating infection rates, and maintain availability of healthcare resources.

In parallel with the previous influenza pandemics, pregnant women are at greater risk of adverse outcomes. In a large US cohort study, pregnant women were 1.5 times more likely to require intensive care and had 1.7 times greater risk of needing mechanical ventilation in comparison to age-matched non-pregnant women [11]. Factors such as pre-existing maternal co-morbidities, chronic hypertension, diabetes, raised body mass index, advanced maternal age, smoking, and non-Caucasian ethnicities have been found to further contribute to a higher risk of developing adverse outcomes [12]. The risk of maternal complications is greater as the gestation advances [13,14]. Interestingly, pregnant or recently pregnant women were more likely to be asymptomatic than non-pregnant women [12]. Furthermore, reports suggest that vertical transmission of the virus is possible [15,16]. Whilst the figures differ between various studies, maternal COVID-19 may be associated with increased risk of pre-eclampsia, delivery by caesarean section, preterm birth, and stillbirth [17–21]. There was a stronger association with the latter during the period when the Delta (SARS-CoV-2 B.1.617.2) variant was predominant compared to that during the pre-Delta period [22]. The caveat is that not all mothers were tested for infection, and many individuals were asymptomatic. Thus, the true prevalence of adverse outcomes is unknown. Nonetheless, of the approximately 20% of women who required general anaesthesia for caesarean section, two-thirds were necessitated by maternal respiratory compromise. There is limited literature to suggest that maternal COVID-19 has additional adverse effects in neonates apart from those related to prematurity [20–23].

Prevention is the key. The Royal College of Obstetricians and Gynaecology (RCOG) strongly recommends the COVID-19 vaccination in pregnancy. There is good evidence to show high levels of protection provided with two doses of the vaccine [24–26]. This is evident in hospitalisation numbers, with only 0.4% of the 1714 pregnant women admitted between February and September 2021 in the UK having received both vaccine doses. Moreover, none of the 235 pregnant women admitted to the intensive care unit had received two doses of the vaccine [27]. A review of 823 pregnant women admitted with COVID-19 in Scotland reported similar findings [27,28]. There is currently not much evidence regarding the efficacy of the booster vaccine, especially as we continue to encounter more variants. Women should be counselled regarding the efficacy and safety of mRNA vaccines; there have been no safety concerns for pregnant women published to date, and the rate of side effects is similar to that in the non-pregnant population [29–32].

Guidelines are constantly evolving as our understanding of this virus and its impact continues to grow. At the time of writing, the RCOG recommends [14]:

- Vaccination (two doses and booster) with pregnant women being categorised as a priority group.
- Women with a $SpO_2 \geq 94\%$ without desaturation on exertion, respiratory rate $\leq$20 breaths/min, HR $<$ 110 bpm and of low clinical concern can be managed in the community. Otherwise, they require admission to hospital.
- Thromboprophylaxis: Both patients managed in the community and inpatients require a venous thromboembolism (VTE) risk assessment. COVID-19 scores one as current systemic infection on the VTE risk assessment as does immobility and dehydration; if appropriate, women should be started on at least a course of prophylactic low molecular weight heparin according to weight.
- For women who are admitted to hospital:
  - The following investigations should be considered: Bloods (FBC, U&E, LFT, LDH, coagulation, ferritin, troponin, ABG), ECG, ECHO, CT/CTPA, influenza testing and anti-spike (anti-S) SARS-CoV-2 antibodies if required for neutralising monoclonal antibody decisions
  - Sepsis should be considered and managed if necessary
  - Oxygen therapy: saturations should be maintained at >94%
  - Steroids: Women with an oxygen requirement should receive 10 days of corticosteroids: either oral prednisolone 40 mg once daily or IV hydrocortisone 80 mg twice daily if they are not needed

in the planning for preterm birth. If steroids are needed for preterm delivery, two doses of 12 mg of intramuscular dexamethasone 24 h apart are recommended prior to the 10-day course.

- If there is deterioration with increasing oxygen requirements (saturation <93% and/or respiration rate >22 per min):
  - A multidisciplinary approach should be considered.
  - In women with hypoxia (oxygen saturation <92% on air or those requiring oxygen therapy) and CRP >75, tocilizumab or sarilumab are recommended.
  - Neutralising monoclonal antibodies can be considered in women who do not have SARS-CoV-2 antibodies and are either hospitalised with symptomatic infection or with very high-risk factors in the community.

Tocilizumab and sarilumab are interleukin-6 receptor antagonists. They have been shown to improve outcomes, including mortality and the risk of mechanical ventilation, in patients hospitalised with COVID-19 who are either hypoxic (oxygen saturation <92% on air) and/or with systemic inflammation as indicated by a CRP >75 [33,34]. However, whilst previous use of tocilizumab in pregnancy outside the COVID-19 situation has shown no evidence of either teratogenicity or fetotoxicity, there are no data regarding the safety of sarilumab in pregnancy or during breastfeeding [35–37].

Severe acute respiratory syndrome (SARS) epidemic

The 2002–2004 SARS epidemic was one which quietly spread and greatly affected healthcare workers, who accounted for 31% of cases [38]. It was the first of its kind in the 21st century, a readily transmissible and potentially fatal disease that hinted at the potential of a virus spreading along the routes of international air travel. It reportedly affected 8347 individuals with an estimated mortality rate of 10% [39]. In comparison to the H1N1 influenza A and COVID-19 pandemics, there were relatively much fewer documented cases of SARS. Nevertheless, it highlights the susceptibility of pregnant women to viral pulmonary infections and the need for raised awareness and close monitoring.

A review of 12 pregnant women who contracted SARS in Hong Kong during 2002 showed adverse obstetric outcomes such as pregnancy losses in over half of women who presented during their first trimester. Comparatively, 4 out of 5 women who were affected after 24 weeks of gestation had a preterm birth [39]. Other similarly sized studies and case reports have demonstrated an increased risk of admission to the intensive care unit and subsequent intubation and raised mortality rates when compared to non-pregnant women with SARS infection [40–42]. There has been no evidence to suggest vertical transmission of SARS. A study that looked at the placental pathology of seven affected mothers found no abnormalities in that of two mothers who had recovered from the SARS infection in their first trimester [43]. In comparison, they noted areas of avascular chorionic villi in the placentas of two mothers who had been affected in their third trimester, and increased subchorionic and intervillous fibrin in the placenta of three mothers who had an acute SARS infection at the time of delivery [43]. Interestingly, the babies born of the former two affected mothers during the third trimester had foetal thrombotic vasculopathy and intrauterine growth restriction [43].

Whilst the small cohort numbers mean there is a paucity of data regarding treatment approach, a valuable lesson learned from the SARS epidemic was the necessity for robust infection control practices to contain the spread of an airborne virus and effective contact tracing [44].

Influenza A

Of the three types of influenza viruses affecting humans, A and B cause the annual seasonal epidemics, with only the former known to cause pandemics. The clinical course of influenza A in healthy individuals can range from mild self-limiting disease to severe disease requiring hospitalisation. The disease burden of the annual 'flu season' is significant, with approximately >600 million cases globally, of which 3 to 5 million are severe, leading to an estimated 500, 000 deaths [5].

Influenza A can be further categorised based on its hemagglutinin (H) and neuraminidase (N) subtypes. The causative agent of the most recent influenza pandemic in 2009 was the H1N1 influenza A

virus. Historically, data from previous pandemics in 1918 and 1957 show disproportionately high rates of mortality among pregnant women, ranging between 27 and 45% in 1918 and nearly 20% in 1957 [45–47]. The increased vulnerability of pregnant women was again highlighted during the H1N1 pandemic, who accounted for 5% of all influenza-related deaths in a cross-sectional US report [48]. Given that pregnant women amount to 1% of the population, this demonstrates significant risk compared to the general population [49]. Moreover, the likelihood of hospitalisation is increased by 3–7 times across pregnant women at all stages of gestation [50–53]. Women with co-morbidities and those in their third trimester appeared to be at risk of more severe disease, accounting for the greatest proportion of admissions to the intensive care unit in comparison to the remaining pregnant cohort [48,54]. The increased risk of complications has also been demonstrated during the interpandemic periods [51,55]. Adverse pregnancy outcomes, namely pregnancy loss and preterm birth were found to be associated with pneumonia secondary to influenza infection [45,56,57]. Moreover, whilst transplacental transmission of influenza is rare, some animal studies suggest that effects such as malformations especially in the central nervous system and craniofacial development and behavioural changes may be secondary to the maternal inflammatory response and hyperthermia [58,59]. This may account for the association with long-term effects such as schizophrenia, Parkinson disease and childhood leukaemia [60–62].

Studies in the US and UK demonstrated that pregnant women diagnosed with H1N1 influenza virus in 2009 who received antiviral treatment within two days of symptom onset compared to after more than four days were less likely to require admission to the intensive care unit and had reduced mortality rates [48,63].

Accordingly, zanamivir (Relenza) or, in severe cases, oseltamivir (Tamiflu) were recommended for any pregnant woman affected by the H1N1 influenza A virus in 2009, in order to shorten the clinical course of the infection and reduce the risk of complications [5]. Considering the potential maternal and foetal effects of influenza A infection during pregnancy, the World Health Organization and UK Health Security Agency (UKSHA) revised their recommendations; pregnant women are now classed as high risk and prioritised for the influenza vaccine.

Varicella

Varicella (chickenpox) is a common childhood infection, which subsequently lends immunity to adults later in life. It is estimated to affect 3 in every 1000 pregnancies [64]. Whilst relatively harmless in children, infection in adulthood, and even more so in pregnancy, is linked with raised mortality and morbidity [65]. In fact, prior to the availability of the vaccine, pregnant women accounted for over a quarter of adult cases [66]. Compared to 5–15% in the general population, approximately 10% of pregnant women with varicella develop pneumonia, and the mortality rate has been reported to be just below 50% compared to 11% in the non-pregnant population [67].

Infection carries not only significant maternal consequences but also foetal and neonatal sequala in the form of congenital varicella syndrome (CVS). The incidence of CVS varies depending on gestation with an estimated rate of 0.55% and 1.4% in the first and second trimester, respectively [68]. The latest associated gestation has been at 28 weeks [69–71]. Infection in the latter stages of pregnancy can lead to neonatal varicella. Thus, establishing the mother's immunity status is essential if she has been exposed to chickenpox or shingles. Non-immune mothers who come into contact with an infected individual are advised to seek medical advice [64]:

- Women should be asked about previous chickenpox and shingles infection as part of their antenatal booking appointment.
- If there is an uncertain or no history of previous infection, serum testing (from the booking sample if available) should ideally be carried out.
- However, if the results are not available within 96 h of exposure or the results show lack of immunity, and it is less than 10 days since contact or the appearance of the rash in the index case, varicella zoster immunoglobulin (VZIG) should be administered.

- If the onset of symptoms is between 5 days preceding delivery and 2 days post-partum, the neonate should also receive VZIG.
- For women who develop chickenpox despite VZIG or present within the first 24 h of the appearance of a rash, acyclovir should be considered in those $<20^{+0}$ weeks of gestation but prescribed in those $\geq 20^{+0}$ weeks of gestation.
- Those affected by severe pneumonia or who are at high risk of complications should be referred to hospital and treatment with IV acyclovir should be commenced.
- Varicella vaccination is recommended as part of the pre-pregnancy and postpartum care in women who are found to be seronegative for VZV IgG.

Conclusion

Pregnancy accounts for a period of increased susceptibility to adverse outcomes secondary to viral pulmonary infections. These are likely attributed to the various adaptations that the body undergoes to accommodate the pregnant state. Whilst pandemics serve to remind us of pregnant women belonging to the high-risk group, it is essential to consider this status in interpandemic periods, especially when it comes to managing seasonal or background infections.

Practice points

- Several anatomical, physiological and immunological changes occur in pregnancy.
- Adaptations during pregnancy increase the vulnerability of women to viral infections and their complications.
- Therefore, prevention and early recognition and initiation of management are essential.

Research agenda

- Further research studies should investigate the specific contribution of immunological changes during pregnancy to increased viral infection susceptibility.
- As pregnant women are considered to be high-risk individuals but often excluded from trials, a strong evidence base for interventions such as vaccinations should be developed.

Declaration of competing interest

The authors have no conflicts of interest.

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