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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COVID-19 in Women's health: Epidemiology

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A B S T R A C T

The disease COVID-19 emerged in late 2019 in Wuhan, China, and rapidly spread, causing a pandemic that is ongoing and has resulted in more than two million deaths worldwide. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which spreads effectively by direct contact with an infected person or contaminated surface, droplet or aerosol transmission. Vertical transmission, if it does occur, is rare. Among women of childbearing age, most will have mild or asymptomatic infection; severe illness is uncommon. Severe illness is more common in the later stages of pregnancy, when it is associated with complications, including intensive care admission, maternal death and an increased risk of iatrogenic preterm birth. Women who are older, from minority ethnic groups, who are overweight or obese, who have comorbidities or who live with socioeconomic deprivation are more likely to experience severe illness than women without these characteristics.

Introduction

In December 2019, a novel coronavirus emerged in Wuhan, China. The virus rapidly spread in China, and then internationally, and was declared a pandemic by the World Health Organisation in March 2020. At the time of writing, this pandemic is ongoing. The virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes the disease named coronavirus disease 2019 (COVID-19) in a proportion of those infected.

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This article describes the epidemiology of SARS-CoV-2: the virus, its transmission, transmission in different settings, measures to mitigate transmission, including vaccination and its effect on women, pregnant women and newborn infants.

The COVID-19 pandemic

Background to the pandemic

The 20th and early 21st century saw the emergence of a number of respiratory viruses that caused epidemics and pandemics, the most serious of which was the 'Spanish' influenza pandemic in 1918–2020 which resulted in an estimated 50 million fatalities worldwide [1]. There was, prior to the emergence of SARS-CoV-2, broad expectation of a similar pandemic in the near future [2,3].

Coronaviruses

Coronaviruses are enveloped viruses with a single-strand RNA genome, which cause respiratory and intestinal infection in humans, other mammals and birds. When observed using an electron microscope, spike projections from the virus membrane appear like a crown, giving the name *coronavirus* from the Latin 'corona' [4,5].

Seven coronaviruses are known to infect humans. Of these, four are responsible for the 'common cold' upper respiratory tract illness, which is usually mild and self-limiting, but can cause severe illness in the very young, the very old and the immunosuppressed; these were first described in the 1960s. In the first 19 years of the 21st century, two new coronaviruses emerged in humans: SARS-CoV in 2002–2003 in Guangdong province, China [6,7] and Middle East respiratory syndrome coronavirus (MERS-CoV) in the Middle East in 2012 [8]. These coronaviruses likely originated in bats and were transmitted to humans through civets in wet markets and dromedary camels, respectively [5]. Both led to limited epidemics of severe illness with a high level of deaths: SARS-CoV to 26 countries, with more than 8000 reported cases and 774 deaths, while MERS-CoV was mostly confined to the Middle East with 2494 cases and 858 deaths [9].

Emergence and spread of COVID-19

The initial outbreak of COVID-19 consisted of a cluster of patients with viral pneumonia in Wuhan, Hubei Province, China at the end of 2019. It is likely that the virus originated in bats [10]. It is unknown when SARS-CoV-2 first was transmitted to humans, and whether there was an intermediate vector.

The number of new infections generated per day by each infected person, in a population where everyone is vulnerable to be infected and controls on transmission are not in place (R*t*) has been estimated at between 2 and 4 [11–13]. A symptomatic individual with mild–moderate disease is likely to be infectious for 24–48 h prior to symptom onset. At 10 days following the onset of symptoms, 94% of individuals are no longer infectious [14].

The spread of COVID-19 has been tracked using genomic surveillance [15,16]. When SARS-CoV-2 spreads from person to person, the virus accumulates small mutations, due to copying errors, merging of two different strains infecting the same host, or the host's immune response [17]. Together, these mutations create genomic 'fingerprints', which have been shared within the scientific community in an unprecedented manner [18]. This has allowed confident reporting of the origin of local and national outbreaks, and an understanding of international spread [19,20]. Cases of COVID-19 have now been reported in every continent except Antarctica, with over 115 million cases and over 2.5 million deaths as of March 6, 2021 [21].

Mutations and variants of SARS-CoV-2

SARS-CoV-2 is an RNA virus which is still in the process of adaptation to a human host; mutations affecting the transmission rate and clinical characteristics are expected [17]. While RNA viruses

replicate more than DNA viruses, coronaviruses mutate less frequently than other RNA viruses as they encode a correcting enzyme, which modifies some of the errors which occur during viral replication [22].

At the time of writing, new variants of SARS-CoV-2 which are considered to be potentially more transmissible have emerged in the UK, South Africa and Brazil. These variants include a mutation to the receptor binding domain, which means they bind more easily to the human receptor (ACE2) for SARS-CoV-2. This may make them more transmissible. The UK variant is estimated to be 56% more transmissible (95% CI: 50%–74%) than the previous dominant variants [23].

Transmission

Methods of transmission from person to person

Transmission of respiratory viruses occurs through three routes: (1) droplet transmission of respiratory secretions of an infected person, who is in close (considered by international authorities to be one or 2 m) or direct contact, (2) direct contact with a contaminated surface and (3) airborne transmission of smaller particles or droplets, suspended in air, which last longer and transmit further than droplets [24].

For SARS-CoV-2, there has been ongoing debate about the relative importance of these three routes of transmission. Droplet transmission, through close or direct contact with an infected person, is considered to be the primary route of transmission [16,24,25]. Early in the pandemic, spread from contaminated surfaces or objects (fomites) was considered potentially significant; recent evidence suggests that this contributes less to transmission than initially thought [26]. There is an accumulation of evidence that airborne transmission over longer distances, particularly in indoor spaces, is also important in the spread of SARS-COV-2 [27–29].

Vertical transmission

There is at present insufficient evidence to confirm that vertical (mother to child, either in utero or peripartum) transmission of SARS-CoV-2 occurs [30].

Shah et al. [31] proposed a set of criteria for determining whether an infection with SARS-CoV-2 could be considered congenital:

(1) the mother has a positive polymerase chain reaction (PCR) test for SARS-CoV-2 either prenatally or within 2–3 weeks of birth;
AND
(2) the baby
   a. Has a positive PCR test within 12 h of birth;
OR
   b. Is symptomatic of SARS-CoV-2 infection and there is evidence of SARS-COV-2 infection (by PCR test) in one of umbilical cord blood or amniotic fluid prior to rupture of membranes.

There have been case reports and small case series where these criteria are met in different settings around the world [32–35]. These are considered to represent possible cases of vertical transmission.

If it occurs, vertical transmission is rare. In a surveillance study that identified 66 babies infected with SARS-CoV-2 in the first wave of infection in the UK, only two (3%) of infections were considered to have possibly occurred vertically [32]. The likelihood of transmission appears not to be affected by mode of birth, method of feeding or whether the woman and baby are cared for together [36].

Methods to control transmission

Methods to control transmission are focussed on (1) reducing the number of contacts between individuals; (2) where contact occurs, reducing the likelihood of it resulting in infection and (3)

identifying infected persons and isolating them from contact with others [13,37,38]. Social distancing, hand washing and the use of masks and of other personal protective equipment (PPE), such as eye protection, gloves and gowns have been shown to reduce transmission [39,40]. Large-scale societal interventions, such as the lockdowns imposed in many countries around the world, have been demonstrated to be necessary to control local epidemics [13].

Transmission in different settings

Transmission of SARS-CoV-2 occurs most often in poorly ventilated, enclosed spaces where people have frequent close contact with others.

The likelihood of transmission in a particular setting is estimated as the secondary attack rate, defined as the probability of a new infection occurring in a group of close contacts of an infected person. The highest rate of secondary infection occurs in household contacts: systematic reviews suggest that the secondary attack rate within households is 16–22% [41–43]. There is also an important role for 'superspreader' events, where a large number of people are infected by a single or several infected individuals. These typically occur at events where there is a large amount of social contact: important examples include weddings, bars and sporting events [44].

Considerations in healthcare

Within healthcare settings, implementation of many of the elements of transmission reduction is challenging if not impossible. Care of patients and others accessing care necessarily involves a high number of contacts between individuals, many of which cannot comply with social distancing guidelines. While the estimated secondary attack rate within healthcare settings is 0.7%–3.5% in systematic reviews [42,43], there is substantial heterogeneity between study estimates. The authors of one review noted that the studies available came from high and middle income countries, where PPE is likely to be readily available; in settings where this is not available, the transmission level is likely to be higher [43].

Vaccination

Vaccines for SARS-CoV-2 offer the most likely method of limiting transmission and thus ending the pandemic. As of March 2021, 13 COVID-19 vaccines are currently approved for use in any country [45]. These can be split into vaccines that contain only part of the virus (the 'spike protein' subunit) attached to a vector; and those which contain the whole, inactivated virus.

Vectored vaccines include those developed by Pfizer/BioNTech, Moderna and AstraZeneca. Some of these, including those developed by Pfizer and Moderna, contain messenger RNA which encodes the SARS-CoV-2 spike protein antigen [46,47]. This is delivered into host cells which then express the spike protein, stimulating the production of a neutralising antibody and cellular immune response. Others, such as that developed by AstraZeneca, use viral vectors to encode the SARS-CoV-2 spike protein antigen [48]. These proteins are then expressed by the vector, stimulating a similar immune response.

Vaccines containing inactivated virus include the Chinese Sinopharm [49].

Although the vaccines licenced by EU and American bodies have passed assessments of reproductive toxicity using animal models, which look at both the fertility of the animals after exposure and teratogenicity during pregnancy, at the time of writing, there exists no human trial data about the safety of using these vaccines in pregnancy [50].

Effects of SARS-CoV-2 infection

The median incubation period of SARS-CoV-2 infection is estimated as 5.1 (95% CI 4.5–5.8) days, with the 95% upper percentile estimated as 11.7 (95% CI 9.7–14.2) days [51,52].

A significant proportion of individuals infected with SARS-CoV-2 will have no symptoms. A systematic review estimated the proportion of infected individuals who remain asymptomatic throughout their infection to be 20% (95% CI: 17–25%).

The presentation of COVID-19 is heterogeneous, with a broad range of symptoms. Predominant symptoms are cough, sore throat, fever, myalgia or arthralgia, fatigue, headache and anosmia or ageusia (loss of senses of smell or taste, respectively). However, symptoms can also include nasal congestion, rash and gastrointestinal effects, such as anorexia, nausea and vomiting, and diarrhoea [53–55].

Effect on all women

A large study in the UK population estimated that men were substantially more likely to die from COVID-19 than women (HR 1.59, 95% CI 1.53 to 1.65) [56]. Severe symptoms, suggesting pneumonia and marked hypoxia, are more common in older people, the immunosuppressed and those with chronic conditions, such as diabetes, cancer or chronic lung disease [56]. Severe illness, such as that requiring intensive care unit (ICU) admission, is relatively uncommon in women of reproductive age [57].

While for many, the symptoms of COVID-19 improve quickly, it is evident that a substantial proportion of sufferers have prolonged symptoms ('long' or 'post acute' COVID-19) [58,59]. In one survey, a quarter of those age 18–34 and nearly half of those age 50 or over were still experiencing symptoms two weeks following infection [59].

Effect on pregnant women

Pregnant women do not appear more likely to contract the infection than the general population. Similar to the general population, most pregnant women who are infected with SARS-CoV-2 will remain asymptomatic or experience only mild or moderate cold/flu-like symptoms. The PregCOV-19 Living Systematic Review is a programme to synthesise evidence on COVID-19 in pregnancy [30]. This review, which contained information on more than 11,000 women, found that the most common symptoms of COVID-19 in pregnant women were fever (40%) and cough (39%). Less frequent symptoms were dyspnoea, myalgia, ageusia and diarrhoea, each present in more than 10% of women. In a small number of studies reporting universal screening, 74% (95% CI 51–93) of women were asymptomatic at the time of testing [30].

Pregnant women in the late stages of pregnancy appear to be more likely to experience severe morbidity. A UK registry study found that most women admitted to hospital with severe symptoms of COVID-19 in the first wave in the UK were in the late second or third trimester [60]. An analysis of women in French hospitals showed that those in the second half of pregnancy, from 20 weeks of gestation, were five times more likely to be admitted to ICU than those in the first half of pregnancy [61]. A large study from the USA, which included 406,446 women hospitalised for childbirth, of whom 6380 (1.6%) had COVID-19 (identified using hospital coding), found that women who gave birth with COVID-19 were at a substantially increased risk of ICU admission (3.3% of women), mechanical ventilation (1.3%) and death (0.1%) than those without COVID-19 [62].

For women who are seriously unwell, there is a substantially increased risk of iatrogenic preterm birth: a large study which included global cohorts estimated a preterm birth rate among infected women of 16.2% [63]. The UK Obstetric Surveillance system found that women admitted to hospital with symptomatic SARS-CoV-2 infection were 11 times (aOR 11.43, 95% CI 5.07–25.75) more likely to have an iatrogenic preterm birth [64].

For pregnant women at earlier gestations, there is little conclusive evidence of increased risk. In some populations and studies, it has been concluded that all pregnant women are at increased risk; however, these studies do not stratify by gestation [65–67]. Some reassurance can be obtained for women in early pregnancy by noting the very small numbers of pregnant women at earlier gestations included in registry studies, and the increased risk being restricted to women at later gestations where gestation is recorded [60,63].

Effect on babies in the neonatal period

The course of infection in neonates is mild [32,68–70]. A UK registry study demonstrated that of 66 infected babies, 28 (42%) had severe COVID-19 disease, defined as babies who had an abnormal x ray in

the context of both clinical and biochemical signs of infection, and a positive PCR test for SARS-CoV-2. Of these 66 babies, one (2%) died of a cause unrelated to COVID-19, and 88% were discharged home at the time of follow-up [32].

Risk factors for severe SARS-CoV-2 infection

The COVID-19 pandemic has further exposed marked inequalities in healthcare outcomes between individuals from less affluent socioeconomic groups and from non-White ethnic groups. Risk factors that appear to be associated with the likelihood of severe illness are as follows:

- Being from a Black, Asian and minority ethnic (BAME) background
- Being overweight (body mass index (BMI) 25–29 kg/m^2) or obese (BMI 30 kg/m^2 or more)
- Comorbidity, including pre-existing diabetes and chronic hypertension
- Increased age, including for pregnant women aged 35 years or older
- Living in areas or households of increased socioeconomic deprivation [56,60].

In addition to these, the risk of becoming infected with COVID-19 is greater in individuals who are more exposed by working in healthcare or other public-facing occupations [71].

The estimates of association with these risk factors are summarised in Table 1, based on a large systematic review which did not estimate risks associated with the ethnic group [30]. In the UK, a registry study found that compared with a historical cohort of women without SARS-CoV-2 infection, women hospitalised with COVID 19 were more likely to be from BAME groups, even after adjusting for age, comorbidity and BMI (adjusted odds ratio [adjOR] compared with White women: for Black women, 6.24, 95% CI 3.93–9.90; Asian, 4.36, 95% CI 3.19–5.95 and other, 12.95, 95% CI 4.93–34.01) [64].

Ethnic and socioeconomic inequalities

Ethnic and socioeconomic inequalities have been observed across the world in rates of severe illness and death due to COVID-19 [56,72].

Even after controlling for age, comorbidities, sex and deprivation, an analysis of linked UK mortality and primary care records found a significant difference in mortality rates among those from BAME groups (compared with White, Black ethnicity: adjusted hazard ratio (adjHR) 1.71, 95% CI 1.44, 2.02; Asian ethnicity: adjHR 1.62, 95% CI 1.43, 1.82; mixed ethnicity: adjHR 1.64, 95% CI 1.19, 2.26). The same study found a linear relationship between increasing deprivation and risk of death: those in most deprived quintile had a hazard ratio of death of 1.79 (95% CI 1.68, 1.91) compared with the least deprived, following adjustment for age, comorbidities, sex and ethnicity [56]. Individuals from BAME groups comprise 13% of the UK population, but in the first wave of infections accounted for 34% of all ICU admissions [57]. These findings concur with those for pregnant women in registry cohorts [60,64].

In the USA, a systematic review found that African American/Black and Hispanic individuals had higher rates of SARS-CoV-2 infection, hospitalization and death than non-Hispanic White individuals; individuals from Asian groups had similar outcomes to non-Hispanic Whites [72].

Table 1
Estimates of association between risk factors and severe COVID-19 illness in pregnancy, from PregCOV-19 Living Systematic Review [30].

Risk factor	Associated odds ratio of severe COVID-19 illness in pregnancy (95% CI)
Maternal age 35 years and older	1.78 (1.25–2.55)
BMI 30 kg/m^2 and above	2.38 (1.67–3.39)
Chronic hypertension	2.00 (1.14–3.48)
Pre-existing diabetes	2.51 (1.31–4.80)

BMI = Body Mass Index.

Summary

The ongoing COVID-19 pandemic initially emerged in China and since the end of 2019 has spread rapidly globally. COVID-19 is caused by the SARS-CoV-2 virus, which spreads effectively by direct contact with an infected person or contaminated surface, droplet or aerosol transmission. Vertical transmission, if it does occur, is rare. Transmission may be mitigated through protective equipment, isolation and social restrictions, but vaccination offers an important route to reduce infection and ultimately end the pandemic.

Women of childbearing age typically have mild symptoms of COVID-19 and may have asymptomatic infection, with severe illness being uncommon. Pregnant women in the later stages of pregnancy are more likely to experience severe illness including ICU admission; there is no evidence that this also applies to women prior to 20- week gestation. For babies in the neonatal period, the course of infection is mild. Women who are older, from minority ethnic groups, who are overweight or obese, who have comorbidities, or who live with socioeconomic deprivation are more likely to experience severe illness than women without these characteristics.

Practice points

- Clinicians should be aware that pregnant women who are older, from minority ethnic groups, who are overweight or obese, who have comorbidities or who live with socioeconomic deprivation are more likely to experience severe illness than women without these characteristics.
- Pregnant women in the later stages of pregnancy seem to be at higher risk of experiencing severe disease than those at earlier gestations.
- Maternal infection with coronavirus disease 2019 (COVID-19) alone is not an indication for caesarean birth, formula feeding or separation of woman and baby, as the likelihood of transmission appears not to be affected by mode of birth, method of feeding or whether the woman and baby are cared for together.

Research agenda

Important areas for focus for future research include:

- The safety and efficacy of vaccination against coronavirus disease 2019 (COVID-19) in pregnant women
- Persistence of symptoms in pregnant women
- Care for pregnant women with long or sub-acute COVID-19

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