

Review Article

Pandemics and maternal health: the indirect effects of COVID-19

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Summary

Infectious diseases can directly affect women and men differently. During the COVID-19 pandemic, higher case fatality rates have been observed in men in most countries. There is growing evidence, however, that while organisational changes to healthcare delivery have occurred to protect those vulnerable to the virus (staff and patients), these may lead to indirect, potentially harmful consequences, particularly to vulnerable groups including pregnant women. These encompass reduced access to antenatal and postnatal care, with a lack of in-person clinics impacting the ability to screen for physical, psychological and social issues such as elevated blood pressure, mental health issues and sex-based violence. Indirect consequences also encompass a lack of equity when considering the inclusion of pregnant women in COVID-19 research and their absence from vaccine trials, leading to a lack of safety data for breastfeeding and pregnant women. The risk-benefit analysis of these changes to healthcare delivery remains to be fully evaluated, but the battle against COVID-19 cannot come at the expense of losing existing quality standards in other areas of healthcare, especially for maternal health.

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"When you are thinking about a pandemic, you have to differentiate between what comes from being infected and what comes from being affected"

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Introduction

Infectious diseases can directly affect women and men differently, as has been demonstrated by the COVID-19 pandemic [1]. A wealth of data has confirmed a male bias in mortality associated with COVID-19 [2]. Higher case fatality rates in men have been seen in most parts of the world, with notable exceptions including India, Nepal, Vietnam and Slovenia, where higher fatality rates have been observed in women [3, 4]. The reasons behind the male preponderance in mortality are not clearly established. Relevant factors may

include biological aspects, such as stronger immune responses in women and behavioural patterns, for example, smoking, placing men at a greater risk for health complications and death due to COVID-19 [2, 5]. Previous pandemics have had greater morbidity or mortality for women (2009 H1N1 pandemic and the avian influenza (H5N1) pandemic, respectively). In contrast, the 1918 H1N1 pandemic was characterised by higher mortality rates in young adult men.

With any pandemic, the indirect as well as direct health effects need to be evaluated. There is growing evidence that the COVID-19 pandemic's indirect effects have had a more significant adverse impact on women's health. A United Nation Policy Brief commented that *"the pandemic is deepening pre-existing inequalities, exposing vulnerabilities in social, political and economic systems which are in turn amplifying the impacts of the*

pandemic. . .with women being disproportionately affected" [6]. During a pandemic, healthcare services and resources shift to focus on managing patients suffering from the acute effects of infection. Healthcare delivery has necessarily transformed with various strategies, including moving from face-to-face to mostly virtual consultations and new working patterns to cope with staff shortages. While some of the strategies will have the necessary benefit of protecting those vulnerable to the virus (both staff and patients), there may be indirect, potentially harmful consequences, particularly to vulnerable groups. The risk-benefit analysis of these healthcare strategies and transformations remains to be fully evaluated, but the battle against COVID-19 cannot come at the expense of losing existing quality standards in other aspects of healthcare.

Effect of COVID-19 on maternal healthcare

There were concerns at the start of the pandemic that the clinical outcomes for pregnant women with COVID-19 would be worse than the non-pregnant population. Evidence from previous similar viral outbreaks including influenza A/H1N1, severe acute respiratory syndrome and Middle East respiratory syndrome, suggested that pregnant women were at greater risk of severe maternal and neonatal morbidity and mortality, with the risk of critical illness likely being most significant in the third trimester of pregnancy [7–9]. However, evidence to date suggests that the maternal outcomes of pregnant women admitted to hospital with SARS-CoV-2 infection are no worse than the non-obstetric population with the transmission of SARS-CoV-2 to infants being uncommon [10, 11]. The risk of iatrogenic preterm birth and caesarean section was increased and data from case series and meta-analyses have identified a higher proportion of infected women from Black, Asian or minority ethnic groups that needs to be investigated and explained.

The effects of an infectious outbreak on maternal health may have wider consequences than the direct effects of individual infection. Following the onset of the Ebola epidemic in Sierra Leone, there was a decrease in the number of women attending for antenatal and postnatal care and birth at a healthcare facility, with a corresponding 34% increase in the facility-based maternal mortality ratio and a 24% increase in the stillbirth rate [12]. Accepting the obvious income disparities between Sierra Leone and other parts of the world, this does highlight the potential harm associated with indirect effects.

Statistical modelling can help to inform healthcare policy decisions during a pandemic. The Lives Saved Tool developed by the Johns Hopkins Bloomberg School of

Public Health is modelling software used since 2003 to estimate the impact of scaling up health interventions (e.g. expanding or replicating innovative pilot or small-scale projects to reach more people or broadening the effectiveness of an intervention) [13, 14]. It has evolved to be used to understand and define the causes of measured or observed declines in mortality in relation to specific activities. Robertson et al. used the Lives Saved Tool to investigate the potential indirect effects of the COVID-19 pandemic on maternal mortality in low- and middle-income countries by measuring the additional indirect maternal deaths that could be attributed to COVID-19 pandemic response strategies [15]. The authors modelled three possible scenarios of reducing the coverage of essential maternal and child health services in 118 low- and middle-income countries. The scenarios ranged from least severe (presumed small reductions in the availability of health workers and supplies due to the reallocation of resources to the pandemic response) to most severe (disruptions in the health system, presumed governmental restrictions on movement, forcing families and non-essential workers to stay at home possibly limiting access to routine antenatal care). They estimated additional deaths for a single month and then extrapolated this figure for 6 and 12 months. The least severe scenario (healthcare coverage reductions of 9.8–18.5% over 6 months), would result in 12,200 additional maternal deaths over 6 months (or 24,400 in 12 months). The most severe scenario (healthcare coverage reductions of 39.3–51.9% over 6 months), would result in an additional 56,700 maternal deaths over 6 months (or 113,400 in 12 months). These additional deaths would represent an increase of 8.3–38.6% maternal deaths per month, across the 118 countries. These are stark figures, but alongside the numerical estimates of excess indirect mortality, the authors estimated the reduced coverage of four major obstetric interventions (parenteral administration of uterotonics, antibiotics, anticonvulsants and clean birth environments) accounted for approximately 60% of additional maternal deaths. This information can be used to support more effective targeting of resources.

The COVID-19 pandemic has challenged healthcare systems worldwide. Adaptations to the challenges of COVID-19 have included the extensive reorganisation of the delivery of maternity care. In the UK, the NHS' clinical guide for anaesthesia service reorganisation during the coronavirus pandemic has highlighted obstetrics as an area that cannot decrease clinical activity. Despite this, a survey conducted to explore maternity services' modifications across the UK in response to COVID-19, found substantial and heterogeneous maternity service modifications [16].

These primarily affected antenatal and postnatal services, but also some intrapartum services. In total, 70% of respondents reported a reduction in antenatal appointments and 56% reported a reduction in postnatal appointments, with 89% using remote consultation methods. There were significant changes in specialist maternity care services with widespread uptake of home blood pressure monitoring (79%), but this was almost always for women with an established hypertensive disorder. Few units undertook home blood pressure monitoring for women at higher risk of a hypertensive disorder and no unit reported that this monitoring was undertaken as part of routine antenatal care. A reduction in emergency antenatal presentations was experienced by 86% of units. It is too early for the impact of these changes on maternal outcomes to be evident. Some reassurance can be taken from an analysis of Hospital Episode Statistics examining the stillbirth rate in England during the pandemic's first wave [17]. There was no evidence of an increase in stillbirths regionally or nationally during the first wave of COVID-19 compared with the same months in 2019, despite variable community SARS-CoV-2 incidence rates in different regions. The authors highlight that these are early data and that it will be essential to continue to monitor pregnancy outcomes in the future. However, countries including India and Nepal have reported an increase in stillbirth rates during the pandemic [18, 19]. It has been postulated that this may have resulted from indirect effects such as maternal reluctance to attend hospital when needed, for example, with reduced fetal movements, for fear of contracting infection. Public information campaigns have an essential role in addressing womens' concerns and reassuring them that it is safe to come to the hospital for emergency obstetric care [18].

Anaesthetic practice in maternity care during the COVID-19 pandemic

With the deployment of anaesthetic staff to support critical care services, there were concerns that the anaesthetic service to labour wards may be compromised, for example, reduced availability of labour epidural analgesia. The Obstetric Anaesthetists' Association surveyed consultant service leads for obstetric anaesthesia. The survey comprised questions about the size and location of the participants' hospitals and details regarding labour epidural availability since the start of the COVID-19 crisis [20]. The majority of units (92%) reported no restriction in access to labour epidural analgesia during the COVID-19 crisis: six units (3%) reported a restriction in access to labour epidural analgesia; three stated it was due to anaesthetist availability;

two stated that it was due to personal protective equipment availability; one stated it was due to delivery unit management; and one attributed it to equipment/drug availability issues [20]. The availability of a labour epidural service plays an essential part in safety in maternity units, enabling the opportunity for rapid anaesthesia for intrapartum caesarean section and reducing the need for general anaesthesia. This is particularly relevant with COVID-19, as general anaesthesia and intubation are regarded as aerosol-generating procedures and potentially increase infection risk to healthcare workers. Bhatia et al. analysed anaesthetic information for 2480 caesarean sections across six maternity units from April to July 2020 (during the first wave of the pandemic in the UK) [21]. They compared it with data from 2555 caesarean sections performed at the same hospitals over a similar period in 2019. During this period, the overall caesarean section rate increased (28.3 to 29.7%). During the same period, the authors found significant reduction in general anaesthetic rates across the six hospitals (7.7 to 3.7%, $p < 0.0001$). They also found that the conversion rates of neuraxial (spinal and epidural) anaesthesia to general anaesthesia were reduced (1.7 to 0.8%, $p = 0.012$), with the most significant reduction seen in category 1 (immediate threat to maternal or fetal life) caesarean sections. The authors attributed these changes to anaesthetic decision-making, the use of recommendations from national anaesthetic guidelines and on-site consultant anaesthetist support. This latter point was perceived as a particularly important factor, with on-site out-of-hours consultant anaesthetist support systems established in 80% of the hospitals analysed. The main 'advantage' of general anaesthesia over neuraxial anaesthesia for caesarean section is that of reliable speed, which is of particular relevance in the context of the urgency of the category 1 caesarean section. The results and implications of this study, therefore, need to be interpreted with some caution until neonatal outcome data have been studied, as any reduction in general anaesthesia rates can only be viewed as successful if it does not come at the cost of increased neonatal morbidity and mortality [22].

Pandemic research and vaccination in pregnant women

While there is consensus on the need to include pregnant and breastfeeding women in research, they are frequently not included in clinical trials, particularly those with pharmacological interventions [23]. Investigators may not include pregnant women in trials for various reasons, including concerns about potential harm to the woman or developing fetus, the altered pharmacokinetics associated

with pregnancy and the possibility of heterogeneity related to hormonal cycles that might impact the intervention being studied. One of the ethical principles of research is 'equity', founded on the ethical principle of justice as a basis for study participant selection, in that "*particular individuals, groups or communities should neither bear an unfair share of the direct burdens of participating in research nor should they be unfairly excluded from the potential benefits of research participation*" [24]. It is, therefore, potentially unethical not to include pregnant women. The paradox of wanting to protect pregnant women while simultaneously not including them in clinical research prevents the development of evidence about the safety of drugs in pregnancy and therapeutic options available to pregnant women [25]. Despite international initiatives to address this longstanding problem including recommendations from the Task Force on Research Specific to Pregnant Women and Lactating Women, aimed at changing the social-cultural barriers around the inclusion of pregnant women in research, practical strategies to promote progress in this area remain limited [26].

The COVID-19 pandemic has highlighted the inequity of trial inclusion for pregnant women. A review of international trial registries identified 927 COVID-19 studies [27]. Of these, the majority (52%) explicitly excluded pregnancy, 46% did not mention pregnancy and only 16 (1.7%) were pregnancy-specific. Of the trials which included pregnant women, only three were randomised controlled drug trials. A notable success of a COVID-19 drug trial that has effectively and actively included pregnant women is the randomised evaluation of COVID-19 therapy (RECOVERY) trial [28]. Existing data already supported the use of some treatment arms of the trial in pregnancy; from its role in HIV treatment lopinavir-ritonavir has already been established as safe in pregnancy and similarly with hydroxychloroquine, which is used to treat lupus during pregnancy. Additionally, one arm of the study was modified for pregnant women, so that the adverse fetal effects reported with multiple dexamethasone courses could be avoided. Prednisolone or hydrocortisone (agents which have low placental transfer) were used in place of dexamethasone. This trial has effectively demonstrated how projects can be modified to include pregnant women and should serve as a template for other projects.

The advent of an effective vaccine against COVID-19 has been recognised as a significant step towards bringing the pandemic to an end [29]. Pregnant women have not been included in all COVID-19 vaccine trials, but the question of whether to offer pregnant or breastfeeding women the vaccine is essential. Globally, 70% of health

workers and first responders are women, many of whom may be pregnant or planning a pregnancy when COVID-19 vaccines become widely available (www.unwomen.org/en/digital-library/publications/2020/09/gender-equality-in-the-wake-of-covid-19). In the USA, the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine have all recommended that COVID-19 vaccines should not be withheld from women who are pregnant or lactating and want to be vaccinated, despite a lack of safety data in these populations [30–32]. The Centers for Disease Control and Prevention also advises that women do not need to avoid pregnancy after receiving the Pfizer-BioNTech COVID-19 vaccine. The three organisations acknowledge the lack of safety data and highlight that mRNA vaccines are not live vaccines and are unlikely to pose a risk for pregnant women. The Society for Maternal-Fetal Medicine recommends that pregnant and lactating women have access to COVID-19 vaccines in general and have advocated for the inclusion of pregnant or lactating women in vaccine trials. They emphasise the role of consent, "*pregnant individuals should be given the opportunity, along with their obstetric provider, to weigh the potential risk of severe maternal disease against the unknown risk of fetal exposure and make an autonomous decision about whether or not to accept vaccine until pregnancy safety data are available*". In the UK, the Joint Committee on Vaccination and Immunisation has advised that whilst the available data do not indicate any safety concerns about the use of COVID-19 vaccines during pregnancy, there is insufficient evidence to recommend routine COVID-19 vaccination during pregnancy; however, the option for vaccination should be considered for pregnant women categorised as being clinically extremely vulnerable or who are frontline health or social care workers [33]. The Joint Committee on Vaccination and Immunisation has also advised that breastfeeding women should be offered vaccination if otherwise eligible, for example, a frontline healthcare worker. Since the advent of vaccination programmes for COVID-19 at the end of 2020, there has been increased concern about equitable access to adequate supplies of the available vaccines for low- and middle-income countries. Despite efforts to co-ordinate global access to vaccines through the COVAX Facility, a global collaboration bringing together governments, global health organisations, manufacturers, scientists and other relevant parties, there is some evidence that vaccine supply for low- and middle-income countries might lag behind that of high-income countries [34, 35]. The ultimate success of vaccines in bringing an end to the pandemic will

rely upon the commitment of high-income countries sharing in an equitable distribution of COVID-19 vaccines across the world [34].

Mental health, violence against women and social deprivation

Mental health conditions are the leading cause of pregnancy-associated deaths between 6 weeks and a year after giving birth in the UK [36]. Furthermore, the COVID-19 pandemic may have an adverse effect on the mental health of individuals without a history of mental health disorders; though, in contrast, the pandemic does not seem to increase symptom severity in people with pre-existing mental health disorders [37]. Women and young people have been found to have worse mental health outcomes during the lockdown response to the pandemic and women who are pregnant, postpartum or vulnerable to partner violence are at high risk for developing mental health problems during the pandemic [38, 39]. Mental health concerns for women during the pandemic may be exacerbated by social stresses including loss of work (women are more likely than men to have lost their jobs during the pandemic), increased caring duties within homes and lack of opportunities for social interaction and support [40]. The Royal College of Obstetricians and Gynaecologists recommendations highlight that mental well-being can and should be assessed at every contact a woman has with her maternity team, even when appointments are conducted remotely [41].

A further indirect consequence of the COVID-19 pandemic relates to sex-based violence. One in four women will experience domestic violence in their lifetime, with abuse during pregnancy or soon after the birth of their baby occurring in nearly 10% of all women [42]. It is well recognised that pregnancy triggers and frequently accelerates domestic violence, with women from ethnic minorities and marginalised groups being particularly vulnerable [43]. There is some evidence of an increase in domestic violence against women during the pandemic, with factors including stay-at-home orders and economic dependence contributing [43, 44]. This has been alongside a pandemic-related reduction in essential support services such as crisis centres and hotlines [45]. Routine enquiries should be made to every woman during antenatal appointments where their partner is not present; the increase in remote appointments has led to concern by healthcare professionals that violence will be masked during the pandemic. Together this acts as a perfect storm to further increase the risk of sex-based violence towards pregnant women and new mothers.

Finally, it is recognised that social deprivation, which can be compounded by ethnic minority status, leads to inequalities in maternal mortality and maternal morbidity. These inequalities and the risk that they pose for maternal health are likely to be exacerbated by the COVID-19 pandemic.

Conclusion

Beyond the direct effect of illness, the COVID-19 pandemic will amplify and accentuate existing health and socio-economic inequalities both in the UK and globally. These inequalities will lead to increased risk of indirect adverse effects on women's well-being and were recognised by the United Nations early during the pandemic [6]. Women are vulnerable to these inequalities and are likely to bear the health burden of the indirect effects of COVID-19, with these effects continuing to remain imprinted long after the rollout of a vaccination program. There needs to be an enjoined effort to ensure that existing inequalities are addressed as a priority as part of any national and international recovery programmes during and after the pandemic.

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