Were pregnant women more affected by COVID-19 in the second wave of the pandemic?

At the emergence of the COVID-19 pandemic in 2020, there was justified concern that this disease might have similar effects on pregnant women as influenza or other coronavirus infections. During the 2009 H1N1 influenza pandemic, influenza mortality in pregnant women in the USA was 4·3%.[1] In global analyses,[2,3] maternal deaths from severe acute respiratory syndrome or Middle East respiratory syndrome have been reported in 13% (n=24) and 40% (n=10) of published case reports, respectively. Reassuringly, US data[4] from the first wave of the COVID-19 pandemic (from January to June, 2020) show that death from COVID-19 during pregnancy was low (0·19%) and consistent with that of non-pregnant women of childbearing age (0·25%). However, by September, 2020, findings from a systematic review and meta-analysis of global data[5] suggested that pregnancy is a significant risk factor for hospitalisation and more severe illness, with a critical care admission odds ratio for pregnant women with COVID-19 compared with infected women of childbearing age of 2·13 (95% CI 1·53–2·95) and an invasive ventilation odds ratio of 2·59 (2·28–2·94).

Since September, 2020, a second wave in the UK appears to have had a more marked impact on pregant women. At the Royal Brompton Hospital in London, one of five commissioned centres in England for severe acute respiratory failure that offer extracorporeal membrane oxygenation (ECMO), we have treated pregnant and peripartum women with severe COVID-19 disease since March, 2020. The numbers of pregnant and peripartum women with severe COVID-19 disease increased during the second wave, and it appears that more of these individuals are requiring admission to intensive care and are being considered for ECMO.

Since March 26, 2020, we have received 96 ECMO referrals for women aged 16–49 years with COVID-19. 34 referrals were made in the first wave (before Sept 1, 2020) and 62 in the second wave (Sept 1, 2020–Jan 30, 2021; appendix). Of the referrals in the first wave, four (12%) of 34 were for peripartum women (and three for post-partum women), with three managed conventionally and one retrieved on ECMO. By contrast, peripartum women accounted for 19 (31%) of 62 referrals (12 for post-partum women) in the second wave, with ten managed conventionally, six retrieved on ECMO, and three that did not meet the National Health Service (NHS) criteria for ECMO, resulting in conventional management at the referring hospitals). ECMO referrals for peripartum women were significantly more common during the second wave than during the first wave (p=0·047 using Fisher's exact test).

External evidence supports our observation. The latest Intensive Care National Audit & Research Centre report[6] from March 5, 2021, highlighted an increase in the number of pregnant or recently pregnant women (ie, within 6 weeks) aged 16–49 years requiring admission to intensive care between the first wave (70 [March 1–Aug 31, 2020]) and second wave (277 [Sept 1, 2020–March 4, 2021]; appendix).[6] These admissions represent 8·9% and 13·5% of all women aged 16–49 years, and 0·6% and 1·2% of all patients who were admitted to intensive care with COVID-19 in the respective waves. In addition, since Aug 31, 2020, a greater proportion of women aged 16–49 years requiring invasive ventilation within 24 h of admission were pregnant or recently pregnant (87 [14%] of 625 during the first wave *vs* 31 [8%] of 376 during the second wave).[6] These findings reflect our experience at the Royal Brompton Hospital, although not identifying those pregnant or peripartum women that were critically ill with COVID-19 as a proportion of all pregnant or peripartum women infected with COVID-19 limits the conclusions that can be drawn. Further studies comparing this cohort's outcomes in the first and second waves are necessary.

The observed increase pregnant women with severe COVID-19 could relate to the emergence of a more pathogenic strain of SARS-CoV-2. However, preliminary analysis[7] suggests there is no evidence that the B.1.1.7 variant that originated in the UK at the onset of the second wave is particularly more infective or causes more severe disease in pregnant women specifically than other variants do. This trend could also be explained by an increase in the total number of COVID-19 cases in the second wave, resulting in more pregnant women being infected. This postulation is consistent with UK data showing that 340 000 cases were reported between Jan 30 and Aug 31, 2020 (ie, the first wave), whereas 3 800 000 cases were reported between Sept 1, 2020, and Feb 24, 2021 (the second wave). Case reporting, however, is likely to have been affected by differences in the availability of testing and in overall reporting between the first and second waves. More tests were done during the second wave, with laboratories increasing their testing capacity. Alternatively, it is possible that our experience reflects preliminary data from Spain,[8] where the number of hospitalised pregnant women during the second wave was ten times higher than in the first wave, while the total number of patients hospitalised only increased by 30% during the same timeframe, suggesting that this trend might not be entirely explained by an increase in total number of cases. At present, therefore, the extent to which these factors might have contributed to the increase of severe disease in pregnant women remains unclear.

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See **Online** for appendix

For **NHS adult ECMO service specification** see https://www.england.nhs.uk/publication/extra-corporeal-membrane-oxygenation-for-respiratory-failure-in-adults/

For more on **COVID-19 cases in the UK** see https://coronavirus.data.gov.uk/details/cases

For more on **SARS-CoV-2 testing in the UK** see https://coronavirus.data.gov.uk/details/testing

Focused research is required for further clarification regarding these potential causes.

The medical literature indicates that maternal COVID-19 affects pregnancy outcomes, with increased incidences of iatrogenic preterm births and caesarean section births due to maternal or fetal compromise, or both.[5,9] No increase in rate of neonatal deaths has been reported, but a possible relationship between COVID-19 and stillbirth is contentious, with one London hospital reporting an increased incidence of stillbirth during the pandemic.[5,10] Reassuringly, UK and US registry data, alongside regional and national data for England alone, suggest that this is not the case.[11,12] Additionally, convincing evidence suggests that vertical transmission of SARS-CoV-2 occurs and is a relatively common route of transmission for those neonates diagnosed with COVID-19 immediately after birth.[13] Infection of this cohort appears to occur primarily through postnatal exposure (70·5%), but a significant proportion of infections might be congenital (5·7%).[13] However, a consensus for the laboratory diagnosis of congenital infection and a mechanism for transmission are yet to be established.

In summary, early data suggest that pregnant and peripartum women are experiencing more severe illness in the second wave of the COVID-19 pandemic than was observed in the first wave. However, the true cause of this change is currently unclear. Further studies are urgently required to define whether the emergence of new variants could be related to this trend and whether public health policies should be modified to enhance protection of pregnant women.

We declare no competing interests. SK and JJS contributed equally and were responsible for the literature search and original drafting. SK was responsible for project administration. SL and PB accessed and verified the data. All authors contributed to the writing and editing and approved the final version for publication.

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