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Gender in the ICU

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Sex, Lies and COVID-19

An overview of the impact of gender on the severity of illness, impact and outcomes of COVID-19.

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The human coronaviruses (HCoVs) include two alpha-CoVs (HCoV-229E and HCoV-NL63) and five beta-coronaviruses (HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome CoV [SARS-CoV], Middle East respiratory syndrome CoV [MERS-CoV], and most recently (β-CoV SARS-CoV-2). Early data relating to the severe acute respiratory Syndrome (SARS) epidemic (2002-2003) suggested that the case fatality rate of infected males is significantly higher than that of females (Karlsberg et al. 2004). However, as the SARS epidemic was contained, this finding was never pursued. More recent data regarding the Middle East Respiratory syndrome (MERS) coronavirus also suggests excess male mortality (Goggins 2004; Alghamdi et al. 2014). The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been proposed to affect men and women differently.

Does It?

Between the first and second pandemic waves, the calculated global employment loss rates for women due to COVID-19 were estimated to be 1.8 times higher than those of men (5.7% vs. 3.1% respectively). Yet even when industry-mix effects were taken into consideration, survey data showed higher loss of employment among women than that expected. Before the pandemic, 46% of the United States workforce was comprised of women. The overall proportion of women among those losing their employment was expected to be 43% whereas unemployment data showed that women comprised 54% of those newly unemployed. Similarly, in India, 20% of the workforce before the pandemic were women. Their calculated proportion of employment loss was estimated at 17% while unemployment surveys showed they were actually 23%. The gendered nature of work across industries explains only one-fourth of the difference in employment loss rates for men and women. The lack of systemic progress to resolve societal barriers for women probably explains the rest (McKinsey Global Institute 2020). Gender-equality in society is strongly linked to gender equality in work. A typical example during the current pandemic is the availability of women versus men for work once the need for home nursery and schooling arose. So should women or men be staying at home?

In terms of disease infectivity, men were often overrepresented in early publications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Guan et al. 2020; Grasselli et al. 2020). This led to the misconception that men are more susceptible to infection with SARS-CoV-2 than women. More recent, sex-disaggregated data suggests there is probably no difference in disease infectivity. The Global Health 50/50 project reports almost equal global numbers of men and women having a confirmed diagnosis of infection with SARS-CoV-2 (i.e. based on laboratory testing) (https://globalhealth5050.org/the-sex-gender-and-covid-19-project/). This finding could easily be biased by differences in access to testing. Whether this is indeed the case remains unclear; reports from non-selective screening programmes are conflicted with some showing male predominance of varying proportions (Teherán et al. 2020; Stringhini et al. 2020) and some showing equal prevalence among men and women (Slot et al. 2020; Pollán et al. 2020).

With regards to disease severity and case-fatality rates, there have recently been several important findings. Although coronaviruses have been reported to cause respiratory, enteric, hepatic, and neurological diseases in various animal species, until recently beta-HcoVs were typically associated with self-limiting upper respiratory infections in immune-competent human hosts and occasional pneumonias in immune-compromised or older hosts (Letko 2020; Woo et al. 2005). The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), seems to be an exception to this rule and in the clinical manifestations of this disease lies a real difference between men and women.

Results from observational studies almost consistently show overrepresentation of males among COVID-19 patients with severe disease, among COVID-19 intensive care unit admissions and among those who die (Penna et al. 2020; Gebhard et al. 2020). Two meta-analyses of observational studies strengthened this impression, showing that when compared to women, the unadjusted proportions of men presenting with severe disease, admitted to an intensive care unit and dying are all higher. At the time of this writing, no well conducted, sex-stratified analyses have been conducted with regards to these observed differences. Both meta-

analyses also noted that adjusted analyses could not be conducted due to lack of data (Lakbar et al. 2020; Ortolan et al. 2020). However, specifically among SARS-CoV-2 stroke patients, the modified Rankin Score of patients surviving to hospital discharge has been noted to be worse in male versus female patients even after adjustment (Trifan et al. 2020).

Several explanations have been put forward for the worse disease severity in males. The viral surface spike (S-) protein of SARS-CoV-2 enters host cells by binding to the ACE2 receptor. The transmembrane protease, serine 2 (TMPRSS2) splits the S-protein, which increases viral attachment to cell membranes (Hoffmann et al. 2020). Both ACE2 and TMPRSS2 have been proposed as modulators of the susceptibility of men and women to SARS-CoV2 (Penna et al. 2020).

ACE2 receptors are prevalent in lung cells and may also be found in the endothelium of blood vessels in the myocardium and brain. However, the receptor for ACE2 is primarily expressed in the testis (i.e. spermatogonia; Leydig and Sertoli cells). ACE2-positive spermatogonia express more genes associated with viral reproduction and transmission (Wang and Xu 2020). Male mice are more susceptible to SARS-CoV than age-matched females; they have higher virus titers, more vascular leakage and alveolar oedema and accumulate more inflammatory monocyte macrophages and neutrophils in the lungs and ultimately die more. These differences between male and female mice increased with advancing age and decreased when females underwent ovariectomy or were treated with an oestrogen receptor antagonist (Channappanavar et al. 2017). A protective effect of oestrogen receptor signalling may also be plausible with regards to SARS-CoV-2 as cell mediators of the immune response (i.e. monocytes, macrophages, neutrophils) express surface oestrogen receptors. This receptor mediates the production of type I and III interferon, thereby creating a state of decreased innate immune inflammatory response and increased immune tolerance and antibody production (Mauvais-Jarvis et al. 2020; Suba 2020). Indeed women with severe COVID-19 have been shown to have a lesser rise in inflammatory biomarkers (Mussini et al. 2020; Qin et al. 2020).

TMPRSS2 protein is highly expressed in prostate secretory epithelial cells, and its expression is dependent on androgen signals (Afshari et al. 2020). TMPRSS2 has been proposed to be involved in genetic susceptibility to H1N1 and A (H7N9) influenzas (Cheng et al. 2015.) and probably also plays a role in male susceptibility to SARS-CoV2 (Qiao et al. 2020).

> **"sex-disaggregated data suggests there is probably no difference in disease infectivity between genders"**

So What Happens During Pregnancy?

A cytokine-tolerant environment between mother and fetus prevents activation of natural killer cells against fetal cells. This environment is created by T-helper type 2 cells which mediate hormonal suppression of inflammatory cytokine production and cellular activation (Littauer and Skountzou 2018). The rise in oestrogen that accompanies pregnancy increases the T-helper type 2 cell response (Kourtis et al. 2014). At the same time, T-helper cells also moderate the humoral immune response to large extracellular pathogens via interleukin secretion.

Compared to pregnant women with no infection, those with symptomatic or asymptomatic SARS-CoV2 infection seem to have an increased rate of complications not during pregnancy, but after delivery (Prabhu et al. 2020). This preliminary observation suggests that the overall post-partum reduction in hormonal levels is accompanied by a parallel decrease in protection against SARS-CoV-2.

At the time of this writing, only four papers have compared the laboratory findings of pregnant women with and without COVID-19 and these have shown normal rather than elevated white blood cell counts in pregnant women with the disease (Areia and Mota-Pinto 2020). COVID-19 disease also seems to manifest similarly in pregnant and recently pregnant women and in the general population, i.e. fever, chills, cough, dyspnoea, headache, lethargy, joint or muscle pain, sore throat, diarrhoea, nausea and vomiting (Knight et al. 2020). Yet anxiety regarding disease susceptibility seems rife. Once diagnosed with clinical disease, the age-matched hospitalisation rate of women with COVID-19 is almost five times higher among those who are pregnant than among those who are not [31.5% versus 5.8%] (Ellington et al. 2020).

Whether this concern is justified remains to be seen. Systematic review of the literature shows that 4% (95% CI 2%-7%) of pregnant and recently pregnant women attending or admitted to hospital for any reason and diagnosed as having suspected or confirmed COVID-19, were also admitted to an intensive care unit. Most of these women received invasive mechanical ventilation (3%, 95% CI 1%-5%) and almost one in eight also required extracorporeal mechanical oxygenation (ECMO) support (0.4%, 95% CI 0.1%-0.9%) (Allotey et al. 2020). Maternal deaths due to COVID-19 have also been described in developed (Knight et al. 2020; Ellington et al. 2020; Blitz et al. 2020) and developing (Hantoushzadeh et al. 2020; Takemoto et al. 2020) countries. Unfortunately pregnant women have been almost consistently excluded from COVID-19 trials (Einav et al. 2020). Therefore treatment for pregnant women with COVID-19 remains largely supportive. Steroids may be administered for either circulatory shock or the acute respiratory distress syndrome (ARDS). Anticoagulation is of particular importance as pregnancy is a hypercoagulable condition and there is no evidence for increased risk of bleeding

even with full anticoagulation (Jacobson 2020; D'Souza et al. 2017). In advanced pregnancy with severe hypoxaemia, the advantages of caesarean delivery should be weighed against the potential risk of bleeding as support with EMCO may be required. In case ECMO is initiated after surgery, anticoagulation may be withheld for a limited period (Bideerman et al. 2017).

Whether the relation between SARS-CoV-2 infection and preterm birth and perinatal death is mediated by or coincidental to the higher rates of caesarean delivery and or pre-eclampsia remains to be elucidated (Di Mascio et al. 2020). At this time there is no clear evidence of placental infection or definitive vertical transmission of SARS-CoV-2 (Edlow et al. 2020). However, fetal and neonatal outcomes may still potentially be affected by the indirect effects of prolonged maternal hypoxaemia and by placental transmission of inflammatory cytokines, particularly IL-6 which has been tied to neonatal neurodevelopment (Rudolph et al. 2018).

In conclusion, more women have become unemployed during the current pandemic. This trend is counterproductive as pathophysiological and epidemiological findings suggest that despite a similar susceptibility to SARS-CoV2 infection, women are less likely to suffer from severe COVID-19 disease. Pregnancy seems to be accompanied by an increased protective hormonal effect but regardless of disease severity there may be a higher likelihood of postnatal maternal complications. No vertical transmission of the disease to the fetus has been shown but severe maternal disease may expose the fetus to secondary adverse effects.

Take Home Messages

1. Between the first and second pandemic waves, the calculated global employment loss rates for women due to COVID-19 were estimated to be 1.8 times higher than those of men (5.7% vs. 3.1% respectively).
2. Sex-disaggregated data suggests there is probably no difference in disease infectivity between genders.
3. Compared to pregnant women with no infection, those with symptomatic or asymptomatic SARS-CoV-2 infection seem to have an increased rate of complications not during pregnancy, but after delivery.
4. No vertical transmission of the disease to the fetus has been shown but severe maternal disease may expose the fetus to secondary adverse effects.

Conflict of Interest

Sharon Einav is a member of the European Society of Intensive Care diversity task force. ■

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