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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Short communication

Preterm birth: Potential risk factor for greater COVID-19 severity?

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The novel coronavirus disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a major health (& economic) issue across the globe. As of June 20th, more than eight and a half million human infections have been confirmed worldwide. While the exact pathophysiology is still investigated, significant individual variability in the disease severity and subsequent consequences has been demonstrated. The respiratory distress syndrome related to SARS-CoV-2 infection seems highly specific with a desaturation despite sometimes an absence of dyspnea and distinct manifestations like large intrapulmonary shunt or vascular abnormalities such as thrombosis and increased angiogenesis (Ackermann et al., 2020). Current evidence from large prospective COVID-19 patients cohort studies suggests that the key independent risk factors for mortality and severe complications include higher age, male sex and chronic comorbidities, predominantly related to obesity and metabolic dysfunctions (Liang et al., 2020). Fast identification of “more-at-risk” populations is key for optimization of therapy selection and timing, especially when health care system capacities are limited.

One such, to-date neglected population that is potentially more »vulnerable« to COVID-19 consists of prematurely born individuals. Given that preterm birth prevalence is currently estimated at approximately 10 % births worldwide, the potential consequences of prematurity relate to a significant part of the population. We argue, that three important features associated with prematurity constitute the basis of such probable vulnerability: First, the detrimental long-term consequences on respiratory system development, control and function. Second, higher levels of (and possibly reduced tolerance to) oxidative stress and third, potentially elevated Angiotensin-converting enzyme (ACE2) activity/expression.

Prematurity can provoke life-long adverse sequelae in numerous physiological systems but might predominantly affect the respiratory system. Importantly, recent accumulating evidence suggests that the respiratory drive/control might be particularly compromised under hypoxemic conditions. Indeed, it is well established that the ventilatory response to hypoxic stimuli is blunted in prematurely born individuals as compared to their full-term born and physical capacity matched counterparts (Bates et al., 2014; Debevec et al., 2019). Whilst the exact mechanisms of prematurity-related altered resting cardiorespiratory control and carotid chemoreceptor dysfunction remain unknown, perinatal hyperoxia was hypothesized to be the key underlying factor.

Other anatomical and functional consequences of prematurity might even further exacerbate the observed respiratory dysfunction. The reduced ventilatory response to hypoxia may lead to greater systemic hypoxemia. This can be particularly problematic in already hypoxemic clinical populations. Hypoxemia is a defining feature of COVID-19 that is independently associated with in-hospital mortality (Xie et al., 2020) and might importantly underline the disease-related respiratory challenges and end-point outcomes in this cohort. Whilst other factors associated with COVID-19 also importantly modulate the ventilatory drive (i.e., higher metabolic drive related to fever & inflammation) the potentially blunted hypoxic ventilatory response and subsequently greater systemic hypoxemia in prematurely born individuals should be considered when managing COVID-19 patients.

Recently, it has been speculated that the hypoxemia and associated pulmonary pathology observed in COVID-19 patients may arise from a reduced oxygen-sensing capacity in pulmonary arteries and in carotid bodies (Archer et al., 2020). The resulting dysfunctional regulation of ventilation may be particularly deleterious in combination with pre-existing deficits of the ventilatory response, as is the case in prematurely born individuals.

It is well established that oxygen sensing in the lung and carotid bodies depends on mitochondrial function. The known vulnerability of mitochondria to oxidative stress suggests an additional feature of prematurity to be relevant for impaired oxygen sensing and COVID-19 severity; potentially higher oxidative stress levels as compared to full-term born individuals (Filippone et al., 2012; Martin et al., 2018). This difference in redox balance has indeed been hypothesized to be directly involved in the modulation of the ventilatory response to hypoxaemia in prematurely born persons.

Inflammation related to COVID-19 further increases oxidative stress, while oxidative stress, in turn, can promote inflammation. A basal redox regulation deficit thus might increase the risk to get trapped in this detrimental feedforward loop. Oxidative stress furthermore leads to oxidized phospholipids, commonly present in COVID-19 patient lungs. Oxidized phospholipids have been linked to coagulation abnormalities and low platelet counts, which are associated with adverse outcome of COVID-19 (Merad and Martin, 2020). Given that COVID-19 risk factors/conditions are commonly characterized by high oxidative

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stress levels it seems plausible that redox balance deficits are among the underlying mechanisms of vulnerability to COVID-19. Therefore, the potentially altered oxidative stress status linked to prematurity must be considered as it might exacerbate the clinical status.

Finally, accumulating evidence indicates that prematurity might also be associated with higher ACE2 activity and/or expression (South et al., 2018). ACE-2 is known to be directly involved in SARS-CoV-2 cell-binding, representing the main host cell receptor for all human pathogenic coronaviruses including SARS-CoV-2. Thus, the higher ACE2 activity/expression in the prematurely born individuals might result in greater COVID-19 severity. One also has to bear in mind that the prematurity-related higher ACE2 activity might be additionally heightened by potential hypertension or diabetes drug therapies which often include ACE inhibitors and/or angiotensin II receptor blockers, both upregulating ACE2.

In summary, prematurely born COVID-19 patients could be particularly vulnerable to both infection and adverse outcome. High ACE2 activity levels may enable enhanced virus-binding, thus increasing infection risk. A pre-existing adverse redox balance could then contribute to the aggravation of inflammatory mechanisms by oxidation of different biomolecules including phospholipids, incidentally exacerbating vascular and lung injury. Oxidative damage to oxygen-sensing mitochondria in conjunction with COVID-19-related hypoxemia and prematurity-associated ventilator response deficits may synergistically deteriorate the health status facilitated by a potentially compromised respiratory system of the prematurely born individual. We believe that the above-summarized data and mechanisms observed in prematurely born individuals should be considered when managing/treating COVID-19 patients. As no sound epidemiological data currently exist on the topic, future epidemiological and experimental efforts are urgently warranted to elucidate the relationship between prematurity and COVID-19 severity and thereby optimize therapeutic approaches for this, up-to-now neglected, population.

Author contribution statement

All authors contributed to the preparation and writing of the Letter. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest related to the topic of this Letter.

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Tadej Debevec[a,b], Johannes Burtscher[c], Grégoire P. Millet[c,*]
[a] *Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia*
[b] *School of Life Sciences, Faculty of Medicine and Health Sciences, Nottingham University, Nottingham, United Kingdom*
[c] *Institute of Sport Sciences, University of Lausanne, Lausanne, Switzerland*
E-mail address: gregoire.millet@unil.ch (G.P. Millet).

* Corresponding author.