When it comes to coronavirus and biology - sex matters

Scott Nelson[1], Martina Capuzzo[2], and Antonio LaMarca[2]

[1]University of Glasgow
[2]University of Modena and Reggio Emilia Faculty of Medicine and Surgery

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Scott M Nelson, MD PhD[1,2]

Martina Capuzzo[3]

Antonio La Marca, MD PhD[3]

[1]School of Medicine, University of Glasgow, UK

[2]NIHR Bristol Biomedical Research Centre, Bristol, UK

[3]Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy

Corresponding author:

Prof Scott M Nelson University of Glasgow New Lister Building Glasgow Royal Infirmary Glasgow G31 2ER, UK +44 (0)141 201 8581 Scott.Nelson@glasgow.ac.uk

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The male dominance in COVID19 morbidity and mortality figures has been a consistent feature from the early reports emerging from Wuhan, to national intensive care data, through to more recent comprehensive population mortality data. Men are more than twice as likely to become severely ill and require intensive care than women and at least twice as likely to die, with further widening of the mortality discordance with increasing age. These differences do not appear to be caused by differential rates of infection, as equal numbers of men and women catch SARS-CoV-2. Nor do they appear to reflect clustering of unhealthy behaviour and comorbidities in men, as even after adjustment, male sex is associated with a hazard ratio (HR) of death from COVID19 of HR 1.99, (95%CI 1.88-2.10)[1]. These sex-specific differences in severity and fatality were also observed for the 2002-2003 SARS-CoV outbreak, and the Middle East respiratory syndrome (MERS)-CoV[2]. So, what underlies this sex-specific susceptibility difference for pathogenic coronaviruses? Several early lifestyle theories were proposed, but rather more fundamental sex-specific discordances in steroid hormones, x-linked genes and the innate immune response are likely to underlie this sexual dimorphism.

SARS-CoV-2 pathology and links to sex steroids

Direct antigen testing and seroprevalence studies both support equivalent rates of SARS-CoV-2 infection between men and women, but whether men then go onto exhibit larger viral loads is unknown. The possibility of sex-specific differences in efficiency of viral entry, and replication was suggested from inoculation studies of SARS-CoV virus, in which viral titres were greater in lungs of infected male mice as compared to females despite equivalent inoculation loads[3]. This is biologically plausible as the transmembrane serine protease 2 (TMPRSS2) which SARS-CoV-2 uses for S protein priming, is down-regulated by oestradiol and strongly

upregulated in lung cell lines by androgens at concentrations regularly found in men. There is less clarity over modulation of angiotensin-converting enzyme 2 (ACE2) – the cell entry receptor engaged by SARS-CoV-2, as this is down regulated in the kidneys but not in lungs by 17β oestradiol, and is induced in human atrial tissue by oestradiol[4]. However, whether tissue specific differences in oestradiol dependent ACE2 expression may contribute to sex-specific differences observed in extrapulmonary complications is still untested for SARS-CoV-2[1].

Sexual discordance in the progression of respiratory infections is well recognised, and the less severe COVID19 progression observed in females may be attributable to the differential regulation of sex hormones on innate immune cells in the lungs, which will impact on both the initial proinflammatory / effector phase but then also resolution/repair phase which will drive subsequent complications [5]. Direct experimental evidence for a hormonally mediated discordant immune response for coronaviruses was derived from a mouse model of SARS-CoV, with male mice exhibiting enhanced vascular leakage and alveolar oedema as compared to female counterparts [3]. These histological changes were accompanied by increased accumulation of inflammatory monocyte macrophages (IMM) and neutrophils in the lungs, with experimental IMM depletion reducing male mortality. That oestrogen and not androgens mediated these sex specific differences, was supported by ovariectomy or treatment with an oestrogen receptor antagonist, as both increased female mortality with a concomitant increase in pulmonary IMMs. In contrast, male gonadectomy or treatment with an anti-androgen, did not alter male disease outcome[3]. Detailed immune phenotyping of exposed individuals will further enlighten the sex-specific innate and adaptive immune responses that will support vaccine development.

Hormonal stratification of COVID-19 risk categories

Women exhibit highly dynamic oestrogen trajectories across their lifespan, from the initial pre-pubertal surge, to the regular cyclical fluctuations with menstruation, the substantive increases with pregnancy followed by post-partum resolution, and then the dramatic declines observed with the onset of menopause or in the pathogenic state of premature ovarian insufficiency. The scale of these changes is immense, with pregnancy oestradiol levels frequently exceeding 1,000pg/ml as compared to 30 to 400pg/ml for ovulating premenopausal women, and almost undetectable levels in post-menopausal women. Progesterone levels exhibit a 10-fold increase in across the menstrual cycle with formation of the corpus luteum, with a further 10-fold increase during pregnancy, before becoming negligible in the menopause. Female androgen concentrations decline with age, to levels that approximate 50% of peak values, however, even when testosterone is pathologically raised in polycystic ovarian syndrome the values are still a fraction ($\tilde{}1/20^{\text{th}}$) of that observed in males. Notably these hormonal fluctuations underpin stratification of risk for a range of diseases including hormonally sensitive cancers, cardiovascular disease and thromboembolic disease.

Whether these marked changes in sex steroids underlie some of the differences observed for disease progression for different female populations is an area for further study[6]. The relative low impact of SARS-Cov-2 on pregnant women may reflect their relative shielding, or the pregnancy specific sex-steroid mediated differential immune response. The increased incidence of complications post-partum period may reflect resolution of physiological adaption to pregnancy or hormonal changes but recording gestational age or time from delivery is a prerequisite to understand disease course. For the non-pregnant population epidemiological studies should record the contraceptive methods being used and menstrual cycle characteristics, as oestrogen containing oral contraceptive pills, progesterone only pills and implants all frequently stabilise oestrogen levels removing ovulatory fluctuations and early follicular troughs but with differing efficacy. For older women where disease severity is increased, clarification of the independent effect of the menopausal transition on disease progression would be useful as age and reproductive stage may be independent variables in determining disease severity[7]. Whether exogenous hormone replacement therapy is being taken, and if single or combined preparations and dose may be central to help clarify if oestrogen supplementation mitigates risk. Selective oestrogen receptor modulators like tamoxifen, which may increase circulating oestradiol levels with prolonged use, also need to be recorded.

Simply female – does not do justice to the dynamic female reproductive system

Recognition of the sex-based disparity in COVID19, has further highlighted the need for research into sex differences at the most fundamental levels of biomedical services. As we progress, researchers and policy makers must articulate a critical need to go beyond just recording sex and age as a covariate and reflect that women and their flexible hormonal milieu are highly dynamic across their lifecourse. Clarification of the stage of reproductive lifecourse, their menstrual cycle characteristics and use of hormonal modifying medication is fundamental. Only then can we begin to delineate which features are associated with clinical disease progression and prognosis and increase our pace to a healthier population.

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Contribution to Authorship

ALM, MC and SMN conceived the idea and SMN provided a first draft with all authors, editing and approving the final manuscript. All authors accept responsibility for the paper as published.

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