

1 Extended abstract from IGM webinar May 6, 2021 Gender differences in COVID-19 pandemic around the world

Sex differences in COVID-19: from animal models to clinical data

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Around the world, while males and females are equally likely to test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), males are significantly more likely to be hospitalized, admitted into intensive care units, and die from the 2019 coronavirus disease (COVID-19).¹⁻³ Although globally there are similar proportions of males and females testing positive for SARS-CoV-2, there are a number of gender-associated differences with behavior (e.g., acceptance of public health measures that limit virus spread),⁴ occupations,⁵ and access to healthcare for testing⁶ that contribute to regional differences in SARS-CoV-2 exposure between the sexes.

Gender differences (i.e., social construct that defines norms for men and women) are separate from but complementary to biological sex differences that are mediated by sex chromosome complement, differential reproductive tissues, and differential concentrations of sex steroid hormones. The enrichment of the X chromosome for immune response genes,⁷ combined with the presence of sex steroid hormone receptors on diverse innate and adaptive immune cells and the presence of hormone response elements in the promoters of numerous immune response genes can give rise to sex differences in immunity to viruses.⁸ Consequently, there are sex differences in immunity to SARS-CoV-2, control of virus replication, development of immunopathologies, and long-term protection.⁹ Males consistently have greater proinflammatory cytokine production (e.g., IL-6 and CRP) than females in the context of COVID-19.³ Older males with COVID-19 have lower CD8+ T cell activity (e.g., IFN- γ production and proliferation),¹⁰ but have greater antiviral antibody responses¹¹ than females.

Animal models are integral for studying the impact of biological sex on the pathogenesis of SARS-CoV-2. In golden Syrian hamsters infected with a clinical isolate of SARS-CoV-2, male hamsters experience greater morbidity and develop more extensive pneumonia than females.¹² Treatment of male hamsters with estradiol does not alter pulmonary damage. During the recovery phase of infection, females mount greater antibody responses in both plasma and respiratory tissues. The development of an animal model to study COVID-19 sex

differences will allow for a greater mechanistic understanding of the SARS-CoV-2 associated sex differences seen in the human population.

Keywords. SARS-CoV-2, golden Syrian hamsters, electronic health records, convalescent plasma.

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