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MAYO CLINIC  
PROCEEDINGS

In the Limelight: August 2020



As in the June and July 2020 issues, this month's feature highlights five articles on COVID-19 that appear in the current print and online issue of *Mayo Clinic Proceedings*. These articles are also featured on the *Mayo Clinic Proceedings*' YouTube Channel ([https://youtu.be/xWJNrf2\\_Dr0](https://youtu.be/xWJNrf2_Dr0)).

**PREGNANCY, SARS-CoV-2, AND COVID-19**

Beginning with the recognition that in prior pandemics, susceptibility to infection and attendant mortality were higher in pregnant as compared with nonpregnant women, Narang et al comprehensively review in the present issue of *Mayo Clinic Proceedings* the susceptibility to SARS-CoV-2 that may occur in the pregnant state and the manifestations and outcomes when such infection occurs in pregnancy. Homeostasis is maintained in pregnancy by a spectrum of hemodynamic, immunologic, and metabolic adaptations, and aspects of such essential responses may predispose to infection with SARS-CoV-2. For example, despite the fact that in normal pregnancy the renin-angiotensin-aldosterone system is upregulated, normal pregnancy is characterized by systemic and regional vasodilation and hyperperfusion mediated, in part, by increased production of the vasodilating peptide angiotensin-(1-7). This peptide is produced from angiotensin II by ACE2, a membrane receptor normally expressed by diverse cells in health, and one that is induced in normal pregnancy; this enables the vasodilation seen in pregnancy. Remarkably, ACE2 is one of the two cell surface receptors co-opted by SARS-CoV-2 to gain cellular entry. Once SARS-CoV-2

invades and replicates within cells, expression of ACE2 decreases. The consequences of such processes are several. First, increased ACE2 expression in pregnancy may predispose to infection with SARS-CoV-2. Second, the attendant reduction in ACE2 expression once SARS-CoV-2 infection occurs may impair production of angiotensin-(1-7) and the vasodilation that this peptide sustains. Third, infection of endothelial cells with SARS-CoV-2 may cause endothelial dysfunction, the latter predisposing to vasoconstriction, inflammation, and thrombosis. Fourth, such processes are further heightened by the relative deficiency of angiotensin-(1-7), as the latter is also anti-inflammatory and anti-thrombotic. The net effect of such processes is not only a predisposition to SARS-CoV-2 infection in pregnancy, but also to such complications in pregnancy as systemic hypertension and preeclampsia. Narang et al also discuss how the altered immune profiles, depending upon the trimester of pregnancy, may either predispose to infection with SARS-CoV-2 or to the cytokine storm engendered by such an infection. Physiologic changes in the respiratory tract in pregnancy (such as congestion and accumulating secretions in the upper airways) may also predispose to SARS-CoV-2 infection, while the usual dyspnea of pregnancy may cloud the appreciation of dyspnea in the pregnant patient as a warning symptom of impending COVID-19. Narang et al review the available data in pregnant patients infected with SARS-CoV-2 regarding maternal disease, obstetrical outcomes, and neonatal outcomes. Drawing upon guidelines issued by relevant societies devoted to



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obstetrical and fetal care, and by the Centers for Disease Control and Prevention and World Health Organization, Narang et al distill such information so as to provide current guidelines regarding prenatal/antepartum, intrapartum, and postpartum care. The article also discusses the implications of COVID-19 in particular pregnant patient populations and broadly outlines the treatment of COVID-19 in pregnant patients. All of these clinical sections include syntheses and summaries of information in clear tabular form. Narang et al are to be commended for this comprehensive, clearly written, and timely review of the impact of the current pandemic on pregnant patients.

Narang K, Enninga EAL, Gunaratne MDSK, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. *Mayo Clin Proc.* 2020;95(8):1750-1765.

#### SEX DIFFERENCES IN OUTCOMES IN COVID-19

Susceptibility to and adverse outcomes in COVID-19 may be underpinned by a number of conditions that include, among others, diabetes, cardiovascular disease, systemic hypertension, chronic lung disease, chronic kidney disease, hepatic disease, chronic debilitation, and an immunocompromised state. Additionally, it is becoming increasingly clear that sex differences are also determinants of outcomes in COVID. In the present issue of *Mayo Clinic Proceedings*, Alkhouli et al examine this issue by utilizing the COVID-19 Research Network, a database available through TriNetX, the latter representing a globally based, health care-dedicated research network. In this study, men, comprising 43% of a total population of approximately 15,000 patients, exhibited, as compared with women, increased all-cause mortality and decreased cumulative probability of survival. Because several risk factors for COVID-19 (including diabetes, hypertension, coronary artery disease) were more prevalent in men, propensity score matching analyses were conducted—this demonstrated that men still evinced increased all-cause mortality and decreased cumulative probability of survival. Finally,

two sensitivity analyses were performed to assess whether the worse outcomes in men reflected their older age or differential usage of angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs). Propensity score matching in patients 50 years or older and in patients not taking ACEi/ARBs demonstrated the cumulative probability of survival was again lower in men. Alkhouli et al conclude that men, as compared with women, exhibit a higher mortality in COVID-19, a susceptibility that cannot be simply explained by age or other relevant risk factors. Possible explanations for this sex-dependent outcome in COVID-19 are provided by the accompanying article by Al-Lami et al in the same issue of *Mayo Clinic Proceedings*. As these authors point out, the immune system in women, as compared with men, broadly considered, is more robust and reactive, rendering the former relatively more resistant to infectious diseases. This may reflect, in part, the fact that a large number of immune regulatory genes congregate on the X chromosome. A salient additional consideration is that sex hormones themselves can mitigate inflammatory responses, and a substantive pathobiologic basis for COVID-19 and its complications resides in the vigorous proinflammatory processes that ensue after infection with SARS-CoV-2. Estrogens exert anti-inflammatory effects, including inhibition of activation of the proinflammatory transcription factor, NF- $\kappa$ B, the latter possibly representing a pathway for tissue injury in COVID-19. Estrogen can also induce cytoprotective genes. Such properties of estrogens may not only contribute to the relative protection of premenopausal women against, for example, atherosclerotic coronary artery disease, but also for the better outcomes of younger women as compared with similarly aged men in COVID-19. Testosterone, itself, exerts anti-inflammatory effects as well as trophic effects on skeletal muscle; an age-dependent decline in testosterone in men may lead to heightened inflammation as well as impairment in respiratory muscular function when COVID-19 occurs in older

men. In sum, worse outcomes in men as compared with women in COVID-19 are likely multifactorial representing the integrative effects of a greater prevalence of comorbid conditions, sex-dependent genetic determinants of immune responses, and cellular effects and prevailing levels of sex hormones.

Alkhouli M, Nanjundappa A, Annie F, Bates MC, Bhatt DL. Sex differences in COVID-19 case fatality rate: insights from a multinational registry. *Mayo Clin Proc.* 2020;95(8):1613-1620.

Al-Lami RA, Urban RJ, Volpi E, Algburi AMA, Baillargeon J. Sex hormones and novel coronavirus infectious disease (COVID-19). *Mayo Clin Proc.* 2020;95(8):1710-1714.

#### NECESSITY AND INNOVATION IN TIMES OF CRISIS

There is a time honored adage that necessity is the mother of invention, and in the present issue of *Mayo Clinic Proceedings*, Farrugia and Plutowski discuss how the exigencies of the current COVID-19 crisis can germinate innovative strategies that may prove beneficial in the short and long term. Innovation in such circumstances, as emphasized by the authors, is underpinned by and emerges from the willingness to take risks; the dedicated application of science and technology; a cohesiveness of focus and effort among medical centers, research institutions, and the biotechnology and pharmaceutical industries; the application of information technology; public-private partnerships; and, importantly, collaboration with governmental agencies. Farrugia and Plutowski provide examples of how such collaboration has enabled a number of

important initiatives including the molecular and serologic testing for the disease, clinical trials of potential therapies, vaccine development, the application of artificial intelligence, and the growth of digital health care. As noted by the authors, constraints against in-person health care caused by COVID-19 led to the rapid and extensive application of telehealth and virtual care, the latter representing a form of health care now reimbursed by Centers for Medicare & Medicaid Services. Such growth and gains in telehealth would likely not have occurred in the foreseeable future had there not been these challenges posed by COVID-19. Illustrating this power of telehealth/telemedicine in the present issue of *Mayo Clinic Proceedings* is the article by Laskowski et al which provides for practitioners a detailed virtual musculoskeletal examination with clear text and relevant pictures and videos. In concluding their *Perspective*, Farrugia and Plutowski underscore the view that, out of the profound challenges and loss created by the COVID-19 crisis, a united purpose, a steadfast resolve, and a concerted effort can enable the emergence of innovative strategies and solutions, including the untapped and enduring potential of digital health care systems.

Farrugia G, Plutowski RW. Innovation lessons from the COVID-19 pandemic. *Mayo Clin Proc.* 2020;95(8):1574-1577.

Laskowski ER, Johnson SE, Shelerud RA, et al. The telemedicine musculoskeletal examination. *Mayo Clin Proc.* 2020;95(8):1715-1731.

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