Current Commentary

Sex, Hormones, Immune Functions, and Susceptibility to Coronavirus Disease 2019 (COVID-19)–Related Morbidity

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), uses two primary receptors, type II transmembrane serine protease and angiotensin-converting enzyme-2, for priming and cellular invasion, respectively. Both proteins have been demonstrated to be present in different concentrations in females and males, which may explain a mechanism for the reported higher case-fatality rate in males. Despite the known sex difference in COVID-19 disease mortality, preliminary data suggest there are certain female populations, including pregnant and menopausal women and possibly polycystic ovarian syndrome patients who are more susceptible to COVID-19–related morbidity. This commentary analyzes the interplay between sex differences, hormones, and the immune function in each of these populations with respect to the risk and severity of COVID-19 and proposes biological rationales to explain these differences.

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the pandemic viral disease outbreak that originated in Wuhan, China, in December 2019. As of September 2020, the Centers for Disease Control and Prevention (CDC) reported 4.9 million cases of COVID-19 in the United States.[1] Ninety-seven percent of these cases were reported with sex (male or female): 2.5 million female (51.8%) and 2.3 million male (48.2%).[1] Among these cases, the overall case-fatality rate was 2.9%, of which 46% of the deaths were females and 54% were males.[1] Although there is a higher infection rate for females in the United States, it appears that the severity and subsequent death rate is worse in males.

The Global Health 5050 database, as of September 2020, reports COVID-19 data from 119 countries, of which 42 countries reported a greater rate of COVID-19 infection in females.[2] Furthermore, an increased male/female case-fatality ratio ranging from 1.01 to 3.84 times greater was reported in 63 of the 75 countries for which detailed demographics were available.[2] The highest male/female ratio was observed in Myanmar, Tunisia, Thailand, Albania, and Wales.[2] It is important to acknowledge, however, that each country employed a unique entity to report data, making it difficult to analyze COVID-19 incidence and case-fatality reporting on a global platform.[2]

Not only are there sex differences in COVID-19 incidences and mortality, but differences are also observed at the cellular level after infection with SARS-COV-2. Severe acute respiratory syndrome coronavirus 2 is an enveloped positive sense RNA

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virus that enters the body through its interaction between the S-protein on the virus' surface and the angiotensin-converting enzyme-2 (ACE-2) molecules, inducing a cellular response.[3] Before interaction with ACE-2, the S-protein is primed by a type II transmembrane serine protease.[4] Angiotensin-converting enzyme-2 and type II transmembrane serine protease have been demonstrated to be present in different concentrations in females and males.[3,4] Angiotensin-converting enzyme-2 expression levels have been shown to be higher in males than females.[4] In the lungs, there are several cell types that express ACE-2.[3] In males there are at least five different cell types with ACE-2 expression, compared with only two to four cell types in females.[3] Furthermore, male gonadal cells including spermatogonia, Leydig, and Sertoli cells have an increased presence of ACE-2 compared with female gonadal cells.[5] Type II transmembrane serine protease is an androgen-regulated cell surface protease that is predominantly expressed in prostate epithelium, spermatogonia, and spermatids.[6] Coronavirus disease 2019 is a viral disease that uses two primary receptors for priming and cellular invasion, both of which are more prevalent in males comparatively.

Despite the recognized sex differences in COVID-19 disease mortality, there are certain female populations who are more susceptible to COVID-19–related morbidity. This commentary discusses the potential hormonal and immune system differences between sexes that may account for differences in incidences and case-fatality rates. There are certain female populations, including pregnant and menopausal women and possibly patients with polycystic ovarian syndrome (PCOS) who may be susceptible to COVID-19–related incidence and morbidity.

PREGNANCY

The June 25, 2020, Morbidity and Mortality Weekly Report from the CDC reported that SARS-CoV-2 infection in pregnancy was associated with increased hospitalizations, intensive care unit admissions, and mechanical ventilation, but not death (Table 1).[7] Factors that may contribute to increased disease severity in pregnancy relate to normal physiologic changes including airway edema, elevated diaphragm, and increased oxygen consumption as well as an overall immunocompromised state.[8] In addition, the postpartum progesterone withdrawal may further increase risk of viral susceptibility.

Progesterone exerts antiinflammatory effects via inhibition of nuclear factor kappa beta.[8] It also decreases inflammatory cytokines: tumor necrosis factor-alpha, interferon-gamma, and interleukin (IL) 12, and increases antiinflammatory cytokines such as IL-10. Influenza A virus, similar to SARS-CoV-2, primarily infects respiratory epithelial cells leading to the production of proinflammatory cytokines and chemokines.[8,9] An animal study showed significant improvement in influenza A morbidity and mortality among female rats on progesterone who had prior surgical progesterone depletion via oophorectomy.[9] The authors of the study concluded that progesterone reduces pulmonary inflammation, improves lung function, repairs damaged lung epithelium, and facilitates overall faster recovery from influenza A virus infection.[9] Of note, the influenza viral load was unaffected, implying progesterone acts primarily on the downstream inflammatory reaction.[9] Pregnancy is a high progesterone state, and the postpartum period is a relatively progesterone depleted state. The rapid withdrawal of progesterone in the postpartum period may create a relative decrease in protection from inflammation in the lung conducive to SARS-CoV-2.

Early studies from China reported that most severe cases in pregnant women occurred after delivery–when progesterone withdrawal rapidly occurs. However, this was a small sample (N=9).[10] More recently, a study from New York City showed that approximately one of three (14/43) pregnant patients who tested positive for SARS-CoV-2 were asymptomatic, but 6 of 13 discharged asymptomatic patients developed symptoms within 7 days.[11] More compelling is a prospective observational cohort study (N=427) by Knight et al,[12] which showed that 81% (342/427) of women admitted with SARS-CoV-2 were in the third trimester or peripartum. Sixty-two percent (266/427) of these patients delivered in the hospital. Forty-one admitted women experienced severe disease states requiring critical care or extracorporeal membrane oxygenation; of note, 80% (33/41) were in the postpartum period.[12] The article, however, did not discuss whether the 33 postpartum patients' deliveries were spontaneous or initiated by worsening respiratory function.

It is difficult to assess the role of low progesterone in viral infection susceptibility because the third trimester and peripartum patients with COVID-19 were grouped in the study design.[12] However, the majority of the patients who experienced severe symptoms were in the postpartum period, supporting the hypothesis of increased disease severity with progesterone withdrawal.[12] It is important to note that the small sample size reported in the aforementioned study may be affected by ascertainment bias. Additional high-powered studies should be conducted to further support the correlation described.

Table 1. Rates of Hospitalization, Intensive Care Unit Admission, Mechanical Ventilation, and Death Among Females Aged 15–44 Years With Coronavirus Disease 2019 (COVID-19) With Respect to Pregnancy Status

Outcome	Pregnant (n=8,207)	Nonpregnant (n=83,205)	RR (95% CI)
Hospitalization	2,587 (31.5)	4,847 (5.8)	5.4 (5.1–5.6)
ICU admission	120 (1.5)	757 (0.9)	1.5 (1.2–1.8)
Mechanical ventilation	42 (0.5)	225 (0.3)	1.7 (1.2–2.4)
Death	16 (0.2)	208 (0.2)	0.9 (0.5–1.5)

RR, risk ratio; ICU, intensive care unit.
Data are n (%) unless otherwise specified.
Modified from Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769–75. doi: 10.15585/mmwr.mm6925a1

Progesterone-only contraceptives, medroxyprogesterone acetate injectables, levonorgestrel intrauterine devices, subdermal implants, and progestin-only pills can potentially be used in the immediate postpartum progesterone withdrawal period. These agents replace endogenous progesterone production with a synthetic progestin, which binds to progesterone receptors longer and may create a unique immune response. The injectable form is readily administered immediately after delivery in accordance with the CDC recommendations.[13] We present a theoretical framework for the use of progestin-only contraceptives that may be extrapolated to include combined hormonal contraceptive therapy given their use of synthetic progestins. One study assessed COVID-19 disease with respect to the use of combined hormonal oral contraceptives, which demonstrated a protective effect for symptomatic COVID-19 disease.[14] The primary study population were premenopausal women. However, the study did not include a subset analysis of postpartum patients. Therefore, further studies and trials should be completed to assess the theoretical role of hormonal contraceptive therapy in mitigating the risk of severe COVID-19 in the postpartum period.

Not only is pregnancy associated with increased progesterone levels, but also with increased levels of estrogen. Estrogen receptors are expressed on T and B cells, natural killer cells, macrophages, dendritic cells, and neutrophils.[15] These receptors are regulated by the changes in hormones in the menstrual cycle, pregnancy, and menopause. Low levels of estrogen have been associated with a Th1 response, which is predominantly a cellular-based immune response producing IL-6 among other pro-inflammatory cytokines.[15] In contrast, higher doses of estrogen have been associated with a humoral response, with notably increased Th2 and subsequent IL-4, IL-5, and IL-10 cytokine production.[15]

Therefore, in pregnancy, there are immune changes due to the increased levels of estrogen. Specifically, there is a shift from the Th1–Th2 balance to more Th2 predominance.[16] The elevated levels of estrogen in pregnancy act on the immune function cells to upregulate a humoral response via the Th2 shift.[16] However, there is a reduced activity and quantity of NK cells and T cells despite the shift towards a Th2 class. These factors may increase susceptibility to SARS-CoV-2 infection.

A possible additional factor to explain the increased disease severity in pregnancy is the increased expression of ACE-2. One study reported that there was a two-fold increase in ACE-2 expression in the kidney, placenta, and uterus of pregnant patients compared with nonpregnant women.[15,17,18] As noted, the ACE-2 protein serves as a key regulator of viral entry in SARS-CoV-2 infection. Thus, increase in ACE-2 during pregnancy heightens the risk for SARS-CoV-2 infectivity.

MENOPAUSE

Menopause reflects a change of the reproductive hormone levels in women. During this phase, estrogen and progesterone levels decrease as luteinizing hormone and follicle stimulating hormones increase.

It is well known that COVID-19 has globally affected men more severely than women. Despite the increased mortality among men, we have also seen an alarming effect on female mortality. Scully et al[19] demonstrated the relationship of age and COVID-19 mortality rates desegregated by sex (Fig. 1). For women, there is an initial increase in COVID-19–associated case-fatality that begins at age 50 years, notably coinciding with the age of menopause and many other comorbidities. A more pronounced increase in COVID-19 case-fatality is seen in women older than age 70 years, where the case-fatality rate

approaches that of men. Before 70 years of age, men across all age groups had approximately twice the case-fatality rate compared with women.[20]

An explanation for the decreasing mortality gap between sexes with increasing age may be attributed to the hormonal changes that occur after menopause. These changes include decreased levels of estrogen and increased androgen production from the adrenal glands. Estrogen has demonstrated protective effects on the immune system, and androgen receptor activation has been implicated in viral infectivity as previously described.

Another theory posed by Marquez et al[20] suggests that the increased mortality with age is due to a decline in immune function. This article notes two significant immune declines throughout the lifetime. The first decline is observed in both sexes to occur approximately at age 40 years; the second and more pronounced decline occurs near age 70 years. The latter decline shows that men experience the decline 5 years earlier than women.[20] Coincidentally, the median age of COVID-19 mortality was 82 years for women and 78 years for men. This difference in immune decline may be attributed to genetic components, changes in adaptive or innate immunity, and hormonal effect.

The genetic aspect may be the result of the presence of two X-chromosomes in females, which allows for random X inactivation and the presence of a larger pool of genetic material to create immune responses.[20] Recent studies on female lymphocytes using knock-out techniques have shown that X-chromosome inactivation is predisposed to become partially reactivated.[21] Both female T and B cells, therefore, have biallelic expression increasing transcription of X-linked immune-related genes.[22] This provides mechanistic evidence to link X-chromosome inactivation to female bias observed with enhanced immunity and autoimmunity susceptibility.[22]

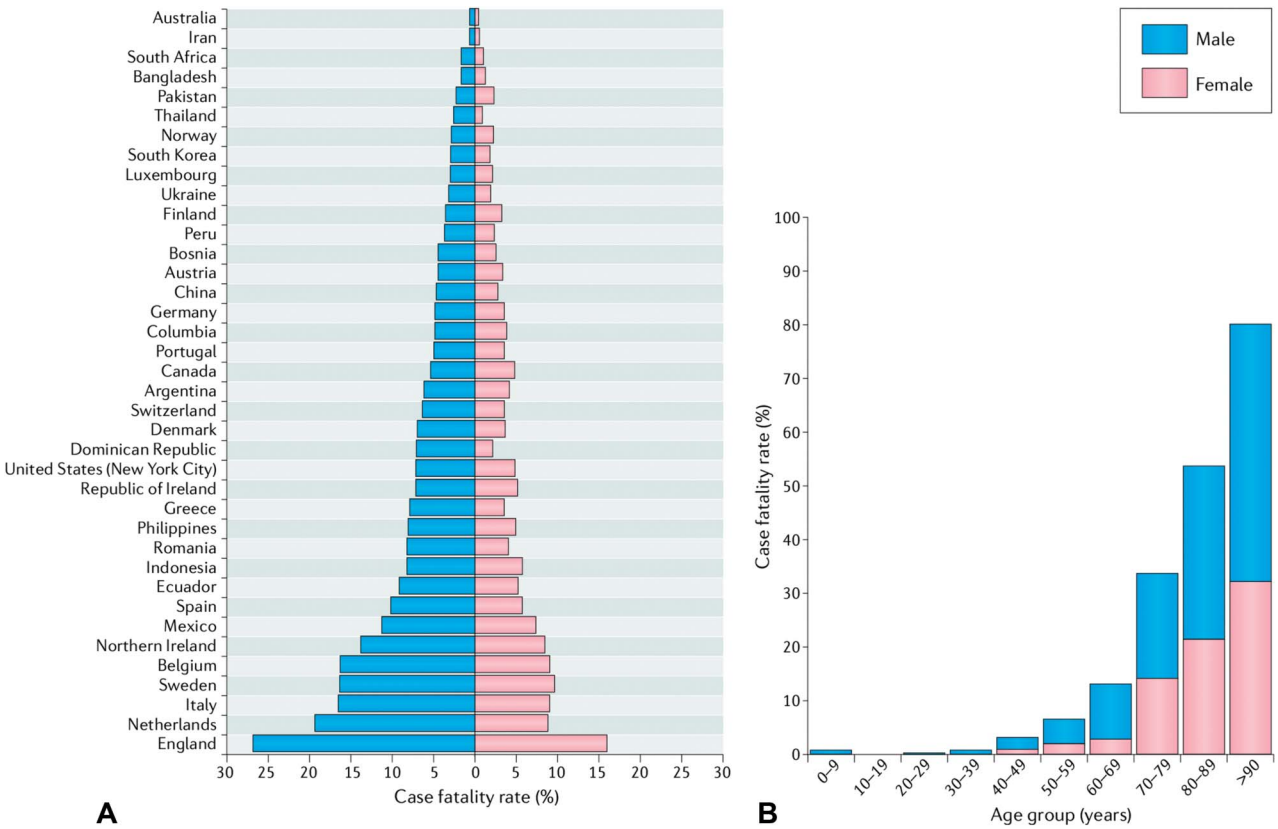

Fig. 1. Case-fatality rate by gender, age, and country. **A**. Coronavirus disease 2019 (COVID-19) case fatality rates for males and females across 38 countries or regions reporting sex-disaggregated data on COVID-19 cases and deaths. **B**. Average COVID-19 case fatality rates for males and females stratified by age. The data were obtained from Global Health 50/50 and official government websites of each respective country on 7 May and 8 May 2020. Reprinted by permission from Springer Nature: Nat Rev Immunol. 2020; 20(7):442–447 (Considering how biological sex impacts immune responses and COVID-19 outcomes. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL, 2020).

Gotluru. Coronavirus Disease 2019 (COVID-19) and Sex. Obstet Gynecol 2021.

Estrogen receptors are present on multiple immune function cells and act in a dose dependent manner. Menopause is a relatively low estrogen state favoring the Th1 innate cellular response.[15] The innate cellular response is characterized by pro-inflammatory cytokines including IL-6, among others. Marquez et al notes that males have increased inflammation correlating with levels of IL-6, which increases in males faster than females.[20] Women experience a distinct increase in IL-6 after menopause. We postulate that menopausal women have similar increases in IL-6 as males. Perhaps this increased inflammatory state is a predisposing factor to the classic cytokine storm seen in severe COVID-19.[15]

POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome is an altered hormonal state that predominantly affects females of childbearing age (typically 14–50 years). The important features of this syndrome are hyperandrogenism, numerous ovarian cysts, and irregular anovulatory menstrual cycles.[23] The prevalence of PCOS in the female population varies from 4% to 21% depending on the criteria.[23]

In a recent article by Kyrou et al[24], the similarities between patients with PCOS and high-risk patients with COVID-19 are reviewed. The classic patient with PCOS has a higher prevalence of comorbidities such as metabolic syndromes including heart disease, hypertension, diabetes mellitus, and obesity.[24,25] Metabolic syndromes have been directly associated with increased COVID-19 morbidity and mortality.[24,25]

According to epidemiologic studies, females who are of childbearing age are at decreased risk of contracting COVID-19 and have a decreased case-fatality rate.[19] Despite the seemingly protective factor of childbearing age, the subset of patients within this category who have PCOS may be at increased risk of COVID-19 disease and severity due to associated hyperinflammation and hyperandrogenism.[24] The caveat to this hypothesis is that it is difficult to independently assess the contribution of PCOS as a risk factor due to the overlap of metabolic syndrome in the male and female populations.

Polycystic ovarian syndrome is a hyperinflammatory state that makes patients more prone to activate pro-inflammatory pathways in response to infection.[24] It is often correlated with obesity with a prevalence rate of 50–80%.[26] Obesity and increased peripheral adipose tissue lead the body to experience lipotoxicity: the ectopic presence of lipid in nonadipose tissue where it induces oxidative stress.[27] This can be directly related to insulin resistance and inflammation.[27] Coronavirus disease 2019 has been strongly associated with the development of a cytokine storm syndrome producing pro-inflammatory cytokines (tumor necrosis factor-alpha, IL-6, IL-7, IL-8, and others).[20] It can be postulated that the existing inflammatory state of PCOS can more readily trigger a characteristic cytokine storm, exacerbating the COVID-19 infection.

Not only is PCOS a state of hyperandrogenism in which there are higher levels of androgens, but it is also a state of increased androgen sensitivity.[28] Androgens play an indirect role in viral entry via androgen receptor activation. When androgen receptor activation occurs, type II transmembrane serine protease is upregulated.[28] Type II transmembrane serine protease serves as a primer for the spike protein of SARS-CoV-2, which then interacts with ACE-2 for viral entry.[3,4] The increased levels and sensitivity to androgens could potentially directly affect the susceptibility to COVID-19 in patients with PCOS.[28] In theory, patients with PCOS may be at greater risk of contracting the virus and require increased surveillance by their health care professional. Despite multiple hypotheses that suggest that patients with PCOS are more susceptible to COVID-19 disease, there are no clinical data reported regarding this association. To further investigate the correlation of COVID-19 disease in patients with PCOS, we suggest that patients with PCOS be prospectively studied among a cohort of age-matched patients with similar incidences of comorbidities.

It may be useful to stratify future studies of COVID-19 infection and severity rates in patients with PCOS. Spironolactone (an antiandrogenic) is prescribed as one of the treatments for patients with PCOS with hyperandrogenic symptoms, but it is infrequently used.[29] It has been considered as therapy in patients with COVID-19 given the antiandrogenic properties and the effect on decreasing type II transmembrane serine protease expression. Liaudet et al suggest the potential use of spironolactone to prevent severe COVID-19 is due to its antiinflammatory effects through inhibition of the mineralocorticoid receptor.[30] However, spironolactone increases ACE-2 expression, which is a key factor in viral entry. This hypothesis should also be assessed in patients without PCOS who exhibit comorbidities associated with COVID-19 disease. For example, spironolactone is a common treatment for patients with hypertension or cardiac failure. In this subset of patients, COVID-19 infectivity and severity when on spironolactone therapy compared with a control group should be assessed.

SUMMARY AND CONCLUSION

There are female populations that should be considered at increased risk of COVID-19 infection and disease severity, including patients who are pregnant and are postmenopausal. Patients with PCOS may also represent a population that is at higher risk of infection, but there is a paucity of data to confirm this correlation. This commentary serves to analyze the interplay between hormones and immune function in each of these female populations with respect to COVID-19 risk, develops biological hypotheses for these relationships, and explores potential therapeutic interventions. We recognize the following limitations within this commentary: there are individuals who are not represented by binary sex, and, as of November 2020, there are no data on patients with PCOS and COVID-19. A literature review using the terms polycystic ovarian disease, PCOS, COVID-19, and SARS-CoV-2 was completed in PubMed, Cochrane Libraries, ClinicalTrials.gov, and HealthData.gov, and yielded no data comparing patients with PCOS and COVID-19.

REFERENCES

1. Centers for Disease Control and Prevention. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. Accessed September 13, 2020. https://covid.cdc.gov/covid-data-tracker/#demographics
2. Global Health 5050. The COVID-19 sex-disaggregated data tracker. Accessed September 27, 2020. https://globalhealth5050.org/the-sex-gender-and-covid-19-project/the-data-tracker/?explore=variable
3. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med 2020;202:756–9. doi: 10.1164/rccm.202001-0179LE
4. Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacol Res 2020;157:104833. doi: 10.1016/j.phrs.2020.104833
5. Salonia A, Corona G, Giwercman A, Maggi M, Minhas S, Nappi RE, et al. SARS-CoV-2, testosterone and frailty in males (PROTEGGIMI): multidimensional research project. Andrology 2020 May 5 [Epub ahead of print]. doi: 10.1111/andr.12811
6. Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 2014;4:1310–25. doi: 10.1158/2159-8290.CD-13-1010
7. Ellington S, Strid P, Tong V, Woodworth K, Galang R, Zambrano L, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status–United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769–75. doi: 10.15585/mmwr.mm6925a1
8. Hall OJ, Klein SL. Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. Mucosal Immunol 2017;10:1097–107. doi: 10.1038/mi.2017.35.
9. Hall OJ, Limjunyawong N, Vermillion MS, Robinson DP, Wohlgemuth N, Pekosz A, et al. Progesterone-based therapy protects against influenza by promoting lung repair and recovery in females. PLoS Pathog 2016;12:e1005840. doi: 10.1371/journal.ppat.1005840
10. Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. N Engl J Med 2020;382:e100. doi: 10.1056/NEJMc2009226
11. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM 2020;2:100118. doi: 10.1016/j.ajogmf.2020.100118
12. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107. doi: 10.1136/bmj.m2107
13. Centers for Disease Control and Prevention. US selected practice recommendations (US SPR) for contraceptive use, 2016. Accessed September 19, 2020. https://www.cdc.gov/reproductivehealth/contraception/mmwr/spr/summary.html
14. Costeira R, Lee KA, Murray B, Christiansen C, Castillo-Fernandez J, Lochlainn MN, et al. Estrogen and COVID-19 symptoms: associations in women from the COVID Symptom Study. medRxiv 2020. doi: 10.1101/2020.07.30.20164921.
15. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg 2015;109:9–15. doi: 10.1093/trstmh/tru167.
16. Zhao X, Jiang Y, Zhao Y, Xi H, Liu C, Qu F, et al. Analysis of the susceptibility to COVID-19 in pregnancy and recommendations on potential drug screening. Eur J Clin Microbiol Infect Dis 2020;39:1209–20. doi: 10.1007/s10096-020-03897-6.
17. Levy A, Yagil Y, Bursztyn M, Barkalifa R, Scharf S, Yagil C. ACE2 expression and activity are enhanced during pregnancy. Am J Physiol Regul Integr Comp Physiol 2008;295:R1953–61. doi: 10.1152/ajpregu.90592.2008.
18. Groban L, Wang H, Sun X, Ahmad S, Ferrario CM. Is sex a determinant of COVID-19 infection? Truth or myth? Curr Hypertens Rep 2020;22:62. doi: 10.1007/s11906-020-01073-x.
19. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 2020;20:442–7. doi: 10.1038/s41577-020-0348-8
20. Márquez EJ, Trowbridge J, Kuchel GA, Banchereau J, Ucar D. The lethal sex gap: COVID-19. Immun Ageing 2020;17:13.
21. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genomics 2019;17:13. doi: 10.1186/s12979-020-00183-z
22. Wang J, Syrett CM, Kramer MC, Basu A, Atchison ML, Anguera MC. Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. Proc Natl Acad Sci U S A 2016;113:E2029–38. doi: 10.1073/pnas.1520113113
23. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016;106:6–15. doi: 10.1016/j.fertnstert.2016.05.003.
24. Kyrou I, Karteris E, Robbins T, Chatha K, Drenos F, Randeva HS. Polycystic ovary syndrome (PCOS) and COVID-19: an

overlooked female patient population at potentially higher risk during the COVID-19 pandemic. BMC Med 2020;18:220. doi: 10.1186/s12916-020-01697-5

25. Morgante G, Troìa L, De Leo V. Coronavirus disease 2019 (SARS-CoV-2) and polycystic ovarian disease: is there a higher risk for these women? J Steroid Biochem Mol Biol 2020;205: 105770. doi: 10.1016/j.jsbmb.2020.105770
26. McCartney CR, Marshall JC. CLINICAL PRACTICE. Polycystic ovary syndrome. N Engl J Med 2016;375:54–64. doi: 10.1056/NEJMcp1514916
27. Brennan KM, Kroener LL, Chazenbalk GD, Dumesic DA. Polycystic ovary syndrome: impact of lipotoxicity on metabolic and reproductive health. Obstet Gynecol Surv 2019;74:223–31. doi: 10.1097/OGX.0000000000000661
28. Wambier CG, Goren A, Vaño-Galván S, Ramos PM, Ossimetha A, Nau G, et al. Androgen sensitivity gateway to COVID-19 disease severity. Drug Dev Res 2020;81:771–6. doi: 10.1002/ddr.21688.
29. Alpañés M, Álvarez-Blasco F, Fernández-Durán E, Luque-Ramírez M, Escobar-Morreale HF. Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: a one-year randomized clinical trial. Eur J Endocrinol 2017;177:399–408. doi: 10.1530/EJE-17-0516
30. Liaudet L, Szabo C. Blocking mineralocorticoid receptor with spironolactone may have a wide range of therapeutic actions in severe COVID-19 disease. Crit Care 2020;24:318. doi: 10.1186/s13054-020-03055-6

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