Sex differences in COVID-19 course and outcome: progesterone should not be neglected

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LETTER TO THE EDITOR

Sex differences in COVID-19 course and outcome: progesterone should not be neglected

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TO THE EDITOR: Almost immediately after the pandemic outbreak in China, sex differences in COVID-19 vulnerability and clinical presentation were observed (9, 17, 23), indicating some protective mechanism in females. A reasonable biological explanation was offered by well-known estrogen ability to boost immune response and likely modulate angiotensin-converting enzyme 2 (ACE2) expression (4, 6, 18, 22), which should imply a lower rate of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in females because of the more robust immune response. However, recent retrospective studies using large, pooled sex-disaggregated data from countries worldwide find no differences in the number of COVID-19 cases between the sexes, but higher severity [according to the number of hospitalizations and intensive care unit (ICU) admissions] and case fatality in males (7, 16). Male-to-female COVID-19 case fatality ratios, obtained from different countries, were found to be relatively uniform and range between 1.7 and 1.8 (7), supporting universal biological mechanisms responsible for reduced case fatality rate in females, independent of demographic and sociocultural factors. Interestingly, the male case fatality predominance was shown to be most pronounced in the middle age group and to linearly decline in the higher age groups (7), suggesting a loss of females' physiological protective factor/s during aging. The main pathophysiological event strongly associated with fatal outcome in COVID-19 patients is cytokine release syndrome (cytokine storm) development, triggered by the uncontrolled hyperimmune response (1, 14, 20), which may actually be aggravated by immunostimulatory effects of estrogen. In the recent study, severe COVID-19 patients on respiratory support who were treated with dexamethasone showed significantly reduced 28-day mortality compared with usual care group (19), emphasizing the beneficial effects of immunosuppression in alleviating COVID-19 severity. In that terms, lower COVID-19 vulnerability in females could be provided by progesterone, rather than estrogen. Namely, progesterone is well known for its immunosuppressive and anti-inflammatory effects (6, 13, 15, 18) that could mitigate hyperinflammatory reaction counteracting cytokine storm development. Progesterone has been shown to stimulate T regulatory cell (Treg) differentiation, restrain Th17 responses but enhance interferon-alpha (IFN-α) pathways (10, 13, 18), which all together could be of particular importance for keeping the viral replication under control, but without excessive and self-reinforcing inflammation. Furthermore, animal studies showed progesterone ability to promote lung repair and recovery by inducing epidermal growth factor amphiregulin (Areg), protecting thus adult female mice against lethal Influenza A virus (IAV) infection (11, 15). Progesterone was also found to be effective in the mitigation of noninfectious inflammatory lung injuries in animal models, where even inhalation of progesterone provided protection (5).

Most of the progesterone immune effects are achieved through the progesterone receptor (PR), which is widely distributed on the immune cells and acts by the transrepression manner to inhibit proinflammatory gene transcription (10). However, owing to the considerable pleiotropism, progesterone can bind and activate other steroid receptors, preferably glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), but with less potency than the original ligands (10). Knowing the physiological effects of the corresponding hormones, some potentially protective effects of progesterone during SARS-CoV-2 infection could be also attributed to the progesterone-mediated activation of GRs and MRs. The beneficent effect of GRs activation is in line with the aforementioned reduction of mortality in dexamethasone-treated severe COVID-19 patients (19). Moreover, recent studies on animal models suggest that progesterone immunomodulatory impact on T cell response is achieved strictly by means of GRs (12). On the other hand, by increasing blood volume, progesterone-mediated MR activation could reduce constitutive renin secretion from juxtaglomerular cells and consequently decrease the production of proinflammatory and profibrotic angiotensin II (Ang II) molecule. This thesis is supported by a recent clinical study showing that females require a lower dose of ACE inhibitors than males to achieve a satisfactory therapeutic effect (21). Withal, progesterone has been found to decrease cell infection by human immunodeficiency virus (HIV) retaining viral particles in the endosomal-type vesicles and preventing thus "trapped" virus to spread (2, 3). Previous studies also showed that progesterone is able to inhibit fluid phase endocytosis-mediated HIV cellular uptake (3). Besides, a recent study on the SARS-CoV-2 protein interaction map found that progesterone can antagonize endoplasmic reticulum Sigma receptors that are implicated in trafficking and assembly of viral components, eventually disrupting endocytic pathway exploited by the SARS-CoV-2 (8).

Although the role of progesterone in the context of SARS-CoV-2 infection has been somewhat neglected and rarely discussed so far, the available data strongly indicate progesterone importance in establishing sex disparity of COVID-19 course and outcome. Moreover, cumulative

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evidence points to the protective role of progesterone during SARS-CoV-2 infection nominating it for drug repurposing consideration (8).

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AUTHOR CONTRIBUTIONS

H.J. conceived and designed research; H.J. drafted manuscript; H.J. edited and revised manuscript; H.J. approved final version of manuscript.

REFERENCES

1. **Abdin SM**, **Elgendy SM**, **Alyammahi SK**, **Alhamad DW**, **Omar HA.** Tackling the cytokine storm in COVID-19, challenges and hopes. *Life Sci* 257: 118054, 2020. doi:10.1016/j.lfs.2020.118054.
2. **Carrière F**, **Longhi S**, **Record M.** The endosomal lipid bis(monoacylglycero) phosphate as a potential key player in the mechanism of action of chloroquine against SARS-COV-2 and other enveloped viruses hijacking the endocytic pathway. *Biochimie* S0300-9084(20)30129-2, 2020. doi:10.1016/j.biochi.2020.05.013.
3. **Chapuy-Regaud S**, **Subra C**, **Requena M**, **de Medina P**, **Amara S**, **Delton-Vandenbroucke I**, **Payre B**, **Cazabat M**, **Carriere F**, **Izopet J**, **Poirot M**, **Record M.** Progesterone and a phospholipase inhibitor increase the endosomal bis(monoacylglycero)phosphate content and block HIV viral particle intercellular transmission. *Biochimie* 95: 1677–1688, 2013. doi:10.1016/j.biochi.2013.05.019.
4. **Conti P**, **Younes A.** Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J Biol Regul Homeost Agents* 34: 339–343, 2020. doi:10.23812/Editorial-Conti-3.
5. **Fei X**, **Bao W**, **Zhang P**, **Zhang X**, **Zhang G**, **Zhang Y**, **Zhou X**, **Zhang M.** Inhalation of progesterone inhibits chronic airway inflammation of mice exposed to ozone. *Mol Immunol* 85: 174–184, 2017. doi:10.1016/j.molimm.2017.02.006.
6. **Gargaglioni LH**, **Marques DA.** Let's talk about sex in the context of COVID-19. *J Appl Physiol (1985)* 128: 1533–1538, 2020. doi:10.1152/japplphysiol.00335.2020.
7. **Gebhard C**, **Regitz-Zagrosek V**, **Neuhauser HK**, **Morgan R**, **Klein SL.** Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* 11: 29, 2020. doi:10.1186/s13293-020-00304-9.
8. **Gordon DE**, **Jang GM**, **Bouhaddou M**, **Xu J**, **Obernier K**, **White KM**, **O'Meara MJ**, **Rezelj VV**, **Guo JZ**, **Swaney DL**, **Tummino TA**, **Hüttenhain R**, **Kaake RM**, **Richards AL**, **Tutuncuoglu B**, **Foussard H**, **Batra J**, **Haas K**, **Modak M**, **Kim M**, **Haas P**, **Polacco BJ**, **Braberg H**, **Fabius JM**, **Eckhardt M**, **Soucheray M**, **Bennett MJ**, **Cakir M**, **McGregor MJ**, **Li Q**, **Meyer B**, **Roesch F**, **Vallet T**, **Mac Kain A**, **Miorin L**, **Moreno E**, **Naing ZZC**, **Zhou Y**, **Peng S**, **Shi Y**, **Zhang Z**, **Shen W**, **Kirby IT**, **Melnyk JE**, **Chorba JS**, **Lou K**, **Dai SA**, **Barrio-Hernandez I**, **Memon D**, **Hernandez-Armenta C**, **Lyu J**, **Mathy CJP**, **Perica T**, **Pilla KB**, **Ganesan SJ**, **Saltzberg DJ**, **Rakesh R**, **Liu X**, **Rosenthal SB**, **Calviello L**, **Venkataramanan S**, **Liboy-Lugo J**, **Lin Y**, **Huang XP**, **Liu Y**, **Wankowicz SA**, **Bohn M**, **Safari M**, **Ugur FS**, **Koh C**, **Savar NS**, **Tran QD**, **Shengjuler D**, **Fletcher SJ**, **O'Neal MC**, **Cai Y**, **Chang JCJ**, **Broadhurst DJ**, **Klippsten S**, **Sharp PP**, **Wenzell NA**, **Kuzuoglu-Ozturk D**, **Wang HY**, **Trenker R**, **Young JM**, **Cavero DA**, **Hiatt J**, **Roth TL**, **Rathore U**, **Subramanian A**, **Noack J**, **Hubert M**, **Stroud RM**, **Frankel AD**, **Rosenberg OS**, **Verba KA**, **Agard DA**, **Ott M**, **Emerman M**, **Jura N**, **von Zastrow M**, **Verdin E**, **Ashworth A**, **Schwartz O**, **d'Enfert C**, **Mukherjee S**, **Jacobson M**, **Malik HS**, **Fujimori DG**, **Ideker T**, **Craik CS**, **Floor SN**, **Fraser JS**, **Gross JD**, **Sali A**, **Roth BL**, **Ruggero D**, **Taunton J**, **Kortemme T**, **Beltrao P**, **Vignuzzi M**, **García-Sastre A**, **Shokat KM**, **Shoichet BK**, **Krogan NJ.** A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 583: 459–468, 2020. doi:10.1038/s41586-020-2286-9.
9. **Guan WJ**, **Ni ZY**, **Hu Y**, **Liang WH**, **Ou CQ**, **He JX**, **Liu L**, **Shan H**, **Lei CL**, **Hui DSC**, **Du B**, **Li LJ**, **Zeng G**, **Yuen KY**, **Chen RC**, **Tang CL**, **Wang T**, **Chen PY**, **Xiang J**, **Li SY**, **Wang JL**, **Liang ZJ**, **Peng YX**, **Wei L**, **Liu Y**, **Hu YH**, **Peng P**, **Wang JM**, **Liu JY**, **Chen Z**, **Li G**, **Zheng ZJ**, **Qiu SQ**, **Luo J**, **Ye CJ**, **Zhu SY**, **Zhong NS**; **China Medical Treatment Expert Group for Covid-19.** Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382: 1708–1720, 2020. doi:10.1056/NEJMoa2002032.
10. **Hall OJ**, **Klein SL.** Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. *Mucosal Immunol* 10: 1097–1107, 2017. doi:10.1038/mi.2017.35.
11. **Hall OJ**, **Limjunyawong N**, **Vermillion MS**, **Robinson DP**, **Wohlgemuth N**, **Pekosz A**, **Mitzner W**, **Klein SL.** Progesterone-based therapy protects against influenza by promoting lung repair and recovery in females. *PLoS Pathog* 12: e1005840, 2016. doi:10.1371/journal.ppat.1005840.
12. **Hierweger AM**, **Engler JB**, **Friese MA**, **Reichardt HM**, **Lydon J**, **DeMayo F**, **Mittrücker HW**, **Arck PC.** Progesterone modulates the T-cell response via glucocorticoid receptor-dependent pathways. *Am J Reprod Immunol* 81: e13084, 2019. doi:10.1111/aji.13084.
13. **Hughes GC.** Progesterone and autoimmune disease. *Autoimmun Rev* 11: A502–A514, 2012. doi:10.1016/j.autrev.2011.12.003.
14. **Jakovac H.** COVID-19 and vitamin D—Is there a link and an opportunity for intervention? *Am J Physiol Endocrinol Metab* 318: E589, 2020. doi:10.1152/ajpendo.00138.2020.
15. **Kadel S**, **Kovats S.** Sex hormones regulate innate immune cells and promote sex differences in respiratory virus infection. *Front Immunol* 9: 1653, 2018. doi:10.3389/fimmu.2018.01653.
16. **Kragholm K**, **Andersen MP**, **Gerds TA**, **Butt JH**, **Østergaard L**, **Polcwiartek C**, **Phelps M**, **Andersson C**, **Gislason GH**, **Torp-Pedersen C**, **Køber L**, **Schou M**, **Fosbøl EL.** Association between male sex and outcomes of Coronavirus Disease 2019 (Covid-19)—a Danish nationwide, register-based study. *Clin Infect Dis* ciaa924, 2020. doi:10.1093/cid/ciaa924.
17. **Mo P**, **Xing Y**, **Xiao Y**, **Deng L**, **Zhao Q**, **Wang H**, **Xiong Y**, **Cheng Z**, **Gao S**, **Liang K**, **Luo M**, **Chen T**, **Song S**, **Ma Z**, **Chen X**, **Zheng R**, **Cao Q**, **Wang F**, **Zhang Y.** Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* ciaa270, 2020. doi:10.1093/cid/ciaa270.
18. **Moulton VR.** Sex hormones in acquired immunity and autoimmune disease. *Front Immunol* 9: 2279, 2018. doi:10.3389/fimmu.2018.02279.
19. **RECOVERY Collaborative Group**; **Horby** P, **Lim** WS, **Emberson** JR, **Mafham** M, **Bell** JL, **Linsell** L, **Staplin** N, **Brightling** C, **Ustianowski** A, **Elmahi** E, **Prudon** B, **Green** C, **Felton** T, **Chadwick** D, **Rege** K, **Fegan** C, **Chappell** LC, **Faust** SN, **Jaki** T, **Jeffery** K, **Montgomery** A, **Rowan** K, **Juszczak** E, **Baillie** JK, **Haynes** R, **Landray** MJ**.** Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med*, 2020. doi:doi:10.1056/NEJMoa2021436.
20. **Romagnoli S**, **Peris A**, **De Gaudio AR**, **Geppetti P.** SARS-CoV-2 and COVID-19: From the Bench to the Bedside. *Physiol Rev* 100: 1455–1466, 2020. doi:10.1152/physrev.00020.2020.
21. **Santema BT**, **Ouwerkerk W**, **Tromp J**, **Sama IE**, **Ravera A**, **Regitz-Zagrosek V**, **Hillege H**, **Samani NJ**, **Zannad F**, **Dickstein K**, **Lang CC**, **Cleland JG**, **Ter Maaten JM**, **Metra M**, **Anker SD**, **van der Harst P**, **Ng LL**, **van der Meer P**, **van Veldhuisen DJ**, **Meyer S**, **Lam CSP**; **ASIAN-HF investigators**; **Voors AA.** Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet* 394: 1254–1263, 2019. doi:10.1016/S0140-6736(19)31792-1.
22. **Suba Z.** Prevention and therapy of COVID-19 via exogenous estrogen treatment for both male and female patients. *J Pharm Pharm Sci* 23: 75–85, 2020. doi:10.18433/jpps31069.
23. **Zhao S**, **Cao P**, **Chong MKC**, **Gao D**, **Lou Y**, **Ran J**, **Wang K**, **Wang W**, **Yang L**, **He D**, **Wang MH.** COVID-19 and gender-specific difference: analysis of public surveillance data in Hong Kong and Shenzhen, China, from January 10 to February 15, 2020. *Infect Control Hosp Epidemiol* 41: 750–751, 2020. doi:10.1017/ice.2020.64.