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Sex Hormones May Be Key Weaponry in the Fight Against COVID-19

Why male patients are at greater risk of severe complications from the Coronavirus

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With Franck Mauvais-Jarvis MD, PhD

Sex differences are routinely observed in comorbidities associated with a poor COVID-19 outcome. Many conditions such as heart disease, hypertension, obesity, and diabetes have distinct sex differences even in the absence of COVID-19. A recent article by Franck Mauvais-Jarvis MD, PhD, Director of the Diabetes Discovery Research and Sex-Based Medicine Laboratory at Tulane University Health Sciences Center and colleagues reviewed the direct role that sex hormones have on immunomodulation in reference to corona virus infections.

It's a pattern that was observed during the SARS-COV and MERS outbreaks, and is present in the current Coronavirus pandemic. Dr. Mauvais-Jarvis says:

> "The observation that men have more severe COVID-19 outcomes is likely to be multifactorial, including the fact that women usually mount a stronger immune response to viral infections. This difference in immune response is due to genetic differences in sex chromosomes and possibly the immunomodulation by sex hormones."

When it comes to corona viruses, men are at greater risk than women

SARS, severe acute respiratory syndrome, is the illness produced by the SARS-COV corona virus which spread across international lines in 2002. Data suggests that sex and age were two independent risk factors for SARS-related mortality. Being male increased the relative risk of death by more than 60%.

MERS, Middle Eastern respiratory syndrome, is also caused by a corona virus and had a substantial outbreak in 2012. A study from Saudi Arabia found that among 425 infected patients, men made up 62% of the cases and had a fatality rate of 52%. Women, on the other hand, had a case fatality rate of only 23%. This pattern was also seen in Korea, where 60% of cases were in men. Most interestingly, this study found that women were more likely to be exposed to the virus because of their higher numbers in the healthcare field, but they still accounted for only 40% of cases. The authors then theorized that women might be less susceptible to MERS infection than men.

COVID-19, our most recent corona virus outbreak, is caused by the SARS-COV2 virus, a close cousin to SARS-COV. Data from the international community, including China, Italy, and the UK, all support the theory that SARS-COV2 infected men are more likely to have severe COVID-19 symptoms and fatal outcomes compared to infected women.

Using data collected at New York City area hospitals between March 1 to April 4, 2020, a new study found that in COVID-19 patients sufficiently sick to require hospitalization, 60% were men. For those admitted to the ICU, 66% were also men. The difference between men and women was also reflected in the COVID-19 mortality rates, and was present at every age point except the youngest subsets.

responses have been observed for some time, though relatively understudied. The pandemic and differences in COVID-19 morbidity and mortality by age and sex have raised attention to these questions, and to the therapeutic potential of sex hormones as short-acting immune modulatory drugs in fighting infectious diseases."

Androgens could put men at a disadvantage

Recently a pattern has emerged among male COVID-19 patients suggesting that male pattern baldness (androgenetic alopecia) is associated with positive SARS-COV2 infections and a more severe COVID-19 outcome. It's hypothesized that androgens, a key player in this form of baldness, may also be involved in the sex differences observed in COVID-19 patients.

The SARS-COV2 virus gains entry into cells using the ACE2 receptor, facilitated by the serine protease, transmembrane protease, serine 2 (TMPRSS2), an androgen dependent enzyme. TMPRSS2 is up-regulated in prostate cancer. A study by Chakravarty et al. found that men with prostate cancer were more likely to be intubated when infected with SARS-COV2 than men with other cancers. Furthermore, they had a greater likelihood of dying than other male cancer patients. An Italian study confirms that cancer in general is a risk factor for SARS-COV2 infection and that men with prostate cancer are at greater risk than other types of cancer. However, androgen-deprivation therapy seemed to have a protective effect in prostate cancer patients, reducing the likelihood of infection even below that of other cancers.

Can sex hormones be used to combat COVID-19?

There are multiple clinical trials (https://clinicaltrials.gov/ct2/results?pg=1&load=cart&id=NCT04365127+OR+NCT04374279+OR+NCT04359329+OR+NCT04539626+OR+NCT04509999+OR+NCT04531748+OR+NCT04446429+OR+NCT04475601) underway seeking to determine if sex hormones can be used to combat COVID-19. Currently active studies include:

NCT 04359329 (https://clinicaltrials.gov/show/NCT04359329) : This study will be comparing a short 7-day course of estradiol (100mg) using a transdermal patch compared to standard care, based on random assignment. They are recruiting patients positive for COVID19 or presumptive positive, both adult men (>= 18yo) and older women (>=55 yo). The primary outcomes are rates of hospitalizations, transfer to ICU, intubations, and mortality. Investigators from Stony Brook University Hospital in New York are heading up this clinical trial.