Letter to the Editor

Valentina Corda, Federica Murgia and Giovanni Monni*

COVID-19 vaccine: the gender disparity

https://doi.org/10.1515/jpm-2021-0246
Received May 13, 2021; accepted June 1, 2021;
published online June 14, 2021

Keywords: Covid-19; gender; vaccination.

To the Editor,

Gender factors are a key variable which influences the vulnerability to infectious diseases as well as the drug response and immune system modulation. The prevalence and severity of bacterial, viral, and parasitic infections is higher in males, whereas women react more vigorously and effectively to both infections and vaccines [1].

Unfortunately, gender medicine, as many other fields of medical science, has been greatly challenged by the currently ongoing COVID-19 pandemic. The mortality rate of the previous coronavirus epidemic outbreaks was significantly higher for men, compared to women. In line with these findings, SARS-CoV-2 infection showed a lower incidence of severe cases and mortality amongst women. Moreover, previously published studies based on gender analysis report lower mortality and complication rates in women compared to men [2].

The mechanisms responsible for this scenario can be summarized in several main points: the active regions of X chromosomes together with the sex hormones could play a pivotal role in modeling the type, extent, and duration of inflammatory responses and possibly explain the low risk and better prognosis of the SARS-CoV-2 infection in women.

Diverse evidence suggested a distinct phenotypic expression of the cellular system essential for the interaction between SARS-CoV-2 and target tissues in both sexes. In particular, the access to the host cell by COVID-19 begins with the interaction between the Spike protein exposed on the viral capsid and the host protein Angiotensin-converting enzyme (ACE2), whose expression and activity differ according to sex, as is well-known. This phenomenon can be determined in part by the action of sex hormones and in part by the chromosomal set [3].

Interestingly, the gene encoding for ACE2 is located in a region which eludes the inactivation of the X chromosome, generating a potentially genetic unbalance in the two sexes. Furthermore, the Leydig and Sertoli cells express ACE2 much more markedly than the ovary.

Gender is also a biological variable of great impact in the modulation of the immune response. While estrogens can stimulate or inhibit immune responses depending on the levels achieved, testosterone suppresses them.

However, these observations are just a part of a vaster and more complex picture consisting of biological, behavioral, and social aspects that can significantly influence the impact of the disease and its consequences. Having taken this into consideration, it would be reasonable to hypothesize gender-based differences in the vaccination response. Indeed, the cellular response to some vaccinations is also greater in women [4].

Adverse reactions to vaccinations are more frequent and often more serious in women due to the stronger female immuno-reactivity. Despite the widely documented evidence of gender diversity in immune responses, this key point would seem somewhat neglected in terms of design, dosage, and management of drugs and vaccines.

Based on the published reports, the COVID-19 vaccine safety issue has not been adequately addressed in terms of gender variability if we consider the data analysis from the agencies for the approval of the four vaccines currently administered worldwide [5–9].

Furthermore, it is still unclear whether the stronger immuno-reactivity in women could be potentially associated with a longer lasting or overall superior protection from COVID-19.

Obviously, the consideration of the female sex in the design of drugs and vaccines could be further hindered by hormonal fluctuations, pregnancy, and breastfeeding, but this cannot justify such a deficiency.

***Corresponding author: Giovanni Monni**, MD, Department of Obstetrics and Gynecology, Prenatal and Preimplantation Genetic Diagnosis, Fetal Therapy, Microcitemico Pediatric Hospital "A. Cao", via Edward Jenner SNC, Cagliari 09121, Sardinia, Italy,
Phone: +39 070 52965546/7, Fax: +39 070 52965514,
E-mail: prenatalmonni@tiscali.it
Valentina Corda and Federica Murgia, Department of Obstetrics and Gynecology, Prenatal and Preimplantation Genetic Diagnosis, Fetal Therapy, Microcitemico Pediatric Hospital "A. Cao", Cagliari, Sardinia, Italy

Understanding the gender related mechanisms underlying the COVID-19 pandemic should not be considered an additional option for research but a fundamental aspect which will guarantee the best tailored health policy for each woman, globally.

Therefore, it is essential:

- To obtain further knowledge on gender differences in response to vaccinations and the mechanisms involved by identifying, for example, the sex-related biomarkers (sex hormones, vitamin D, micro RNA, and methylation patterns) that can predict the response to vaccines;
- To optimize the health surveillance programs of healthcare workers who are predominantly women;
- To implement gender-specific prevention programs;
- To better define shared prevention programs for pregnant and breastfeeding women.

These considerations are of vital importance in disadvantaged populations and in poor communities, where women are most vulnerable [10].

The aim of this observation is not only to identify the controversial issues of vaccination and gender disparity but to open new horizons towards optimizing the research by offering vaccination of more fitting design.

Acknowledgments: The authors of this manuscript would like to thank Fondazione di Sardegna and Boyana Petrova Tsikalova, MA in English Philology for editing assistance.
Research funding: None declared.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Not applicable.
Ethical approval: Not applicable.

References

1. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626–38.
2. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 2020;8:e20.
3. Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS- CoV-2 receptor. Pharmacol Res 2020;157:104833.
4. Fink AL, Klein SL. The evolution of greater humoral immunity in females than males: implications for vaccine efficacy. Curr Opin Physiol 2018;6:16–20.
5. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. Lancet Infect Dis 2021;21:e26–35.
6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. For the C4591001 clinical trial group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383: 2603–15.
7. Baden LR, El Sahly HM, Essink B, Kotlon K, Frey S, Novak R, et al. For the COVE study group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
8. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111.
9. Sadoff J, Le Gars M, Shukarev G, Heerwgh D, Truyers C, de Groot AM , et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med 2021;13:NEJMoa2034201.
10. Gausman J, Langer A. Sex and gender disparities in the COVID-19 pandemic. J Wom Health 2020;29:465–6.