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Effects of gender on the efficacy and response to COVID-19 vaccination; a review study on current knowledge

Ali Rastegar Kashkouli[1*], Mohsen Jafari[1], Pourya Yousefi[1]

Abstract
Vaccination is one of the most important public health strategies to reduce mortality and morbidity of various infectious diseases. The COVID-19 pandemic was declared, on March 11, 2020, since then, the virus has spread rapidly, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have played the main substantial role in advancing the management of the COVID-19 pandemic. As is well known, sex/gender-related differences affect vaccine efficacy, response, and acceptability. This review aims to compare the effects of sexual dimorphism and gender-related differences factors on the efficacy, responses, and acceptance of the COVID-19 vaccines. As far as the COVID-19 vaccine effectiveness is concerned, both males and females with the COVID-19 vaccine showed consistent and impressive efficacy; although males showed slightly greater efficacy, there was no significant correlation between the efficacy of the COVID-19 vaccine and their sex or gender differences. Consequently, to reduce adverse reactions in females, sex differences should be considered in the design of the COVID-19 vaccine. It is also essential to conduct pragmatic trials to verify whether sex differences in vaccine response and efficacy vary with age.

Keywords: SARS-CoV-2, COVID-19, Gender and/or sex differences, Sexual dimorphism, Vaccine, Adverse reaction
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Introduction

Vaccination is one of the most important public health strategies to reduce mortality and morbidity of various infectious diseases (1). As is well known, sex/gender-related differences affect vaccine efficacy, adverse events, and acceptability (2). As a result of the differential response of the immune system to vaccination between males and females, many factors are involved, including the effect of sex hormones on the immune system as well as genetics and epigenetics (3). In this review, sexual dimorphism is described in the context of innate and adaptive immune responses to COVID-19 vaccine, expression of X-linked genes, and sex hormone levels.

Sexual dimorphism and vaccine adverse events

Sex (i.e., the biological diversity amongst males and females) and gender (i.e., cultural and societal norms related to being male or female) influence responses, efficacy, and acceptance of the vaccination (4). Studies have shown that vaccine acceptance is frequently lower among females (5) but, once vaccinated, elicits a more significant antibody response and lasts longer as compared to males (4). Vaccines often trigger greater inflammatory, antibody, and cell-mediated immune responses in females, which makes them more susceptible to autoimmune disease. This might be one of the reasons why females have a higher rate of adverse reactions and a lower probability of vaccine acceptance than males (6).

According to a study that evaluated relevant data from 1990 to 2016, about 83% of anaphylactic reactions to vaccines among adults (19-49 years) were reported in females (7).

Data from the Centers for Disease Control and Prevention (CDC) that studied the side effects of the H1N1 vaccine in adults aged 20 to 59 years indicated that females were four times more likely than males to experience hypersensitivity reactions after vaccination. Female-biased efficacy of vaccines and more adverse events following vaccination may be attributed to these differences (8). In an attempt to explain the differences in vaccine response between the sexes, a number of biological mechanisms have been proposed.

Effects of sex hormones on immunological response to vaccines

The level of sex-related steroids, including testosterone, estrogens, and progesterone, differ between sexes; females generally have higher quantities of estrogen and progesterone, while males typically have higher levels of testosterone (9). Several steroid hormones, particularly

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[1]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
***Corresponding Author:** Ali Rastegar Kashkouli, Email: dralirastegar97@gmail.com

Implication for health policy/practice/research/ medical education

Despite considerable biological and behavioral differences between males and females, we found no significant correlation between sex differences and efficacy.

testosterone, estradiol, and progesterone, affect immune function (10). Estradiol stimulates B cell antibody production, which is one of the possible mechanisms for females producing high levels of antibodies before reproductive senescence (11). Males with higher testosterone levels had faster lipid metabolism and less antibody response to vaccinations (4). Interestingly, half of the promoters of the active genes in adult female T cells respond directly to estrogen, suggesting estrogen can regulate their expression and activity (12).

Effects of genetics and epigenetics on immune responses to vaccines

A major part of the mammalian genome express microRNAs (miRNAs), and some studies have shown that miRNAs affect vaccine responses (13). The X chromosome has a number of genes that regulate immune function; these may play a role in sex-specific reactions to vaccines. While the Y chromosome only contains two miRNAs, the X chromosome has a greater number of miRNAs (accounts for 10% of the human genome's ~800 miRNAs) (14). Females with incomplete X inactivation express more miRNAs, which may affect how differently males and females respond to vaccines (4).

COVID-19 vaccination during the pandemic

As we know, the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak was first detected in Wuhan, China, in December 2019. On February 11, 2020, the World Health Organization (WHO) announced this disease due the SARS-CoV-2 as coronavirus disease (COVID-19), then exactly one month later, on March 11, 2020, the COVID-19 pandemic was declared(15). Since then, the virus has spread rapidly, and as of October 13, 2022, 620 301 709 confirmed cases of COVID-19, including 6 540 487 deaths, have been reported to the WHO (15). With 12 782 955 639 vaccine doses administered as of October 13, 2022, SARS-CoV-2 vaccines are the utmost important advance in the management of the SARS-CoV-2 pandemic (15, 16).

The effectiveness and care of vaccines in individuals are affected by sex-related factors by different mechanisms. The subject the sex-related efficacy and safety is currently highlighted following the rapid development of SARS-CoV-2 vaccines (17). In fact, it is difficult to draw a comprehensive assumption regarding the association of sex to vaccine efficacy and safety because sex-disaggregated data for SARS-CoV-2 vaccines are still disorganized and incomplete. Additionally, recent studies seldom comprised sex-disaggregated data analysis in their study designs (18).

This review aims to compare the effect of sexual dimorphism and gender/sex-related differences factors on the efficacy, responses, and acceptance of the COVID-19 vaccines.

Search strategy

The studies were identified using the PubMed database, EMBASE, Scopus, and DOAJ and, published until October 10, 2022.

The search was performed by using the following keywords: Gender and/or sex differences, Sexual dimorphism, Vaccine, Adverse reaction, COVID-19, SARS-CoV-2.

Clinical trials, systematic reviews, and retrospective and prospective studies were included. Three authors reviewed all study abstracts. Studies were included if sex/gender differences in response to the vaccine were reported. Studies written in languages other than English were excluded. All selected studies were qualitatively analyzed.

Effects of sex difference on COVID-19 vaccine adverse events

Vaccine efficacy and safety reports have enabled the use of pharmacovigilance methods and the documentation of rare adverse-effects not initially considered during clinical trials for COVID-19 vaccines (19). The CDC reported that of the 13.7 million initial doses of the COVID-19 vaccine inject into to Americans, females accounted for only 61.2% (or 8 436 863) of the 13 794 904 vaccine recipients, while 79.1% (or 5413) of the 6994 registered side effects were related to females (19). As a previous study has shown, after the injection of the mRNA COVID-19 vaccines in the U.S. between December 14, 2020 and January 18, 2021, 44 of the 47 participants who reported anaphylactic reactions to the Pfizer-BioNTech vaccine as well as 19 of the 19 participants who reported different side effects to the Moderna vaccine were female (20,21).

Likewise, Swissmedic assessed 1,953 cases of adverse effects from approximately 2.8 million doses of Moderna and Pfizer-BioNTech vaccines injected in Switzerland (as of May 4, 2021). As stated in their report, 69.2% of side effects, ranging in severity from mild (e.g., erythema around the injection site) to severe (e.g., mortality) were reported by females and 27.8% by males. Indeed, the preliminary data described above suggest that the risk of adverse events after vaccination against COVID-19 is higher in females than males (22). Based on the latest studies, COVID-19 vaccination has been linked to thrombotic events such as cerebral venous sinus thrombosis (CVST) and thrombocytopenia through immunological signals. According to the CDC's Vaccine Adverse Reporting System (VAERS), 22 of 28 confirmed cases of thrombosis with thrombocytopenia in the United States after the Jansen vaccine were females (out of approximately

8.7 million doses injected through May 7, 2021) (23). Furthermore, the European Medicines Agency (EMA) acknowledged that AstraZeneca and Janssen vaccines might cause thrombotic episodes. According to the EMA's report of about 34 million initial doses of AstraZeneca vaccine prescribed in Europe and the UK by April 4, 2021, there have been approximately 169 cases of CVST and 53 cases of splanchnic vein thrombosis reported after the first dose of the vaccine was administered (16). As reported by the European Union Pharmacopoeia database, the incidence of thrombocytopenia or thrombosis is less than one per 10 000 of cases (24, 25). Since female participants are more likely to develop autoimmune disorders and have more adverse vaccine reactions due to their stronger immune responses, vaccination programs worldwide are significantly limited by the lack of sex-related guidelines on this subject (26,27).

COVID-19 vaccine efficacy according to sex

We conducted a PubMed search for safety and/or efficacy data in peer-reviewed studies from phase III vaccine trials, and the following results were obtained. The Pfizer/BioNTech vaccine efficacy was demonstrated to be (96.4%) in males and (93.7%) in females (28). The efficacy of the Moderna vaccine was (95.4%) in males and (93.1%) in females (29). Regarding Sputnik V, studies reported the efficacy of the vaccine (94.2%) in males and (87.5%) in females (30). The Janssen vaccine efficacy by administration of a single dose was observed in males (69.8%) and females (60.3%) (31). Sex classification for the AstraZeneca vaccination was not provided (32). The overall effect of the COVID-19 vaccine was 95.1% and 92.3% in males and females, respectively (33). The trials found that the COVID-19 vaccine was highly influential in both males and females, and there were no significant sex-related differences in vaccine efficacy. The data are summarized in Table 1.

Studies that provided data on the COVID-19 vaccine's sex-specific efficacy indicated that the vaccine's effectiveness was slightly greater in males than in females (33).

Biological factors such as immunity, hormones, and genetics may influence vaccine response the by sexes (34). This can also be related to behavioral variables such as immunization, opportunity and willingness, as well as potential risk exposure in the workplace (4,35).

COVID-19 vaccines showed to be effective in both males and females, without consisting of their age. SARS-CoV-2 infections can be prevented by COVID-19 vaccines with efficacy ratings over 90%. Additionally, a statistical study of the raw data from the COVID-19 vaccine population revealed no significant correlation between sex differences and efficacy. The systematic review and meta-analysis conducted by Zhu et al supports our findings (33). Furthermore, Dagan et al demonstrated that vaccine efficacy across age groups was equivalent for SARS-CoV-2 infection in sex-specific subpopulations (36).

Additional data

Another factor that affects the immune system's response is age, which should also not be overlooked. The immune system changes and evolves throughout life. In this regard, the immune system's function gradually declines with age (37). A chronic low-grade proinflammatory state is one of the most well-recognized characteristics of the aging immune system and may be more prevalent in females (34).

Sex differences in immune responses throughout the life course

There is evidence that newborn males have higher numbers of natural killer cells, monocytes, and basophils as well as stronger innate inflammatory responses to stimulation than females, verifying that infant males have stronger natural immunity (4). The sex-differentiated immune system does not change during childhood as compared to infancy, but it changes during puberty, possibly as a result of the development of sex steroids increase the sex-differentiated immune system. Compared to adult males, females exhibit higher inflammatory responses, antibody responses, and T-cell activation and proliferation (38,39). The number and activity of B cells and T cells typically decline with age more quickly in males than in females (40). Regardless of age, females tend to have a higher antibody response to stimuli (41).

In the same studies, safety data were stratified only by age. Safety analysis for the Pfizer-BioNTech vaccine showed that systemic adverse events (e.g., headache, fatigue) were more common in younger vaccine recipients than in older subjects, while local reactions (e.g., pain)

Table 1. Summary of study data for approved COVID-19 vaccines efficacy

Vaccine	Total participants (N)	Males (%)	Females (%)	Efficacy in All	Efficacy in females	Efficacy in males	Adverse Reactions (N)	References
Pfizer-BioNTech (BNT162)	37 706	51	49	95%	93.7%	96.4%	8408	(28)
Moderna (mRNA1273)	28 207	52.6	47.4	94.1%	93.1%	95.4%	7340	(29)
Sputnik V (GamCOVID-Vac)	19 866	61.2	38.8	91.6%	87.5%	94.2%	122	(30)
Janssen (Ad26. COV·S)	39 321	54.9	45	66.1%	60.3%	69.8%	-	(31)
AstraZeneca (AZD1222)	11 636	44.7	55.3	-	-	-	6736	(32)

were reported more among older participants (>55 years) than among younger participants (16-55 years) (28).

The Moderna vaccine's safety analyses also showed that younger subjects (18-65 years old) experienced more injection-site and systemic adverse events than older participants (42). Meanwhile, age stratification was not mentioned for the AstraZeneca vaccine (32).

Unfortunately, the majority of vaccine trials have excluded the elderly, pregnant women, post-menopausal women, and children in favor of healthy adults between the ages of 18 and 65 (43). As a result, to ensure safety, immunogenicity, and efficacy in vaccine trials and to account for the disparate mortality rate by sex in people over 60, both gender and the elderly must be taken into account. It's still a problem when it comes to vaccine effectiveness in vulnerable and underrepresented groups, such as older and female populations (44).

Discussion

This narrative review investigated sexual dimorphism in response to the COVID-19 vaccines. At this time of global health emergency, as different types of vaccines for COVID-19 are developed and administered, disparities in vaccine response due to sex dimorphism biases in efficacy and adverse effects of vaccine should be considered, and sex-specific doses should be tested. According to our study, both males and females significantly benefited from the COVID-19 vaccine (33).

In addition, statistical analysis of the raw data of the vaccinated population showed that although the efficacy was slightly higher in males than females, there was no significant relationship between sex differences and the efficacy of the COVID-19 vaccine. The systematic review and meta-analysis by Zhu et al confirms our findings (33). Additionally, Dagan et al confirmed our findings by demonstrating that the estimated vaccine efficacy for confirmed SARS-CoV-2 infection in subpopulations defined by sex was consistent with similar efficacy across age groups (36). Therefore, the effect of sex differences on the efficacy of the COVID-19 vaccines has not yet been confirmed. To ascertain the effects of antibody response in different sexes and ages, National policies should consider various aspects of improving the clinical quality of vaccines and promote the equitable distribution of COVID-19 vaccines, which can provide a better vaccination experience for the public and increase willingness to be vaccinated.

Conclusion

Despite considerable biological and behavioral differences between males and females, we found no significant correlation between sex differences and efficacy. The impact of sex differences on the protective response and the efficacy of various vaccine types in different age groups will need to be confirmed by further pragmatic trials.

Authors' contribution

Conceptualization: ARK.
Validation: ARK, MJ, PY.
Investigation: ARK, MJ, PY.
Resources: ARK.
Data curation: ARK, MJ, PY.
Writing—original draft preparation: ARK, MJ, PY.
Writing—reviewing and editing: ARK, MJ, PY.
Visualization: ARK.
Supervision: ARK.
Project management: ARK.

Conflicts of interest

The authors declare no conflict of interest related to the subject matter or materials discussed in this article.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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