Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Sex differences in the incidence of anaphylaxis to LNP-mRNA COVID-19 vaccines

On February 17, 2021, Japan started vaccinating healthcare workers with the Pfizer-BioNTech lipid nanoparticle (LNP)-mRNA COVID-19 vaccine. Among total 79 anaphylaxis cases, 70 cases have been reported in women (89.9%) after 1,096,698 doses of the vaccine until April 4, 2021 [1]. Since the initiation of COVID-19 mass vaccination globally, there have been reported cases of anaphylaxis associated with Pfizer-BioNTech and Moderna LNP-mRNA COVID-19 vaccines. Recent surveillance data in the US reported 66 cases of anaphylaxis after administering > 17 million doses of the two LNP-mRNA vaccines between December 14, 2020, and January 18, 2021 [2], with a striking female predominance (95.4%) in the reported cases of vaccine-associated anaphylaxis. According to the US Center for Disease Control and Prevention, 63% of the vaccinations were administered to women until January 14. Another report confirmed the female predominance of anaphylaxis cases in over 60,000 doses of LNP-mRNA vaccinations; 15 (94%) of the 16 confirmed cases were women [3]. According to EudraVigilance, a reporting system of suspected adverse drug reaction in the EU, 88.1% of anaphylaxis cases (including both anaphylactic reaction and anaphylactic shock) after administering Pfizer-BioNTech LNP-mRNA COVID-19 vaccines was found in women (as of April 10, 2021) [4]. Although vaccine-associated anaphylaxis is known to be slightly more common in women [5], this sexual disproportion is quite notable with LNP-mRNA COVID-19 vaccines. The surveillance data strongly suggest that women are more prone to anaphylaxis to LNP-mRNA COVID-19 vaccines.

Although the exact cause of vaccine-associated anaphylaxis with the LNP-mRNA vaccines is still unknown, a polyethylene glycol (PEG)-conjugated lipid derivative in the LNPs is suspected to be the causative agent [6]. The PEG-conjugated lipids are common in two LNP-mRNA COVID-19 vaccines: ALC-0159 in the Pfizer-BioNTech vaccine and PEG2000-DMG in the Moderna vaccine. These lipids are essential for the *in vivo* stability of mRNA-containing LNPs. PEGs are also common ingredients in pharmaceutical, food, and cosmetic products; thus, certain populations may have already been exposed, sensitized, and developed pre-existing immunity against PEGs. Although PEG is generally considered a well-tolerated and non-antigenic ingredient, some people can be hypersensitive to PEG and experience acute allergic reactions upon exposure to the PEG-related products.

PEG-associated anaphylaxis is considered to be a very rare event. The underlying mechanism of PEG-associated anaphylaxis is largely unknown, although IgE-dependent and IgE-independent mechanisms have been proposed [7]. One possible explanation for the sex imbalance is that sensitization to PEG is more common in women due to the relatively frequent exposure to PEG-containing products, such as cutaneous exposure to cosmetics or the use of medications such as contraceptive injections. Pre-existing anti-PEG antibodies have been reported to be associated with severe allergic reactions upon administration of a PEGylated drug [8], suggesting that prior exposure to the PEG-containing products may sensitize individuals and establish anti-PEG hypersensitivity. The female-biased severe allergic reaction against LNP-mRNA COVID-19 vaccines is partly supported by the higher prevalence of anti-PEG antibodies in women than in men [9]. Another possible explanation includes hormonal differences such as the role of estrogen which may be an important factor in allergic immunological responses. Experimental data in rodents showed that estradiol enhances mast cell activation and allergic sensitization while progesterone suppresses histamine release but potentiates IgE formation [10].

Although some countries report the number of anaphylaxis cases associated with COVID-19 vaccines, the proportion of cases based on sex is not always reported. Special attention should be given to the female predominance associated with LNP-mRNA COVID-19 vaccines. Vaccination plays a crucial role in a global pandemic situation; therefore, it is important to understand the pathophysiology of the severe allergic reactions against the LNP-mRNA COVID-19 vaccines and the reason for their female predominance. It seems worthwhile to investigate whether the individuals who experienced an anaphylactic reaction against the LNP-mRNA COVID-19 vaccine had a pre-existing immunity against PEG, by performing the skin prick test or measuring anti-PEG antibodies, especially anti-PEG IgE. It is also presumed that vaccination with PEG-containing LNP-mRNA vaccines may elicit an anti-PEG immunity in naive individuals and hamper the future use of PEG-containing products. Therefore, if we are able to identify individuals with a predisposition to anaphylaxis, precautionary measures may be taken such as additional monitoring, and the use of other types of COVID-19 vaccines can be considered for those individuals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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