HEMOSTASIS AND THROMBOSIS

Review

Thrombosis and bleeding after COVID-19 vaccination: do differences in sex matter?

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Gender medicine deals with differences in approach to diagnostic work-up and management according to gender. Although the issue is relevant in every field of medicine, it is often neglected. However, the recent SARS-CoV-2 pandemic has made consideration of gender even more urgent. In fact, available literature has suggested a higher number of deaths among infected men than in women and more side effects in women than in male recipients of certain anti-COVID-19 vaccines. This review examines sex-disaggregated data on thrombotic and bleeding events associated with vaccination against COVID-19. Thrombotic complications are by far more frequently reported than bleeding events after vaccination and are mostly observed in young women receiving viral-vectored vaccines. However, detailed data that could help better stratify the risk according to sex/gender are generally lacking. Likewise, overall bleeding complications and those associated with a specific vaccine are mainly reported as aggregated data, including thrombocytopenia that is reported to occur in the presence or absence of thrombotic complications. Such information is important as it underlines the need to differentiate between thrombocytopenia with and without thrombosis because management and prognosis differ according to the association of thrombotic events. Here, we highlight how the lack of disaggregated data has led to the publication of conflicting information about adverse events by sex in recipients of viral-vectored vaccines. Lastly, we examine the possible mechanisms underlying vaccine-associated thrombotic and bleeding complications according to sex/gender.

Keywords: *thrombosis, hemorrhage, vaccination, COVID-19, sex/gender-disaggregated data.*

INTRODUCTION

As of 11 February 2022, there had been 404,910,528 confirmed cases and 5,783,776 deaths due to the novel coronavirus disease 2019 (COVID-19) reported worldwide. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The advent of vaccines against the infection has saved a significant number of lives. By 7 February 2022, a total of 10,095,615,243 vaccine doses had been administered[1].

COVID-19 is now considered a systemic disease, as it may affect different organs. Signs and symptoms range from mild to severe acute respiratory distress syndrome to a severe multisystem inflammatory syndrome[2].

Among other manifestations, thrombotic events, both arterial and venous, as well

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as hemorrhagic complications, have been reported[3]. Thrombocytopenia has been described as being potentially associated with COVID-19 disease and/or vaccination. In recipients of vaccines against COVID-19, venous thromboses at unusual sites, such as cerebral sinus vein thrombosis (CVST) or splanchnic vein thrombosis (SVT), have been reported, sometimes in association with thrombocytopenia (thrombosis thrombocytopenia syndrome [TTS]). They seem to be more frequent in women under 55 years of age[4] and are observed approximately 5-30 days (d) after vaccination with virus-vectored vaccines (i.e., ChAdOx1 nCoV-19, Astra-Zeneca [Cambridge, UK] and Ad26.COV2.S Janssen [Beerse, Belgium])[5].

Greinacher *et al.* described the physio-pathological mechanisms underlying TTS that are similar to those described in patients developing heparin-induced thrombocytopenia (HIT)[6]. Indeed, in both situations, immunoglobulin G class platelet-activating antibodies are directed against the platelet chemokine, platelet factor 4 (PF4).

Sarah Hawkes, co-director of Global Health 50/50, observed that "The COVID-19 pandemic has shone a light on the importance of sex and gender in a way that few other conditions have managed to do". However, in spite of this, the largest COVID-19 trials sometimes did not include any analysis according to sex[7]. Likewise, few sex-disaggregated data are available in literature on thrombotic events or bleeding complications after administration of vaccines against COVID-19. This analysis is important because, for example, vaccine studies showed that cisgender females develop a higher antibody response and, in turn, higher efficacy and more side-effects, suggesting the need for sex-differentiated dosing regimens[8].

We reviewed the available literature to investigate the presence of sex/gender-disaggregated data with regard to thrombotic and bleeding events following vaccination against COVID-19.

MATERIALS AND METHODS

We reviewed data published before 31 December 2021 focusing on adverse events in recipients of vaccines against SARS-CoV-2. Articles were searched on the PubMed and Embase electronic bibliographic databases. We identified articles using a combination of the following keywords or MeSH terms: COVID-19 vaccines; adenovirus vaccines; women; gender; sex; thrombosis; venous thromboembolism; pulmonary embolism; hemorrhage; hemophilia; antibodies; thrombocytopenia; risk factors; cardiovascular; outcomes; hormones; oral contraceptives; hormone replacement therapy; infertility; assisted reproduction; estrogens; progestins; pregnancy; postmenopausal. Our search identified a total of 146 citations (*search strategies and results are available upon request*). Articles were preliminarily defined as eligible if they: 1) were directly related to the review topic; 2) had a clear statement of aim; 3) were published in peer-reviewed journals; and 4) were in English. No geographical restrictions were applied. A first level screening of articles extracted from electronic databases was carried out by reading titles and abstracts. Subsequent critical assessment of eligible full-text articles was based on an appraisal of relevance of topic, defined clinical questions, study methodology, description of findings, and significance and possible impact of the findings on the review topic. Care was taken to exclude duplicate articles. Two co-authors (EG and RN) dealt with the literature extractions from chosen databases, while the other authors independently reviewed and appraised the extracted literature. Out of the initial selection of 134 articles, 110 were included in the final analysis (**Figure 1**).

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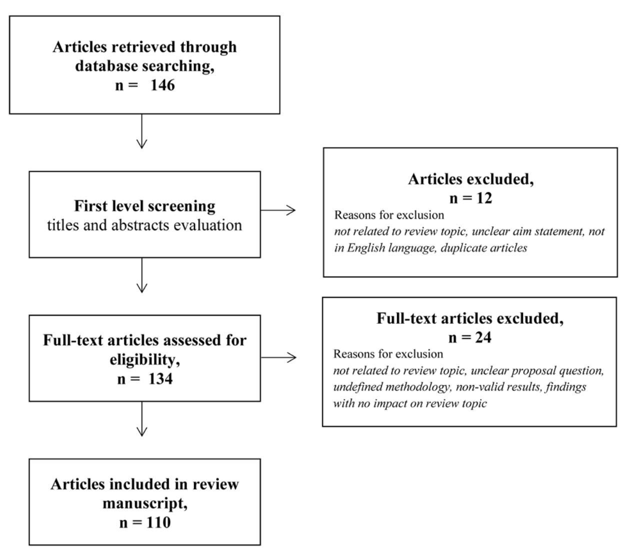

Figure 1 - Flowchart

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RESULTS

Thrombotic risk by type of vaccine and sex-gender disaggregated data

We first analyzed data on thrombotic events according to type of vaccine used, and searched for details on sex- and gender-related data. Three systematic reviews reported data on CVST and/or thrombosis and TTS, defined as the occurrence of CVST or thromboses at unusual sites associated to thrombocytopenia (**Table I**). Palaiodimou *et al.* included 69 studies and found 370 CVST out of

Table I - *Studies on thrombotic risk in recipients of COVID-19 vaccines*

First author, Journal[Ref] Type of study	Date of publication	Vaccine	CSVT	TTS	Other information
Pottegard A, BMJ[12] Population-based	May 2021	Viral vectored	Morbidity ratio 20.25 (8.14-41.73)	Morbidity ratio for any thrombocytopenia/coagulation disorders 1.52 (0.97 to 2.25)	Morbidity ratio for arterial events: 0.97 (95% CI 0.77-1.20) Morbidity ratio for VTE: 1.97 (1.50-2.54)
Bikdeli B, 2021, JAMA[11] Surveillance	July 2021	Viral vectored	3.6 (**99**% CI: 2.7-4.8) per million recipients	n.a.	MHRA No sex-disaggregated data
Simpson CR Nat Med[16] Population-based (with nested-incident matched case-control and self-controlled case- series analysis)	July 2021	Viral vectored and m-RNA	Not informative data	n.a.	No association with VTE for both types of vaccines Arterial events in viral vectored vaccine recipients aRR 1.48 (95% CI 1.12-1.96)
Cari L J Autoimm[13] Eudra Vigilance European database	August 2021	Viral vectored and m-RNA	Increase of SAE rate in subjects 18–64-years *vs* >64 years: mean (95% CI) Viral vector recipients 5.7 (5.1-6.2) mRNA recipients 2.0 (1.7-2.3)	Increase of SAE rate in subjects 18-64 years *vs* >64 years: mean (95% CI) Viral vectored recipients 2.5 (2.3-2.7) mRNA recipients 1.9 (1.6-2.2)	Splanchnic vein thromboses increase of SAE rate in subjects 18-64 years *vs* >64 years: mean (95% CI) Viral vectored recipients 4.0 (3.7-4.3) mRNA recipients 2.1 (1.8-2.4) Sex-disaggregated raw data (see Figures 2, 3 and 4)
Palaiodimou L, Neurology[9] Systematic review	October 2021	Viral vectored	370 patients (69 studies) Women proportion pooled estimate 75% (95% CI 69-80%) 28% of those with post-vaccination CVST died during hospitalization (pooled rate 28%; 95% CI 21-36%; 14 studies)	72 patients (12 studies) TTS was independently associated with a higher likelihood of CVST when compared to patients without TTS with thrombotic events after vaccination (OR 13.8; 95% CI 2.0-97.3) Women with TTS -CSVT proportion pooled estimate 75% (95% CI 69-81) Women with any TTS 71% (95% CI 62-80%)	All venous and arterial thromboses were eligible. Women among patients with any thrombotic event, 69% (95% CI 60-77%)
Hafeez MU, Clin Appl Thromb Hemost[10] Systematic review	October 2021	Viral vectored and m-RNA	n.a.	59 studies F/M: 51/18 63 out of 69 (91.3%) occurred after viral vector vaccine	
Klein NP, JAMA[14] Surveillance	October 2021	m-RNA	Excess cases in risk interval 0.2 (–1.1 to 0.5) per million doses	Excess cases in risk interval 1.0 (–4.6 to 1.4) per million doses	MHRA No sex-disaggregated data
Uaprasert N, Thromb J[28] Systematic review and meta-analysis	November 2021	Viral vector ed and m-RNA	n.a.	n.a.	8 RCTs included No increased risk of thromboembolism, and death from thromboembolism. No sex-disaggregated data

CI: confidence interval; MHRA: Medicines and Healthcare Products Regulatory Agency; aRR: adjusted relative risk; VTE: venous thromboembolism; RCT: randomized controlled trials; TTS: thrombosis and thrombocytopenia syndrome; n.a.: not applicable.

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4,182 patients with any thrombotic event in association with SARS-CoV-2 vector-based vaccine[9]. Seventy-two additional cases of TTS were also reported; among them, the pooled proportion of CVST was 51% (95% confidence interval [CI] 36-66%; I^2=61%). TTS was independently associated with a higher likelihood of CVST when compared to patients without TTS with thrombotic events after vaccination (odds ratio [OR] 13.8; 95% CI: 2.0-97.3; I^2=78%). The pooled mortality rates of TTS and TTS-associated CVST were 28% (95% CI: 21-36%) and 38% (95% CI: 27-49%), respectively.

Thrombotic complications developed within two weeks of exposure to vector-based SARS-CoV-2 vaccines (mean interval 10 d; 95% CI: 8-12).

A systematic review with post-hoc analysis reports similar findings with a significant association between TTS (during arterial or venous thrombosis) and death[10]. Platelet nadir and D-dimer peak were strong predictors of death (Area Under Curve: 0.646 and 0.604, respectively).

Regarding sex data, the pool estimate in women was 75% (95% CI: 69-80%) for CSVT and 75% (95% CI: 69-81%) for TTS. TTS was shown to mostly affect young women (i.e., under 45 years of age) (69%; 95% CI: 60%-77%), even in the absence of prothrombotic risk factors[9].

Notably, authors report that diagnosed thrombophilia or use of the contraceptive pill were not associated with an increased incidence of TTS[9,10]; however, detailed results were not shown.

A surveillance study reports the rate of CVST in US associated with viral-vector-based vaccines according to publicly reported data[11]. This study summarizes findings published by the Medicine and Healthcare Regulatory Agency (MHRA) but does not show sex/gender disaggregated data.

A sample largely represented by women was described in a population-based study carried out in Norway and Denmark. In this analysis, authors compared 28-d rates of hospital contacts for incident arterial events, venous thromboembolism, thrombocytopenia/coagulation disorders and bleeding among recipients of viral-vectored vaccines with those expected based on sex- and age-specific background rates. The study found a higher rate of CVST with a standardized morbidity ratio of 20.25 (8.14-41.73); the reported excess in vaccinated people was 2.5 (0.9-5.2) events per 100,000 vaccinations.

As stated, this sample was largely represented by women (77.6 in Norway and 80.1 in Denmark) in whom no excess rate of thrombocytopenia/coagulation disorders or other outcomes were observed. Notably, the analysis carried out in men highlighted no excess rate of venous thromboembolism, with a standardized morbidity ratio of 0.67 (0.22-1.56)[12].

Post-hoc analyses showed that the proportion of women who redeemed a prescription for hormone therapy (oral contraceptives or oestradiol) during the year before cohort entry was slightly lower than that observed in the background population[12]. However, authors do not give any additional information on adverse events in this sub-group or any details on the type of hormone therapy administered.

Cari *et al.*[13] performed an interesting analysis that aimed to take into account gender data. They used the data of the Eudra Vigilance European database registered up to 16 April 2021 to calculate the incidence of thrombocytopenia, bleeding, and thromboses in recipients of ChA (i.e., virus-vectored vaccine) and of BNT162b2 (i.e., m-RNA vectored vaccine). Of note, they defined adverse events as those with "blood clots and/or thrombocytopenia", whereas the European Medicines Agency (EMA) investigated adverse events due to "blood clots and thrombocytopenia". CSVT, SVT and/or thrombocytopenia were categorized as thrombo-hemorrhagic events.

The most relevant finding was that all these symptoms were found with the virus-vectored vaccine and not with the m-RNA vaccine[13]. Although the European Center for Disease Prevention and Control database did not report separate numbers of vaccine doses administered in women and in men, authors calculated the woman: man ratio based on data on the sex of recipients reported by some European countries. Therefore, in a scenario where the women: men ratio is 3 : 2, the risk of Serious Adverse Event (SAE) was highest in women and men in the age range 18-24 years for recipients of adeno-virus vaccine (approx. 50 events per million doses). **Figure 2** shows SAE and deaths per million doses by type of vaccine.

In the age ranges 25-49 years and 50-59 years, the SAE risk in women remained high, whereas that in men of the same age decreased. Similar SAE risk was observed in women and men aged >59 years who received adeno-virus vaccine (approx. 15-25 SAEs per million doses). **Figures 3**, **4** and **5**

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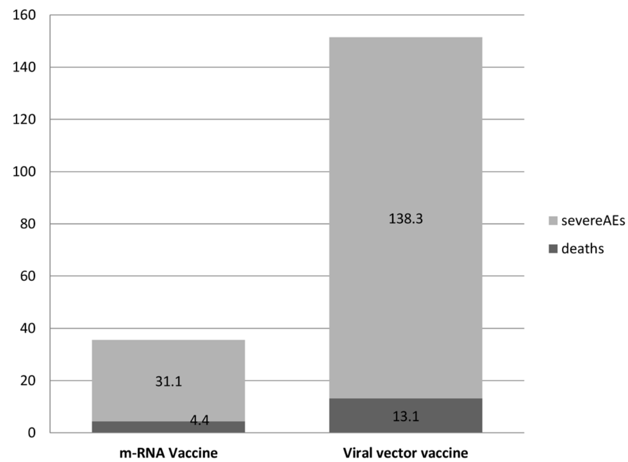

Figure 2 - Severe adverse events (SAEs) and deaths by type of vaccine
Absolute number of SAEs and death per million of administrated doses.

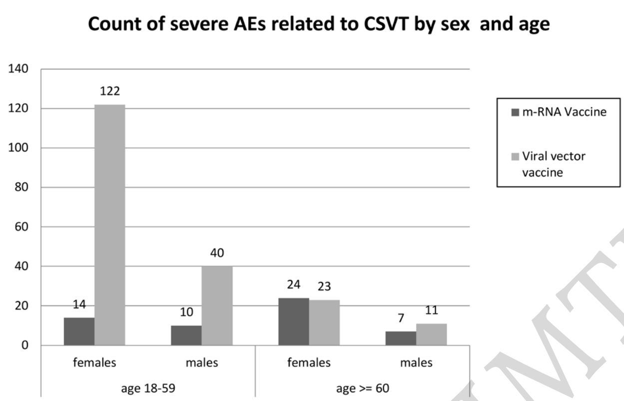

Figure 3 - Severe adverse events (SAEs) related to cerebral sinus vein thrombosis (CSVT) by sex and age (adapted from Cari *et al.*[13])
Figure shows the absolute number of SAEs related to CSVT in males and females divided into two age groups: 18-59 years *vs* ≥60 years.

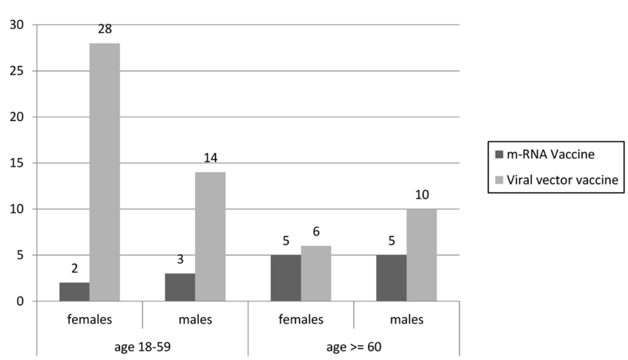

Figure 4 - Severe adverse events (SAEs) related to splanchnic vein thrombosis (SVT) by sex and age (adapted from Cari *et al.*[13])
Figure shows the number of SAEs related to SVT in males and females divided into two age groups: 18-59 years *vs* ≥60 years.

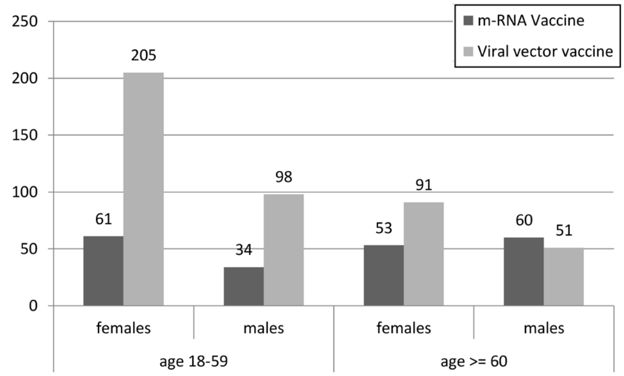

Figure 5 - Severe adverse events (SAEs) related to thrombocytopenia by sex and age (adapted from Cari *et al.*[13])
Figure shows the number of SAEs related to thrombocytopenia in males and females divided in two age groups: 18-59 years *vs* ≥60 years.

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show SAEs related to CSVT, SVT and thrombocytopenia by sex and age, as reported by Cari *et al*.

Consistent with these findings, an interim analysis of surveillance data carried out in the USA for mRNA-only vaccines[14] found that the incidence of thrombosis (arterial and venous, including pulmonary embolism) or TTS were not significantly higher 1-21 d post vaccination compared with 22-42 d post vaccination. Unfortunately, these authors did not show sex/gender-disaggregated data.

Arterial thromboses are reported in some studies (**Table II**). A Scottish national population-based analysis among 2.53 million people who received their first doses of SARS-CoV-2 vaccines found an increased risk of arterial thromboembolic events in viral-vector recipients. This risk was associated with increasing age (especially over 60 years), male sex, presence of certain comorbidities (such as heart failure, coronary heart disease, peripheral vascular disease, severe mental illness, sickle cell disease, prior stroke, type 1 and 2 diabetes and chronic kidney disease)[1].

Hemorrhagic risk by type of vaccines and sex-gender disaggregated

In a population-based cohort study involving more than 80,000 participants, the overall risk of hemorrhagic events in recipients of virus-vectored vaccine 0-27 d after vaccination was 1.48 (95% CI: 1.12-1.9). Recipients of the first dose of adenovirus vaccines were at higher risk of skin bleeding events (3.2 *vs* 0.2% of mRNA vaccine recipients; OR 16.0, 95% CI: 7.5-34.1). Similarly, nose and gingival bleedings were significantly more frequent in recipients

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Table II - *Systematic reviews, surveillance and population-based studies on hemorrhagic risk in recipients of COVID-19 vaccines*

First author, Journal[Ref] Type of study	Date of publication	Vaccine	Risk of bleeding events	Type of bleeding	Other information
Pottegard A, BMJ[12] Population-based	May 2021	Viral-vectored	Morbidity ratio for any bleeding 1.23 (0.97-1.55).	/	All venous and arterial thromboses and bleedings were eligible
Simpson CR Nat Med[15] Population-based	July 2021	Viral-vectored and m-RNA	Adjusted RR 1.48 (95% CI 1.12-1.96) in viral-vector vaccine recipients	(ITP) in viral-vector vaccine recipients: adjusted RR 5.77 (95% CI 2.41-13.83)	Nested-incident-matched case-control Self-controlled case- series analysis Males are predicted to develop thrombotic and hemorrhagic events (included ITP) with adjusted RR 1.31 (95% CI 1.23-1.39)
Cari L J Autoimm[13] Eudra Vigilance European database	August 2021	Viral-vectored and m-RNA	33 and 151 SAEs/1 million doses in mRNA-and viral-vector vaccine recipients, respectively	Increase in SAE rate in subjects 18-64 years *vs* >64 years Viral vector recipients mRNA recipients Gastrointestinal bleeding Viral vector recipients 1.6 (1.5-1.8) mRNA recipients 1.6 (1.3-1.8) Cerebral bleeding Viral vector recipients 1.4 (1.3-1.5) mRNA recipients 0.6 (0.6-0.7)	
Trogstad L Vaccine[17] Population-based (self-reported side-effects)	September 2021	Viral-vectored and m-RNA	0.2% recipients of single dose mRNA vaccine reported skin bleeding *vs* 3.2% recipients of a single-dose viral-vectored vaccine. OR 16.0, 95% CI 7.5-34.1)	ORs for nose and gingival bleeding 8.0 (4.0-15.8) and 9.3 (4.3-20.0), respectively	Among recipients of viral-vectored vaccine, 3.5% (152/4,365) women reported skin bleeding as opposed to 1.4% (11/767) among men, OR 2.5 (95% CI 1.3-4.6)
Alghamdi AN, Frontiers in Med[18] Questionnaire-based	October 2021	Viral-vectored and m-RNA			Some details on hormonal status
Uaprasert N, Thromb J[28] Systematic review and meta-analysis	November 2021	Viral-vectored and m-RNA	n.a.	n.a.	8 RCTs included No increased risk of hemorrhage, and death from hemorrhage No sex- disaggregated data

CI: confidence interval; VTE: venous thromboembolism; ITP: idiopathic thrombocytopenic purpura; RCT: randomized controlled trials, n.a.: not applicable.

of viral-vectored vaccines with an adjusted OR of 7.0 (95% CI: 3.5-13.9) and 8.1 (3.7-17.6), respectively[15].

When we focused on occurrence of thrombocytopenia or idiopathic thrombocytopenic purpura (ITP), we found that a first dose of virus-vectored vaccine was associated with a small, although significant, increase of ITP[16]. The Scottish national population-based study revealed a potential association between recipients of a first dose ChAdOx1 vaccination and occurrence of ITP. The adjusted risk ratio for ITP was 5.77 (95% CI: 2.41-13.83) with an estimated incidence of 1.13 (0.62-1.63) cases per 100,000 doses.

Women have a significantly higher risk of bleeding episodes. Indeed, Trogstad *et al.* found that 3.5% (152/4,365) women receiving adeno-viral vectored vaccine experienced skin bleeding as opposed to 1.4% (11/767) among men, with an OR of 2.5 (95% CI: 1.3-4.6). Notably, 37% reported prolonged duration of skin bleeds (10% lasting 3-4 weeks), 14% nose bleeds (3.7% lasting 3-4 weeks), and 26.5% gingival bleeds (10.2% lasting 3-4 weeks)[15].

On the other hand, Simpson *et al.* refer to male sex as a predictor of ITP and hemorrhagic events (not specified) within 28 d post vaccination with an adjusted rate ratio of 1.31 (1.23-1.39). These findings are intriguing because,

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similar to other autoimmune diseases, ITP has an overall ratio of women to men of 3-4 to 1 in other clinical contexts[17]. A single study reported abnormal menstrual cycle (delayed/increased hemorrhages or pain) in 0.98% (18/1,846) m-RNA and 0.68% (7/1,028) viral-vector vaccine recipients[18].

Why are women more exposed to thrombocytopenia and CSVT than men?

It is well known that women are more prone than men to several autoimmune diseases, and it has been hypothesized that exposure to hormonal changes during pubertal development are responsible for the gender bias in autoimmune diseases[19-21]. Gene-gene and gene-environment interactions are responsible for the susceptibility to develop autoimmune disease. Furthermore, environmental factors, exposure to infectious agents, chemicals or dietary components confer susceptibility to autoimmune disease, whereas other factors, such as sunlight, can protect from the development of these conditions[22]. Sex hormones, and particularly estrogens, modulate immune response in humans through sex hormone receptors found on immune system cells such as T cells, B cells, and monocytes. Depending on the context, estrogens can either promote inflammation by enhancing Th1 or increase the regulatory arm of the adaptive immune response by promoting anti-inflammatory/regulatory Th2-type[23]. Therefore, it is not surprising that estrogens show an ability to increase antibody responses to vaccines, infections and autoantigens by activating B cells, while androgens have the opposite effect[24]. Megakaryocytes contain mRNA for estrogen receptors and this suggests a potential mechanism through which sex hormones may mediate gender differences in platelet function and thrombotic diseases[25]. Taken together, all these findings indicate that estrogen can favor an exaggerated response of platelets or their precursors to vaccines, with ITP as a possible consequence. These data are consistent with the knowledge that ITP is secondary to autoantibodies targeting multiple platelet glycoproteins. Changes in hormonal status through different stages of life can explain different platelet susceptibility to vaccine and, in turn, the higher prevalence of young women among those who develop thrombocytopenia and vein thrombosis after vaccination against COVID-19. Interestingly, in the animal model (sheep) the expression of alfa and beta receptors in the brain and pituitary gland is influenced by circulating estrogen concentrations, and is acutely regulated in response to cerebral hypoperfusion[26]. A lower blood flow in cerebral veins, especially in certain menstrual phases[27], together with estrogen-mediated hyper-response to vaccine, might be responsible for the higher prevalence of thrombocytopenia associated to CSVT in women after COVID-19 vaccination.

CONCLUSIONS

This review highlights the much more frequent reports of thrombotic complications compared to bleeds after vaccinations against SARS-CoV-2. These adverse events are mostly observed in young women who are administered with viral-vectored vaccines. In young women, sex steroids and the immune system likely affect the increased risk of thrombotic events. As for several autoimmune diseases, we need to collect additional data on specific side-effects of vaccines, especially those with adeno viral vectors. The immune reaction promoted by virus-vectored vaccine may lead, not only to thrombocytopenia and cerebral/splanchnic venous thrombosis, but also to other thrombotic and thromboembolic SAEs.

Bleeding events are mainly reported as aggregated data, with the exception of ITP and thrombocytopenia. This latter can occur in the presence or absence of thrombotic complications; therefore, we must be careful when differentiating between thrombocytopenia occurring with thrombosis and that occurring without, because we may have to adopt different approaches to management, follow-up and prognosis. There are conflicting data on the prevalence of bleeding events according to sex in recipients of viral-vectored vaccines. Indeed, one study showed a higher risk of bleeding episodes in women, while other investigators found that males are predicted to develop hemorrhagic events.

Future reporting of sex/gender-disaggregated data and a discussion of how sex factors influence outcomes would benefit the decision-making process for both regulatory agencies and the general public, and help in the design of mass vaccination programs[8].

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RESEARCH AGENDA

Out of 45 COVID-19 randomized controlled trials whose results were published in December 2020, only eight reported the impact of sex or gender[7]. All trials reported numbers of men and women participants, but only eight examined whether results differed among women and men. Likewise, sex/gender-disaggregated data in vaccine recipients are lacking, although preliminary information suggests that such an analysis is essential.

It is unknown why women frequently show cerebral or splanchnic vein thrombosis in association with thrombocytopenia. In this context, there are no sex/gender-disaggregated data on the development of anti-PF4 antibodies after virus-vectored vaccine exposure or on the underlying pathophysiological mechanism(s). We urgently need data on the possible role of hormonal status in those who develop thrombosis or bleeds.

It is important to consider that platelets are probably the most important player in the pathogenesis mechanism of both thrombotic and bleeding complications. Therefore, future studies should focus especially on platelets and on global tests, such as thrombin generation assays.

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AUTHORSHIP CONTRIBUTION

Conceptualization: EG, SuCh, SeCa, RN; methodology: EG; formal analysis: EG, RN; original draft preparation: EG, SuCh; writing, review and editing: EG, SuCh, SeCa, RN; All others read, critically revised and approved analysis and final draft.

The Authors declare no conflicts of interest.

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APPENDIX 1

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- Maria Novella Luciani, Ministero della Salute, Direzione Ricerca e Innovazione in Sanità, Rome, Italy

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