THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 11

RESEARCH ARTICLE

Potential Association of Covid-19 mRNA Vaccination and Infections with the Antiphospholipid Antibody Syndrome

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OPEN ACCESS

PUBLISHED
30 November 2024

CITATION
Balbona, EJ., Neuenschwander, J., et al., 2024. Potential Association of Covid-19 mRNA Vaccination and Infections with the Antiphospholipid Antibody Syndrome. Medical Research Archives, [online] 12(11). https://doi.org/10.18103/mra.v12i11.6049

DOI
https://doi.org/10.18103/mra.v12i11.6049

ISSN
2375-1924

ABSTRACT

Antiphospholipid Syndrome (APS) is an autoimmune reaction in which the immune system produces antibodies to specific phospholipids that are found in normal cells. Three specific antiphospholipid autoantibodies (APLs) characterize the antiphospholipid syndrome. The three diagnostic biomarkers of APS are the lupus anticoagulant (LA), the anticardiolipin antibody (aCL), and the anti-β2-glycoprotein-1 antibodies (B2GP1). The diagnostic criteria for APS require the presence of clinical thrombotic manifestations as well as the continued presence of antiphospholipid antibodies over at least a 12-week period. The prolonged period of observation required for diagnosis is an impediment to the recognition of APS and explains its subsequent low incidence of diagnosis in the inpatient setting. We hypothesize that undiagnosed post-COVID and/or post-COVID vaccine APS could be a factor in the rise in acute heart conditions and sudden unexplained deaths in otherwise healthy individuals, as well as other adverse health events. Therefore, we argue that clinicians must be more aware of APS and that clinical events that are temporally linked to or subsequent to either COVID-19 or SARS-CoV-2 mRNA vaccine exposures should be assessed for evidence of APS.

Keywords: Antiphospholipid Syndrome (APS); SARS-CoV-2; SARS-CoV-2 mRNA vaccines; Autoimmunity; VAERS; Thrombosis; Infertility.

1. Introduction

To date, more than four billion people worldwide (27% of the world's population) have been fully vaccinated against SARS-C0V-2 infection and nearly five billion people have received at least one Covid-19 vaccination.[1]. The development of these new gene-therapy-based products was expedited, and emergency use authorization (EUA) was granted in response to the fear generated in the early days of the COVID-19 pandemic. The typical time-consuming pharmacokinetic, biodistribution, and safety studies were abbreviated or not done for the sake of expediency.[2]

COVID-19 viral pneumonia disproportionately affected the old and infirm, who represented the vast majority of the first-year deaths from COVID-19 infections.[3] In light of this, we would expect that subsequent years would show a sharp decline in population mortality. However, following the introduction of the mRNA-based COVID-19 vaccines, an unexpected rise occurred in the mortality of the young and healthy, who were not at high risk from the COVID-19 virus. In the United States, mortality rates in the second half of 2021 among individuals aged 25-44 was 84% higher than their baseline rate. During this period, many of these individuals were required to obtain COVID-19 vaccines in order to remain employed.[4]

Despite these trends, there has been a remarkable lack of interest in the physiological basis of this phenomenon. Many of these excess deaths have occurred due to sudden cardiac arrests in otherwise healthy individuals. Contemporaneous with these excess deaths, there have also been clear signals from vaccine adverse events reporting systems such as VAERS. Small studies of unexpected sudden deaths have demonstrated evidence of microvascular disease, systemic inflammation, and autoimmunity, as well as thrombosis.[5-7] Many of these features are shared with the clinical manifestations of Antiphospholipid Syndrome.[8-12]

Phospholipid molecules have a hydrophilic end as well as a hydrophobic end. The two poles self align based on their charges similar to oil in water. The hydrophilic poles are positively charged and form the outer and inner surfaces of bilayer membranes. The hydrophobic poles form the interior of the bilayered phospholipid sheets that compose all cell membranes. The phospholipid hydrophilic ends facing out and the neutral ends facing the inner membrane layer. This is an effective structure for keeping cell contents inside the cell while protecting its integrity. The unique structure of phospholipids makes them crucial components of living cell membranes. Any process that alters their function can have adverse consequences, as is the case in APS.

The authors undertook this project to evaluate whether there was a link between the COVID mRNA vaccines and reports of antiphospholipid syndrome and antibodies related to APS within the VAERS system. We also reviewed the published literature to determine potential mechanisms unique to the mRNA vaccine structure that might induce this syndrome.

2. Features of Antiphospholipid Syndrome

Antiphospholipid Syndrome (APS) is a well-recognized autoimmune reaction in which the immune system produces antibodies to specific phospholipids that are found in normal cells. The syndrome, now known as APS, was first recognized by Dr. Graham Hughes in 1983. He described unusual thromboses in his lupus patients with circulating antiphospholipid autoantibodies.

Three specific antiphospholipid autoantibodies (APLs) characterize the antiphospholipid syndrome. The three diagnostic biomarkers of APS are the lupus anticoagulant (LA), the anticardiolipin antibody (aCL), and the anti-β2-glycoprotein-1 antibodies (B2GP1).[9]

APS produces a prothrombotic state that results in pathognomonic clinical manifestations such as venous thrombosis as well as arterial thromboses. The exuberant systemic thrombosis seen in APS can result in multiorgan damage, including the interruption of blood flow to the lungs, heart, liver, kidneys, brain, bone, and skin. The resulting clinical manifestations may include: deep venous thrombosis, pulmonary embolus, heart attack, stroke, liver, spleen, and kidney infarcts, neurologic changes, bone fractures, miscarriage, and skin findings such as Raynaud's and livedo reticularis.[8-10] The most severe presentation of antiphospholipid syndrome is known as *Catastrophic* Antiphospholipid Syndrome or simply "CAPS," which is often life-threatening and involves multiple systemic thromboses within a short time period.[10,11,13,14]

The diagnostic criteria for APS require the presence of clinical thrombotic manifestations as well as the continued presence of antiphospholipid antibodies over at least a 12-week period. This prolonged period of observation required for diagnosis is likely an impediment to the recognition of APS and explains its subsequent low incidence of diagnosis, especially in the inpatient setting. Nevertheless, only the persistence of APL antibodies is associated with thrombotic risk.

Several factors can lead to the development of APL antibodies. Transient and low-risk APL elevations may occur following exposure to certain medications, infections, or vaccinations. It should also be noted that low levels of APLs can be found in 2 to 5% of normal individuals as well as those with recognized autoimmune diseases.[11]

In an analysis of the WHO international database, Gérardin et al. reported that various medications, including antiarrhythmics, anti-seizure, anti-hypertensive, and even antibiotics, can result in the production of APLs and induce APS.[15] Viral infections are also associated with APS, as are bacterial infections, including those of mycoplasma and streptococcus.[15] Viral infections such as EBV, CMV, HBV, HCV, HIV, and SARS-CoV-2 viral infection have all been associated with the development of APLs.[15] A review study on this topic stated that the prevalence of APL in COVID-19 disease can be as high as 50%.[16]

3. Is there a link between APS and COVID-19/mRNA vaccines?

Vaccinations and their adjuvants also may result in the antiphospholipid syndrome. APS has been reported in association with the hepatitis B and hepatitis A vaccines,

typhoid, seasonal influenza, and tetanus toxoid vaccines.[15]. Case reports also implicate the COVID-19 mRNA vaccines as capable of producing APLs and the antiphospholipid syndrome.[13,14,17]

Possible mechanisms for the development of APL-based thrombophilia include activation of a type-1 interferon response, molecular mimicry, and cytokine activation, as well as induction of the innate immune and complement cascades.[11] Since the antigens presented to the immune system in infection and vaccination are by design very similar, the induction of APLs in acute SARS-CoV-2 viral infections implicate the risk of the induction of APLs and, thus, APS in the SARS-CoV-2 mRNA vaccinated.[11,12]

Indeed, several studies have documented the production of antiphospholipid antibodies during early SARS-CoV-2 infection.[11,12] We suspect the presentation of similar antigens with COVID-19 vaccinations may be concerning regarding APS risk via the innate immune-thrombotic response.

A study of COVID-19 patients by Dima et al. found that 41% of those with early SARS-CoV-2 infections without evidence of thromboses were positive for the APL "Lupus Anticoagulant" (LA) antiphospholipid antibodies. In these patients, the presence of LA autoantibodies was also shown to correlate with the severity of disease as well as the level of inflammation seen as measured by C-reactive protein (CRP).[12] Case reports of COVID-19 mRNA vaccine-associated antiphospholipid syndrome do exist in the literature but are not widely known or well recognized.[13,14,17-19]

The production of APLs stimulates several proinflammatory and prothrombotic pathways. For example, the β2-glycoprotein I (B2GP1) antibody can bind endothelial cells and result in APL-mediated damage with the expression of endothelial adhesion molecules that bind leukocytes and platelets. Notably, the B2GP1 antibody has homology with infectious agents and is understandably very immunogenic.

The endothelium is rich in angiotensin converting enzyme type II (ACE2) receptors and, as such, is the unintentional target of both COVID-19 and the SARS-CoV-2 mRNA vaccine products. The endothelium is also the substrate on which the immunothrombotic system regulates the delicate balance involved in our innate immunity and the clotting cascade. When damaged, the endothelium transitions from its baseline antithrombotic status to a prothrombotic state. The exposure of von Willebrand's factor (WF) and Platelet Activating Factor (PAF) from damaged endothelium promotes platelet aggregation and the release of Tissue Factor (TF) from endothelial cells, stimulating the coagulation cascade and inflammation. Thus, APLs promote endothelial dysfunction, which results in the thrombogenic state that characterizes the antiphospholipid syndrome.

Cardiologists have recognized the role of APLs in cardiac inflammation. Cardiovascular events are the leading cause of morbidity and mortality in APS.[20] The term "antiphospholipid antibodies" may be a misnomer, since, in many cases, the pathogenic antibodies in APS target proteins that associate with phospholipids, most notably, β2GPI, rather than phospholipids themselves.[21] β2GPI modulates hemostasis and the complement system, and it plays an important role in vascular injury associated with APS.[22] Perricone and Shoenfeld's book, The Heart in Systemic Autoimmune Diseases, (2017) states that "β2GPI is an abundant plasma glycoprotein that binds to phospholipids and is involved in clotting mechanisms and lipid pathways in chronic diseases related to endothelial cell dysfunction, such as systemic lupus (SLE), antiphospholipid syndrome (APS), and ankylosing spondylosis (AS)."[23]

4. APS, mRNA vaccines, and infertility

APS can cause primary infertility in part through its negative effects on the endometrium.[24.] It has been shown experimentally that antiphospholipid antibodies greatly increase endometrial stromal cell decidualization, senescence and inflammation, leading to increased risk to miscarriage.[25] These effects were mediated by toll-like receptor 4 (TLR4) and MAP kinase (MAPK) signaling, along with cytokine-induced reactive oxygen species (ROS).[25] Studies on mice have shown that the spike protein induces TLR4 upregulation in mice.[26]

Proinflammatory cytokines are induced after COVID-19 vaccination, particularly after the second dose.[26] Elevated levels of the TNF-α cytokine following vaccination were associated with both increased antibody production and increased adverse reactions.[27] Antiphospholipid antibodies induce elevated expression of TNF-α in the decidual tissues, causing rapid increases in TNF-α levels both in the decidua and systemically.[28]

Most studies on the effects of COVID-19 vaccines on pregnancy outcomes are under-powered. However, studies involving patients undergoing infertility treatment have detected significant effects of prior vaccination for COVID-19. A cohort study involving 3,052 women undergoing *in vitro* fertilization (IVF) treatment found a statistically significant reduced pregnancy rate for those who had received a SARS-CoV-2 vaccine within 60 days prior to IVF treatment.[29] A meta-analysis involving pooling of results from several previous studies on pregnancy outcomes for assisted reproductive technology (ART) found a statistically significant difference between vaccinated and unvaccinated groups ($p = 0.029$). These authors concluded: "It can, therefore, be postulated that the administration of the SARS-CoV-2 vaccine may have an impact on the frequency of pregnancies in individuals undergoing ART, with a significantly higher prevalence observed in those who had not received the vaccine"[30, p. 12] It should be noted that miscarriage is a common complication of the antiphospholipid syndrome.[31]

5. Analyses from the VAERS database

The FDA's Vaccine Adverse Event Reporting System (VAERS) is a national early warning system designed to detect vaccine post-marketing adverse reactions. Anyone can report an event, and vaccine manufacturers are required to report all events that come to their attention. It is widely agreed that adverse events are grossly under-reported in VAERS, although it is difficult to estimate exactly what percentage is reported.[32]

Nonetheless, VAERS can be useful for finding patterns that suggest atypical or unexpected reactions that deserve further attention by medical providers. A

strategy that can be used to evaluate risk for a particular symptom from a particular vaccine is to normalize event counts against the number of reports mentioning that reaction among other vaccines. This strategy was used in a paper that evaluated risk for several different adverse reactions reported in cases where a COVID-19 vaccine was administered, compared to the number of cases reported for all vaccines.[33] The researchers found 8,281 cases in 2021 related to myocarditis, cardiac arrest, arrhythmias, myocardial infarction and cardiac failure, of which 97.7% were associated with the COVID-19 vaccines. Table 4 in that paper reported that 98.7% of 7,451 cases of various types of thromboses were associated with the COVID-19 vaccines.[33.] Both cardiac issues and thrombosis are linked to APS.

The article by Seneff, et al. showed that, overall, 93% of all cases reported in 2021 were related to COVID-19 vaccines. By comparing the estimated total number of COVID-19 vaccines administered with the total number of flu vaccines, the authors were able to predict that COVID-19 cases should have only accounted for 32.6% of all cases, if all vaccines were equally likely to be associated with events.[33] This can only be interpreted to mean that COVID-19 vaccines elicit many more adverse reactions than traditional vaccines. Concerningly, there have been more adverse reactions and deaths reported to VAERS for the COVID vaccines than for all other vaccines combined, over the past 32 years.[4]

Here, we perform a similar analysis from VAERS, focusing on symptoms that are known to be associated with APS. Cardiolipin antibodies are the most common antiphospholipid antibody, and they are commonly used to diagnose APS. There were 120 cases where either "CARDIOLIPIN ANTIBODY" or "CARDIOLIPIN ANTIBODY POSITIVE" or both were listed for COVID-19 vaccines. Of these, 39 also included the "symptom" "CARDIOLIPIN NEGATIVE." So, we found 81 cases where cardiolipin antibodies were not negative. In addition, there were 27 cases where APS was listed as a symptom, and none of these overlapped with the cardiolipin reports. Interestingly, none of the other vaccine reports in 2021 besides COVID-19 vaccines listed either cardiolipin antibodies or APS as symptoms.

Other APS-linked symptoms include deep vein thrombosis and pulmonary thrombosis, along with the related conditions, pulmonary embolism, pulmonary hypertension and intracardiac thrombus. These can form one interrelated group of symptoms associated with APS. A second set of associated symptoms are related to issues during pregnancy, including preeclampsia, spontaneous abortion, and foetal death. Neuropathy is another common feature observed in association with APS.[34] and we included peripheral neuropathy, carpal tunnel syndrome, inflammation and C-reactive protein, a marker of inflammation, in this category. Results are presented in Table 1.

Table 1: Various adverse reactions reported in VAERS for the year 2021, with tallies of counts for COVID-19 vaccines and all vaccines, as well as the percentage of reactions that were associated with COVID-19 vaccines.

Reaction	Count COVID-19 2021	Count ALL 2021	Percent COVID-19
Thrombosis & Pulmonary Disease			
APS / Cardiolipin Antibody	108	108	100%
Pulmonary Hypertension	118	119	99.2%
Pulmonary Embolism	3024	3060	98.8%
Pulmonary Thrombosis	593	606	97.9%
Deep Vein Thrombosis	2222	2243	99.0%
Intracardiac Thrombus	102	104	98.1%
Issues in Pregnancy			
Preeclampsia	60	63	95.2%
Abortion	1067	1090	97.9%
Foetal Death	112	115	97.3%
Neuropathy & Inflammation			
Peripheral Neuropathy	1151	1226	93.9%
Seizure	4413	4686	94.2%
Carpal Tunnel Syndrome	132	136	97.\%
Inflammation	3407	3572	95.4%
C-reactive Protein Increased	1877	1942	96.7%

APS is highly associated with deep vein thrombosis. Statistically, as many as 20% of cases of deep vein thrombosis are associated with antiphospholipid antibodies.[35] There were over two thousand cases of deep vein thrombosis reported in 2021 in VAERS, and 99% of them were associated with COVID-19 vaccines.

The research literature also links APS to increased risk to pulmonary hypertension and pulmonary embolism, which are also risks linked to thrombosis.[36,37] Overwhelmingly, VAERS reports in 2021 where these conditions occurred were associated with COVID-19 vaccines.

An unusual but rare symptom associated with APS is intracardiac thrombosis. Dhibar et al. described a case study and conducted a literature analysis reporting on 28 published case studies describing intra-cardiac thrombosis linked to APS.[38] In VAERS, there were 104 cases of intracardiac thrombus reported in 2021, of which only two were *not* associated with COVID-19 vaccines.

It is well established that APS is associated with increased risk to spontaneous abortion, foetal death, and preeclampsia.[39-41] All three of these symptoms were

highly over-represented in COVID-19 vaccine reports compared to all other vaccines (see Table 1).

6. Possible mechanisms tying mRNA vaccines to APS

Current knowledge about the pathophysiology of the SARS-CoV-2 infection itself suggests the potential mechanism tying mRNA vaccination and the development of APS. From early in the pandemic, it was apparent that the infection itself had the potential to induce issues with clotting and vascular health. This was particularly true of patients with severe COVID-19, where levels of anti-cardiolipin (aCL) and anti-platelet glycoprotein antibodies correlated with the severity of disease.[42] These autoimmune antibodies are a part of an APS diagnosis, which requires the presence of symptoms along with certain autoimmune antibodies, including aCL antibodies, β2GPI, and/or lupus anticoagulant.[43] There are multiple reports confirming the increase in APS type antibodies with COVID with at least one study correlating the level of aCL directly with the circulating level of cell-free DNA, a classic damage associate molecular pattern (DAMP). Elevation of cell-free DNA occurs with increased disease severity. In this study, the rate of at least one APS antibody in 157 patients with severe COVID was 54.8% with aCL being present in over 50% of those cases.[44] This cascade of symptoms appears to be a direct result of reactivity to the spike protein subunit of the SARS-CoV-2 virus with levels of autoimmune antibodies relating to the level of spike antibody response and the severity of disease.[42]

With the advent of mRNA-driven vaccines that function to create spike protein, we would expect to see the same type of response. A study of the impact of the mRNA COVD vaccine at one month and three months after vaccination (no pre-vaccine data was studied) demonstrated a 7% rate of IgG aCL antibodies, a 23% rate of aβ2GPI antibodies and a 7% rate of anti-phosphatidylserine/prothrombin IgM antibodies in health care workers that had been vaccinated.[45] This suggests a connection between the vaccine and the production of autoimmune APS type antibodies. However, a separate study suggested that the presence of broad autoantigen recognition (autoimmune antibodies) by a patient was associated with better COVID outcomes, suggesting that the autoimmune response is part of a robust immune activation by the spike protein.[46]

There appear to be multiple possible mechanisms for this autoimmune response. The first is the most common explanation—molecular mimicry between sequences of the spike protein and various human antigens. Others have predicted a significant homology with the spike protein and multiple human antigens based on the amino acid sequence of both.[47] This has been confirmed in a study utilizing human monoclonal antibodies to the spike protein and demonstrated a high degree of reactivity of those antibodies to phospholipids (reactivity to β2GPI was not tested).[48] Molecular mimicry appears to be at least one confirmed mechanism for vaccine-induced APS.

The second possibility is the release of DAMPs from mRNA transfected cells undergoing some type of cell death. The degree of this process would be dependent on the amount of mRNA delivered and the resulting spike protein production. Given that the level of aCL antibodies was correlated with cell-free DNA in COVID infections, this theory has support.[44] mRNA, itself, can be considered a DAMP, but the pseudouridine modification of vaccine mRNA allows it to escape the normal activation of toll like receptors (TLRs) and not create the same reaction.[49] This makes the vaccine mRNA unlikely to act as a DAMP to promote autoimmunity.

A third possible mechanism is from the lipid nanoparticle (LNP) carrier. The mRNA vaccines use different types of lipids in the LNP including a cationic ionizable phospholipid. The mRNA/LNP vaccine complex has been shown to induce expression of IL-1β, interferon-γ (IFN-γ), and IL-6. This complex is recognized by TLRs and this will induce type 1 IFNs, which induce a cytotoxic immune response.[50] The ionizable cationic lipid in the LNP has been shown to act as an adjuvant, resulting in immune activation. The fact that this is a cationic phospholipid results in cell membrane interactions that induce an oxidative stress response and can add to the adverse impact.[50] This impact of the LNP and its contribution to immune activation cannot be overemphasized: this was a dose limiting issue with the development of LNP delivery systems for the treatment of cancer.[51] This immune activation can induce autoimmunity through an "innocent bystander" mechanism in which the immune system will develop temporary autoimmune antibodies due to exposure to damaged cells.

The final mechanism is one of amplification of subclinical autoimmunity. Many otherwise healthy people can carry levels of autoimmune antibodies without symptom. A recent study from Germany suggested that aCL and aβ2GPI antibodies were positive in 1.8% and 4.8% of a selection of healthy adults, respectively.[52] Specific immune activation by these vaccines would result in an increase in those levels to a point where they could trigger a clinical syndrome.

One other consideration with mRNA vaccines: there have been studies suggesting that the vaccine induces a far greater antibody response to the spike protein than does the natural infection with SARS-CoV-2. This increase is more pronounced if a person has had a previous SARS-C0V-2 infection prior to vaccination and if they have had more than one vaccine.[53] Because the vaccine will mimic the impact of the spike protein in COVID disease, it is likely that this increase in antibody production will result in an increase in the autoimmune antibodies (including aCL and aβ2GPI) at a far greater rate than what is expected with natural infection.

7. Screening for antiphospholipid antibodies

No consensus exists on which patients should be screened for the presence of antiphospholipid antibodies. Screening should be considered standard of care following pathognomonic complications such as serial miscarriage or arterial thromboses. Tan et al. reports that they are also appropriate in the setting of an unprovoked venous thrombosis, especially at "unusual sites", in those younger than age 45.[54]

Both the SARS-CoV-2 virus and the mRNA vaccines are

known to elicit APLs and the antiphospholipid syndrome. Consequently, "APS-like" manifestations in an appropriate clinical setting should warrant further studies for APLs. Clinical events that are temporally linked to or subsequent to either COVID-19 or SARS-CoV-2 mRNA vaccine exposures should be assessed for evidence of APS.

Individuals with chronic APLs (up to 5% of the population) and those with known autoimmune disease such as Lupus may be at particularly high risk for the complications of APS. Indeed, a case of catastrophic antiphospholipid syndrome has been reported following Pfizer's SARS-CoV-2 mRNA vaccination in a 35-year-old female with Lupus and chronic APS.[14] Since APS can be life-threatening, pre-exposure counseling may be necessary.

8. Conclusion

COVD-19 infections were notorious for generating adverse vascular and cardiac events, many of these due to intravascular thrombosis. The rise in excess mortality in 2020 with the first two waves of SARS-CoV-2 infections was expected. What was unexpected was the rise in excess deaths in 2021, particularly in young, healthy individuals. Many of the excess deaths seen in this younger population were not from a viral pneumonia, but from vascular/cardiovascular events. Given that one significant difference between the environment in 2020 and in 2021 was the widespread introduction of the mRNA COVID vaccines, the question of whether mRNA vaccines could be involved with this increase in all-cause mortality must be considered.

We know from the literature that both COVID-19 and the mRNA COVID vaccines can induce the types of inflammatory and thrombotic events that have been associated with this excess mortality. Since APLs are also strongly associated with abnormal thrombosis, they would be a prime suspect for involvement in these cases.

Our review of the VAERS data from 2021 demonstrated that the COVID vaccine was associated with 98.7% of all reports of thrombosis and 97.7% of reports of myocarditis, cardiac arrest, arrhythmias, myocardial infarction and cardiac failure. All reports in the same time frame that included terms such as APS or cardiolipin antibody in this same data set were solely linked with the COVID vaccine. A further review demonstrated a high correlation between COVID vaccination and pulmonary hypertension (99.2%), pulmonary embolism and thrombosis (98.8% and 97.9%), deep vein thrombosis (99.0%) and intracardiac thrombosis (98.1%). Because APLs are highly correlated with and causative of abnormal clotting, this data suggests that the COVID vaccines may be related to these events through the induction of APLs and APS. In light of the association between APS and adverse pregnancy outcomes, this was also investigated through VAERS data. COVID vaccination was highly associated with pre-eclampsia (95.2% of reports), spontaneous abortion (97.9%) and fetal death (97.3%).

These associations between COVID/COVID-19 vaccination and APS are further supported by viable mechanisms. There is published evidence of homology between spike protein and phospholipids as well as documented binding of human monoclonal antibodies against spike protein to human phospholipids.

We propose that there exists sufficient evidence for COVID/COVID-19 vaccine associated autoimmunity and of their induction of antiphospholipid antibodies to raise concerns. The possibility of "APS-like" illness and potentially life-threatening complications requires greater physician awareness of APS and of the need to screen for the antiphospholipid syndrome.

Conflicts of Interest: None

Funding: Stephanie Seneff received funding for this research from Quanta Computer, Inc. Taiwan, under grant number 6950759. All other authors received no funding.

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