

**Short Communication**
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## Combined Hormonal Contraception and the Adenoviral Vector Covid-19 Vaccines

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### ABSTRACT

There are at least 4 different types of covid-19 vaccines that are available worldwide. The most widely used ones are the mRNA genetic vaccine and the viral vector vaccine. In the midst of the COVID-19 pandemic and after the administration of millions of those vaccines globally over few months, several national health authorities across Europe decided to pause the administration of the chimpanzee adenovirus-vectored vaccine1 (ChAdOx1nCoV-19, AZD1222; Oxford/AstraZeneca) after sporadic reports of severe cases of thrombocytopenia, bleeding, or thrombosis in those who received this vaccine. This complication has been identified as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) that affects mostly woman under the age of 55 years at a rate of 1:100,000 vaccine doses. Combined hormonal contraceptives (CHC) are known to carry the risk of thrombosis in certain high-risk population. Accordingly, women taking those contraceptives raised their concern of getting such vaccine.

This review will attempt to explain the different mechanisms of thrombosis which abolish any link between the VITT complication and the use of CHC. Reassuring statements from authoritative agencies are also included.

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### Introduction

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) held their meeting on 18 March 2021 with the German Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut) governing the production of AstraZeneca vaccine to evaluate the very rare events observed by some EU member countries in temporal association with vaccination with the COVID-19 Vaccine AstraZeneca, in particular blood clots, bleeding, and platelet deficiency [1].

They reviewed 62 cases of cerebral venous sinus thrombosis (CVST) and 24 cases of splanchnic vein thrombosis reported in the EU's Drug Safety Database, 18 of which were fatal.

Two weeks later, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) reported their own statistics that among more than 20 million people who have been vaccinated in UK with the Oxford/AstraZeneca vaccine, 79 cases developed this rare clinical syndrome. Out of those 44 developed CVST, 35 had other forms of thrombosis; 19 died. An incidence of 0.0004% or in other words around one case per 250 000 people vaccinated, and one death in a million [2].

**The EU-UK issued the following joint statement** "the benefits of the vaccine in combating SARS-CoV-2 pandemic and associated COVID-19 disease continue to outweigh the risk of adverse events.

It was decided to include a warning about these very rare events in the technical and use information. The vaccine is not associated with an increase in the overall risk of thromboembolic events in vaccinated individuals. There is no evidence of a quality defect - that is, an association of specific batches or manufacturing at specific sites of the vaccine with the observed thromboembolic events".

On 30 April 2021, the US published their first 18 cases of the same clinical syndrome related to another adenoviral vector covid-19 vaccine (Ad26.COVS COVID-19 vaccine; Janssen/Johnson & Johnson). All were symptomatic under 60 years of age and mostly White women who developed their symptoms between 6-15 days postvaccination. 12 had CVST and the rest suffered non-CVST thrombosis. Approximately 7 million doses of this vaccine had been administered nationwide, and 3 out of the 18 died giving an incidence of less than 3 in a million and one fatality in every 2 million administered doses, which is far less than the European figures related to Oxford/AstraZeneca vaccine. Consequently, CDC's Advisory Committee on Immunization Practices (ACIP) reaffirmed its interim recommendation for use of the Ad26. COVS COVID-19 Janssen/Johnson & Johnson vaccine in all persons aged 18 years or older in the US [3].

Furthermore, we have to keep in mind that the risk of thrombosis and thrombocytopenia is much higher with covid-19 infection than these extremely rare events which are occurring with the vaccine. A study found that, in people with covid-19, the overall prevalence of pulmonary embolism was 7.8% and deep vein

thrombosis (DVT) 11.2%. Of those who ended up in intensive care, 23% developed DVT. Covid-19 also led to strokes in around 1.6% of people, and an estimated 30% of people with covid-19 will get thrombocytopenia [4].

### What is VITT?

Adenoviral vector COVID-19 vaccines, including the Oxford AstraZeneca/Covishield/ Vaxzevria vaccine and the Janssen/Johnson & Johnson vaccine, are associated with immune thrombosis that is similar to heparin-induced thrombocytopenia (HIT). A very rare form of thrombosis (primarily cerebral venous thrombosis) associated with thrombocytopenia was observed in a very small number of vaccinated individuals predominantly under the age of 55 years following vaccination with such vaccine. This phenomenon has been referred to as **Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)**, also known as Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) and Thrombotic Thrombocytopenia Syndrome (TTS). It is called VITT to distinguish it from classical thromboembolic events without thrombocytopenia [5].

Although we started to see cases reported in older adults and men, all original cases were women who developed symptoms between 4 to 28 days after vaccination. The estimated incidence of VITT according to recent publications ranges from 1 case per 26,000 to 1 case per 127,000 doses of Oxford AstraZeneca administered. The rate is lower with Janssen/Johnson & Johnson vaccine (1 case per 500,000 vaccine doses administered).

Hence, the Canadian National Advisory Committee on Immunization (NACI) has recommended that the AstraZeneca/ Covishield or Janssen/Johnson & Johnson vaccine may be offered to Canadians 30 years of age and older, while mRNA vaccines to younger ones. The reason is that more than 180 million doses of BNT162b2 or mRNA-1273 vaccines administered so far, and this clinical syndrome (VITT) has not been reported.

Since VITT appears to be immune-mediated and linked to a very specific antigen without affecting the coagulation cascade, then most probably it does not augment the risk of thrombosis in individual with classical risk factors for thrombosis, such as thrombophilia, a family history of thromboembolism, a personal history of arterial or venous thrombosis, autoimmune disease, thrombocytopenia without a history of thrombosis, or who is on CHC or pregnant.

Screening, diagnosis, and treatment of VITT are summarized in Table 1.

**Table 1: Screening, Diagnosis and Treatment of VITT**

Screening and Diagnosis	<ol style="list-style-type: none"> <li>1. Presence of Post-vaccine symptoms within 4-28 days, such as severe headache, blurred vision, seizure, chest pain with difficult breathing, swollen legs, unusual bleeding, multiple bruises, or red or pale legs)</li> <li>2. CBC: platelet count is &lt; 150 x 10<sup>9</sup>/L.</li> <li>3. VITT is suspected if the above is present, then proceed with: <ol style="list-style-type: none"> <li>a. Blood film (Clear, no platelet clumping)</li> <li>b. D-dimer (elevated)</li> <li>c. Diagnostic imaging (depends on complaints, but commonly R/O CVST by CT +/- MR brain &amp; venogram.</li> <li>d. Heparin Induced Thrombocytopenia (HIT) Antibody Test</li> </ol> </li> <li>4. Consult Hematologist</li> </ol>
Treatment	Once VITT was suspected, platelet transfusions and anticoagulation with any kind of heparins should be avoided. Empirically, direct oral factor Xa inhibitors such as edoxaban, rivaroxaban, apixaban should be started.

### Mechanism of Thrombosis

Thrombosis can either be arterial or venous. While accelerated atherosclerosis is the underlying event for arterial thrombosis, immobility and procoagulant states are the predisposing factors for venous thrombosis.

VITT is a thrombosis that is associated with immune thrombocytopenia. These patients produce antibodies against platelet factor 4 which induce massive platelet activation, reducing the platelet count and causing thrombocytopenic thrombosis [6]. Symptoms usually appear late after vaccination because of the time needed for the antigen to stimulate the production of specific antibodies. This is a similar mechanism to HIT, except that VITT does not require heparin as a trigger. This is characterized by immune mediated destruction and impaired synthesis of platelets resulting normally in bleeding tendency. However, thrombosis may also occur in such unique pathological process. Patients with chronic and active diseases are particularly at risk of thrombosis due to accelerated atherosclerosis as in any autoimmune conditions, leading to arterial thrombosis. It is important to note that treatment with IVIG to prevent platelet destruction may increase the risk of thrombosis due to increasing blood viscosity and thrombin production at the same time. Venous thrombosis may result from circulating platelets microparticles that promote thrombin formation, regardless whether the patient is taking the CHC or not.

Estrogen can increase plasma fibrinogen and the activity of coagulation factors in the blood, leading to a procoagulant status that can only be of threat to develop a clot in certain high-risk groups, such as acquired or inherited thrombophilia patients or those with venous stasis; but not the majority of general population. This estrogen related risk of thrombosis is equally seen in any CHC, including the pill, the ring, and the patch.

While the pill is contraindicated in patients with thrombophilia and or history of thrombosis, the likelihood of pill-associated venous thromboembolism (VTE) in general female population is considered very low, especially when compared to thrombosis risk associated with pregnancy and postpartum which is ten times more. VTE risk from taking the pill is estimated to be 1:2000 women each year; and that associated with air travel was estimated to be 1:1000 [7].

### The Adenoviral Vector COVID-19 Vaccine and CHC

Despite that most of the cases occurring in women under the age of 55, not all those who developed VITT were taking CHC. Hence, CHC is unlikely to cause the clotting. It seems that the VITT associated antibodies are specifically strong activators of the platelets, leading to the typical presentation of thrombosis and thrombocytopenia. Minor modulating factors like the pill may have probably very little influence on the thrombotic outcome if any. The driving force of the severity of VITT is the strength of the antibody and not minor co-factors. Looking for predisposing factors, apart from genetic makeup, the gender may come next as for unknown reasons we see more autoimmune diseases in women than men. While scientists around the world working to understand this complication, VITT remains a minor association with covid vaccines. Potluri reported that flu vaccine-induced antibody responses were increased in females by estradiol and decreased in males by testosterone [8]. However, Young women have a higher risk of developing certain types of blood clots regardless of their vaccine status.

Adenoviral vector COVID-19 vaccines may cause VIIT, but due to different pathophysiological process, CHC is unlikely to

precipitate or aid the development of VITT. Other conditions, which might be thrombotic risks for CHC, are not obvious risks in this VITT condition. In other words, VITT is not more common in people with a history of thrombosis, with a family history of VTE, with thrombocytopenia, or pregnant women because VITT does not develop through the same process as usual types of bleeding or thrombosis. Obviously, those on various forms of hormonal contraception should not be concerned about receiving Adenoviral vector COVID-19 vaccines. Lastly, getting the vaccine while being on a form of CHC will not double a woman's chance of thrombosis.

### Current Positions

I would like to caution the reader that these positions might change at any time as the science of this new disease is evolving. The Canadian Stated: "none of the currently approved 5 COVID-19 vaccines in Canada (AstraZeneca is one of them) increase the risk of blood clots overall" [9].

The UK scientific authorities similarly stated that for Oxford AstraZeneca vaccine: "Blood clots are extremely rare and benefits outweigh risks" [10]. Moreover, "Women aged under 30 years are not going to receive the Oxford AstraZeneca vaccine following MHRA guidance" [11].

The Faculty of Sexual and Reproductive Health specified that "we do not recommend that combined contraceptive users stop their contraception when they receive their first or second COVID-19 vaccine. Currently, there is no evidence that ongoing or very recent use of combined hormonal contraception affects risk of this specific type of blood clot with low platelets occurring after the first dose of the AstraZeneca COVID-19 vaccine" [12]. Finally, for those who are not convinced with these reassuring scientific evidences and professional statements, there is always a room for switching from CHC to non-estrogen containing long-acting reversible contraceptives or progesterone only pill.

### Conflict of Interest

The author would like to report no conflict of interest.

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