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Estrogen-Eluting Ring for Contraception and Possible Issues of Severe Pulmonary Emboli

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG **Alexander Santos**
ABCDE **Christopher R. Chew** 
ABCD **Anthony Hatoum**

Graduate Medical Education, Northeast Georgia Medical Center, Gainesville, GA, USA

Corresponding Author: Alexander Santos, e-mail: as194115@pcom.edu
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Patient: Female, 27-year-old
Final Diagnosis: Pulmonary embolism
Symptoms: Chest pa • dyspne
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine • Pulmonology

Objective: Rare coexistence of disease or pathology





Background: This case report demonstrates the relationship of an estrogen-eluting vaginal ring and thrombosis. There have been multiple reports in the literature demonstrating this scenario, but it is normally found that the patient is taking the medication orally. In this unique report we present the case of a patient with an acute severe pulmonary embolus while using an estrogen-eluting vaginal ring, with no other significant risk factors.

Case Report: A 27-year-old African American woman who came to the Emergency Department due to new shortness of breath and tachycardia. She was discovered to have a pulmonary embolus found on CTA pulmonary. On further questioning, the patient noted using an estrogen-eluting ring for contraception.

Conclusions: We postulate that her use of this estrogen-eluting ring likely played a large part in her developing a pulmonary embolus, as this patient had little to no risk of developing a pulmonary embolism.

Keywords: Estrogens • Pulmonary Embolism

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Background

Various methods are used for birth control: hormonal, barrier technique, intrauterine, withdrawal, and sterilization. Hormonal contraception can come in the form of vaginal rings, intrauterine devices, injections, implants, combined oral tablets, and patches. Estrogen-containing contraceptives also cause a 3- to 5-fold increase in venous thromboembolism. A 2015 meta-analysis noted a 1.6 times higher risk of arterial thrombosis causing myocardial infarction and stroke when compared to the population not taking COCs (combined hormonal contraceptives) [1]. While estrogen-containing oral contraceptives have been noted to cause venous thromboembolisms, there is less evidence that vaginal rings containing estrogen cause venous thromboembolisms. The vaginal ring contains 2.7 mg of ethinyl estradiol and 11.7 mg of etonogestrel, which secrete around 0.015 mg/day of ethinyl estradiol and 0.120 mg/day of etonogestrel. Ethinyl estradiol is a synthetic estrogen and etonogestrel is considered a progesterone-mimicking compound. The mechanism of action of these hormones is by inhibition of gonadotropins and prevention of ovulation. There are additional effects on cervical mucus of increased risk of blood clot events such as deep vein thrombosis, pulmonary embolus, loss of eyesight from clots, heart attack, and stroke. According to the company's risk analysis, patients using their hormone-eluting ring have a risk of developing a clot range of 3-12 in 10 000 women-years compared to 1-5 in 10 000 women-years in non-hormonal contraception therapy [3]. There was a large, prospective, controlled, non-interventional cohort study of the 'NuvaRing' and combined oral contraceptives, showing similar incidence of thromboembolic events during routine clinical use, and commenting that there is a lack of awareness of the actual thromboembolic risk [4]. In the present study we present a patient with no known history of thrombophilia who is currently using a hormone-eluting vaginal ring, which resulted in significant thromboembolic disease.

Case Report

The patient was a 27-year-old African American woman with past medical history of hypertension controlled on Amlodipine 5 mg, depression, and generalized anxiety disorder, who presented to the Emergency Department with shortness of breath and chest pain. The patient endorses that she is not married, denies tobacco, E-cigarette, or smokeless tobacco use, and has a BMI of 35.7. The patient's essential hypertension developed prior to using the hormone-eluting vaginal ring and was not related to the estrogen ring. She reported she engages in moderate physical activity (around 30 min of moderate-intensity activity at least 3 times a week). The patient states that the chest pain was pleuritic in nature and started the day before her visit to the Emergency Department (ED). She denied recent travel, long periods of inactivity, recent surgery, or any

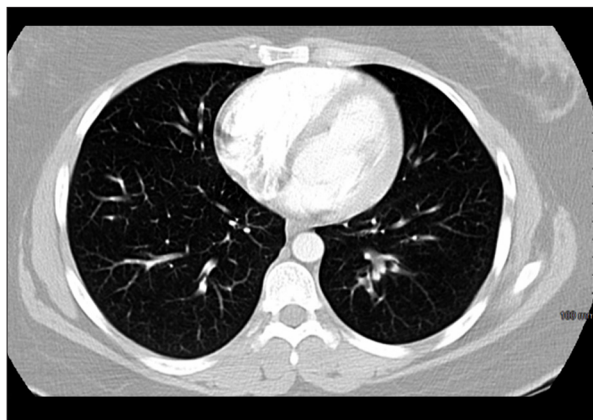


Figure 1. CTA pulmonary.

past medical history of thromboembolism. She additionally endorsed no family history of congenital thrombophilias or autoimmune diseases.

While in the ED, the patient had a venous blood gas taken, which noted a pH of 7.47 and pCO₂ 32.3 mm Hg. Additional labs taken while in the ED noted a hemoglobin of 13 g/dl, platelet count of 172 k/uL, INR 1.5, PT 17.1 s, AST 11 U/L, ALT 22 U/L, and albumin 3.8 g/dL. No leukocytosis or anemia was present on the CBC. Due to the patient's shortness of breath and feeling of palpitations, an electrocardiogram was completed, which was significant for sinus tachycardia. Due to concern of respiratory pathology, an X-ray of the chest was taken, which showed no acute cardiopulmonary disease. As the patient's oxygen requirement began to increase and she continued to have tachycardia on telemetry with no infectious etiology identified on the physical exam, a CTA pulmonary was performed in the ED (**Figure 1**). The CTA pulmonary showed extensive bilateral pulmonary emboli in both main pulmonary arteries that extend into the right upper middle and lower lobes of the pulmonary arteries and the left upper and left lower lobe of the pulmonary arteries. A lower extremity venous duplex scan was performed, which did not reveal any deep vein thrombosis. Due to fear of additional thrombi in the ventricles or atria of the heart, a transesophageal echocardiogram was performed, which showed left ventricular ejection fraction at 50-55%, normal left ventricular diastolic function, and normal right ventricular systolic function. She was subsequently started on heparin infusion for 4 days, then transitioned to apixaban for 6 months duration. The patient had an immediate recovery of symptoms after a few days of treatment and was discharged from the hospital. It was also recommended that she discuss alternative contraceptive methods with her gynecologist.

It was revealed throughout the patient's hospital course that she had been using an estradiol-eluting vaginal ring for the last 2 years as her means of contraception. Upon discharge, the patient visited her PCP for further workup, and her cardiologist

antibody IgA, IgM, and G were negative (<2.0 U/mL), as were Beta-2 Glycoprotein 1 Ab IgA, IgM, IgG (<2.0 U/mL), prothrombin (Factor II) 20210G.A mutation, and factor V Leiden (R506Q).

Discussion

This case study shows the possibility of a high-risk medication such as an estrogen-eluting vaginal ring causing thromboembolism. This form of contraception releases estrogen, which is slowly reabsorbed systemically via the vaginal tissue. There have been multiple cases in the literature noting estrogen-containing birth control associated with an increase in thromboembolic events.

Due to advances in research in thrombosis, the scientific community has a better understanding of oral contraceptives and their effects on coagulation. A randomized, cycle-controlled, cross-over study showed increased plasma levels of coagulation factors VII, VIII, and X, as well as increased levels of fibrinogen and prothrombin when oral contraceptives were being used, and also noted decreased levels of factor V [5,6]. Increases in factor V levels via estrogen use have similar effects to that in factor V Leiden, including increased risk of thromboembolism.

Use of oral contraceptives can decrease levels of antithrombin, which is an inhibitor of several activated coagulation factors and TEPI (triatomine extrinsic pathway inhibitor). Protein C activity is also impacted. Women on oral contraceptives containing estrogen may have lower APC-independent anticoagulation activity protein S than in women using third-generation oral contraceptives.

Etonogestrel, which is a progesterone receptor agonist, is also eluted in this form of contraception. This medication inhibits contraception by inhibiting ovulation and secondarily increasing cervical mucus viscosity, which inhibits sperm penetration. Multiple studies have been conducted on etonogestrel-containing vaginal rings and cardiovascular risk. A prospective, controlled study performed in the United States and 5 European countries assessed 66 489 woman-years of data for incidence

of venous thromboembolism. The results noted a Cox regression analysis with users with combined OCPs of 0.9 and 0.8 for VTEs (95% confidence intervals [CLs] 0.5-1.6 and 0.5-1.5) and 0.8 and 0.7 (95% CLs 0.2-2.5 and 0.2-2.3) for arterial thromboembolism. This suggests the estrogen component is the main reason for VTE risks and not the etonogestrel [7]

A similar report on venous thromboembolic events (VTEs) in 3 women using novel hormone-eluting rings with no extensive personal or family history of VTEs found 1 of the patients in review had heterozygous genetic findings of factor V Leiden and the other 2 had transient lupus anticoagulant. This publication additionally lists a group of studies reporting VTEs in women using the NuvaRing, but all of the studies note that the women using the ring had additional risk factors or were unsure of risk factors. The present study is important because this patient had no known risk factors for developing a VTE [8].

Conclusions

We report the case of a patient with no risk for VTE other than the use of a hormone-eluting vaginal ring, coming to the hospital with signs and symptoms of pulmonary emboli and found to have a large PE. Additional awareness is needed regarding young patients presenting with similar symptoms, and emergency physicians should suspect serious VTE as a likely culprit in patients with drug-eluting rings as a form of contraception. This case report should also reinforce the importance of questioning patients about their contraception use and the many forms they come in. Multiple studies have noted the general safety of the ring and low risk profile of such vaginal medications. There is likely a need for increased awareness of estrogen-eluting medications for contraception and how they may play a role in development of VTEs.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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