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Case Report

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Pulmonary Embolism in a Healthy Woman using oral contraceptive containing ethinyl estradiol: A Case Report

Evelin Jimenez MD, Lauren Alcantara Navarro MD, Sahar S Abdelmoneim MD MBA*, Abelardo Broceta Martinez, MD, Manuel Gonzalez Cruz, MD, Odalys Frontela, M.D.

From the Division of Internal Medicine, Larkin Palm Spring Community Hospital, Hialeah, Florida

***Corresponding author:** Sahar S Abdelmoneim MD MBA, Odalys P Frontela, MD, Division of Internal Medicine, Larkin Palm Spring Community Hospital, 1475 W 49th Pl, Hialeah, FL 33012.USA.

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Abstract

Background: *Combined oral contraceptive (COC) use has been associated with venous thromboembolism (VTE) (i.e., deep venous thrombosis and pulmonary embolism). The risk for VTE has been evaluated for many estrogen doses and progestogen types contained in COC with an increased risk of VTE for females taking third generation COCs (containing desogestrel, drospirenone, or gestodene) than the use of second-generation COCs (containing levonorgestrel).*

Case Description: *We present a case of an obese (BMI 34.33 kg/m2) nulligravid 20-year-old female with no significant past medical history who developed a pulmonary embolism one year after using third generation COCs (Lo Loestrin and Estarylla) without any additional risk factors for thrombosis. The patient presented with palpitations for a day along with chest pain, shortness of breath. Two weeks prior to the onset of palpitations, she reported having a pain in her left lower extremity. Lower extremities vein doppler revealed no evidence of deep vein thrombosis in both lower extremities. Chest computed tomography angiography (CTA) showed extensive bilateral pulmonary emboli (PE) including a large embolus at the right pulmonary artery and bilateral patchy irregular ground glass opacities. Transthoracic Echocardiography showed a positive McConnell's sign of the right ventricular free wall akinesis with sparing of the apex. The patient was started on full anticoagulation with a heparin drip for 48 hours, with uncomplicated hospital course. Long term oral anticoagulants were prescribed.*

Conclusion: *All oral contraceptives are associated with some risk of venous thromboembolism, which should be taken into consideration when these drugs are prescribed. The effect size depended both on the progestogen used and the dose of ethinyl estradiol. Presenting symptoms vary amongst individuals, thus proper diagnostic workup is necessary. Anticoagulation is the mainstay of PE treatment both in the in-hospital treatment phase and after hospital discharge and should be initiated as soon as the diagnosis of PE is suspected.*

Introduction

Combined estrogen-progestin oral contraceptives (COCs) are known to provide reliable contraception benefits. COCs contain an estrogen component and one of a dozen different progestins. Like any other drug, COCs are not free from risks. Women taking COCs have, as with any other hormonal contraception, an increased risk of venous thromboembolism (VTE). Women taking COCs have a higher risk of developing deep vein thrombosis (DVT), usually in the legs, which in turn may lead to pulmonary embolism, a known serious complication. It is estimated that the risk of VTE increases 3 to 5 times in individuals using second-generation COCs and up to 6 to 8 times in those using third generation COCs [1].The presence of an associated risk factor (e.g., thrombophilia) increases this risk in these individuals. We present a 20-year-old young woman, with unremarkable past medical history, presenting with the diagnosis of Pulmonary Embolism (PE) without the evidence of deep vein thrombosis (DVT) or inherited risk factors one year after taking Lo Loestrin and Estarylla. We also report a brief review of Literature. The patient presented in this case report gave informed consent and is aware that there are no patient-identifying details in the text or images submitted.

Case Description

A 20-year-old woman who is a non-smoker, college student, and with no significant past medical or surgical history, presented to

our emergency room for persistent palpitations of 1 day duration. The palpitations were associated with a stabbing like chest pain rated 7/10 in severity, and mild shortness of breath at rest. Of note, the patient reported history of left lower extremity pain with no swelling two weeks prior to the onset of palpitations. OB/Gyn history was significant for regular menstrual cycle of 28 days with menstruation lasting 5 days. Menstrual flow was moderate and menstrual pain was tolerable. Contraceptive history included OCPs for a year for contraception. She started taking Lo Loestrin (norethindrone acetate 1 mg, ethinyl estradiol 10 mcg and ethinyl estradiol 10 mcg) for 3 months. She then switched over to Estarylla (norgestimate 0.25 mg and ethinyl estradiol 0.035 mg) for the last 9 months. Her family history was significant for a history of unprovoked PE in her father at the age of 58 years old. On physical examination, BMI was 34.33 Kg/m^2, BP 145/88 mmHg, pulse rate 143/min, respiratory rate 24/min with oxygen saturation at 97% on 2L NC. Patients appeared lethargic. Pulmonary examination showed a decreased breath sounds at the right side and pleuritic chest pain on deep inspiration. Lower extremities examination was unremarkable with no significant skin color changes, edema, or asymmetry. Calculated Well's score was 7.5 points (i.e.: high-risk for PE) while Geneva score was 8 points (i.e.: moderate risk for PE). Chest X-ray (Figure 1) showed normal cardiac silhouette and no focal pulmonary consolidations or pleural effusions. Initial ECG (Figure 2) showed sinus tachycardia. A Lower extremity vein doppler ultrasound was performed and revealed no evidence of deep vein thrombosis in both lower extremities. Laboratory workup on admission revealed elevated D -Dimer at 3.70 µg/mL (normal <0.55 µg/mL), and protein S activity was decreased at 56% (normal 60% to 130%). Other labs including Lupus anticoagulant and Factor V Liden, CBC, CMP, Coagulation profile, liver function test, cardiac Troponin -I, high sensitivity CRP, Sed rate, and arterial blood gases were all within normal limits. Two-dimensional transthoracic echocardiography (Figure 3) showed mild right ventricular pressure overload with flattening of the interventricular septum in the parasternal long axis view while the modified apical right ventricular focused view showed right ventricular strain, and positive McConnell's sign (right ventricular free wall akinesis with sparing of the apex). Chest computed tomography angiography (CTA) showed patchy irregular ground glass opacities bilaterally, extensive bilateral pulmonary emboli including a large embolus at the right pulmonary artery, main pulmonary artery trunk dilatation, and evidence of subsegmental extension of the embolus as shown in Figure 4. The patient was admitted to the ICU and was started on full anticoagulation with a Heparin drip titrated per unit protocol for 48 hours. Her hospital stay was uncomplicated, and she was clinically and hemodynamically stable. The patient was discharged on Eliquis 10 mg PO BID for 7 days followed by 5 mg PO BID for 21 days, followed by 2.5 mg PO BID for 6 months, with instruction to follow up outpatient with her primary care physician.

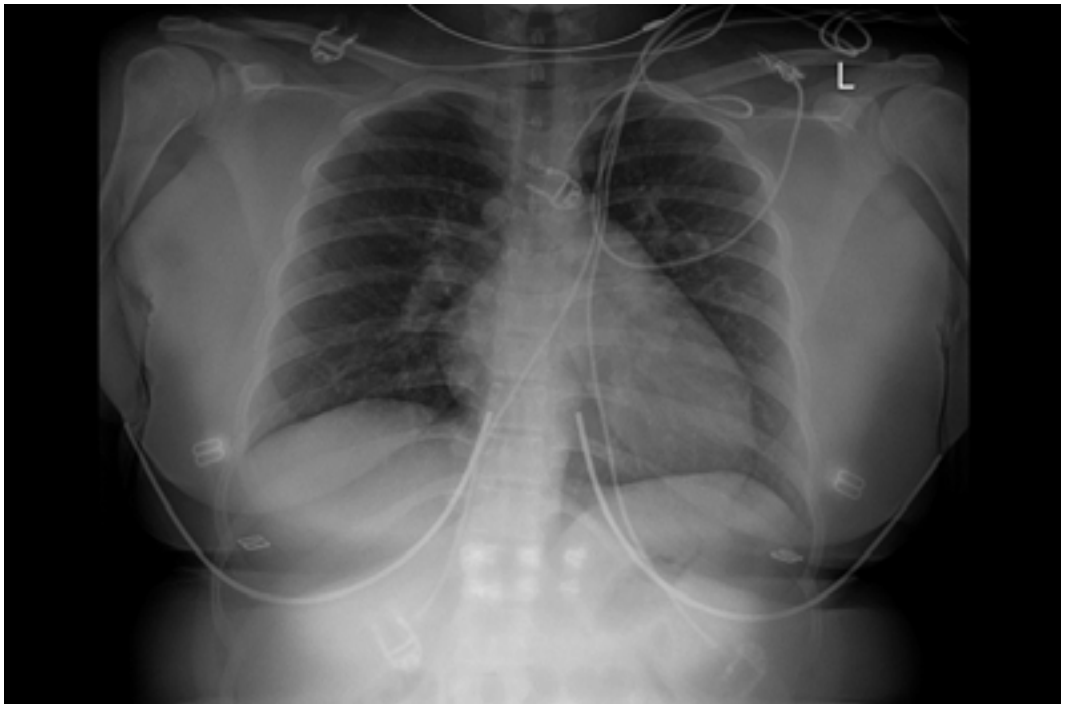

Figure 1: Chest X-ray: showing normal cardiac silhouette and no focal pulmonary consolidations or pleural effusions.

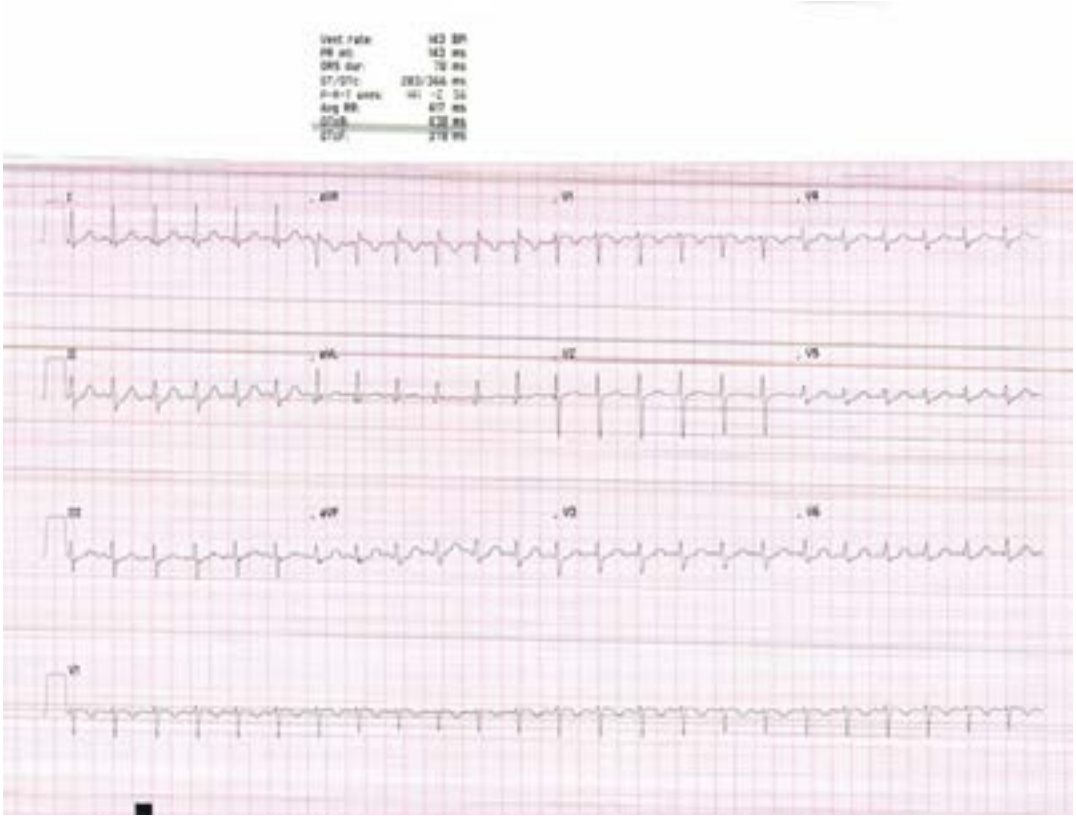

Figure 2: ECG showing sinus tachycardia.

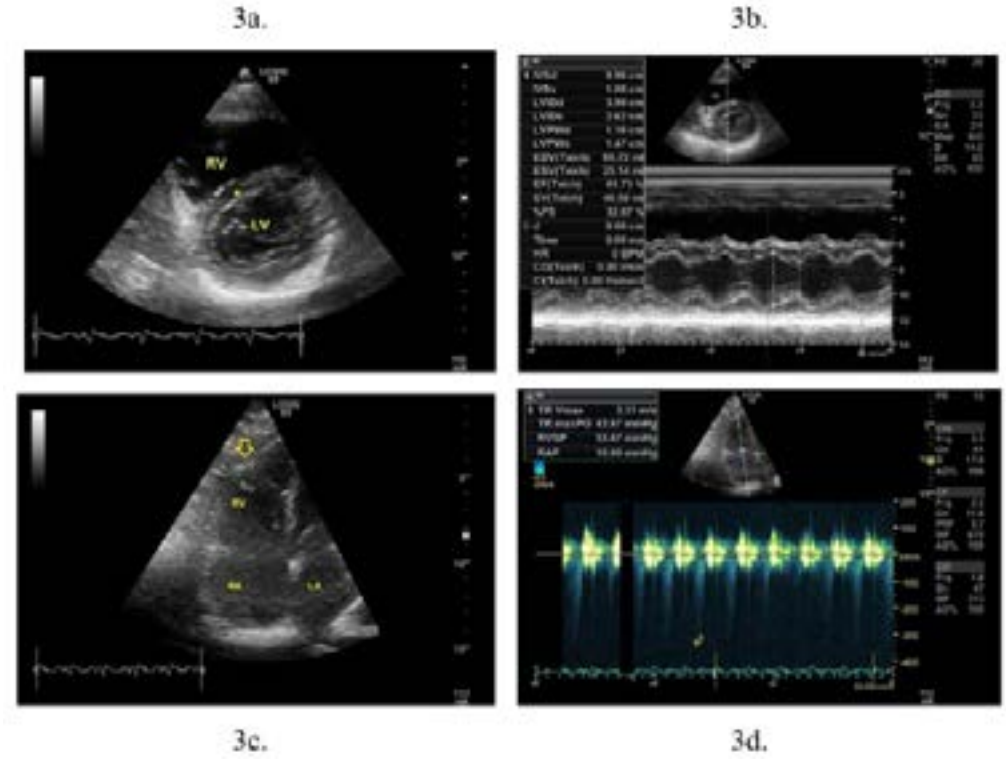

Figure 3: Two-dimensional transthoracic echocardiography image. A) Parasternal short axis view at papillary muscle level showing mild right ventricular pressure overload with flattening of the interventricular septum; B) Parasternal long axis view showing septal deviation due to pressure overload in right ventricle; C) Modified apical right ventricular focused view showing right ventricular strain, and positive McConnell's sign : right ventricular free wall akinesis with sparing of the apex; D) Continuous wave doppler showing mild tricuspid regurgitation.

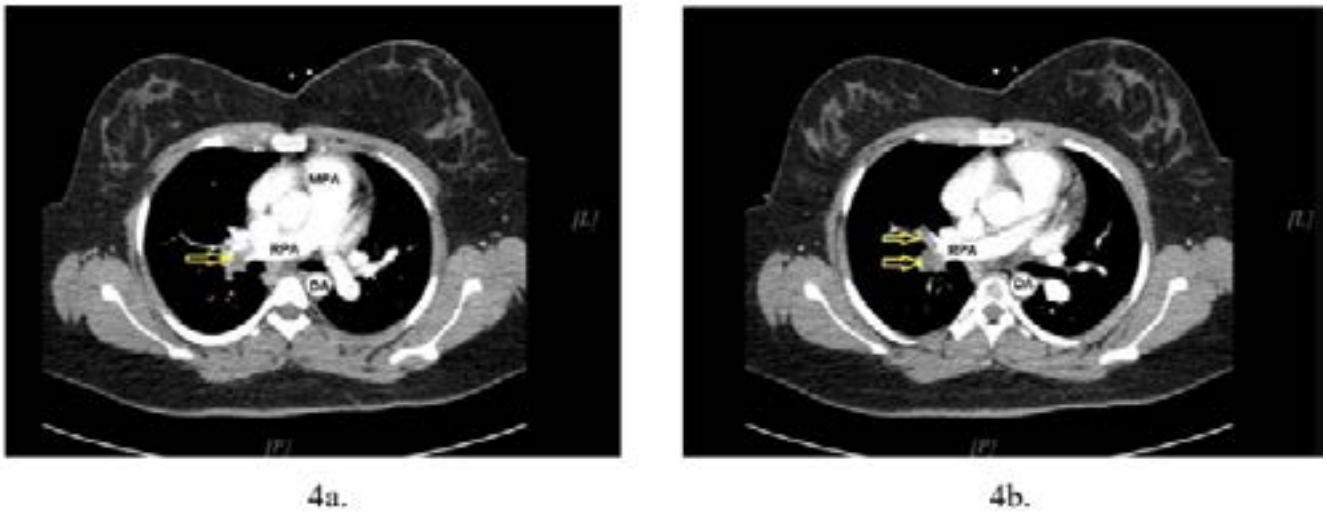

Figure 4: Computed tomography angiogram of the chest, axial images showing extensive bilateral pulmonary emboli including a large embolus at the right pulmonary artery (arrow). **A)** There is enlargement of the pulmonary arterial trunk. Main pulmonary artery trunk is dilated. Additionally, a patchy irregular ground glass opacities bilaterally is noted; **B)** evidence of subsegmental extension of the embolus. MPA, main pulmonary artery; RPA, right pulmonary artery; DA, descending aorta.

Discussion

An effective and convenient method of contraception is the use of COCs. COCs are also known to help treat premenstrual syndrome, headaches, and acne, as well as decrease the risks of ovarian and endometrial cancer [1]. Using COCs also increases the risks of certain life-threatening conditions including Venous thromboembolism (VTE) and ischemic stroke, particularly among women with inherited thrombophilia. Inherited thrombophilia's are seen mainly in Factor V Leiden deficiency, antithrombin or protein C/S deficiency. Acquired thrombophilia is seen with risk factors including but not limited to, obesity, smoking, combined oral contraceptive use, surgery, trauma, inflammation, and chronic medical illnesses such as hypertension or diabetes mellitus [2].

VTE is often a rare event in young women although the risk is increased in association with a new COCs. Studies have shown that the risk of VTE related to the use of COCs needs to be considered as a cause of PE among very young females. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 women [3]. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer but usually gradually disappears after use is discontinued [1].

Estrogens have many different effects on the coagulation system [3, 4]. These include increases in the levels of procoagulant factors VII, X, XII, and XIII and reductions in the anticoagulant factors' protein S and antithrombin [3, 4]. Increased levels of activators and decreased activities of inhibitors may contribute to arterial and venous thrombotic complications seen in predisposed COCs users [2]. Our patient, for example, had decreased free protein S activity (at 56%), which has been shown to be significantly affected by hormonal status, a commonly known estrogenic effect on the coagulation system. Furthermore, it is postulated that the underlying pathogenesis of a PE is like the generation of a thrombus: Virchow's triad of venous stasis, endothelial injury, and a hypercoagulable state [5]. Thus, a pulmonary embolism can arise even in the absence of a deep vein thrombosis, much like our patient.

The thought behind VTE and OCP use up until 1995 was that the progestin component of COCs did not contribute to the risk, with an exclusive attribution to ethinyl estradiol. Thus, the dose of estrogen was lowered from 100 mcg to 35 -50 mcg in the newer generation pills which led to the reduction of venous thrombosis. Over time, new pill formulations were developed to try to improve patient safety and to decrease adverse effects. As a result, newer hormones were incorporated into the formulations. Initially this was done by changing the progesterone integral of the pill, but more recently, combined pills have been developed with newer estrogens as well. Based on the hormonal content, they were divided into classes; first, second, third, and fourth generations. First generation pills, while no longer in use, contain estrogen mestranol and progesterone norethindrone. Second generation pills contain estrogen ethinyl estradiol and progesterone levonorgestrel or norethisterone. Third generation pills contain the estrogen ethinyl estradiol and progesterone desogestrel or gestodene. Fourth generation pills contain either ethinyl estradiol and progesterone drospirenone, or a different estrogen 17 B estradiol with nomegestrol acetate, or estradiol valerate and dienogest [1, 3]. Various studies published between 1995 and 1996 reported the increased risk of VTE for females taking third generation COCs (containing desogestrel, drospirenone, or gestodene) than the use of second-generation COCs (containing levonorgestrel). The thrombosis risk for contraceptives with drospirenone (fourth generation) was found to be higher than for combined oral contraceptives with second generation progestogens [5]. A summary of unique case reports of DVT/PE of varying symptomatology in young females taking COCs is shown in Table 1.

Table 1: A summary of unique case reports of DVT/PE of varying symptomatology in young females taking COCs.

	Age	Symptoms	Results
Park et al. (5)	23	Pleuritic chest pain	D-dimer: 1.65 CTPA: pulmonary embolism in the basal segmental branch of right lower lobe
Kim et al. (9)	24	Left inguinal pain and edema of left leg	DVT: diffuse DVT below the level of the left external iliac vein CTPA: pulmonary embolism in bilateral basal pulmonary arteries
Piparva et al. (10)	29	Pain and swelling of left leg	DVT: early DVT
Our case	20	Chest pain, palpitations, sob, vomiting, diarrhea	D-dimer: 3.7 CTPA: extensive bilateral pulmonary emboli including a large embolus at the right pulmonary artery

Once a PE is suspected, a determination of pretest probability using either the Wells or Geneva scores may be used [7]. In cases of low and intermediate pretest probability for PE, testing D-dimer is helpful because a negative result may be used to rule out PE. In cases of high-risk pulmonary embolism, confirmatory diagnosis is made by CT pulmonary angiography or echocardiography. In our case, the patient had a Well's score of 7.5 points, placing her at a high-risk for PE and a Geneva score of 8 points, placing her at a moderate risk for PE. In both instances, further workup with D-dimer testing, echocardiography (Figure 3) and CT (Figure 4) were performed, leading us to the diagnosis of PE.

Anticoagulation is the mainstay of PE treatment both in the in-hospital treatment phase and after hospital discharge. Because the first three months after a VTE is the period that has the highest risk of recurrent thrombosis, interruptions of anticoagulation should be limited. Long-term treatment consists of anticoagulation therapy for 3-6 months, with discontinuation at 3 months if the provoked PE is due to a treatable or transient risk factor [7]. Our patient was initially started on a Heparin drip for 48 hours and discharged on Eliquis 10 mg PO BID for 7 days followed by 5 mg PO BID for 21 days, followed by 2.5 mg PO BID for 6 months, with instruction to follow up with her primary care physician.

In summary, all oral contraceptives are associated with some risk of venous thromboembolism, which should be taken into consideration when these drugs are prescribed [8]. In this study, we reported a case of pulmonary embolism in an obese 20-year-old nulligravid woman who was using third generation COCs without additional risk factors for thrombosis. This case emphasizes on the importance to individualize the choices of COCs and screen for risk factors in young and healthy women in aim to decrease the incidence of developing VTE from low-dose formulations of COCs [9,10].

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