

## Pulmonary embolism secondary to inappropriate use of oral contraceptive therapy: a case report

### Pulmonary embolism secondary to inappropriate use of oral contraceptive therapy: a case report

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#### RESUMEN

Mujer de 41 años que ingresa al hospital por cuadro clínico sugestivo de tromboembolismo pulmonar, el cual fue confirmado por AngioTAC. No había antecedentes de eventos tromboembólicos previos, tabaquismo, estasis venosa ni de lesión vascular (anticoagulante lúpico y anticardiolipinas negativo). Como único factor de hipercoagulabilidad que se documenta es el consumo de un anticonceptivo oral que contenía drospirenona y etinilestradiol desde un año atrás. La paciente fue anticoagulada con enoxaparina y se recuperó sin secuelas y actualmente se encuentra en manejo ambulatorio con warfarina. El uso de anticonceptivos orales en combinación se debe realizar con precaución en pacientes mayores de 35 años, en buena medida por el aumento del riesgo de eventos tromboembólicos asociado al incremento en la síntesis hepática de algunos factores de coagulación. Por lo tanto, éste representa un caso de reacción adversa severa, potencialmente fatal y prevenible.

**Palabras clave:** embolia pulmonar; anticonceptivos orales combinados; efecto secundario; reacciones adversas.

## ABSTRACT

Forty-one year old female admitted to the hospital because of symptoms and signs suggestive of pulmonary thromboembolism which was confirmed by CT angiography. There was no history of prior thromboembolic events, smoking, venous stasis or vascular lesion (negative lupus anticoagulant and anticardiolipins). The only documented hypercoagulability factor was the use of an oral contraceptive containing drospirenone and ethinylestradiol for the last year. The patient was treated with anticoagulants such as enoxaparin and she recovered without sequelae; she is currently under treatment with warfarin as an outpatient. It is known that the use of combined oral contraceptives in patients over 35 years old requires caution, largely due to higher risk of thromboembolic events associated with increased hepatic synthesis of several coagulation factors. Therefore, this case represents a potentially fatal and preventable severe adverse reaction.

**Keywords:** pulmonary thromboembolism; combined oral contraceptives side effects; adverse reactions.

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## BACKGROUND

Combined oral contraceptives (COC) are associated with an increased risk of venous thromboembolism (VTE)<sup>1</sup> and the most probable mechanism is the estrogen induction of hepatic plasma proteins involved in coagulation. It has been reported that the risk is double that of non-users, but that the total risk is low.<sup>2</sup>

The risk of thromboembolism varies according to the degree of exposure to estrogen and the type of progestin used. Many COC, especially those containing drospirenone, or other third or fourth generation progestins, have been associated with an increased risk of VTE.<sup>2</sup>

On square, the four generations of progestins are presented.

Drospirenone is a derivative of 17 alpha spironolactone. In rats, rabbits and in man, it is a progestational receptor agonist, and a mineralocorticoid and androgen receptor antagonist, without effect on the glucocorticoid receptor and the estrogen receptor. In normally menstruating women, 2-3 mg drospirenone per day, taken from day 5 to 25 of the cycle, inhibit ovulation, lead to a slight natriuresis, and a mild compensatory activation of the renin-angiotensin-aldosterone system. The COC containing drospirenone has favorable effects in certain conditions as premenstrual syndrome and acne, possibly due to its antiandrogenic effects.<sup>3</sup>

Regarding pharmacokinetics, drospirenone has an oral bioavailability of 76-85 %, with a Tmax between 60-90 min. Its mean terminal half-life is about 30-35 h, leading to steady state concentrations in plasma after 10 days of application. All metabolites (not dependent of Cytochrome P450) are hormonally inactive and are excreted by the kidney. Drospirenone does not bind to sex hormone binding globulin or to corticoid binding globulin, but to other plasma proteins. The free fraction in serum of drospirenone is about 5 %.<sup>3</sup>

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Although two studies published in 2007 entitled EURAS<sup>4</sup> and INGENIX<sup>5</sup> did not report a significant increased risk of VTE in women using COCs containing drospirenone compared to COCs containing other progestins (e.g. levonorgestrel), other two analytical studies published in 2009 confirmed the association, and led to the statement of a warning by the Food and Drug Administration (FDA).<sup>6-8</sup> These studies found an increased VTE risk 1,5 to 2 fold higher in women using COCs containing drospirenone compared with other progestins. This led to several labeling changes on 2010 and 2011, to state an increased risk of VTE in COCs containing drospirenone.<sup>5</sup> Other regulatory agencies such as European Medicines Agency (EMA) and Health Canada took similar measures.<sup>9</sup>

Risks factors of venous thromboembolism associated with COC are linked with smoking, obesity and AB blood group,<sup>10</sup> as well as alcohol consumption, ethnic group and thrombotic comorbidities.<sup>11</sup>

Based on the results of the MEGA case-control by Hylckama Vlieg et al,<sup>8</sup> the relative risk (RR) of VTE in women <30 years was 3,1 (CI 2,2 to 4,6), while it was 5,0 (CI 3,8 to 6,5) for women between 30 and 40 years. For women between 40 and 50 years as our patient, RR was 5,8 (CI 4,6 to 7,3), almost double than women younger than 30 years old. This lead to the FDA to indicate that the risk may be higher in patients older than 35 years,<sup>6</sup> despite of the recommendations of the World Health Organization and the American College of Obstetricians and Gynecologists which advise the use of COCs in women over 40 years nonsmokers without arterial hypertension associated.<sup>1,2</sup> Therefore, this case illustrates a potentially preventable severe adverse drug reaction, and illustrates the importance of identifying possible cautions prior to begin hormonal contraception.

## CASE PRESENTATION

Forty-one year old female who presents with sudden sharp chest pain for the past 20 minutes, with a 10/10 intensity on the visual analog scale (VAS). The pain radiated to the lumbar region and was associated with dyspnea. She did not present syncope or hemoptysis. She was using birth control with drospirenone-ethinylestradiol 3 mg/0,02 mg since august 2013 until july 2014 when the pulmonary thromboembolism (PTE) was diagnosed. There was no history of prior thromboembolic events, smoking, dyslipidemia, recent surgery, travelling, venous stasis or vascular lesion. She was not taken any other drugs or herbal medicines.

The patient was admitted conscious, alert, and hydrated, with signs of respiratory difficulty: tachypnea and intercostal retractions. Heart Rate: 110 per minute, Respiratory Rate: 26 per minute, Blood Pressure: 85/48 mmHg, Temperature: 37,7 °C, Body Mass Index: 24 kg/m<sup>2</sup>, pulse oximetry: 94 % at 28 % inspiratory oxygen fraction.

Normochromic, moist oral mucosa, without jugular distension, neck masses or lymphadenopathies, tachycardic cardiac sounds, right basal hypoventilation and pain on superficial palpation of the right costal cage. Abdomen soft without masses or organomegaly. No edemas or signs of deep venous thrombosis and no motor or sensory neurological deficit. Glasgow coma scale 15/15.

## INVESTIGATIONS

EKG: sinus tachycardia without signs of ischemia or necrosis.

The complete blood count showed mild leukocytosis and anaemia. Platelet count, thromboplastin time and prothrombin time between normal limits. Lipid profile was not performed.

Normal renal function and electrolytes.

Chest x-ray showed: right basal parenchymal opacity and increased vascular markings.

Arterial gases showed respiratory alkalosis with moderately altered oxygenation.

The CT angiogram showed: pulmonary thromboembolism with right basal parenchymal opacity related to pulmonary ischemia without tomographic signs of right ventricular dysfunction.

Lupus anticoagulant and anticardiolipins: negative.

## DIFFERENTIAL DIAGNOSIS

Musculoskeletal pain, Pleuritis, Pericarditis, Hyperventilation, Acute Coronary Syndrome, Anxiety disorders, Cardiac tamponade, Pneumothorax, Pulmonary Edema, and Pulmonary Hypertension.

## TREATMENT

She was treated initially at the ICU with IV fluids, enoxaparin, morphine, omeprazole and oxygen by nasal cannula, when she was referred to internal medicine ward

## OUTCOME AND FOLLOW-UP

She was discharged four days after admission because her PTE had improved. Currently the patient is asymptomatic and without functional limitations. The COC was withdrawn definitely and she was considering surgical sterilization. She was treated with warfarin 5 mg during six months after out, with an INR target of 2-3. Recommendations for prevention of PTE were not discontinue warfarin, not to restart COC, not smoking, maintaining a healthy weight, to report of signs of venous insufficiency appear or she would make long journeys. Anticoagulated patient care (INR control, diet, use of concomitant medications, fall prevention) and warning signs of thromboembolic disease (pain and lower limb edema, chest pain, dyspnea).

## CAUSALITY ASSESSMENT

Regarding causality assessment we used the Naranjo algorithm<sup>12</sup> and World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale,<sup>13</sup> with the following results:

*Naranjo's Algorithm:*

1. Are there previous conclusive reports on this reaction? Yes +1
2. Did adverse event appear after the suspected drug was given? Yes +2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes 0
4. Did the adverse reaction appear when the drug was readministered? Not known or not done 0
5. Are there alternative causes that could have caused the reaction? No +2
6. Did the reaction reappear when a placebo was given? Not known or not done 0
7. Was the drug detected in any body fluid in toxic concentrations? Not known or not done 0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Not known or not done 0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Not known or not done 0
10. Was the adverse event confirmed by any objective evidence? Yes +1

Score: 6, Probable adverse drug reaction

*WHO-UMC scale*

Probable/Likely Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Rechallenge not required.

## DISCUSSION

A PTE case probably associated with the use of a COC containing drospirenone is reported. It is noteworthy that the FDA and other drug regulatory agencies had issued a warning regarding of an increased risk of thromboembolic events for this drug, higher than other progestins.

In this manner, a review published by the FDA in 2011 entitled: "Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints"

found that the risk of VTE could be higher in women between 35 and 55 years old who take COCs containing drospirenone, (the age range of our patient).<sup>14</sup>

However, another FDA review published in 2012 found conflicting evidence regarding the risk of VTE associated with the use of COCs containing drospirenone.<sup>15</sup> According to some epidemiological studies, the risk of VTE can be up to 3 times higher in women who take COCs containing this progestin, compared to users who take COCs with different progestins. However, other studies that were part of the FDA review did not confirm this association.<sup>15</sup>

On the other hand, one of the most important studies aimed at evaluating the safety of drospirenone versus levonorgestrel and other progestins included in COCs included 58 674 women who were followed for 142 475 women-years of observation, finding that the odds ratio of VTE for drospirenone was 1,0 and 0,8 for levonorgestrel.<sup>4</sup> In the same way, the studies by Lidegaard et al. and van Hylckama Vlieg et al. confirmed the association.<sup>7,8</sup>

On the whole, Martinez et al systematic review<sup>17</sup> published in 2012 confirmed a slight increase in risk in patients using COCs containing drospirenone compared to levonorgestrel (RR 1,26, 95 % CI: 1,03-1,52).

Other risk factors include age, thrombogenic mutations (women with a Factor V Leiden mutation may have a risk of VTE up to 35 times higher), personal or family history of VTE, pregnancy and postpartum (increased risk up to 3 to 6 weeks after giving birth), obesity, length of long trips, and travelling at high altitudes (more than one week at more than 4 500 meters above sea level).<sup>1,2</sup> Other than age, none of these risk factors could be documented in this patient. Similarly, drugs associated with thromboembolic disease such as neuroleptics, hormone replacement therapy, non steroideal anti-inflammatory drugs, among others, were not reported in this case.

Although this adverse reaction is more frequent in the first four months of contraceptive use,<sup>6</sup> it is remarkable that in our patient the event presented a year after having begun the medication.

## LEARNING POINTS/TAKE HOME MESSAGES

1. Always consider the possibility of thromboembolic events in patients using oral contraceptives.
2. Evaluate very well the risk factors for thromboembolic events and weigh the benefit/risk ratio before prescribing oral contraceptives.
3. Recognize that age over 40 years is a possible caution for the use of oral contraceptives.
4. The use of drospirenone as a COC carries a slightly higher risk of VTE than other progestins.
5. Remember that a new medicine is not necessarily safer or more effective than those that already exist for certain indication

**Square.** Classification of synthetic progestins

Classification by structure/generation	First	Second	Third	Four
Estranes	Ethinodiol diacetate (with ethinyl estradiol: Demulen <sup>®</sup> ) Norethindrone (Micronor <sup>®</sup> ) Norethindrone acetate (Aygestin <sup>®</sup> )	-	-	-
Gonanes	Norgestrel (Ovrette <sup>®</sup> )	Levonorgestrel (Norplant <sup>®</sup> ; with ethinyl estradiol: Alesse <sup>®</sup> , Nordette <sup>®</sup> )	Desogestrel (with ethinyl estradiol: Desogen <sup>®</sup> ) Gestodene Norgestimate (with ethinyl estradiol: Ortho-Cyclen <sup>®</sup> , Ortho Tri-Cyclen <sup>®</sup> )	
Pregnanes	Medroxyprogesterone acetate (Provera <sup>®</sup> )	-	-	
17-spironolactone derivatives	-	-	-	Drospirenone (Yaz <sup>®</sup> , Yazmin <sup>®</sup> )

Adapted from: Apgar BS, Greenberg G. Using Progestins in Clinical Practice. Am Fam Physician. 2000;15:1839-46.

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