

# Venous thromboembolism during air travel in pregnant women

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## Abstract

**Introduction.** Air travel (AT) has become an integral part of modern life, including for pregnant women who may need to travel for a variety of reasons. While the overall risk of venous thromboembolism (VTE) during AT is low, specific populations, such as pregnant women, face significantly higher risks. This study explores the relation between air travel and VTE in pregnant women, by examining the risk factors, epidemiology, and preventive strategies. **Objectives.** To analyze the incidence of VTE in pregnant women during air travel, identify associated risk factors, and evaluate prophylactic measures to mitigate these risks. **Methodology and Resources.** A comprehensive review of existing literature was conducted, focusing on studies related to the incidence of VTE in air travel, especially in pregnant women. Data from epidemiological and review studies were reviewed to assess the risk factors and the efficacy of prophylactic measures, including mechanical and pharmacological interventions. **Results and Discussion.** The review indicates that pregnant women are at an elevated risk for VTE, especially during flights that last longer than 6 hours. Contributing factors include venous stasis, hypercoagulability, and hypoxia. Prophylactic measures, such as the use of graduated compression stockings and low molecular weight heparin (LMWH), are recommended for high-risk individuals, although routine pharmaco-

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logical prophylaxis is not generally indicated. **Conclusion.** The study highlights the importance of a personalized risk assessment for pregnant women who plan to travel by air. While general preventive measures should be universally recommended, pharmacological prophylaxis should be reserved for high risk travelers. Further research is needed to refine the guidelines for pregnant travelers and ensure their safety.

**Keywords:** thrombosis; pregnancy; anticoagulants; air travel.

## Introduction

Air travel (AT) has become increasingly common and accessible in recent decades and has become part of the lives of women, including pregnant ones, who need to travel for work, leisure, or even as part of their employment in the airline industry.<sup>1</sup> In 2015, approximately 3.5 billion people were estimated to have traveled by air worldwide, a 6.8% increase compared to the previous year.<sup>2</sup> In Brazil, over the past 10 years, with the exception of 2016, the number

of passengers on commercial flights has followed the global growth trend. According to the National Civil Aviation Agency (ANAC), in 2016, around 115 million Brazilians were transported on domestic and international flights.<sup>3</sup> The increase in the number of passengers has been accompanied by an increase in medical issues related to AT, especially in long-haul or long-distance flights. Overall, the most frequently reported medical issues have been hypoxia, infectious diseases, jet lag, anxiety crises, and venous thromboembolism (VTE).<sup>4</sup> Generally, the risk of VTE during air travel is not high; however, it can be significant in some specific groups, such as pregnant women.<sup>5-7</sup>

## Epidemiology

Defining which VTE episodes are directly related to AT can be difficult, since there is no general consensus about the maximum time interval between the landing of the aircraft and the diagnosis of VTE that characterizes such an association.<sup>2-4</sup> Initial studies were based on isolated clinical data with no laboratory or ultrasound confirmation, and the definition of what constituted a long-distance flight varied greatly.<sup>4,7</sup>

Another factor complicating a more consistent epidemiological analysis is that studies tend to be rather specific, with some exclusively reporting the incidence of deep vein thrombosis (DVT) and others focus only on pulmonary embolism (PE), while a smaller number encompasses both factors.

The incidence and prevalence of VTE also vary according to the method used for diagnosis, and also whether it was measured through active search, for example, in asymptomatic patients, or if it was conducted only in symptomatic patients who sought medical assistance after a flight. Nevertheless, a direct relation appears to exist between the duration of the flight and VTE, which mostly manifests itself within the first two weeks after landing, within four days on average, and with the risk persisting for up to four weeks.<sup>3,8</sup>

A meta-analysis of 14 studies involving 4,055 episodes of DVT, published in 2009, showed that the pooled overall relative risk is 2.8 times higher in long AT. Furthermore, the absolute risk of symptomatic DVT in the 8 weeks following a long-haul flight is one episode in 4,500 flights.<sup>8</sup> Such data, therefore, do not suggest universal and widespread practices of VTE prophylaxis during AT, although, risks can increase significantly in some passenger profiles.

A cohort study involving 7,592 employees of large corporations who traveled regularly for about 4.4 years showed that the risk of VTE can increase up to 20 times in passengers who have recently undergone surgery, and up to 18 times in those diagnosed with an active cancer.<sup>8</sup>

The incidence of VTE after flights lasting longer than 4 hours is of one event in 4,656 flights,<sup>5,9</sup> and around 0.5% after those lasting over 8 hours, in low and medium-risk passengers. Severe episodes of PE immediately after flights of up to 8 hours are extremely rare. On flights lasting longer than 12 hours, this figure is five episodes per million.<sup>10</sup>

## Air travel and venous thromboembolism

The association between AT and VTE has been recognized for more than 70 years. In the 1970s, the increase in the number of flights that transported passengers in positions that often require prolonged immobility, led to the coining of the term “economy class syndrome”. However, VTE can affect passengers in any aircraft seating class.<sup>11</sup> At least eight risk factors can be related to

VTE during AT: flight duration exceeding 6 hours; age higher than 40; use of oral contraceptives (OC) or hormone replacement therapy (HRT); gravidic-puerperal cycle; chronic venous disease; obesity (body mass index [BMI] >30kg/m<sup>2</sup>); acquired or genetic thrombophilias; and extremes of stature.<sup>12,13</sup> Combinations of these factors increase the risk; for example, an overweight woman using OC has a risk of VTE after a long flight 60 times higher than a woman without these factors.<sup>6</sup>

## Aircraft-related VTE risk factors

### Hypoxia

For financial reasons, most commercial flights maintain an atmospheric pressure (AP) inside the aircraft similar to an altitude between 1,800 and 2,400 meters above sea level, since maintaining higher AP requires greater fuel consumption due to increased aircraft weight.<sup>4</sup> Prolonged passenger exposure to this hypoxia can trigger the activation of the extrinsic coagulation pathway through microparticles carrying tissue factor<sup>14,15</sup> and raise serum concentrations of factor VIII and plasminogen activator inhibitors (PAI) 1.<sup>16</sup> Nevertheless, the clinical impact seems to be restricted to passengers with associated risk factors, such as thrombophilias or OC users.<sup>15</sup>

### Position during travel

In addition to causing compression of the popliteal vein for long periods, venous stasis caused by sitting in a position with limited space between rows that do not allow regular movement of the feet and lower limbs can trigger a coagulation cascade during AT.<sup>4,14,17,18</sup> This factor is more evident in people taller than 1.90 meters, since they remain in more restricted positions, and in those shorter than 1.60 meters, in whom compression of the popliteal vein occurs because their feet do not touch the ground and remain in a hanging position.<sup>17,18</sup>

### Dehydration

During AT, the cabin humidity is generally low. In a study evaluating 18 flights, the relative average air humidity in the cabin was 10.3%. For purposes of comparison, the relative humidity ranges between 40 and 60% indoors at sea level, and between 70 and 90% outdoors.<sup>19</sup> Moreover, dehydration can be intensified by regular consumption of alcoholic beverages, coffee, and teas, which induce diuresis.<sup>4</sup> Based on these data, passengers are advised to increase their fluid intake to prevent VTE.<sup>19,20</sup> Contradicting these findings, some studies do not support the hypothesis that, in isolation, fluid loss during AT contributes to VTE formation.<sup>15,19</sup>

### Flight duration

Although there is no consensus regarding the exact duration for a flight to be considered long-haul, a clear relationship exists between VTE and flights lasting longer than 6 hours. The risk of VTE increases 2.3 times in long flights compared to short flights, and rises by 26% for every two hours of flight.<sup>2,4</sup> The estimated risk of fatal PE is 0.5/106 for flights over 3 hours and 1.3/106 for flights over 8 hours.<sup>1</sup>

### Class type and seat location

Although the term “economy class syndrome” is systematically used as a synonym for AT-related VTE, the risk factors for passengers traveling in any class — economy, business or first

— remain basically equal.<sup>4,22</sup> However, the risk of VTE doubles for passengers seated by the window compared to those seated in the aisle, especially obese passengers, for whom the risk increases sixfold.<sup>6,22</sup>

## Passenger-associated risk factors

### Gender

No statistical differences in VTE between males and females were found in several studies.<sup>23</sup> However, Lapostolle et al. published a cohort study that indicates that the female sex constitutes an independent risk factor for VTE after long-duration AT that is three times higher than in males (0.61 vs. 0.20 per 1 million passengers).<sup>24</sup>

### Others

Recent surgery, cancer, acquired and genetic thrombophilias, oral contraceptives, and HRT are considered additional risk factors for passengers engaging in long-distance AT.<sup>4,5,8,22,25-27</sup>

### Pregnancy

Pregnant women present the three etiopathogenic components of Virchow's triad: a) venous stasis, due to compression of the inferior vena cava and left common iliac vein by the gravid uterus and decreased venous tone due to the myorelaxant action of progesterone; b) hypercoagulability, secondary to the induction of hepatic synthesis of coagulation FVII, FVIII, and FX by placental estriol, increased fibrinogen and PAI I and II, and decreased protein S synthesis; and c) endothelial injury, which occurs during nidation, endovascular remodeling of the utero-placental arteries, and with the delivery.<sup>28,29</sup> These changes, which are important to protect women from bleeding during childbirth, predispose to VTE.<sup>29,30</sup>

Recent data showed that approximately 44% of women have traveled during pregnancy, among which around 66% sought some form of counseling.<sup>31</sup>

In the absence of obstetric complications or comorbidities, AT is generally safe for pregnant women.<sup>31</sup> Most airlines allow boarding up to the 36th week of pregnancy, although some restrict international flights during the early stages due to the risk of spontaneous abortion.<sup>32</sup>

Nausea and hyperemesis gravidarum, common complications in the first trimester, can exacerbate dehydration due to fluid loss and the inability to replenish fluids, as well as limit ambulation, all of which favor the development of VTE.<sup>31</sup>

In the third trimester, the risk of VTE may increase due to excess weight or obesity, restricted mobility, preeclampsia, or even the onset of premature labor during AT.<sup>31</sup>

The frequency of VTE specifically in pregnant women who are traveling is still unknown.<sup>6,30</sup> The MEGA 5 study showed that the risk of VTE during the first two trimesters of pregnancy is slightly elevated. However, this risk increases in the third trimester by 9 times and in the first six weeks postpartum by 20 to 80 times.<sup>5,33</sup>

In any case, the estimated risk of VTE of 0.3 to 1/1,000 for pregnant women, means that pharmacological prophylaxis is not routinely recommended, although general measures should be encouraged.<sup>6,28,31</sup>

## VTE prophylaxis during AT in pregnant women

The risk level of each passenger should be individually defined.<sup>31</sup> Preventing VTE during pregnancy, based on guidelines that take into account risk factors, and subsequently instituting mechanical and/or pharmacological prophylaxis is the best strategy to reduce this complication.<sup>12,28-31</sup>

### General measures

All pregnant and postpartum women should be encouraged to adopt a range of measures to mitigate the risk of VTE in flights that exceed 4 hours. These include: choosing aisle seats to facilitate movement; regular ambulation; plantar dorsiflexion exercises every 30 minutes while seated; wearing comfortable and non-restrictive clothing; maintaining good fluid intake; avoiding diuretic beverages; and keeping the space under the seat free for better foot movement.<sup>10,12,23,28,31-34</sup>

### Graduated compression elastic stockings (GCES)

GCES, up to knee height and with a compression between 14 and 30mmHg at the ankle, reduce venous stasis and the incidence of VTE in intermediate or high-risk patients, including pregnant women. These stockings are especially useful for those with contraindications to anticoagulants and/or a high risk of bleeding.<sup>36</sup> Contraindications for using GCES include: substantial lower limb edema; severe peripheral arterial disease or neuropathy; dermatitis; significant lower limb deformities; and congestive heart failure.<sup>38</sup>

### Pharmacological prophylaxis

The pharmacological prophylaxis of VTE during AT has been a subject of debate, both regarding which medications to use (and their doses) and the patient profile that should receive them.<sup>11,12,39</sup> No indication exists for routine use in pregnancy, and only some profiles, considered to be of high risk, may benefit from this measure.<sup>10,39</sup>

### Acetylsalicylic acid (ASA)

The effectiveness of ASA in VTE prophylaxis is limited, and its side effects, such as bleeding, can be severe. Furthermore, ASA crosses the placental barrier and, therefore, should not be recommended.<sup>12,23</sup>

The LONFLIT III study showed that passengers with high-risk of VTE who used 400mg of ASA 12 hours before the flight and for three days after landing did not have protection against VTE, whereas the use of enoxaparin (1mg/kg, 2 to 4 hours before flight) reduced the prevalence of VTE (evaluated by Doppler ultrasound) from 4.8 to 0%.<sup>11</sup>

### Low molecular weight heparin (LMWH)

LMWH is used in the prophylaxis and treatment of VTE during the gravidic-puerperal cycle, since it does not cross the placental barrier and possesses an excellent efficacy-to-safety ratio. LMWH is, therefore, the drug of choice in pregnant women at high risk of VTE during long-distance AT. Enoxaparin (0.5mg/kg, subcutaneously before the flight) is the most widely used substance due to its practicality, rapid onset of action, and protection for at least 16 hours.<sup>6,12,34-39</sup>

## Direct oral anticoagulants (DOACs)

DOACs have gradually replaced warfarin and LMWH in the prophylaxis and treatment of VTE due to their posological advantages and excellent efficacy-to-safety profile. In addition, they do not require routine laboratory monitoring.<sup>40</sup> The rapid onset of action and short half-life of DOACs are characteristics that would be relevant to preventing VTE during AT.<sup>2,39</sup> Since there are no studies corroborating this indication, however, DOACs are still considered off-label.<sup>2,39,40</sup> Moreover, they are contraindicated throughout the gravidic-puerperal cycle and during breastfeeding, because they cross the placental barrier and are excreted in breast milk.<sup>40</sup>

## Final message

Air travel, especially flights lasting more than 6 hours, poses various risks for pregnant women, one of the most feared of which is venous thromboembolism. All pregnant women who plan to take a long-distance flight should seek medical advice on the risks to safety and health both for themselves and their fetuses, including VTE prevention through general measures and, potentially, pharmacological prophylaxis.

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