



## Review article

# Economy class syndrome: what is it and who are the individuals at risk?



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### ABSTRACT

The term 'economy class syndrome' refers to the occurrence of thrombotic events during long-haul flights that mainly occur in passengers in the economy class of the aircraft. This syndrome results from several factors related to the aircraft cabin (immobilization, hypobaric hypoxia and low humidity) and the passenger (body mass index, thrombophilia, oral contraceptives or hormone replacement therapy, cancer), acting together to predispose to excessive blood coagulation, which can result in venous thromboembolism. Several risk factors, both genetic and acquired, are associated with venous thromboembolism. The most important genetic risk factors are natural anticoagulant deficiencies (antithrombin, protein C and protein S), factor V Leiden, prothrombin and fibrinogen gene mutations and non-O blood group individuals. Acquired risk factors include age, pregnancy, surgery, obesity, cancer, hormonal contraceptives and hormone replacement therapy, antiphospholipid syndrome, infections, immobilization and smoking. People who have these risk factors are predisposed to hypercoagulability and are more susceptible to suffer venous thromboembolism during air travel. For these individuals, a suitable outfit for the trip, frequent walks, calf muscle exercises, elastic compression stockings and hydration are important preventive measures. Hence, it is essential to inform about economic class syndrome in an attempt to encourage Brazilian health and transport authorities to adopt measures, in partnership with the pharmaceutical industry, to prevent venous thromboembolism.

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## Introduction

Venous thromboembolism (VTE) is a clinical condition that involves two related situations, venous thrombosis and

pulmonary embolism.<sup>1</sup> It affects approximately 2–3 people per 1000 individuals per year. VTE is the third cause of death by vascular diseases, only surpassed by myocardial infarction and ischemic stroke. In addition, it is the most common cause of preventable death in hospitalized patients.<sup>2,3</sup>

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The term 'economy class syndrome' refers to the occurrence of thrombotic events during long-haul flights, mainly in economy class passengers. This syndrome results from several factors related to the aircraft cabin (immobilization, hypobaric hypoxia and low humidity) and to the passenger (such as obesity, thrombophilia, oral contraceptive use, hormone replacement therapy and cancer), that act together predisposing to excessive blood coagulation, which can result in VTE.<sup>4</sup>

Several risk factors, both genetic and acquired, are associated with VTE. The most important genetic risk factors are natural anticoagulant deficiencies: (1) Deficiency of antithrombin, protein C or protein S; (2) Factor V (FV) Leiden, which is resistant to protein C inactivation; (3) The G20210A mutation in the prothrombin gene, which leads to an increase in gene expression and prothrombin plasma levels; (4) The C10034T mutation in the fibrinogen gene, which produces a variant form of fibrinogen; and (5) Non-O blood group (A, B and AB) as individuals have higher von Willebrand factor and factor VIII plasma levels than O group subjects and have increased risk of thrombosis.

Acquired risk factors include age, pregnancy, surgery, obesity, cancer, hormonal contraceptives and hormone replacement therapy, antiphospholipid syndrome, infections, immobilization and smoking.<sup>5,6</sup>

### Venous thromboembolism and air travel

Data from the Brazilian National Civil Aviation Agency (ANAC) revealed that the number of passengers carried by civil aviation in 2015 surpassed 100 million.<sup>7</sup> Tables 1 and 2<sup>8-10</sup> show the main domestic and international flights in and from Brazil in 2015. The aircraft microenvironment provides very specific conditions, such as reduced oxygen tension, immobilization (in general, people are in tight uncomfortable seats) and circadian dysrhythmia, due to differences in time zones (jet lag).

**Table 1 – Major domestic flights of Brazil in 2015.**

Route	Passengers (millions)	Mean flight time
São Paulo (CGH) – Rio de Janeiro (SDU)	4.05	1 h
São Paulo (CGH) – Brasília (BSB)	2.23	1 h 45 min
São Paulo (GRU) – Salvador (SSA)	2.2	2 h 20 min
São Paulo (GRU) – Porto Alegre (POA)	2.02	1 h 35 min
São Paulo (GRU)–Recife (REC)	1.98	3 h 30 min
São Paulo (CGH) – Belo Horizonte (CNF)	1.82	1 h 20 min
São Paulo (CGH) – Porto Alegre (POA)	1.7	1 h 35 min
São Paulo (CGH) – Curitiba (CWB)	1.52	1 h 00 min
São Paulo (CGH) – Brasília (BSB)	1.35	1 h 45 min
Rio de Janeiro (GIG) – Salvador (SSA)	1.34	2 h 15 min
Total	20.21	

**Table 2 – Major international flights from Brazil in 2015.**

Destination	Passengers (millions)	Mean flight time <sup>a</sup>
USA	5.38	11 h
Argentina	3.07	2 h 50 min
Portugal	1.54	11 h
Chile	1.41	4 h
Spain	0.98	12 h
France	0.97	14 h
Germany	0.84	15 h
Peru	0.65	5 h 30 min
Uruguay	0.62	2 h 40 min
United Kingdom	0.59	12 h
Italy	0.50	12 h

<sup>a</sup> Flight time departing from the city of São Paulo.

These factors may disturb the passenger's health, causing fatigue, anxiety and nausea.<sup>11,12</sup>

The first cases of VTE associated with air travel were reported in 1954, and since then, other cases have been described.<sup>4</sup> The vast majority of victims suffer pulmonary embolism and/or deep vein thrombosis, but cases of subclavian vein thrombosis,<sup>13</sup> cerebral vein thrombosis,<sup>14</sup> stroke and arterial thrombosis<sup>15</sup> have also been reported.

The actual incidence of VTE in air travel is unknown. It is difficult to arrive at an estimation given that this condition may be asymptomatic or may develop days or even weeks after the flight.<sup>16</sup> In a cohort of healthy subjects, the absolute risk of VTE on flights lasting more than 4 h was 1 in 6000.<sup>17</sup> A meta-analysis<sup>18</sup> involving 14 studies reported 4055 cases of VTE in trips lasting up to 8 h. These studies included both air and overland trips with the follow-up time after the journey ranging from two to eight weeks. The relative risk of VTE was 2.8 [95% confidence interval (95% CI): 2.2–3.7] and at each increment of 2 h in travel time, there was an approximate 18% increase in the risk of VTE. Considering only air travel, this risk increased to 26%, suggesting a cumulative effect of flight time in the genesis of VTE.

MacCallum et al.<sup>19</sup> demonstrated that on flights lasting less than 4 h, the risk of VTE is approximately two times higher compared to non-traveler subjects [odds ratio (OR): 2.20; 95% CI: 1.29–3.73] and remained high in the four subsequent weeks. In long-haul flights (greater than 12 h as one or more flights), the risk of VTE is around three times higher (OR: 2.75; 95% CI: 1.44–5.28). After 12 weeks, no time-flight effect was observed in the occurrence of thrombotic events.

A number of factors associated both to the aircraft or passengers have been singled out as responsible for triggering VTE.<sup>20</sup> Stasis and hypercoagulability, two components of Virchow's triad, have a crucial role in the occurrence of thromboembolism in flights.<sup>18</sup>

The factors associated with the aircraft include:

- Hypobaric hypoxia: The hypoxia caused by reduced air pressure in the aircraft cabin contributes to VTE. At sea level, normal atmospheric pressure is 760 mmHg, which corresponds to a partial oxygen pressure of 159 mmHg. Under these conditions, oxygen saturation in healthy individuals is 95%. In the cockpit of an aircraft at flight altitude,

the pressure is usually 570 mmHg and the partial oxygen pressure is 125 mmHg, resulting in oxygen saturation of 90–93%. However, in the elderly and people with lung and/or heart diseases, reductions of up to 80% of oxygen saturation can occur. The relative hypoxia in the aircraft leads to a decrease in fibrinolytic activity and the release of venous relaxation factors, which help to increase the hemostasis.<sup>12</sup>

- Low humidity: The relative humidity inside the aircraft is approximately 10%, while at sea level is 30–40%. Low humidity is associated with increases in plasmatic and urinary osmolarity, which result in hemoconcentration that favors VTE.<sup>12</sup>

The main passenger-related factors are:

- Immobilization: Lack of movement in the sitting position during the flight results in hemostasis of the lower limbs predisposing the individual to VTE.<sup>12</sup> An evaluation of coagulation biomarkers showed that there is an increased generation of thrombin during flights lasting more than 8 h; this does not occur in other situations where the subject is immobilized in the sitting position. It suggests that there is an additional mechanism resulting in hypercoagulability during flights.<sup>20</sup>
- Body mass index (BMI) and height: In obese subjects (BMI > 30 kg/m<sup>2</sup>), there is a reduction in blood flow in the lower limbs, favoring hemostasis. It has been observed that individuals at the extremes of stature (>1.90 m or <1.60 m) have an increased risk of VTE during air travel.<sup>12</sup>
- Thrombophilia: The presence of genetic thrombophilia is an independent risk factor for VTE. Martinelli et al. reported that the risk of VTE is 6.6 (95% CI: 3.9–11.3) times higher in patients with thrombophilia, compared to individuals without these mutations. In patients with thrombophilia, the risk of VTE was 16.8 times higher (95% CI: 3.8–74.7), compared to non-thrombophilic, non-travelers, which suggests a synergistic interaction resulting in an increase in thrombotic risk.<sup>21</sup>
- Oral contraceptives and hormone replacement therapy: The use of oral contraceptives increases the risk of VTE by about fourfold in the general population (OR: 4.2; 95% CI: 1.9–9.3). A synergistic association between air travel and oral contraceptive use in the genesis of VTE can be inferred since the occurrence of thrombosis is high in women under oral contraceptives use during or after air travel (OR: 23.4; 95% CI: 2.6–11.2). Similarly, hormone replacement therapy predisposes to VTE.<sup>2</sup>
- Cancer: It is well established that cancer patients have an increased risk of developing VTE throughout the history of the disease, mainly in the first three months after the initial diagnosis (OR: 53.5; 95% CI: 8.6–334.3).<sup>22</sup> Kuipers et al.<sup>23</sup> estimated that the presence of a malignant disease is associated to an 18-fold increase in thromboembolic risk during flights.
- Other factors: Although it is admitted that factors such as diabetes and smoking are associated with a hypercoagulable state,<sup>24</sup> there is a lack of studies about the association of these conditions and the incidence of VTE during flights.

## Pregnancy, air travel and venous thrombosis

Pregnancy progresses with important physiological changes in the hemostatic system, which determines a hypercoagulable state. These adaptive changes aim to prepare the maternal organism to the great hemostatic challenge of placenta expulsion and simultaneous disruption of numerous blood vessels to prevent excessive bleeding.<sup>25</sup>

Literature data suggest that 1:6000 young passengers without risk factors for thrombosis have a risk of symptomatic VTE in a four-hour flight.<sup>26</sup> Pregnant women in four-hour flights have a thromboembolic risk five to ten times higher than non-pregnant women have. This risk rises exponentially on long-haul trips, by around fourfold and eightfold if the flight time exceeds eight or 12 h, respectively.<sup>26</sup>

For pregnant women with thrombophilia who fly over 4 h, the thromboembolic risk is 1:200. For women with Factor V Leiden in homozygosis or those heterozygosis for both Factor V Leiden and the prothrombin mutation, the risk is about 1:40.<sup>26</sup> In addition to genetic thrombophilia, parturients with an acquired thrombophilia such as antiphospholipid syndrome also have an increased risk for VTE. These findings raise the debate about the relevance of the adoption of pharmacological prophylaxis in pregnant women while flying.<sup>27,28</sup>

It has been reported that hypoxia during flights and, consequently trophoblastic injury, favors the occurrence of preterm birth and intrauterine death, especially in pregnant women aged over 35 years, with preeclampsia, abruptio placentae or intrauterine growth restriction.<sup>29</sup>

Aware of the risks, many commercial airlines allow pregnant women to travel only up to the 36th week of pregnancy. Other companies make restrictions for international flights in early pregnancy and require evidentiary documentation of gestational age or state that cases should be evaluated individually. Pregnant civilian or military crewmembers should check with regulatory bodies with regard to restrictions on their professional activities. However, the main concern with pregnant women of airlines is associated with the risk of labor during the trip, which could disrupt or interrupt the flight. In addition, there is a lack of skilled professionals to manage obstetric complications occurring aboard.<sup>27</sup>

Obstetricians advise at-risk pregnant women not to fly. All pregnant women should be informed of the obstetric emergencies that can occur in the first and third trimesters of pregnancy and it is prudent to avoid travel during these periods.<sup>30</sup>

Currently, with the progressive increase in the possibility of air travel given by the expansion of routes and drop in ticket prices, the risk of venous thrombotic events associated with long hours of immobilization during air travel has emerged as a topic to be discussed. Preventive measures are extremely important. Passengers should be informed of potential risks and encouraged to exercise regularly, with short walks in the aisles, and to avoid dehydration. It is controversial as to whether drinking alcoholic beverages increases the risk of thromboembolic events, but it may contribute to dehydration and there is still the possibility of fetus damage during pregnancy. Thus, the intake of alcoholic beverages must be discouraged.<sup>29</sup>

**Table 3 – Risk categories for the occurrence of thromboembolic events.**

Risk	Risk category
Low	Age over 40 years, obesity, inflammatory disease, recent minor surgery (within three days)
Moderate	Varicose veins, decompensated heart failure, recent acute myocardial infarction (within six weeks), hormone therapy (including contraceptives), pregnancy or the postpartum period, lower limb hemiparesis, lower limb trauma (within six weeks)
High	Previous venous thromboembolism, known thrombophilia, recent major surgery (within six weeks), prior stroke, cancer, family history of venous thromboembolism.

The choice of a suitable outfit for the trip is also important and must prioritize comfort, avoiding tight garments with elastic. Adequate hydration should be encouraged.<sup>27</sup>

Individual risk stratification is essential to define the most appropriate measures. The Aerospace Medical Association (AsMA) has published guidelines on the use of prophylaxis in individuals who travel by air. The risk groups defined in these guidelines are shown in Table 3.<sup>31</sup> Pregnancy and the puerperium are defined as moderate risk. For individuals with moderate risk, the guidelines suggest acetylsalicylic acid associated or not with compression stockings.<sup>32</sup> However, the evidence about acetylsalicylic acid use is controversial as it crosses the placenta and therefore it cannot be recommended prophylactically in pregnant women according to the American College of Chest Physicians Guidelines.<sup>33</sup>

Elastic compression stockings exert graduated pressure of the lower limb with greater pressure at the ankle. When combined with muscle activity, they direct the blood flow from the superficial venous system to the deep system, reducing venous stasis and potentially preventing the occurrence of venous thrombosis. A Cochrane systematic review included nine randomized trials (2821 individuals) comparing flyers who used compression stockings with those who did not (seven studies in low- or medium-risk individuals). The study noted a significant reduction in the risk of asymptomatic travel-related deep venous thrombosis with the use of compression stockings (OR: 0.10; 95% CI: 0.05–0.25).<sup>15</sup> The tolerability of compression stockings was good in all studies and no adverse effects were reported with the exception of superficial thrombophlebitis.<sup>15,34</sup>

For high-risk individuals, frequent walking, calf muscle exercises and compression stockings should be encouraged.<sup>27,31</sup>

Despite the fact that thrombophilia constitutes a major risk factor for VTE, routine screening is not recommended in pregnant women, since there are multiple risk factors in pregnant women (even though each individual factor is not associated to high risk).<sup>35</sup>

Considering the large extension of the Brazilian territory, thrombosis during long overland trips (with immobilization in a sitting position) should be expected however only one

case report was found in the Brazilian literature concerning the occurrence of a thromboembolic event.<sup>36</sup>

## Final considerations

In the context of Brazil, the majority of domestic flights last less than 2 h, although trips from the south to the north and northeast can last from 8 to 10 h. With respect to international travel, most flights are of long duration and thus represent a greater risk of VTE. Despite this, there is no data about Brazilian individuals who travel with a risk of hypercoagulability or about VTE related to flights.

It is essential to inform about economic class syndrome in an attempt to encourage the Brazilian health and transport authorities to adopt some measures, in partnership with the pharmaceutical industry, to prevent venous thromboembolism.

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