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# Do pregnant women have a higher risk for venous thromboembolism following air travel?

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## Abstract

International travel has become increasingly common and accessible, and it is part of everyday life in pregnant women. Venous thromboembolism (VTE) is a serious public health disorder that occurs following long-haul travel, especially after air travel. The normal pregnancy is accompanied by a state of hypercoagulability and hypofibrinolysis. Thus, it seems that pregnant women are at a higher risk of VTE following air travel, and, if they have preexisting risk factors, this risk would increase. There is limited data about travel-related VTE in pregnant women; therefore, in the present study, we tried to evaluate the pathogenesis of thrombosis, association of thrombosis and air travel, risk factors and prevention of VTE in pregnant women based on available evidences. Pregnancy is associated with a five- to 10-fold increased risk of VTE compared with nonpregnant women; however, during the postpartum period, this risk would increase to 20–80-fold. Furthermore, the risk of thrombosis is higher in individuals with preexisting risk factors, and the most common risk factor for VTE during pregnancy is a previous history of VTE. Pregnant women are at a higher risk for thrombosis compared with other women. Thus, the prevention of VTE and additional risk factors should be considered for all pregnant women who travel by plane.

**Key Words:** Hypoxia, pregnancy, stress, travel, venous thromboembolism

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## INTRODUCTION

Approximately two billion passengers undertake international and domestic air travel each year.<sup>[1,2]</sup> Today, travel by plane has become increasingly common

and accessible, and it is part of everyday life in pregnant women who have to travel as a requirement for their jobs or who work as flight attendants or aviators (civilian and military). The incidence of pregnancy during travel is 0.93 per 1000 travelers.<sup>[3]</sup> Although air travel during pregnancy does not seem to pose a significant risk to the pregnancy, and it is generally considered to be safe, and most commercial airlines allow pregnant women to fly up to 36 weeks of gestational age, information on the effect of air travel on early pregnancy loss, organogenesis and pregnancy outcomes is limited.<sup>[4,5]</sup>

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary thromboembolism

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(PTE), is a serious public health disorder that may occur following long-distance air travel. The term of travel-related thrombosis is used to indicate VTE that occurs during or within 4 weeks after long-haul travel, and a subgroup of air-travel thrombosis was referred to thrombosis that occurs when the main part of the journey was undertaken by plane.<sup>[6]</sup> However, according to the guidelines of the British Committee for Standards in Haematology (BCSH), VTE may be attributable to travel if it occurs up to 8 weeks following the journey.<sup>[7]</sup>

Previous studies documented that travel-related thrombosis is more common in women;<sup>[8,9]</sup> however, data about thrombosis in pregnant women following air travel is limited. Therefore, in this study, we tried to evaluate the pathogenesis of thrombosis, association of thrombosis and air travel, risk factors and prevention of VTE in pregnant women based on the available evidences.

### Association of thrombosis and pregnancy

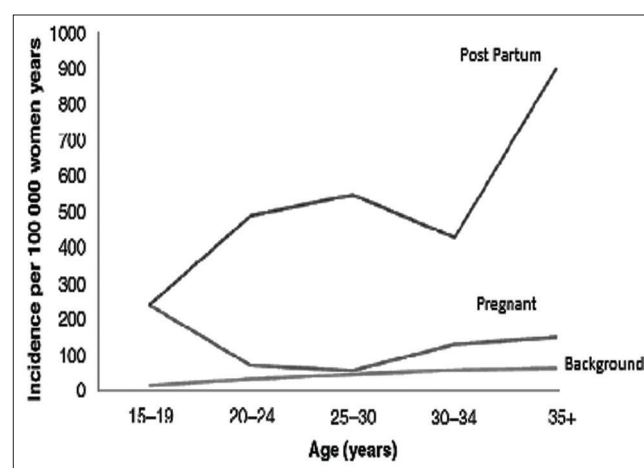
As well as a significant expansion in plasma volume, normal pregnancy is accompanied by major changes in the maternal hemostatic system. The net effect of all these is to create a state of hypercoagulability and hypofibrinolysis. During pregnancy, plasma levels of fibrinogen, von-Willebrand factor (VWF) and factors VII, VIII, IX and X increase, while plasma level of protein S and platelet fall. Subsequently, these changes lead to a significant increase in the activity of the hemostatic system.<sup>[10-12]</sup> Plasminogen activator inhibitor type-1 levels increase five-fold.<sup>[11]</sup> Also, the levels of plasminogen activator inhibitor type-2, which is produced by the placenta, increase significantly during the third trimester,<sup>[13]</sup> and markers of thrombin generation such as prothrombin F1 + 2 and thrombin-antithrombin complexes are increased.<sup>[14]</sup> Many of coagulation changes take 6–8 weeks to return to normal after delivery.<sup>[10]</sup> Also, mechanical obstruction by the uterus, decreased mobility and vascular injury may make pregnant women more prone to thrombus formation.<sup>[14]</sup>

Therefore, the hypercoagulability state during pregnancy and the postpartum period can increase the risk of thrombus formation and, in some women, may contribute to pregnancy complications, such as DVT, PTE, pregnancy loss, preeclampsia and intrauterine growth restriction. A study showed that women with a history of DVT during pregnancy had a lower quality of life, even after a long period after delivery.<sup>[15]</sup>

Pregnancy is associated with a five- to 10-fold increased risk of thrombus formation compared with

non-pregnant women.<sup>[10,16,17]</sup> Heit *et al.* in a large study evaluated pregnant and postpartum women with VTE first diagnosed between 1966 and 1995, and found that the overall relative risk for VTE was 4.29 (95% confidence interval [CI]: 3.49–5.22). Jacobsen *et al.* in a register-based case-control study showed that the incidence of VTE among pregnant women was 1 per 1000 pregnancies.<sup>[18]</sup> Pomp *et al.* in the MEGA study found that the risk of VTE was five-fold (odds ratio [OR]: 4.6; 95% CI: 2.7–7.8) increased during pregnancy compared with nonpregnant women. Also, they observed a 14-fold increased risk of DVT of the leg compared with a six-fold increased risk of PTE.<sup>[19]</sup> The risk of VTE is highest in the third trimester of pregnancy.<sup>[12,19,20]</sup> The MEGA study showed that the risk of venous thrombosis during the first two trimesters of pregnancy slightly increased, but the risk was increased nine-fold during the third trimester compared with nonpregnant women.<sup>[19]</sup> Interestingly, during the first 6 weeks after delivery, the risk of VTE is 20–80-fold higher<sup>[18,19,21]</sup> and, in the first week, it is 100-fold higher.<sup>[21]</sup> Also, the incidence of VTE rose with increased age [Figure 1].<sup>[22]</sup>

Events of DVT in pregnant women are more common in the ileofemoral, and are left sided.<sup>[14,23,24]</sup> Although the true mechanism of more frequent left-sided DVT during pregnancy is unknown, it is thought to be attributable to a relative stenosis of the left common iliac vein where it lies between the lumbar vertebral body and the right common iliac artery.<sup>[25,26]</sup> During pregnancy, acute VTE should be suspected when symptoms and signs consistent with possible VTE occur, such as unilateral and usually left-sided leg pain and swelling, lower abdominal pain, low-grade pyrexia, dyspnea, chest pain and hemoptysis.<sup>[24]</sup> The VTE is a multifactorial disorder, and the risk of thrombosis is



**Figure 1:** The risk of venous thromboembolism is higher in pregnant women, especially in the postpartum period, and increases with increased age<sup>[22]</sup>

higher in individuals with preexisting risk factors. The most common risk factor for VTE during pregnancy is previous history of VTE (OR: 24.8; 95% CI: 17.1–36). Others include immobility, body mass index more than 30 kg/m<sup>2</sup>, smoking, weight gain more than 21 kg, multiparity, age more than 35 years, preeclampsia, preeclampsia with fetal growth restriction, assisted reproductive techniques, twin pregnancy, antepartum hemorrhage, postpartum hemorrhage, cesarean section, blood transfusion and medical conditions such as systemic lupus erythematosus, heart disease, anemia, active infection or varicose veins.<sup>[24,27]</sup>

### Association of air travel and thrombosis

A direct relation between VTE development and long-distance air travels has been documented in previous studies. Kuipers *et al.* in a systematic review showed that long-distance travel increases the risk of VTE approximately two- to four-fold. The absolute risk of a symptomatic event within 4 weeks of flights longer than 4 h is 1/4600 flights. The risk of severe pulmonary embolism (PTE) occurring immediately after air travel increases with duration of travel, up to 4.8 per million in flights longer than 12 h.<sup>[28]</sup> Chandra *et al.* in a meta-analysis evaluated 14 studies (11 case-control, two cohort and one case-crossover), and subsequently found that travel is associated with a three-fold higher risk for VTE, with a dose-response relationship of 18% higher risk for each 2-h increase in travel duration.<sup>[29]</sup> The WRIGHT project in phase 1 reported that long-distance air travel (more than 4 h) approximately doubled the risk of VTE. The absolute risk of VTE per more than 4-h flying, in healthy individuals, is 1 in 6000, rising to about 1 to 1000 travelers for multiple flights (taken in the 4-week exposure period) and longer journeys.<sup>[30]</sup> Furthermore, travel-related thrombosis is more common in women. Lapostolle *et al.* systematically reviewed the records of all patients with confirmed PTE after arrival at the Roissy-Charles-de-Gaulle Airport (Paris, France) during a 13-year period, and observed that although the proportion of men to women in long-distance travel was 50.5–49.5%, PTE was more frequent in women (78%).<sup>[8]</sup>

### Flight-specific factors related to VTE

It was suggested that VTE in a plane could occur following immobilization by sitting for several hours.<sup>[31]</sup> Travelers could be sitting on narrow seating in the plane (especially in economic class), resulting in a cramped position during prolonged flights. This position for a long period can lead to venous stasis and DVT.<sup>[32,33]</sup> Prolonged immobility in a sitting position can lead to reduction of velocity of venous blood flow up to 2/3 in the lower limbs, which may be sufficient to activate a prethrombotic state.<sup>[34]</sup> Also,

this position causes more venous stasis because of external compression from the seat and by kinking the popliteal veins, especially in elderly and obese travelers.<sup>[35]</sup> Venous stasis induces hemoconcentration and depressed fibrinolytic activity, contributing to a prethrombotic state.<sup>[35]</sup>

Other factors such as hypobaric hypoxia, dehydration, excessive alcohol or coffee, lower air pressure and lower humidity may affect the coagulation system.<sup>[28,35-37]</sup> Hypoxia associated with decreased cabin pressure can lead to thrombosis formation. Above sea level, the atmospheric pressure is 101 kPa and oxygen makes up 21% of the inspired air. Therefore, the partial pressure of oxygen is 21.2 kPa. Normally, when red blood cells pass through the lung, 95% of them are saturated with oxygen. Thus, the oxygen saturation in healthy individuals is 95%. At a high altitude, when the partial pressure of oxygen decreases, most hemoglobin is deoxygenated and the oxygen saturation of hemoglobin decreases. During air travel, the cabin pressure drops to 75.8 kPa, which is equivalent to an altitude of 2400 m above sea level. Consequently, oxygen saturation can fall as low as 90–93%, and even to 80% in passengers who are asleep.<sup>[35,38,39]</sup>

The hypobaric hypoxia (which is the decrease in air pressure and induction of relative hypoxia) reduces fibrinolytic activity and leads to release of relaxing factors from the vein wall that may enhance venous stasis.<sup>[40,41]</sup> Also, hypoxia after long-distance air travel triggers systemic inflammation and platelet activation, leading to more coagulation induction and degranulation of platelets.<sup>[42]</sup> Also, activation of endothelial cells of the valve pocket sinus of the veins by hypoxia would lead to surface expression of adhesion receptors that facilitate the binding of circulating leukocytes, which induce expression of the potent procoagulant protein tissue factor that triggers thrombosis formation.<sup>[43]</sup> Some believe that hypobaric hypoxia was a more likely explanation for thrombus formation during long-distance air travel than any of the other factors.<sup>[31,42]</sup>

Low humidity at around 15% within the cabin of the plane is another factor that can stimulate the development of thrombosis. The relative humidity in the cabin gradually falls on high altitude and prolonged flights, although sweating and moisture from travelers will cause it to increase.<sup>[35]</sup> The noticeable effect of low humidity on travelers, such as drying of the skin and mucous membranes, is seen after 3–4 h of flight.<sup>[44]</sup> Also, alcohol or coffee consumption (which promotes diuresis), together with the lower humidity of the cabin, may lead to some degree of dehydration and a consequent thrombus formation.<sup>[35,45]</sup>



### Association of air travel-related VTE in pregnant women

We did not find a study that evaluated the risk of thrombosis in pregnant women who travel by air; however, it is thought that this is not a rare combination. Therefore, the true frequency of VTE during long-distance flights in pregnancy is unknown.

It is true that the risk of VTE in an air women traveler who is not using oral contraceptives is about 1 in 5000 passengers (based on the Kuipers *et al.* study),<sup>[9]</sup> and this risk would be increased five-fold during pregnancy (based on the MEGA study),<sup>[19]</sup> in other words, this would lead to a risk of 1 per 1000 pregnant women travelling by air. Interestingly, if we considered a 60-fold increase in the risk of VTE within a 3-month postpartum period compared with nonpregnant women (based on the MEGA study),<sup>[19]</sup> the risk of thrombosis following air travel would be 12 per 1000.

Cannegieter and Rosendaal evaluated the association of pregnancy and air travel-related VTE in a review article recently. They used results from studies performed in air travelers and pregnant women separately to estimate the risk of the combination; subsequently, they estimated that this risk was between 0.03% and 0.1%.<sup>[4]</sup>

On the other hand, majority of the guidelines considered pregnancy as a potential risk factor of VTE during air travel and recommended thrombosis prevention during travel. Based on an updated international consensus statement published in 2008, the travelers were divided into three groups (low, moderate, and high) regarding the level of probability of VTE development and in this classification pregnancy or post-partum period was considered as a moderate risk factor.<sup>[6]</sup> The British Thoracic Society (BTS) in 2011 also considered pregnancy or the postpartum period as a moderate risk factor, especially following long-haul air travel.<sup>[46]</sup> In the recent guidelines of the American College of Chest Physicians (2012), the pregnant women was considered as traveler at increased risk of VTE.<sup>[47]</sup>

### Prevention

The American College of Obstetricians and Gynecologists (ACOG) committee did not recommend air travel generally at any time during pregnancy for women who have medical or obstetric conditions that may be exacerbated by flight or those that could require emergency care. They recommended that pregnant travelers should consider the duration of the flight and should be informed that the most common obstetric emergencies occur in the first and third

trimesters. To minimize the risk of VTE following long-distance flights, they advice that wearing support stockings, moving their legs periodically, avoiding restrictive clothing, getting out of their seat and walking for a few minutes and staying hydrated should be practiced.<sup>[5]</sup>

The Royal College of Obstetricians and Gynaecologists' recommendations for prevention of VTE following long-haul air travel (more than 4 h) are listed in Table 1. They advice no specific measures for short-haul journeys. Furthermore, they recommended that pregnant women with additional risk factors for thrombosis, such as a previous DVTs, symptomatic thrombophilia (such as antiphospholipid syndrome or DVT and a heritable thrombophilia), morbid obesity or medical problems such as nephrotic syndrome, specific pharmacological prophylaxis with low-molecular weight heparin (LMWH) in the doses recommended for antenatal prophylaxis, should be considered for the day of travel and several days thereafter, if the woman is not already on LMWH. However, the appropriate duration of such thromboprophylaxis is not established and is a matter for clinical judgment based on the perceived magnitude and duration of risk for the individual woman.<sup>[48]</sup>

As mentioned above, pregnancy alone was considered as a moderate risk factor for thrombosis following long-distance air travel in the Hall meeting (2007) and BTS guidelines (2011). But, if the pregnant woman had additional risk factors, then she was considered as a high-risk traveler. In Tables 2 and 3, the risk factors and recommendations for prevention of VTE following travel are shown based on the Hall meeting and the BTS guidelines.<sup>[6,46]</sup> The recent guidelines of the American College of Chest Physicians (2012) also considered pregnancy as a risk factor for VTE following long-haul air travel (more than 4 h) and recommended ambulation or sitting in an aisle seat if feasible and avoiding dehydration. Other recommendations are listed in Table 4.<sup>[47]</sup> All the above guidelines did not recommended aspirin alone as VTE prophylaxis, primarily because more effective methods of prophylaxis are readily available and

**Table 1: Royal college of Obstetricians and Gynaecologists' recommendations for flight VTE prophylaxis in pregnant women**

Have an aisle seat to facilitate ease of movement
Take regular walks around the cabin and/or;
Carry out in-seat exercises approximately every 30 minutes on a medium or long-haul flight
Maintain a good fluid intake and minimize caffeine and alcohol intake to avoid dehydration
Make a specific individualized risk assessment for thrombosis in pregnant women who are flying

VTE: Venous thromboembolism

**Table 2: Risk factors and recommendations for prevention of travel-related VTE based on the Hall meeting<sup>[6]</sup>**

Risk group	Risk factors	Recommendations
Low-risk group	In passengers without additional personal risk factors (as listed below), every prolonged journey is associated with a slightly increased but indeterminate risk	General measures  Perform regular leg exercises, e.g., ankle movements, isometric exercises and walking. During travel by car and bus, take regular breaks to walk around Maintain normal fluid intake (at least 250 mL every 2 h) and avoid excessive alcohol consumption Avoid the use of tranquilizers and sleeping pills while in a sitting position
Medium-risk group	The following factors may increase the individual risk for VTE. The presence of two or more factors may increase the risk in a supraadditive fashion: Pregnancy or postpartum period  Age over 60 years  Documented thrombophilia/family history of VTE Large varicose veins, chronic venous insufficiency Oral contraceptives, hormone replacement therapy Obesity (body mass index >30 kg/m <sup>2</sup> )	General measures, as for the low-risk group  Graduated compression stockings (compression at least 10–20 mmHg but 20–40 mmHg in subjects with chronic venous insufficiency) In special cases, consider low-molecular weight heparin, as for the high-risk group
High-risk group	The presence of the following factors is associated with particularly high risk Previous VTE  Manifest malignant disease or other severe illness Immobilization (e.g., limb in plaster cast) Recent major surgery	General measures, as for the low-risk group  Graduated compression stockings (compression at least 10–20 mmHg but 20–40 mmHg in subjects with chronic venous insufficiency) Consider low-molecular weight heparin or fondaparinux

VTE: Venous thromboembolism

**Table 3: Risk factors and recommendations for prevention of travel-related VTE based on the BTS guidelines<sup>[46]</sup>**

Risk group	Risk factors	Recommendations
Low-risk group	All passengers not in the categories listed below	Passengers should avoid excess alcohol and caffeine-containing drinks, and preferably remain mobile and/or exercise their legs during the flight (D)
Medium-risk group	Family history of VTE, past history of provoked VTE, thrombophilia, obesity (BMI >30 kg/m <sup>2</sup> ), height >1.90 m or <1.60 m, significant medical illness within the previous 6 weeks, cardiac disease, immobility, pregnancy or estrogen therapy (including hormone replacement therapy and some type of oral contraception) and postnatal patients within 2 weeks of delivery	These patients should be advised to wear below-knee elastic compression stockings in addition to recommendations for low-risk passengers. In addition, they should be advised against the use of sedatives or sleeping for prolonged periods in abnormal positions. (D) Passengers with varicose veins may be at a risk of superficial thrombophlebitis with use of stockings; the risk/benefit ratio here is unclear
High-risk group	Past history of idiopathic VTE, those within 6 weeks of major surgery or trauma and active malignancy	Pre-flight prophylactic dose low-molecular weight heparin should be considered or formal anticoagulation to achieve a stable INR between 2 and 3, for both outward and return journeys, and decisions made on a case-by-case basis. The recommendations are in addition to the general advice for those at low to moderate risk (D)  Patients who have had a VTE should ideally not travel for 4 weeks or until proximal (above-knee) deep vein thrombosis has been treated and symptoms resolved, with no evidence of pre- or postexercise desaturation (D)

INR: International normalized ratio; VTE: Venous thromboembolism; BMI: Body mass index

there is an association with potential hemorrhagic complications.

## CONCLUSION

Normal pregnancy and the postpartum period are accompanied by major changes in the maternal

hemostatic system, where the net effect is to create a state of hypercoagulability and hypofibrinolysis. Pregnancy is associated with a five- to 10-fold increased risk of VTE compared with nonpregnant women; however, during the postpartum period, this risk could increase to 20–80-fold. Furthermore, the risk of thrombosis is higher in individuals with

**Table 4: Recommendations of the guidelines of the American College of Chest Physicians for prevention of travel-related VTE<sup>[47]</sup>**

For long-distance travelers at increased risk of VTE, we suggest frequent ambulation, calf muscle exercise or sitting in an aisle seat if feasible (Grade 2C)

For long-distance travelers at increased risk of VTE, we suggest use of properly fitted, below-knee graduated compression stockings providing 15–30 mmHg of pressure at the ankle stockings during travel (Grade 2C)

For all other long-distance travelers, we suggest against the use of graduated compression stockings (Grade 2C)

For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C)

VTE: Venous thromboembolism

preexisting risk factors, and the most common risk factor for VTE during pregnancy is previous history of VTE. Therefore, pregnant women are at a higher risk for thrombosis compared with other women. Thus, the prevention of VTE regarding additional risk factors should be considered for all pregnant women who travel by plane (more than 4 h).

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