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LOWER EXTREMITY BLOOD FLOW VELOCITY IN PREGNANT WOMEN

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ABSTRACT

The data demonstrate that venous blood volume flow in the lower extremities was higher in the 10 obese pregnant women compared with the 10 nonobese pregnant women in our study. Future research is warranted in both the antepartum and postpartum periods to further delineate the changes in venous hemodynamics during pregnancy. Thus, the increased risk of VTE among obese pregnant women may not be caused by venous stasis.

KEYWORDS: Lower Extremity Blood Flow Velocity, Pregnant.

INTRODUCTION

Venous thromboembolism (VTE)is defined as deep vein thrombosis (DVT), pulmonary embolus, or both. Pregnant women are four to five times more likely to develop VTE than nonpregnant women. 1,2 In 2011 alone, thrombotic pulmonary embolism (PE) was responsible for 9.8% of maternal deaths.3 Obesity complicates up to one-third of pregnancies in the United States,[1] substantially increasing the risk of VTE.1,5 James et al reviewed more than 9 million pregnancy admissions and reported an odds ratio of 4.4 (95% CI 3.4–5.7) for the development of VTE in obese pregnant women.[2]

Changes in blood flow during pregnancy are likely to play a role in the development of venous insufficiency and thromboembolic events.[3] Venous insufficiency and varicose disease were observed in 43% and 72.7% of pregnant women, respectively. Additionally, 50% of pregnant women complained of lower limb edema.[4] One mechanical factor that affects venous return is the growing uterus. In the supine position, the uterus presses on the inferior vena cava, resulting in reduced venous return.[5]

However, the major factors causing pregnancy-related blood vessel changes are pregnancy-related hormonal and physiological changes.1 The total volumes of blood, plasma, and erythrocytes increase during pregnancy to provide an increased blood supply to the uterus and placenta. The total blood volume of 4,000 mL prior to pregnancy increases to 5,300 mL at week 36 of gestation.

During pregnancy, the number of white blood cells and blood coagulation also increase. Furthermore, a reduction in vein wall tension can cause stagnation of blood and swelling of the legs and women with a predisposition may develop varicose veins. Additionally, vein dilatation and exposure to collagen fibers can cause endothelial damage and lead to blood clot formation.[6]

A previous study shows that blood flow velocity is statistically lower in pregnant women with venous insufficiency. Nevertheless, a substantial reduction in velocity during the last trimester of pregnancy was also observed in healthy pregnant women, reaching its peak at week 36 of gestation.

Background

Peripheral vascular disease becomes symptomatic when insufficient blood flows to tissue during exercise results in reduced oxygen supply, which causes claudication. Severe reduction in flow leads to rest pain, ulceration, and gangrene. The ankle-brachial index gives an estimate of the pressure gradient across all stenoses, but therapeutic planning is usually based on x-ray angiography. The relationship of the morphologic appearance of individual stenoses by angiography to hemodynamic effects has been shown to be weak[7], and the estimation of the hemodynamic effect of multiple stenoses in series is even more problematic. Evaluation of morphology alone does not take into account the large effect of the flow rate through stenosis on its hemodynamic significance, which is especially important with the increased flow rate induced by exercise. Quantitative measures of the volumetric flow rate may provide useful information in the evaluation of peripheral vascular disease. Although impaired arterial blood flow determines lower extremity ischemia, it has been difficult to quantify, and clinicians have relied on measures of blood pressure, Doppler velocity or Doppler waveform analysis. However, no definitive study has been successful in correlating the degree of area reduction with the peak systolic velocity or peak systolic Doppler shift. More invasive catheterization techniques are also currently used clinically to quantify arterial flow and to assess vessel patency to determine the cause of extremity ischemia. During the

past 50 years, there have been dramatic advances in the development of ultrasonic techniques to study vascular disorders.[8] Duplex Doppler ultrasound now allows estimation of volumetric blood flow noninvasively and without the use of contrast agents or ionizing radiation.[9]

Several epidemiological studies have given strong advice to the hypothesis that obesity is a risk factor for both chronic venous insufficiency (CVI) and venous thromboembolism (VTE).[10] Obesity plays a key role in the development of metabolic syndrome with a cluster of cardiovascular risk factors. Excess body weight has also been related to various alterations in the coagulation system including impaired fibrinolytic activity and elevated plasma concentrations of clotting factors. These alterations in endothelial function and coagulation are thought not only to be relevant for arterial but also for venous thrombosis. In addition to these mechanisms, obesity is thought to predispose venous stasis, which is a trigger of both deep VTE and CVI. Central abdominal obesity is thought to be associated with increased intraabdominal pressure (IAP) caused by abdominal fat.[11] Arvidsson and coworkers showed that the pressure in the iliofemoral vein in morbidly obese patients is significantly higher compared to non-obese subjects. Likewise, it has been shown that surgical weight reduction decreases urinary bladder pressure, a surrogate marker of IAP. Elevated IAP, therefore, might impede venous backflow in the iliofemoral veins resulting in venous stasis and vein distension of the lower limbs favoring valve dysfunction and thrombosis. To our knowledge, there are no human in-vivo studies aimed at proving this assumption. Color-coded duplex sonography (CCDS) allows a non-invasive and accurate flow assessment of the veins of the lower limbs. We hypothesized that venous flow characteristics of the lower limbs differ between obese and non-obese subjects inasmuch as obese subjects exhibit lower flow velocities and larger vein diameter and that abdominal obesity correlates with venous hemodynamic changes.[12]

METHODS

Criteria for inclusion were pregnant patients aged 18 years with estimated gestational ages 37 weeks. Exclusion criteria included personal history of VTE (regardless of etiology), development of VTE during the current pregnancy, thrombophilia, bleeding disorder, thrombophlebitis, marked varicosities, history of recurrent stillbirth, intrauterine growth restriction, any indication for emergency delivery, known major fetal abnormality or genetic syndrome, multiple gestations, and the use of therapeutic or prophylactic low molecular

weight heparin (LMWH) or unfractionated heparin during the current pregnancy. Participants were recruited in July 2018 and were stratified into two groups based on body mass index (BMI):

- nonobese (<30 kg/m2)
- and obese (30 kg/m2)

RESULTS AND DISCUSSION

Pregnant women are 4 to 5 times more likely to develop venous thromboembolism than women who are not. This predisposition to develop venous thromboembolism results from the hypercoagulable state of pregnancy that has likely evolved to protect women from hemorrhage during miscarriage and childbirth. While the leading cause of maternal death in the developing world is hemorrhage, in the United States, where death from hemorrhage is prevented, the leading cause of maternal death is a thromboembolic disease.[13] Besides death, venous thromboembolism can cause significant acute and chronic morbidity. In addition to the immediate morbidity associated with venous thromboembolism, there is long-term morbidity associated with the post-thrombotic syndrome. The majority of women who suffer from venous thromboembolism during pregnancy develop sequelae that range from edema and skin changes to recurrent thromboses and ulceration.

Table I Frequency of venous thromboembolic events by type and timing in gestation

	DVT	PE	Both	Total (%)
Pregnancy admissions n = 9,058,162	5929	1033	215	7177 (50%)
Postpartum admissions n = 73,834	5397	1466	295	7158 (50%)
Total (%)	11,326 (79%)	2499 (17%)	510 (4%)	14,335 (100%)

Table II Rate of venous thromboembolic events by age

Age	No. of cases	Per 1000 deliveries	95% CI
< 20	1399	1.47	(1.33-1.61)
20-24	3201	1.58	(1.50-1.66)
25-29	3667	1.67	(1.59-1.75)
30-34	3424	1.73	(1.63-1.83)
35-39	2067	2.13	(1.97-2.29)
40 +	577	2.75	(2.36-3.14)

Peripheral vascular disease is a common clinical problem that requires intervention when distal ischemia produces severe symptoms. Because arterial blood volume is directly related to ischemia, quantification might be helpful in evaluating the severity of disease, even in asymptomatic patients. Such methodology might be applied clinically to aid in earlier recognition of vascular disease.

The results of studies suggest that obesity impacts lower limb venous properties. The diameter of the femoral vein was significantly greater in obese compared to non-obese subjects. This could be interpreted as a result of elevated IAP transmitted to the femoral veins and leading to vein wall extension.

Increased stasis and reduced forward flow velocity might be a consequence. Indeed, we also found significantly different hemodynamic properties between obese and non-obese subjects.

A hypercoagulable state is experienced by all women during pregnancy and may be influenced by hormonal changes, venous stasis, weight gain, and impaired motility during pregnancy. Obesity is considered a risk factor for VTE formation in pregnancy, but the mechanism is not well understood.[14] Several studies have identified a relationship between obesity and varicose vein formation, particularly in women. Obesity is associated with increased intra-abdominal pressure, which in theory could impede venous flow in the lower extremities.

Willenberg et al6 designed a study to demonstrate this concept. Nonobese participants were subjected to an abdominal cuff that, when inflated, increased intra-abdominal pressure. As a surrogate for obesity, this model demonstrated that during cuff inflation, the venous diameter increased and flow and velocity decreased. Furthermore, nonobese participants receiving

compression of the abdomen to 40 mm Hg showed lower extremity vessel changes that were very similar to those of obese participants who were not receiving compression.[15] The venous function was also studied in participants with varicose veins, noting increased venous reflux in obese compared with nonobese persons, again suggesting obesity alone contributes to alterations of venous flow.

According to the American College of Obstetrics and Gynecology, 50% of pregnancy-related VTEs occur during pregnancy, and the other 50% occur in the postpartum period. Additionally, 75 to 90% of VTEs occur in the iliofemoral veins of the left leg.[16] The predominance of clots in the left lower leg is likely due to compression of the left common iliac vein by the overlying right common iliac artery. In nonpregnant individuals, obesity is associated with abnormal venous flow in the lower extremities. Our hypothesis was that obesity during pregnancy would have the same impact or perhaps more with the addition of a gravid uterus. All participants were tested in the late third trimester, a time of expected maximal impact from the combination of pregnancy and BMI. Contrary to the reported findings in nonpregnant obese participants, we did not find decreased venous flow in the obese compared with nonobese pregnant participants.[17] Venous volume flow and TAMV in the left SFV were higher in the obese group compared with the nonobese group. This finding is contrary to Willenberg et al's findings in the nonpregnant population. We do not have a clear explanation for the apparent increased venous blood flow seen in obese pregnant patients when compared with their nonobese counterparts. However, regardless of the cause, it appears that other factors contribute to the increased risk of DVT in obese pregnant women. Obesity is associated with chronic inflammation.

The inflammatory response is a strong trigger for clotting since it results in endothelial injury and activation of factor VII through tissue factor expression in monocytes, neutrophils, and the endothelium. Alternatively, it is possible that obese women may have an abnormal synthesis of natural anticoagulants due to liver dysfunction. Further research is required before any firm conclusions are made. Limited data suggest that obese individuals have superior calf venous muscle pump function compared with nonobese patients.[18] The latter could explain, at least in part, the increased velocity in venous return noticed in this study. A weakness of the study is that we did not assess venous duplex volume flow and TAMV after delivery, which may have demonstrated differences between the two study groups that were not apparent prior to delivery. In fact, there is evidence that VTE risk increases in the

postpartum period. In a study by Jacobsen,[19] the rates of VTE were higher antepartum, whereas PE was more common during the postpartum period. We used a BMI of 30 kg/m2 as our inclusion criteria for the study group. Despite the fact that the control group had BMIs below[20], many were overweight. Findings may have been more dramatic between groups if the control group had normal BMIs. Comparing true normal weight (BMI: 18–25) women to obese women might have demonstrated greater differences in venous hemodynamics.

The strength of our study is that we reduced interobserver variability by employing two credentialed vascular technicians to perform all of the ultrasound examinations. However, our main strength is that, to our knowledge, this is the first study to report Duplex venous volume flow and velocities in a pregnant cohort. We recognize that a larger sample size is necessary to further define normal ranges. It would also be beneficial to define normal ranges in women undergoing a cesarean section, as well as women in the first half of pregnancy and the postpartum period.[21]

We found a higher incidence of pregnancy-related venous thromboembolism, 1.72 per 1000 deliveries, than has been previously reported. While none of the reports are from the US, and none have included as many cases, the previously published figures for the incidence of pregnancy-related venous thromboembolism range from 0.71 to 1.25 per 1000 deliveries.[22]

Data from the Nationwide Inpatient Sample are limited to information derived from discharge abstracts.

Consequently, detailed and precise information on diagnosis and treatment are not available. A potential confounder, therefore, is the difference in the availability and utilization of various imaging or other diagnostic modalities among institutions. A number of cases may go undiagnosed. For that reason, our estimate of the incidence of pregnancy-related venous thromboembolism, although higher than others, may be an underestimate. The improved diagnosis has been shown to increase,[23] rather than decrease, the reported incidence of pregnancy-related thromboembolism.

Half of pregnancy-related venous thromboembolism occurred postpartum. This is similar to the proportion in other series, in which one third to two-thirds of cases occurred postpartum.[24]

We estimated the mortality rate from pregnancy-related venous thromboembolism to be 1.1 per 100,000 deliveries.

This is lower than the previously reported 2 to 3 per 100,000 deaths but these reports included cases of amniotic fluid embolism as well as a pulmonary embolus. We found the case fatality rate for a pulmonary embolus to be 2.4%. This is one-tenth what has been previously reported.20 The probable explanation is that pregnant and postpartum patients are not representative of those who suffer from pulmonary emboli, the majority of whom are likely to be older or have life-threatening comorbidities such as cancer.[25]

The medical conditions with the highest ORs for pregnancy-related venous thromboembolism, not surprisingly, included known thrombophilia, OR 51.8 (38.7-69.2), a history of thrombosis, OR 24.8 (17.1- 36.0), and the antiphospholipid syndrome, OR 15.8 (10.9-22.8). Other conditions with more than a 5-fold increased risk were lupus, OR 8.7 (5.8-13.0), heart disease, OR 7.1 (6.2-8.3), and sickle cell disease, OR 6.7 (4.4-10.1). The presence of these comorbidities may warrant consideration for thromboprophylaxis.[26]

The complication of pregnancy or delivery with the highest OR was transfusion, OR 7.6 (6.2-9.4). DanilenkoDixon et al also identified transfusion as a possible risk factor for pregnancy-related venous thromboembolism.[27]

Transfusion may be associated with venous thrombosis because of the conditions for which the transfusion is indicated, such as anemia, antepartum hemorrhage, or postpartum hemorrhage, or may reflect the severity of a patient's condition. There is evidence, however, that storage and preservation of red blood cells increase their aggregability,[28] which may contribute to an increased risk of thrombosis.

Disorders of fluid, electrolyte, and acid-base balance, OR 4.9 (4.1-5.9), not obvious risk factors for thrombosis, were likely present in critically ill patients who were at risk of thrombosis because of their underlying condition.

We found that postpartum infection increased the risk of thrombosis 4-fold, paralleling findings from Hauth et al, who reported a 4-fold increased risk of venous thromboembolism among women with chorioamnionitis who underwent cesarean delivery.

Several epidemiologic studies have given strong evidence to the hypothesis that obesity is a risk factor for chronic venous insufficiency (CVI) and venous thromboembolism (VTE). Obesity can significantly affect the development of metabolic syndrome with a cluster of cardiovascular risk factors. Excess body weight is also related to alterations in the coagulation system, including impaired fibrinolytic activity and elevated plasma concentrations of clotting factors.4 These alterations in endothelial function and coagulation are thought to be relevant not only for arterial but also for venous thrombosis.5 In addition to these mechanisms, obesity is thought to predispose individuals to venous stasis, which is a trigger of both deep vein thrombosis and CVI. Central obesity is thought to be associated with increased intra-abdominal pressure (IAP) caused by abdominal fat.[29] Arvidsson et al[30] showed that the pressure in the iliofemoral vein in morbidly obese patients was significantly higher than in nonobese individuals. Likewise, surgical weight reduction decreases urinary bladder pressure, a surrogate marker of intra-abdominal pressure.[31]

The elevated IAP is postulated to be transmitted to the extremities by the femoral veins, leading to venous stasis and distensions of the veins of the lower limbs favoring thrombosis and venous valve dysfunction. To our knowledge, however, no human in vivo studies have confirmed this pathophysiologic assumption. Color-coded duplex ultrasound (CCDU) imaging allows for a noninvasive and accurate flow assessment of the veins of the lower limbs. We hypothesized that venous flow characteristics of the lower limb differ between obese and nonobese individuals, inasmuch as obese people exhibit lower flow velocities and a larger vein diameter and that abdominal obesity correlates with venous hemodynamic changes.[32]

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