The hemodynamic effects of pregnancy on the lower extremity venous system

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ABSTRACT

Objective: Pregnancy has significant effects on the lower extremity venous system. Increasing venous pressure and blood volume, in combination with reduced flow rates within the deep veins, predisposes pregnant women to both primary and secondary chronic venous insufficiency (CVI). This review article highlights the specific physiologic and hemodynamic changes that occur during pregnancy and examines the nonpharmacologic, pharmacologic, and invasive interventions that are appropriate for both prophylaxis and treatment of CVI and venous thromboembolism (VTE).

Methods: This study is a review article of the key literature related to VTE and CVI in pregnancy.

Results: Significant hemodynamic changes occur in the lower extremities during pregnancy. Although well documented and essential to fetal development, these changes can have a negative impact on the maternal lower extremity venous circulation. Consequences of pregnancy can result in venous disease only during pregnancy or, particularly in the multiparous patient, can progress to CVI. An abundance of literature and guidelines exist for the management of VTE during pregnancy; however, the quality and extent of literature based around the management of primary CVI during pregnancy are modest at best.

Conclusions: The physiologic changes throughout the arterial and venous systems during pregnancy are well documented. However, there is a paucity of data available to construct guidelines for care, particularly in the pregnant patient with symptomatic superficial venous insufficiency. Further investigation in the form of prospective randomized trials is required to establish appropriate guidelines for treatment. (J Vasc Surg: Venous and Lym Dis 2017;1-9.)

The cardiovascular system undergoes dynamic physiologic changes throughout the course of pregnancy to meet the demands of both the mother and the developing fetus. Although essential for ensuring the appropriate development of the fetus, these changes may reveal previously silent cardiac disease and are associated with several venous diseases in the mother. The burden of disease from venous diseases, in particular, can be high during pregnancy. Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a potentially lethal condition that affects pregnant women nearly five times more often than nonpregnant women. This risk increases even further during the postpartum period. Indeed, VTE is the number one cause of maternal death in developed countries. Chronic venous insufficiency (CVI) is also common during pregnancy. Affected women experience an increased risk of varicose veins, leg pain, edema, itching, skin discoloration, night cramps, and a feeling of heaviness in the legs, with symptoms most pronounced in the third trimester.

Herein, we describe the hemodynamic changes of pregnancy that result in venous disease in addition to potential preventive and treatment strategies.

LOWER EXTREMITY HEMODYNAMICS IN PREGNANCY

The lower extremity venous system is composed of a series of superficial, deep, and perforator veins, all of which act in concert to return blood to the heart. A series of bicuspid one-way venous valves are essential to ensuring that the blood flows in the correct direction, and the contraction of the calf muscle pump assists in propelling the blood toward the heart against the effect of gravity. In a normal (nonpregnant, healthy) individual, the vascular system varies its tone in response to changes in the cardiac output of the heart, and the arterial supply to the lower extremities is relatively evenly matched by venous return. As such, lower extremity swelling is minimized.

Hemodynamic changes

The hemodynamic alterations associated with pregnancy can dramatically alter the function of the lower extremity venous system. An intricate combination of neurologic and hormonal factors results in elevated cardiac output and heart rate and decreased systemic vascular resistance and blood pressure (Table I).
Mean arterial pressure and systemic vascular resistance. Hemodynamic changes during pregnancy occur as early as week 5 of gestation. The greatest fall in mean arterial pressure occurs during the second trimester, when it falls by an average of 8 mm Hg (9%). Systemic vascular resistance progressively decreases during the course of pregnancy, reaching a nadir approximately 30% below nonpregnancy values in the third trimester. After delivery, both mean arterial pressure and systemic vascular resistance return to nonpregnancy values.

Heart rate. Heart rate rises progressively during the course of gestation. The highest value occurs in the late third trimester, when it peaks at approximately 16 beats/min (24%) above nonpregnant values. After delivery, heart rate returns to nonpregnancy values and remains stable across the early and late postpartum periods.

Cardiac output. Cardiac output increases throughout pregnancy as the result of an increase in heart rate and stroke output. A recent meta-analysis investigating the pattern of change in cardiac output during healthy pregnancy demonstrated that it peaks in the early third trimester at an estimated 1.5 L/min (31%) above nonpregnant values. In the early postpartum period, cardiac output quickly returns to nonpregnancy levels because of the reduced maternal cardiovascular demand after delivery. There is a subsequent modest increase in cardiac output in the late postpartum period (approximately 0.63 L/min, or 12%).

Physiologic changes

The physiologic changes that contribute to hemodynamic flux during pregnancy include increased vaso-motor sympathetic activity, increased maternal baroreceptor sensitivity, and an attenuated response to α-adrenergic stimulation. The hormones estrogen, progesterone, and relaxin are all elevated during pregnancy and play a role in systemic vasodilation and increased venous capacitance. Nitric oxide has also been postulated to play a part in mediating systemic vasodilation during pregnancy, but there are conflicting data on the topic, suggesting that it likely does not play a major role.

The renin-angiotensin-aldosterone system is hyperactivated during pregnancy from an early stage as a result of estrogen, relaxin, and progesterone influences. Maternal plasma prorenin levels peak at 10 times nonpregnant levels at approximately 8 to 12 weeks of gestation, whereas active renin levels do not rise until approximately week 20. Estrogen increases the level of angiotensinogen, which in turn increases levels of angiotensin II. High levels of angiotensin II play a critical role in maintaining circulating blood volume, blood pressure, and uteroplacental blood flow. Correspondingly, total blood volume has also been shown to increase by 20% to 100% from pre-pregnancy levels, with the normal rise being estimated at 45%. Erythropoiesis increases the red blood cell mass by up to 40%, thanks in part to the influence of placental lactogen. However, there is a proportionately higher increase in plasma volume, resulting in "physiologic anemia" from hemodilution. As a result of all these changes, pregnant women tend to be in a pseudo-stress-response state at all times, which ultimately leads to lower extremity edema and swelling beyond the normal state.

Flow dynamics

Air plethysmography (APG) and duplex ultrasound have been used in several studies to calculate venous volumes, vein diameters, and flows in pregnant women compared with nonpregnant matched counterparts, with the thought that pregnancy is associated with a propensity for CVI. APG is an accurate, noninvasive means of obtaining data for the assessment of lower extremity venous and arterial perfusion. It is simple to use and quantitative, and it provides a variety of information including venous volume, venous filling index, and ejection fraction, although it cannot be used to identify specific sites of venous reflux. In contrast, duplex ultrasound has the advantage of being able to locate the exact region of reflux in patients with CVI. However, it is much more user dependent than APG. The sensitivity and specificity of APG for diagnosis of CVI range between 58% and 100% and 72% and 98%, respectively, whereas the sensitivity and specificity for duplex ultrasound range between 83% and 90% and 74% and 86%, respectively.

Based on a combination of APG and duplex ultrasound modalities, it appears that both anatomic and functional changes occur in the venous system during pregnancy. Both venous volume and the diameter of the lower
extremity veins have been shown to be significantly greater in pregnant than in nonpregnant women.\textsuperscript{29} The mechanisms contributing to these changes are thought to include elevated levels of estrogen, the reduction in systemic vascular resistance that occurs during pregnancy,\textsuperscript{13} and venous stasis secondary to compression from the gravid uterus on the iliac veins and vena cava.\textsuperscript{30} Similar to the physiologic manifestations observed among patients with May-Thurner syndrome, in whom there is exaggerated compression of the left common iliac vein by the right common iliac artery,\textsuperscript{31} the compression of the uterus on the inferior vena cava (IVC) in pregnant women causes a mechanical obstruction that prevents venous return, thereby leading to venous stasis and subsequent CVI.\textsuperscript{32}

The blood flow dynamics within the lower extremity veins are also affected during pregnancy. The venous filling index, a measure of the rate of filling of calf veins, has been shown to increase in pregnant women compared with nonpregnant women.\textsuperscript{33} However, the outflow fraction, an estimate of proximal venous obstruction, and the ejection fraction, which is a measure for calf pump efficiency, do not significantly change during pregnancy.\textsuperscript{34} Ambulatory venous pressure also appears to remain stable during pregnancy.\textsuperscript{35} Despite this, the blood velocity recorded at the common femoral, superficial femoral, and popliteal veins has been shown to decrease throughout gestation, with the nadir of flow occurring in the third trimester.\textsuperscript{36} As noted before, this is likely a manifestation of a mechanical venous outflow obstruction that results from compression of the IVC by the uterus.\textsuperscript{32} Taken together, these findings suggest that whereas the calf veins fill more rapidly during pregnancy, the venous return mechanisms remain stable or decrease. As a result, the overall efficiency of the lower extremity venous system is compromised, leading to venous pooling, endothelial damage, and subsequent CVI. These changes are cumulative, meaning that multiparous women have repetitive insults to their venous outflow systems, therefore resulting in a greater risk of subsequent CVI.\textsuperscript{35}

**Hypercoagulable state**

The components of Virchow’s triad (venous stasis, endothelial injury, and hypercoagulability), which predispose to thrombosis, all occur during pregnancy.\textsuperscript{36} Venous stasis is due to the pressure influence of the uterus on the IVC and iliac veins and is also affected by an overall decrease in blood pressure and systemic vascular resistance that occurs secondary to the influence of the neurohormonal mechanisms activated during pregnancy. Endothelial injury results from stress placed on blood vessel walls secondary to increased plasma volume, which is mediated by the activation of the renin-angiotensin-aldosterone system and influenced by estrogen and relaxin. This is evident on the basis of findings of increased lower extremity vein diameter during pregnancy. Finally, Virchow’s triad is completed in pregnancy by the establishment of a hypercoagulable state (Table II). The concentrations of coagulation factors V, VII, VIII, IX, X, and XII and the adhesive protein von Willebrand factor rise significantly, in addition to heightened fibrinogen levels. There are also critical changes in the anticoagulation system, manifested by increased plasminogen activator, decreased protein S, and increased resistance to activated protein C. In addition, fibrinolysis is impaired because of increased plasminogen activator inhibitor, decreased tissue plasminogen activator, and acquired antithrombin deficiency.\textsuperscript{37} These changes are believed to reflect preparation for delivery by protecting the mother from excessive bleeding but also serve to put the woman in a prothrombotic state throughout the peripartum period. As a result, pregnant women are at increased risk for VTE and other venous diseases compared with nonpregnant women.

**VENOUS DISEASES DURING PREGNANCY**

**Primary CVI**

**Epidemiology.** Primary CVI is venous insufficiency that is a result of intrinsic structural and biochemical abnormalities of the vein wall. A number of major epidemiologic studies have looked at the incidence and prevalence of CVI within the general population.\textsuperscript{36,39} According to data from the San Diego Population Study, primary CVI affects approximately 10% to 35% of adults in the United States.\textsuperscript{38} Pregnancy, along with obesity, history of DVT, smoking, and family history, is a well-described risk factor for venous reflux and subsequent CVI.\textsuperscript{40}

In the pregnant population, primary CVI is evident in up to 80% of women, with the majority of affected individuals reporting symptoms of leg edema and pain, night cramps, numbness, and itching.\textsuperscript{41} Onset occurs in the first trimester in 80% of cases, and symptoms classically worsen after each successive pregnancy.\textsuperscript{42} Varicose veins,

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**Table II. Coagulation changes in pregnancy**

<table>
<thead>
<tr>
<th>Procoagulant factors</th>
<th>Anticoagulant factors</th>
<th>Adhesive proteins</th>
<th>Fibrinolytic proteins</th>
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<tbody>
<tr>
<td>I, V, VII, VIII, IX, X</td>
<td>Soluble thrombomodulin</td>
<td>von Willebrand factor</td>
<td>Plasminogen activator inhibitor, types 1 and 2</td>
</tr>
<tr>
<td>XI</td>
<td>Protein S</td>
<td>Protein C</td>
<td>Tissue plasminogen activator</td>
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which represent Clinical, Etiology, Anatomy, and Pathophysiology class 2 disease, affect up to 40% of pregnant women with primary CVI.23 The risk of CVI increases with each additional pregnancy, and symptoms are most pronounced during the third trimester when the hemodynamic effects of pregnancy are most altered. Potential complications associated with CVI and subsequent varicose veins include thrombosis, inflammation of the vein (thrombophlebitis), and bleeding.

**Nonpharmacologic treatment.** Treatment for CVI during pregnancy can be divided into pharmacologic and nonpharmacologic methods. As with treatment of CVI in nonpregnant individuals, nonpharmacologic approaches are used first in an effort to minimize the need for more invasive measures. Nonpharmacologic methods to manage primary CVI in pregnancy include compression garments, rest, leg elevation, reflexology, water immersion, and foot massage.6,43-45

Compression therapy acts to improve the drainage of superficial venous blood, thus reducing the risk of overdistention and decreasing symptoms of CVI while also potentially preventing thrombosis in high-risk patients.46-48 However, there is a paucity of evidence evaluating the efficacy of compression therapy for the treatment of primary CVI during pregnancy. In one trial by Thaler et al comparing the use of prophylactic compression stockings with no treatment among 42 healthy pregnant women, use of compression stockings did not prevent the emergence of gestational varicose veins but did significantly decrease the incidence of saphenous vein reflux at the saphenofemoral junction and improve leg symptoms.49,50 Similarly, a trial by Jamieson et al evaluating the use of thigh-high compression stockings in the immediate postpartum period found a statistically significant reduction in the diameter of the common femoral vein with a concomitant increase in the rate of venous blood velocity after only 30 minutes of compression therapy. These findings suggest that compression therapy is a successful strategy to reduce venous stasis and thus decrease the risk of CVI in the postnatal period.51 Compression therapy is advantageous in that it is inexpensive and easily applied. Its major limitation is user noncompliance, which limits its effectiveness.52

Among the other nonpharmacologic techniques to manage CVI in pregnancy, single studies have shown that reflexology may reduce CVI symptoms compared with rest.46 and water immersion may reduce symptoms of leg edema compared with no treatment.19 Refluxology is a natural ancient therapy whereby a specific thumb and finger pressure technique is applied to reflex points in the feet, hands, and ears to elicit potential areas of disorder in the body. Lymphatic reflexology is an adapted version of this technique that mimics the lymphatic drainage action of the body to help move extravascular fluid in the edematous foot and leg using these pressure points combined with massage.44 Water immersion is similar to lymphatic reflexology but uses hydrostatic pressure exerted uniformly on all sides of the foot and lower leg to drive extravascular fluid into the intravascular space.45 Whereas a small number of reports suggest a possible benefit with these treatment modalities, they have not been validated. Therefore, their use for treating CVI in pregnancy should be considered nonstandard.

**Pharmacologic treatments.** Pharmacologic techniques for the treatment of primary CVI include the use of phlebotonics and are usually reserved for Clinical, Etiology, Anatomy, and Pathophysiology class 2 disease and greater (ie, varicose veins).

Phlebotonics are a class of venoactive medications that are purported to increase venous tone and to prevent edema, although the mechanism of action is poorly understood. In 1975, Bergstein53 performed a randomized controlled trial comparing the efficacy of O-(β-hydroxyethyl)rutoside, an oral phlebotonic medication, with placebo for the treatment of varicose veins during pregnancy. The patients in the rutoside group experienced a small but significant improvement in lower extremity swelling and a significant reduction in varicose vein symptoms, and there were no reported adverse effects to the pregnant women or neonates.53 More recently, there have been data demonstrating a possible fetal growth promotion effect associated with rutoside treatment in pregnant women, leading to concerns about the fetal safety of flavonoid derivatives.54 Overall, there is weak evidence to support the use of rutosides for anyone with CVI, and given the intrauterine risks associated with the drug, they should be used with extreme caution as a means of relieving severe varicose vein symptoms during pregnancy.

The treatment of superficial thrombophlebitis (STP) during pregnancy is similar to that for nonpregnant patients and ranges from compression therapy and nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain and inflammation to systemic anticoagulation and surgical intervention (ie, ligation and stripping of the vein). Surgical intervention has not been shown to significantly reduce the risk of STP extension or recurrence compared with anticoagulation,55 but it is more effective than compression bandaging alone.56 Of the anticoagulants studied, fondaparinux has been shown to significantly reduce the incidence of VTE, STP extension, and STP recurrence.57 Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) have been shown to reduce STP extension and recurrence without significantly altering VTE incidence.57 Warfarin is contraindicated in pregnancy because it crosses the placenta and can result in severe physical and neurologic developmental disorders in the fetus (ie, warfarin embryopathy) and increases the risk of fetal intracranial hemorrhage.51 NSAIDs have been shown to be as effective as LMWH.
The severity of the STP influences the treatment modality that is most appropriate. DVTs are present in as many as 40% of patients with STP, so all affected patients should undergo a lower extremity duplex ultrasound examination as part of their workup. Obtaining a duplex ultrasound examination is also helpful for assessing the extent of STP and its proximity to the saphenofemoral junction. Based on the 2012 guidelines of the American College of Chest Physicians, patients with STP of the lower limb that is <3 cm from the saphenofemoral junction or 5 cm in length should be treated with a prophylactic dose of fondaparinux or LMWH for 45 days. Other indications for systemic anticoagulation include severe symptoms, involvement of the greater saphenous vein, current or prior history of VTE or superficial venous thrombosis, active cancer, and recent surgery. Lesser burdens of disease, such as STP affecting branch varicosities, should be treated more conservatively with NSAIDs. In patients with superficial venous thrombosis who are treated with anticoagulation, fondaparinux is preferred to prophylactic LMWH whenever possible because of the higher quality available evidence for fondaparinux.

Secondary CVI

Epidemiology. In pregnant women, the most common cause of secondary CVI is acute VTE. Pregnancy is known to predispose women to acute VTE, with an incidence ranging from 0.08 to 7.13 per 1000 pregnancies. Acute VTE includes DVT, which occurs in 0.4 to 6.1 per 1000 pregnancies, and PE, which occurs in approximately 1.1 per 1000 pregnancies. More than half of cases (56%) occur during the third trimester; the remainder are fairly equally distributed between the first and second trimesters (21% and 23%, respectively). Patients undergoing cesarean section delivery are at particularly high risk for VTE, presumably because of the double hit of a hypercoagulable state and surgery; women who undergo cesarean section are four times more likely to develop a DVT than are women who undergo a vaginal delivery. The majority of DVTs in pregnant women occur in the left lower extremity, which is thought to be the result of a May-Thurner syndrome that is exacerbated by the impaired venous return observed with pregnancy. Women who develop VTE during pregnancy are at risk for development of post-thrombotic syndrome or secondary CVI; up to 35% of women who experience a DVT during pregnancy may go on to develop secondary CVI. As such, the prevention, early diagnosis, and effective treatment of VTE in pregnancy women are essential to avoid longer term complications.

VTE prevention during pregnancy. Chemical prophylaxis against the formation of VTE in the antenatal period has been evaluated in the literature. In 2004, the Thromboprophylaxis in Pregnancy Advisory Group attempted to conduct a randomized controlled trial comparing the use of LMWH with placebo for antenatal or postcesarean section thromboprophylaxis. In a more recent Cochrane database systematic review, there was insufficient evidence to support the use of thromboprophylaxis during pregnancy and the early postnatal period. In addition, there were reports of treatment side effects with anticoagulation, including fetal loss, thrombocytopenia, vaginal bleeding, and threatened and incomplete abortions, in a subset of studies analyzed. As a result of these data, the use of thromboprophylaxis during routine pregnancy is not currently supported.

Although there are no data to support the use of VTE prophylaxis in routine pregnancy, there is a subgroup of women in whom this may be beneficial. Women with inherited thrombophilias, including factor V Leiden, prothrombin gene mutation, and antiphospholipid antibody syndrome, are at significantly higher risk for VTE than the general population is. Guidelines from the American College of Obstetricians and Gynecologists recommend that women with a known thrombophilia without prior VTE be observed with clinical vigilance in the antepartum period and receive 6 weeks of prophylaxis with LMWH or warfarin in the postpartum setting. In the event that women with a known thrombophilia have incurred a prior VTE, both antepartum and postpartum prophylaxis is recommended with LMWH. Women with antiphospholipid antibody syndrome are also advised to take low-dose aspirin in addition to LMWH because of the elevated risk of pregnancy loss through placental thrombosis as a consequence of antiphospholipid antibodies. A further strategy in patients at high risk of VTE formation is the insertion of an IVC filter, with recent data suggesting that it can be used safely in pregnancy.

VTE treatment during pregnancy. The appropriate treatment of VTE that develops during gestation is systemic anticoagulation for 3 months, with therapy continued for an additional 6 to 8 weeks post partum if the 3-month treatment time ends before delivery. These recommendations apply to a VTE that develops at any point during the pregnancy. Several acceptable anticoagulation treatment modalities exist, including LMWH, UFH, and fondaparinux. As mentioned before, warfarin is contraindicated in pregnancy. There are limited data about the efficacy and safety of other oral anticoagulants during pregnancy, such as the direct thrombin (IIa) inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Thus, these should be avoided in pregnant women.

In cases in which anticoagulation is contraindicated, such as heparin-induced thrombocytopenia, heparin allergy, significant bleeding, or recent neurosurgery, or in the event of progressive VTE despite therapeutic systemic anticoagulation, placement of an IVC filter should...
be considered. IVC filters can be used safely when appropriate during pregnancy, with complication rates similar to those in nonpregnant patients. In pregnant or young women undergoing IVC filter placement, suprarenal placement is often recommended to avoid compression of the filter by the gravid uterus and to prevent filter fracture or dislodgment during uterine contractions. Suprarenal placement also protects against VTE of the dilated ovarian veins and has not been shown to increase risk of renal failure compared with infrarenal placement. Concerns that radiation exposure during IVC filter placement may cause fetal morbidity are unfounded; the International Commission on Radiological Protection cites no concern for significant effects to the developing human fetus for radiation doses lower than 100 mGy, which is considerably higher than the 12 mGy reported during IVC filter placement. Regardless, abdominal lead shields and use of intravascular ultrasound may minimize radiation exposure to pregnant patients during IVC filter placement if the patient or physician desires. Filter retrieval and complication rates in pregnant women appear to be similar to those in the general population, and filter retrieval should be timed on the basis of the individual patient’s indications. The optimal time for filter retrieval in the postpartum patient is unknown.

For patients with extensive iliofemoral DVT, catheter-directed thrombolysis (CDT), pharmacomechanical thrombolysis (PMT), and operative venous thrombectomy may be considered. In most cases, these treatments are employed post partum. Indeed, pregnancy, obstetric delivery, and lactation are considered to be relative or absolute contraindications to CDT, depending on the professional guideline used. The main concern for CDT during pregnancy relates to the estimated 175 to 245 mGy radiation dose that is required for the procedure, which is associated with a childhood cancer risk of up to 2%. Despite these risks, a study reported successful outcomes in 13 women who underwent CDT or PMT (n = 11) or venous thrombectomy (n = 2) for extensive iliofemoral DVT during pregnancy (weeks 8-34 of gestation). The authors reported using pelvic lead shields, focal fluoroscopy, and limited angiography to minimize radiation exposure to the fetus. All patients treated experienced a substantial improvement in symptoms; recurrent DVT was rare, and 12 of the 13 patients delivered healthy infants at term. Notably, 73% of the patients treated with CDT or PMT underwent venoplasty and stenting of the involved iliac veins, which is similar to the rate of flow-limiting iliac vein stenosis after CTD or PMT in postpartum individuals with iliofemoral DVT. May-Thurner syndrome was diagnosed in approximately one-third of patients. Taken together, these findings suggest that iliofemoral DVT in pregnancy is the result of a mechanical venous outflow obstruction similar to but not synonymous with May-Thurner syndrome.

In the event of a life-threatening PE during pregnancy, options for treatment include intravenous UFH, thrombolysis, thrombectomy, and surgical embolectomy. Thrombolytics have been used with successful outcomes for both the mother and fetus. Although most of the data on this topic are limited to case reports, in general there is consensus that the potential complication rates of thrombolytic therapy are acceptable in light of the underlying disease. Further investigation, perhaps in the form of a study by the Vascular Low Frequency Disease Consortium, is needed to provide comprehensive recommendations about the indications for and contraindications to thrombolysis in the pregnant population.

DISCUSSION

The maternal vascular system undergoes dynamic and extensive change during pregnancy, and the resulting stress places the mother at increased risk for development of lower extremity venous disease. It is important for physicians to comprehend the full extent of the hemodynamic factors that contribute to the increased risk of lower extremity venous disease as well as the most appropriate and effective evidence-based management options.

Strategies exist to manage the lower extremity venous disease associated with pregnancy. Unfortunately, the quality and extent of literature based around the management of primary CVI during pregnancy are modest. Some of the challenges with collecting data on treatment options during pregnancy are the ethical concerns for potential harm to both the mother and the fetus, challenges with collecting appropriate informed consent, and issues with ensuring clinical equipoise in study designs. As a result, there is a lack of large, prospective, randomized controlled trials and a paucity of data regarding the long-term outcomes for both women and their babies resulting from pharmacologic interventions routinely used in nonpregnant individuals with primary and secondary chronic CVI. Based on the available literature, rutosides are the most effective intervention to reduce the symptoms of varicose veins during pregnancy. However, this finding is based on a single study from 1975, with limited data about the safety of the drug during pregnancy. Both reflexology and water immersion were found to reduce the symptoms of leg edema; however, these findings were based on single studies that have not been reproduced. Compression garments can also be helpful for symptom control and are an inexpensive tool that can be easily applied.

The relative risk of VTE occurrence during pregnancy is elevated, although the absolute risk remains minimal, which is why routine VTE prophylaxis is not recommended in current guidelines. Moreover, there are serious risks associated with systemic anticoagulants, including the chance of fetal loss. In women with acquired thrombophilia, specific recommendations include hypervigilance...
during the antenatal and postnatal periods, with the addition of prophylactic LMWH in the event that a prior VTE has occurred.36

A DVT during the course of pregnancy should be managed with 3 months of treatment with UFH, LMWH, or fondaparinux. In the event that 3 months of treatment is completed before delivery, it should be continued for 8 weeks post partum. Warfarin should be avoided as it crosses the placenta and can result in fetal morbidity and mortality. In addition, other non-vitamin K oral anticoagulants should be avoided because of a lack of data surrounding their safety in pregnancy. In the rare event that a life-threatening PE should occur during pregnancy, it is appropriate to manage it with intravenous UFH, thrombolysis, or thrombectomy, depending on a facility’s resources. Pregnant patients with uncomplicated DVT during pregnancy can be managed appropriately according to the anticoagulation guidelines noted before, but we recommend that patients in whom an IVC filter or thrombolysis or thrombectomy is being considered be managed at larger centers with the ability to provide multidisciplinary care from obstetric, maternal-fetal medicine, hematology, and vascular surgery expertise. Pregnant patients with known thrombophilia should also be managed in an institution that can provide close collaboration with the hematology service to tailor treatment, as there is a paucity of data on this subset population.

CONCLUSIONS
Pregnancy has significant effects on the lower extremity venous system. Increasing venous diameters and blood volume, in combination with a reduced flow rate within the deep veins, predisposes pregnant women to both primary and secondary CVI. The prophylaxis and treatment of VTE have been studied extensively in pregnancy, and management guidelines have been published by professional organizations including the American College of Obstetricians and Gynecologists. Further research is required to look at the potential effectiveness and long-term safety profiles of new oral anticoagulants in the mother and fetus. In addition, there is a need for randomized controlled trials to investigate potential treatment strategies to relieve the symptoms associated with varicose veins and venous stasis.

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Conception and design: JH
Analysis and interpretation: JT, CH, JH
Data collection: JT, CH, JH
Writing the article: JT, CH, JH
Critical revision of the article: JH
Final approval of the article: JT, CH, JH
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Overall responsibility: JH
JT and CH contributed equally to this article and share first authorship.

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