Managing iliofemoral deep venous thrombosis of pregnancy with a strategy of thrombus removal is safe and avoids post-thrombotic morbidity

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Background: Extensive deep venous thrombosis (DVT) during pregnancy is usually treated with anticoagulation alone, risking significant post-thrombotic syndrome (PTS) in young patients. Catheter-directed thrombolysis (CDT) and operative venous thrombectomy have been safely and effectively used in nonpregnant patients, demonstrating significant reduction in post-thrombotic morbidity. This report reviews short- and long-term outcomes of 13 patients with extensive DVT of pregnancy treated with a strategy of thrombus removal.

Methods: From 1999 to 2013, 13 patients with iliofemoral DVT during pregnancy were offered CDT, pharmacomechanical thrombolysis (PMT), and/or venous thrombectomy. Gestational age ranged from 8 to 34 weeks. Fetal monitoring was performed throughout hospitalization. Radiation exposure was minimized with pelvic lead shields, focal fluoroscopy, and limited angiographic runs. Follow-up included objective vein evaluation using venous duplex and PTS assessment using the Villalta scale.

Results: CDT and/or PMT were used in 11 patients. Two patients underwent venous thrombectomy alone, and one patient had operative thrombectomy as an adjunct to CDT and PMT. Each patient had complete or near-complete thrombus resolution and rapid improvement in clinical symptoms. Eight of 11 having CDT or PMT underwent venoplasty and stenting of the involved iliac veins. Twelve of the 13 delivered healthy infants at term. One patient opted for termination of her pregnancy. Mean patient and gestational ages were 26 years and 26 weeks, respectively. Mean follow-up was 1.3 years, with only one recurrence. Duplex ultrasonography demonstrated patent veins in all but one patient and normal valve function in 10 patients. Eleven patients had Villalta scores ≤5 (considered normal), with a mean score of 0.7.

Conclusions: Extensive DVT of pregnancy can be effectively and safely treated with a strategy of thrombus removal, resulting in a patent venous system, normal valve function in many, prevention of PTS, and reduction in recurrence. (J Vasc Surg 2014;59:456-64.)

Deep venous thrombosis (DVT) is a significant cause of morbidity during pregnancy and the postpartum period. Venous thoemoembolic disease complicates approximately 1 to 2 per 1000 pregnancies, with maternal age, comorbidities, and mode of delivery influencing the risk. Treatment options range from management with heparin anticoagulation alone until delivery to catheter-based thrombolytic techniques or operative thrombectomy. However, extensive DVT during pregnancy is usually treated with anticoagulation alone, risking significant post-thrombotic morbidity.

A recent systematic review of anatomic distribution of DVT in 124 pregnant patients reported that 87 (71%) patients had proximal thrombosis, and of these, 56 (64%) had thrombus involving the iliofemoral veins. Iliofemoral DVT is associated with a high risk of post-thrombotic syndrome (PTS), a debilitating condition that reduces quality of life and often worsens over time. The prospect of post-thrombotic morbidity in this cohort of young and otherwise healthy women should motivate physicians to consider a strategy of thrombus removal.

Adopting a strategy of thrombus removal and restoring patency to the iliofemoral segment reduces short- and long-term morbidity in iliofemoral DVT patients. The combination of early clot removal with catheter-based techniques or contemporary venous thrombectomy, correction of underlying residual stenosis with balloon venoplasty and/or stenting, and systemic therapeutic anticoagulation is becoming the preferred treatment option for iliofemoral DVT in the nonpregnant patients in centers with appropriate expertise.

DVT of pregnancy is uniformly treated with only anticoagulation, regardless of its extent. Even when pregnant patients present with phlegmasia cerulea dolens, the most common clinical presentation of iliofemoral DVT, vascular surgeons fail to offer venous thrombectomy, and interventionalists avoid catheter-based techniques of thrombus removal for fear of treatment-related pregnancy complications.

We have observed that patients with extensive DVT of pregnancy who have persistent pain and edema with
anticoagulation and leg elevation can be managed safely and effectively with a strategy of thrombus removal. The purpose of this report is to objectively describe the treatment and outcome of 13 consecutive patients treated with either catheter-based techniques or operative thrombectomy for iliofemoral DVT of pregnancy.

METHODS

Between 1999 and 2013, 13 patients were referred for management of extensive DVT during pregnancy. All patients were initially managed with systemic anticoagulation and leg elevation and had persistent pain and edema after 2 to 14 days of treatment. After failing initial anticoagulation and elevation, patients were offered a strategy of thrombus removal. Patient data were collected and retrospectively reviewed to evaluate treatment and pregnancy outcomes. The study was approved by the institutional review board. All patients presented with extensive lower extremity DVT involving the iliofemoral venous segments and had swollen limbs from the inguinal ligament distally that were painful and had bluish discoloration, classically known as phlegmasia cerulea dolens. All were offered a strategy of thrombus removal. Patient data were collected and retrospectively reviewed to evaluate treatment and pregnancy outcomes. The study was approved by the institutional review board. All patients were monitored with electrocardiography, pulse oximetry, and vital signs by experienced interventional nurses. Obstetrical nurses oversaw the fetal monitors measuring fetal heart rate and uterine contractions during the procedures. Radiation exposure was minimized. The patient’s abdomen and pelvis were shielded with a lead apron when possible, and low-frame (four to six frames per second) pulse fluoroscopy with fluoro-save were used during all interventions. Digital subtraction angiographic runs were kept to a minimum and confined to the inferior vena cava (IVC) and iliac veins. The field of fluoroscopy was tightly collimated. Fluoroscopic image hold was used for documenting and filming. Foley catheters were used in all patients.

Most patients were able to tolerate a prone or semi-decubitus position. The preferred access site for percutaneous interventions was the ipsilateral popliteal vein, but two patients required additional posterior tibial vein access at the ankle level due to DVT extending below the popliteal vein into the calf veins. Internal jugular or contralateral common femoral vein access was used when IVC filter placement was required, which occurred when free-floating clot protruding into the vena cava was noted during venography. Optional Gunther-Tulip filters (Cook Medical, Bloomington, Ind) were placed in the suprarenal IVC, with retrieval performed after delivery.

All access sites were prepped with 4% chlorhexidine and draped in the usual fashion. Veins were accessed using ultrasound guidance and 4-F micropuncture needles (Cook Medical). Following venography, a 6- to 8-F access sheath was placed in the popliteal vein, and the clot was traversed with a hydrophilic guidewire. An intravascular ultrasound catheter (Volcano, San Diego, Calif) was occasionally used to evaluate the extent of central venous thrombosis or to guide stent placement.

PMT was performed using an 8-F Trellis catheter (Covidien, Mansfield, Mass) to perform isolated segmental PMT or a 6-F AngioJet catheter (Medrad, Warrendale, Pa) used for rheolytic thrombectomy, occasionally supplemented
with traditional balloon maceration. Eight- to 20-mg recombinant tissue plasminogen activator (rt-PA) was used in the initial session. In 10 of 11 patients treated with CDT and/or PMT, additional rt-PA infusion was required overnight. CDT was performed using a 4- to 5-F Unifuse catheter (Angiodynamics, Latham, NY) or a 6-F EKOS ultrasound-accelerated thrombolysis catheter (EKOS Corp, Bothwell, Wash), with rt-PA infused at 1 mg/hr diluted in 35-mL (EKOS) or 50- to 100-mL saline (Unifuse). When necessary, and upon completion of successful lysis, self-expanding stents were deployed to treat an underlying chronic stenosis of the common iliac (14-16 mm) and external iliac veins (12-14 mm); stents used included Zilver (Cook Medical), Luminex (Bard, Tempe, Ariz), and Wallstent (Boston Scientific, Natick, Mass). In one particularly challenging case, the patient required overlapping stent grafts (10 × 60, 10 × 40) in the femoral and common femoral vein segments.

Patients received 4000 to 7000 units of heparin during the procedure and were therapeutically anticoagulated with heparin postprocedure. They were discharged on enoxaparin 1 mg/kg every 12 hours for the duration of pregnancy, and converted to vitamin K antagonists postdelivery to a target international normalized ratio of 2.0 to 3.0. Anticoagulation was continued for a minimum of 12 months. When anticoagulation was discontinued, patients were placed on aspirin 81 mg daily. Following intervention, leg compression with 30- to 40-mm Hg ankle gradient below-knee stockings was applied, and patients were ambulated. Follow-up consisted of objective evaluation of the veins using segmental venous duplex and assessment of the presence and severity of their PTS using the Villalta scale.

RESULTS

All patients presented with acute occlusive iliofemoral DVT causing lower extremity symptoms of pain, swelling, bluish discoloration, and heaviness, most with the typical clinical presentation of phlegmasia cerulea dolens. All patients were initially treated with therapeutic anticoagulation and leg elevation for 2 to 14 days and had persistent pain and edema. Three patients had such severe pain and swelling that they could not ambulate. One patient, treated for 9 days with heparin prior to referral, had a painful flexion contracture of her knee. Mean age was 26 years (range, 19-35 years) and mean gestational age was 26 weeks (range, 6-34 weeks). Two patients were in the first trimester, two in the second, and nine in the third trimester. It was the first pregnancy for nine patients. All patients had iliofemoral involvement, two of whom had thrombus extending into their popliteal and tibial veins, and two had thrombus involving their vena cava. Figs 1-8 summarize the most challenging patient in our series, who was also the most instructive regarding pathophysiology, residual thrombus, and inflammation of the vein wall.

CDT or PMT techniques were used in 11 patients. Two patients with iliofemoral DVT declined thrombolytic therapy but consented to operative venous thrombectomy. A third patient had operative thrombectomy as an adjunct to PMT to remove persistent thrombus. Two patients had successful lytic therapy antepartum; however, venoplasty and stenting were delayed until the postpartum period. Because of uterine compression on the iliac veins and cava, the presence or absence of intrinsic iliac vein stenosis was not certain in these patients. They were anticoagulated until delivery and had repeat iliocavagrams postpartum. The repeat venograms demonstrated residual iliac vein stenoses, which were then dilated and stented.

IVC filters were placed in two patients due to nonocclusive thrombus in the vena cava at presentation, and postpartum filter retrieval was successful in one. All patients had complete or near-complete thrombus resolution with rapid
improvement in clinical symptoms. Twelve of 13 patients delivered healthy infants at term. One patient was noncompliant with her low-molecular-weight heparin (LMWH) after discharge and was readmitted with recurrent femoropopliteal DVT 1 week later. This patient elected to terminate her pregnancy.

The mean skin dose of radiation, based on a readout of the C-arm, was 447 mGy (range, 86-815 mGy). Actual patient dosimetry can be different based on location of the patient and table movement. The readout of an external dosimeter placed on the patient’s pelvis overlying the fetus was available in one patient. The dosimeter recorded 55.3 mGy compared with 86 mGy displayed by the C-arm readout. This suggests a 55% overestimation of the skin dose by the C-arm.

There were three minor complications, which were puncture site hematomas. One patient required a single blood transfusion. Two major complications occurred in one patient: gross hematuria, which was attributed to trauma of a Foley catheter, required three transfusions postlysis, while the patient was on heparin. The same patient developed a left popliteal artery pseudoaneurysm, which was successfully obliterated with compression ultrasound. One patient was lost to follow-up after treatment and successful delivery.

Mean follow-up was 1.3 years (range, 1-74 months). Venous duplex ultrasonography demonstrated patent veins in 12 of 13 patients and normal valve function in 10 (77%). Eleven (85%) patients had Villalta scores < 5, indicating a normal evaluation. Three patients had uneventful subsequent pregnancies, all managed with subcutaneous LMWH during pregnancy and the peripartum period. There were no pregnancy or postpartum complications. One patient who discontinued her anticoagulation prematurely developed recurrent DVT.

DISCUSSION

Venous thromboembolic disease remains a significant cause of morbidity during pregnancy and the postpartum period. The relative risk of developing venous thromboembolism is increased fivefold during pregnancy and the postpartum period, with the incidence ranging from 1 to 2 per 1000 pregnancies. Venous thromboembolic events occur more frequently during the last 20 weeks of pregnancy, especially among the youngest (15-19 years) and the oldest (> 35 years) women. The incidence of DVT during pregnancy is three times higher than that of pulmonary embolism.

Most physicians and guideline writing committees recommend treating DVT of pregnancy with anticoagulation alone. The use of CDT techniques is suggested only in cases of life-threatening pulmonary embolism. Although several reports have demonstrated that DVT of pregnancy treated with anticoagulation alone resulted in

Fig 3. Residual thrombus in the femoral vein was treated overnight with the ultrasound-accelerated EkoSonic thrombolytic system (EKOS Corp, Bothell, Wash) infusing 1-mg recombinant tissue plasminogen activator (rt-PA) per hour.
a high propensity for post-thrombotic morbidity and impaired quality of life.\textsuperscript{16-18} A 16-year follow-up of DVT of pregnancy in 25 patients treated medically reported that 52% had no clinical signs of venous disease.\textsuperscript{19} However, the precise extent and burden of clot was not well described.

CDT and PMT techniques have demonstrated good results in the nonpregnant population.\textsuperscript{9,11,20-23} A recently reported randomized trial showed that patients treated with CDT had less PTS than those treated with anticoagulation alone, and that patient benefit was related to the patency of the iliofemoral venous system.\textsuperscript{23} Unfortunately, only 37% in the anticoagulation arm and 45% in the thrombolysis arm were treated for iliofemoral DVT. This may explain why the number needed to treat to avoid PTS was seven. Clinically relevant bleeding complications occurred in 8%. Reports of thrombolysis for treating DVT in pregnancy are relatively few and primarily consist of case reports.\textsuperscript{24-26} A literature search performed by Leonhardt et al\textsuperscript{26} included 28 reports of thrombolysis with rt-PA used to treat venous thromboembolism during pregnancy; however, only three of the 28 reports described treatment of DVT, all of which were successful. We believe our series of 13 consecutive patients treated with strategies of thrombus removal for iliofemoral DVT of pregnancy (11 with catheter-directed rt-PA) is the largest report to date. Our patients were thought to be at particularly high risk of PTS because of the extensive nature of their clot and their persistent symptoms and signs despite therapeutic anticoagulation and leg elevation.

Pregnancy is considered a relative contraindication to thrombolytic therapy. However, the amount of plasminogen activator actually delivered with current techniques is a fraction of that delivered with systemic therapy. Some have expressed concern about the transfer of thrombolytic agents across the placenta; however, the large molecular weight of most thrombolytic agents indicates they are

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image1.png}
\caption{Repeat venography demonstrated a patent iliac system but (A) segmental continued segmental obstruction of the proximal femoral vein. Venoplasty resulted in recoil. A recommendation was made for operative venous thrombectomy.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Operative exposure revealed a markedly inflamed and thickened vein wall measuring 4 mm in thickness (A). B, Following removal of the adherent thrombus, a bovine pericardial patch was used to close the venotomy and the patient was maintained on heparin via a catheter in her popliteal vein and returned to the intensive care unit.}
\end{figure}
unlikely to cross the placenta during treatment. All patients in this series treated with catheter-based techniques received rt-PA, which has the largest molecular weight of the available thrombolytic agents. Furthermore, most patients were treated with CDT or PMT techniques, thereby localizing the delivery of rt-PA to the affected venous segments and minimizing its systemic lytic effect.

Systemic thrombolytic therapy has been used during pregnancy to treat stroke, pulmonary embolism, thrombosis of prosthetic cardiac valves, and myocardial infarction. No maternal or fetal toxicity is evident at a 1-mg/kg dose, which is larger than the doses used in our patients.

Operative venous thrombectomy has been shown to restore luminal patency, eliminate the embolic source, and reduce post-thrombotic morbidity in patients with iliofemoral DVT. Pillny et al reported on 97 women with DVT of pregnancy treated with operative venous thrombectomy. Although there were no maternal deaths, there were five fetal deaths at 2 to 10 weeks due to abruption of the placenta. This is likely a reflection of the underlying pathophysiology leading to the patients’ thrombotic event rather than a complication of treatment. At a mean follow-up of 6 years, 56% of women had no post-thrombotic symptoms, 36% had mild symptoms, and 8% had severe PTS. Three of our patients were treated successfully with operative venous thrombectomy.

Diagnostic evaluation should be pursued with compression ultrasonography, magnetic resonance imaging, and venography, with limited patient exposure to computed tomography scans due to the associated radiation dose. D-dimer levels naturally increase during pregnancy and may also be elevated in certain pregnancy complications such as abruption, preeclampsia, and sepsis. As in most nonpregnant patients, the value of a D-dimer test is when it is normal, not when it is elevated. If DVT is suspected, LMWH or unfractionated heparin should be started immediately, especially if confirmatory diagnostic tests are delayed. A negative duplex scan of the infrainguinal veins does not rule out the presence of more proximal clot if iliac veins are not visualized, and further testing should be considered. Anticoagulation, leg elevation, and compression should be used in all patients with DVT.

Once the diagnosis is confirmed, imaging of the vena cava is essential if a strategy of thrombus removal is to be implemented. If nonocclusive thrombus is present in the vena cava, a suprarenal optional IVC filter will be inserted, with plans for retrieval after delivery. During treatment, all measures to prevent radiation exposure were implemented. These included: (1) reduced rate pulsed fluoroscopy;
(2) focused fluoroscopy; (3) limited angiographic runs; and (4) filming performed in an anterior-posterior manner rather than an obliquely or angled position. Most of our patients were exposed to two iliocavagrams and one to two unilateral venograms, which roughly amounts to 0.942 rads, well below the dose levels (5 rads) demonstrated by epidemiologic studies that show risk for fetal injury. It was gratifying that 85% of our patients had no evidence of PTS on long-term follow-up. Comerota et al recently reported that in patients with iliofemoral DVT treated with CDT, PTS was linearly correlated with the amount of residual thrombus at the end of CDT.

Patients with iliofemoral DVT have the largest burden of thrombus. A systematic review by Hull et al reported that when patients are treated with anticoagulation alone, recurrence occurs significantly more frequently in patients with large thrombus burdens. Douketis et al reported that recurrence in patients with iliofemoral DVT occurred 2.4 times more frequently than in patients with infrainguinal DVT. One would have expected a 35% to 40% recurrence rate in our patients if they were treated with anticoagulation alone. Since only one (8%) experienced recurrence, 92% had patent veins, and 77% had normal valve function, our results suggest that successful thrombus removal is important in reducing subsequent venous thromboembolic events. Aziz et al recently reported a significant correlation of recurrent DVT with the thrombus burden remaining at the end of CDT. These observations by Aziz are supported by the patients in the present study. The implications of recurrence are substantial, since patients with recurrent DVT are generally treated with lifelong anticoagulation with its attendant inconvenience and risks.

CONCLUSIONS

Iliofemoral DVT in pregnancy can be treated safely with a strategy of thrombus removal to reverse short- and long-term morbidity. Operative and catheter-based techniques can be tailored to the specific needs of the patient.
Pharmacomechanical methods such as isolated segmental thrombolysis and ultrasound-accelerated thrombolysis lessen exposure to lytic agents and shorten treatment duration. Successful thrombus clearing avoids post-thrombotic morbidity and appears to reduce recurrence in these otherwise healthy young women.

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Conception and design: AC, SH, ST
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