

## Upper extremity deep vein thrombosis after *in vitro* fertilization treated with ultrasound accelerated catheter directed thrombolysis

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Upper extremity deep vein thrombosis (UEDVT) is an important clinical entity, presenting with an increased risk for developing fatal pulmonary thromboembolism. A 32-year-old woman was admitted to our hospital complaining swelling and pain of the right upper extremity for five days. The patient was diagnosed as primary infertility and underwent *in vitro* fertilization after stimulation with gonadotropin-releasing hormone analog one month prior to her admission. An ultrasound scan showed thrombosis of the right brachiocephalic and subclavian veins with partial obstruction of the lumen. The patient was successfully treated with EkoSonic<sup>®</sup> Mach4e Endovascular device with an overnight infusion of recombinant human tissue plasminogen activator. Catheter-directed thrombolysis may represent a potential therapeutic alternative for patients with severe UEDVT, particularly in those in whom medical management fails or conventional thrombolytic therapy and surgical thrombectomy are contraindicated or considered extremely risky.

Keywords: Catheter directed thrombolysis; deep vein thrombosis; *in vitro* fertilization; ultrasound.

Upper extremity deep venous thrombosis (UEDVT) is a serious disease, which is based on the pathogenesis and in view of the individual patient's prognosis and must be divided into primary and secondary presentations.<sup>[1]</sup> Primary UEDVT is a rather benign disease with an excellent prognosis, having only a minor potential of developing disabling post-thrombotic syndrome (PTS). Secondary UEDVT, on the other hand, typically occurs in older patients with severe comorbidities, mainly related to indwelling central venous catheters and cancer. It may also present during pregnancy or as a complication of assisted reproductive techniques. As a consequence of the underlying diseases, prognosis of secondary UEDVT remains poor.<sup>[2]</sup>

Regardless of the etiology, the cornerstone of therapy is anticoagulant treatment with low molecular weight heparin or unfractionated heparin and vitamin K antagonists to prevent thrombus progression and pulmonary embolism. Due to the lack of evidences, the optimal duration of treatment still remains unclear.<sup>[2,3]</sup>

Recent advances in catheter-based interventions have led to the development of a variety of minimally invasive endovascular strategies to remove venous thrombus.

Ultrasound accelerated catheter-directed thrombolysis (UACDT) has been developed to resolve the existing thrombus in a rapid and complete manner.

This technique integrates high frequency, low intensity ultrasound (US) with standard CDT to accelerate clot dissolution, reducing treatment time as well as the incidence of thrombolysis-related complications.<sup>[4,5]</sup> It is hypothesized that catheter-directed thrombolysis for UEDVT provides an effective solution with less severe PTS than during traditional anticoagulation. Herein, we report a case of UEDVT following *in vitro* fertilization (IVF) who was successfully treated with UACDT.

### CASE REPORT

A 32-year-old woman was admitted to our hospital with complaints of swelling and painful right upper extremity during the preceding five days. The patient was previously diagnosed with primary infertility and underwent IVF after stimulation with a gonadotropin-releasing hormone analogue one month prior to her admission. On admission, the patient described a tight, painful swelling of her face, upper chest, and arms. The patient history also revealed slight swelling

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of the neck and face lasting for a month, mainly noticed during morning hours, which resolved later during the day. On clinical examination, her body temperature was 37.2 °C, pulse was 78 beats/min, respiratory rate was 18 breaths/min, blood pressure was 116/70 mmHg, and oxygen saturation was 94% on room air. She was plethoric with deep swelling of her face, neck and right arm. Her heart sounds were normal and abdomen was soft and non-tender without any evidence of mass or organomegaly. Complete blood count and biochemistry results were also normal. Chest X-ray produced unremarkable findings with no evidence of pneumothorax, consolidation, tracheal deviation, pleural effusion, or mediastinal widening. An ultrasound scan showed thrombosis of brachiocephalic and subclavian veins with partial obstruction of the lumen (Figure 1a).

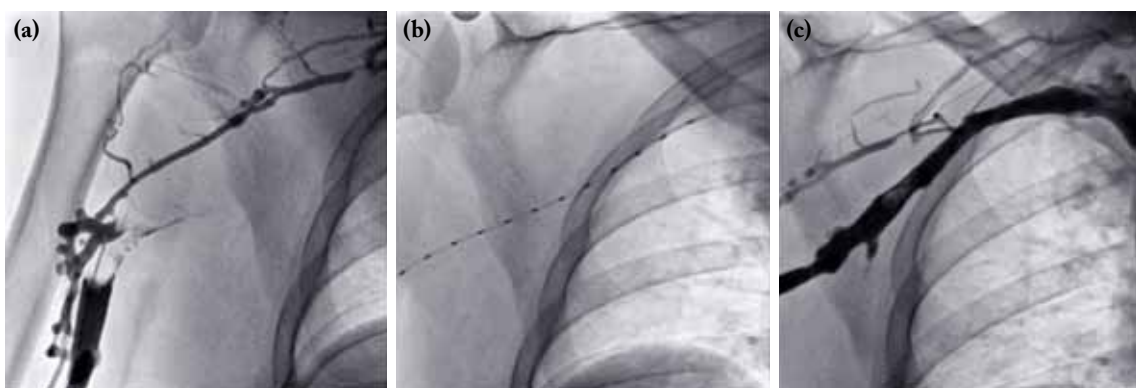
The patient underwent UACDT using the EKOS EkoSonic Endovascular System (EKOS Corporation, Bothell, WA), which consisted of a 5.2 F, 106 cm long infusion catheter, an ultrasonic core wire, and a control unit with catheter interface cables. We preferred a 30 cm length treatment zone catheter in our case, which was appropriate for the thrombus length. The drug delivery catheter was navigated over a 0.035-inch guide wire, therefore, the treatment zone traversed the entire clot and the tip exited the thrombus. After final positioning, the guide wire was exchanged for a matching ultrasonic core wire containing a series of US transducer elements (2.2 MHz, 0.45 W) distributed 1.0 cm apart to evenly deliver US energy radially along the distal coaxial infusion zone (Figure 1b). After priming the drug lumens of the catheter with sub-therapeutic heparin (1,000 U/mL), continuous

infusion of thrombolytic agent was initiated through the side-holes of the infusion delivery catheter using Alteplase (Actilyse, Boehringer Ingelheim GmbH, Germany), a recombinant human tissue plasminogen activator, at a 5 mg bolus, followed by an ultrasound accelerated infusion at 0.02 mg/kg/h over 14 hours. Normal saline, which included 1 mg Alteplase, was infused via a coolant port connected to the central lumen (and discharging from the distal end) at a rate of 35 mL/hr to dissipate any small amount of heat-generated by the US energy. The energy was delivered via the core wire with simultaneous infusion of the thrombolytic drug. Fibrinogen and activated partial thromboplastin time (aPTT) levels were taken every six hours during thrombolytic infusion.

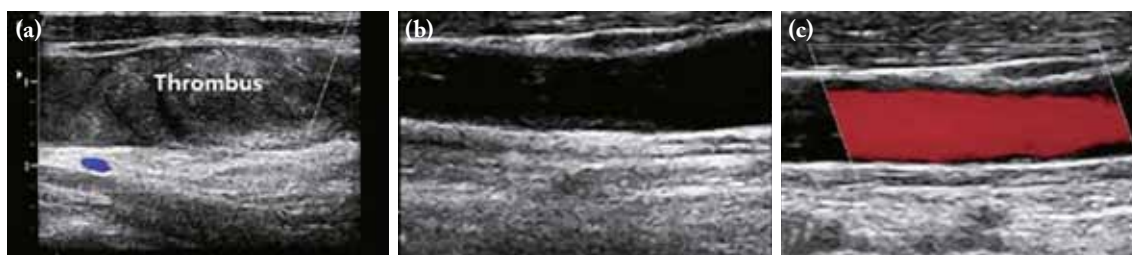
The patient was monitored at the intensive care unit and post-procedure venography was performed prior to removing the introducer. Venography showed excellent flow in the subclavian and brachiocephalic vein (Figure 1c). There were no bleeding complications due to the treatment. The patient was discharged on the second postoperative day on vitamin K antagonist therapy for six months. The follow-up US scan showed normalized subclavian vein and upper extremity veins (Figure 2). Her symptoms improved immediately after the UACDT and she continues to be symptom-free a week after the procedure.

## DISCUSSION

Compared to lower extremity DVT, UEDVT is an uncommon disease representing about 10% of all DVTs.<sup>[1]</sup> It can be associated with mechanical or anatomical factors (e.g. insertion of central venous



**Figure 1.** (a) Venography showing the absence of filling of the subclavian and brachiocephalic vein, consistent with thrombosis. (b) EKOS catheter with a 30 cm treatment length was placed into the thrombus (note the radiopaque ultrasound transducers). (c) Final venogram showing complete resolution.



**Figure 2.** (a) The longitudinal image of the right neck shows thrombosis of the right subclavian vein with obstruction of the lumen. (b, c) The follow-up ultrasound scan reveals normalized subclavian vein.

catheters or narrowing of veins by cervical rib) and hypercoagulable states (e.g. anti-thrombin deficiency, malignancy and anti-phospholipid syndromes).<sup>[2]</sup> In addition, UEDVT can be associated with pulmonary embolism (PE) with reported incidence rates of about up to one third of all patients.<sup>[3]</sup> Since our patient's vital signs were normal and there was little clinical evidence of PE, the possibility of PE was considered to be low. Moreover, echocardiographic examination showed normal right ventricular function and normal pulmonary arterial pressure.

It has been assumed that thrombolytic therapy for UEDVT may reduce the risk of long-term complications, especially the troubling PTS, characterized by chronic arm and hand aching and swelling due to early restoration of venous patency, thereby minimizing damage to vessel valves and endothelium. Recent retrospective<sup>[6]</sup> and prospective<sup>[7,8]</sup> cohort studies of conventional anticoagulant therapy for unselected UEDVT reported to be 27% to 44% mild PTS and almost no severe PTS. Although some cohort studies have evaluated short-term efficacy, adverse events, and reocclusion rates, we found no reports assessing the development of PTS after initial UACDT with subsequent conventional anticoagulant therapy for UEDVT.

Due to its rarity and possible variations in anatomical obstruction associated with UEDVT, there is no unique and unequivocal management strategy. Most patients are unresponsive to anticoagulation alone, which appears to be effective only in the mildest cases. However, life-long anticoagulation following definitive endovascular therapy may be important to reduce the incidence of reocclusion and may play a role in maintaining collateral circulation.<sup>[9]</sup>

Endovascular stents have become the treatment of choice for acute symptom relief of such patients. When stent placement is difficult or dangerous due

to the presence of a large amount of thrombus, thrombectomy, or thrombolysis should be attempted prior to stent deployment. On the other hand, stent placement for treatment of UEDVT is not devoid of complications. Infections, pulmonary embolus, stent migration, hematoma at the insertion site, bleeding, and rarely, perforation or rupture of the venous structures resulting in death, have been previously reported.<sup>[10]</sup>

As thrombus is deemed to be the cause of the upper extremity deep venous obstruction, removing it using UACDT with a low dose of thrombolytic agent may result in reduced risk of hematoma, gastrointestinal bleeding, and shorter length of hospital stay with all the relevant cost and comorbidities. To overcome the limitations posed by long-term treatment and high-drug doses in catheter directed thrombolysis, UACDT enhances drug permeation through thrombus by disaggregating the fibrin matrix, exposing additional plasminogen receptor sites to the thrombolytic agent.<sup>[4,5]</sup> The US energy affects thrombus in the entire venous segment, increasing the probability of complete thrombus clearance. The significant benefit of complete thrombolysis, compared to partial lysis, has been demonstrated in previous studies of standard thrombolysis.<sup>[11]</sup> Therefore, the ability of this technique to penetrate and resolve the entire thrombus may potentially lead to increased long-term patency rates and better long-term outcomes.

Recent literature data have shown a potential benefit of adjuvant angioplasty and stent implantation of the residual venous stenosis in patients with UEDVT.<sup>[12]</sup> Also, Alteplase has a high-degree of safety with few complications when delivered by a catheter rather than the traditional systemic infusion.

In conclusion, UACDT may represent a potential therapeutic alternative in patients with severe UEDVT, particularly in those in whom medical management

fails or conventional thrombolytic therapy and surgical thrombectomy are contraindicated or considered extremely risky.

### Declaration of conflicting interests

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