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CASE REPORT

Assisted reproduction in a patient with Klippel-Trenaunay syndrome: management of thrombophilia and consumptive coagulopathy

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Abstract Klippel-Trenaunay Syndrome (KTS) is a rare, sporadic triad of congenital malformations involving an extensive port wine stain, soft tissue or bone hypertrophy and underlying venous and/or lymphatic malformation involving an extremity. Pregnancy is known to exacerbate KTS complications and can put women at increased obstetrical risk due to deep venous thrombosis and other thromboembolic events. Here we report a case of a patient with KTS who achieved a pregnancy through in vitro fertilization (IVF) using her own eggs and a gestational surrogate in the setting of hypercoagulability and chronic consumptive coagulopathy.

Keywords Klippel-Trenaunay Syndrome · Coagulopathy · In Vitro Fertilization

Klippel-Trenaunay Syndrome (KTS) is a rare, sporadic triad of congenital malformations involving an extensive port wine stain, soft tissue or bone hypertrophy and underlying venous and/or lymphatic malformation involving an extremity. Of major clinical importance is that pulmonary embolism and thrombosis occur in KTS. Treatment is complicated and multidisciplinary and often includes the prevention of vascular and orthopedic complications.

Capsule A woman with Klippel-Trenaunay Syndrome who achieved parenthood through in vitro fertilization (IVF) using a gestational surrogate in the setting of hypercoagulability and chronic consumptive coagulopathy.

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Since 1989 there have been 21 reported cases of pregnancy in patients with KTS. Pregnancy is known to exacerbate KTS complications and can put women at increased obstetrical risk. Therefore physicians often recommend for patients to avoid pregnancy [1]. Patients with KTS have increased risk of deep venous thrombosis and other thromboembolic events [2, 3]. Baskerville reported a post operative embolic complication rate 10 times higher for patients with KTS likely due to venous pooling [2]. Inadequate venous return due to vascular malformation in the pelvis and/or lower extremity can be compounded by pregnancy. Patients may also have abnormalities in their fibrinolytic system [2, 3]. Inherited thrombophilic conditions have been reported in KTS patients and may contribute to their thrombotic tendency [4]. In addition, large hemangiomas and varicosities can trap large amounts of blood and destroy platelets; activating the coagulation cascade which results in localized intravascular coagulopathy [5, 6]. Disseminated intravascular coagulopathy resulting in major episodes of bleeding has also been reported in KTS patients [7].

Here we report a case of a patient with KTS who achieved a pregnancy through in vitro fertilization (IVF) using her own eggs and a gestational carrier in the setting of hypercoagulability and chronic consumptive coagulopathy.

Case report

A 29 year old G0 with a known history of KTS presented to the Yale Fertility Center with the desire for pregnancy and for pre-conceptual counseling. Her KTS lesion consisted of an extensive blue birthmark on her right leg and vulva and a large vascular abnormality

involving her right leg and pelvis. Subsequently, her right leg was severely underdeveloped in length. She also had extensive swelling on the right vulva.

An MRI/MRA showed innumerable, abnormal, late filling, dilated venous structures in the subcutaneous and deep tissues of the lower extremity and flank causing abnormal venous drainage. Two large abnormal varices, measuring 3.8×2.3 and 6×4×3 cm, were noted. There was a question of parametrial involvement on the right side of the uterus.

Her past medical history was notable for a chronic consumptive coagulopathy (due to KTS), in the absence of abnormal bleeding. Factor V Leiden heterozygosity and MTHFR homozygosity C677T and a normal homocysteine were detected by laboratory evaluation.

Pre-conceptual obstetric counseling and risk assessment revealed that due to her vascular malformation, the patient is at increased risk for worsening of her baseline consumptive coagulopathy, thrombosis and significant increases in the size of her vascular abnormalities during a pregnancy. After extensive discussion about the risks of carrying a pregnancy with this condition, and the potential need for an inferior vena cava (IVC) filter, the patient elected to use a gestational carrier.

Materials and methods

A long luteal phase protocol, using a gonadotropin releasing hormone (GnRH) agonist was used. After down-regulation, 150 units of FSH daily were used for ovarian stimulation. The patient was stimulated for 12 days and had an maximum serum estradiol level of 2,980 pg/ml. Ten oocytes were obtained after retrieval from the left ovary and 5 fertilized. On day 3 after retrieval, two 8-cell grade 1 embryos were transferred to a gestational carrier, and resulted in a singleton intrauterine pregnancy. Preimplantation genetic diagnosis (PGD) was not offered, as the specific gene that causes KTS has not yet been identified.

Anticoagulation using prophylactic doses of unfractionated heparin (UFH) heparin was initiated prior to and following the retrieval (Table 1). In the days prior to retrieval, anticoagulation was directed at inhibiting consumptive coagulopathy in the setting of extensive venous malformation, and ultimately decreasing risk of bleeding during retrieval; UFH was discontinued 12 h prior to the procedure. Anticoagulation prior to and following retrieval was also directed at decreasing the thromboembolic risk in the setting of elevated serum estradiol, Factor V heterozygousity, and venous malformation (Table 1).

Results

Successful management of consumptive coagulopathy perioperatively in a patient with KTS. A singleton intrauterine pregnancy was achieved in this case, and the gestational carrier delivered a healthy infant at term.

Discussion

KTS is a congenital disease characterized by extensive cutaneous vascular malformations, port-wine stains, and bony or soft tissue hypertrophy which confers increased morbidity during the hypercoagulable hematologic state during pregnancy. Morbidity and mortality is primarily related to the vascular abnormalities, which can result in decreased venous return, thrombophlebitis and thromboembolic disease [8].

Although the etiology of KTS is unknown, it is likely due to a mesodermal abnormality during early fetal development [9]. It has been established that increased angiogenesis is the mechanism leading to the development of the vascular lesions. A mutation in the gene encoding for an angiogenic factor (VG5Q) that causes increased transcription has been identified in some patients with the

Table 1 Management of consumptive coagulopathy and thrombophilia prior to and following retrieval in a woman with a vascular malformation consistent with Klippel-Trenaunay Syndrome

Time	Hematologic Management
Prior to IVF Cycle	Avoid birth control pills due to thrombosis risk. Determine baseline coagulation laboratory values
Initiation of Medications	Start prophylactic unfractionated heparin (10,000U subcutaneous every 12 h with initiation of GnRH agonist OR gonadotropins
Prior to Retrieval	Stop heparin 12 h prior to retrieval
After Retrieval	Admit to hospital for overnight observation. Re-start prophylactic unfractionated heparin 10–12 h after retrieval (10,000U subcutaneous every 12 h) and once intrabdominal bleeding has been ruled out.
Long Term	Continue prophylactic unfractionated heparin for 1 month

syndrome [10]. Most often a unilateral lower limb is affected [11], and affects men and women equally.

Hematologic management of patients with KTS undergoing IVF is critical for patient safety during this 'elective' procedure. In addition to being hypercoagulable, patients with KTS may have coagulation defects that predispose to bleeding due to consumption of coagulation factors in the venous malformation. In such cases, anticoagulation with low molecular weight heparin should begin with the administration of gonadotropins and can even start earlier with GnRH agonist treatment. Both medications can increase the risk of clot formation. There are case reports of venous thromboembolism with the use of GnRH agonists [12, 13]. In addition, gonadotropins cause a sharp rise in estrogen levels, which also increases the risk of thromboembolism [14]. A stimulation protocol using a GnRH antagonist for pituitary suppression, or a Tamoxifen or Letrozol protocol could also be used to achieve lower serum estradiol levels, with decreased clotting risk [15, 16]. Antagonist protocols have been shown to be equivalent to agonist protocols in terms of reproductive success in women undergoing infertility treatment with IVF [15].

To our knowledge, data on the optimal timing and duration of anticoagulation that optimally adresses risks of bleeding and thrombosis in this clinical scenario is lacking. The protocol that is being reported in the current manuscript was to withold anticoagulation 12 h prior to retrieval and to resume 10–12 h after retrieval, aiming to balance risks of bleeding and thrombosis. It is noteworthy that resumption of anticoagulation should only begin once intra-abdominal bleeding has been ruled out. Overnight hospitalization after retrieval is suggested to closely observe the hemodynamic state of the patient. Prophylactic anticoagulation is recommended for 1 month after retrieval.

In this case, a patient with a vascular malformation resembling KTS with chronic consumptive coagulaopathy and hypercoagulability underwent IVF, which required strict hematologic management. A singleton intrauterine pregnancy was achieved in this case, and the gestational carrier delivered a healthy infant at term. Since IVF's inception more than 30 years ago, the field has significantly advanced, allowing successful reproductive outcomes in challenging patients.

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