

Klippel-Trenaunay Syndrome Prenatal Diagnosis: Two Case Reports and a Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCE 1 **HuiTing Fang**
C 2 **Yujie Li**
F 1 **Jin Zhang**
A 1 **Jun Xiao**

1 Department of Ultrasound, The People's Hospital of Kaizhou District,
Chongqing, PR China
2 Department of Urology, The People's Hospital of Kaizhou District,
Chongqing, PR China

Corresponding Author: Jun Xiao, No. 8, Ankang Road, Hanfeng Sub-district, Kaizhou District, Chongqing City, China
Phone: 86-19541110224, e-mail: kaizhoucsk@163.com
Financial support: None declared
Conflict of interest: None declared

Case series

Patients: Female, 24-year-old • Female, 29-year-old

Final Diagnosis: Klippel-Trenaunay syndrome

Symptoms: Abnormal hypertrophy of the limbs

Clinical Procedure: —

Specialty: Obstetrics and Gynecology • Radiology

Objective: Congenital defects / diseases

Background: Klippel-Trenaunay syndrome (KTS) is an exceedingly rare congenital disorder attributed to a sporadic mutation in the *PIK3CA* gene, which impairs normal blood and lymphatic vessel development. The syndrome is classically defined by a triad of congenital features: cutaneous port-wine stains, venous malformations, and progressive limb hypertrophy. Prenatal recognition of KTS is uncommon, and its sonographic features can overlap with other congenital vascular anomalies, making early diagnosis challenging.

Case Reports: This report reviews 2 cases of prenatally diagnosed KTS at our institution. In both fetuses, prenatal ultrasound demonstrated marked swelling and thickening of the soft tissues within the right thigh. Within these hypertrophic soft tissues, tortuous and dilated arterial and venous channels were visualized; some veins exhibited a honeycomb-like structural pattern. Color Doppler imaging revealed abundant intralesional blood flow signals. Following induced abortion, gross anatomical examination of both fetuses disclosed reddish skin discoloration over the right lower extremity. The diagnosis of KTS was established based on concordant prenatal ultrasound findings and post-abortion macroscopic anatomical evaluation.

Conclusions: The diagnostic cornerstone of prenatal KTS lies in the sonographic detection of disproportionate soft-tissue and bony overgrowth accompanied by characteristic vascular malformations. It is equally imperative to rigorously differentiate these ultrasound findings from those of other overgrowth syndromes and vascular anomalies, and to assess for potential severe complications that may affect perinatal prognosis. An accurate prenatal diagnosis, coupled with multidisciplinary perinatal management involving obstetricians, geneticists, and neonatal specialists, is essential for optimizing pregnancy counseling and improving overall clinical outcomes.

Keywords: Diagnosis • Hypertrophy • Klippel-Trenaunay-Weber Syndrome

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/953517>

 1853  —  2  16



Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher

Introduction

The classic triad of port-wine stains (98%), lymphatic or venous abnormalities (72%), and asymmetrical limb hypertrophy (67%), is the hallmark of Klippel-Trenaunay syndrome (KTS), a rare congenital condition. The lungs, large intestine, bladder, liver, and other parts of the body, particularly the limbs and trunk, may be affected [1]. KTS shows an equal male-to-female ratio. Clinical manifestations vary widely, ranging from mild symptoms to life-threatening bleeding and embolism. Involvement can be unilateral (85%), bilateral (12.5%), or cross-bilateral (2.5%) [2]. Additionally, 10% of patients have concurrent upper- and lower-limb involvement [2].

Recent studies have linked KTS to somatic *PIK3CA* mutations, which activate the PI3K/AKT pathway and promote cell overgrowth via mTORC2 dysregulation [3,4]. These mutations arise during embryonic angiogenesis, accounting for the vascular phenotypes observed. KTS is now classified within the *PIK3CA*-related overgrowth spectrum (PROS), a group of overgrowth syndromes with overlapping clinical features and diverse *PIK3CA* mutations. In the past, a thorough medical history and postnatal clinical examinations diagnosed the majority of cases [5]. The degree of vascularization, visceral involvement, lesion extent, hemangioma progression rate, and gestational age at diagnosis all affect the prognosis of KTS. To diagnose KTS, a thorough prenatal ultrasound scan and follow-up are essential. To provide the newborn with the proper medical care, the expectant mother may also choose to give birth in a hospital under specific conditions [6]. An essential technique for the intrauterine diagnosis of KTS is ultrasound examination [2]. This report describes 2 cases of prenatal ultrasound diagnosis of KTS.

Case Reports

Case 1

The patient was a 24-year-old Asian woman, G1P0, at 19+3 weeks of gestation, with an unremarkable past medical history. She reported no history of previous illness, exposure to radiation or harmful substances, or drug or food allergies. Hypothyroidism, autoimmune thyroiditis, and a possible threatening abortion were discovered in the early stages of pregnancy. Following this, progesterone and euthyrox was administered orally on a daily basis. Given the increased thrombotic risk associated with pregnancy, anticoagulant therapy was recommended to protect the fetus; however, the patient declined treatment. The nuchal translucency ultrasound examination (NT) at 11+4 weeks revealed no clear abnormalities. A 4-dimensional ultrasound examination at 19+3 weeks of pregnancy showed no discernible thickening of the skin layer, but the

fetus's right lower limb's soft tissue was enlarged. The calf was greater in circumference than the thigh. The enlarged soft tissue of the lower leg contained many cystic echoes of varying sizes. In the lower leg, the arteries and veins appeared tortuous, and the veins were markedly thickened. No arteriovenous fistula was identified. It was possible to discern some lower extremity veins feeding into the wider azygos vein. The inferior vena cava was likewise enlarged. The bilateral thighs and the femurs within them could be seen, as well as the bilateral lower legs and the tibia and fibula within them. The feet could also be seen, and there were no abnormalities in the lengths, thicknesses, or other features of the femurs, tibias, and fibulas. The differential diagnosis included Parkes-Weber syndrome (PWS) and congenital lipomatous overgrowth, vascular anomalies, epidermal nevi, and skeletal deformities (CLOVES) syndrome. PWS was excluded by the absence of high-flow arterio-venous fistula, as our case showed low-flow venous malformations. CLOVES syndrome was ruled out due to the lack of adipose overgrowth, spinal abnormalities, and high-flow vascular lesions. Ultrasound suggested abnormal swelling of the right lower limb of the fetus, suggesting KTS (**Figure 1**). The expectant woman made the decision to have an induced abortion after consulting with a prenatal diagnostician. A baby girl weighing 405 g was delivered. Her skin was wine red and her right lower limb was noticeably swollen. The autopsy and genetic tests were declined by the expectant mother and her relatives. However, based on the results of prenatal ultrasound examination and postnatal gross anatomy, the 3 classic features of KTS—port-wine stains, venous malformations, and limb hypertrophy—were present. Therefore, the diagnosis of KTS was established. Regular follow-up was then carried out. The pregnant woman is now pregnant again, almost a year after the induced abortion. As of right now, there are no anomalies in the fetus's NT examination, early pregnancy stage, or 4-dimensional ultrasound examination.

Case 2

The patient was a 29-year-old Asian woman, G2P1, at 24+5 weeks of gestation, with an unremarkable past medical and family history. During the early stages of pregnancy and NT examination, no clear abnormalities were discovered. At 24+5 weeks of pregnancy, a 4-dimensional ultrasound examination was conducted. There was no discernible thickening of the skin layer, but the soft tissue on the right thigh was swollen and thickened. The thickened soft tissue contained tortuous, dilated arteries and veins, some of which exhibited a honeycomb-like appearance. However, no definite arteriovenous connection was identified. Venous drainage from the lower extremity was observed to ascend and drain into a dilated great saphenous vein, and the inferior vena cava was also noted to be enlarged. The abdominal cavity's right iliac arteries were enlarged and had a convoluted path. Additionally, the

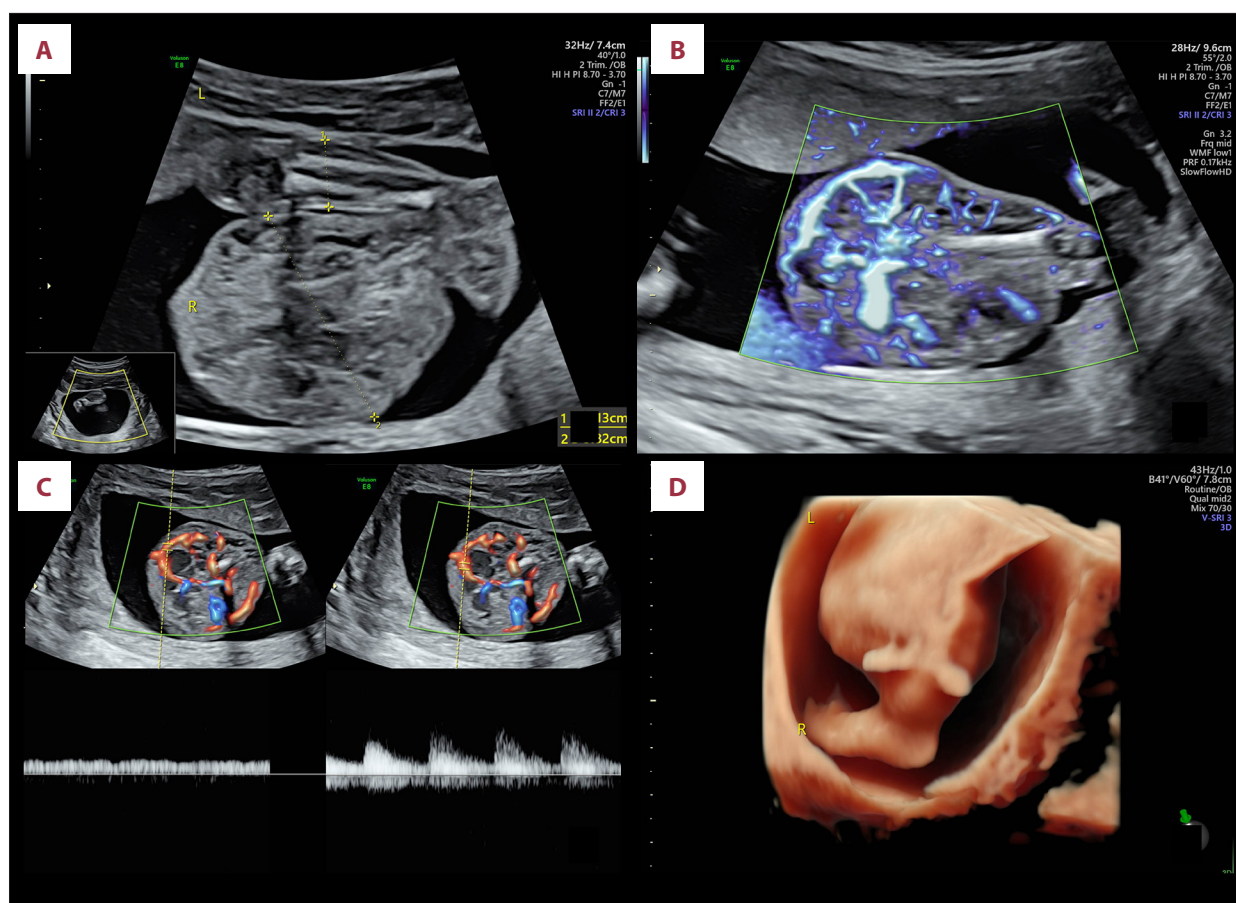


Figure 1. Case 1: (A) Multiple cystic echoes of different sizes are visible inside the fetus's right lower limb, which has enlarged and swelled soft tissue, with the thickest portion measuring around 38 mm. (B) Color Doppler flow imaging: The soft tissue of the fetus's right calf exhibits thickened and twisted arteriovenous veins, together with abundant blood flow signals. (C) Pulsed-wave Doppler: Arterial and venous flow signals were observed within the soft tissues of the fetal right lower limb; however, no arteriovenous fistula was identified. (D) Four-dimensional imaging: The fetus's right lower limb's soft tissue is noticeably enlarged and thickened.

size of the heart relative to the chest cavity was elevated to roughly 0.48. Abnormal sound images of the right lower limb of the fetus do not rule out the possibility of KTS in the fetus (Figure 2). The differential diagnosis included PWS and vascular pigmented nevus hamartoma syndrome. PWS was excluded by the absence of arteriovenous fistulas and cardiac complications. Vascular pigmented nevus hamartoma syndrome was ruled out because our case lacked cutaneous pigmentation and showed significant limb overgrowth, which is atypical for this entity. The expectant woman made the decision to have an induced abortion after seeking advice at the prenatal diagnosis clinic. A baby boy weighing 765 g was born. The right lower limb was noticeably larger and the baby had dark red flesh. The autopsy and genetic testing were rejected by the family members. Based on the results of prenatal ultrasound examination and postnatal gross anatomy, the patient exhibited the 3 classic clinical features of KTS, namely port-wine stains, venous malformations, and limb hypertrophy.

Therefore, the diagnosis of KTS was confirmed. After the abortion, a postnatal pelvic ultrasound examination was performed, and no gross abnormal echoes were detected.

Discussion

In 1900, KTS was described by Klippel and Trenaunay as a vascular malformation (red spots, varicose veins) affecting the soft tissues and bones of one or more limbs because of excessive proliferation. Case 1 and case 2 both meet the definition of this triad of symptoms. However, compared with previous literature cases, these 2 cases were limited to the right lower limb and did not have any other serious complications. Only case 2 had an increased chest-to-abdomen ratio. Due to the rarity of the pathological features of KTS and its overlap with other genetic syndromes, prenatal diagnosis of KTS should be differentiated from the following 4 diseases. First, PWS is the

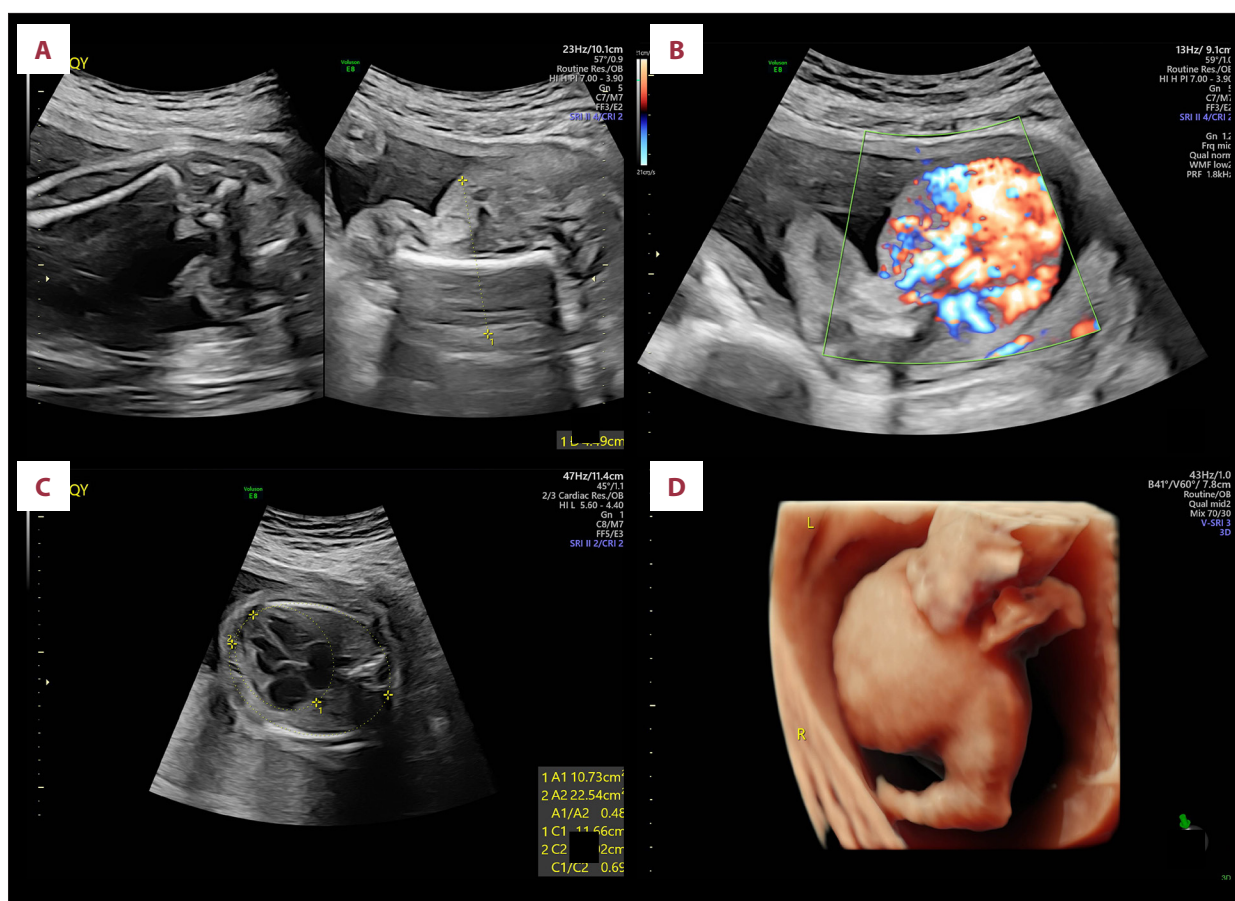


Figure 2. Case 2 (A) The fetus's right thigh's soft tissue is enlarged and thickened. (B) Color Doppler flow imaging: The thickened soft tissue of the fetal right thigh contained tortuous, thickened arteries and veins with prominent internal blood flow signals, some showing a honeycomb-like configuration. (C) It is evident the size of the heart relative to the chest cavity was elevated, reaching a value of roughly 0.48. (D) Four-dimensional imaging: The fetus's right lower limb's soft tissue is noticeably enlarged and thickened.

most similar disease to KTS, as both present the triad of capillary malformations, varicose veins, and limb overgrowth [7,8]. The key difference lies in their hemodynamic nature: KTS is a low-flow venous/lymphatic malformation, whereas PWS is characterized by high-flow arteriovenous fistulas, with arterial phase veins appearing earlier on imaging [7]. PWS is caused by *RASA1* gene mutations, and its risk of heart failure, bleeding, and thromboembolic events is significantly higher than that of KTS [7,9]. The name "Klippel-Trenaunay-Weber syndrome" has been historically abandoned to avoid confusion with PWS [8]. Second, CLOVES syndrome mainly affects the trunk and is accompanied by excessive fat tissue growth, tethered spinal cord, scoliosis, and kidney abnormalities (such as Wilms tumor), whereas KTS usually does not present these manifestations [10]. Both belong to the *PIK3CA*-related overgrowth spectrum (PROS) [9]. Third, Proteus syndrome is characterized by progressive overgrowth that worsens with skeletal deformities, and it often accompanies lung diseases, whereas the limb hypertrophy in KTS is mainly soft-tissue and bone hypertrophy

and progresses relatively slowly [8,10]. Fourth, Sturge-Weber syndrome is characterized by vascular malformations that are almost all located in the brain, and patients often have cognitive developmental delays and ocular abnormalities, whereas KTS usually does not present these manifestations [10].

The perinatal manifestations of KTS are diverse, ranging from asymptomatic port-wine stains to life-threatening complications. Prenatal ultrasound is the primary diagnostic method, and most cases are detected in the second trimester to late pregnancy (after 18 weeks), with the earliest prenatal description reported at 14 weeks [5]. In terms of perinatal complications, fetal edema and polyhydramnios indicate the need for close ultrasound follow-up. Severe complications such as Kasabach-Merritt phenomenon (a thrombocytopenic coagulation disorder) can lead to high-output heart failure and fetal edema, resulting in a poor prognosis for the fetus [11]. Due to the rarity of KTS (with an incidence of approximately 1 in 27 500 to 1 in 100 000) [11,12], there are limited large-scale

data on long-term survival rates. Current evidence indicates that the accuracy of prenatal diagnosis has a significant impact on the outcome. A study found that children with an accurate prenatal diagnosis had no perinatal deaths, whereas the neonatal mortality and morbidity rates of misdiagnosed cases were significantly higher [13].

In terms of treatment response, the surviving children can undergo interventional therapy and achieve good results. In the study by Singh et al, the live-born children in that group received multiple courses of image-guided sclerotherapy, and the lesions shrank significantly. The appearance and mobility of the limbs were close to normal. However, if severe complications occur during the fetal stage (such as fetal edema or heart failure), the prognosis is very poor [11]. In addition, perinatal management requires attention to the choice of delivery method. Pregnant women with KTS have significant risks of thrombosis and bleeding. The delivery method should be individually decided after a comprehensive assessment by a multidisciplinary team including obstetrics, vascular surgery, anesthesiology, and hematology [12,14]. Currently, there are fewer than 50 reported cases in the literature on prenatal diagnosis of KTS. Based on the existing evidence, KTS itself is not an absolute indication for pregnancy termination, and an individualized assessment based on the severity of prenatal manifestations is required. However, Hergesell et al [15] pointed out that if prenatal ultrasound shows changes consistent with KTS, termination of pregnancy may be discussed, given that the risk of fatal complications after delivery is high. This viewpoint emphasizes the value of prenatal ultrasound

in assisting reproductive decisions. Prenatal ultrasound-guided diagnosis and genetic counseling can assist in making informed decisions and optimize perinatal care planning [16].

Conclusions

The core of prenatal diagnosis of KTS lies in identifying abnormal growth of soft tissues and bones and vascular malformations through ultrasound, and strictly differentiating these findings from other diseases. It also involves determining the presence of severe complications. Precise prenatal diagnosis and multidisciplinary perinatal management are crucial for improving outcomes.

Department and Institution Where Work Was Done

Department of Ultrasound, The People's Hospital of Kaizhou District, Chongqing, PR China.

Patient Permission/Consent Declarations

Written informed consent for publication of the case details and accompanying images was obtained from each patient.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

- Asghar F, Aqeel R, Farooque U, et al. Presentation and management of Klippel-Trenaunay syndrome: A review of available data. *Cureus*. 2020;12:e8023
- Ivanitskaya O, Andreeva E, Odegova N. Prenatal diagnosis of Klippel-Trenaunay syndrome: Series of four cases and review of the literature. *Ultrasound*. 2020;28:91-102
- Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). *Exp Dermatol*. 2016;25(1):17-19
- Martinez-Lopez A, Salvador-Rodriguez L, Montero-Vilchez T, et al. Vascular malformations syndromes: An update. *Curr Opin Pediatr*. 2019;31(6):747-53
- Wang SK, Drucker NA, Gupta AK, et al. Diagnosis and management of the venous malformations of Klippel-Trenaunay syndrome. *J Vasc Surg Venous Lymphat Disord*. 2017;5:587-95
- Sreekar H, Dawre S, Petkar KS, et al. Diverse manifestations and management options in Klippel-Trenaunay syndrome: A single centre 10-year experience. *J Plast Surg Hand Surg*. 2013;47:303-7
- Nirwal H, Singh P, Singh SP, Parihar A. Imaging Klippel-Trenaunay and Parkes Weber syndromes: A unilateral limb overgrowth case series. *S Afr J Rad*. 2025;29(1):a3246
- Naganathan S, Tadi P. Klippel-Trenaunay-Weber Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [updated 2023 Aug 8; cited 2026 Aug 30]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK558989/>
- Ishikawa K, Yamamoto Y, Funayama E, et al. Wound-healing problems associated with combined vascular malformations in Klippel-Trenaunay syndrome. *Adv Wound Care (New Rochelle)*. 2019;8(6):246-55
- Maag BC, Towbin RB, Schaefer CM, Towbin AJ. Klippel-Trenaunay syndrome. *Appl Radiol*. 2024;(5):10-13
- Singh N, Mandelia A, Nigam N, et al. Fetal Klippel-Trenaunay-Weber syndrome: Antenatal diagnosis and postnatal management. *J Indian Assoc Pediatr Surg*. 2023;28(5):387-91
- Silva Correia IF, Hussain M, Johnson JA. Obstetric management for pregnant women with Klippel-Trenaunay syndrome: A UK case report and review of the literature. *Int J Gynaecol Obstet*. 2025;168(2):484-86
- Hatjis CG, Philip AG, Anderson GG, Mann LI. The in utero ultrasonographic appearance of Klippel-Trenaunay-Weber syndrome. *Am J Obstet Gynecol*. 1981;139(8):972-74
- Meenakshi Menon R, Tirkey RS, Stephen E, et al. The management of pregnancy for a woman with bilateral Klippel-Trenaunay syndrome: A case report. *Case Rep Womens Health*. 2026;49:e00795
- Hergesell K, Kroger K, Petruschkat S, et al. Klippel-Trenaunay syndrome and pregnancy. *Int Angiol*. 2003;22(2):194-98
- Orlandi G, Sarno L, Angelino A, et al. Klippel-Trenaunay-Weber syndrome: Prenatal diagnosis and review of the literature. *J Clin Ultrasound*. 2025;53(3):535-46