# Venous thromboembolic and bleeding complications among pregnant women with Klippel-Trenaunay syndrome

Elizabeth K. Marvin, MD,[a] Jennifer J. Schoch, MD,[b] Henry Nguyen, MD,[a] Katelyn R. Anderson, MD,[a] David J. Driscoll, MD,[c,d] Carl H. Rose, MD,[e] Emily C. Bendel, MD,[f] and Megha M. Tollefson, MD[a,c]
*Rochester, Minnesota, and Gainesville, Florida*

***Background:*** Klippel-Trenaunay syndrome (KTS) is a vascular malformation overgrowth syndrome characterized by capillary malformation, venous malformation, and limb overgrowth, with or without lymphatic malformation. Patients are at an increased risk of hemorrhage and venous thromboembolism (VTE). Consequently, women with this condition often are counseled to avoid pregnancy, but minimal data are available on the relationship between pregnancy, VTE, and bleeding risk.

***Objective:*** To review the risk of VTE and bleeding in pregnant and nulligravid women with KTS.

***Methods:*** A retrospective medical record review was performed of women with KTS, aged ≥18 years, evaluated at Mayo Clinic Rochester, Minnesota, from August 1945 to April 2018.

***Results:*** We identified 75 women with ≥1 pregnancy and 64 nulligravid women. VTE prevalence was 14 of 70 (20%) for women with a history of pregnancy and 16 of 64 (25%) for nulligravid women ($P$ = .93). Among the 70 women with a history of pregnancy, 7 of 18 VTE events (39%) occurred in association with pregnancy, with VTE affecting 7 of 151 pregnancies (4.6%). Significant bleeding prevalence was 6 of 70 (8.6%) for women with a history of pregnancy and 6 of 64 (9.4%) for nulligravid women ($P$ = .54).

***Limitations:*** This was a retrospective review.

***Conclusion:*** The prevalence of VTE and bleeding was similar in patients with KTS, irrespective of pregnancy status. (J Am Acad Dermatol 2019;81:1277-82.)

***Key words:*** bleeding; deep vein thrombosis; hemorrhage; Klippel-Trenaunay syndrome; pregnancy; pulmonary embolism; venous thromboembolic.

Klippel-Trenaunay syndrome (KTS) is a rare, congenital, vascular malformation overgrowth syndrome characterized by capillary malformation, venous malformation, and limb overgrowth, with or without lymphatic malformation.[1] The vascular malformations can involve internal organs in addition to the skin.[2,3] KTS has recently been associated with activating mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene.[4] Disorders with the *PIK3CA* mutation have been previously associated with coagulopathy.[5]

Complications of KTS include venous thromboembolism (VTE) in addition to bleeding, stasis dermatitis, and cutaneous ulceration. Historically, clinicians have often considered KTS a relative contraindication to pregnancy out of concern for a theoretical increased risk of hemorrhage or VTE secondary to physiologic changes such as increased cardiac output, leg edema, and elevated venous pressure.[6-8]

From the Department of Dermatology, Mayo Clinic, Rochester[a]; Department of Dermatology, University of Florida, Gainesville[b]; Department of Pediatric and Adolescent Medicine,[c] Division of Pediatric Cardiology,[d] Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology,[e] and Department of Vascular and Interventional Radiology, Mayo Clinic, Rochester.[f]
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Reprint requests: Megha M. Tollefson, MD, 200 1st St SW, Rochester, MN 55902. E-mail: tollefson.megha@mayo.edu.
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Few investigators, however, have examined the magnitude of the effect of pregnancy on the risk of VTE and bleeding in women with KTS, and until recently, data were mostly anecdotal or derived from small case series. In April 2017, a cross-sectional study was published using surveys to assess the complications of pregnancy in 43 women with KTS, concluding that pregnant women with KTS are at increased risk of severe complications, including deep vein thrombosis, pulmonary embolism (PE), and postpartum hemorrhage (PPH), compared with pregnant women in the general population.[7]

Given the limited data on KTS and pregnancy, clinicians who care for women with KTS cannot appropriately estimate relative obstetric risks and outcomes. This study aimed to increase our understanding of the risks associated with KTS and pregnancy by examining the prevalence of complications in pregnant women and nulligravid women with KTS.

**CAPSULE SUMMARY**

- Klippel-Trenaunay syndrome imparts an increased risk for venous thromboembolic and bleeding complications compared with the general population.
- Among women with Klippel-Trenaunay syndrome, the prevalence of venous thromboembolic or bleeding complications does not appear to be influenced by pregnancy.

## METHODS

### Study design

A retrospective medical record review was performed on a cohort of >400 patients with KTS evaluated at the Mayo Clinic in Rochester, Minnesota, from August 1945 to April 2018. KTS was defined by strict International Society for the Study of Vascular Anomalies criteria as a vascular malformation syndrome consisting of a capillary malformation, venous malformation, and limb overgrowth, with or without lymphatic malformation.[1] Clinical information was extracted from the medical records by 3 physicians, and clinical photographs were used when available to help establish the validity of the diagnosis. The Mayo Clinic Institutional Review Board reviewed and approved this study (approval #12-007022).

### Study participants

All women aged ≥18 years in the KTS cohort were identified. Exclusion criteria included age <18 years and men with KTS. Women ≥18 years were subsequently grouped by those with a history of pregnancy and those with no documented history of pregnancy. For each group, data were collected on medical history, treatments, complications, and outcomes.

### Data analysis

Categorical features are reported with frequency counts and percentages, and *t* tests were used to compare means between groups. For calculations involving the prevalence per pregnancy, only pregnancies resulting in delivery were included (ie, excluding pregnancies that ended prematurely owing to miscarriage <20 weeks' gestation). Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

The postpartum period was defined as within 6 weeks after delivery. VTE was defined as a deep vein thrombosis, PE, or both. When calculating the number of events per pregnancy, a deep vein thrombosis with concurrent PE was counted as 1 event (not 2). Significant bleeding was defined as requiring a blood transfusion, requiring an intervention, such as dilation and curettage or hysterectomy, or being documented as severe or excessive based on clinical judgment.

The extent of each vascular malformation was determined by the number of anatomic sites involved. The anatomic sites were categorized as head/neck, trunk, upper extremity, lower extremity, hand, foot, and buttocks/perineum/genitalia. Family history of VTE was not formally assessed.

## RESULTS

There were 267 potential patients with KTS identified by the Hospital International Classification of Diseases Adapted codes, and 634 potential patients with KTS were identified through clinical notes. From the initial 901 patients identified, patients were subsequently excluded if they did not have evidence in the medical record of KTS based on strict International Society for the Study of Vascular Anomalies criteria. This left 410 patients with KTS, and of these, 139 women aged ≥18 years were identified. Of the 75 women with a history of pregnancy, 5 were excluded from the analysis due to inadequate documentation. The remaining 70 women and 187 pregnancies were included for data analysis. All 64 nulligravid women were

*Abbreviations used:*

KTS: Klippel-Trenaunay syndrome
PE: pulmonary embolism
PPH: postpartum hemorrhage
VTE: venous thromboembolism

included in the analysis. Results are summarized in Tables I and II.

### Venous thromboembolism

In the women with a history of pregnancy, VTE was experienced by 7 women (10.0%) during pregnancy (n = 2) or in the postpartum period (n = 5) and in 7 of 151 (4.6%) total pregnancies. An additional 7 women (10.0%) with a history of pregnancy did not experience VTE during pregnancy or postpartum but had a VTE complication in their lifetime. Lifetime VTE prevalence for those with at least 1 pregnancy was 20.0% (14 of 70).

In the pregnancy group, 7 VTE events occurred during pregnancy or postpartum, and 11 VTE events occurred outside of pregnancy, so among the 70 women with a history of pregnancy, 7 of 18 VTE events (39%) occurred in association with pregnancy. Mean age of the first VTE in this group was 39.2 years (standard deviation, 13.6 years; range, 21-65 years). There were 29 documented cesarean sections and 1 documented VTE after cesarean section. VTE occurred in 16 of the 64 nulligravid women (25%). Mean age of the first VTE was 26.0 years (standard deviation, 9.9 years; range, 15-47 years). There was no statistically significant difference in prevalence of VTE between the 2 groups ($P$ = .93); however, the difference in mean age of the first VTE between the 2 groups was statistically significant ($P$ = .01). The mean number of vascular malformation sites involved was 1.73 (standard deviation, 0.64) in women with a history of VTE and 1.74 (standard deviation, 0.88) in women without a history of VTE ($P$ = .97).

### Bleeding

Significant bleeding occurred in 6 of 70 women (8.6%) with a history of pregnancy; in 4 of these women, this occurred during pregnancy or postpartum. Vascular malformation involved the uterus in 3 of the 70 women, 2 of whom were in the group of 4 who experienced significant bleeding during pregnancy or postpartum. When events per pregnancy were calculated, PPH complicated 2 of 151 pregnancies (1.3%). Two women (2.9%) only experienced significant bleeding outside of the pregnancy or postpartum period, and 1 woman experienced VTE and bleeding complications associated with pregnancy. Mean age of the first significant bleeding event was 27.8 years (standard deviation, 9.0 years; range, 5-59 years).

Significant bleeding occurred in 6 of the 64 women (9.4%) in the nulligravid group. One woman had a vascular malformation involving her uterus but had no documented bleeding complications. Two women experienced VTE and bleeding complications. The mean age of the first significant bleeding event was 15.3 years (standard deviation, 2.7 years; range, 5-24 years). The difference in prevalence of bleeding complications between the groups was not statistically significant ($P$ = .54). There was also no statistically significant difference in mean age of first bleeding event ($P$ = .24). The mean number of vascular malformation sites involved was 2.25 (standard deviation, 0.97) in women with a history of bleeding and 1.69 (standard deviation, 0.80) in women without a history of bleeding complications ($P$ = .03).

Regarding anticoagulant use, 3 women with no history of VTE before pregnancy were treated with prophylactic unfractionated or low-molecular-weight heparin during pregnancy and postpartum, and 1 additional woman, also without a history of VTE, was treated with low-dose aspirin throughout her pregnancies and low-molecular-weight heparin postpartum; none experienced VTE or bleeding complications during pregnancy or postpartum. No women in the nulligravid group were prescribed anticoagulant medications for reasons other than development of a VTE.

### Other complications

Twenty-one women (30%) reported worsening symptoms of pain, swelling, or increased varicosities during or after pregnancy. There were 36 pregnancies (19.3%) that ended in miscarriage. One woman who miscarried had a uterine vascular malformation. One patient underwent 5 medically recommended abortions in the first trimester owing to perceived risk of continuing a pregnancy with KTS. No patient deaths occurred secondary to VTE or bleeding complications in the women with a history of pregnancy. One death occurred in the nulligravid group secondary to VTE. This patient had an extensive case of KTS involving her thorax, abdomen, and extremities and died of a PE at age 21.

No statistically significant difference was found between the nulligravid women and women with a history of pregnancy regarding the extent of vascular malformations. A mean number of 1.63 sites (standard deviation, 0.76) were involved in women with a

**Table I.** VTE and bleeding complications in women with Klippel-Trenaunay syndrome

| Variable | Patients | | Risk factors (No.) |
|---|---|---|---|
| | No. | % | |
| History of pregnancy | 70 | | |
| VTE | | | |
| Pregnancy or postpartum | 7 | 10.0 | Morbid obesity (1) |
| | | | Postoperative (1) |
| | 3* | | Postoperative (1) |
| In lifetime, except pregnancy or postpartum | 7 | 10.0 | Factor XII deficiency and homozygous factor V Leiden (1) |
| | | | Heterozygous factor V Leiden (1) |
| | | | Postoperative (3) |
| Significant bleeding | | | |
| Pregnancy or postpartum | 4 | 5.7 | None |
| | 2† | | None |
| In lifetime, except pregnancy or postpartum | 2 | 2.9 | None |
| Nulligravid | 64 | | |
| VTE | 16 | 25.0 | Postoperative (3) |
| | | | Morbid obesity (1) |
| | | | OCPs and smoking (1) |
| | | | Heterozygous factor V Leiden (1) |
| Significant bleeding | 6 | 9.4 | None |

*OCPs*, Oral contraceptive pills; *VTE*, venous thromboembolism.
*Number of patients with additional VTE that was outside of pregnancy or postpartum
†Number of patients with additional significant bleeding event outside of pregnancy or postpartum.

**Table II.** Risk of lifetime VTE and lifetime bleeding compared with extent of vascular malformation

| History of pregnancy | Patients, No. (%) | Lifetime VTE, No. (%) | Lifetime bleeding, No. (%) |
|---|---|---|---|
| Pregnancy | | | |
| 1 location | 37 (52.9) | 7 (50) | 3 (50) |
| 2 locations | 23 (32.9) | 7 (50) | 1 (16.7) |
| 3 locations | 9 (12.9) | 0 | 1 (16.7) |
| 4 locations | 1 (1.4) | 0 | 1 (16.7) |
| 5 locations | 0 | … | … |
| Nulligravid | | | |
| 1 location | 26 (40.6) | 4 (25) | 0 |
| 2 locations | 24 (37.5) | 9 (56.3) | 3 (50) |
| 3 locations | 11 (17.2) | 3 (18.8) | 3 (50) |
| 4 locations | 2 (3.1) | 0 | 0 |
| 5 locations | 1 (1.6) | 0 | 0 |

*VTE*, Venous thromboembolism.

history of pregnancy versus 1.86 sites (standard deviation, 0.89) in nulligravid women ($P = .11$).

## DISCUSSION

In the general population, VTE occurs in approximately 1 in 1000 pregnancies.[9] Consistent with the general population, VTE complications were more common postpartum than during pregnancy.[10,11] Horbach et al[7] compared pregnant women with KTS to a general unaffected population-based cohort and found the relative risk of VTE in pregnancy was 106 to 109 ($P < .0001$). In our study, nulligravid women with KTS were used as a reference population, and although the prevalence of VTE was increased in both KTS and also increased in pregnancy, the increase in this cohort did not seem to be cumulative. Among the 70 women with a history of pregnancy, 7 of 18 events (39%) occurred in association with pregnancy, with VTE affecting 7 of 151 pregnancies (4.6%). Of note, in this cohort we did not make comparisons to the general population. Our findings suggest that there is no difference in the

frequency of VTE or bleeding events between women with ≥1 pregnancy and nulligravid women with KTS.

Although the difference did not reach statistical significance, the prevalence of VTE was slightly higher in the nulligravid women with KTS than in those who became pregnant. A possible explanation is that women who experienced a VTE early in life may have been discouraged from conceiving because of perceived recurrence risk, and our results confirmed a significant difference between the mean ages of the first VTE between the 2 groups. Moreover, compared with women with a history of pregnancy, there was a higher percentage of nulligravid women with vascular malformations involving ≥2 anatomic locations; thus, women may have been discouraged from conceiving because of the extent of their malformation, although no statistically significant difference was found. There was also no statistically significant difference found comparing women with and without a history of VTE and the extent of their vascular malformations.

Similar to VTE, pregnancy did not seem to affect the prevalence of bleeding complications. However, age at onset of significant bleeding could again be a contributing factor, because women with significant bleeding may be discouraged from conceiving. Although the difference between the mean ages of the first bleeding event was not statistically significant, all nulligravid women were aged <25 years when their first event occurred, and the mean age was younger compared with the previously pregnant group. Moreover, all of the nulligravid patients had significant bleeding involving the urogenital tract; thus, the anatomic location of bleeding may have influenced their decision to avoid conception. A significant association was also found between the number of vascular malformation anatomic sites involved in women with a history of bleeding versus women with no history of bleeding complications; thus, those with more extensive involvement were more likely to experience bleeding.

In the general population, PPH complicates 1% to 5% of all deliveries, which is similar to the finding in this study of 1.3%.[12] Theoretically, PPH is a major concern for women with KTS because vascular malformations may involve the uterus, because of the presence of coagulopathy, or because women may be on anticoagulation for VTE prophylaxis.[3,6] Horbach et al[7] found that PPH occurred in 9 of 40 women (22.5%), which compared to their reference population, represented a relative risk of 1.81 and was not statistically significant. That the PPH rate in our population was not higher than in the general population is reassuring.

Although bleeding and VTE risk are the most pressing concerns, this cohort of women also experienced other symptoms and complications. Exacerbation of existing symptoms is a common counseling point in women with KTS who become pregnant and has been previously described.[7,13,14] Spontaneous abortion occurred at a rate similar to the general population (15%-20%).[15] In addition to the common genetic etiologies, miscarriages in this population may be secondary to vascular malformations involving the uterus, affecting implantation, or to thrombotic events within the placenta.[16] Vascular malformations involving the uterus have also been suggested to result in fetal growth restriction, but fetal risks are still largely unknown.[17]

This study offers insight into the prevalence of VTE and bleeding complications in pregnant women with KTS. A strength of this study was the ability to include nulligravid women with KTS as a comparative cohort. The primary limitation is the historical retrospective cohort design. By comparing pregnant women to nulligravid women with KTS, we were able to demonstrate that the prevalence of VTE or bleeding complications is not increased in women with a history of pregnancy.

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