Nine Successful Pregnancy Outcomes in a Woman With Vascular Ehlers-Danlos Syndrome: A Case Report and Literature Review

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ABSTRACT

Introduction: The vascular form of Ehlers-Danlos syndromes occurs due to alterations in the *COL3A1* gene. It has been associated with major vascular and hollow organ complications, leading to increased morbidity and mortality rates with pregnancy.

Case Presentation: We report a woman (gravida 9, para 9) diagnosed with vascular Ehlers-Danlos syndrome in her 70s after bowel rupture. Genetic testing revealed a null mutation in *COL3A1* that is predicted to result in haploinsufficiency. Preceding diagnosis, she had 9 pregnancies with minimal complications.

Discussion: While no evidence-based guidelines for obstetric care in vascular Ehlers-Danlos syndrome have been well-established, patients often are counseled and followed as high-risk pregnancies.

Conclusions: Null mutations resulting in haploinsufficiency likely have lower pregnancy risks than reported in the literature for vascular Ehlers-Danlos syndrome overall. Thus, understanding the specific *COL3A1* mutation may help optimize counseling regarding pregnancy and facilitate decision-making regarding management.

INTRODUCTION

Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders affecting the skin, joints, blood vessels, and hollow organs.[1] Mutations in genes that encode for fibrillar collagen or collagen-processing enzymes are associated with EDS. Although this family of conditions share certain features, they are distinguished by the protein affected, mode of inheritance, and the frequency in the population (Table).[2,3] Vascular Ehlers-Danlos syndrome (vEDS) is considered the most life-threatening type. Inherited in an autosomal-dominant manner, major complications include arterial dissection or rupture and spontaneous bowel perforation that can lead to sudden death.[4] Individuals with vEDS have a reported median lifespan of 51 years, with the first major complication typically appearing in the third decade of life.[5] Its clinical features include easy bruising, thin-translucent skin, early-onset varicose veins, and facial features, including thin vermillion of the lip, deep-set eyes, decreased subcutaneous tissue, and attached ear lobes.[3,6]

Women with vEDS are at an additional risk of significant morbidity and early mortality due to pregnancy-related complications, including uterine rupture, hemorrhage, premature rupture of membranes, tears, lacerations, and wound dehiscence after cesarean delivery.[7] Vessel rupture is the leading cause of maternal mortality in the prenatal and perinatal period.[8] Murray et al[7] found the per delivery mortality rate of women with vEDS to be nearly 300 times the pregnancy-related death rate in the general US population.

Pathogenic mutations in the *COL3A1* gene cause vEDS;[2] however, the survival rate depends on the type of mutation.[5] The most commonly reported mutations are missense mutations, followed by splice site mutations and in-frame insertions and deletions.[9] These mutations result in a dominant negative effect due to the production of misfolded type III collagen.[2] Null mutations are rarer, occurring in about 5% of all vEDS cases.[3] These mutations result in little, if any, functional protein product from the affected allele, resulting in an overall reduction of type III collagen. Thus, null mutations do not induce a dominant negative

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Table. Common Types of Ehlers-Danlos Syndrome [a]

Type (Abbreviation)	Clinical Features	Mode of Inheritance	Protein Affected	Genetic Mutation	Incidence
Classic (cEDS)	Skin hyperextensibility, tissue fragility, generalized joint hypermobility, easy bruising, atrophic scarring.	Autosomal dominant	Type V collagen, type I collagen	*COL5A1* *COL5A2*	1 in 20,000
Vascular (vEDS)	Arterial rupture in youth, bowel perforation, uterine rupture, thin translucent skin, Prominent eyes, thin face, nose, lobeless ears, joint hypermobility only in minor joints	Autosomal dominant	Type III collagen, type I collagen	*COL3A1*	1:50,000 to 100,000
Hypermobile (hEDS)	Generalized joint hypermobility., skin hyperextensibility, unexplained striae, recurrent or multiple abdominal hernias, mild atrophic scarring.	Autosomal dominant	Unknown	Unknown	1:5,000 to 1:20,000

[a] Adapted from Malfait et al[10] and Joseph et al.[11]

effect, but rather result in haploinsufficiency due to the reduction of the amount of normal collagen produced. Consequentially, individuals with null mutations often have a less severe clinical course and are clinically differentiated from those with other types of mutations by, on average, a 10- to 15-year delay in onset of complications, as well as better vascular prognosis. Some individuals are noted to have few clinical manifestations—even into the ninth decade of life. In a cohort of 1231 cases, patients with null mutations were compared to those with splice site and missense mutations, and although the median survival age for vEDS was 51 years, those with null mutations had the longest survival of all individuals.[5]

Few cases in the literature describe patients with vEDS who have had multiple successful pregnancies or have been diagnosed with the condition in their senior years. Rarer still are cases where patients experience both. Due to its severity, vEDS is typically diagnosed based on clinical findings and earlier in life; however, our case describes a patient who had 9 successful deliveries and was only diagnosed in her 70s after a bowel rupture. This variation in presentation from the norm in our patient is due to differences in the genotype-phenotype correlation in *COL3A1* gene mutations. Her presentation would historically be considered atypical for vEDS, attributing to her long diagnostic odyssey. This attenuated phenotype of vEDS in regard to her obstetrical outcomes and longevity can be explained by the presence of the null mutation. Through genetic testing, clinicians are able to provide an individualized clinical picture based on the specific type of mutation, allowing for greater insight into obstetrical options, medical management, and natural history of the condition for the patient and their family.

CASE PRESENTATION

The patient is a 72-year-old, gravida 9, para 9, White woman. At the age of 70, she had an emergency colostomy due to bowel perforation. During the procedure, the surgeon noted extreme tissue friability and referred her to genetics due to clinical suspicion of a connective tissue disorder. The woman demonstrated physical features of vEDS, including thin vermillion of the lips, lobeless ears, thin bridge of nose, deep-set prominent eyes, and translucent skin (Figure 1). In addition, large, tortuous varicose veins on her hands, knees, and lower legs were noted (Figure 2). She reported a history of easy bleeding, bruising, and fragile skin as early as 10 years of age. She reported a history of significant menorrhagia; joint pain involving her knees and hips; joint hypermobility including her hands, knees, and elbows; hypotension; and early onset varicosities beginning at age 19. She had 2 surgeries (vein embolization and hip arthroplasty), both of which occurred in her 60s without complications. There was no prior history of internal complications and no suspicion of her having a connective tissue disorder prior to her acute bowel perforation. While she did not have complications from her colostomy procedure, it was noted that her wound took much longer than expected to heal. Due to tissue fragility, future reanastomosis was not considered an option.

While retrospective review of her medical history was highly suggestive of vEDS, her pregnancy history was not. Notably, she had 9 vaginal deliveries between the ages of 20 and 45, with only 2 reported complications. Her first pregnancy resulted in preterm premature rupture of membranes (PPROM) at 33 weeks gestation, and her seventh pregnancy resulted in significant postpartum anemia requiring a blood transfusion. All other pregnancies were delivered at term with no complications, prolonged hospital stay, or significant vaginal tearing. With each pregnancy, she reported that varicosities enlarged and returned to baseline after delivery.

A review of the family history revealed that while no one else had previously been suspected to have a connective tissue disorder, her maternal relatives had features of vEDS. Her mother reportedly had prominent, early-onset varicose veins, easy bleeding, and bruising. She had 2 uncomplicated pregnancies with vaginal deliveries. She had a reported myocardial infraction in her 50s but passed away in her 90s. Our patient's eldest son died in a motor vehicle accident at age 52 and had a history of poor wound healing and frequent injuries. Of note, our patient did experience PPROM when she was pregnant with him. His son was reported to have facial features similar to our patient, as well as reported easy bleeding and bruising.

Because the medical and family history was strongly suggestive of vEDS, sequencing and deletion/duplication analysis of *COL3A1* was completed, revealing a pathogenic mutation (c.4011+1G>T) that affects a donor splice site in codon 49 of *COL3A1*. This mutation is predicted to disrupt RNA splicing, likely resulting in haploinsufficiency due to the lack of production of a viable protein product. While this mutation has not been reported in the literature, a similar mutation (c.4011+1G>A) affecting the same nucleotide has been described as pathogenic.[8]

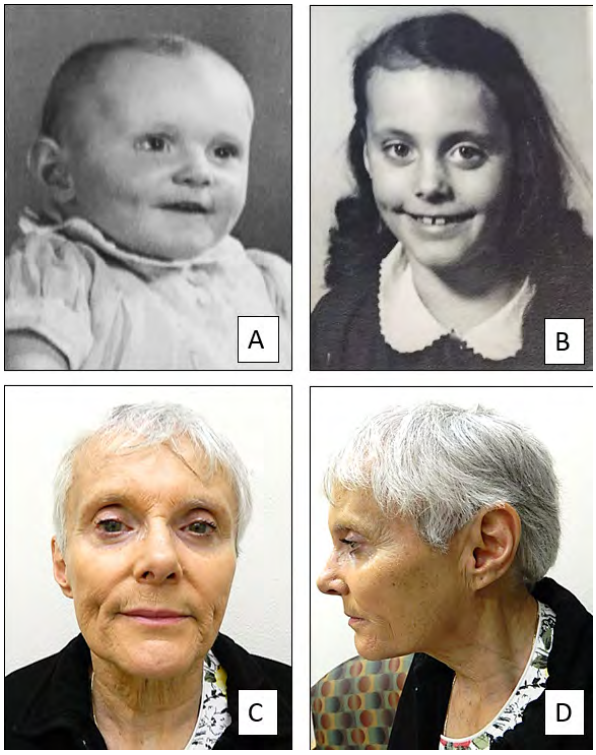
DISCUSSION

There is substantial discussion in the medical literature regarding optimal pregnancy management strategies in vEDS. Our literature review of pregnancy-related risks and complications in vEDS found earlier studies, such as those by Lurie et al,[8] quote maternal mortality rates to be as high as 20% for pregnant women with vEDS. These studies resulted in recommendations for a very conservative approach to pregnancy for vEDS patients, establishing the widely held belief among many health professionals that pregnancy should not be considered in vEDS due to the high morbidity and mortality rates. In a survey of 775 women with EDS in 2014, 62.5% of women with vEDS responded that "they were told by a health care provider to not conceive due to EDS."[12]

However, there have been studies as early as 1996 (Table 1) that found no cases of maternal death in their cohort of 12 women with 22 total pregnancies.[13] Various analyses and case reports have since been published in the literature that continue to debate the level of risk of pregnancy in vEDS. One study reported finding a 0% maternal death rate in their cohort of 13 women with 23 total deliveries and few severe complications.[14] Various other published case series and reports have reported few pregnancy complications for women with vEDS,[15] including a family with a protein-altering mutation in which there were 6 uneventful pregnancy outcomes.[1] Many of these studies do not account for age or type of mutation when discussing pregnancy outcomes in vEDS.

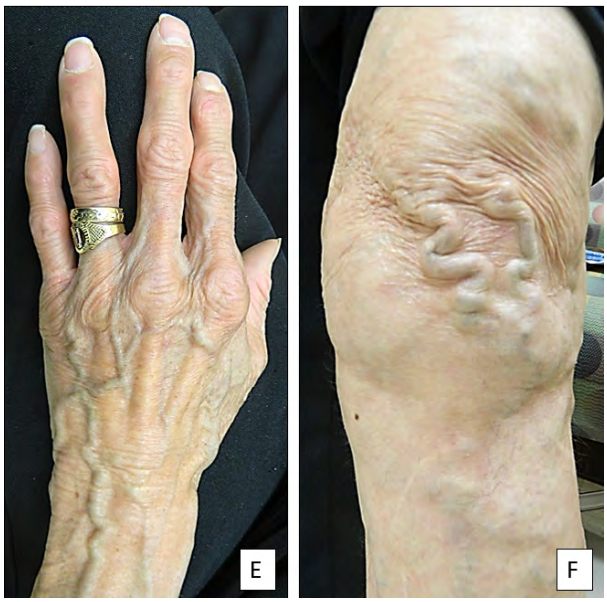
Although the overall risk for pregnancy-related mortality and complications is increased in women with vEDS, the maternal mortality rate may be reduced for those specifically with a null mutation. In a review of a cohort of 526 women of reproductive age with vEDS, Murray et al[7] found that in 616 deliveries, there were 30 pregnancy-related deaths consistent with a maternal mortality rate of 5.3%. A majority of their cohort included women with missense mutations and splice site mutations, but there were no reported pregnancy-related deaths for the 21 women (and 51 deliveries) with null mutations. Additionally, they found no significant difference in the comparison of survival in parous and nulliparous women with vEDS. They also enrolled 38 women into an interview study that found that 46% of their deliveries were uncomplicated; 35 of these women (with 76 delivered pregnancies) had protein-altering mutations. Among women with

Figure 1. Features of Vascular Ehlers-Danlos Syndrome Throughout the Patient's Life



The thin vermillion of the lips and bridge of the nose can be noted as can the deep-set eyes and lobe-ess ears.

Figure 2. Varicose Veins



Tortuous varicose veins are also a sign of vascular Ehlers-Danlos syndrome; seen on the patient's hands and knees.

predicted dominant negative mutations, there were 5 maternal deaths reported, 4 due to arterial dissection or rupture and 1 due to cesarean delivery wound dehiscence. The 3 women with null mutations were not included in further analysis due to the attenuated phenotype; however, it was noted that 2 had third- or fourth-degree lacerations, and 1 had a preterm delivery. They found that for women who did not have a vEDS-related complication prior to pregnancy, pregnancy itself did not add further risk.[7]

Currently there are no established, evidence-based guidelines for treatment and management of pregnancy for women with vEDS.[7] For patients electing to continue their pregnancies, elective cesarean delivery between 32 and 36 weeks gestation has been recommended to minimize hemodynamic risks that can lead to aortic rupture or dissection during labor and delivery; there remains limited evidence for outcomes for cesarean or vaginal deliveries.[7] Cesarean delivery carries with it a risk of wound dehiscence, which is a factor associated with the maternal mortality rate in vEDS. These enduring discrepancies in the literature, as well as contrasting recommendations for pregnancy care, require a more personalized approach to obstetric care for women with vEDS.

In our case, the patient suffered no major complications from vEDS until the seventh decade of life and had 9 successful pregnancies—all with vaginal deliveries—and only two minor complications. As far as we know, there are no reports of women with vEDS reported in the literature with as many successful pregnancies and as few complications. This case exemplifies the differences in pregnancy outcomes for women with vEDS due to genotype-phenotype variation—specifically null mutations—and, in turn, the value of genetic assessment for tailored care management during pregnancy. This woman's pregnancy and medical history is consistent with reports of better pregnancy outcomes for women with null mutations[5,7] and, as seen in other studies, is in contrast with prior reports of high pregnancy-related morbidity risks.[8] As further favorable reports regarding obstetric outcomes for women with vEDS are collected in the literature, the current trends of discouraging pregnancy, consideration of termination of pregnancy, or recommendation for early delivery via cesarean birth for women with a clinical diagnosis of vEDS will likely evolve. Instead of relying only on the clinical diagnosis of vEDS, using a person's medical, obstetric, and family history, together with the specific *COL3A1* mutation type, will help tailor care management and counseling surrounding pregnancy.

CONCLUSION

This case highlights the importance for a personalized approach to pregnancy management for women with vEDS and the value in confirming both the presence and the nature of the specific *COL3A1* mutation when evaluating risks and complications in pregnancy.

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