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Obstetric Management of Loeys-Dietz Syndrome

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Abstract

Background—Loeys-Dietz syndrome is associated with arterial tortuosity and aortic dissection. Pregnancy may be a period of increased risk for aortic dissection.

Case—A 16 year-old primigravida was referred to our center with a family history of aortic dissection. Loeys-Dietz syndrome was suspected and genetic testing confirmed the *TGFβ2* (c. 988C>T) mutation. A cesarean delivery was performed at 36 weeks gestation with no cardiovascular complications. In this case, the uterine vessels were significantly tortuous and this may be an additional finding in Loeys-Dietz syndrome.

Conclusion—Women with Loeys-Dietz syndrome warrant special consideration in obstetric management secondary to the risk for aortic dissection. A multi-disciplinary team with knowledge about connective tissue disorders and expertise in aortic surgery is recommended to coordinate maternal obstetrical and cardiovascular care.

Introduction

Loeys-Dietz syndrome is an autosomal dominant connective tissue disorder caused by mutations in *TGFβR1*, *TGFβR2*, *TGFβ2*, *TGFβ3* and *SMAD3* genes. The syndrome is characterized by vascular, skeletal, craniofacial and cutaneous features (Box 1).¹ However, the minimum clinical criteria for diagnosis of Loeys-Dietz syndrome has not been defined and there is a broad spectrum of features and severity.² Because some individuals have minimal characteristics, a family history of aortic dissection and genetic testing are additional diagnostic criteria.

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Limited data derived from Loeys-Dietz syndrome registries, case series and case reports indicate that the rate of aortic dissection in women with Loeys-Dietz syndrome is elevated during pregnancy, likely due to hemodynamic and hormonal changes, and may be as high as 1.5-6%.^{2,3} This rate is much higher than the rate in the general population (0.0004%) and comparable to the rate in women with Marfan syndrome.⁴ The European Society of Cardiology (ESC) and American College of Cardiology (ACC) acknowledge that pregnancy is a high risk time for women with aortic disease, with most dissections occurring in the third trimester (50%) or postpartum (33%).^{5,6} Because aortic dissection in pregnancy is associated with a high mortality rate, it is essential to identify these high-risk women preconception or early in pregnancy. In this specific case, we highlight the obstetric management of Loeys-Dietz syndrome.

Case

A 16-year-old primigravida was referred to our tertiary care center at 18 weeks gestation with a possible history of some form of Ehlers Danlos syndrome, based on arachnodactyly and hypermobile joints, as well as aortic root dilation and a small perimembranous ventricular septal defect (VSD). Her family history was significant for aortic dissections in two distant maternal relatives. On physical examination, she was petite (height 155 cm, pre-pregnancy weight 44 kg), and had minor dysmorphic features including dolicocephaly, arachnodactyly, malar hypoplasia, soft translucent skin and hypertelorism. By echocardiography her aortic root measured 3.6 cm (Z-score, which accounts for body size, of 4.1 standard deviations above the mean). Other findings included a small restrictive perimembranous VSD, mild pulmonary artery dilation (2.8 cm, Z-score 2.8), normal estimated right ventricular pressure (16 mm Hg plus right atrial pressure), no evidence of mitral valve prolapse and trivial mitral and tricuspid regurgitation. Based on these features, a family history of aortic dissection, and genetic testing of a maternal relative with aortic dissection revealing a pathogenic TGF β 2 mutation (c.988C>T), a diagnosis of Loeys-Dietz syndrome was suspected. The patient then had molecular testing which revealed that she was heterozygous for the known familial pathogenic variant. Of note, although her mother and maternal grandmother were obligate carriers of the same mutation, they had only mild aortic root dilation, and no history of aortic events.

A multi-disciplinary team including maternal fetal medicine, genetics, cardiology, cardiovascular surgery, anesthesia, neonatology, transfusion medicine, and nursing, met to plan the method and timing of delivery and to make contingency plans in the case of aortic dissection. A non-contrast magnetic resonance angiogram (MRA) was ordered from head to pelvis to evaluate for additional aneurysms however this could not be completed secondary to patient anxiety. In accordance with ACC and ESC guidelines, the size of her aortic root was followed with transthoracic echocardiography every 4-8 weeks, and remained unchanged.^{5,6} She was also treated with metoprolol for heart rate control. Fetal growth scans every 4 weeks confirmed normal fetal growth. She underwent a fetal echocardiogram secondary to the concern for congenital cardiac anomalies and no significant cardiovascular findings were seen.

The third trimester was complicated by complaints of sudden chest pain and dyspnea on several occasions. Each time she was in normal sinus rhythm with a stable aortic root size (3.6 cm). A CT angiogram identified tortuous vertebral vessels with a vertebral tortuosity index (VTI) of 19 (normal <10). Although these episodes were felt to be due to anxiety and panic attacks, because of the complex care required for this patient, inconsistent compliance and her living two hours from the tertiary care center, the decision was made to hospitalize the patient at 32 weeks until her planned delivery. She had a magnetic resonance imaging (MRI) of the spine for anesthesia preparation that showed dural ectasias at S-1-S-2 levels.

Because dissection has been reported with an aortic root of 3.5 cm in Loeys-Dietz syndrome patients, and in consideration of the increased vertebral tortuosity index and increased risk of aortic dissection with third trimester hemodynamic changes, the consensus of the multidisciplinary team was to recommend delivery by planned cesarean at 36 weeks so that delivery could occur under controlled conditions with maximum resources available. Recovery and postpartum care was planned to occur in the cardiac intensive care unit with telemetry due to risk of postpartum cardiac arrhythmia that has been described in women with Marfan syndrome (OR 10.64) and in close proximity to the cardiac operating rooms.⁷

After arterial and central line placement, the patient underwent a primary low transverse cesarean delivery at 36 weeks gestation with a slowly titrated epidural to avoid hemodynamic fluctuations. She delivered a live-born female infant (1 and 5 minute Apgars 8 and 9, birth weight 2689 grams) with an estimated blood loss of 750 ml. Intra-operatively, there was significant uterine vessel tortuosity noted (Figure 1). After delivery, she was started on losartan in addition to metoprolol as prophylaxis against further aortic root dilation. She had an echocardiogram on post-operative day 1 and an MRA on post-operative day 4 that showed no evidence of further aortic root dilation or dissection. She was offered long-term reversible contraception but declined. She was discharged on post-operative day 5. The infant was tested for the TGF β 2 mutation and was negative. Although cardiology follow-up was scheduled at 6 weeks and 3 months postpartum, she did not come to the visits despite being contacted several times. By report of other family members, she has not had any aortic events 18 months after delivery.

Discussion

This case demonstrates that a patient with Loeys-Dietz syndrome can have a successful pregnancy when closely monitored by a multi-disciplinary team. Additionally, this case suggests that, although not previously reported, uterine vessel tortuosity may be an additional phenotypical finding in Loeys-Dietz syndrome.

Arterial tortuosity, defined as an artery that has multiple turns, is present in head and neck vessels in 84-100% of individuals with Loeys-Dietz syndrome.^{1,2} A quantitative measure of vertebral tortuosity, the vertebral tortuosity index, has been examined in patients with Loeys-Dietz and Marfan syndrome with a higher tortuosity score associated with earlier age of aortic dissection and death.^{2,8} Our case suggests that vascular tortuosity extends to the uterine vessels and may be an additional phenotypical finding, although isolated uterine vessel tortuosity is non-diagnostic because it can occur in the general population. One of the

limitations with a qualitative assessment of tortuosity is that interpretation can vary between observers. Thus, future studies to determine whether increased tortuosity of the uterine arteries is seen in the majority of women with Loeys-Dietz syndrome and to develop a quantitative measurement of uterine artery tortuosity on imaging, similar to other developed indexes, should be considered.⁸ This quantified tortuosity score, if found to be associated with poor cardiovascular outcomes during pregnancy or in the long-term period, could potentially be used for preconception counseling about the risk of pregnancy in that individual or be used in the planning for timing and method of delivery.

Pregnancy management in women with Loeys-Dietz syndrome requires a multi-disciplinary team with knowledge of connective tissue disorders, including access to cardiac surgeons with expertise in aortic surgery; the management guidelines are outlined in Table 1. Although in Marfan syndrome, the greatest risk of pregnancy-associated aortic events occur when the maximum aortic dimension is greater than or equal to 4.0-4.5 cm, aortic diameter criteria have not been well-studied in Loeys-Dietz syndrome pregnancies and aortic dissections have been reported at diameters as small as 3.1 cm in a patient with prior aortic surgery and 3.5 cm in a patient without prior surgery.^{2,4} Therefore, until more data is available to estimate aortic dissection risk in patients with Loeys-Dietz syndrome, caution should be taken in pregnant women with aortic dilation and this syndrome.

Treatment with beta-blockers and angiotensin-receptor blockers (ARBs), outside of pregnancy in children and young adults, reduces the rate of aortic root dilation and improve survival, however a recent meta-analysis refutes these benefits.^{9,10} ARBs cannot be used during pregnancy secondary to teratogenic risks. Beta-blocker use in pregnancy is associated with fetal growth restriction; metoprolol is specifically recommended as it is thought to have the least, detrimental effect on fetal growth.¹¹

The method and timing of delivery in women with Loeys-Dietz syndrome is controversial and no guidelines have been established. Because of an early study reporting uterine rupture before term (2 of 12 women, 17%), some experts recommended early cesarean delivery to avoid this potential risk.¹ These patients generally tolerate surgical manipulation, and thus differ from patients with vascular Ehlers-Danlos syndrome who have poor tolerance of surgery and fragile tissues. However, larger, and more recent studies in Loeys-Dietz syndrome have not shown that vaginal delivery increases the risk of uterine rupture, thus vaginal delivery may be considered.^{2,3} Because of the lack of rigorous data, a consensus of a multidisciplinary team should determine the timing and mode of delivery for each patient individually until there is more information. Because of the peripartum risk of aortic dissection and cardiac arrhythmias, postpartum observation in a higher level of care setting should be considered. The ACC and ESC recommend cardiovascular imaging post-delivery and at 6 months postpartum.^{5,6} Contraception should be offered to the patient prior to discharge, although minimal data is available regarding the ideal contraceptive methods in Loeys-Dietz syndrome women.

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References

1. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *NEJM*. 2006; 355(8):788–798. [PubMed: 16928994]
2. Jondeau G, Ropers J, Regalado E, Braverman A, Evangelista A, Teixedo G, et al. International registry of patients carrying TGFBR1 or TGFBR2 mutations: results of MAC (Montalcino Aortic Consortium). *Circ Cardiovasc Genet*. 2016; 9(6):548–558. [PubMed: 27879313]
3. Tran-Fadulu V, Pannu H, Kim DH, Vick GW, Lonsford CM, Lafont AL, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. *J Med Genet*. 2009; 46(9):607–613. [PubMed: 19542084]
4. Goland S, Elkayam U. Cardiovascular problems in pregnant women with Marfan syndrome. *Circulation*. 2009; 119(4):619–623. [PubMed: 19188522]
5. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal*. 2011; 32(24):3147–3197. [PubMed: 21873418]
6. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiology*. 2010; 55(14):e27–e129.
7. Hassan N, Patenaude V, Oddy L, Abenhaim HA. Pregnancy outcomes in Marfan syndrome: a retrospective cohort study. *Am J Perinatology*. 2015; 30(2):123–130.
8. Morris SA, Orbach DB, Geva T, Singh MN, Gauvreau K, Lacro RV. Increased vertebral artery tortuosity index is associated with adverse outcomes in children and young adults with connective tissue disorders. *Circulation*. 2011; 124(4):388–396. [PubMed: 21730308]
9. Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *NEJM*. 2014; 371(22):2061–2071. [PubMed: 25405392]
10. Gersony DR, McCloughlin MA, Jin Z, Gersony WM. The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: a meta-analysis. *Int J Cardiology*. 2007; 114(3):303–308.
11. Tanaka K, Tanaka H, Kamiya C, Katsuragi S, Sawada M, Tsuritani M, et al. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. *Circulation Journal*. 2016; 80:2221–2226. [PubMed: 27593227]

Teaching Points

1. Loeys-Dietz syndrome is an autosomal dominant disorder with a known risk of aortic and arterial aneurysm and dissection; this risk is thought to be elevated in the peripartum period. Although the third trimester and postpartum period are the times of greatest risk, the optimal gestational age for delivery and delivery method have not yet been determined.
2. Loeys-Dietz syndrome is characterized by vascular, skeletal, craniofacial and cutaneous features, however, the minimum clinical diagnostic criteria have not been established. Family history of aortic dissection and molecular testing of *TGFBR1*, *TGFBR2*, *SMAD3* and *TGFB2* contribute to the diagnosis. A clinical suspicion for Loeys-Dietz syndrome warrants a referral to a cardiovascular geneticist.
3. Vessel tortuosity in head and neck is a hallmark finding for this disorder and may extend to the uterine vessels. Identification of women with Loeys-Dietz syndrome prior to or early in pregnancy is important to allow for adequate surveillance of aortic disease and to ensure delivery at a tertiary care center with expertise in aortic surgery.

Box 1**Clinical Findings Associated With Loeys- Dietz Syndrome****Vascular**

- Dilatation or dissection of the aorta or other arterial aneurysms
- Arterial Tortuosity

Skeletal

- Pectus excavatum or pectus carinatum
- Scoliosis or cervical spine malformations or instability and dural ectasia
- Joint laxity or contracture (mostly in fingers)
- Arachnodactyly (long, slender fingers)
- Talipes equinovarus (club foot)

Craniofacial

- Hypertelorism (widely spaced eyes)
- Bifid uvula or uvula with wide base or prominent ridge
- Cleft Palate
- Malar hypoplasia or retrognathia
- Blue sclera
- Craniosynostosis

Cutaneous

- Translucent skin
- Easy bruising
- Dystrophic scarring

Figure 1.

A illustrates the appearance of the uterine vessels in our patient with Loeys-Dietz syndrome. In contrast, **B** shows the appearance of the uterine vessels in an unaffected individual.

Table 1**Management Recommendations for Loeys-Dietz in Pregnancy**

Time of Pregnancy	Recommendations	Level of Evidence
Preconception	<ul style="list-style-type: none"> Assessment of aortic and cardiovascular health <ul style="list-style-type: none"> Echocardiogram to assess aortic root size Computerize tomography (CT) or magnetic resonance angiogram (MRA) to assess vascular tree Assessment of spine <ul style="list-style-type: none"> cervical spine stability, vascular malformations, dural ectasia Magnetic resonance imaging (MRI) of spine Counseling about risk of aortic dissection in pregnancy <ul style="list-style-type: none"> Aortic root < 4 cm- lower risk of aortic dissection Aortic root 4cm- higher risk of aortic dissection Counseling about hereditability of disorder to children <ul style="list-style-type: none"> Autosomal-dominant, variable expressivity Genetic testing options available in pregnancy Titration off angiotensin-receptor blocker to beta-blocker Consideration of prophylactic aortic root surgery <ul style="list-style-type: none"> Aortic Root >4–4.5 cm 	I C I C I C I C I C IIb C
1 st Trimester	<ul style="list-style-type: none"> Assessment of aortic root size with echocardiogram <ul style="list-style-type: none"> Echocardiogram every 4–8 weeks in pregnancy Assessment of vascular tree and spine (if not pre-conception) Multi-Disciplinary Team with Cardiothoracic Surgery <ul style="list-style-type: none"> Discuss antepartum and postpartum care Plan delivery method and timing Contingency plan in case of aortic dissection Strict blood pressure control with beta-blocker 	I C I C I C I C
2 nd Trimester	<ul style="list-style-type: none"> Level II ultrasound at 18–20 weeks Fetal echocardiogram at 22–24 weeks 	I C I C
3 rd Trimester	<ul style="list-style-type: none"> Fetal growth scans every 4 weeks until delivery Anesthesia Recommendations <ul style="list-style-type: none"> Consultation with anesthesia in 3rd trimester Regional anesthesia can be difficult secondary to scoliosis, dural ectasia Delivery <ul style="list-style-type: none"> Vaginal delivery is favored <ul style="list-style-type: none"> Aortic root < 4 cm (I C) Aortic root 4–4.5 cm with epidural, expedited 2nd stage Cesarean delivery should be considered <ul style="list-style-type: none"> Significant aortic root enlargement during pregnancy Aortic root > 4.5 cm Aortic root 4- 4.5 cm 	I A I C I C IIa C IIa C I C IIb C
Postpartum	<ul style="list-style-type: none"> Close observation with telemetry Assessment of aortic root and vascular tree <ul style="list-style-type: none"> Echocardiogram <ul style="list-style-type: none"> 1st week after delivery 6 months CT or MRA Contraception <ul style="list-style-type: none"> Contraceptive counseling is recommended No data exists about optimal methods of contraception Breast Feeding <ul style="list-style-type: none"> Lactation contributes to aortic dissection in Marfan mouse model, however there is no human data on effect of lactation on aortic dissection risk Beta-blocker is safe for breastfeeding Angiotensin receptor blocker (ARB) is not recommended 	NA * I C I C NA * NA * I C I C
Acute Aortic Dissection	<ul style="list-style-type: none"> Contrast tomography (CT) angiogram is the preferred imaging for rapid diagnosis of aortic dissection, regardless of pregnancy stage 	I B

* NA=No available data