CASE REPORT

Proposed Management Policy for Pregnant Women with Loeys-Dietz Syndrome Following Prophylactic Aortic Root Replacement Based on Experience from a Tertiary Care Center

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Summary

Loeys-Dietz syndrome (LDS) is a connective tissue disorder with a high incidence of aortic dissection (AD). After treating two previously reported cases of postpartum AD in women with LDS following prophylactic aortic root replacement (ARR), we succeeded in managing a 30-year-old primigravida with no AD during her peripartum period. On the basis of the patient’s stated desire to conceive during preconception counseling, a multidisciplinary team was assembled. She conceived naturally after receiving prophylactic ARR and beta-blocker treatment. Multidisciplinary patient care included precise blood pressure management, continuation of beta-blocker treatment, cardiovascular assessment with echocardiogram, regional anesthesia during labor, prevention of lactation, and resumption of angiotensin II receptor blocker therapy immediately after delivery. On the basis of our assessment of three cases, including this case, and a literature review, we propose a peripartum management strategy for patients with LDS following prophylactic ARR.

Key words: Heritable connective tissue disorder, Pregnancy, Aortic dissection, Preconception counseling

Loeys-Dietz syndrome (LDS) is a rare autosomal dominant connective tissue disorder characterized by thoracic aortic aneurysms, cleft palate, hypertelorism, and arterial tortuosity.1,2 Pathogenic mutations in TGFBR1, TGFBR2, SMAD3, TGFBR2, TGFBR3, or SMAD2 are known to cause different disease phenotypes, some of which involve severe aortopathy that may lead to aortic dissection (AD).3,4 Because it has been only 16 years since this disease was recognized, there have been limited reports of pregnancies in women with LDS. Several recent case series have reported favorable outcomes of pregnancy in LDS5-8; however, pregnancies that occurred following prophylactic aortic root replacement (ARR) had a high risk of peripartum AD. To the best of our knowledge, four out of six patients with LDS with a history of ARR, including two patients from our institution, were reported to have had AD postpartum4-7 and required additional monitoring compared with those without ARR. In contrast to the presence of pregnancy treatment recommendations for patients with Marfan syndrome (MFS), a connective tissue disorder that shares common features with LDS, no pregnancy management guidelines exist for women with LDS.8,9 Russo, et al. reported a management protocol for pregnant women with LDS9; however, those with pregnancies following ARR require additional care. After treating two cases of AD in patients with LDS following ARR, we describe the management of our third case of a woman with LDS who received prophylactic ARR prior to conception and did not develop peripartum AD. On the basis of a literature review and our experience from these three cases, we propose a perinatal management strategy following prophylactic ARR for women with LDS.

Case Report

A 30-year-old primigravida with LDS was referred to our preconception clinic. We had previously diagnosed the patient with LDS at age 26 years, based on characteristic physical features and suspected mutation of the TGFBR2 gene (c.1145 G > A, p.Ser382Asn: rs863223844). Two months prior to her preconception appointment, at age 29 years, she had received prophylactic ARR for a sinus of Valsalva aneurysm measuring 41 mm in diameter. Gynecological inspection showed an intramural fibroid measuring 4 cm in diameter in the anterior uterine wall. The patient confirmed her desire to conceive following a thorough exploration of our management policy for patients with LDS, which covered the following possible conditions: possible peripartum Stanford type B AD, autosomal inheritance in offspring, possible reduced fetal growth due

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to continued beta-blocker treatment during pregnancy, use of epidural anesthesia during labor, lactation prevention, resumption of angiotensin II receptor blocker (ARB) therapy after delivery, and a 14-day postpartum hospital stay. Conception was confirmed 21 months after preconception counseling. During this time interval, the patient was treated with oral bisoprolol (5 mg/day).

At the first prenatal appointment (32 days postmenses), the uterine fibroid was 68 × 67 mm in size. Other clinical findings were unremarkable, except for mild aortic regurgitation (AR) that had been detected in her echocardiography 12 months after ARR surgery. Echocardiography that was repeated at 3-month intervals after week 10 of gestation showed no remarkable changes and was characterized by an ejection fraction > 60%, mild AR, and no dilatation of the remaining aorta. The pregnancy course was uneventful except for bleeding caused by colonic diverticulitis that responded to conservative treatment. The patient’s blood pressure was stable at approximately 100–110/50–60 mmHg throughout pregnancy, without any change in the daily 5-mg bisoprolol dosage. The patient was admitted for labor induction at 37th weeks of gestation to avoid labor onset that could limit access to a full multidisciplinary team, including a cardiovascular surgeon. Administration of oxytocin on the following day to induce labor was unsuccessful. Cesarean section was performed (blood loss, 1150 mL; surgical time, 63 minutes) and a fibroid measuring 9 cm in diameter was observed in the anterior uterine wall above the lower uterine segment, which contained tortuous arteries that are a characteristic finding of LDS.10 A male neonate, weighing 2115 g, with an Appgar score of 8/9 (1 and 5 minutes, respectively), was delivered.

One day postpartum, the patient was administered oral cabergoline (1 mg) to stop lactation and oral losartan (50 mg/day) to supplement bisoprolol therapy (5 mg/day) for maintenance of systolic blood pressure < 120 mmHg. During her 16-day postpartum hospital stay, the patient’s blood pressure was stable at 80–100/50–60 mmHg with temporal use of nicardipine (20 mg) when systolic blood pressure exceeded 120 mmHg. The patient had no symptoms suggestive of AD during her hospital stay, and a computed tomography scan on postpartum day 8 showed no signs of aortic dilatation or AD. Echocardiography on postpartum day 8 showed no worsening of mild AR compared with the preconception state. The patient was discharged on postpartum day 16 and had no complications, including those for Stanford type B AD, at follow-up, 12 months after delivery.

Discussion

LDS was first reported in 2004–2005 as a condition that shared features with MFS; however, it was found to have a more aggressive course than MFS.11 Several recent case series report outcomes of pregnancies complicated by LDS. Frise, et al. summarized reported cases of pregnancy in patients with LDS and found only two cases of AD and one death of unknown cause in 213 pregnancies for 91 women with no history of ARR.12 Cauldwell, et al. reported 20 pregnancies in 13 women with LDS, including one woman with a history of ARR after her first pregnancy; however, no AD occurred in their cohort.13 Including the report from Cauldwell, et al., in which precise history is unknown, there were only six cases of pregnancy in patients with LDS with a history of ARR, and four of these patients had AD after delivery.17 These results indicate that patients with LDS with a history of ARR must be informed of risks prior to pregnancy, because they require special attention during pregnancy and after delivery.

Recent ESC Guidelines illustrate that patients with LDS are at high risk and require expert counseling prior to conception; however, there are no management guidelines for the peripartum period, as there are for MFS.8 Because our patient was followed up by doctors specializing in MFS-related diseases, she was referred to the obstetrics department for preconception counseling. After thorough explanation of pregnancy risks (including AD and autosomal inheritance) and our management policy, the patient stated her intent to conceive. Our management policies include continuation of beta-blockers during pregnancy, use of epidural anesthesia during labor, use of forcepts delivery to limit pushing, strict blood pressure control throughout the peripartum period, echocardiography in every trimester and after delivery, prevention of lactation, use of ARB after delivery, and a 14-day hospital stay after delivery. Lactation prevention has been controversial for the past decade; however, based on a report from Habashi, et al., which showed that lactation prevention in MFS model mice reduced the incidence of postpartum AD from 91.1% to 25.9% and the growth of the ascending aorta,10 we added lactation prevention to our management policy in 2019. With regard to the report of Habashi, et al., this may also reduce the risk of future AD by preventing postpartum aortic deterioration. Furthermore, we recommend the combination of ARB and beta-blockers postpartum, because ARB shows great promise as an antihypertensive medication for inhibiting aortic growth in MFS and potentially for aiding postpartum AD inhibition. Treatment with ARB can be resumed soon after delivery, because the patient is not allowed to breastfeed in that period.

We reported that pregnant patients with MFS are at high risk for Stanford type B AD following ARR, because three of five patients who underwent ARR prior to conception had AD during the third trimester or postpartum period.15 Because women with LDS are more prone to AD compared with those with MFS, it is reasonable to consider that these patients with LDS are at a high risk for AD following ARR. Table I shows the clinical outcomes of eight pregnancies in six patients with LDS after ARR, including the present case, of which three (Table I, cases 1-3) were from our institution. Interestingly, all patients had AD after delivery, which implies that efforts to prevent AD should focus on the postpartum period. Our first case (Table I, case 2) involved severe AD that extended to the vertebrobasilar arteries and resulted in the death of the patient 20 days after delivery.9 The present case was the second case we managed with postpartum lactation prevention, after adding postpartum lactation prevention to our peripartum management policy for LDS in...
Table I. Review of Perinatal Outcomes of Patients with LDS Following ARR

| Case | Age at delivery (years) | Genetic mutation | History of ARR | Age of ARR (years) | Aortic root diameter at ARR (mm) | Use of beta-blocker during pregnancy | Use of ARB postpartum | Delivery (weeks) | Mode of delivery | Onset of AD | Outcome | Lactation | References |
|------|------------------------|------------------|----------------|-------------------|-------------------------------|-------------------------------------|----------------------|-----------------|-----------------|-----------|---------|-----------|------------|
| 1    | 30                     | TGFBR2           | VSARR          | 29                | 41                            | Yes                                 | Yes                  | 37              | CS              | (-)       | Live    | No        | This report |
| 2    | 23                     | TGFBR2           | VSARR (-)      | NA                | NA                            | No                                  | No                   | 38              | CS              | 3 days    | Live    | Yes       | Fujita, et al. |
|      |                        |                  |                |                   |                               |                                     |                      |                 |                 | postpartum |         |           |            |
| 3    | 28                     | TGFBR2           | VSARR          | 20                | 55                            | Yes                                 | No                   | 37              | CS              | 5 days    | Dead*   | Yes       | Shitara, et al. |
| 4    | 43                     | TGFBR1           | VSARR          | 25                | 48                            | Yes                                 | NA                   | 35              | CS              | 2 days    | Live    | Yes       | Braverman, et al. |
| 5    | 37                     | TGFBR2           | VSARR          | 17                | 50                            | Yes                                 | NA                   | 34              | CS              | 1 day after discharge | Live | Yes | Braverman, et al. |
| 6    | 26                     | TGFBR2           | VSARR          | 21                | 45                            | Yes                                 | NA                   | 34              | CS              | (-)       | Live    | NA        | Braverman, et al. |
| 7    | NA                     | NA               | NA (-) VSARR   | NA                | NA                            | NA                                  | NA                   | NA              | NA              | (-)       | Live    | NA        | Cauldwell, et al. |

LDS indicates Loeys–Dietz syndrome; ARR, aortic root replacement; ARB, angiotensin II receptor blocker; AD, aortic dissection; VSARR, valve-sparing aortic root replacement; CS, Cesarean section; and NA, not available. * This patient died 20 days postpartum.

Table II. Perinatal Management Recommendations for LDS Following ARR

| Preconception counseling | During pregnancy | During labor | Postpartum |
|--------------------------|------------------|--------------|------------|
| Autosomal dominant inheritance | Continuation of beta-blocker | Regional anesthesia | Prevent lactation |
| Assessment of aortic root dilation and heart function | Fetal growth ultrasound (every 2 weeks) | Follow obstetric indication | Combination of ARB with beta-blocker |
| Discuss peripartum risks | Maternal echocardiogram (every 3 months) | Instrumental delivery to prevent pushing | CT scan and echocardiogram (1 week postpartum) |
| Switch ARB to beta-blocker | | Strict BP management of sBP < 120 mmHg | Hospital stay for 7–14 days |

LDS indicates Loeys–Dietz syndrome; ARR, aortic root replacement; ARB, angiotensin II receptor blocker; CT, computed tomography; BP, blood pressure; and sBP, systolic blood pressure. * Cesarean delivery may be considered upon discussion between the multidisciplinary team and the patient.

2019. Our first case (Table I, case 3) had Stanford type B AD on postpartum day 8 and had previously received prophylactic ARR at age 20 years for a 55-mm aortic root dilatation, suggesting a more aggressive phenotype compared with that of other women who had received ARR (Table I). Because this patient’s blood pressure was stable, she was not administered ARB until after postpartum AD development; however, we added ARB to beta-blocker treatment immediately after delivery in our management protocol after observing the results of her therapy. Postpartum ARB may have been another factor in preventing AD in the present case.

The patient in the present case received valve-sparing ARR (VSARR), as did other pregnant women with LDS in the previous reports shown in Table I. In our institute, aortic root reimplantation (David procedure) with wrapping of the remaining distal ascending aorta is chosen for VSARR to avoid a future risk of Stanford type A AD. VSARR is highly recommended for aortic root dilatation over 40 mm in women with LDS who plan to conceive, according to surgical guidelines for the prevention of peripartum aortic events and thromboembolic and bleeding complications related to anticoagulant therapies. However, aortic valve cusps in patients with LDS tend to be thinner and more fragile than those in patients with MFS. Therefore, ARR with a composite graft of a prosthetic valve (Bentall procedure) is needed in cases where aortic valves cannot be spared. It should be noted that our perinatal management only applies to patients with LDS following VSARR; thus, those following the Bentall procedure may have a different outcome and require thorough prenatal counseling prior to conception.

In summary, we propose a management strategy for pregnant women with LDS following ARR, as shown in Table II. Women with LDS without a history of ARR seem to have favorable pregnancy outcomes; however, because fatal AD occurs in 1%-2% of these women, we used the same protocol for each LDS pregnancy after thorough discussion with the patient. Considering the beneficial effect of lactation for both mother and newborn, lactation prevention in MFS-related diseases has been controversial; however, given the promising results observed by Habashi, et al. in mice, the option to prevent lactation should be discussed with women with LDS regardless of...
the history of ARR.

Disclosure

Conflicts of interest: The authors declare no conflicts of interest.

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