

Loeys-Dietz Syndrome and pregnancy: two case reports and literature review

Síndrome de Loeys-Dietz e gravidez: dois casos clínicos e revisão da literatura

Sara Vargas¹, Oana Moldovan², Filipa Lança³, Mónica Centeno⁴, Luísa Pinto⁴
Hospital de Santa Maria, Centro Hospitalar e Universitário de Lisboa Norte

Abstract

Loeys-Dietz syndrome is a rare autosomal dominant connective tissue disorder characterized by vascular, skeletal, craniofacial and cutaneous abnormalities. During pregnancy, women with this syndrome have an increased risk of aortic aneurysm and dissection, preterm birth, uterine rupture and postpartum hemorrhage. Appropriate preconceptional, pregnancy and postpartum evaluation, counseling and surveillance by a specialized and multidisciplinary team might improve maternal and pregnancy outcomes. We present two cases of pregnant women with this syndrome surveilled at a tertiary high-risk obstetrics center. Both delivered at term without *major* complications.

Keywords: Pregnancy; Cardiovascular Diseases; Loeys-Dietz Syndrome; Pregnancy Complications

INTRODUCTION

Loeys-Dietz syndrome (LDS) is a recently recognized and rare autosomal dominant connective tissue disorder with widespread systemic involvement that may resemble Marfan syndrome^{1,2}. However, the clinical criteria for LDS' diagnosis have not yet been defined and there is a broad spectrum of clinical features and severity.

It is most commonly caused by genetic mutations in the genes encoding transforming growth factor receptors (TGFB 1/2), but it may also comprise heterozygous mutations in its ligands (TGFB 2/3) as well as in genes encoding the decapentaplegic homolog (SMAD 2/3)^{3,4}.

It is characterized by vascular (arterial tortuosity, aneurism and dissection), skeletal (*pectus excavatum* or *pectus carinatum*, cervical instability, joint laxity or contracture), craniofacial (hypertelorism, bifid uvula, cleft palate, craniosynostosis) and cutaneous (translucent skin, easy bruising, dystrophic scarring) abnormalities^{1,3}.

During pregnancy, women with this syndrome have an increased risk of aortic aneurysm, rupture and dissection (higher in the third trimester and peripartum period), uterine rupture, preterm birth and postpartum hemorrhage^{2,5}.

Appropriate preconception, pregnancy and postpartum evaluation, counseling and surveillance by a specialized and multidisciplinary team might improve maternal and pregnancy outcomes.

The ideal management of these patients during pregnancy is limited by the paucity of data in the literature. We present two cases of pregnant women previously diagnosed with this syndrome whose pregnancies were surveilled at a tertiary center and who delivered at term without *major* complications.

An informed consent was obtained from both patients and the protocols in use in our working center regarding patients' data publication were followed.

1. Interna de Formação Específica de Ginecologia e Obstetrícia, Departamento de Obstetrícia, Ginecologia e Medicina da Reprodução, Centro Hospitalar e Universitário de Lisboa Norte - Hospital de Santa Maria, Lisboa, Portugal

2. Assistente Hospitalar Graduada de Genética Médica, Serviço de Genética Médica, Centro Hospitalar e Universitário de Lisboa Norte - Hospital de Santa Maria, Lisboa, Portugal

3. Assistente Hospitalar Graduada de Anestesiologia; Departamento de Anestesiologia; Centro Hospitalar e Universitário de Lisboa Norte - Hospital de Santa Maria, Lisboa, Portugal

4. Assistente Hospitalar Graduada de Ginecologia e Obstetrícia; Departamento de Obstetrícia, Ginecologia e Medicina da Reprodução, Centro Hospitalar e Universitário de Lisboa Norte - Hospital de Santa Maria, Lisboa, Portugal

CASE REPORT

Case 1

A 31-year-old Caucasian primiparous woman was referred to our obstetric outpatient unit at seven weeks of gestation. LDS diagnosis was based on her family's history (her grandfather and uncle suffered a sudden death) and confirmed by genetic testing before pregnancy, with identification of the familial mutation in the TGFBR 1. A stable sinusal aortic dilation (41mm) was also diagnosed during follow-up but she was not taking any medication before pregnancy. She did not present any symptoms or dysmorphic features besides long limbs. There was also a medical history of asthma and one episode of spontaneous pneumothorax (submitted to bilateral pleurodesis and partial lobectomy). Cardiologic, pneumonologic and genetic pre pregnancy counseling was performed. Pregnancy risks were explained and the preconceptional echocardiogram and magnetic resonance revealed a sinusal aorta of 41 mm and an ascending aorta diameter of 27 mm. No prophylactic medical therapy was initiated before pregnancy. Obstetric, genetic, cardiac, pneumonologic and anesthetic evaluation and counseling were provided during pregnancy. Further obstetrical appointments were not needed but more attention was given to symptoms of cardiovascular deterioration. The parents decided not to do invasive prenatal diagnosis. An ascending aortic dilation (43mm) was diagnosed at 15 weeks' gestation and bisoprolol 1.25 mg/day was then initiated. Monthly echocardiographic evaluation was performed and revealed stability of this lesion until the end of the pregnancy. Fetal ultrasound and echocardiogram were normal. No other complications were noticed. An elective cesarean under general anesthesia was electively performed at 37 weeks (male newborn with 2600 g and Apgar score at 5th minute of 9). After the delivery there was an early postpartum hemorrhage that was treated with medical therapy (1g of tranexamic acid and 20 IU of oxytocin infusion) and hemostatic uterine sutures. The immediate recovery occurred in the post anesthesia care unit. There was no need for other interventions and the subsequent postpartum period was uneventful. We didn't advise against breastfeeding and propranolol 10 mg was maintained during the puerperium.

Case 2

A 29-year-old Caucasian primiparous woman with an uneventful medical history besides a known familial

SMAD3 heterozigotic mutation (her father suffered from an aortic dissection at 57 years old) and migraine was referred to our obstetric outpatient unit at ten weeks of gestation. She did not have symptoms or dysmorphic features of LDS but the diagnosis was confirmed by genetic testing before pregnancy. Cardiologic, neurologic and genetic pre pregnancy counseling was performed. Pregnancy risks were explained and the preconceptional echocardiogram and computed tomography angiogram were normal (maximum aortic diameter of 25.9 mm). No prophylactic medical therapy was initiated before pregnancy. Obstetric, genetic, cardiac, neurologic and anesthetic evaluation and counseling were provided during pregnancy. Based on a high risk screening for trisomy 21 and preeclampsia, prophylaxis with acetylsalicylic acid (150 mg/day) was initiated and a chorionic villous sample was performed (46 XY). The parents refused to do any other genetic testing. Further obstetrical appointments were not needed but more attention was given to symptoms of cardiovascular deterioration. Monthly echocardiographic evaluations did not reveal any abnormality but prophylactic bisoprolol 2.5 mg was initiated in the third trimester. Fetal ultrasounds and echocardiogram were normal. An elective cesarean was performed at 37 weeks under general anesthesia (male newborn with 2700 g and Apgar score at 5th minute of 10). The immediate recovery occurred in the post anesthesia care unit without complications. We didn't advise against breastfeeding and propranolol 10 mg was maintained during the puerperium.

DISCUSSION

LDS is a connective tissue disorder with widespread systemic involvement that may affect women during reproductive age. Its real prevalence is unknown and its prognosis is variable depending on clinical disease expression and treatment.

The paucity of guidelines and studies that include a large number of women makes pre and postnatal care challenging. Therefore, guidance for these pregnancies is mostly extrapolated from information pertaining to other aortopathies and from a limited number of case reports^{3,6}. Nevertheless, as these pregnant women are at increased risk of adverse maternal and pregnancy outcomes, they should be surveilled at tertiary high-risk obstetrics centers.

Multidisciplinary teams including obstetricians, car-

diologists, anesthesiologists, cardiovascular surgeons, geneticists, neonatologists and eventually others if there are more comorbidities are crucial for better outcomes during pregnancy in women with LDS^{2,5,6}. Prenatal diagnosis and pre-implantation genetic diagnosis should be discussed with the parents⁷. Although not all abnormalities can be detected with prenatal screening, fetal echocardiographic evaluation should be performed in order to exclude cardiac abnormalities.

Since aortic dissection is the leading cause of mortality, preconception counseling is recommended and pregnancy is contraindicated for women with an ascending aorta >45 mm. Even though, there is approximately a 10% risk of dissection when the aortic dimension is above 40 mm and 1% risk with normal aorta⁶.

Pregnant women with this syndrome should be monitored by echocardiography at regular intervals (4 to 12 weeks, depending on the severity of dilation) and for six months after delivery⁸. Beta blockers should always be considered and strict blood pressure control (under 130/80mmHg) is recommended⁹. Fetal growth should also be monitored. In the first case described, and despite a normal preconceptional echocardiographic evaluation of the ascending aorta, an enlargement was noticed for the first time at 15 weeks of pregnancy. Subsequent surveillance confirmed that there was no progressive aortic dilation and allowed for the progression of the pregnancy until term. Progressive aortic root dilation may justify the pregnancy's termination and surgical treatment if the fetus is viable. Before fetal viability, maternal thoracic surgery can be performed with the fetus *in utero*.⁸

Besides all the possible complications previously mentioned, these women can also have dural ectasia and cervical spine abnormalities and anesthetic planning should be performed before delivery^{3,10}. The patient should be submitted to a lumbar magnetic resonance with contrast if one decides to perform an epidural anesthesia.

Although vaginal delivery could be considered in selected patients without aortic dilation >40mm, early delivery by elective cesarean section may reduce the cardiovascular stress of labor and delivery that might predispose to aortic dissection². In the majority of cases described in the literature, cesarean section was the main mode of delivery⁵. Despite these facts and regardless of the risk of uterine rupture, currently there are no comparative studies and no guidelines that recommend cesarean section delivery for all women with LDS¹¹. When considering vaginal delivery, one should

maintain a low threshold for epidural anesthesia and instrumental extraction¹².

We decided to perform elective cesarean sections at term and under general anesthesia, focusing on the maintenance of intraoperative hemodynamic stability and minimal intraoperative blood loss. Despite this, in one of the cases there was a postpartum hemorrhage that was promptly resolved with medical therapy and hemostatic sutures. In this setting, medical teams should always be prepared for further intervention. Uterotonics that might interfere with blood pressure control should be avoided and oxytocin infusion should be preferred to bolus. Tranexamic acid might reduce further bleeding¹⁰.

After delivery, it is important to recognize that the risk of aortic pathology persists and maternal follow-up must be continued, even after hospital discharge¹¹. Initially, the recovery should happen in the post anesthesia care unit with standard hemodynamic monitoring for 24 hours. Some authorities advise against breastfeeding due to the effect of natural oxytocin on maternal blood pressure but there is no consensus.

These cases highlight the need for multidisciplinary specialist management of women with LDS at tertiary high-risk obstetrics centers before, during and after pregnancy, as this strategy probably ameliorates maternal and pregnancy outcomes.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interests.

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ENDEREÇO PARA CORRESPONDÊNCIA:

Sara Vargas
saravargasp@gmail.com

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