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NEWS AND VIEWS

Ehlers–Danlos syndrome and other heritable connective tissue disorders that impact pregnancies can be detected using next-generation DNA sequencing

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Abstract
Ehlers–Danlos syndromes (EDS) are a genetically heterogeneous group of inherited connective tissue disorders classified into six major types with a variable collection of findings and different inheritance patterns. Although complications occur in about one-half of pregnancies in women with EDS, the majority can have a good outcome if managed appropriately. Classic EDS is characterized by joint hypermobility, loose skin with poor healing and easy bruising, musculoskeletal problems with chronic pain and at risk for pre-term delivery. In addition, the vascular form of EDS can have cardiac anomalies, aneurysms, gastrointestinal perforation and uterine rupture during pregnancy. Due to overlapping features among the connective tissue disorders, it is difficult to categorize the disorder into specific types without detailed genetic testing which is now available through advanced genomic technology using next-generation DNA sequencing, searching genomic databases and bioinformatics approach. Therefore, obstetrical complications are variable but relate to specific connective tissue disorders requiring an exact diagnosis. There are several dozen genes causing connective tissue disorders that are currently available for testing using next-generation sequencing and bioinformatics to provide pertinent care, treatment and surveillance of the affected pregnant woman but also for her at-risk fetus related to the specific heritable condition.

Keywords Connective tissue disorders impacting pregnancies · Ehlers–Danlos syndrome and obstetric complications · Advanced genomic technology and next generation sequencing · Genetic screening

Ehlers–Danlos syndromes (EDS) represent a heterogeneous group of inherited connective tissue disorders. There are six major types of EDS including classic (Type I and Type II) with defects in Type 5 collagen; hypermobile (Type III), vascular (Type IV) with abnormal Type 3 collagen; kyphoscoliosis (Type VI) with lysl hydroxylase deficiency; arthrochalasia (Type VII) with deficiency of Type 1 collagen and dermatosparaxis (Type VII) with procollagen N-proteinase deficiency in Type 1 collagen. Most of the EDS types have in common hypermobility including joint dislocations/subluxations, blood pressure instability, other musculoskeletal problems and pain. Mitral valve prolapse, aortic root dilation or aneurysms are reported as well as possible early pregnancy termination due to premature rupture of membranes or an incompetent cervix [1, 2].

Classic EDS is characterized by joint hypermobility, loose skin (often described as "soft" or velvet-like), easy bruising, and slow wound healing with atrophic scars. Features of vascular EDS include a high risk of arterial rupture, aneurysms, gastrointestinal perforation, and uterine rupture during pregnancy [3]. Several patients will be difficult to categorize into specific classes due to overlapping features and will require detailed genetic testing. Obstetrical complications related to connective tissue disorders are variable and the literature about labor and delivery descriptions are sparse including for EDS. However, there is evidence that the risk of pre-term labor is higher than seen in the general population. Successful vaginal deliveries and caesarian sections are well documented in patients with hypermobile EDS [4–7]. Delivery and post-partum related risks include ante-partum and post-partum hemorrhage, aneurysms, blood pressure instability and poor healing [8]. Patients with vascular EDS, in particular, are at a higher risk for severe maternal

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complications [9–13]. Some of these complications may be avoided by caesarian section but risks should be noted for the fetus whom may be similarly affected, and the diagnosis addressed postnatally by evaluating the presence of the targeted gene variant seen in the mother.

About 5% of deaths in women with EDS have disease-related complications in pregnancy with 50% of those deaths occurring in the first pregnancy. Although complications occur in about one-half of the pregnancies, they can be managed and lead to a good outcome in the majority of cases [13, 14]. Knowing the type of connective tissue disorder such as EDS can help the obstetrician better manage and advise on treatment on a case by case situation. Precautions are especially important for patients with vascular EDS and illustrated by a case report in the literature of a patient with vascular EDS undergoing a caesarian section with spinal anesthesia [15].

Although EDS is classified into several types, delineation and relationship with causative gene variants is now testable in the clinical setting with advances in genomic technology and genomics-driven approaches using next-generation sequencing (NGS). DNA sequencing gene panels and deletion/duplication analysis are available for greater than 67 disease-causing genes for connective tissue disorders. These genes are: ABCC6, ACTA2, ADAMTS2, ADAMTS10, ADAMTSL2, ALDH18A1, ATP6V0A2, ATP7A, B3GALT6, B4GALT7, BGN, C1R, C1S, CBS, CHST14, COL1A1, COL1A2, COL2A1, COL3A1, COL5A1, COL5A2, COL9A1, COL9A2, COL9A3, COL11A1, COL11A2, DSE, EFEMP2 (FBLN4), ELN, FBLN5, FBN1, FBN2, FKBP14, FLCN, FLNA, FOXE3, GORAB, LOX, LTBP4, MED12, MFAP5, MYH11, MYLK, NOTCH1, NOTCH2, PKD1, PKD2, PLOD1, PRDM5, PRKG1, PTDSS1, PYCR1, RIN2, SKI, SLC2A10, SLC39A13, SMAD2, SMAD3, SMAD4, SMAD6, TAB2, TGFB2, TGFB3, TGFBR1, TGFBR2, TNXB and ZNF469. This gene panel can be performed commercially using saliva samples for DNA isolation (e.g., University of Nebraska Medical Center—Human Genetics Laboratory, Omaha).

Many connective tissue genes can cause well-known conditions besides EDS that impact pregnancies, including care and management, treatment, surveillance and risk for a similarly affected fetus such as Marfan syndrome (FBN1), Stickler syndrome (COL2A1, COL9A1, COL11A1), Loeys–Dietz syndrome (TGFB3, TGFBR1, SMAD3), familial thoracic aortic aneurysm (MYLK, PRKG1, ACTA2, MFAC5, FOXE3), cutis laxa (FBLN5, PYCR1, LTBP4) and osteogenesis imperfecta (COL1A1, COL1A2). The classic form of EDS involves COL5A1 and COL5A2, vascular EDS involves COLA31 and the hypermobile form involves TNXB [16]. Classic EDS occurs between 1 in 5000 to 1 in 20,000 individuals [17]. Because of overlapping features in the types of EDS, one cannot be sure of the diagnosis or frequency without genetic testing including NGS of connective tissue disorder gene panels as other conditions involving separate genes may present with different outcomes, healthcare issues and genetic counseling risks as high as 50% for autosomal dominant connective tissue disorders.

Current estimates of individuals with a diagnosis of EDS without advanced genetic testing indicate that classic EDS represents 30% of those affected, hypermobile EDS accounts for 35% and vascular EDS is seen in 10–30%. The estimated overall prevalence of EDS is 1 in 5000 [18]. The vascular form carries a high risk of maternal morbidity and mortality estimated at 25% predominantly due to spontaneous arterial rupture [19–21]. Genetic testing of women with features of a connective tissue disorder and identification of the specific type of EDS (or other related disorder based on the gene variant found) will impact genetic counseling (as high as 50% for several connective tissue disorders), treatment and surveillance during an established pregnancy. To assess hypermobility, the Beighton scale is used and recorded as a numerical score with a maximal score of 9 [22]. The score includes passive dorsiflexion of bilateral fifth fingers beyond 90° (2 points), passive bilateral apposition of both thumbs to flexor aspects of forearms (2 points); hyperextension of both elbows beyond 180° (2 points); hyperextension of the both knees beyond 180° (2 points); and forward flexion of the trunk with palms of hands resting on the floor upon forward flexion of the trunk (1 point). The Beighton hypermobility score should be determined upon the initial examination before or during early pregnancy for each woman. If the score is ≥ 5, then a connective tissue disorder should be pursued with genetic testing ordered using NGS for comprehensive connective tissue disorder gene panels, readily available by commercial laboratories. The genetic testing results and laboratory interpretation would impact the rest of the pregnancy with follow-up, evaluation, obstetric management and care. With the fetus at a potential 50% risk depending on the inheritance pattern of the disease-causing connective tissue gene and variant identified, the care of the newborn may also be impacted requiring specialized care, testing and surveillance.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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