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REVIEW

Skin Ultrastructural Clues on the Impact of Ehlers-Danlos Syndrome in Women

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ABSTRACT

Ehlers-Danlos syndrome is heterogeneous in its genetic origins, molecular defects, and ultrastructure of connective tissues (CT). It frequently represents underdiagnosed heritable conditions. The altered mechanical functions of the involved tissues lead to variable combinations of increased skin distensibility and elasticity, joint laxity and CT fragility. In addition, EDS women commonly suffer from some gynecologic and obstetric disorders. In most instances, the diagnosis is based on selected clinical criteria. Dermal ultrastructural changes show representative patterns suggesting some EDS types: the collagen and elastic fibres are altered in the dermis, ligaments, vessel walls and internal organs. Although EDS is presumed to be a rare condition, physicians should view the disease outside the limits of conventional medical practices. Women are at risk of adverse pregnancy outcomes and various menstrual abnormalities. A multidisciplinary approach is usually welcome.

Key words: Collagen; Elastic fibre; Ultrastructure; Skin; Gynecology-obstetric disorder; Tenascin; Decorin; Dermatan sulfate

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INTRODUCTION

In many instances, the connective tissue (CT) of the dermis represents a structure composed of a set of some molecular structures showing a specific organization corresponding to a model for other soft tissue architectures. In particular, structural changes found in the different types of Ehlers-Danlos syndrome (EDS) are expressed in the skin[1] and in various organs including the female genital tract.

The aim of the present review was to revisit the implications of EDS in selected gynecologic and obstetric conditions.

REGULAR STRUCTURE OF THE DERMIS

The regular dermis is composed of distinct interconnected anatomical compartments corresponding to the subepidermal band, the adventitial and reticular compartments, as well as the hypodermal strands. The main bulk of the CT corresponds to the reticular portion that contains of abundant fibres, namely the collagen and elastic fibres.

The subepidermal band is a very thin fibrous tissue abutted to the basement membrane. It contains thin fibres running parallel to the dermoepidermal junction and intermingled with arcades of anchoring fibrils. The adventitial dermis comprises (a) the papillary dermis, that is the outermost portion of the dermis molded and abutted to the subepidermal band, and (b) the periadnexal dermis surrounding each sweat gland and sebaceous gland, as well as every hair follicle. The thick reticular dermis, runs from the bottom of the papillary dermis, located at the level of the superficial vascular plexus, to the subcutaneous fat. It is composed of two subunits called the mid and deep dermis.

The subepidermal band and the adventitial dermis are made of thin and loose collagen and elastic networks. Cells and proteoglycans are proportionally more abundant in the adventitial than in the reticular compartment.

Collagen fibres represent by far the most abundant component of the normal dermis. In the subepidermal band, they are present as a finely woven meshwork mostly oriented parallel to the skin surface whereas they are almost perpendicular to that direction in the adventitial dermis. They are grouped inside thick, interlacing and interconnected bundles in the reticular dermis where they are nearly parallel to the skin surface. So-called reticulin fibres are argyrophilic and correspond to thin collagen fibres. They are quite abundant in the subepidermal band and in the adventitial dermis, and they form a basket-like network surrounding collagen bundles in the reticular dermis. The mid reticular dermis is more compact than the deep zone which contains the largest collagen bundles of the skin.

Normal collagen fibres forming a bundle are rather uniform in shape and size. However, there are possibly wide variations in the aspect and area of the cut surface of the fibres in some CT disorders. These changes are best perceived by the combination of electron microscopy and computerized image analysis. Two main changes are roughly distinguished[2]. On the one hand, wide variations are occasionally present in the diameter of rounded fibres. This is commonly encountered in sclerotic conditions. On the other hand, some other disorders are associated with the presence of collagen fibres showing cauliflower shape sections. Their aspect ranges from serrated fibres to spider-like or hieroglyphic aggregates with branching arms[3]. They have been reported in a set of disorders including EDS[3,4].

Using polarization microscopy, it is possible to detect the orientation of small particles having one dimension that is small in comparison with the wavelength of the light. Thus, collagen fibres are positively birefringent. This property is enhanced by the sirius red stain. The specificity and the sensitivity of such a staining procedure do not identify any molecular nature of the collagen types[5]. It remains that the sirius red stain is obviously a method useful for visualizing the CT organization under polarized light.

Elastic fibres form a distinct network anchored to collagen bundles and to basement membranes. They are composed of microfibrils of glycoproteins embedded in elastin. Bundles of microfibrils called oxytalan fibres are present nearly basement membranes in the subepidermal band. They are connected to elaunin fibres of the adventitial dermis containing a small amount of elastin, which are in turn in continuity with the elastic fibres. Fully mature elastic fibres are only found in the deep reticular dermis. Oxytalan fibres are revealed after oxidation with oxone by elastic tissue stains. Nonsulfated glycosaminoglycans (hyaluronic acid) are stained with colloidal iron and alcian blue at pH 3, but not at pH 0.5. They present metachromasia with toluidine blue at pH 3, but not at pH 1.5. Sulfated glycosaminoglycans (dermatan sulfate, heparan sulfate) are revealed by these stains irrespective of the pH.

The above mentioned characteristics of the dermis vary according to the age and location on the body. Chronological aging of the dermis first alters the open network of fibres and bundles. The interwoven, randomly oriented pattern is altered into a loose or a more densely packed structure with variable amounts of non-fibrous matrix. Progressively, the packing of collagen fibres in bundles is disrupted. Later on, bundles become no more recognizable. Such an evolution toward atrophy is markedly boosted by cortisosteroids.

Photoaging represents those changes that occur in sun-exposed skin. Its aspects are strikingly different form those of chronologically aged skin. It is characterized by the development of solar elastosis involving the upper and mid reticular dermis, and by densification of subepidermal band (grenz zone). Deposits of acid proteoglycans are also different in the elastotic material from non exposed skin of young and aged individuals.

CURRENT CLASSIFICATION OF EDS TYPES

Globally, EDS is clinically recognized by various combinations of increased skin distensibility and hyperelasticity, extendable joint laxity, and some aspects of CT fragility. At present, some EDS patients are identified by molecular biology. Some EDS types are characterized by a single defined and specific genetic mutation. Other EDS clinical types are associated with a few distinct molecular alterations. Furthermore, a few EDS types share similar gene mutations. Still other clinical types have not been identified by molecular means. Therefore, such methods are not fully satisfactory for routinely identifying a number of EDS cases.

Most often, the clinical examination allows the identification and the distinction of various EDS types, particularly in the most severe presentations. By contrast, the mild clinical manifestations are commonly underestimated, and EDS diagnosis is frequently missed. Conventional histopathology of the skin brings some information about the structure of the fibrous collagen network and the aspect of elastic fibres. Immunohistochemistry looking for the aspect of Factor XIIIa dermal dendrocytes brings further insight in the tensegrity of these dermal cells that look unstimulated in most EDS cases[6]. The ultrastructure of the fibre networks is another means that has been particularly used in various EDS types and some related disorders[2,7,8].

Six main EDS types are curently recognized following clinical characteristics, specific underlying molecular defects, and patterns of inheritance. They correspond to the classic, hypermobile, vascular, kyphoscoliosis, arthorchalasia, and dermatosparaxis types, respectively. Other much less frequently seen forms include spondylocheirodysplasia EDS and musculocontractural EDS, whereas a few other additional rare variants of EDS have also been described. Some cases remain, however, unclassified. The classic and hypermobile types are the most frequent EDS conditions[9]. Major and minor characteristics are identified in most different EDS type.

In EDS classic type, most of the mutations are disclosed in COL5 A1 and COL5 A2 genes with some exceptions related to COL 1 and tenascin -X (TNX) mutations[1,10-12]. Increased skin distensibility is a major diagnostic criterion for the EDS classic type. It is commonly assessed by the easy pulling up the skin of the forearm until feeling resistance. It is better evaluated by measuring the actual tensile strength of the skin[13]. Atrophic scars, violaceous scar hyperpigmentation, exophytic molluscoid tumors, and easy bruising are common. Spheroids correspond to small, hard, freely moveable fibrotic and calcified fat lobules in the hypodermis.

Joint hypermobility is present at variable extent in EDS. It is conveniently assessed according to the Beighton scale[9,14,15]. A score reaching or over 4 or 5/9 is common in EDS. However, such score interpretation is occasionally uncertain. In fact, a number of women and children, as well as some Asian people exhibit extendable joint laxity. In addition, all joints are not assessed in the Beighton score. Furthermore, joint hypermobility becomes commonly less prominent with aging as a result of pain, sequels of traumas and surgery.

The EDS hypermobile type (former EDS III) is commonly the least severe but one of most frequent EDS types. Hypemobile EDS, and its probable related condition called family benign joint hypermobility syndrome, appear commonly as an underdiagnosed EDS hypermobile type[16]. Sporadic mutations, including COL5 A1 and TNX-B haploinsufficiency, were reported in a few hypermobile EDS, but mutations remain undisclosed in most cases. Hypermobile

EDS exhibits minimal skin changes[16-24]. Skin looks velvety and discretely hyperextensible. Scars are commonly atrophic. Striae distensae and pyezogenic papules are present in both EDS classic and hypermobile types. EDS hypermobile type and fibromyalgia are possibly related[25,26]. Absence of the lingual and inferior labial frenula was pointed up in EDS hypermobile type[27,28].

The EDS vascular type (former EDS IV) is characterized by thin, translucent, but not overextensible skin, associated with atrophic scars, easy bruising, increased risk of pneumothorax and arterial ruptures[29,30]. It is an autosomal dominant inherited disorder caused by type III procollagen gene (COL3A1). Hands and feet commonly exhibit acrogeria appearance. Pregnant women with vascular EDS are at increased risk of uterine and arterial rupture during the peripartum period, with high maternal morbidity and mortality rates[29, 31].

Distinct other EDS types are exceptional. Hypotonia, early onset scoliosis, risk of ocular rupture, and increased mortality in pregnancy occur in kyphoscoliotic EDS (EDS VI A)[32]. Skin distensibility is moderately increased, and scars are widened. In various EDS including the kyphoscoliotic type, arterial rupture is a cause of fatal outcome[33]. The musculocontractural EDS VIB presents disctinct craniofacial abnormalities, contractures of fingers and toes, widened scars, severe wrinkling as well as gastrointestinal and genitourinary manifestations. The impaired manifestations result from various genetic defects involving dermatose sulfate[34]. EDS arthorchalasia patients suffer from congenital hip dislocations and increased risk of fractures. Laxity, doughy and extreme skin fragility, poor wound healing and typical facies are major signs of human dermatosparaxis (EDS VII C), combined with premature rupture of membranes in pregnancy and spontaneous rupture of internal organs[4,35,36]. The rare EDS periodontitis variant (EDS VIII) associated classic EDS type features, periodontitis, early loss of adult dentition and leg ulcers[37].

Diverse conditions resemble EDS some aspects. One exemple is given by the cervical artery dissection of young adults[38]. Neural outcomes are typically the issue.

EDS-ASSOCIATED GYNECOLOGIC DISORDERS

EDS women are prone to various ailments including irregular menses, metrorrhagias, dysmenorrhea, dyspareunia, and vulvodynia. Chronic pains represent common neurologic complaints. They commonly represent the issue of joint laxity and dislocation. Involvement of the S2-S4 joints is responsible for the Alcock canal syndrome with pelvic pain increased by sitting.

PREGNANCY AND POST-PARTUM COMPLICATION

Preterm premature rupture of fetal membranes (PPROM) is another condition occuring, before 37 weeks of gestation and without prior labor[39]. The multifactorial causes and cofactors involved in PPROM include infections, tobacco smoking and poor socioeconomic factors. Idiopathic human PPROM is considered as an EDS subtype caused by abnormal decorin expression[3,41]. Decorin expression is regulated in normal fetal membranes, and is decreased in PPROM-related preterm birth compared to preterm birth unrelated to PPROM. In preterm with PPROM, the presence of infection is associated with significant decorin downregulation compared to preterm with PPROM without infection. The absence of decorin or the deregulation of decorin downstream pathway components alter the transcription factor p-Smad-2. PPROM is associated with a reduction in amnion collagen content, probably related to disturbance in collagen metabolism[40,42,43]. Hence, some CT disorders including EDS possibly alter fetal membranes inducing PPROM and miscarriages. Indeed, there is an increased incidence of preterm delivery and late abortions in some EDS patients[39]. The incidence is higher when the fetus is affected[44].

Severe dorsal and pelvic pains and bleeding are frequent complaints in pregnant EDS women. Major post-partum complications such as intestinal and vascular ruptures are present in vascular, kyphoscoliotic and dermatosparaxis EDS[45-48]. In contrast, pregnancy outcome remains often unaffected in EDS hypermobile type[49]. Nevertheless, some complications have been reported[50] including abnormal fetal presentations, dehiscence and delayed wound healing, uterus atonia, hemorrhage, pelvic prolapse, deep venous thrombosis and coccyx dislocation. Pelvic prolapse possibly occurs in nullipara.

DIAGNOSIS

The EDS spectrum should be suspected in front of atrophic enlarged scars and ecchymoses. The diagnosis and classification of EDS are mainly set up form typical clinical signs. Increased skin distensibility defines the ability of the skin to be stretched beyond normal limits, and rapidly returning to its original position. It is mostly important in EDS classic type. Different methods are available for assessing any abnormal skin tensile functions[13].

The Beighton score should be adequately assessed for joint laxity. Personal and familial history should be considered including preterm birth, and hip or shoulder congenital dislocations. Yet, some patients do not meet the current clinical EDS criteria. Updating the EDS nosology is welcome, for unifying available and updated diagnostic criteria.

Gene mutations are presently not yet disclosed in each EDS patient, in part due to some technical limitations in sequencing methods. Any clear phenotype-genotype correlation is established at present. Indeed, in the majority of cases of EDS classic type, collagen V mutations are identified, although distinct collagen I mutations as well as TNX defects have been reported. The latter alteration is further responsible for EDS hypermobile type. Therefore, other investigations should be carried on to establish any EDS diagnosis. Histopathological dermal changes with shrinkage of Factor XIII a+ dermal dendrocytes are observed in the EDS classic type[6] and in dermatosparaxis[4].

DERMAL ULTRASTRUCTURE CLUES

The dermal ultrastructural abnormalities are of diagnostic relevance, and they occasionally suggest the EDS type[2]. The number of dermal collagen bundles showing obvious ultrastructural changes is variable among EDS samples. In typical EDS, collagen bundles are composed of fibres exhibiting variable cross-sectional shape and area with uneven interfibre spacing out (Figure 1). In some cases of EDS hypermobile type, collagen fibres exhibit uniform large diameters. Some collagen fibres show serrated, and irregular contours as well as flower-like cross-sections (Figure 2). Unusual collagen fibres orientations appear erratic (Figure 3), associating twisted, hook-like, S-shaped, and ring-shaped structures[51]. The hieroglyphic pattern is specific for dermatosparaxis (Figure 4)

The ultrastructure of elastic fibres is commonly altered in EDS[52,53]. They have frayed contours, internal microcavities (Figure 5), elastotic

changes, and uneven distribution of electron-dense inclusions in the amorphous elastin matrix. The amount in microfibrils is variable at the periphery of the elastic fibres. They are clustered to the side of microcavities, or present as homogeneous structures or target-like figures. The proportion of altered elastic fibres differs among patients and appears unrelated to age and photo-exposure.

Granulo-filamentous deposits are found in variable amounts inside the interfibre spacing out of the collagen structures. In addition, thick stellate globules, presumably hyaluronic acid, and focal granulo-filamentous deposits are commonly disclosed in the interstitial matrix. The presumably hyaluronic acid globules are generally single, but they occasionally form chains or networks.

In EDS, type-specific ultrastructural alterations are not disclosed in collagen and elastic fibres, except for the hieroglyphic-shaped fibre cross-sections of the EDS dermatosparaxis type[2,4,35,54]. In spite of heterogeneity in both the structural and biochemical abnormalities, the pattern combinations of changes and the overall ultrastructure of the dermal changes are of diagnostic relevance. They occasionally suggest the EDS type. Furthermore, they speedily contribute to the diagnosis before getting the information form genetic screening.

Ultrastructural changes are more obvious inside the reticular dermis where collagen fibres show aspects of flower-like, unraveled, serrated, twisted and hieroglyphic fibres. In EDS classic type, the flower-like collagen fibres are rare and dispersed among round-section fibres. Their size is altered and their morphometric aspect suggests an uncontrolled fibrogenesis[3]. In EDS hypermobile type, the size of the flower-like collagen fibres is commonly smaller[16]. Collagen fibres are commonly misoriented. In most cases of EDS hypermobile type, other dermal components exhibit changes such as abnormal elastic fibres, granulo-filamentous deposits and presence of large stellate hyaluronic acid-like globules. The dermis in the EDS vascular type is slimmer to about one third. Collagen bundles and other dermal components appear loosely organized. Both the collagen bundles and their fibres are thin. Composite, notched or hiergoglyphic fibres are absent. Elastic fibres appear branched or fragmented, and they appear increased in numbers. Fibroblasts exhibit dilated endoplasmic reticulum filled with some granular material.

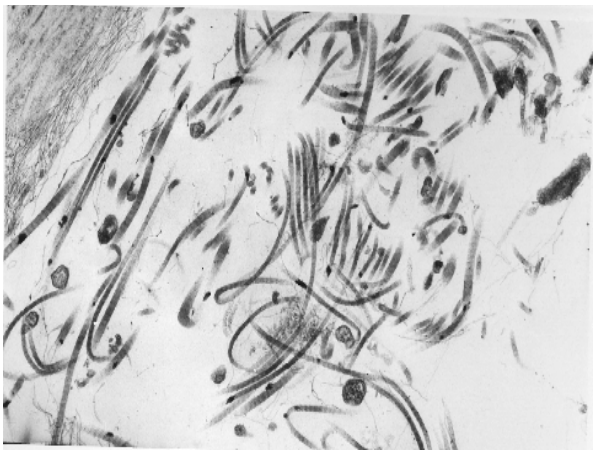

Figure 3 Misoriented loose collagen fibres.

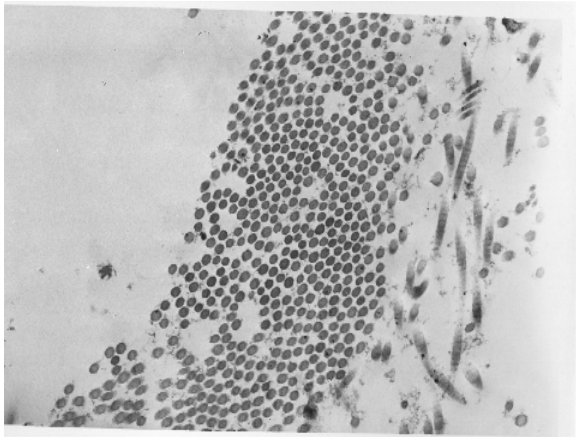

Figure 1 Irregular collagen fibre spacing out in a bundle

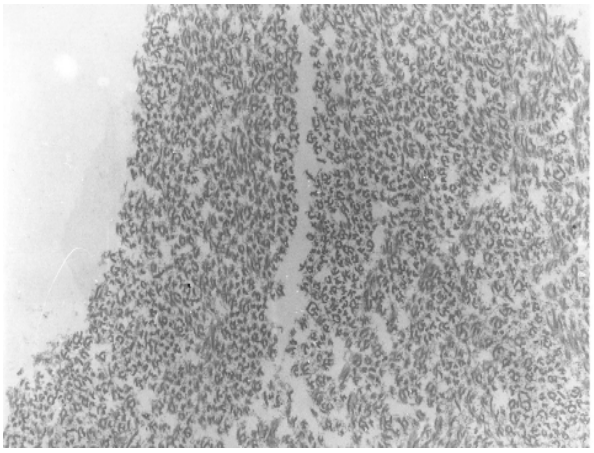

Figure 4 Hieroglyphic collagen fibres in dermatosparaxis.

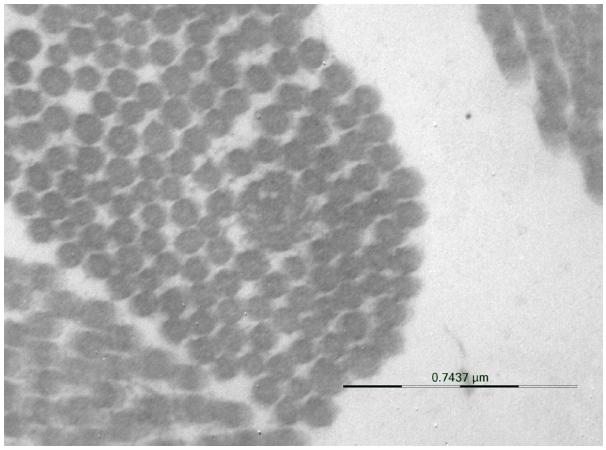

Figure 2 Large flower like fibre in a bundle of rounded collagen fibres.

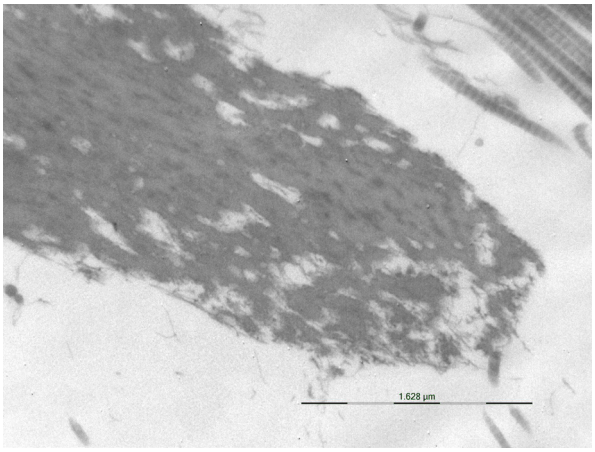

Figure 5 Elastic fibre with microcavities.

MANAGEMENT

Typing EDS and identifying their potential complications in women represent facets on important aid for familial counseling and management of diverse pains in women. It is important for these patients and their relatives to consider that pain is not always limited to a psychosomatic background.

Prenatal counseling is of the utmost importance, particularly in EDS vascular and kyphoscoliotic types, as well as in some cases of the classic type associated with the risk of arterial rupture. Indeed they present important life-threatening complications. The risk of severe morbidity and the increased mortality in parturients with vascular EDS has warranted some recommendations for modified labor management, particularly regarding the mode and timing of delivery. At present, there is however no consensus about the timing and mode of delivery for pregnant vascular EDS women. By contrast, there is a lack or only benign complications in EDS hypermobile type. However, the diagnostic established before pregnancy helps to map out specific management procedures and reduces some post-partum complications. Cesarean section helps minimizing the risk of pelvic prolapse. Because of weakening in wound healing, waiting time before removal of suture stitches after cesarean or episiotomy is commonly extended.

Prophylaxis helps reducing the risk of cardiovascular dysautonomia during general anesthesia and cerebrospinal fluid leakage in peridural anesthesia. The risk of pregnancy-related complications is increased in women with vascular EDS compared with the general population. However, survival data indicate that pregnancy does not appear to affect overall mortality compared with nulliparous women with vascular EDS.

CONCLUSIONS

A number of gynecologic and obstetric complications possibly take place in EDS women. Physicians should pay special attentive to a series of signs of this heterogeneous syndrome. Some cutaneous signs, including increased skin distensibility and presence of velvety translucent skin and atrophic scars, should evoke EDS diagnosis. Determination of the EDS type is basically rooted on the sound evaluations of the clinical presentation. It is further established or confirmed by dermatopathology, particularly ultrastructural observations of the dermis. In some cases, particularly in the classic and vascular types, the identification of specific genetic mutations is particularly useful.

Determination of EDS types is important for reproductive counseling and pregnancy management. It is advisable to get a preconceptional diagnosis for adequate management of these patients. It remains that the EDS clinical phenotype is occasionally disturbing and associated with an unusual genotype. Such presentations suggest heterozygous variants of unknown significance. For management, a mutldidisciplinary approach and consideration of phenotype is recommended, rather than any procedure based on genotype alone.

There is an increased prevalence of obstetric and gynecologic issues encountered by women with EDS than in the general population. Additionally, rates differ significantly among the most common EDS types with vascular lesions having the highest rates of adverse pregnancy outcomes and gynecologic dysfunctions. Although EDS vascular type is a rare condition, it is critical that physicians be aware of this disease because it presents unique management challenges.

Obstetric guidelines are not fully established for EDS patients. The management should be made individually according to the EDS severity. In EDS classic and hypermobile types, maternal and fetal outcomes are generally favorable, but maternal complications related to the abnormal CT, occur more often than in the general population. EDS vascular and kyphoscoliotic types, as well as some cases of the classic type, are occasionally associated with severe maternal morbidity and even mortality.

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CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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