Ehlers-Danlos Syndrome in Pregnancy: a Review

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Abstract

Ehlers-Danlos syndrome (EDS) is a group of connective tissue disorders that can result in a range of complications during pregnancy. Pregnant EDS patients generally have a favourable outcome, but those with vascular EDS are more likely to suffer from severe maternal complications. Early diagnosis of EDS and subtype characterization can aid in pre-pregnancy counselling, planning of antenatal care, risk assessment of obstetric and neonatal complications, and influence both obstetric and anaesthetic management of these patients. This piece aims to outline the obstetric implications of classical, hypermobile, and vascular EDS, and review the current literature regarding their optimal obstetric management.

TWEETABLE ABSTRACT

EDS affects obstetric management, especially in vEDS. Evidence is limited, but recommendations are provided.

KEYWORDS

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Medical conditions in pregnancy

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BACKGROUND

Ehlers-Danlos syndrome (EDS) is the name given to a group of monogenic conditions with variable systemic manifestations that predominantly affect the skin, joints, ligaments, vasculature, and internal organs.[1] Common clinical features among different types of EDS include joint hypermobility, frequent joint dislocations, and skin hyperextensibility. Although various mutations and types of EDS exist, most forms of EDS result from a genetic mutation in collagen proteins or enzymes involved in collagen biosynthesis or organisation.[2] Inheritance is usually autosomal dominant, with *de novo* mutations being relatively common, and estimates of prevalence range from 1 in 20,000 to nearly 10 in 5,000.[3–5]

Considering the multisystemic effects of EDS on the body, it is not surprising that the condition complicates pregnancy and delivery. A recent population-based retrospective study examining EDS in pregnancy suggests that the overall prevalence is 7 per 100,000 births on average during the period studied, with prevalence increasing every year – likely due to recent advances in EDS classification and genetic techniques.[6] In this cohort examining 1,042 pregnant patients with EDS, pregnancy in EDS was associated with intrauterine

growth restriction and higher rates of maternal death and obstetric complications, including prematurity, cervical incompetence, antepartum haemorrhage, and placenta praevia.[6] Despite the higher prevalence of complications associated with EDS in pregnancy, there is limited evidence and guidance regarding the optimal management of individuals with EDS. This piece aims to provide an overview of the obstetric implications of the most common forms of EDS, namely the classical, hypermobile, and vascular types, and review the current literature regarding their optimal obstetric management.

CLASSIFICATION OF EDS

Categorization of the Ehlers-Danlos syndromes began in the late 1960s and was formalized in the Berlin nosology. Over time, it became apparent that the diagnostic criteria established previously did not discriminate adequately between the different types of Ehlers-Danlos syndromes. With advances in technology, the genetic and molecular basis of several Ehlers-Danlos syndromes were uncovered, adding a new dimension to the classification of this group of disorders. Consequently, a revised classification named the "Villefranche Nosology" was published in 1997 with defined diagnostic criteria and laboratory findings whenever possible for each type.[7] This simplified classification has facilitated an accurate diagnosis of the Ehlers-Danlos syndromes and has contributed to the delineation of phenotypically related disorders. Except for the hypermobility type, the genetic mutations involved have been identified and can be precisely identified by specific testing. Since then, with the development of genetic analysis techniques, such as next-generation sequencing, and greater research into EDS, new mutations and subtypes have been discovered. These new findings have culminated in the new 2017 international classification of EDS, which is summarised in Table 1.[2]

TYPES OF EDS AND EFFECTS OF EDS ON PREGNANCY

Classical and Hypermobile EDS

Classical EDS (cEDS) and hypermobile EDS (hEDS) account for most individuals diagnosed with EDS. cEDS is an autosomal dominant disorder typically caused by a mutation in collagen type V (COL5A1, and COL5A2), although some patients may have abnormalities in collagen type I (COL1A1).[2] Collagen type V is mainly found as a heterotrimer along with collagen type I in various tissues, including skin, tendon, bone, and the cornea.[8] Consequently, the dominant clinical manifestations include skin hyperextensibility, atrophic scarring, poor wound healing, and joint hypermobility. Similarly, hEDS is an autosomal dominant condition characterised by joint hypermobility, although the exact genetic mechanisms are yet to be discovered.[5] As the molecular mechanisms are largely unknown, diagnostic criteria for hypermobility EDS (hEDS) is based on strict clinical findings of generalized joint hypermobility and evidence of syndromic features (skin hyperextensibility, smooth velvety skin, atrophic scarring), musculoskeletal complications, and/or family history.[2]

Although pregnancy is generally well-tolerated in patients with cEDS and hEDS, the conditions have wide-ranging obstetric implications for the mother and the foetus. For the mother, the pregnancy-related release of relaxin can exacerbate joint hypermobility and pain, especially within the pelvic region.[9,10] Interestingly, it was found that prematurity and premature rupture of membranes were twice as more common in foetuses with EDS with healthy mothers, compared to foetuses without EDS in EDS-affected mothers. This suggests that amnion-related abnormalities could mediate higher rates of prematurity, especially in cEDS as collagen types I and V are known components of the amnion.[8,11] Cervical insufficiency could also contribute, with collagen types I and V playing a key role in the structural integrity of the cervix.[12] Finally, with pelvic connective tissue hypermobility and poor tissue healing, cEDS and hEDS pregnancies experience higher rates of perineal tearing, postpartum haemorrhage, pelvic prolapse and incontinence following delivery.[13–15] For the foetus, although no formal studies on intrauterine growth restriction (IUGR) in specifically cEDS or hEDS have been performed, large population studies on EDS in general and case studies have demonstrated IUGR in both conditions.[6,16,17] This is thought to be associated with placental defects, with a case study demonstrating IUGR in cEDS related to abnormal placental vascular resistance.[17]Further research needs to

be done to elucidate the prevalence and mechanisms of IUGR in cEDS and hEDS.

Considering these complications, it may be beneficial to advise pregnant women with cEDS and hEDS about the risks of IUGR, PROM and premature labour, and adequate screening for the former should be done. Cervical length screening and cervical cerclage may be helpful in managing cervical insufficiency. Echocardiography should be completed to monitor for known aortic root dilation, considering its high prevalence in both cEDS and hEDS, and the cardiovascular stresses of pregnancy.[18] Early identification can lead to a prompt referral and appropriate management, minimising further risks. Regarding delivery options, no clear evidence for or against vaginal or caesarean sections currently exist in the literature.[15,19] For vaginal delivery, prompt episiotomy should be considered to prevent excessive perineal damage and should be repaired by an experienced individual due to the tissue fragility in cEDS and hEDS.[15] Furthermore, considering the joint hypermobility and propensity for dislocation, special care must be taken to prevent hip or knee dislocation in the peripartum period, especially when regional anaesthesia is utilised. It must also be noted that studies have demonstrated reduced efficacy of regional anaesthesia in hEDS, and careful anaesthetic input is advised.[20,21]For hEDS specifically, additional attention may be needed in individuals who suffer from postural orthostatic tachycardia syndrome (PoTS), characterised by orthostatic tachycardia without hypotension and symptoms. PoTS can complicate delivery due to haemodynamic instability, especially in vaginal delivery with epidural anaesthesia and in caesarean sections. Karthikeyan and Venkat-Raman recommend combined spinal-epidural anaesthesia for caesarean delivery.[15]Finally, considering the risk of postpartum haemorrhage in cEDS and hEDS, prophylactic desmopressin (DDAVP) and tranexamic acid, along with postpartum oxytocin may be beneficial.[15] However, it is important to note the effectiveness of these interventions has not yet been examined in clinical trials, and the extent of the benefit is unclear. Further work needs to be done in order to formalise management guidance in patients with cEDS and hEDS.

Vascular EDS

Vascular EDS (vEDS) is arguably the most life-threatening form of EDS. It is an autosomal dominant disorder of connective tissue caused by mutation of the COL3A1 gene which encodes the pro-alpha-1 chains of type III collagen.[22] Type III collagen is found within the skin, vessel walls and viscera, and is responsible for structural integrity.[23] As such, individuals with vEDS are prone to vascular rupture (i.e. aortic dissection), organ rupture (i.e. bowel perforation, uterine rupture) and fistulae formation (i.e. carotid-cavernous sinus fistulae).[24] These conditions form the major criteria for clinical diagnosis of vEDS according to the 2017 EDS guidelines.[2] Clinical suspicion can also be raised on characteristic facial features, thin translucent skin, talipes equinovarus, congenital hip dysplasia, and increased bruising, although these features are often recognised in retrospect.[2,24]

Due to these complications, vEDS is seen as the most life-threatening form of EDS. The significance of these problems is magnified in pregnancy and especially during the peripartum period when uterine contractions begin to appear. The contractions themselves increase stress on a structurally weaker uterus, increasing the risk of uterine rupture, and also facilitate increase in blood volume, heart rate, and blood pressure, which can increase the risk of vessel rupture and dissection[25]. Valsalva-associated increases in abdominal pressure during contractions can also increase vascular and organ transmural pressures, increasing the risk of vessel and hollow organ rupture.[26] As such, it is not surprising that pregnancy-related deaths in women with vEDS occur in around 5% of deliveries, which is nearly 300 times the maternal mortality rate in the local population studied.[27] Interestingly, pregnancy and delivery do not seem to alter survival rates overall according to the largest survival analysis to date, contrary to the established opinion that pregnancy should not be considered in vEDS due to the mortality risk.[27,28]

In addition to EDS-specific complications, there is a greater prevalence of obstetric complications in women with vEDS. Pre-term births have been reported to occur with a prevalence of 19%, likely associated with cervical insufficiency and/or preterm PROM.[27,29] Due to the fragility of the skin and connective tissues, 3rd and 4th-degree perineal tears are almost 20-fold more prevalent in vaginal deliveries in vEDS[27]. Finally, postpartum haemorrhage is also reported to be more common, possibly due to greater vascular rupture, higher

rates of uterine rupture, and problems with haemostasis secondary to platelet aggregation dysfunction.[24,30]

Despite the risks associated with vEDS, formal obstetric guidelines on vEDS do not yet exist, perhaps due to the rarity of the condition making it difficult to conduct controlled trials and build a solid evidence base. A multidisciplinary approach, including input from cardiovascular and genetic specialists, is likely to improve outcomes for patients. The European Society of Cardiology (ESC) recommends that celiprolol, a β_1-adrenoreceptor antagonist and β_2-adrenoreceptor agonist, be used in pregnancy.[28] Celiprolol has been demonstrated to reduce vascular complications in an open randomised trial and an observational study, although both studies have significant limitations.[31,32] In theory, the tocolytic β_2-agonist action could also be beneficial in preventing premature contractions and delivery associated with vEDS. From a genetic point a view, it may be valuable to genetically screen for patients with vEDS in high-risk groups (i.e. positive family history) or on clinical suspicion. For instance, Murray and colleagues argue that being aware of the risk associated with vEDS can direct clinicians to manage pregnancy and delivery in tertiary care settings.[27] Moreover, considering the differences in survival depending on the mutation type, genetic testing may be able to help guide clinical decision-making.[33] However, this may be difficult to implement as de-novo mutations in COL3A1 are common, and as the majority of women are genetically diagnosed after pregnancy.[27]Many case reports describe the first presentation of vEDS in the perinatal period. Patients have presented with severe and often deadly complications including uterine rupture as a primigravida, coronary artery dissection, aortic dissection, and inferior vena cava rupture.[34–37]

In terms of obstetric management, early elective caesarean section, with prophylactic DDAVP and tranexamic acid to support haemostasis and sufficient transfusion preparation, is thought to minimise complications although no empirical studies have been performed to assess this[29]. Theoretically, caesarean section would minimise labour-related risks and enable greater haemostasis control. However, caesarean section is also not without excess risk in vEDS. With fragile vessels and organs, arterial damage and haemorrhage are more likely and bowel rupture can occur during the procedure.[38] The risk of wound dehiscence is likely increased due to the thin and friable skin.[39]Anaesthesia choice is also a key factor, with local and generalised anaesthesia having distinct advantages and disadvantages. Neuraxial blockade poses a risk of perforation, nerve injury, hematoma.[29,40] Techniques such as single-shot spinal anaesthsia may not provide sufficient anaesthetic coverage to manage intraoperative haemorrhage and organ rupture.[41] On the other hand, generalised anaesthesia may face difficulties with intubation, as atlantoaxial sublaxation has been reported in patients with vEDS, and a greater risk of ventilation-associated pneumothorax due to lung tissue fragility.[40,42,43] Nonetheless, both Orphanet UK emergency guidelines and Wiesmann and colleagues' recommendations for anaesthesia in vEDS suggest the use of generalised anaesthesia due to the potential risks of neuraxial blockade and lack of clear evidence of benefit.[29,42] If the patient proceeds with vaginal delivery, epidural anaesthesia may be beneficial in reducing excess maternal effort and the pain-associated sympathetic response, which can increase blood pressure.[37] Again, haemostasis support with tranexamic acid and DDAVP is likely to be beneficial. Orphanet UK guidelines for vEDS recommend that steps be taken to strengthen the perineum and to strongly avoid using forceps, considering tissue fragility and risk of severe perineal tearing.[42] Finally, regardless of caesarean or vaginal delivery, patients should be closely monitored in hospital in the postnatal period for delayed complications.

CONCLUSION

With a wide range of phenotypes in EDS, combined early clinical and accurate molecular diagnosis can have a profound effect on the management of pregnant patients with EDS. As molecular diagnosis has become more widely available, subtyping EDS patients has become more accessible and the estimated prevalence is growing. One of the issues in studies investigating outcomes of pregnancy in EDS is the lack of clearly distinguished subtypes. Relying solely on isolated case reports does not provide a full picture of the scale of obstetric complications, with selection and reporting bias being a key issue. Regardless, certain dominant obstetric features in the classical and hypermobile subtypes have emerged: prematurity from cervical insufficiency or PROM, pelvic girdle pain or issues related to the pelvic floor. Perhaps of greater consequence, vascular EDS predisposes a significant risk of vessel rupture and perineal tears and may benefit from early caesarean

delivery with specialist anaesthetic input. It is clear that further prospective research needs to be conducted in individuals with specific subtypes of EDS. With this in mind, the current review has attempted to highlight the obstetric complications of each subtype and to suggest potential management considerations based on clinical features and the limited evidence base.

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JK: writing, editing

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TABLE CAPTION LIST

Table 1: Types of Ehlers-Danlos Syndrome, adapted from Malfait et al.[2]

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