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# More Than Hypermobility: Understanding Ehlers-Danlos Syndrome in Women – A Literature Review

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## ABSTRACT

Hypermobile Ehlers-Danlos Syndrome (hEDS) is one of 13 recognised subtypes of inherited connective tissue disorders known as Ehlers-Danlos syndrome. It is the most common form, accounting for 80-90% of cases. The disease is estimated to affect 1 in 5000 people, with a gender ratio of 10 women to 1 man. This paper aims to evaluate the symptoms and manifestations of hEDS in women and to identify the factors that lead to delayed or missed diagnosis. The higher prevalence of hEDS in women, the observed later diagnosis in girls during childhood, and the significant negative consequences of diagnostic delays require a greater focus on earlier diagnosis and proper management. Greater educational efforts directed at clinicians are needed to ensure timely identification and appropriate care for women with hEDS.

**Keywords:** hEDS, hypermobile Ehlers-Danlos Syndrome, women, hypermobility

## 1. INTRODUCTION

Ehlers-Danlos Syndromes (EDS) are a diverse group of inherited connective tissue disorders primarily characterized by abnormalities in collagen synthesis. This leads to fragility of soft connective tissues and widespread manifestations throughout the body, including the ligaments, joints, blood vessels, skin, and internal organs. There are 13 recognized subtypes of EDS. The hypermobile form (hEDS) is the most common, accounting for an estimated 80–90% of EDS cases. Unlike most other EDS subtypes, hEDS currently has no identifiable associated genetic mutation, and its diagnosis relies on a set of clinical criteria. Generalized Joint Hypermobility (GJH) and Hypermobility Spectrum Disorders (HSDs) are related conditions, with HSDs being the most common forms of symptomatic GJH, as well as hEDS.

Ehlers-Danlos syndrome (EDS) is estimated to affect 1 in 5,000 individuals worldwide, with a ratio of 10 women for every one man. Despite this, one study focusing on children with HSD or hEDS found that boys received their diagnosis, on average, just over two years earlier than girls in the hEDS group (mean age at diagnosis was 6.82 years for boys vs. 8.71 years for girls). Similarly, in the HSD group, boys were diagnosed about one year earlier than girls (Kindgren et al., 2021). Additionally, the prevalence of hEDS may be significantly higher than previously estimated, possibly affecting 0.75–2% or even up to 3.4% of the population (Gensemer et al., 2021). These calculations suggest millions of undiagnosed women who are not receiving appropriate treatment for their symptoms and are at risk of serious medical consequences due to complications of undiagnosed hEDS.

Up to 56% of patients with EDS receive a misdiagnosis, and 70% undergo inappropriate treatments, with diagnosis taking as long as 28 years from symptom onset (Glans et al., 2021). Girls are often diagnosed later than boys, despite the higher prevalence in women, and these diagnostic delays contribute to worsening health outcomes and prolonged suffering.

This paper aims to evaluate the symptoms and manifestations of hEDS in women and to identify the factors that lead to delayed or missed diagnosis. The higher prevalence of hEDS in women, the observed later diagnosis in girls during childhood, and the significant negative consequences of diagnostic delays require a greater focus on earlier diagnosis and proper management. Efforts to raise awareness amongst medical professionals are crucial.

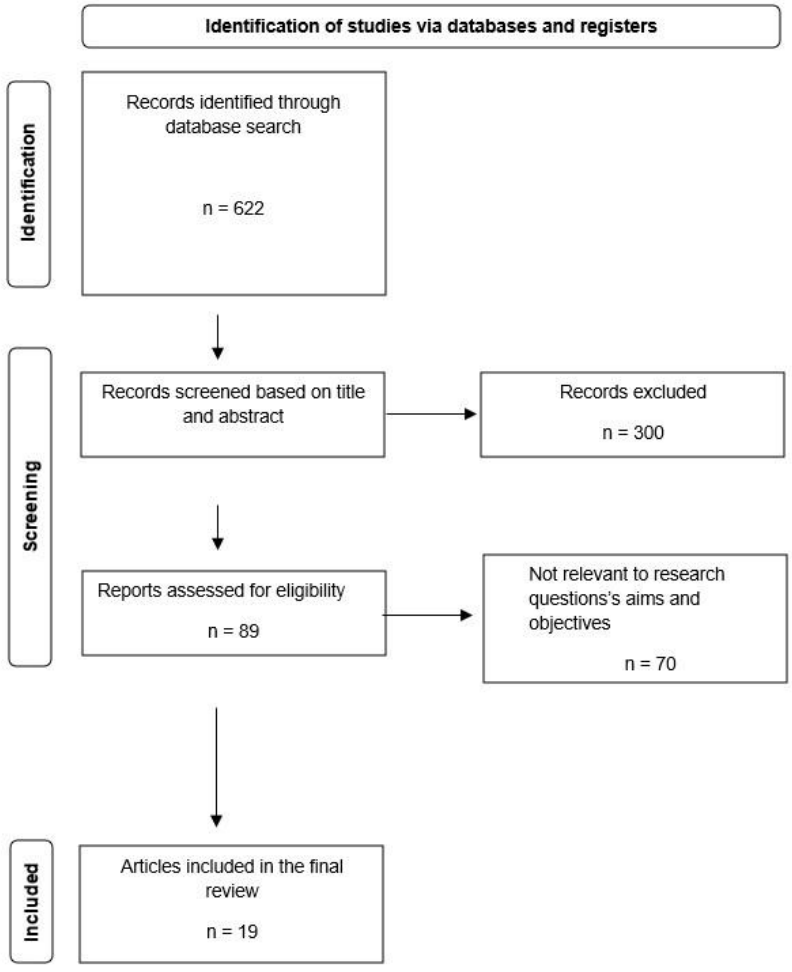


**Figure 1**. PRISMA 2020 flow diagram of study selection

## 2. REVIEW METHODS

A systematic search of PubMed was conducted for scientific papers published between January 2015 and June 2025, using the terms "hypermobile Ehlers-Danlos syndrome," "hEDS," and "women." This yielded 389 records. Additional older publications were considered only if recent evidence was insufficient. All 389 records were screened by title and abstract. A total of 300 records were

excluded at this stage for not meeting the eligibility criteria (non-hEDS population, non-female cohorts, unrelated comorbidities, case reports, or not published in English).

The remaining 89 articles were retrieved for full-text assessment. Of these, 70 were excluded due to insufficient clinical relevance (e.g., narrative overviews, mixed connective tissue disorders without specific hEDS subgroup analysis, editorials, or inadequate data on women).

In total, 19 studies satisfied the inclusion criteria and were included in the analysis. Analysis of these studies focused on shared themes, reported clinical features, and areas where further investigation is needed in relation to hEDS in women. A PRISMA 2020 flow diagram summarizing the selection of studies is displayed in Figure 1.

## 3. RESULTS & DISCUSSION

**Early Symptomatic**

Hypermobile Ehlers-Danlos syndrome (hEDS) is characterized by generalized joint hypermobility (GJH) and joint instability resulting from the laxity of ligaments, joint capsules, and tendons. This inherent laxity makes joints more prone to injury. In childhood, often the first phase of hEDS progression, individuals may experience frequent dislocations and subluxations, even in the absence of pain. These can also occur with minimal trauma. Early complications also include sprains and soft tissue lesions. Such injuries are highly relevant to activities involving movement and impact, such as sports, and may lead to the first doctor referrals for patients with hEDS.

In hEDS, the hypermobility is systemic and pathological, making individuals inherently vulnerable to injuries from forces that would be considered normal or minor for others. It is crucial to assess patients who present with these injuries for hEDS, since GJH often precedes systemic manifestations, which can further complicate the diagnostic process (Hakim et al., 2017; Gensemer et al., 2021).

**Systemic Manifestations**

Outside symptoms commonly associated with hypermobile Ehlers-Danlos syndrome (hEDS), such as joint hypermobility, affected patients present with a plethora of other symptoms that can mimic various other conditions, which makes the diagnosis even more challenging.

Cardiovascular and autonomic dysfunction (dysautonomia) are significant and frequent comorbidities of hEDS. Postural Orthostatic Tachycardia Syndrome (POTS) is a manifestation characterized by an exaggerated increase in heart rate upon standing, accompanied by a minimal or no drop in blood pressure. Proposed mechanisms for dysautonomia in hEDS include increased vascular and venous compliance. Lax connective tissue can lead to blood pooling in the lower extremities when upright, thereby affecting vasoconstriction and venoconstriction. This can result in orthostatic intolerance (Gensemer et al., 2021).

There is a strong and consistently reported association, as well as a high concurrence rate, between hEDS (and generalized joint hypermobility, GJH) and POTS. Some studies report that 18 up to 31% of POTS patients have hEDS, and 24% have GJH without meeting full hEDS criteria. Symptoms resembling POTS can also occur in hEDS patients due to possible brainstem or cervical cord impingement caused by Chiari malformation or craniocervical instability. Compared with the general population, these conditions appear more frequently in individuals with hEDS (Qarajeh et al., 2021). Since POTS symptoms—light-headedness, visual disturbances, palpitations, and nausea—are not unique, they may resemble psychiatric disorders such as anxiety or panic attacks. This similarity highlights the importance of cautious differential diagnosis in hEDS. Mild Mitral Valve Prolapse (MVP) and Aortic Root Dilatation (ARD) are also sometimes observed. Aforementioned conditions are included in the diagnostic criteria, although they are less common than in other EDS types (Riley, 2020).

Patients with hEDS may also experience Mast Cell Activation Syndrome (MCAS), where mast cells are overactive and degranulate inappropriately, causing too much histamine release and widespread symptoms. The most common symptoms of MCAS are fatigue, urticaria, and other skin manifestations, gastrointestinal symptoms such as nausea and vomiting after consuming certain products. The mechanism connecting hEDS to MCAS is thought to involve mast cells residing in connective tissue, which are changed by improper formation of collagen (Gensemer et al., 2021).

Joint hypermobility disorders have also been linked to neurodivergence. In attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) populations the prevalence of hEDS is significantly increased compared to populations without neurodevelopmental changes. It is inconclusive whether the two aforementioned conditions are related to each other or just commonly comorbid. There is a lack of understanding of factors leading to the development of ADHD, ASD, and hypermobility disorders, although genetic factors seem to be largely involved in these conditions (Csecs et al., 2022).

Gastrointestinal (GI) dysfunction is a highly prevalent comorbidity in patients with hEDS, although it is not yet considered a diagnostic criterion. Symptoms include abdominal pain, bloating, nausea, reflux, vomiting, and altered bowel habits. Dysmotility and delayed gastric emptying (gastroparesis) are notably of higher incidence in populations with hEDS and POTS (Riley, 2020). An impaired systemic sympathetic response may lead to increased postprandial mesenteric blood flow and splanchnic capacitance. Abnormal collagen organization in the smooth muscle of the gastrointestinal tract has been linked to anatomical complications such as diverticulosis, rectoceles, and prolapse. Increased permeability of gut mucosa, possibly driven by defects in the extracellular matrix (ECM) as well as increased abdominal visceral mobility due to lax peritoneal ligaments, may also play a role.

Gastroparesis is a chronic condition marked by delayed gastric emptying without any mechanical blockage. It has a known association with hEDS and POTS. While often underreported, gastroparesis seems to occur at a noticeably higher rate in these groups compared to the general population. Autonomic dysfunction (dysautonomia) is highlighted as a primary contributor to GI problems in hEDS and POTS. This dysregulation of sympathetic inhibitory responses may lead to uncoordinated GI activity (Gensemer et al., 2021; Gerogiannis, 2020). GI symptoms can be severe enough to cause reduced oral and fluid intake, leading to dehydration and malnourishment, which can directly worsen POTS symptoms.

**Pain And Fatigue**

Chronic pain is nearly universal in hEDS patients, progressing over time. It can be neuropathic, stemming from nerve stretch or compression due to joint laxity (Sundelin et al., 2017; Gerogiannis, 2020).

Chronic fatigue is a prevalent and vital symptom in hEDS. It is defined as fatigue lasting more than 6 months, not due to exertion, not substantially alleviated by rest, and causing significant impairment in activities. There is a considerable overlap in the symptoms and findings of hEDS and chronic fatigue syndrome (CFS). An important challenge is that CFS diagnostic criteria often require fatigue to be "unexplained by other conditions." Therefore, a diagnosis of hEDS might formally exclude a CFS diagnosis, or conversely, hEDS is likely substantially underdiagnosed in patients labeled with CFS. In patients with hEDS, fatigue may be driven by a combination of poor sleep quality, chronic pain of different origins, autonomic dysfunction like POTS, gastrointestinal and urological difficulties, psychological conditions such as depression or anxiety, low physical fitness, and nutritional shortfalls. Generalized hyperalgesia and a deficit in endogenous pain inhibitory control have been reported (Hakim et al., 2017; Gensemer et al., 2021).

Because hEDS affects multiple body systems, individuals are at increased risk for overlapping disorders, including CFS, MCAS, POTS, and a variety of gastrointestinal problems. Because these conditions share many features, diagnosing them can be difficult. Managing Ehlers-Danlos syndrome is therefore best approached through coordinated, multidisciplinary care.

**Table 1**: Multisystem Involvement in hEDS.

| System | Key Symptoms & Manifestations | Clinical Concerns | References |
|---|---|---|---|
| **Musculoskeletal** | Joint hypermobility; Dislocations/subluxations; Chronic pain; Early osteoarthritis | Injury risk; Physical therapy needs | Gensemer et al., 2021; Lee & Strand, 2017 |
| **Cardiovascular/ANS** | Postural orthostatic tachycardia syndrome (POTS); Orthostatic intolerance; Mitral valve prolapse (MVP); Aortic root dilatation | May mimic anxiety; Requires cardiac evaluation | Riley, 2020; Glans et al., 2021; Cederlöf et al., 2016 |
| **Gastrointestinal** | Reflux; Gastroparesis; Bloating; Constipation/diarrhea | Risk of malnutrition, dehydration; Often misdiagnosed as IBS or eating disorder | Gerogiannis, 2020; Wu & Ho, 2024 |
| **Gynecological/Obstetric** | Dysmenorrhea; Menorrhagia; Recurrent miscarriage; Pelvic organ prolapse (POP) | Pregnancy complications; Requires individualized obstetric care | Hakim et al., 2017; Karthikeyan & Venkat-Raman, 2018 |
| **Urological** | Incontinence; Bladder diverticula; Vesicoureteral reflux (VUR); Recurrent urinary tract infections (UTIs) | Early onset pelvic floor disorders | Riley, 2020; Gensemer et al., 2021 |
| **Neurological/Pain** | Headaches; Neuropathic pain; Brain fog; Temporomandibular joint (TMJ) instability | May be mistaken for psychosomatic; Often co- | Fajardo-Jiménez et al., 2022; Lee & |

| | | | |
|---|---|---|---|
| | | occurs with fatigue and dysautonomia | Strand, 2017; |
| **Dermatological** | Skin fragility; Easy bruising; Poor wound healing | Surgical complications; Risk of scarring, dehiscence | Hugon-Rodin et al., 2016; Riley, 2020; |
| **Immunological** | Mast cell activation syndrome (MCAS); Rashes; Hives; Food/environmental sensitivities | Often overlaps with allergies; Can affect multiple systems | Gensemer et al., 2021 |
| **Psychiatric/Neurodivergent** | Anxiety; Attention-deficit/hyperactivity disorder (ADHD); Autism traits; Depression | Risk of mislabeling as functional or somatic; May delay hEDS diagnosis | Riley, 2020; Song et al., 2021 |

**Ehlers-Danlos Syndrome in Women**

Women living with hypermobile Ehlers-Danlos syndrome (hEDS) or hypermobility spectrum disorders (HSD) commonly face reproductive health difficulties. These may appear as gynecological issues, complications during pregnancy, or problems after childbirth (Table 2). Unfortunately, the presentation is often overlooked, which can delay diagnosis and limit the quality of management provided. The lack of training regarding women's hEDS manifestations further adds to these challenges.

Women with hEDS frequently report significant gynecological complaints, including menorrhagia reported by 76% of women in one study (Hugon-Rodin et al., 2016). This is often due to capillary fragility and weakness of the perivascular connective tissue, rather than clotting disorders. Dysmenorrhea is present in 72% of women, and notably, its frequency does not significantly decrease with age or after deliveries, unlike idiopathic dysmenorrhea. In women with hEDS, 61% of those who had engaged in sexual activity reported dyspareunia. The overlap with symptoms typically attributed to endometriosis can lead to diagnostic errors and sometimes even unwarranted or risky surgical treatment. Studies indicate that the actual rate of endometriosis is not increased in the Ehlers-Danlos syndrome (EDS) population (3–6%). This suggests that the symptom overlap may be the reason for overdiagnosis (Karthikeyan & Venkat-Raman, 2018; Hugon-Rodin et al., 2016).

Women with hEDS exhibit a markedly higher incidence of both spontaneous abortion—reported in approximately 28% of pregnancies—and recurrent miscarriage, with 13% of affected women experiencing three or more losses with the same partner. The underlying pathophysiology remains poorly understood. Proposed mechanisms include increased uterine contractility, cervical insufficiency, and implantation abnormalities. Although some questionnaire-based studies have suggested elevated rates of preterm birth (exceeding 21%), findings from larger, population-based studies have been inconsistent. For example, a Swedish cohort study reported no significant increase in preterm delivery (3.2% in the hEDS group vs. 4.9% in controls) (Sundelin et al., 2017). However, women with EDS are at a higher risk for cervical incompetence (over three times the risk), a known risk factor for preterm birth, likely due to structurally altered collagen in the cervix. Close cervical surveillance during pregnancy is recommended for these women. Pregnant women with EDS have an increased risk of antepartum hemorrhage and are more than twice as likely to experience placenta previa. This is related to their tissue fragility.

Further research is warranted to clarify the relationship between connective tissue disorders such as EDS and abnormal placentation. Cesarean sections are reported more frequently in women with EDS, typically for common obstetric indications such as arrested labor. At the same time, psychological concerns can shape decision-making; many women express fear of joint instability or dislocation during childbirth, which may alter delivery planning. Choosing the optimal delivery route is complex. Vaginal births may proceed with unusual rapidity, but fragile tissues increase the likelihood of major perineal injury. Cesarean delivery, while often considered, also presents distinctive risks for these patients. Complications such as poor wound healing, dehiscence, and incisional hernias are more common and are often made worse by the connective tissue fragility associated with the condition. Delivery decisions in hEDS are best made on a case-by-case basis rather than by following fixed guidelines. During operations, minimizing trauma through delicate handling and reinforced closure lowers complication risk. Another difficulty is that some patients respond poorly to local anesthetics, so the usual doses may fail to provide full relief. Consequently, higher doses or more frequent administration of anesthetics might be necessary during interventions such as episiotomy repairs or cesarean sections. Female patients with EDS typically have longer postpartum hospital admissions. It is suspected to be an effect of higher rates of C-sections and preterm deliveries observed in this group of patients (Spiegel et al., 2020; Karthikeyan & Venkat-Raman, 2018).

Pelvic Organ Prolapse (POP) is considerably more common in women with EDS and Joint Hypermobility Syndrome (JHS), with prevalence estimates ranging from 29% to 75% in EDS and around 73% in JHS. Furthermore, these women tend to experience POP at an earlier age and with greater severity than those in the general population. POP can complicate the postpartum period in affected patients. Urinary incontinence (UI) is also common, affecting 50–60% of EDS patients and 40–73% of JHS patients, with a significant impact on quality of life. Pediatric studies also show an increased prevalence of UI in children with generalized joint hypermobility.

Bladder diverticula and Vesicoureteral Reflux (VUR) are frequently reported in EDS patients. VUR is significantly increased in children with generalized joint hypermobility and is often more severe than in the general population. Recurrent urinary tract infections are also reported, particularly in those with bladder diverticula. Nocturia and dysuria have been reported, as well as bladder hypocontractility and non-neurological vesico-sphincter disorders (Glans et al., 2021; Gensemer et al., 2021).

There is a strong hormonal influence on hEDS symptoms, with a divergence in sex ratio from adolescence. A considerable number of women (approximately 52%) report a worsening of hEDS symptoms during puberty, which may be related to rapid growth or increased estrogen levels. Symptoms can also intensify during the perimenstrual phase, throughout pregnancy, and in the postpartum period. Conversely, some women report improvement in symptoms after menopause and with the use of progestin-only contraceptives. Ligament laxity in the general population is known to be influenced by hormones such as estrogen, progesterone, relaxin, and testosterone, with increased laxity and an increased risk of injury during high-estrogen phases of the menstrual cycle. Although hormonal effects on joint laxity are well documented in the general population, comparable studies in hEDS remain scarce, leaving important gaps in understanding female-specific manifestations. (Gensemer et al., 2021; Francis & Dickton, 2021).

**Lactation-Specific Challenges**

In women with hypermobile Ehlers-Danlos syndrome (hEDS), hypermobility can cause dislocations or subluxations with surprisingly little pressure — for example, during breastfeeding, especially when adjusting how the breast is held. Simple daily activities, like washing one's hair, can sometimes lead to shoulder dislocations—particularly in the postpartum period, when changes in breast weight may increase the risk. Skin fragility presents an additional challenge, with bruising or tearing potentially resulting from an improper latch or infant biting. Moreover, ligament laxity can lead to "shearing injuries" as breast tissue moves. Raynaud's syndrome, which frequently occurs in Ehlers-Danlos syndrome (EDS), can worsen nipple and breast pain. Finally, abnormal collagen may affect how the smooth muscle in the breast functions, making milk let-down difficult or sometimes causing milk to flow too forcefully. For many new mothers with EDS, fatigue is intensified by the combined burden of chronic pain and poor sleep. Yet, the literature on lactation support for this population remains sparse, which poses difficulties for healthcare providers as well as patients (Gensemer et al., 2021; Wu & Ho, 2024).

Taken together, the multisystem involvement of hEDS shapes reproductive health across a woman's lifespan. Greater clinical awareness and collaboration across specialties are essential to improve diagnosis and long-term outcomes.

**Table 2**: Clinical Features of Hypermobile Ehlers-Danlos Syndrome (hEDS) Across the Lifespan

| Life Stage | Key Clinical Features | Clinical Implications | References |
|---|---|---|---|
| **Childhood** | Joint hypermobility; sprains and dislocations; gastrointestinal (GI) and bladder dysfunction | Often labeled as clumsy; boys are diagnosed earlier than girls | Cederlöf et al., 2016; Gensemer et al., 2021 |
| **Adolescence** | Worsening symptoms, particularly in girls; dysmenorrhea; postural orthostatic tachycardia syndrome (POTS); mast cell activation syndrome (MCAS); neurodivergence (attention-deficit/hyperactivity disorder [ADHD], autism traits) | Hormonal influence becomes more significant; possible misdiagnosis as psychiatric conditions | Riley, 2020; Hugon-Rodin et al., 2016; |
| **Adulthood** | Chronic pain and fatigue; POTS; MCAS; GI dysfunction; misdiagnosis or medical gaslighting | Long delays in diagnosis; requires multidisciplinary care | Gerogiannis, 2020; Wu & Ho, 2024 |
| **Pregnancy** | Miscarriage; cervical insufficiency; cesarean section (C-section) and delivery complications | Requires individualized care plans; increased anesthesia risks and wound healing difficulties | Spiegel et al., 2020; Lee & Strand, 2017 |
| **Postpartum** | Pelvic organ prolapse; incontinence; breastfeeding-related joint and skin problems | Increased risk of injury; lack of guidelines for lactation in hEDS | Cederlöf et al., 2016; Gensemer et al., 2021 |

| | | | |
|---|---|---|---|
| **Menopause** | Symptom stabilization; reduced flexibility but persistent pain | Hormonal changes may ease symptoms for some patients | Gensemer et al., 2021; Francis & Dickton, 2021 |

**Interdisciplinary Challenges Posed by the Disease**

Some complications seen in patients with Ehlers-Danlos syndrome (EDS) could potentially be avoided if the condition were identified earlier. For example, issues often arise during surgery—mainly due to fragile tissues, delayed wound healing, or other systemic factors (Table 1). These risks show why a broad, team-based approach is needed, from the planning stage through recovery (Glans et al., 2021; Cederlöf et al., 2016).

Ehlers-Danlos syndrome (EDS) is characterized by fragile connective tissues—especially in the skin and blood vessels—and abnormal collagen production. These characteristics can complicate surgical procedures and raise the likelihood of complications. During surgery, minimizing blood loss and tissue damage requires gentle handling and meticulous wound closure. Individuals with EDS, especially those with the hypermobile (hEDS) or classical subtypes, often show delayed wound healing, fragile scars, and poor scar quality. These features raise the likelihood of complications such as wound dehiscence and incisional hernia. To counter this, non-absorbable sutures are generally left in place for double the usual period. Because of increased capillary fragility and weakness of the surrounding connective tissue, these patients are also prone to bruising, spontaneous ecchymosis, and hematoma formation, all of which heighten surgical risks. Intraoperative bleeding and significant intraperitoneal adhesions have been reported in gastrointestinal surgery for EDS patients (Cederlöf et al., 2016; Wu & Ho, 2024).

There is a generally higher failure rate for surgical repair and increased postoperative complications in EDS patients. Recurrence of pelvic organ prolapse (POP) and stress urinary incontinence (SUI) post-surgery has also been observed.

Patients affected by hEDS may exhibit reduced or insufficient efficacy of local anesthetics, resulting in diminished or shorter-lasting pain relief. This needs to be considered for procedures requiring local infiltration, such as episiotomy repair, or for epidural/spinal analgesia, which may require higher doses or more frequent top-ups. The exact mechanism is poorly understood. Managing the airway during intubation can be especially difficult in women with a history of temporomandibular joint (TMJ) dysfunction or dislocation, or those with cervical spine instability, both common in populations affected by EDS. Fragility of the mucosa and collapse of fibroelastic tissue can add further difficulty during these procedures (Song et al., 2021; Gerogiannis, 2020). For this reason, a comprehensive airway evaluation should be carried out before any intervention. Because of joint hypermobility and ligament laxity, patients are at risk of joint dislocations or subluxations even with minimal pressure during surgical positioning. Skin injuries resulting from mechanical stress, traction, or pressure can also occur. Using a low-rebound mattress can help reduce the risk of pressure-related skin damage

Cardiovascular autonomic problems are common in EDS, and one example is postural orthostatic tachycardia syndrome (POTS), where patients may experience dizziness from a sudden drop in blood pressure and a sharp rise in heart rate when standing. Because epidural anesthesia induces peripheral vasodilation, it has the potential to exacerbate POTS symptoms such as hypotension (Table 1). Awareness of these risks is important for anesthetists (Hugon-Rodin et al., 2016; Wu & Ho, 2024).

Evaluating current complaints, surgical history, and family background plays a key role in anticipating complications. Patients need to be counseled about risks specific to EDS, such as impaired healing, bleeding tendencies, and anesthesia-related concerns. Multidisciplinary input from surgical, anesthetic, rheumatologic, gynecologic, genetic, and pain teams is strongly advised (Karthikeyan & Venkat-Raman, 2018; Fajardo-Jiménez et al., 2022).

**Diagnostic Difficulties**

Although it is estimated that 1 in 5,000 people suffer from the condition, the prevalence of hypermobile Ehlers-Danlos syndrome (hEDS) may be significantly higher than previously estimated, possibly affecting 0.75–2% or even up to 3.4% of the population. There are multiple factors contributing to the delay or misdiagnosis. The diagnosis of hEDS is primarily clinical, as there is currently no identifiable genetic mutation or confirmatory test for the vast majority of cases. This makes physician awareness and adherence to the specific diagnostic criteria crucial. Recent changes to the classification of Ehlers-Danlos syndrome (EDS) and the reclassification of joint hypermobility syndrome (JHS) may have further complicated diagnosis and consistent understanding among practitioners. While there may be a gradual increase in awareness, the current body of evidence suggests that physician awareness of hEDS is still notably insufficient, contributing to significant diagnostic and management challenges for patients (Hugon-Rodin et al., 2016; Wu & Ho, 2024).

Many hEDS symptoms are non-specific and can be mistaken for other conditions (Table 1). The chronic, systemic nature means symptoms may be insidious, developing slowly and making early diagnosis difficult. Many symptoms of hEDS, such as chronic pain,

fatigue, gastrointestinal issues, and autonomic dysfunction, are also common in a range of psychiatric conditions, like anxiety and depression, and functional gastrointestinal disorders. These overlaps can lead to misdiagnosis, attributing hEDS symptoms primarily to an eating disorder like anorexia nervosa, or to somatisation disorders. Joint hypermobility, a key feature, can decrease with age, while pain and fatigue may worsen. As patients age, obvious features of hEDS often diminish, leaving clinicians with fewer visible cues to guide diagnosis (Table 2). (Karthikeyan & Venkat-Raman, 2018; Cederlöf et al., 2016).

Without a clear diagnostic marker, physicians must rely on variable and sometimes subtle clinical signs, a process further complicated by the generally low level of professional awareness about hEDS.

## 4. CONCLUSION

Since hypermobile Ehlers-Danlos syndrome (hEDS) is more common in females and diagnoses in girls frequently occur later in childhood, or even far into adulthood, combined with the significant consequences of delayed recognition, it is crucial to prioritize earlier identification within this group. Timely diagnosis offers the possibility of better management, reduction of hormone-driven symptom aggravation, and improved daily functioning for patients.

There appears to be limited research on how hormonal factors affect symptom presentation in women with hEDS, which may be slowing progress in developing the interdisciplinary care these patients require. More focused research is needed—particularly on topics such as lactation and the specific functional and structural changes related to urological involvement. Reliable biomarkers remain a missing piece in the diagnostic process. Progress in this area, together with deeper insight into the genetics of hEDS, could eventually guide more effective therapeutic strategies.

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The authors declare that there is no conflict of interest.

**Data and materials availability**

All data sets collected during this study are available upon reasonable request from the corresponding author.

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