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EHLERS–DANLOS SYNDROME AND PREGNANCY: CURRENT STATE OF KNOWLEDGE, RISKS AND OBSTETRIC COMPLICATIONS

Abstract

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders caused by abnormalities in its structure and functional properties, which may significantly affect the course of pregnancy, childbirth, and the postpartum period. Clinical manifestations and the degree of risk of obstetric complications depend on the specific EDS subtype, necessitating an individualized approach to the management of affected patients. This article presents the current state of knowledge and summarizes the scientific literature on the main clinical subtypes of EDS, their manifestations during pregnancy, and their potential impact on maternal and perinatal outcomes. The major obstetric risks are reviewed, including preterm birth, preterm prelabor rupture of membranes, postpartum hemorrhage, traumatic soft tissue injuries, impaired wound healing, as well as pain and joint hypermobility, which may complicate pregnancy. Particular attention is paid to the vascular subtype of EDS, which is associated with an increased risk of arterial rupture and dissection, uterine rupture, and other potentially life-threatening complications. Current approaches to preconception counseling, genetic diagnosis, individual risk assessment, antenatal surveillance, and delivery planning are analyzed, taking into account the clinical subtype of the disorder and the patient's obstetric history. The importance of timely diagnosis, interdisciplinary collaboration among obstetricians and gynecologists,

geneticists, and other relevant specialists, as well as the early detection of potentially dangerous conditions, is emphasized. It is concluded that optimizing the management of pregnant women with EDS requires an individualized approach, further accumulation of clinical data, and high-quality research to clarify maternal and perinatal risks and improve evidence-based recommendations for pregnancy management and mode of delivery.

Keywords: Ehlers–Danlos syndrome, pregnancy, vascular subtype, obstetric complications, maternal mortality, perinatal outcomes, preconception counseling, delivery.

Problem statement. Ehlers–Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders characterized by impaired structural integrity and manifested by joint hypermobility, skin hyperextensibility, and increased tissue fragility. According to the international classification, 13 EDS subtypes are recognized, differing in their genetic mechanisms, clinical manifestations, and prognosis. The hypermobile, classical, and vascular subtypes are of particular clinical importance, with the vascular subtype being associated with an increased risk of arterial and internal organ rupture [1, 2, 4].

Pregnancy in women with EDS presents a particular challenge in obstetric practice because connective tissue abnormalities may affect the course of gestation, childbirth, and the postpartum period. Clinical manifestations may worsen as a result of physiological hormonal and mechanical changes during pregnancy, contributing to joint pain, musculoskeletal instability, and pelvic girdle pain. At the same time, obstetric risks depend on the EDS subtype, individual phenotype, comorbidities, and the presence of vascular involvement [2, 3].

Analysis of recent research and publications. According to current research, pregnant women with Ehlers–Danlos syndrome (EDS) may have an increased incidence of preterm birth, preterm prelabor rupture of membranes, postpartum

hemorrhage, traumatic perineal injuries, and impaired healing of surgical wounds. The vascular subtype of EDS requires particular attention, as pregnancy may be associated with life-threatening complications, including arterial dissection or rupture, uterine rupture, and massive hemorrhage. A systematic review by Haem et al., published in 2024, confirmed the high risk of severe maternal complications associated with the vascular subtype, while also highlighting the limitations of the available evidence and the need for individualized counseling [1].

The relevance of this issue is also determined by the difficulty of establishing a timely diagnosis, the variability of clinical manifestations, and the lack of clearly defined obstetric management strategies for certain EDS subtypes. The hypermobile subtype often remains undiagnosed until pregnancy, whereas the vascular subtype requires particularly thorough risk assessment at the preconception stage. Additional challenges include the limited number of large prospective studies, the heterogeneity of published findings, and the absence of a universal management algorithm applicable to all pregnant women with EDS [2–5].

Therefore, investigating current evidence on EDS during pregnancy is important for improving preconception counseling, assessing maternal and perinatal risks, and developing individualized strategies for pregnancy and childbirth management. Interdisciplinary collaboration among obstetricians and gynecologists, medical geneticists, cardiologists, and anesthesiologists enables the timely identification of potentially life-threatening conditions and optimization of care for women with this disorder.

Purpose of the article. The aim of this study is to summarize current evidence on pregnancy outcomes in women with EDS, particularly those with the vascular subtype (vEDS); identify the main pathophysiological mechanisms underlying the associated risks; and analyze the frequency and spectrum of obstetric and perinatal complications. To achieve this aim, publications were searched in the PubMed/MEDLINE, Scopus, and Cochrane Library databases, including systematic reviews, meta-analyses, cohort

studies, and clinical practice guidelines. The study seeks to substantiate the need for an individualized approach to pregnancy management, multidisciplinary surveillance, and genetic counseling for patients with EDS in order to reduce maternal and perinatal morbidity and mortality.

Presentation of the main material of the study. Ehlers–Danlos syndrome (EDS) is a group of inherited connective tissue disorders characterized by abnormalities in the structure or function of collagen and associated proteins. The main clinical manifestations include joint hypermobility, increased skin extensibility and fragility, a predisposition to bruising, and impaired wound healing. The severity of these features varies depending on the genetic variant underlying the disorder, resulting in considerable clinical heterogeneity [2, 6].

According to the 2017 international classification, 13 EDS subtypes are recognized, most of which have an established molecular genetic basis. The pathogenesis of the disorder is associated with abnormalities in the synthesis, maturation, structure, or organization of extracellular matrix components. The genetic cause has been identified for most subtypes, whereas no specific genetic marker has yet been established for the hypermobile subtype. Consequently, its diagnosis is based on clinical criteria after other conditions have been excluded [6, 7].

During pregnancy, the hypermobile, classical, and vascular subtypes of EDS are of particular importance because they differ in the nature of potential complications and the level of obstetric surveillance required.

Hypermobile EDS (hEDS) is characterized by generalized joint hypermobility, joint instability, recurrent subluxations, chronic pain, and various extra-articular manifestations. During pregnancy, pelvic girdle pain, joint discomfort, and functional limitations may worsen. Cases of preterm prelabor rupture of membranes, preterm birth, perineal trauma, and postpartum hemorrhage have also been reported; however, the strength of evidence and the incidence of individual complications remain

uncertain. An important aspect of care is the assessment of associated manifestations, including orthostatic intolerance and pelvic floor dysfunction [2, 8].

Classical EDS (cEDS) is primarily characterized by skin hyperextensibility, atrophic scarring, a predisposition to bruising, and increased tissue fragility. In obstetric practice, these features are relevant because of the potential risk of perineal trauma, soft tissue lacerations, and impaired healing of postpartum or postoperative wounds. Accordingly, attention should be paid to the condition of the skin and tissues, the history of wound healing, and the risk of bleeding when planning childbirth [2, 9].

Vascular EDS (vEDS) is the subtype associated with the greatest potential risk of severe maternal complications. It is primarily associated with pathogenic variants in the COL3A1 gene, which impair the formation of type III collagen. This subtype is characterized by fragility of the arteries and hollow organs, thin translucent skin, easy bruising, and a predisposition to spontaneous vascular injury. Pregnancy may be complicated by arterial dissection or rupture, rupture of hollow organs or the uterus, and massive hemorrhage. Therefore, establishing the diagnosis before pregnancy, providing genetic counseling, and developing an individualized obstetric management plan are of fundamental importance [7, 9].

Other rare EDS subtypes, including kyphoscoliotic EDS, arthrochalasia EDS, and dermatosparaxis EDS, may also be associated with marked tissue fragility, severe joint instability, or vascular abnormalities. However, evidence regarding their effects on pregnancy is limited and is derived primarily from case reports and small case series. Consequently, risk assessment should be based on the specific phenotype, genetic diagnosis, and associated medical conditions rather than solely on the general diagnosis of EDS [6, 7].

Thus, determining the clinical subtype of EDS is a key step in obstetric risk assessment. In the hypermobile and classical subtypes, the main focus is on pain, joint instability, tissue trauma, and wound healing, whereas the vascular subtype requires particular vigilance for life-threatening vascular and organ complications. At the same

time, the limited evidence available for many EDS subtypes highlights the need for individualized, multidisciplinary pregnancy management.

The course of pregnancy in women with EDS is characterized by variable clinical manifestations and depends on the disease subtype, the severity of connective tissue abnormalities, and the presence of comorbid conditions. Potential complications include miscarriage, preterm prelabor rupture of membranes (PPROM), preterm birth, hemorrhage, traumatic injuries to the birth canal, and impaired wound healing. However, the evidence regarding the incidence of these conditions remains limited, and study findings are heterogeneous [1, 2].

Preterm prelabor rupture of membranes (PPROM) has been reported in 4.1%–54% of pregnancies. Studies suggest that the presence of a pathogenic *COL3A1* variant in the fetus may be a stronger predictor of PPROM and preterm birth than EDS in the mother. Because the fetal membranes (amnion and chorion) originate from fetal tissues and their strength depends partly on type III collagen, inheritance of a pathogenic variant by the fetus may predispose to premature membrane rupture even when the mother is unaffected [10, 11].

Impaired structural integrity of connective tissue is considered one of the possible mechanisms underlying an increased susceptibility to PPROM. However, the association between EDS, cervical insufficiency, and preterm birth has not been conclusively established. In women with the hypermobile subtype, research findings are conflicting; therefore, the diagnosis alone is insufficient justification for prophylactic cervical cerclage or other interventions in the absence of additional clinical indications [2, 9].

Increased tissue fragility, a tendency to bruise, and possible abnormalities in hemostasis may contribute to bleeding during childbirth and in the postpartum period. In women with the classical subtype, particular attention should be paid to the risk of perineal tears, soft tissue injuries, and impaired wound healing. Nevertheless, postpartum hemorrhage should not be attributed solely to the presence of EDS.

Established obstetric causes, including uterine atony, retained placental tissue, and birth canal trauma, must also be considered [2, 9].

The highest risk of severe maternal outcomes is associated with vascular EDS. A systematic review by Haem et al., published in 2024, analyzed six studies involving 412 pregnancies in women with the vascular subtype. The miscarriage rate was 13.8%, the preterm birth rate among live births was 8.8%, and the rate of obstetric anal sphincter injuries was 11.3% in studies reporting this outcome. The overall maternal mortality rate was 5.7% in the five studies with available data on this outcome [1]. These estimates should be interpreted cautiously because of the small number of studies, differences between cohorts, and the possible influence of historical data collected before advances in genetic diagnosis and specialized obstetric care.

The main causes of maternal death in this group included vascular rupture or dissection and uterine rupture. The peripartum and postpartum periods are particularly hazardous, as hemodynamic changes and physical stress may be accompanied by acute complications. Therefore, pregnancy in women with confirmed vascular EDS requires individualized planning involving specialists in medical genetics, cardiology, vascular medicine, and obstetrics [1].

In a systematic review by Almheiri et al. (2026), which examined maternal and fetal outcomes of pregnancy in women with vascular Ehlers–Danlos syndrome (vEDS), 11 observational studies were analyzed. The authors identified the vascular subtype as the form associated with the highest risk of severe maternal complications, including arterial rupture and dissection, uterine rupture, and postpartum hemorrhage. Maternal mortality rates in individual included studies ranged from 0.10% to 50%, while preterm birth rates ranged from 8.9% to 48.8%. This variability reflects the heterogeneity of the study populations, differences in study designs, and the inclusion of historical data. Therefore, these figures should not be interpreted as pooled estimates of risk. Perinatal complications described in the studies included preterm birth, low birth weight, stillbirth, and neonatal complications. The authors also highlighted a possible

association between fetal genetic status, *COL3A1* gene variants, and adverse pregnancy outcomes, although further research is needed to confirm the prognostic significance of these factors [10].

Potential adverse outcomes for the fetus and newborn include prematurity, low birth weight, and complications associated with preterm delivery. The risk of transmitting EDS to offspring depends on the specific subtype and its inheritance pattern. Most subtypes are inherited in an autosomal dominant manner, although autosomal recessive forms also exist. In cases of autosomal dominant inheritance, the risk of transmitting the pathogenic variant to offspring is generally 50% in each pregnancy. Genetic counseling allows individual risks and reproductive planning options to be discussed [6, 9].

Thus, obstetric risks associated with EDS are not the same for all patients. In the hypermobile and classical subtypes, key priorities include pain management, prevention of tissue trauma, and appropriate postpartum care. In the vascular subtype, the priority is to prevent and promptly identify potentially life-threatening vascular and organ complications. This risk stratification provides the basis for further consideration of pregnancy management strategies and the choice of mode of delivery.

Pregnancy planning for women with EDS should include determination of the clinical subtype, assessment of individual risks, and discussion of potential maternal and perinatal complications. Medical genetic counseling is particularly important, including identification of the pathogenic gene variant in vascular EDS and assessment of the likelihood of transmitting it to offspring. Women with vascular EDS should receive preconception counseling from a multidisciplinary team, taking into account their family history, genetic variant, previous vascular events, and vascular imaging findings. The 2025 European Society of Cardiology (ESC) guidelines emphasize the need for individualized discussion of the high risks associated with pregnancy in women with this subtype [12].

Ogawa et al. (2022) demonstrated the clinical importance of timely differential diagnosis of EDS subtypes through the management of a twin pregnancy in a 20-year-old patient. The disorder was suspected at 19 weeks of gestation because of joint hypermobility, skin hyperextensibility, and a significant family history, including the sudden death of the patient's mother due to a cardiovascular rupture. As the vascular subtype of EDS is associated with a risk of life-threatening complications, molecular genetic testing was performed, which revealed no pathogenic variant in the *COL3A1* gene. Based on the clinical criteria, the patient was diagnosed with the hypermobile subtype of EDS. Due to worsening pain and difficulties with continuing the pregnancy, a cesarean section was performed at 34 weeks of gestation, and both infants were born healthy. This case highlights the importance of early clarification of the EDS subtype, genetic counseling, and individualized obstetric management, while also demonstrating that pregnancy may be associated with considerable clinical challenges even in the absence of the vascular subtype [14].

The antenatal surveillance strategy should be determined by the clinical subtype of EDS, comorbidities, and previous obstetric complications. In women with the hypermobile subtype, assessment should include the severity of joint and pelvic pain, mobility, pelvic floor function, tolerance of physical activity, and the need for supportive therapy. In the presence of vascular abnormalities or relevant clinical indications, cardiac assessment and instrumental evaluation of the vascular system should be performed. Particular attention should be paid to symptoms that may indicate an acute vascular complication, as well as signs of preterm prelabor rupture of membranes and preterm labor. However, the intensity of surveillance should be tailored to individual risk, as no universal protocol has been established for all EDS subtypes [2, 8].

The management of labor and delivery depends on the EDS subtype, obstetric circumstances, and the presence of vascular complications. In women with the hypermobile subtype, vaginal delivery may be appropriate in the absence of obstetric

contraindications. Consideration should be given to the possibility of rapid labor, perineal trauma, and joint instability. Gentle tissue handling, appropriate planning of analgesia, and selection of a safe maternal birthing position may help reduce the risk of injury [2].

In women with vascular EDS, the risks of arterial complications, uterine rupture, and severe hemorrhage necessitate particular caution. Based on the available evidence from systematic reviews, the 2025 European Society of Cardiology (ESC) guidelines recommend planning cesarean delivery at 37 weeks of gestation to avoid the substantial physical strain associated with pushing during labor [1, 12, 13]. This decision should be made in advance by a multidisciplinary team, taking into account the genetic variant, vascular status, and obstetric history. Nevertheless, the evidence regarding the optimal mode of delivery remains limited; therefore, the potential risks and expected benefits should be discussed on an individualized basis.

Following delivery, blood loss, the condition of the birth canal, and the surgical wound, if cesarean delivery was performed, should be monitored. In women with EDS, potential tissue fragility, impaired wound healing, pain, and pelvic floor dysfunction should be taken into account. In the vascular subtype, particular vigilance is required for acute vascular complications during the peripartum period. The postpartum follow-up plan should include assessment of physical recovery, rehabilitation needs, and genetic counseling regarding future pregnancies [2, 8, 12].

Thus, pregnancy management in women with Ehlers–Danlos syndrome should be based on differentiated risk assessment, early interdisciplinary counseling, and individualized delivery planning. The vascular subtype requires particular attention, whereas in the hypermobile and classical subtypes, the main objectives are to prevent tissue trauma, manage symptoms, and ensure adequate postpartum recovery.

Conclusions. Ehlers–Danlos syndrome is a clinically heterogeneous group of inherited connective tissue disorders that may increase the risk of obstetric and perinatal complications, depending on the clinical subtype. The vascular subtype poses

the greatest life-threatening risk to the mother because of its association with arterial rupture, uterine rupture, and massive hemorrhage. Pregnancy management in these patients requires preconception genetic counseling, individualized risk assessment, and multidisciplinary surveillance. The choice of mode of delivery should be based on the EDS subtype, obstetric history, and clinical circumstances. Further research is needed to clarify the incidence of complications and improve evidence-based recommendations for pregnancy management in women with different EDS subtypes.

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