The Ehlers-Danlos Syndromes – complex multisystem disorders with OB/GYN consequences

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Disclosures

- I have no conflicts of interest
- I would like to thank and acknowledge Dr Clair Francomano, one of the premier geneticists in the US regarding EDS (and my best friend from Kindergarten). We have given joint talks in the past and some of the following slides were used in those talks. Some information was also from a titled "OB/GYN and EDS/HDS", given at the EDS conference in Baltimore, MD, by Natalie Blagowidow, MD 2018

EDS Multidisciplinary Center of Excellence

-First Clinic day was 11/7/19

We have seen >4000 patient visits in 5 years. This represents >900 unique patients. Our patients come predominantly from Colorado, and its surrounding states but we have been referred patients from 27 states across the US as far away as Massachusetts, Washington state, and California. We see patients up to age 30.

- -Running at "full capacity", 2 1/2 full days per month

We collaborate with the Hypermobiliity clinic in the Dept of Genetics (which sees patients ages 5-21) so that we only schedule patients with the confirmed clinical dx of EDS. I also see patients who are birth-5 yr's and > 30 yr's for consultation, and see patients with more rare forms of EDS.

Ehlers-Danlos Syndromes

- These are a group of hereditary disorders, all involving the connective tissue
- There are 14 different types, and these have a wide range of differing presentations
- The underlying gene(s) causing 13 of these types are known
- These genes affect the structural proteins of the connective tissue and the enzymes involved in the processing of these proteins.
- The genes underlying the hypermobile type of EDS (hEDS) are not yet known**. There are 62 genes which have been identified in my CO patients who meet criteria for hEDS, some of which will be covered in this talk.**

Malfait F, Francomano C, Byers P et al. 2017. The 2017 International Classification of the Ehlers-Danlos Syndromes. Am J Med Genet Part C Semin Med Genet 175C:8-26.

Disorders of fibrillar collagen primary structure and processing , folding and crosslinking			
Classical EDS	COL5A1/COL5A2	Type V collagen	AD
Vascular EDS	COL3A1	Type III collagen	AD
Cardiac-valvular EDS	COL1A2	Type I collagen (total absence of α2 chain)	AR
Arthrochalasia EDS	COL1A1/COL1A2	Type I collagen (N-propeptide processing)	AD
Dermatosparaxis EDS	ADAMTS2	ADAMTS-2	AR
Kyphoscoliotic EDS-PLOD1	PLOD1	Lysyl hydroxylase 1	AR
Kyphoscoliotic EDS-FKBP14	FKBP14	FKBP22	AR
Disorders of structure and function of the myomatrix, the interface between muscle and ECM			
Classical-like EDS	TNXB	Tenascin-X	AR/AD
Myopathic EDS	COL12A1	Collagen XII	AR/AD
Disorders of glycosaminoglycan biosynthesis			
SpEDS_B4GALT7	*B4GALT7*	β4GalT7 (Galactosyltransferase I)	AR
SpEDS_B3GALT6	*B3GALT6*	β3GalT6 (Galactosyltransferase II)	AR
MC-CHST14	*CHST14*	Dermatan 4-sulfotransferase 1	AR
MC-DSE	*DSE*	Dermatan sulfate epimerase 1	AR
Disorders linked to aberrant intracellular processes			
spEDS_SLC39A13	*SLC39A13*	ZIP13	AR
Brittle Cornea Syndrome	*ZN469/PRDM5*	ZNF469/PRDM5	AR
Disorders of complement pathway			
Periodontal EDS	*C1r/C1s*	C1R/C1S	AD

The three most common forms of EDS seen in adults are hEDS, cEDS and vEDS

Classic EDS (cEDS): caused by variants in COL5A1 and COL5A2. Skin is the target organ and is fragile with abnormal scars, stretch marks, poor wound healing and elasticity. Patients may have joint hypermobility and the mild form of cEDS can be indistinguishable from hEDS. Classic EDS can also be caused by biallelic variants in TNXB.

Vascular EDS (vEDS): caused by variants in COL3A1. Skin may be very fragile but the most concerning issues can be life-threatening including spontaneous perforation of the intestine or an abdominal organ, spontaneous perforation of vasculature including the aorta, and uterine rupture during pregnancy

Hypermobile EDS (hEDS)

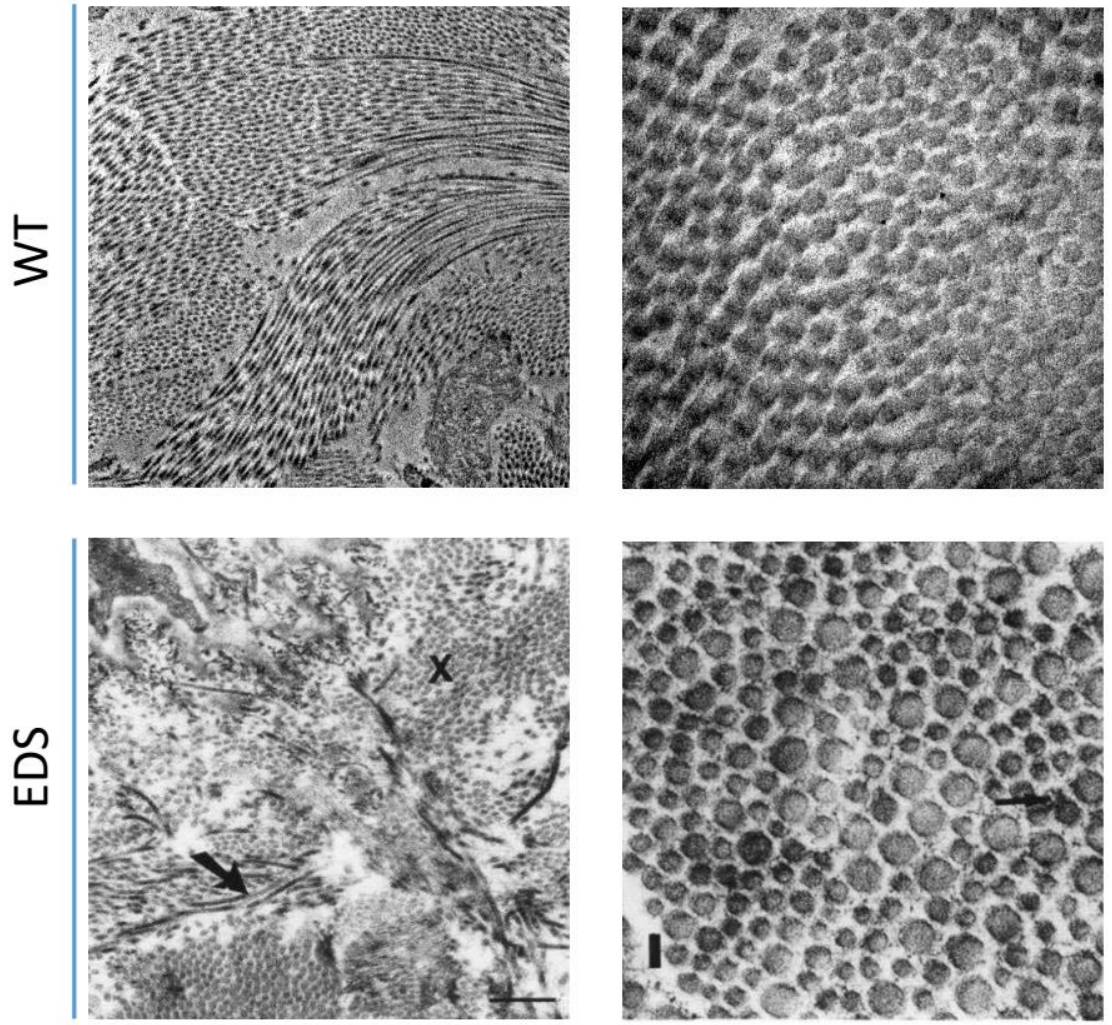
- hEDS is the most common form of EDS, estimated to occur with an incidence of 1:5,000-1:7,000 individuals. It is predominantly seen in females (80% of my patients), and the diagnosis is based on meeting clinical criteria published in 2017 in adults. Pediatric prepubertal patients older than 5 are diagnosed with a new pediatric set of criteria published in 2023. (Tofts et al)
- There is NOT one gene associated with hEDS. Patients who don't meet all criteria for hEDS may be given a diagnosis of Hypermobility Spectrum Disorder (HSD).
- The presentation of hEDS includes generalized joint hypermobility and skin abnormalities. There are common comorbidities including dysautonomia (POTS), chronic pain, GI complaints, headaches, and autoimmune issues. Anxiety and depression are common, and the incidence of gender dysphoria and autism are more common in patients with hEDS/HSD than in the general population.

What has been learned about the molecular findings in patients with hEDS

Hypermobile EDS is a CLINICAL Diagnosis, and there are many genes (62 and counting) which can cause patients to have findings and symptoms compatible with hEDS.

- Abnormalities of Collagen have long been known to cause other types of EDS. With increased ability to do molecular testing, we have determined that the following Collagen genes can cause what has been diagnosed as hEDS:
- COL1A1 and COL1A2 – *mutations usually cause Osteogenesis Imperfecta (OI) but can also cause hEDS*
- COL 5A1 and COL5A2 – *mutations usually cause Classic EDS, but can also cause hEDS*
- COL6A1 and COL12A1 – *mutations can cause a severe presentation of joint hypermobility, hypotonia, and congenital myopathy. Patients with COL12A1 variants may have significant dysautonomia.*
- COL3A1 mutations cause Vascular EDS, which has a different presentation than hEDS and often more severe complications.
- MOST patients with hEDS have negative gene testing on the EDS panel, but molecular variants can be identified on other panels including the Connective Tissue Panel, the Neuromuscular panel, and on WES/WGS, when appropriately detailed information is provided to the testing lab.

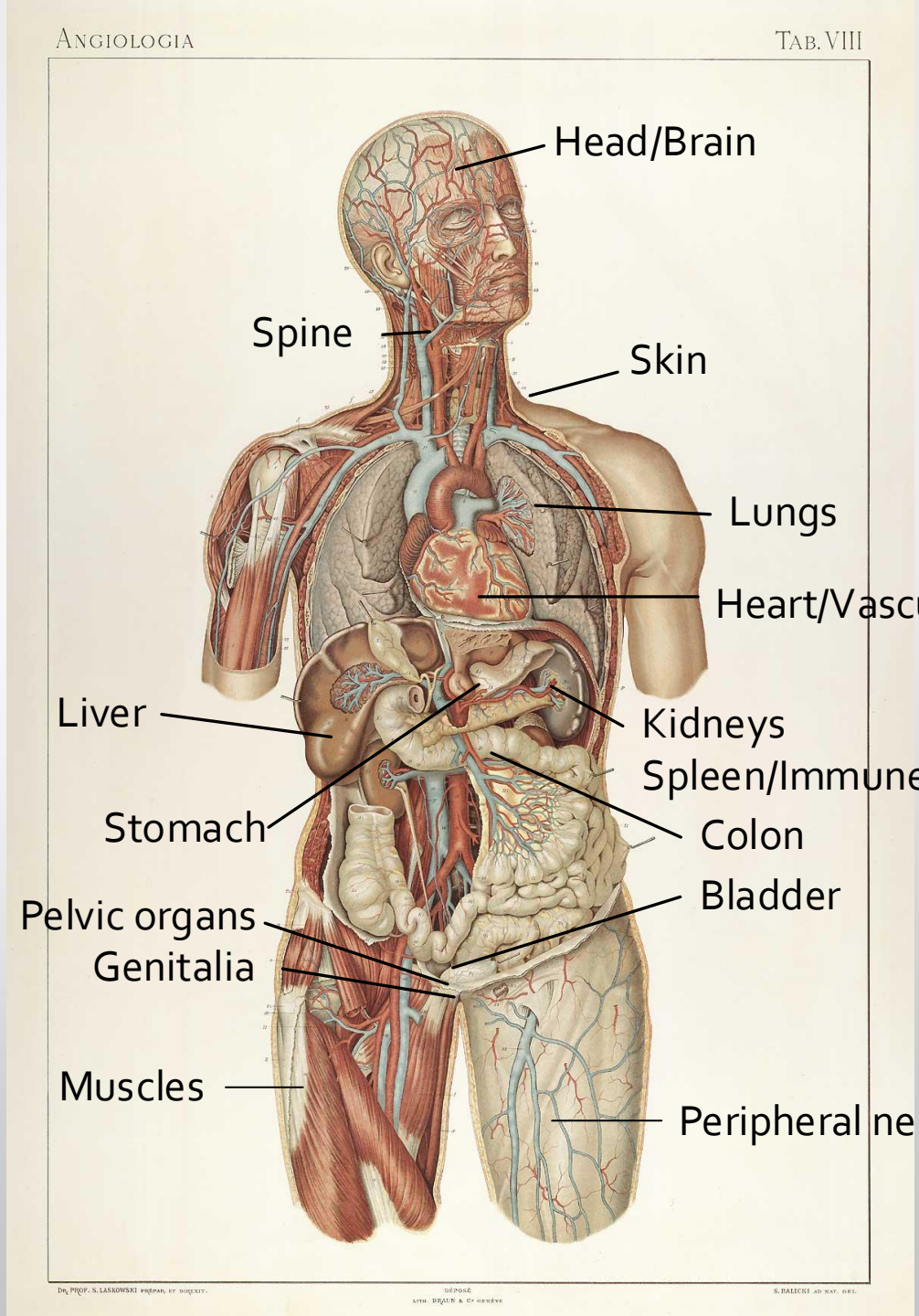
Collagen structure is affected in EDS



Meyer et al., 1988


Beighton score
Give yourself 1 point
for each of the manoeuvres you can do,
up to a maximum of 9 points
Can you bend your thumb back
Can you bend your knee backwards?
Can you put your hands flat on the floor with your knees straight?
Can you bend your elbow backwards?
Can you bend your little finger up at 90° (right angle) to the back of your hand?
1 point
www.ehlers-danlos.org
T: 020 8736 5604

Symptoms seen in patients with EDS affect every organ system in the body



UroGyn issues in patients with EDS

Urogenital system and pelvic region contains collagen-rich tissues including the uterus, pelvic ligaments and bladder

- Pelvic complications including pelvic organ prolapse, pelvic floor dysfunction, pelvic or vulvar varicose veins, - possibly endometriosis
- Uterine fibromas and polyps
- Pain: vulvodynia and dyspareunia
- Bladder dysfunction

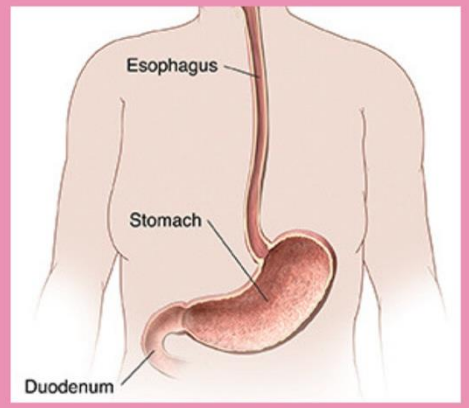
Gilliam, E et al Urogenital and pelvic complications in EDS and associated hypermobility. Clin Genetics 2019 1:97 (1);168-178

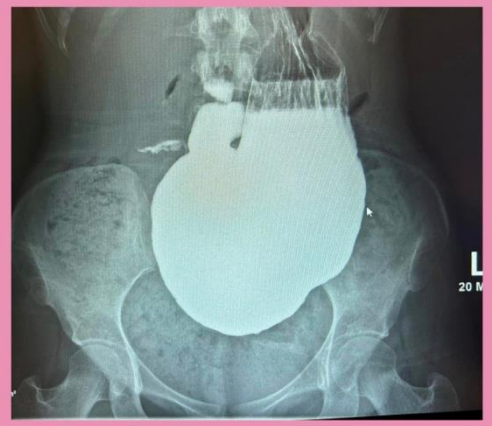
UroGyn issues are common

- GYN issues reported in high number of patients (at least 36%), especially pain, heavy bleeding, dysmenorrhea, dyspareunia and pelvic organ prolapse.
- Urinary symptoms are even more common (41%) including urgency, frequent UTI's, incontinence, Vesico-ureteral reflux (especially in patients with HSD), bladder diverticuli, voiding dysfunction, megacystis, hematuria, bladder outlet obstruction.
- GI issues can complicate evaluation and management including severe constipation and visceroptosis.

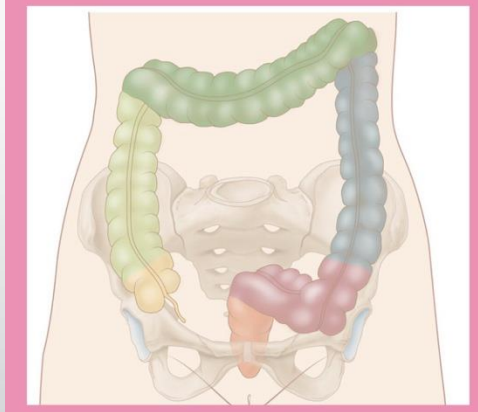
Visceroptosis

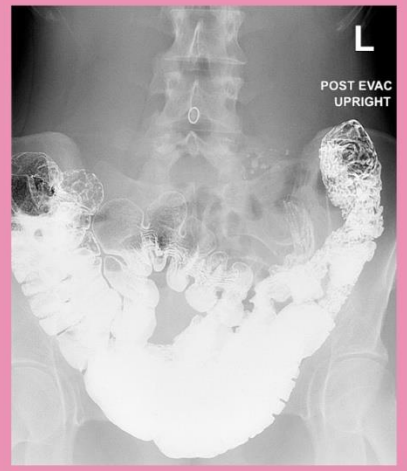
Normal stomach anatomy vs visceroptosis





Normal colon anatomy vs visceroptosis





Pelvic Floor Prolapse

- Risk between 15-30%
- Weakness of pelvic floor can lead to bladder distension, stress urinary incontinence and cystocele
- Can occur in nulliparous patients including teenagers
- Pelvic floor exercises can be helpful

Menorrhagia/Dysmenorrhea

- Bleeding issues are more common in patients with connective tissue disorders.
- Heavy bleeding with periods can lead to iron deficiency and anemia. Menorrhagia reported in 33-75% of patients in various papers.
- Dysmenorrhea has been reported in >90% of patients. NSAID's are primary treatment
- If heavy bleeding is unusual or anemia severe, should consider a Heme eval for a bleeding diathesis. Heme diagnoses may include von Willebrand disease and Hemophilia.

Menstrual Suppression

Treatment interventions include:

OCP's or Progesterone only medication

IUD with progesterone.

Per Hugon-Rodin paper: EDS symptoms improved 25% on progesterone only meds

Vulvodynia/Dyspareunia

- Incidence varies from 32-77%
- Etiology not completely clear – may be related to generalized nerve sensitivity
- Severe vulvar edema may occur during/after intercourse due to friable tissues
- Treatment options include: good skin care, PT, Behavioral approaches including Cognitive behavior therapy and psychotherapy, Kegel exercises and some meds. Of 120 treatments regimented by CureTogether, the most effective included botox, estrogen and trigger point therapy. The least effective included steroid and anti-fungal creams and antibiotics.

Puberty

- Worsening symptoms are often seen with pubertal progression and the onset of menarche. In a series published by Hugon-Rodin of 386 women in 2016, more than 50% of patients with EDS had worsening of symptoms with puberty and 17% of patients didn't develop symptoms of EDS until puberty.
- The role of estrogen is an area being actively studied on our campus, including abnormalities in Matrix Metalloproteins (MMP's), which are important for collagen repair.
- Remember- 80% of patients with EDS are female!!
- Transgender patients who are genetically female, may see improvement in symptoms when started on menstrual suppression and testosterone.

Other GYN Issues

- **Endometriosis –** association with EDS is somewhat controversial. Incidence 6-25%
- **Infertility –** same as in general population – but pregnancy complications higher
- **Menopause –** symptoms improve in 22%
- **Uterine Myomas –** rare – 5-9%

Urological Issues

- Review by Gilliam et al from 2019 looked at 105 studies in 5282 patients, including patients with hEDS, cEDS, vEDS and HSD
- Urinary complications include: incontinence, urgency, VUR, bladder diverticuli, recurrent UTI's, bladder outlet obstruction, hematuria and voiding dysfunction
- From above study, 41% had urinary symptoms, 36% had GYN symptoms, and 9% developed renal issues

Summary of UroGYn issues in patients with EDS

- These are complex patients and the actual underlying diagnoses may involve more than one organ system.
- Patients with classic EDS caused by COL5 variants may present with significant bleeding issues and often require Heme eval and intervention
- Patients with vascular EDS are at risk for intestinal rupture, arterial rupture and uterine rupture during pregnancy. Abdominal and pelvic pain requires immediate evaluation and treatment.

Summary of UroGyn issues in patients with hEDS and HSD

- Despite intense study around the world, the genetic etiology of hEDS/HSD is unknown. There are multiple genes involved including connective tissue disorders, neuromuscular disorders, and autoimmune disorders
- Some patients have neurodiversity, and gender dysphoria. The incidence of this is higher in the population of patients with hEDS than in the general population
- Mental health issues are common including depression and anxiety.

Obstetrical Issues in Patients with EDS

The general obstetrical Issues in patients with EDS are common across all types and are related to tissue fragility.

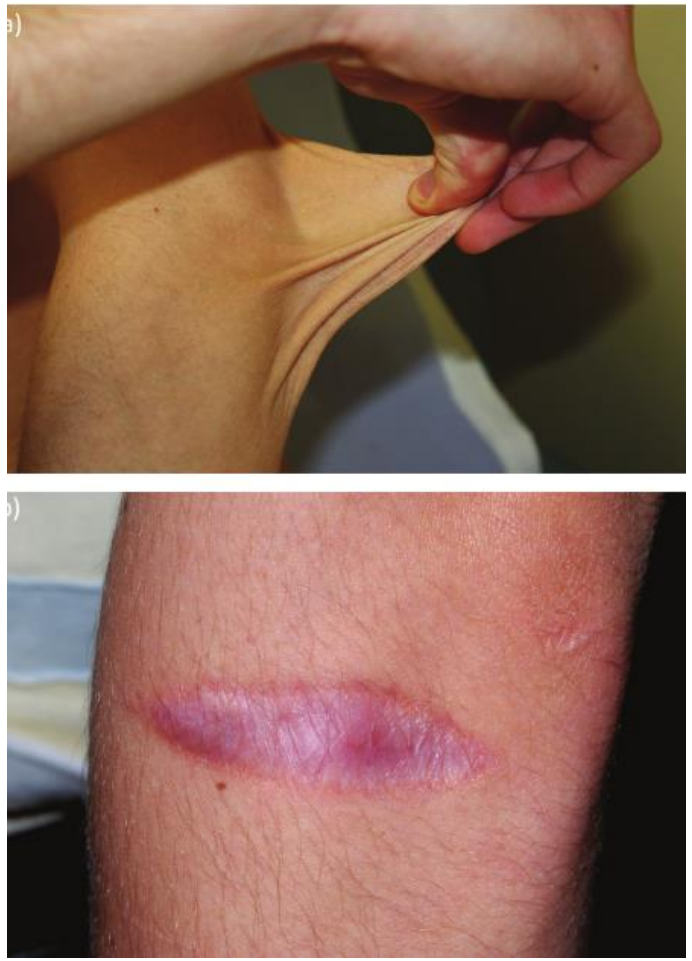
- **Will now separately look at specific issues seen in the 3 main forms of EDS, classic EDS, vascular EDS and Hypermobile EDS (hEDS)/Hypermobility Spectrum Disorder (HSD)**

Classical EDS (cEDS)

cEDS is an autosomal dominant disorder, caused by variants in COL5A1 or COL5A2

The main target organ in cEDS is the SKIN. Patients with cEDS have unusual skin which is soft, stretchy, and heals poorly if injured.

Scars are widened and thin.



OB complications in cEDS

The common OB complications in patients with cEDS include:

- **Easy Bleeding** – this can be caused by poor platelet adherence to abnormal connective tissue, as well as comorbid bleeding disorders including von Willebrand's disease. Patients can have spotting/bleeding during pregnancy and excessive bleeding at delivery
- **Preterm labor and delivery**
- **Prolapse of the pelvic floor and uterus**
- **Complex perineal tears which can require special stitching**
- **Decreased analgesia and response to typical anesthesia – may be helpful to obtain an Anesthesia consult**
- **Worsening GI issues/dysautonomia**

Vaginal vs C/section delivery – often a complex decision!

Vascular EDS (vEDS)

vEDS is an autosomal dominant disorder caused by variants in COL3A1 with a prevalence of 1-9/100,000.

This form of EDS can have lethal consequences, including risk of spontaneous colon perforation, arterial rupture in patients < 40 yo, and development of a carotid cavernous sinus fistula without antecedent trauma.

Pregnancy complications can also be severe and even lethal.

Obstetrical Complications in patients with vEDS

Haem et al reviewed complications of vEDS in the BJOG in June 2024. Per their review of >120 publications of 412 pregnancies, they report:

13.8% risk of miscarriage

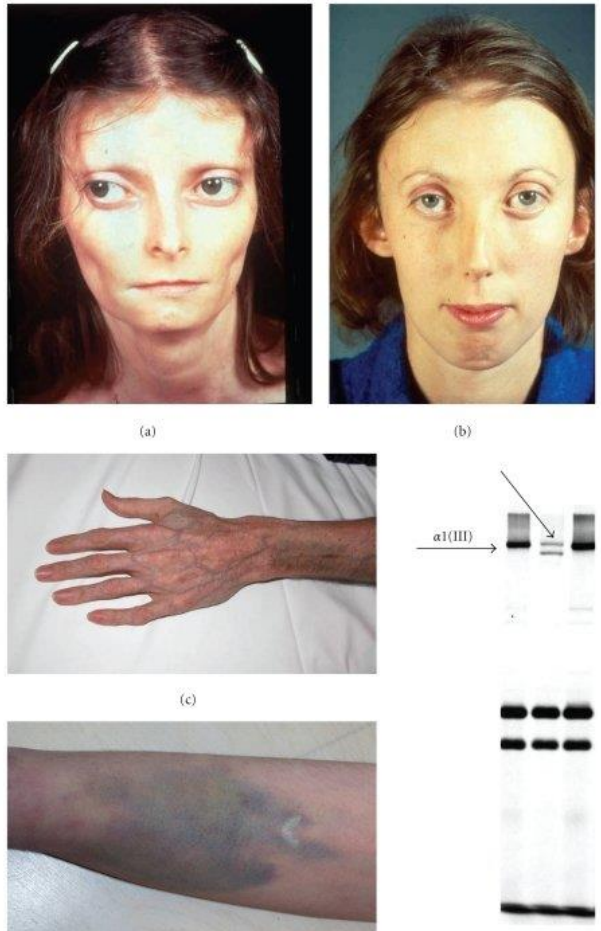
8.8% premature birth

11.3% risk of anal sphincter injury

5.7%maternal mortality rate

Vascular EDS

- Distinctive facial features
- Acrogeria
- Fragile skin with easy bleeding
- Other findings may include
  - Small joint increased ROM
  - Tendon/muscle rupture
  - Spontaneous pneumothorax



OB issues in patients with vEDS

Patients may not have a vEDS diagnosis prior to pregnancy! This can significantly increase risk of complications. It is important to be suspicious based on the patient's PE, and to ask detailed questions about family history. Confirming a vEDS diagnosis requires just a simple blood test.

If the diagnosis of vEDS is known prior to pregnancy:

the risk of pregnancy and delivery need to be clearly counseled.

almost 2/3 of patients choose voluntary childlessness

mode of delivery is important to plan – scheduled C/sect is recommended

85.7% of women who did NOT have a vEDS diagnosis prior to pregnancy had a suggestive family history

Lethal consequences of pregnancy in patients with vEDS

Causes of death in women with vEDS related to pregnancy (5.7% rate)

vascular rupture in 63.6%

uterine rupture in 31.8%

other organ rupture in 4.6% hysterectomy dehiscence

Nonlethal complications reported:

coronary artery dissection, splenic artery rupture, uterine rupture, multiple artery dissection, bladder and venous tears

Complications can be seen in post-partum period, usually within 7 days of delivery, as well as peri-partum. Women need to be observed after delivery for 7 days after delivery.

NO ONE who delivered via a scheduled C/sect died!

Cardiac issues in patients with vEDS

While aortic rupture is a big concern, any artery in the body can spontaneously rupture and lead to death.

The American College of Cardiology assesses particular COL3A1 variants and does not recommend against getting pregnant in patients with null variants and normal vascular imaging. They do recommend treatment with vascular-protective meds such as Losartan and beta-blockers

The European Society of Cardiology advises against pregnancy

OB complications in patients with hEDS/HSD

Hypermobile EDS is the most common type of EDS. Unlike the other forms of EDS, hEDS is a CLINICAL DIAGNOSIS, and cannot be confirmed with molecular testing. The causative genes are not known. The main target organs are the skin and the joints. Most family histories suggest autosomal dominant inheritance.

Hypermobility Spectrum Disorder (HSD) is the diagnosis given to patients who do not fully meet criteria for hEDS. However, they have very similar (but often milder issues) and I treat them as if they are the same.

80% of the patients followed in multiple studies are FEMALE!

OB complications in patients with hEDS/HSD

Molecular testing in patients with hEDS/HSD:

Because there is no one gene causing hEDS, molecular testing is often negative in these patients. However, there is significant overlap between hEDS and other forms of connective tissue disorders. Therefore, it is worthwhile to do molecular testing to be able to confirm a clear diagnosis and to be able to anticipate complications of pregnancy.

As mentioned in the earlier part of this talk, positive gene testing in patients who meet the clinical criteria for hEDS have been found in patients with variants in COL1 (often presenting with Osteogenesis Imperfecta and bony fragility), COL3, who actually have a diagnosis of vEDS (you don't want to miss this!), COL5, who actually have cEDS, TNXB (compound heterozygotes present with a c EDS phenotype, but heterozygotes have an hEDS phenotype), and COL12A1 (these patients have the neuropathic form of EDS and may have complex neurological issues including severe Dysautonomia)

OB complications in patients with hEDS/HSD

A review discussing the OB issues in patients with hEDS and HSD. Nichols-Dempson et al in the AJ OB/GYN from 2019 reviewed over 3 million total births of which 910 were in patients with EDS.

The main complications were:

- increased risk of prematurity
- cervical incompetence
- Antepartum hemorrhage
- placenta previa
- increased incidence of C sect delivery
- prolonged post-partum hospital stays > 7 days

A more recent review by S Pezaro in PLOS one from 2024 cited similar issues.

OB complications in patients with hEDS and HSD

Patients with hEDS/HSD have many comorbidities in addition to skin and joint issues. These may be exacerbated by pregnancy.

- Joint pain and subluxation
- Severe headaches including migraines
- Bleeding disorders
- Dysautonomia
- GI disorders including intestinal dysmotility, severe constipation, GERD
- Pelvic floor weakness and prolapse
- Urological issues including UTI's, incontinence

Summary

- **Ehlers-Danlos syndromes are a complex group of connective tissue disorders, which mostly impact the skin, joints and vasculature.**
- **Depending on the type of EDS the patient has, there can be both obstetrical and UroGYN complications with a wide spectrum of severity.**
- **The vascular form of EDS has the most potentially severe concerns, which include lethal consequences during pregnancy. Many patients with vEDS are not diagnosed prior to pregnancy – important to do a complete physical exam and get a good family history!**
- **Careful planning can help reduce morbidity/mortality in patients with EDS.**

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