Ehlers-Danlos And Pregnancy

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EDS and pregnancy

• Goals
  • Overview of Subtypes
  • Physiology of Pregnancy and relationship to EDS
  • Pregnancy Complications
  • Delivery and Recovery issues
EDS

- 6 major phenotypes with significant overlap
- Clinical features
  - Skin hyperextensibility
  - Joint hypermobility
  - Tissue Fragility
  - Poor wound healing
  - Bruising
- Few can be confirmed with laboratory testing
Subtypes

- EDS Type I & II: **Classic**
  - Autosomal Dominant
  - Type V Collagen
  - MVP and organ prolapse
  - PPROM, prematurity
  - Postop hernia
  - Gene: COL5A1 or A2
  - Locus: 9q34.2-34.3 or 2q31
  - Type II is typically milder
Genetics of Classic Type EDS

- 40-50% have detectable COL5A1 or 2
- 10% have detectable pro1(V) or pro2(V)
- 30% with pro1(V) haploinsufficiency
- A complex work-up and commonly declined
- Potentially increased risk of Amniocentesis complications
Subtypes

- EDS III: Hypermobility
  - Clinical diagnosis
  - Striking Joint findings but less skin changes
  - Recurrent joint dislocations and limb pain
  - Genetics: unknown
Subtypes

- EDS IV: Vascular
  - Autosomal Dominant
  - Type III collagen
  - Vascular markings seen through skin
  - Risk of rupture: vascular, bowel and/or tendon
  - Reduced lifespan
  - Gene: COL3A1
  - Locus: 2q31
Subtypes

- EDS VI: Kyphoscoliosis
  - Autosomal Recessive
  - Lysyl hydroxylase deficiency
  - Retinal detachment
  - Scoliosis
  - Mafans-like with risk of vascular rupture
- Gene: PLOD1
- Locus: 1p36.3-36.2
Subtypes

- EDS VII: Athrochalasia
- AD or AR
- Type I Collagen
- Hyperflaccid joints with normal skin
- Short stature
- Congenital skull fractures and hip dislocation
- COL1A1,2 or ADAMST2
- 17q31-22.5, 7q22.1, 5q23-24
EDS and Genetics

- Overlap makes specific diagnosis challenging
- Genetics consult and maternal testing best done prior to pregnancy since workup may take too much time to offer prenatal diagnosis
- Type VI has been diagnosed by Lysyl Hydroxylase in amniotic fluid
### Layers of amnion chorion

<table>
<thead>
<tr>
<th>Layer</th>
<th>Extracellular-matrix composition</th>
<th>MMP or TIMP produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid</td>
<td></td>
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<tr>
<td>Layer Amnion</td>
<td></td>
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<tr>
<td>Epithelium</td>
<td></td>
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</tr>
<tr>
<td>Basement membrane</td>
<td>Collagen types III, IV, V; laminin, fibronectin, nidogen</td>
<td>MMP-1, MMP-2, MMP-9</td>
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<tr>
<td>Compact layer</td>
<td>Collagen types I, III, V, VI; fibronectin</td>
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<tr>
<td>Fibroblast layer</td>
<td>Collagen types I, III, VI; nidogen, laminin, fibronectin</td>
<td>MMP-1, MMP-9, TIMP-1</td>
</tr>
<tr>
<td>Intermediate (spongy) layer</td>
<td>Collagen types I, III, IV; proteoglycans</td>
<td></td>
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<tr>
<td>Chorion</td>
<td></td>
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<tr>
<td>Reticular layer</td>
<td>Collagen types I, III, IV, V, VI; proteoglycans</td>
<td>MMP-9</td>
</tr>
<tr>
<td>Basement membrane</td>
<td>Collagen type IV; fibronectin, laminin</td>
<td></td>
</tr>
<tr>
<td>Trophoblasts</td>
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</tbody>
</table>

Maternal decidua
Physiology of Pregnancy

• Cardiovascular
  • Increased blood volume
    • 40% increase (from 5-7 L)
    • Peaks around 30 weeks
  • Increased cardiac output
    • 50% increase
    • Pulse up 20%, stroke volume increased by 60%
    • Peaks around 32 wks
Physiology of Pregnancy: Cardiovascular

- Increased venous capacitance
- Increased extracellular fluid volume (4-6 L)
- By term 15% of CO is directed to the uterus
- Renal perfusion increases by 40%
- Posture and Perfusion
  - Supine hypotension syndrome
Physiology of Pregnancy

- Hormonal Changes
  - Progesterone
    - Relaxes vascular, GI and GU smooth muscles
    - Reduces uterine motility
    - Blunts maternal vascular responsiveness
  - Relaxin
    - Cervical integrity
Physiology of Pregnancy

- GI Adaptation
  - GERD and altered gastric emptying
- Musculoskeletal
  - SI and pubic symphysis mobility
  - Increased lumbar lordosis
- Skin
  - Stretch marks and spider angiomata
  - Varicosities
Pregnancy and EDS

• Initial Evaluation
• Maternal Echocardiogram
  • MVP
  • Aortic root diameter
  • Root diameter > 4 cm
• Screening Carotid and Abdominal Aorta Doppler analysis
• Genetics assessment
  • Maternal testing needed to confirm testing is available
Pregnancy and EDS

• Multidisciplinary Approach
  • MFM
  • Genetics
  • Vascular Surgery
  • Cardiology
  • Others (Rheum, Gen Surg, Neurosurg, Ophtho)
Cervix and EDS

- Cervical insufficiency commonly reported
- No cervical insufficiency noted in Dutch cohort
- Case reports of prophylactic cerclage associated with high rate of PPROM and preterm birth
- No recommendation for cerclage
- Consider surveillance and vaginal progesterone
PPROM/Preterm Birth and EDS

• Case series suggest a rate of 25-75%
• Fetal contribution to PPROM
  • PPROM rate 21/43 affected fetus
  • PPROM rate 25/128 affected mom
• Delivery before 37 wks
  • 17/43 if affected fetus
  • 28/128 affected mother

2002:81;293
Fetal Growth and EDS

- Fetal growth restriction has been described in several case reports
- Dutch case cohort
  - No increased frequency
  - Only seen in affected mothers

Pregnancy and EDS

- Beta-blockers to control HR and pulse pressure
- Avoid valsalva or strenuous activity
- Vitamin C supplementation to maximize strength and quality of collagen crosslinking
- Early admission to hospital
Delivery and EDS

• Vaginal Delivery
  • Increased risk for extensive perineal trauma
  • Increased risk for poor episiotomy healing
  • Mediolateral episiotomy
• Cesarean Delivery
  • Incisional hernia
  • Poor skin healing
  • Meticulous hemostasis and retention sutures
Suture vs glue?
Delivery and EDS

• Malpresentation
  • Breech 8% (3% rate at term normally)
  • Face and Brow Presentation seen in 5/46 affected fetuses
• Risk of both protracted and precipitous labors

EDS and Anesthesia

- Neuraxial Anesthesia
  - Risk of epidural hematoma
  - Increased HR and pulse pressure
- General Anesthesia
  - Gingival bleeding
  - Oropharyngeal tissue fragility
  - Pneumothorax
- Pressure point injury
Hemorrhage and EDS

- Capillary and vessel fragility
- Impaired platelet aggregation
- Vascular repair difficult
- Potential for A-V fistula formation
Hemorrhage and EDS

- Obstetric hemorrhage requiring treatment: 20%
- Risk if both mother and neonate affected: 33%
- Uterine atony and lacerations contribute to the high rate
- DDAVP
Neonate and EDS

- 50% of infants to affected mothers
- Floppy baby syndrome: 13%
- Congenital anomalies not increased
- Affected infants frequently not diagnosed at delivery
- Congenital hip dislocation
Classical Type EDS and Pregnancy

- Generally do well during pregnancy
- Multiple reports of episiotomy complications
- Intrapartum/Postpartum hemorrhage
- Operative vaginal delivery may pose an additional risk for perineal trauma
Hypermobility Type and Pregnancy

- No contraindication to pregnancy
- Significant pelvic instability and pain frequently reported
- Case series suggest overall good obstetric outcomes
Vascular Type EDS and Pregnancy

- 167/183 delivered at term
- 12/81 maternal mortalities
  - 5 uterine ruptures
  - 2 intrapartum vessel ruptures
  - 5 postpartum
  - 2 of mortalities occurred in the 6th pregnancy

Pepin, et al. NEJM 2000;342:673
Vascular Type EDS and Pregnancy

- Maternal Mortality:
  - 20% for each pregnancy
  - 38.5% for each pregnant woman
- Spontaneous labor onset: 32-35 weeks
- Spontaneous arterial rupture
  - Subclavian, iliac
- GI Rupture
Kyphoscoliotic EDS and Pregnancy

- Amniotic fluid testing available:
  - Lysyl hydroxylase activity
  - Deoxypyridinoline/pyroxydinoline ratio elevated
- Retinal detachment
- Increased risk for vascular complications
Conclusions

• Vessels at risk due to hormonally induced relaxation
• Increased cardiac output increases risk of vessel rupture
• Pain and joint instability a common maternal complaint
Conclusions

- Kyphoscoliotic and Vascular Types associated with significant risk of maternal mortality
- Spontaneous arterial rupture has been described in pregnancy with minimal trauma
- Echo, Vascular Doppler and MRI
- Tertiary care a necessity
Conclusions

- PPROM and prematurity common and affected fetuses increase the risk
- Prenatal diagnosis complex but improving
- Consider Vitamin C and B-Blocker therapy
- Maternal mortality remains a concern through the postpartum period