The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs

AUGUST 30-31, 2023

BELGIUM

European Reference Network | VASCERN | Gathering the best expertise in Europe to provide accessible cross-border healthcare to patients with rare vascular diseases

Centre de référence des maladies vasculaires rares

EDS ECHO SUMMIT SERIES

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs

PRESENTATION

Pregnancy and vascular EDS:
The Paris experience

SPEAKER

Dr Michael Frank, MD
National Referral Centre for Rare Vascular Diseases, Hôpital Européen Georges Pompidou, AP-HP, Paris, France **michael.frank@aphp.fr**
Chair of the MSA-WG (vascERN)

Conflicts interest

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

Dr Frank has no conflicts of interest to declare in relation with this presentation

Clinical Cases for reflection

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

Case 1

- 30 year-old patient
- Nulliparous
- ***COL3A1***: c.1700 G>A
- No vascular history
- Not compliant to celiprolol (or else)
- Now in a stable relation and considering pregnancy

Case 2

- 38 year-old patient
- Nulliparous
- ***COL3A1***: c.2387 G>A
- Treated w. celiprolol
- Important vascular history:
  - Aorto-iliac dissection
  - Vertebral and ICA dissection and aneurysms
- Considering pregnancy

How to council and advise these 2 patients?

The Ehlers Danlos Society

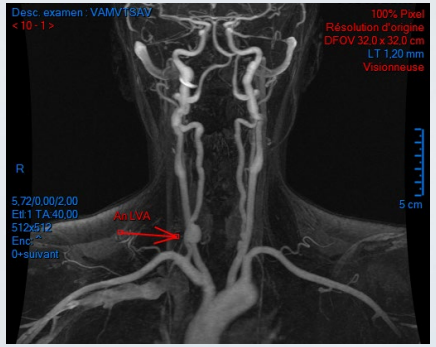
GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

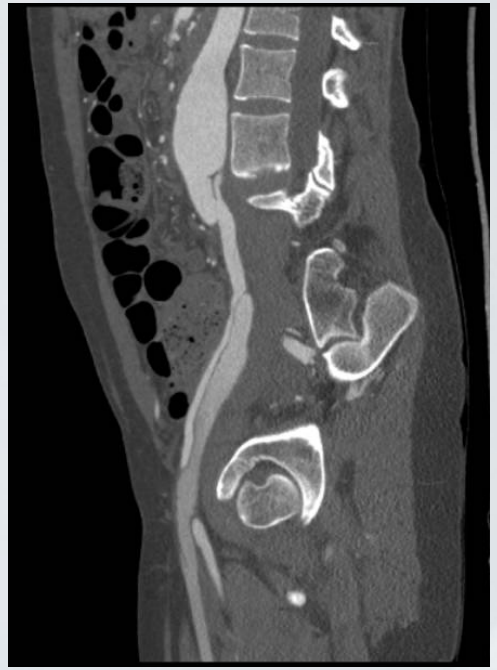
Case 1

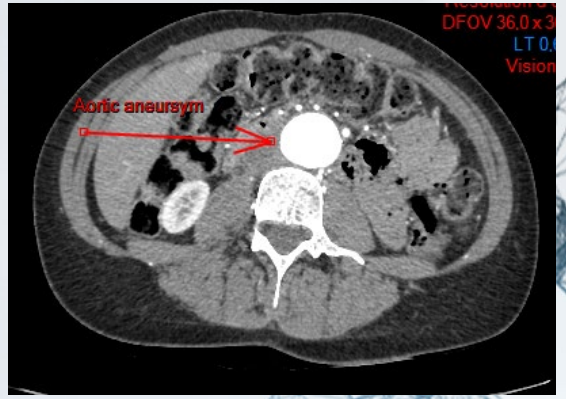
- Vascular work-up
  - Dissection right ICA
  - Aneurysm right vert. Art.
- Family history of vEDS wo. obstetrical events (Mother, Grandmother)

Case 2

- 38 year-old patient
- Nulliparous
- ***COL3A1***:
- Treated w. celiprolol
- Important vascular history:
  - Aorto-iliac dissection
  - Vertebral and ICA dissection and aneurysms
  - Splenic artery rupture
- Considering pregnancy







Maternal mortality in vEDS

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

Pregnancy related death rate 4,9-5,3% per delivery (283 patients, 616 deliveries, 30 deaths)

Pregnancy does not reduce life-expectancy in women with vEDS

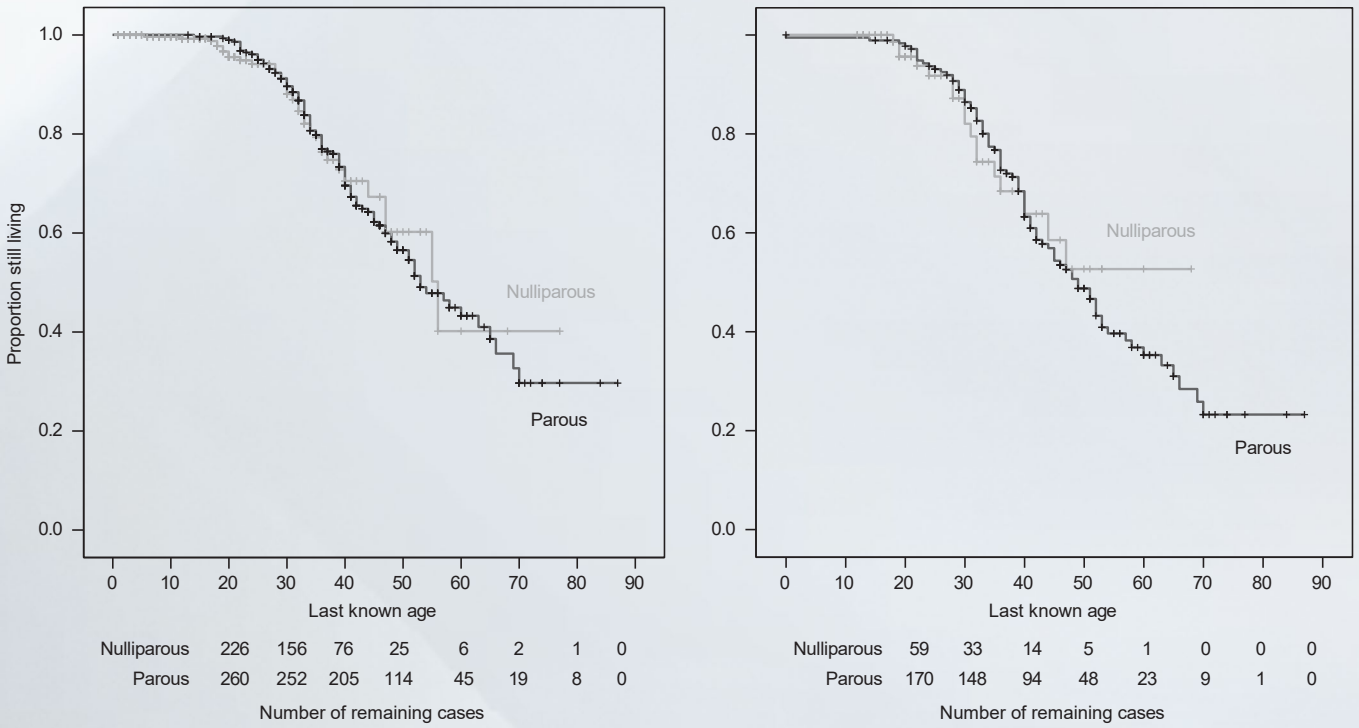


Figure 2 Kaplan–Meier estimates. (**a**) Overall survival of 526 parous (n = 283) and nulliparous (n = 243) women of reproductive age with vEDS; (**b**) overall survival in parous (n = 179) and nulliparous (n = 86) affected female relatives of probands with vEDS. vEDS, vascular Ehlers–Danlos syndrome.

Murray et al. 2014

2018 ESC Guidelines

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:

Strategies & Solutions for Unmet Needs

AUGUST 30-31, 2023

BELGIUM

Pregnancy is a high-risk period for all patients with aortic pathology, which is rare during pregnancy but associated with very high mortality.

Serious vascular complications occur almost exclusively in type IV Ehlers-Danlos syndrome (vascular). Maternal mortality is significant, and relates to uterine rupture and dissection of major arteries and veins. Pregnancy is therefore considered as a very high-risk undertaking and not advised. T hese women should be engaged in a shared decision-making process when contemplating pregnancy.

ESC guidelines for aortic diseases (2018)

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

	Marfan[19,175]	Bicuspid aortic valve[176]	LoeysDietz[182-184]	Turner[178,179]	Vascular Ehlers-Danlos[26]
Location of aneurysm/dissection	Everywhere (sinus of Valsalva)	Ascending aorta	Everywhere	Ascending aorta, arch and descending aorta	Everywhere
Risk of dissection	High: 1–10%	Low: <1%	High:1–10%	High: 1–10%	High: 1–10%
Comorbidity	Dural abnormalities Mitral regurgitation Heart failure Arrhythmias	Aortic stenosis or regurgitation	Dural abnormalities Mitral regurgitation	Low height Infertility Hypertension Diabetes Bicuspid aortic valve Coarctation	Dural abnormalities Uterine rupture
Advise not to become pregnant	Ascending aorta >45 mm (or >40 mm in family his- tory of dissection or sud- den death)	Ascending aorta >50 mm	Ascending aorta >45 mm (or >40 mm in family history of dissection or sud- den death)	ASI >25 mm/m^2	All patients

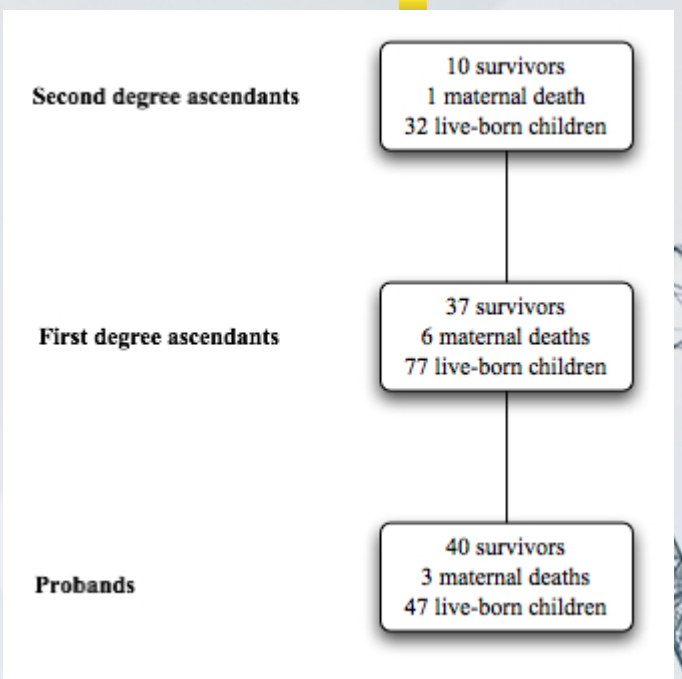
Maternal mortality in France : probands and pedigree analysis (2000-2014)

The Ehlers Danlos Society

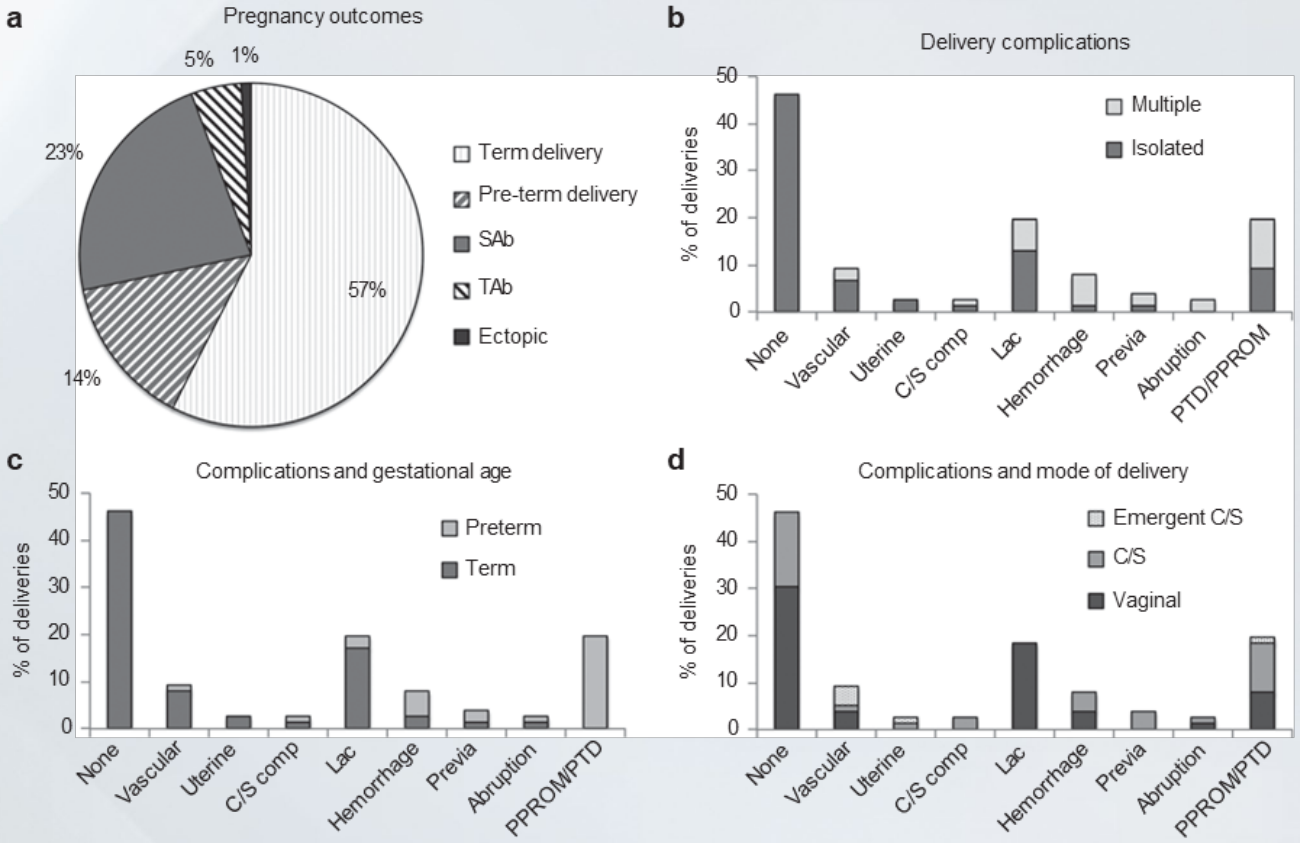
GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

N=75 probands and n=60 families, n=98 parturients with n=156 live-born children

	Live born children	Maternal deaths (all)	Maternal deaths (pregnancy and peripartum)	Late maternal deaths (peripartum to 1 year)	Pregnancy-related mortality Ratio (95%CI)	Late maternal mortality ratio (95%CI)	Overall maternal mortality ratio (95%CI)
2nd degree ascendants	32	1	1	0	3.1[0.1-16.2]	0.0[0.0-0.0]	3.1[0.1-16.2]
1st degree ascendants	77	6	6	0	7.8[2.9-16.2]	0.0[0.0-0.0]	7.8[2.9-16.2]
Probands	47	3	2	1	4.3[0.5-14.5]	2.1[0.1-11.3]	6.4[1.0-20.3]
Probands + 1st degree ascendants	124	9	8	1	6.5[2.8-12.3]	0.8[0.0-4.4]	7.3[3.4-13.3]
Probands + 1st + 2nd degree ascendants	156	10	9	1	**5.8[2.7-10.7]**	0.6[0.0-3.5]	**6.4[3.1-11.5]**



Obstetrical outcomes in n=76 term pregnancies from n=35 women



Murray et al. 2014

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:

Strategies & Solutions for Unmet Needs

AUGUST 30-31, 2023

BELGIUM

Maternal characteristics and obstetrical outcomes in n=61 term pregnancies by n=39 women

	n (%) or Median [Q1-Q3]
Maternal characteristics	
Age at delivery	27 [24-30]
Age at genetic diagnosis	38 [29-44]
vEDS diagnosed before delivery	9 (24)
Total number of pregnancies	82
Type of *COL3A1* variant:	
Glycine substitutions	23 (60)
Splice-site mutations/deletions/duplications	12 (32)
C- or N-terminal mutations	3 (8)
Characteristics of pregnancies and deliveries (life and still-births; n=61)	
Preterm labour	23 (38)
Premature rupture of membranes	12 (20)
Cervix incompetence (5 months)	2 (3)
Preterm births*	24 (40)
Term (weeks of amenorrhea)	36 [33-37]
Arterial events	2 (3)
Bleeding (all)	12 (20)
Hemorrhage requiring blood transfusion	6 (10)
Haemorrhagic shock	4 (7)
Perineal outcome in vEDS patients with vaginal deliveries (n=35)	
Episiotomy	26 (74)
Forceps delivery	4 (11)
Perineal tears (all)	19 (54)
1st degree	4 (21)
2nd degree	6 (32)
3rd degree	8 (42)
4th degree	1 (5)
Duration of pain (days)	13.5 [5-42.5]
Incontinence	4 (11)
urinary	3 (75)
faecal	1 (25)
Duration of incontinence	
from 3 to 6 months	3 (75)
>6 months	1 (25)

The Ehlers Danlos Society
GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

Pregnancy management in France

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

1. Preconception multidisciplinary counseling

- If molecular diagnosis is established
- History of disease and past arterial accident are reviewed
- Arterial imaging is programmed
- Adaptation of treatments if necessary
- Betablockers / celiprolol if applicable, are continued
- Options of prenatal genetic testing are discussed
- The couple is informed about maternal risks

Pathol. Mat. et Grossesse Benachi et al. Elsevier Health Science, 2022

Pregnancy management in France

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

2. Follow-up of pregnancy

- Monthly outpatient visits until 34 WA, then more frequent
- Patient are informed about risk of complications and must sollicit medical attention in case of unusual symptoms. Patient have an emergency care card
- Cervical cerclage is not systematic, but cervix should be measured at 1st trimester fetal echography, at 16WA and 28WA
- Premature rupture of membranes is increased (20%), more frequent when fœtus carries the mutation
- Antenatal corticosteroïds (single course for accelerating lung maturation are systematic (32WA)

There is no systematic arterial monitoring during pregnancy in France

Pathol. Mat. et Grossesse Benachi et al. Elsevier Health Science, 2022

Pregnancy management in France

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

3. Choice of mode of Child Delivery

- No existent litterature on mode of delivery in vEDS
- Final decision relies on the benefit/risk ratio between
  - Risks of vaginal delivery: uterine rupture, high grade perineal tears potentially needing complex repairs
  - Risks of c-section : post-partum hemorrhage, uterine tissular fragility, cutaneous fragility (sutures)
  - Regardless of mode, delivery should be programmed because of the increased risk of complications

A c-section between 35 and 37 WA is often preferred. Vascular surgeons must be informed and on stand-by.

Pathol. Mat. et Grossesse Benachi et al. Elsevier Health Science, 2022

Pregnancy management in France

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

4. Post-partum

- **Timeframe at high risk of complications**
- Progesterone implants should be avoided
- Missing littérature on intrauterine devices
- TE prevention as necessary
- No early dismissal (<5 days)

- Breastfeeding

- Controversial since patients are taking betablockers
- Should not prolonged be over extensive periods

Pathol. Mat. et Grossesse Benachi et al. Elsevier Health Science, 2022

How to council and advise these 2 patients?

The Ehlers Danlos Society

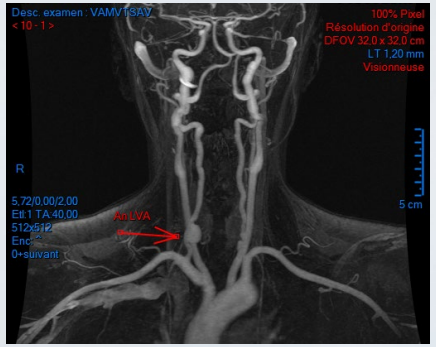
GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

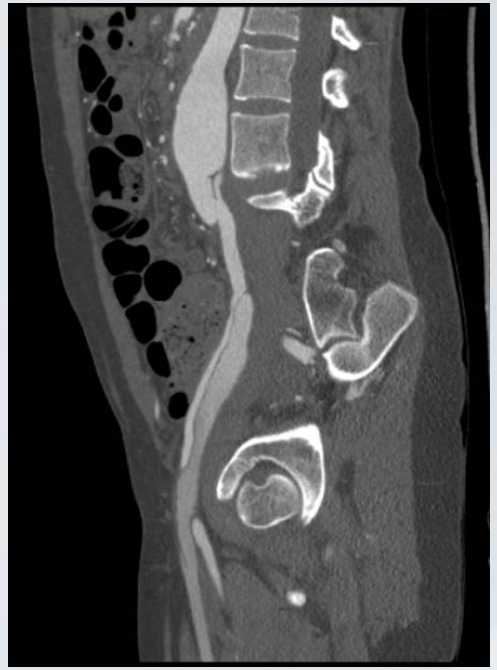
Case 1

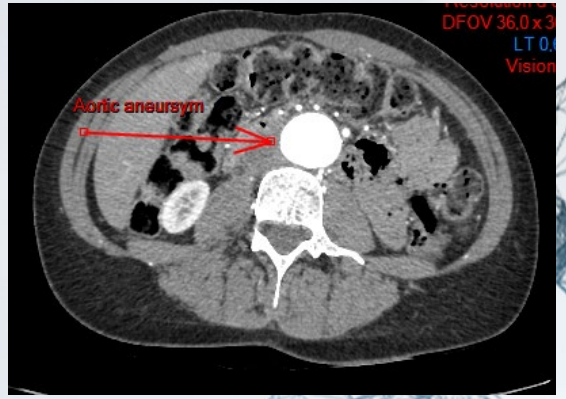
- Vascular work-up
  - Dissection right ICA
  - Aneurysm right vert. Art.
- Family history of vEDS wo. obstetrical events (Mother, Grandmother)

Case 2

- 38 year-old patient
- Nulliparous
- ***COL3A1***:
- Treated w. celiprolol
- Important vascular history:
  - Aorto-iliac dissection
  - Vertebral and ICA dissection and aneurysms
  - Splenic artery rupture
- Considering pregnancy







Clinical Cases : outcomes

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

Case 1

- Spontaneous pregnancy
- Uneventful throughout prgncy
- 1 week prior to programmed c-section:
  - moderate lateralized chest pain for 24h
  - Pneumothorax and PE ruled in emergency
  - Cardiocirculatory collapse by aortic rupture occurred after CTscan
  - Emergency c-section was performed but patient deceased despite surgical stand-by

Case 2

- Spontaneous pregnancy despite contra-indication
- Pregnancy uneventful
- Programmed c-section uneventful
- At day 3 : abdominal aortic rupture resulting in death of the patient despite aortic repair

Maternal morbidity in France : programmed c-sections (2000-2014)

N=14 patients had a standardized follow-up and progammed delivery by c-section
N=8 patients had betablockers (well tolerated)

N=1 died by aortic rupture 1 week prior delivery (patient not compliant to BB)
N=1 patient developped aortic rupture at day +3 PP and deceased despite aortic repair (pregnancy was contra-indicated)

Conclusion

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:
Strategies & Solutions for Unmet Needs
AUGUST 30-31, 2023
BELGIUM

- Pregnancy is a difficult topic in vEDS because of the unpredictable risk of maternal complications
- Multidisciplinary Preconception counseling for the couple is the first most important step when contemplating pregnancy
- Arterial rupture remains unpredictable and any unusual pain during third trimester should prompt imaging of the whole aorta

The Ehlers Danlos Society

GENETICALLY DEFINED EDS:

Strategies & Solutions for Unmet Needs

AUGUST 30-31, 2023

BELGIUM

Thank you for listening