



The
Ehlers
Danlos
Society

GENETICALLY DEFINED EDS:

Strategies & Solutions for Unmet Needs

AUGUST 30-31, 2023

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EDS ECHO SUMMIT SERIES

GENETICALLY DEFINED EDS: Strategies & Solutions for Unmet Needs

PRESENTATION

Preimplantation genetic
testing in genetically defined
types of EDS

SPEAKER

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1. National EDS service London

2. Section of genomics and genetics, Imperial College London



What is pre-implantation genetic testing?



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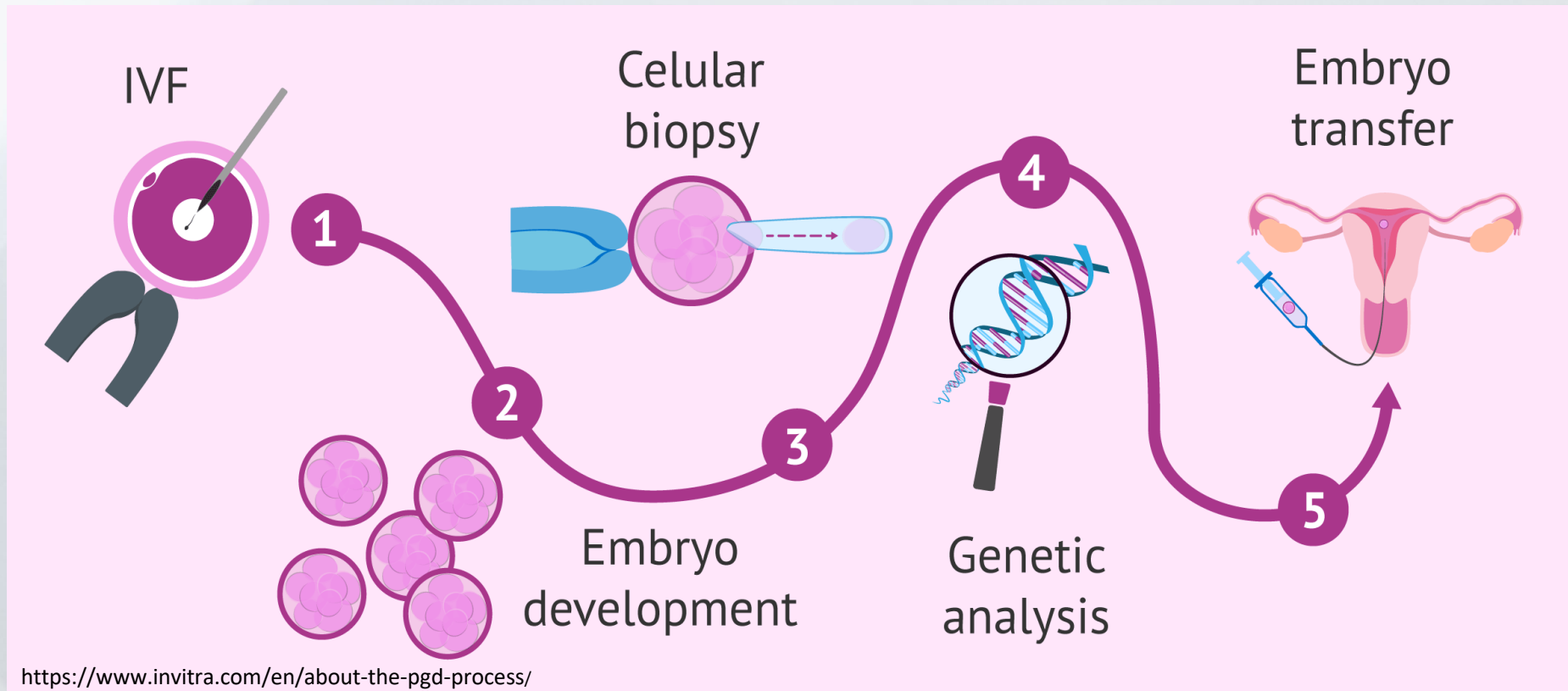
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- Testing for monogenetic disorders, karyotype disorders, chromosomal rearrangements
- Previously called PGD, now called PGT



<https://www.invitra.com/en/about-the-pgd-process/>

Recommendations worldwide

- Available since the 1990s
- There are differences around the world
- The UK is one of the only countries to have an authorising body:
Human Fertilisation and Embryology Authority
- Approved in the UK for:
 - Vascular EDS
 - Classical EDS
 - Periodontal EDS
 - Kyphoscoliotic EDS (PLOD1 or FKBP14)
- More indications being added all the time

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197420/>



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Case Reports > Hum Fertil (Camb). 2014 Jun;17(2):141-4. doi: 10.3109/14647273.2014.903002.

Epub 2014 Apr 24.

In vitro maturation and surrogacy in patients with vascular-type Ehlers-Danlos syndrome--a safe assisted reproductive technology approach

Marie-Eve Bergeron¹, Tim Child, Muhammad Fatum

Affiliations + expand

PMID: 24758138 DOI: 10.3109/14647273.2014.903002

FULL TEXT LINKS



ACTIONS

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CASE REPORT article

Front. Genet., 16 March 2023

Sec. Genetics of Common and Rare Diseases

Volume 14 - 2023 | <https://doi.org/10.3389/fgene.2023.1147607>

This article is part of the Research Topic

Ehlers-Danlos Syndrome: from bedside to bench

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Case report and discussion: Pre-implantation genetic diagnosis with surrogacy in vascular Ehlers-Danlos syndrome



Chloe Angwin^{1,2},



Neeti Ghali^{1,2} and



Fleur Stephanie van Dijk^{1,2*}

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UM

Birth

- unilateral congenital hip dislocation



Age 9

- left anterior cruciate ligament rupture

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Age 27

- haemorrhagic rupture of a liver cyst

Age 28

- right peroneal artery aneurysm

Testing

- *COL3A1* c.2492G>A heterozygous pathogenic variant

Age 29

- right coronary artery dissection complicated by right iliac artery dissection post angiogram

Age 30

- pre-conception counselling (IVF with PGT and surrogacy)

Bergeron et al. 2014

Age 32

- Standard IVF protocol, first round with surrogate

- Splenic artery aneurysm rupture day before oocyte retrieval
- Developed left sided deep vein thrombosis after discharge, managed with anticoagulants and complicated by a liver haematoma

Age 33

- 4 cycles of unstimulated/natural IVF which failed

- Trialled in vitro maturation (IVM)
- used rHCG for oocyte retrieval with monitoring for vascular complications

- Successful oocyte retrieval, successful PGT with unaffected embryos
- failure to implant into surrogate

What then?



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Age 35

- Natural IVF at a private clinic with an alternative surrogate



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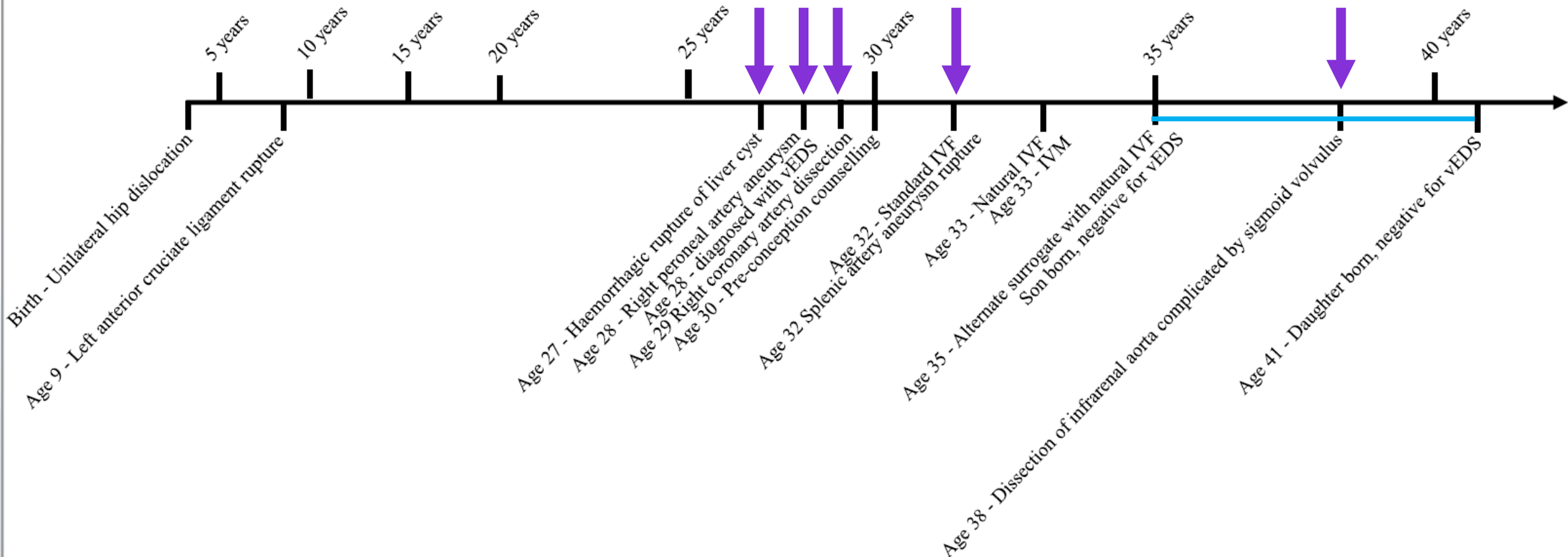
Age 38

- spontaneous dissection of the infrarenal aorta below the inferior mesenteric artery complicated by sigmoid volvulus managed endoscopically.

Age 41

- 20 cycles to retrieve 19 oocytes with PGD
- successful implantation into surrogate
- daughter born and confirmed negative

Case



What have we learned from this case?

- Unclear whether there is a link with hormonal stimulation and arterial events
- Transvaginal egg retrieval had no direct complications for this individual
- We know from clinical experience that many women with vEDS are keen to have biological **and** unaffected children
- PGT offers the only route for families wishing to have unaffected biological children without the 50% risk of termination of pregnancy

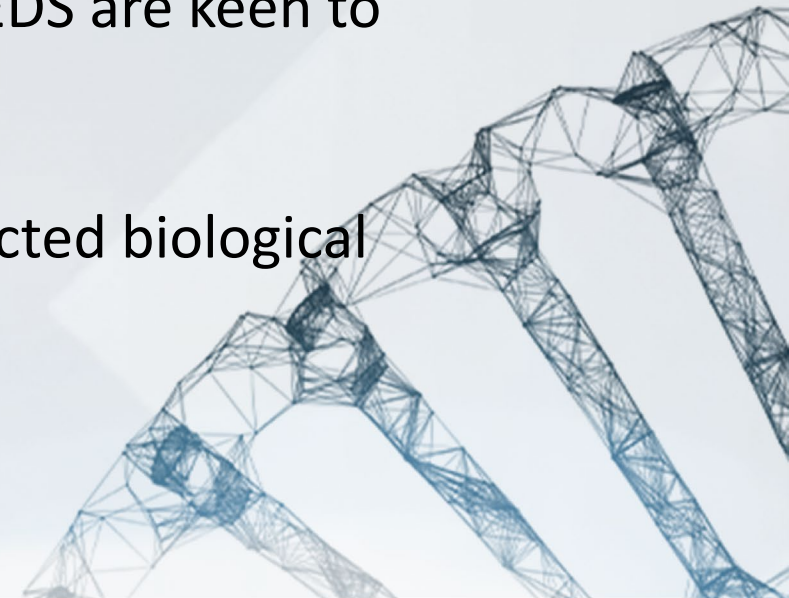


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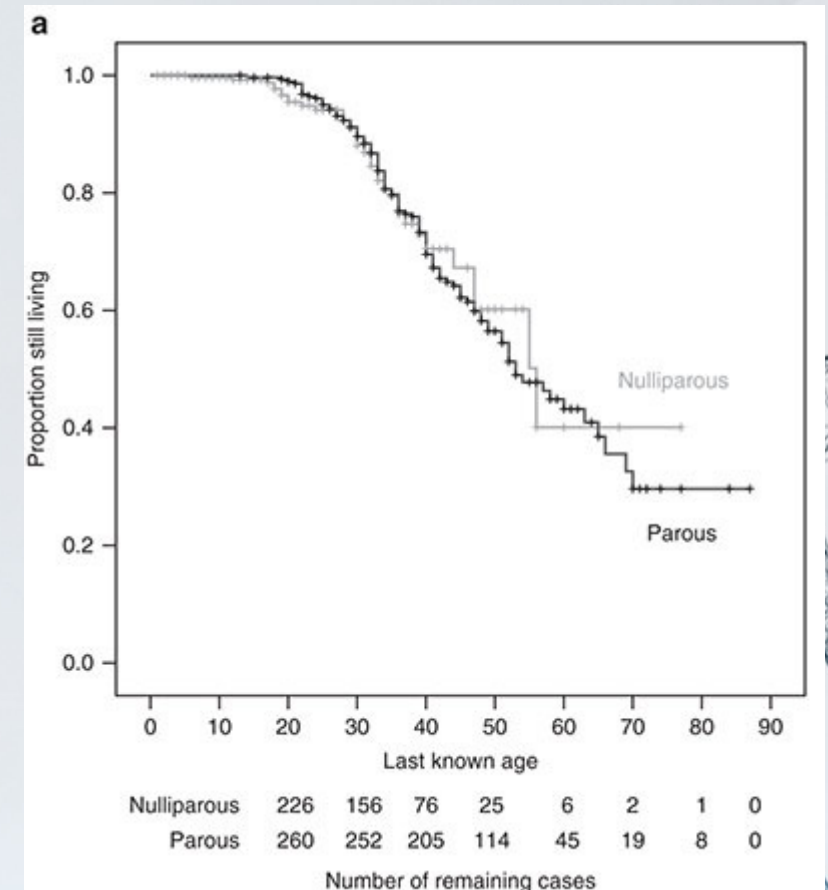
What do we know about pregnancy in vEDS?



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- Mortality in pregnancy for women with vEDS is currently estimated at 5.3% (30/565) (Murray et al., 2014)
 - No difference in survival between parous and nulliparous
 - A smaller interviewed cohort (38 women, 113 pregnancies)
 - 10.6% (12 pregnancies) vEDS diagnosed prior to conception
 - 4.4% (5) deaths: 4 arterial events, 1 previous c-section wound dehiscence
 - 9.7% (11) non-fatal complications: arterial dissections, uterine ruptures, surgical complications, third or fourth degree lacerations, haemorrhage, placental complications
 - 14% (16) premature delivery
- Haploinsufficiency is thought to result in attenuated phenotype (Murray et al., 2014) (27 women, 51 deliveries)
 - No pregnancy related deaths
 - Premature delivery, third or fourth degree lacerations
- Premature birth is more common in vEDS affected fetuses (Stephens et al., 2022) regardless of maternal status



What are the current recommendations?

- The European Society of Cardiology 2018 Guidelines for the management of cardiovascular disease during pregnancy:
 - Pregnancy is considered very high risk and is not recommended in patients with vascular EDS
 - All patients with vEDS should be advised not to become pregnant
 - Celiprolol is recommended for women with vEDS
 - For any woman with high risk cardiovascular disease:
 - Medical termination should be considered up to 9 weeks at reduced doses
 - Surgical termination in an experienced centre is a more appropriate route
 - Any pregnancy should be monitored by a cardiologist and obstetrician
 - C-section is recommended for any vEDS patients who are pregnant
- Human Fertilisation and Embryology Authority:
 - Vascular EDS is approved for PGT



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Bowen et al., 2023

- 1 patient had unsuccessful IVF without complications
- 53 vEDS women with 114 pregnancies
 - Thoracic aortic dissection 1 day after surgical termination of pregnancy at 10 weeks
 - There were 5 significant vascular events in 104 pregnancies (4.8%), 3 of which were fatal (2.9%).
 - 9 babies were delivered to 8 women where vEDS was already confirmed,
 - early delivery with planned c-section under general anaesthetic in a tertiary hospital



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What do we need?

- Up to date pregnancy information in patients with known diagnosis and on current recommended management
- Data on other pregnancy related complications, not just mortality
- Is there variable pregnancy risk along with variation in phenotype/genotype?
- Data on safety of termination either hormonal or surgical
- Data on safety and risk of PGT or IVF procedures.
- The need and desire for further research and evidence has been recently highlighted by the vEDS Research Collaborative Sage et al 2020
 - Four areas: mental health, creating a care team, holistic approach to management, **pregnancy management**



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Thank you
for listening



Our clinical experience

- Unclear about hormonal stimulation and whether that has contributed
- Many women with vEDS are keen to have biological and unaffected children
- Lack of communication and clear understanding of the risks may put this group of patients at further risk as they are unable to make an informed decision around reproduction
- At worst there is potential that this may result in an unmonitored pregnancy



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Discussion

- This patient used a surrogate for the pregnancies
- There is a paucity of up to date information on mortality from pregnancy in EDS
- No evidence that natural IVF egg retrieval procedures increased the risk of vEDS related complications
- Theorised increased risk of arterial events with stimulated IVF not recommended for patients with inherited vascular conditions by the European Society of Cardiology (no recommendation General recommendations from the ESC regarding IVF in women with any cardiovascular disease include careful consideration of hormone dosages to manage or avoid prothrombotic conditions such as ovarian hyperstimulation syndrome and consideration of natural IVF ([European Society of Cardiology, 2018](#)). The ESC guidance makes no specific recommendations regarding egg retrieval risks or surrogacy in cardiovascular disease ([European Society of Cardiology, 2018](#)).



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Risks and benefits

- No guarantee no genetic conditions present
- Can be very expensive
- No formal procedural safety testing for vEDS
- Standard IVF carries potential health risks
 - those affected by cardiovascular disease
 - ovarian hyperstimulation syndrome
- Reassurance no familial variant
- Removes need for termination of affected child
- Mothers avoid risk to themselves from affected fetus



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Recommendations worldwide

Country	PGD available	Regulated by
USA	Yes	Guidelines
UK	Yes	Human Fertilisation and Embryology Authority
France	Yes	Public Health Code— Article L2131-1
Italy	Yes	<i>2004 Rules on Medically Assisted Procreation</i>
Japan	Yes	Guidelines
South Korea	Yes	<i>2005 Bioethics and safety act</i>
Brazil	Yes	Guidelines
South Africa	Yes	Guidelines
Israel	Yes	Guidelines



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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197420/>

Risk of pregnancy in vEDS

- For women with vEDS pregnancy has been reported to carry a 5% risk of death (population risk of 0.2% according to the CDC (USA 2017)) Pepin et al 2000
- vEDS status of the fetus can affect the pregnancy – increased rates of prematurity in affected not affected by maternal status Stephens et al 2022 – PGD is therefore important to ensure surrogate safety
- European Society of Cardiology current guidance advises that pregnancy should be avoided in all women with vEDS (ESC 2018)
- No guidance on assisted reproductive techniques

Data were analyzed from 526 women with vEDS as an update to a previous cohort ([Pepin et al., 2000](#)), comparing 243 nulliparous women against a cohort of 283 women who had had at least one pregnancy ([Murray et al., 2014](#)). Women with vEDS had a pregnancy-related death rate of 4.9%. When stratified for the variant type, protein-altering variants resulted in a 5.3% death rate per delivery (30 deaths in 256 women across 565 delivered pregnancies), while there were no deaths in those women with heterozygous null variants. Importantly, Kaplan–Meier survival curve analysis showed no significant difference in survival



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An alternative to PGD which ensures an unaffected child is invasive prenatal diagnosis (IPD), which would involve termination of any affected fetus ([NHS England, 2014](#)). ESC guidance discusses termination of pregnancy and recommends that for any women with high-risk cardiovascular disease, surgical termination in an experienced center is more appropriate, and medical terminations should be considered only up to 9 weeks using reduced dosages ([European Society of Cardiology, 2018](#)). However, prenatal testing can only be performed accurately after 11 weeks ([Alfirevic et al., 2017](#)). In women with vEDS, non-invasive prenatal diagnosis (NIPD) is currently not possible as the maternal variant will prevent differentiation from the fetus ([Jenkins et al., 2018](#)). Therefore, women with vEDS would have the option of a surgical termination only, which, given their generalized tissue fragility, would be considered a high-risk procedure. Additionally, the procedure of prenatal diagnosis is not without risk, particularly in the context of disorders of tissue fragility, and is also not



Take home messages

- People affected by rare conditions should be able to have informed discussions about reproductive options
- Safety trials are required for IVF (natural vs hormonal)
- Up to date information on safety in pregnancy for all EDS types is required



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Natural IVF

- Natural IVF at a private clinic with an alternative surrogate
- 6 cycles to create four unaffected embryos
 - successful implantation into surrogate
 - son born
 - confirmed negative
- 20 cycles to retrieve 19 oocytes with PGD
 - successful implantation into surrogate
 - daughter born
 - confirmed negative



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