Fabry Findings

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Current guidance issued by the regulatory authorities advise to use treatment for Fabry with caution,[1,2] or to avoid its use altogether[3] during pregnancy.

These recommendations have been based on the limited amount of data available for these treatments in pregnant women or from the findings of earlier studies conducted in animals.

There are a number of published reports describing cases where treatment with enzyme replacement therapy (ERT) has continued during pregnancy.

In this issue, we explore pregnancy and Fabry disease, and present the latest findings on the use of ERT during pregnancy

What is Fabry?

Fabry disease is a rare, genetic condition which is estimated to affect around 1 in 100,000 people.[4]

In Fabry, an absence or reduced level of an enzyme called α-galactosidase A (α-Gal A), means that the body cannot break down certain types of fats, called globotriaosylceramide (GL-3 or Gb3) and plasma globotriaosylsphingosine (lyso-Gb3), and Gb3 builds up in a variety of cells in the body.[4]

This build-up causes damage to tissues and organs and leads to a range of symptoms and complications, which vary from one person to another.[4]

Fabry in women

Until 2001, women were considered, by medical professionals, to be 'asymptomatic carriers' of Fabry disease; that they can pass the disease on to their children without experiencing any of the symptoms themselves.[5]

It is now widely recognised that most women with the mutation in α-Gal A (**heterozygous disease**) experience the disease in the same way that men with the mutation do; with a significant burden of disease and impaired quality of life.[6]

A woman has heterozygous disease

She has the Fabry gene on at least one of her two X chromosomes (XX), one inherited from her mother, one inherited from her father

Information on how Fabry is inherited can be found on page 9.

Information on the variability of Fabry symptoms and complications, and what effect pregnancy has on these, can be found on page 3.

Planning a family

When considering starting a family, individuals with Fabry may wish to consider **genetic counselling**.

Genetic counselling helps individuals and families understand the medical, psychological, social and reproductive implications of having a genetic condition

Fabry and fertility

There is limited information on fertility in individuals with Fabry disease.

One study reported normal hormone levels and fertility in both males and females with Fabry when compared with the general population.[7]

A recent study of males reported that Fabry disease may affect sperm characteristics (e.g. count, shape and movement), but it does not impact hormone function and only slightly reduces fertility rates.[8]

Pregnancy

Testing for Fabry

A number of tests are available to check for Fabry before a child is born:

- Before pregnancy – **pre-implantation diagnosis** of embryos - similar to *in vitro* fertilisation (IVF)
- Week 5 onwards – **free-foetal DNA testing**
- Weeks 10–12 – **chorionic villous sampling (CVS)**
- Weeks 16–17 – **amniocentesis**

Pre-implantation diagnosis is used to check embryos for a known condition in the family before unaffected embryos are implanted into the mother

CVS involves removing and testing a small sample of cells from the placenta

Amniocentesis involves removing and testing a small sample of cells from the amniotic fluid, the fluid that surrounds the unborn baby in the womb

Cells from the baby (free foetal DNA) can be detected in the mother's blood from around five weeks of pregnancy

These cells can be analysed to find out the sex of the foetus

Not everyone chooses to find out if their unborn child has Fabry disease before they are born, instead testing can be carried out at a later stage.

Fabry symptoms

Day-to-day symptoms and complications of Fabry are known to vary from one person to another;[4] some of these **symptoms get worse during pregnancy.**

SKIN

- Sweating less than normal
- Small dark red/purple spots located between the belly button and the knees

KIDNEYS

- Protein in urine
- Decreased kidney function
- Kidney failure

EYES AND EARS

- Hearing loss (in children)
- Ringing in ears
- Cloudy vision (cataracts)

BRAIN AND NERVES

- Burning in the hands and feet
- Intolerance to heat/cold
- Vertigo/feeling dizzy
- Pain
- White matter lesions
- Depression
- Mini stroke
- Stroke

STOMACH AND BOWELS

- Feeling sick/being sick
- Diarrhoea
- Pain/bloating after eating
- Difficulty managing weight
- Feeling full after eating a small amount of food

HEART

- Irregular heart beat
- Enlarged heart
- Heart attack
- Heart failure

OTHER

- Tiredness that is not relieved by rest or sleep
- Shortness of breath
- Cough/wheezing

The effect of pregnancy on Fabry symptoms

A **retrospective study** looking at the impact of Fabry disease on pregnancy found several Fabry-related symptoms worsened during pregnancy. These included: gastrointestinal symptoms, a sensation or burning/pricking/tingling in hands and feet, protein in the urine, headaches and **post-partum** depression.[9]

A retrospective study is one which looks at information or events that have taken place in the past

Post-partum is the period of time after giving birth

Fabry disease treatment and pregnancy

How safe and effective ERT for Fabry disease is during pregnancy and its impact on the unborn child has yet to be established by any of the clinical trials and is unlikely to ever take place due to the low number of patients.

Instead, we rely on patient **case reports** to provide a source of information on this topic.

A case report is a detailed report of the symptoms, signs, diagnosis, treatment and follow-up of an individual patient

Case reports usually describe an unusual or novel occurrence

First reported cases of Fabry treatments in pregnancy

The first case report for agalsidase alfa treatment was published in 2005;[10] this was followed by the first report for agalsidase beta in 2010;[11,12] and in 2018, the first case report for migalastat.[13]

Replagal™ - 2005
Agalsidase alfa

Fabrazyme™ - 2010
Agalsidase beta

Galafold™ - 2018
Migalastat

Fabry and the foetus

There are mixed reports on whether glycosphingolipids, mainly Gb3, are found in the **placenta**;[14] this might be because of differences in disease severity in the mother, disease severity in the child, and the effects of ERT.

The placenta is the structure attached to the lining of the womb that provides oxygen and nutrients to the growing baby, and removes waste products

Gb3 levels in the placenta may be affected by the disease severity of the mother and/or child and ERT

Research news

'Enzyme replacement therapy during pregnancy on Fabry patients. Review of published cases of live births and a new case of a severely affected female with Fabry disease and pre-eclampsia complicating pregnancy' *was published in JIMD Reports.*[15]

The study

'Enzyme replacement therapy during pregnancy on Fabry patients. Review of published cases of live births and a new case of a severely affected female with Fabry disease and pre-eclampsia complicating pregnancy' was published in JIMD Reports.[15]

The study reported a new case report of Fabry disease in a pregnant patient with **pre-eclampsia**, in which ERT was used throughout the pregnancy.

The study also reviewed a further 12 published case reports.

New case report

A pregnancy with pre-eclampsia

+

Review

Pre-eclampsia is a condition that affects some pregnant women, usually during the second half of pregnancy or soon after delivery

Early signs of pre-eclampsia include high blood pressure and protein in urine

Most cases of pre-eclampsia cause no problems and improve after delivery, however, there is a risk of serious complications to both the mother and her baby if it is left untreated

Review of a total of 13 published case studies of live births in women with Fabry; nine of which used ERT during pregnancy

The findings

'Enzyme replacement therapy during pregnancy on Fabry patients. Review of published cases of live births and a new case of a severely affected female with Fabry disease and pre-eclampsia complicating pregnancy'

New case report - a pregnancy with pre-eclampsia

A 38-year-old, first-time mother, who had been diagnosed with Fabry aged 2 years

Medical history

- Stroke, aged 23 years
- High blood pressure
- Reduced renal function
- **Albuminuria**
- **TIA**, aged 32 years

Albuminuria is the presence of albumin (a type of protein) in the urine

TIA stands for transient ischaemic attack

It is sometimes called a mini stroke

ERT

- Started ERT, aged 23 years

A spontaneous pregnancy is one which has occurred naturally, as opposed to one which has happened by medical intervention (e.g. IVF)

Pregnancy

- **Spontaneous pregnancy**
- CVS showed a male child without Fabry disease
- Moderate to severe pre-eclampsia in the **third trimester**, which was successfully managed with medication (for high blood pressure)

The third trimester begins in week 28 of pregnancy and lasts until birth

Birth

- Planned **caesarean** section at 38 weeks + 6 days of **gestation**
- Healthy baby boy delivered
- Without Fabry disease

Gestation is the average length of a pregnancy

In humans this is 40 weeks

A caesarean section is an operation to deliver a baby through a cut made to the abdomen and womb

A caesarean can be planned or done in an emergency if there are problems during a vaginal delivery

Placenta

- No Gb3 accumulation

The findings

'Enzyme replacement therapy during pregnancy on Fabry patients. Review of published cases of live births and a new case of a severely affected female with Fabry disease and pre-eclampsia complicating pregnancy'

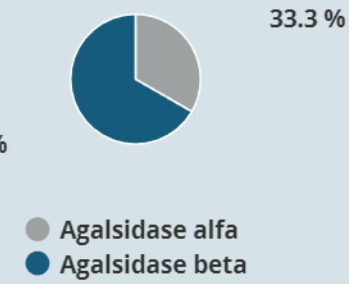
The new case report was reviewed along with a further 12 case studies that had previously been published

13 cases reviewed

In the study population:

- Nine women were treated with ERT during pregnancy
- Six were treated with agalsidase beta
- Three were treated with agalsidase alfa
- The dose of ERT remained unchanged during the pregnancy

Four women had not been treated with ERT during pregnancy



Complications and disease progression

No ERT	ERT
No complications reported	Gestational diabetes and hyperthyroidism; pre-eclampsia
No disease progression reported	Disease progression not disclosed

Two women had complications

Pregnancy outcomes

All babies survived

whether the mother received ERT during pregnancy or not; and whether or not the child had Fabry disease

Gestational diabetes is high blood sugar that develops during pregnancy

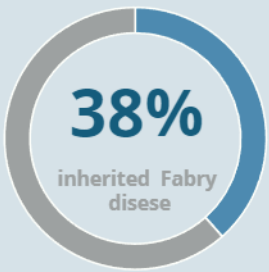
Hyperthyroidism is another name for an overactive thyroid

Placenta

The placenta from six cases (both treated and untreated mothers) was examined for Gb3.

Gb3 was found in tissues from the mother's side of the placenta in all samples tested.

Gb3 was only found in tissues from the foetus' side of the placenta if the foetus had inherited Fabry; this occured in two cases.



Five infants inherited Fabry disease

Findings in brief

'Enzyme replacement therapy during pregnancy on Fabry patients. Review of published cases of live births and a new case of a severely affected female with Fabry disease and pre-eclampsia complicating pregnancy'

- A review of 13 published Fabry pregnancies was performed
- Nine mothers were treated with ERT during their pregnancy at the same dose they received before pregnancy

6 women were treated with agalsidase beta

4 women had no treatment

3 women were treated with agalsidase alfa

- All pregnancies resulted in a live birth

5 infants inherited Fabry disease

- Six placentas were examined from ERT treated/untreated pregnancies

100%

Gb3 was found in tissues from the mother's side of the placenta in all examined

33%

Gb3 was only found in tissues from the foetal side of the placenta if the foetus had Fabry disease

Conclusions

- A review of published case reports of pregnancy in Fabry disease suggests that ERT is safe to use in pregnancy
- Based on these findings, the question is asked whether it is time to reconsider the current 'use with caution' advice in respect to ERT use in Fabry pregnancies

Inheritance

As Fabry disease is an X-linked disorder it can be passed to children by either parent

Fabry is caused by a **mutation** in the α-galactosidase A gene (GLA) on the X chromosome

A mutation is a permanent alteration in the DNA sequence that makes up a gene

'Heterozygous' and 'hemizygous' disease...

Females have heterozygous disease

They inherit two different copies of the X gene, one from each parent

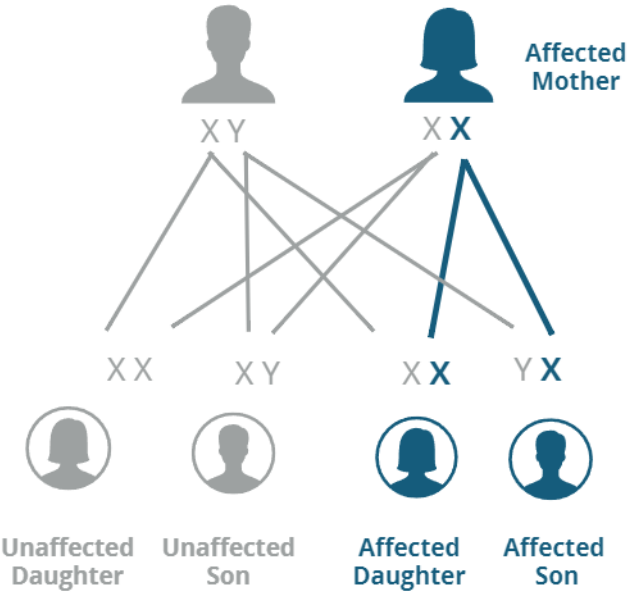
Females can inherit the Fabry gene from either parent

Males have hemizygous disease

They have a single copy of the X gene which is inherited from their mother

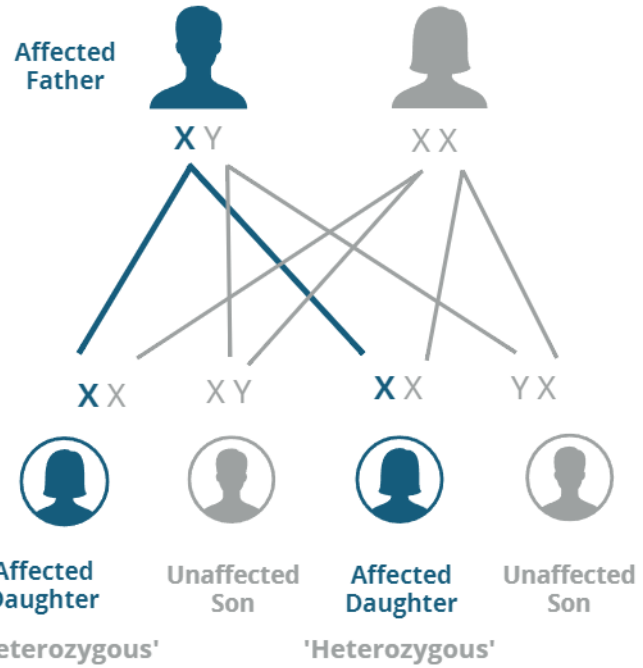
Mother

A mother with Fabry has a 50% chance of passing her **X mutation** to any of her children



Father

A father with Fabry passes his **X mutation** to all of his daughters. His sons do not inherit Fabry because they inherit his Y chromosome



References

1. BNF NICE. Agalsidase alfa [cited 2019 November]. Available from: https://bnf.nice.org.uk/drug/agalsidase-alfa.html#pregnancy.
2. BNF NICE. Agalsidase beta [cited 2019 November]. Available from: https://bnf.nice.org.uk/drug/agalsidase-beta.html#pregnancy.
3. BNF NICE. Migalastat [cited 2019 November]. Available from: https://bnf.nice.org.uk/drug/migalastat.html#pregnancy.
4. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30.
5. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38(11):769-75.
6. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007;9(1):34-45.
7. Hauser AC, Gessl A, Harm F, Wiesholzer M, Kleinert J, Wallner M, et al. Hormonal profile and fertility in patients with Anderson-Fabry disease. Int J Clin Pract. 2005;59(9):1025-8.
8. Papaxanthos-Roche A, Maillard A, Chansel-Debordeaux L, Albert M, Patrat C, Lidove O, et al. Semen and male genital tract characteristics of patients with Fabry disease: the FERTIFABRY multicentre observational study. Basic Clin Androl. 2019;29:7.
9. Holmes A, Laney D. A Retrospective Survey Studying the Impact of Fabry Disease on Pregnancy. JIMD Rep. 2015;21:57-63.
10. Wendt S, Whybra C, Kampmann C, Teichmann E, Beck M. Successful pregnancy outcome in a patient with Fabry disease receiving enzyme replacement therapy with agalsidase alfa. J Inherit Metab Dis. 2005;28(5):787-8.
11. Politei JM. Treatment with agalsidase beta during pregnancy in Fabry disease. J Obstet Gynaecol Res. 2010;36(2):428-9.
12. Germain DP, Bruneval P, Tran TC, Balouet P, Richalet B, Benistan K. Uneventful pregnancy outcome after enzyme replacement therapy with agalsidase beta in a heterozygous female with Fabry disease: A case report. Eur J Med Genet. 2010;53(2):111-2.
13. Haninger-Vacariu N E-HS, Pauler U, Foretnik M, Kain R, Schmidt A, Skuban N, Barth JA, Sunder-Plassmann G., Pregnancy outcome after exposure to migalastat: A case study. 14th Annual WORLDSymposium; 2018; San Diego, CA.
14. Bouwman MG, Hollak CE, van den Bergh Weerman MA, Wijburg FA, Linthorst GE. Analysis of placental tissue in Fabry disease with and without enzyme replacement therapy. Placenta. 2010;31(4):344-6.
15. Madsen CV, Christensen EI, Nielsen R, Mogensen H, Rasmussen AK, Feldt-Rasmussen U. Enzyme Replacement Therapy During Pregnancy in Fabry Patients : Review of Published Cases of Live Births and a New Case of a Severely Affected Female with Fabry Disease and Pre-eclampsia Complicating Pregnancy. JIMD Rep. 2019;44:93-101.

Find out more

Fabry International Network

Fabrynetwork.org

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