Current guidance issued by the regulatory authorities advise to use treatment for Fabry with caution, or to avoid its use altogether 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.

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; 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

**KIDNEYS**
- Protein in urine
- Decreased kidney function
- Kidney failure

**OTHER**
- Tiredness that is not relieved by rest or sleep
- Shortness of breath
- Cough/wheezeing

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.

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.

First reported cases of Fabry treatments in pregnancy

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

Fabry and the foetus

There are mixed reports on whether glycosphingolipids, mainly Gb3, are found in the placenta; 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.
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

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

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

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

New case report - a pregnancy with pre-eclampsia

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

- ERT
  - Started ERT, aged 23 years

Medical history

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

TIA stands for transient ischaemic attack
It is sometimes called a mini stroke

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

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

Gestation is the average length of a pregnancy
In humans this is 40 weeks

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

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

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

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

69% had ERT during pregnancy

33.3 % Agalsidase alfa
66.7 % Agalsidase beta

Complications and disease progression

- No ERT: No complications reported, No disease progression reported
- ERT: Gestational diabetes and hyperthyroidism; pre-eclampsia; Two women had complications
- Disease progression not disclosed

Pregnancy outcomes

All babies survived whether the mother received ERT during pregnancy or not, and whether or not the child had Fabry disease.

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 occurred in two cases.
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...

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

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.

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.

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References


Find out more

Fabry International Network
Fabrynetwork.org

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