The role of inactive follicle stimulating hormone in ovarian dysfunction in galactosemia.

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1) To assess whether galactosemia women with ovarian failure are able to produce estradiol after exogenous (normally bioactive) FSH and LH gift 2) To characterize FSH glycan structures

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine disorders of gonadal function
Study type	Interventional

Summary

ID

NL-OMON31697

Source
ToetsingOnline

Brief title
FSH/Galactosemia

Condition

- Endocrine disorders of gonadal function
- Inborn errors of metabolism
- Ovarian and fallopian tube disorders

Synonym
infertility in galactosemia (inherited metabolic disorder)

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht

Source(s) of monetary or material Support: Ministerie van OC&W,Galactosemie Onderzoek Fonds

Intervention

Keyword: galactosemia, gonadotropins, ovarian dysfunction

Outcome measures

Primary outcome

1) Estradiol response (yes/no) after recombinant FSH and LH. Estradiol response

is defined as (*E2) > 30 pg/ml (Fanchin et al. 1994)

2) FSH glycan structure characterization in galactosemia women

Secondary outcome

Baseline FSH (follicle stimulating hormone), LH (luteinizing hormone) AMH

(anti- Müllerian hormone) and inhibin are measured at baseline. AMH and inhibin

have not been well documented in the galactosemia population. These

measurements can be relevant to the understanding of ovarian dysfunction.

Study description

Background summary

Classical galactosemia is an inborn error of galactose metabolism due to a deficiency of the enzyme galactose-1-fosfate uridyltransferase. Dairy products are rich in galactose. Treatment consists of a lifelong galactose restricted diet (soja diet).
Most females with galactosemia have ovarian dysfunction varying from primary to secondary amenorrhoea due to premature ovarian failure and was first described by Kaufman et al. in 1981. In 75-90% primary amenorrhoea is present and women are infertile.
Until present the mechanism underlying ovarian dysfunction is not clear.
Recent insights point to a possible inactive (follicle stimulating hormone) FSH in these patients.

FSH is such as other hormones a glycoprotein (protein with sugar trees). In classical galactosemia there is a secondary disturbance in glycosylation of proteins (abnormal sugar trees are made). Protein glycan structures (sugar trees) are essential for protein function. In female galactosemia patients, there is preliminary evidence that abnormally glycosylated FSH is present. This abnormal glycosylated FSH can bind to the receptor but it is unable to generate cyclic AMP, acting as an antagonist. The final result is that no estradiol (female hormone) can be produced.
Our hypothesis is that ovarian dysfunction in galactosemia females is due (at least in part) to inactive, abnormally glycosylated FSH.

Clinical relevance: Most women with classical galactosemia are infertile. If ovarian dysfunction is due to inactive FSH, treatment with exogenous FSH and LH could be a possibility in childbearing women. Moreover this finding would be very relevant for the understanding of this disease complication and for possible elucidation of other complications (abnormal glycosylation of other proteins).

Study objective

1) To assess whether galactosemia women with ovarian failure are able to produce estradiol after exogenous (normally bioactive) FSH and LH gift
2) To characterize FSH glycan structures

Study design

Intervention study with before and after measurements and no parallel group

Intervention

Study persons are treated with one subcutaneous gift Menopur, 150 resp 225 IU/day during maximum 20 days. This is registered medication regularly used for ovulation induction in infertility treatment.
Just before the first gift and on day 8, 10, 18 and 20, a blood sample is drawn (vena punction, 10 ml each time).

Study burden and risks

Most women with galactosemia have ovarian dysfunction and are infertile. The mechanism is not yet clear. Female patients often experience this complication as the most distressing problem of their disease.
If we obtain a positive estradiol response in this study after FSH and LH stimulation, we will be a huge step forward in understanding the mechanism underlying this complication and treatment of infertility in this women.
The study lasts a maximum of 20 days and the expected risks of this treatment are, with this relatively low dose, extremely small. The injections and blood

withdrawals are done by the at the patient's home address. In case of complaints, the patient can contact the physician researcher 24 hours/day. Adverse effects of Menopur are described in paragraph 7.2 of the protocol. The participants will be notified of the results of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

galactosemia
ovarian dysfunction

Exclusion criteria

normal ovarian function
endocrinological or gynecological tumors

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2007
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Menopur
Generic name:	Menopausalgonadotropin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	15-09-2006
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	25-10-2006
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-03-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-07-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-07-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-004766-13-NL
CCMO	NL14258.068.06