Levothyroxine for euthyroid women with recurrent miscarriage and positive TPO antibodies: a randomized controlled trial

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First objective: To assess improvement in live birth rate after levothyroxine supplementation. Secondary objective: 1) to test the hypothesis that levothyroxine lowers the risk for miscarriage and preterm birth 2) to test the hypothesis that...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON44997

Source
ToetsingOnline

Brief title
T4LIFE-trial

Condition

- Thyroid gland disorders
- Abortions and stillbirth

Synonym
recurrent miscarriage, thyroid autoimmunity

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Subsidie Fonds

NutsOhra;Subsidie Jan Dekker & dr. Ludgardine Bouwmanstichting;subsidie Schildklier Organisaties Nederland;subsidie ZonMw

Intervention

Keyword: levothyroxine, live birth rate, recurrent miscarriage, thyroid auto-immunity

Outcome measures

Primary outcome

Primary outcome measure: live birth rate.

Secondary outcome

Secondary outcome measures: ongoing pregnancy at 12 weeks (range 11 - 13 weeks), miscarriage rate (miscarriage defined as pregnancy loss before the 20th week of gestation), preterm delivery (preterm birth defined as delivery before 37 weeks of gestation), survival at 28 days of neonatal life, adverse events, subgroup effects of levothyroxine, postpartum thyroid disease (defined as abnormal TSH levels three or six months postpartum).

Study description

Background summary

Recurrent miscarriage (RM) represents a significant health problem. When the definition of RM includes two or more miscarriages, about 5% of couples trying to conceive suffer from RM. A cause for RM is identified in less than 50% of couples.
Unexplained recurrent miscarriage is a condition that affects at least 1300 couples in the Netherlands every year.
Thyroid autoimmunity is prevalent among women of reproductive age and is associated with miscarriage, recurrent miscarriage, preterm birth and maternal post partum thyroiditisTPO-Ab are present in 4-14 % of fertile women. In clinical practice, thyroid antibodies can be found in women with RM. Different prevalence*s have been described varying from 19 till 36 %. Given the high prevalence of TPO-Ab and its association with adverse pregnancy outcomes, is screening for thyroid dysfunction proposed, but not generally accepted. But the

treatment possibilities and effects for women with autoimmunity are thus far unclear.
One trial studied levothyroxine therapy for pregnant euthyroid women with TPO-Ab: a significantly decrease in preterm birth en miscarriage rate was found. This trial didn*t study recurrent miscarriage.
Because no trial is available specific on the topic of recurrent miscarriage we want to perform a RCT on levothyroxine supplementation for women with recurrent miscarriage and thyroid autoimmunity.

Study objective

First objective: To assess improvement in live birth rate after levothyroxine supplementation.
Secondary objective: 1) to test the hypothesis that levothyroxine lowers the risk for miscarriage and preterm birth 2) to test the hypothesis that levothyroxine, compared to placebo, does not incur substantial adverse effects to the mother or the neonate, time to pregnancy (defined as the interval between thyroid function test and the month of conception of the next pregnancy).

Study design

Randomised, double-blind, placebo controlled multicenter study

Intervention

All women will be randomly allocated to receive either levothyroxie tabelts once a day taken orally, or receive placebo tablets. Women will start with medication from the beginning of the study till the end of their next pregnancy.

Study burden and risks

Women with RM receive standard diagnostic care. The risks and burden of participating in the trial are little. The women will use levothyroxine or placebo after finishing the diagnostic work up for recurrent miscarriage and no other cause has been found. The outcome of that particular pregnancy will be followed. The (minimal) risk of participation is the risk of thyroid hormone use. Substantial evidence exists that thyroid hormone supplementation is safe to the mother and foetus as a treatment for hypothyroidism. For the indication thyroid autoimmunity, clinicians sometimes suscribe levothyroxine, no adverse effects are known or described in the literature. Also in earlier studies women with thyroid autoimmunity have been treated with levothyroxine, no adverse effects have been described.

We will monitor the maternal thyroid function in the first and second

trimester to make sure it will stay between the reference intervals for a normal thyroid function.

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

1.Women with unexplained RM and thyroid autoimmunity. Recurrent miscarriage is defined as two or more miscarriages.TPOAb positivity is defined according to the cut off levels of the coordinating or cooperating centres.
2.Age 18 - 42 years at randomisation
3.Willing and able to give informed consent (IC).

Exclusion criteria

1.Antiphospholipid syndrome (lupus anticoagulant and/ or anticardiolipin antibodies [IgG or IgM]) and/ or B2-Glycoprotein IgG or IgM)
2.Other auto-immune conditions, diabetes mellitus, diabetes gravidarum, thyroid disease different then isolated thyroid autoimmunity.
3. Abnormal TSH. This is defined as a TSH level different then the centre specific cut- off levels. (Known thyroid disease different then isolated thyroid autoimmunity)
4.Previous enrolment in the T4LIFE- trial
5. Contraindications to levothyroxine use:
Adrenal or pituitary disorders, untreated
Thyreotoxicosis, untreated
Acute cardiac arrest
Acute pancreatitis
Acute myocarditis

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-01-2013
Enrollment:	190
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Levothyroxine
Generic name:	levothyroxine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-001820-39-NL
CCMO	NL36571.018.12

Study results

Results posted: 14-07-2022

Actual enrolment: 160

Summary results
Trial ended prematurely

First publication
01-01-1900