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Effect of levothyroxine on live birth rate in euthyroid women with recurrent miscarriage and TPO antibodies (T4-LIFE study)

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ABSTRACT

Background: Thyroid peroxidase antibodies (TPO-Ab) in euthyroid women are associated with recurrent miscarriage (RM) and other pregnancy complications such as preterm birth. It is unclear if treatment with levothyroxine improves pregnancy outcome.
Aim: The aim of this study is to determine the effect of levothyroxine administration on live birth rate in euthyroid TPO-Ab positive women with recurrent miscarriage.
Methods/design: We will perform a multicenter, placebo controlled randomized trial in euthyroid women with recurrent miscarriage and TPO-Ab. Recurrent miscarriage is defined as two or more miscarriages before the 20th week of gestation. The primary outcome is live birth, defined as the birth of a living fetus beyond 24 weeks of gestation. Secondary outcomes are ongoing pregnancy at 12 weeks, miscarriage, preterm birth, (serious) adverse events, time to pregnancy and survival at 28 days of neonatal life. The analysis will be performed according to the intention to treat principle. We need to randomize 240 women (120 per group) to demonstrate an improvement in live birth rate from 55% in the placebo group to 75% in the levothyroxine treatment group. This trial is a registered trial (NTR 3364, March 2012).
Here we discuss the rationale and design of the T4-LIFE study, an international multicenter randomized, double blind placebo controlled, clinical trial aimed to assess the effectiveness of levothyroxine in women with recurrent miscarriage and TPO-Ab.

Abbreviations: ATA, American Thyroid Association; CCMO, Central Committee on Research involving Human Subjects; DSMB, Data and Safety Monitoring Board; ESCPG, Endocrine Society Clinical Practice Guideline; ESHRE, European Society of Human Reproduction and Embryology; IRB, Institutional Review Board; IRQ, inter-quartile ranges; ITT, intention to treat; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; RCOG, Royal College of Obstetricians and Gynecologists; RM, recurrent miscarriage; TPO-Ab, thyroid peroxidase antibodies; TSH, Thyroid Stimulating Hormone; T4, levothyroxine; SAE, serious adverse event; SD, standard deviation.

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1. Introduction

Recurrent miscarriage represents a significant health problem. Approximately 5% of couples trying to conceive suffer recurrent miscarriage (RM) [1,2]. Different definitions for RM have been described. In this article recurrent miscarriage has been defined as two or more – not necessarily consecutive – miscarriages [3–8]. Known risk-factors for RM are parental chromosome abnormalities, uterine anomalies and antiphospholipid syndrome [1,9]. Even after comprehensive investigations, no underlying risk factor for RM is identified in ≥50% of couples [1].

The presence of thyroid peroxidase antibodies (TPO-Ab) indicates a state of thyroid autoimmunity and is strongly associated with sporadic and recurrent miscarriages [10]. Thyroid autoimmunity is present in 8–14% among all women at reproductive age [11]. The presence of thyroid peroxidase antibodies is not only associated with miscarriage, but also with other adverse pregnancy outcomes such as unexplained subfertility, preterm birth and postpartum thyroiditis [10]. A higher prevalence of TPO-Ab is reported in women with recurrent miscarriage, varying from 19 to 36% [11–16].

Given the high prevalence of TPO-Ab and its association with RM and other pregnancy complications, screening for thyroid dysfunction in the work-up for RM or during pregnancy is proposed, but not generally accepted. The current guidelines for RM of the European Society of Human Reproduction and Embryology (ESHRE 2006), the Royal College of Obstetricians and Gynecologists (RCOG 2011) and the 'Nederlandse Vereniging voor Obstetrie en Gynaecologie' (NVOG 2007), advise not to screen for thyroid antibodies because no evidence exists for an effective treatment intervention [4,17–19]. The guidelines on thyroid disorders and pregnancy of the Endocrine Society Clinical Practice Guideline (ESCPG 2012) and the American Thyroid Association (ATA 2011) state that screening during pregnancy is not indicated because the treatment possibilities and effects for women with thyroid autoimmunity are thus far unclear [20,21].

Two small, randomized studies, including a total of 160 women with thyroid antibodies evaluated the effect of levothyroxine (T4) treatment on pregnancy outcomes. One trial studied pregnant euthyroid women with thyroid antibodies. The other trial studied women with TPO-Ab undergoing assisted reproduction technologies [22,23]. Both studies showed a reduction in miscarriage rates (36% and 75% relative reductions). One of the studies found a 69% relative risk reduction in preterm births. Both studies did not have an adequate sample size [22,23]. Meta-analysis of these studies showed a non-significant reduction in miscarriage rate, but the studies were too small to draw robust conclusions [19].

Although current RM guidelines do not support the screening for thyroid disorders, since lack of evidence on effective treatment interventions, endocrinologists are eager to prescribe levothyroxine during pregnancy for euthyroid women with TPO-Ab [21,24]. A recent European survey demonstrated that almost 80% of endocrinologists prescribe levothyroxine during pregnancy for women with TPO-Ab in combination with a normal Thyroid Stimulating Hormone (TSH) level [25]. This can result in unnecessary screening and treatment.

The aim of this study is to determine the effect of levothyroxine treatment on live birth rates and pregnancy complications in women with recurrent miscarriage and TPO-Ab. To achieve this, we designed an international randomized double blinded placebo controlled trial with inclusions in multiple centers.

2. Methods

2.1. Study sample

Women with unexplained recurrent miscarriage and thyroid autoimmunity are eligible for the study. Women aged 18 years until 42 years at randomization will be included. Recurrent miscarriage is defined as two or more, not necessarily consecutive, pregnancy losses before 20 weeks of gestational age [5,6]. The definition of miscarriage included documentation of pregnancy by a positive pregnancy test and clinical manifestations of miscarriage (e.g., abdominal pain, cramps, and vaginal bleeding); it does not include the loss of a bio-chemical pregnancy. Women with a history of RM after natural conception or after assisted reproductive technology are both included. All participants receive routine diagnostic work-up for recurrent miscarriage, including testing for antiphospholipid syndrome or thrombophilia if indicated, karyotyping if indicated, testing for uterine abnormalities and TSH and TPO-Ab assessments. Thyroid autoimmunity is defined as euthyroidism (TSH level within the center's reference range) with the presence of TPO antibodies. Euthyroidism will be defined according to the cut-off levels per participating center, as a result of minimal differences in reference ranges between centers due to different assay methods. Cut-off levels will be registered. Most commonly used cut-off levels for TPO antibodies are 60 kIU/L or 100 kIU/L. For TSH, the most commonly used reference interval is 0.5–5.0 mIU/L.

Exclusion criteria are: antiphospholipid syndrome (lupus anticoagulant and/or anticardiolipin antibodies IgG or IgM and/or B2-glycoprotein IgG or IgM positivity), other auto-immune conditions, e.g. diabetes mellitus or other known thyroid diseases, previous enrolment in the T4-LIFE-trial, participation in other (double blind randomized) drug trials, and contraindications for levothyroxine use (acute cardiac arrest, acute pancreatitis or acute myocarditis).

2.2. Setting and design

2.2.1. Participating centers

We will perform an international multicenter randomized, double blind placebo controlled, clinical trial, in the Departments of Obstetrics and Gynecology, in both academic and non-academic hospitals in the Netherlands, Denmark and Belgium. This multicenter study will be carried out within the infrastructure of the Dutch Consortium for studies on women's health. This consortium provides a unique clinical research infrastructure for studies in the field of reproductive gynecology. The trial design is presented in Fig. 1. Inclusion has started in January 2013. Currently, as per July 2015, 64 women have been included in the study.

At the start of the study, it was expected to enroll around 7 women per month. The original estimated duration of the recruitment phase of the study was supposed to be 30 months. When the recruitment started only few centers have been participating. Currently, 14 centers do participate in the Netherlands, one center in Belgium and one center in Denmark. The number of participating centers is still increasing. With the current recruitment rate, it is expected that the total recruitment phase will be 45 months.

2.2.2. Randomization

If after the diagnostic work-up for recurrent miscarriage positive TPO-Ab are detected with a normal TSH level and women match the inclusion criteria, they will be asked to participate. After signing informed consent preconceptually, they will be randomized and allocated to levothyroxine or placebo (double-blinded). Randomization will be done on the internet in a 1:1 ratio, once the patient data have been entered in a web-based database. Randomization will be performed using stratified blocks or minimization with a block size of 4 for two groups.

All assays have their own specific reference intervals and therefore we believe that treatment differences between centers will be minimal. To correct for possible treatment differences randomization will be stratified for study center. All patients will start taking their study medication preconceptually, immediately after randomization.

2.2.3. Blinding

The study is double blinded. The TSH levels will be assessed at three time points: preconceptually, at the first trimester (before the 12th