Project Title:	Efficacy and mechanism of thyroxine treatment on pregnancy and neonatal outcomes in women with thyroid antibodies: A randomised, placebo-controlled, double-blind, multi-centre trial [The TABLET (Thyroid AntiBodies and LEvoThyroxine) Trial]
Project Ref:	09/100/10
Cost:	£1,288,196
Lead Applicant & Institution:	Dr Aravinthan Coomarasamy Birmingham Women's Hospital
Start Date:	01 June 2011
Plain English Summary:	Approximately 11 - 19% of women of child-bearing age have thyroid antibodies. In such women, the risks of a) miscarriage and b) preterm birth are more than doubled compared with those who do not have thyroid antibodies. Miscarriage is the commonest complication of pregnancy, affecting 1 in 5 women. It substantially impacts on physical and psychological wellbeing: research shows that the level of distress associated with miscarriage can be equivalent to that of a stillbirth of a term baby. Preterm birth occurs in 6-10% of pregnancies. Up to 85% of new-born deaths are due to preterm births, and of those who survive, approximately 10% suffer long-term disability. The human cost of preterm birth is therefore enormous; the financial cost of preterm birth is estimated at £939 million/year in the UK. EFFICACY: There is evidence from two small studies that giving thyroxine tablets to women with thyroid antibodies may halve the risk of miscarriages and preterm births. However, the evidence is not strong enough for recommending thyroxine treatment: we surveyed 183 clinicians (endocrinologists and obstetricians), and 85% of them said they required more research before they would be confident to use this treatment in routine practice. We are, therefore, proposing a large and high quality study to settle the question, with live birth beyond 34 weeks of gestation as the primary outcome. MECHANISM: We will study why women with thyroid antibodies are more likely to have miscarriages and preterm delivery, and how thyroxine may be helpful. In pregnancy, the mother's immune response is altered to allow the baby and placenta to develop safely within the womb. Placental development is dependent upon thyroid hormones. We think that women with thyroid antibodies fail to alter their immune response appropriately during pregnancy and that the relatively low thyroid hormone levels affect the development of the placenta. Thus we propose to measure markers of the immune response in the mother as well as in the placenta obtained after delivery.

	WHY IS A TRIAL NEEDED NOW? (a) Thyroxine treatment is cheap (£1.10 for 28 tablet pack), safe, convenient (taken orally), and if our study confirms the benefits shown in the existing preliminary studies, it can save the NHS over £215 million/year, (b) a patient survey supports the study, (c) a clinician survey supports the study, (d) the study is also supported by the following bodies: Miscarriage Association, British Thyroid Association, British Thyroid Foundation, Royal College of Obstetricians and Gynaecologists, Association of Early Pregnancy Units and Early Pregnancy Clinical Studies Group (EP-CSG).
Abstract:	We conducted a systematic review exploring the association between thyroid antibodies and adverse pregnancy outcomes. For miscarriage, we identified 29 studies (9817 women), and 26 of these showed a positive association. Meta-analysis of the 29 studies showed more than doubling in the odds of miscarriage in the presence of thyroid antibodies (OR:2.4, 95% CI: 1.9, 3.1). For preterm birth, we identified 4 studies (2896 women). All studies showed a positive association and meta-analysis found more than doubling in the odds of preterm birth in the presence of thyroid antibodies (OR: 2.7, 95% CI: 1.9, 3.9). The two dominant hypotheses for these observations are that a) thyroid antibodies represent a state of global immune dysfunction and b) thyroid antibodies are associated with relative thyroid insufficiency. There is evidence that thyroxine treatment can alter global immune response directly, and it can also correct any relative thyroid insufficiency. We carried out another systematic review to identify studies of thyroxine replacement to improve pregnancy outcomes in women with thyroid antiboides: two randomised trials, including a total of 187 women, were identified; the studies showed a reduction in miscarriages (RR: 0.48, 95% CI:0.25, 0.92) and preterm birth (RR:0.31; 95% CI:0.11, 0.90) with levothyroxine treatment. However, our UK clinician survey (n=183) found that only 8% (15/183) of clinicians use or intend to use levothyroxine for the prevention of miscarriages in thyroid antibody positive women and that 85% (155/183) do not currently use levothyroxine, but would be willing to recruit into a randomised study. We, therefore, propose a randomised, placebo-controlled, double-blind, multi-centre trial to test the hypothesis that in euthyroid women with thyroid peroxidase antibodies, levothyroxine (50mcg, oral, once daily), started pre-conceptually and continued to the end of pregnancy, compared with placebo, increases live births beyond 34 completed weeks of gestation by at least 10%. Nested within the trial, we will evaluate cytokine levels in the maternal circulation and decidua. We plan to randomise 900 women (450 participants in each arm): To detect a 10% difference in live birth beyond 34 weeks, for an alpha of 5% and power of 80%, 380 women will need to be randomised to each group. However, assuming and adjusting for a worst case scenario of a 15% attrition, the total number of participants required will be 900. The analysis will be by intention to treat, and according to a pre-specified analysis plan. The trial will be co-ordinated by an Accredited Clinical Trials Unit. Twenty one hospitals in the UK will participate in this trial, which will be led by a strong team of researchers with track record in conducting multicentre trials as well as miscarriage, preterm birth and thyroid research. The trial is supported by patients (78 interviewed), Miscarriage Association, British Thyroid Foundation, British Thyroid Association, the RCOG and others. If our study confirms the benefits shown in the existing trials, the NHS can save over £215 million/year.

ISRCTN: (if applicable)	To follow
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