Levothyroxine to increase live births in euthyroid women with thyroid antibodies trying to conceive: the TABLET RCT

Rima K Dhillon-Smith,[1,2,3] Lee J Middleton,[4] Kirandeep K Sunner,[4] Versha Cheed,[4] Krys Baker,[5] Samantha Farrell-Carver,[4] Ruth Bender-Atik,[6] Rina Agrawal,[7] Kalsang Bhatia,[8] Edmond Edi-Osagie,[9] Tarek Ghobara,[7] Pratima Gupta,[10] Davor Jurkovic,[11] Yacoub Khalaf,[12] Marjory MacLean,[13] Chris McCabe,[1] Khashia Mulbagal,[14] Natalie Nunes,[15] Caroline Overton,[16] Siobhan Quenby,[7] Rajendra Rai,[17] Nick Raine-Fenning,[18,19] Lynne Robinson,[3] Jackie Ross,[20] Andrew Sizer,[21] Rachel Small,[9] Alex Tan,[22] Martyn Underwood,[21] Mark D Kilby,[1,3] Kristien Boelaert,[1] Jane Daniels,[23] Shakila Thangaratinam,[22] Shiao-Yng Chan[24] and Arri Coomarasamy[1,2,3]*

[1]Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[2]Tommy's Centre for Miscarriage Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[3]Centre for Women's and Newborn Health, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[4]Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[5]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[6]The Miscarriage Association, Wakefield, UK
[7]University Hospital Coventry, University Hospitals Coventry & Warwickshire NHS Trust, Coventry, UK
[8]Burnley General Hospital, East Lancashire Hospitals NHS Trust, Burnley, UK
[9]Saint Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, UK
[10]Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[11]University College Hospital, University College London Hospitals NHS Foundation Trust, London, UK
[12]Assisted Conception Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
[13]Ayrshire Maternity Unit, University Hospital Crosshouse, NHS Ayrshire and Arran, Kilmarnock, UK
[14]Royal Bolton Hospital, Bolton NHS Foundation Trust, Farnworth, UK
[15]West Middlesex University Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
[16]St Michael's Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[17]St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
[18]Division of Child Health, Obstetrics and Gynaecology, Nottingham, UK
[19]Nurture Fertility, The Fertility Partnership, Nottingham, UK
[20]Early Pregnancy and Gynaecology Assessment Unit, King's College Hospital NHS Foundation Trust, London, UK
[21]The Princess Royal Hospital, The Shrewsbury and Telford Hospital NHS Trust, Telford, UK
[22]Barts Research Centre for Women's Health, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[23]Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK
[24]Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

*Corresponding author a.coomarasamy@bham.ac.uk

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Scientific summary

The TABLET RCT

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Scientific summary

Background

Thyroid autoantibodies, specifically thyroid peroxidase antibodies, have been strongly associated with miscarriage and preterm birth in women with a normal thyroid function. Two small randomised controlled trials showed a reduction in adverse pregnancy outcomes with levothyroxine.

Objectives

The Thyroid AntiBodies and LEvoThyroxine (TABLET) trial was designed to test the hypothesis that, in euthyroid women with thyroid peroxidase antibodies, 50 µg of levothyroxine taken once daily from the point of preconception and continued until the end of pregnancy, compared with placebo, would increase live births beyond 34 completed weeks of pregnancy by at least 10%. A concurrent mechanistic study was conducted to examine if the effect of levothyroxine may be mediated by changes in immune responses.

Design

This was a randomised, double-blind, placebo-controlled, multicentre trial with a mechanistic element to explore causality.

Setting

The trial was conducted in hospital settings across the UK, recruiting from 49 sites between 2011 and 2016.

Participants

Women with a normal thyroid function and with thyroid peroxidase antibodies who were aged between 16 and 41 years, trying for a pregnancy either naturally or through assisted conception, and willing and able to give informed consent were eligible. Women were recruited from three main settings: early pregnancy units following a miscarriage, infertility clinics/assisted conception units and recurrent miscarriage clinics. For the purpose of the trial, women were given a 12-month time frame in which to conceive from randomisation.

Interventions

Each participant in the TABLET trial received either levothyroxine at a dose of 50-µg capsules daily or placebo capsules daily. These were commenced as soon as randomised preconceptually, and continued until the end of a pregnancy, regardless of the timing of the end of the pregnancy. Neither the clinician nor the patient knew which group they were allocated to throughout the trial.

Main outcome measures

The primary outcome was live birth at or beyond 34 completed weeks of gestation. The secondary outcomes included miscarriage; clinical pregnancy at 7 weeks; ongoing pregnancy at 12 weeks; gestation at delivery; mode of delivery; birthweight; appearance, pulse, grimace, activity and respiration (Apgar) scores; congenital abnormalities; and neonatal survival at 28 days of life.

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Methods

Randomisation was performed preconceptually following confirmation of normal thyroid function tests and positivity for thyroid peroxidase antibodies. Participants were randomised in a 1 : 1 ratio. Minimisation was implemented for age (< 35 or ≥ 35 years), number of previous miscarriages (0, 1 or 2, ≥ 3), baseline thyroid-stimulating hormone concentration (≤ 2.5 or > 2.5 mIU/l) and infertility treatment (yes/no) to achieve balanced trial arms. For logistical reasons, the randomisation was also minimised by centre. Randomisation was performed online via a secure internet facility. Women were followed up every 3 months while trying to conceive to check thyroid function and general well-being; once pregnant, they were seen each trimester: 6–8 weeks, 16–18 weeks and 28 weeks. Following delivery, a follow-up telephone call was made after 28 days to assess neonatal outcome. Any abnormal thyroid results were managed appropriately in line with local clinical guidance at the time.

A subset of women were recruited to provide additional serum samples longitudinally for the assessment of 17 different chemocytokines by multiplex enzyme-linked immunosorbent assays.

Results

A total of 19,556 participants were screened for eligibility, with thyroid peroxidase antibody positivity found in 9.5% of participants (1827/19,237). A total of 1420 women were eligible for participation, of whom 952 were randomised between 2011 and 2016; 476 received levothyroxine and 476 received placebo. However, six women from each arm were either withdrawn or lost to follow-up, and so outcome data were available for only 470 in each group. A total of 540 women achieved a pregnancy in the 12-month time frame: 266 women conceived in the levothyroxine arm and 274 in the placebo arm. The baseline data (i.e. age, body mass index, maternal ethnicity, smoking status and parity) of the participants were comparable in the two arms of the trial. The follow-up rate to primary outcome was 940 out of 952 participants (98.7%).

The live birth rate in the levothyroxine group was 37% (176/470) and the rate in the placebo group was 38% (178/470), translating to a relative risk of 0.97 (95% confidence interval 0.83 to 1.14; $p = 0.74$) and an absolute risk difference of –0.4% (95% confidence interval –6.6% to 5.8%).

There was no evidence of a significant difference between the groups for any of the secondary outcomes:

- clinical pregnancy at 7 weeks of gestation – levothyroxine group 89% (237/266) versus placebo group 91% (248/274); relative risk 0.98, 95% confidence interval 0.93 to 1.04; $p = 0.59$
- ongoing pregnancy at 12 weeks of gestation – levothyroxine group 73% (194/266) versus placebo group 73% (200/274); relative risk 1.00, 95% confidence interval 0.90 to 1.11; $p = 0.99$
- miscarriage at < 24 weeks – levothyroxine group 28% (75/266) versus placebo group 30% (81/274); relative risk 0.95, 95% confidence interval 0.73 to 1.23; $p = 0.68$
- ectopic pregnancy – levothyroxine group 1% (3/266) versus placebo group 2% (6/274); relative risk 0.50, 95% confidence interval 0.13 to 1.99; $p = 0.33$
- stillbirth – levothyroxine group 0.4% (1/266) versus placebo group 0% (0/274)
- gestation at delivery – levothyroxine group 38^{+6} versus placebo group 39^{+0}; $p = 0.65$
- birthweight (g) – levothyroxine group 3226 (standard deviation 660) versus placebo group 3262 (standard deviation 668); $p = 0.60$
- no early or late neonatal deaths in either group.

The subset of 49 women (26 in levothyroxine arm and 23 in placebo arm) recruited into the mechanistic study demonstrated that treatment with levothyroxine resulted in some changes in chemocytokine concentrations in the non-pregnant state and in very early pregnancy, but these changes had no bearing on whether or not the pregnancy resulted in a live birth outcome.

Conclusions

The TABLET trial is the largest prospective randomised clinical trial conducted on the subject of thyroid antibodies and pregnancy loss, to our knowledge. The trial was appropriately sized and methodologically robust to conclude that levothyroxine commenced preconceptually in euthyroid women with thyroid peroxidase antibodies is of no benefit. One of the limitations of the trial is that we did not look to explore titrations of levothyroxine dose based on body weight or thyroid-stimulating hormone or thyroid peroxidase antibody concentration. Furthermore, the trial did not explore the effects of levothyroxine in women with subclinical hypothyroidism. Future work could investigate the effectiveness of preconceptual levothyroxine treatment to reduce adverse pregnancy outcomes for women with subclinical hypothyroidism, with or without thyroid peroxidase antibodies. This is currently a particular area of controversy in the subfertility population.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN15948785 and EudraCT 2011-000719-19.

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