

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 Chan²⁴ and
Arri Coomarasamy^{1,2,3*}

¹Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

²Tommy's Centre for Miscarriage Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

³Centre for Women's and Newborn Health, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

⁴Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

⁵Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

⁶The Miscarriage Association, Wakefield, UK

⁷University Hospital Coventry, University Hospitals Coventry & Warwickshire NHS Trust, Coventry, UK

⁸Burnley General Hospital, East Lancashire Hospitals NHS Trust, Burnley, UK

⁹Saint Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, UK

¹⁰Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

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

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

Declared competing interests of authors: none

Published October 2019

DOI: 10.3310/eme06110

Plain English summary

The TABLET RCT

Efficacy and Mechanism Evaluation 2019; Vol. 6: No. 11

DOI: 10.3310/eme06110

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Plain English summary

Miscarriage, the loss of a pregnancy before 24 weeks, affects one in five women. In addition, up to 1 in 10 babies are born too early, between 24 and 37 weeks of pregnancy. Antibodies protect us from viruses and bacteria, but can also be produced against the body's own cells. Thyroid gland antibodies are found in the blood in approximately 1 in 10 women who have no other thyroid problems, and have been linked to a higher risk of miscarriage and early birth. Previous small studies have suggested that giving levothyroxine (a hormone produced by the thyroid gland) to women with thyroid antibodies may reduce the risk of miscarriage. We studied whether or not taking levothyroxine, compared with placebo (dummy drug), increases the chance of delivering a live baby after 34 weeks of pregnancy.

Women who had had a previous miscarriage and wanted to get pregnant, or who were having infertility treatment, were invited to take a blood test for thyroid antibodies. Those who had thyroid antibodies and a normal thyroid function were divided into two groups at random by a computer: 476 received levothyroxine and 476 received an identical placebo. Neither the woman nor her doctor knew which group she was in. Both groups took a daily tablet for up to 1 year while trying to get pregnant, and then until the end of the pregnancy.

Of the 952 women in the study, 540 became pregnant and 354 had a baby after 34 weeks of pregnancy: 37% (176/470) in the levothyroxine group and 38% (178/470) in the placebo group. As the trial was large and of high quality, the research team are confident that levothyroxine does not improve pregnancy success for women with thyroid antibodies and normal thyroid function.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal

Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme funds ambitious studies evaluating interventions that have the potential to make a step-change in the promotion of health, treatment of disease and improvement of rehabilitation or long-term care. Within these studies, EME supports research to improve the understanding of the mechanisms of both diseases and treatments.

The programme support translational research into a wide range of new or repurposed interventions. These may include diagnostic or prognostic tests and decision-making tools, therapeutics or psychological treatments, medical devices, and public health initiatives delivered in the NHS.

The EME programme supports clinical trials and studies with other robust designs, which test the efficacy of interventions, and which may use clinical or well-validated surrogate outcomes. It only supports studies in man and where there is adequate proof of concept. The programme encourages hypothesis-driven mechanistic studies, integrated within the efficacy study, that explore the mechanisms of action of the intervention or the disease, the cause of differing responses, or improve the understanding of adverse effects. It funds similar mechanistic studies linked to studies funded by any NIHR programme.

The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 09/100/10. The contractual start date was in June 2011. The final report began editorial review in June 2018 and was accepted for publication in November 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health and Social Care.

© Queen's Printer and Controller of HMSO 2019. This work was produced by Dhillon-Smith *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Senior Clinical Researcher, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Director, NIHR Dissemination Centre, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk