Validation and development of models using clinical, biochemical and ultrasound markers for predicting pre-eclampsia: an individual participant data meta-analysis

John Allotey,[1,2†] Kym IE Snell,[3*†] Melanie Smuk,[2] Richard Hooper,[2] Claire L Chan,[2] Asif Ahmed,[4] Lucy C Chappell,[5] Peter von Dadelszen,[5] Julie Dodds,[1,2] Marcus Green,[6] Louise Kenny,[7] Asma Khalil,[8] Khalid S Khan,[1,2] Ben W Mol,[9] Jenny Myers,[10] Lucilla Poston,[5] Basky Thilaganathan,[8] Anne C Staff,[11,12] Gordon CS Smith,[13] Wessel Ganzevoort,[14] *et al.*[‡] on behalf of the IPPIC Collaborative Network[§]

[1]Barts Research Centre for Women's Health (BARC), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[2]Pragmatic Clinical Trials Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[3]Centre for Prognosis Research, School of Primary, Community and Social Care, Keele University, Keele, UK
[4]Aston Medical Research Institute, Aston Medical School, Aston University, Birmingham, UK
[5]Department of Women & Children's Health, School of Life Course Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK
[6]Action on Pre-eclampsia (APEC), Evesham, UK
[7]Vice Chancellor's Office, Faculty of Health & Life Sciences, University of Liverpool, Liverpool, UK
[8]Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK
[9]Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre, Clayton, VIC, Australia
[10]Maternal and Fetal Health Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK
[11]Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway
[12]Faculty of Medicine, University of Oslo, Oslo, Norway

[13]Department of Obstetrics and Gynaecology, NIHR Biomedical Research Centre, University of Cambridge, Cambridge, UK
[14]Department of Obstetrics, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

*Corresponding author k.snell@keele.ac.uk
†Joint first authors (both contributed equally)
‡The full list of authors can be found in *Appendix 1*.
§The full list of partners in the IPPIC Collaborative Network can be found in *Acknowledgements*.

Declared competing interests of authors: Gordon CS Smith has received research support from Roche Holding AG (Basel, Switzerland) (supply of equipment and reagents for biomarker studies of ≈£600,000 in value) and Sera Prognostics (Salt Lake City, UT, USA) (≈£100,000), and has been paid by Roche to attend an advisory board and to present at a meeting. He is a named inventor on a patent filed by Cambridge Enterprise (UK Patent Application Number 1808489.7, 'Novel Biomarkers') for the prediction of pre-eclampsia and fetal growth restriction. Ignacio Herraiz reports personal fees from Roche Diagnostics and Thermo Fisher Scientific (Waltham, MA, USA). John Kingdom reports personal fees from Roche Canada (Mississauga, ON, Canada). Lucy C Chappell is chairperson of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) CET Committee (January 2019 to present). Asma Khalil is a member of the NIHR HTA Board (November 2018 to present). Jane E Norman is a member of the NIHR HTA MNCH Panel, and she reports grants from NIHR and Chief Scientist Office Scotland, as well as consultancy fees from and participation in data monitoring committees for Dilafor AB (Solna, Sweden) and GlaxoSmithKline (Brentford, UK). Kajantie Eero reports grants from the Academy of Finland, the Foundation for Paediatric Research, the Signe and Ane Gyllenberg Foundation (Helsinki, Finland), the Sigrid Jusélius Foundation (Helsinki, Finland), the Juho Vainio Foundation (Helsinki, Finland), the European Commission, the NORFACE DIAL Programme, the Novo Nordisk Foundation (Hellerup, Denmark), the Yrjö Jahnsson Foundation (Helsinki, Finland), Foundation for Cardiovascular Research (Zürich, Switzerland) and the Diabetes Research Foundation. Ben W Mol reports fellowship from the National Health and Medical Research Council (Canberra, ACT, Australia), personal fees from ObsEva (Plan-les-Ouates, Switzerland), personal fees and consultancy fees from Merck Sharp & Dohme (Kenilworth, NJ, USA), personal fees from Guerbet (Villepinte, France), travel funds from Guerbet and grants from Merck Sharp & Dohme. Richard D Riley reports personal fees from the British Medical Journal for statistical reviews, and from Roche and the universities of Leeds, Edinburgh and Exeter for training on individual participant data meta-analysis methods. Jacques Massé reports grants from National Health Research and Development Program, Health and Welfare Canada, during the conduct of the study. Paul T Seed is partly funded by King's Health Partners Institute of Women and Children's Health, Tommy's (registered charity number 1060508) and ARC South London (NIHR). The views expressed are not necessarily those of KHP, Tommy's, the NHS, the NIHR or the Department of Health.

Published December 2020
DOI: 10.3310/hta24720

Plain English summary

IPD meta-analysis of pre-eclampsia markers

Health Technology Assessment 2020; Vol. 24: No. 72
DOI: 10.3310/hta24720

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

Plain English summary

What is the problem?

Pre-eclampsia, a condition in pregnancy that results in raised blood pressure and protein in the urine, is a major cause of complications for the mother and baby.

What is needed?

A way of accurately identifying women at high risk of pre-eclampsia to allow clinicians to start preventative interventions such as administering aspirin or frequently monitoring women during pregnancy.

Where are the research gaps?

Although over 100 tools (models) have been reported worldwide to predict pre-eclampsia, to date their performance in women managed in the UK NHS is unknown.

What did we plan to do?

We planned to comprehensively identify all published models that predict the risk of pre-eclampsia occurring at any time during pregnancy and to assess if this prediction is accurate in the UK population. If the existing models did not perform satisfactorily, we aimed to develop new prediction models.

What did we find?

We formed the International Prediction of Pregnancy Complications network, which provided data from a large number of studies (78 studies, 25 countries, 125 researchers, 3,570,993 singleton pregnancies). We were able to assess the performance of 24 out of the 131 models published to predict pre-eclampsia in 11 UK data sets. The models did not accurately predict the risk of pre-eclampsia across all UK data sets, and their performance varied within individual data sets. We developed new prediction models that showed promising performance on average across all data sets, but their ability to correctly identify women who develop pre-eclampsia varied between populations. The models were more clinically useful when used in the care of first-time mothers pregnant with one child, compared to a strategy of treating them all as if they were at high-risk of pre-eclampsia.

What does this mean?

Before using the International Prediction of Pregnancy Complications models in various populations, they need to be adjusted for characteristics of the particular population and the setting of application.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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 HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. 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 *Health Technology Assessment* journal

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

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 14/158/02. The contractual start date was in December 2015. The draft report began editorial review in March 2019 and was accepted for publication in March 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). 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, NETSCC, the HTA 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 HTA programme or the Department of Health and Social Care.

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