A prognostic model, including quantitative fetal fibronectin, to predict preterm labour: the QUIDS meta-analysis and prospective cohort study

Sarah J Stock,^{1*} Margaret Horne,¹ Merel Bruijn,¹ Helen White,² Robert Heggie,³ Lisa Wotherspoon,⁴ Kathleen Boyd,³ Lorna Aucott,⁵ Rachel K Morris,⁶ Jon Dorling,⁷ Lesley Jackson,⁸ Manju Chandiramani,⁹ Anna David,¹⁰ Asma Khalil,¹¹ Andrew Shennan,¹² Gert-Jan van Baaren,¹³ Victoria Hodgetts-Morton,⁵ Tina Lavender,² Ewoud Schuit,¹⁴ Susan Harper-Clarke,¹⁵ Ben Mol,¹⁶ Richard D Riley,¹⁷ Jane Norman⁴ and John Norrie¹

¹Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

²Division of Nursing, Midwifery and Social Work, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

³Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

⁴Medical Research Council Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

⁵Health Services Research Unit, University of Aberdeen, Aberdeen, UK

⁶Institute of Applied Health Research, University of Birmingham, Birmingham, UK

⁷Department of Neonatology, IWK Health Centre, Halifax, NS, Canada

⁸Department of Neonatology, Queen Elizabeth Hospital, Glasgow, UK

⁹Department of Obstetrics and Gynaecology, Guy's and St Thomas' NHS Foundation Trust, London, UK

¹⁰Elizabeth Garrett Anderson Institute for Women's Health, University College London, London, UK

¹¹Department of Fetal Medicine, St George's Hospital, St George's, University of London, London, UK

¹²Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK

¹³Department of Obstetrics and Gynaecology, Amsterdam University Medical Center, Amsterdam, the Netherlands

¹⁴Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

¹⁵Public and patient representative, Teddington, UK

- ¹⁶Department of Obstetrics and Gynaecology, Monash University, Melbourne, VIC, Australia
- ¹⁷Centre for Prognosis Research, Research Institute for Primary Care and Health Sciences, Keele University, Keele, UK

Declared competing interests of authors: Sarah J Stock reports grants from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, non-financial support from Hologic, Inc. (Marlborough, MA, USA), non-financial support from Parsagen Diagnostics, Inc. (Boston, MA, USA) and non-financial support from Medix Biochemica Ab (Espoo, Finland) during the conduct of the study. In addition, Sarah J Stock declares membership of the HTA Programme Funding Committee (General) (2016 to present). Kathleen Boyd reports grants from the NIHR HTA programme and NIHR Public Health Research (PHR) programme outside the submitted work during the conduct of the study. Lorna Aucott declares membership of the PHR Research Funding Board (2017 to present). Rachel K Morris reports grants from the NIHR HTA and NIHR Research for Patient Benefit programmes outside the submitted work during the conduct of the study. Jon Dorling reports grants from the NIHR HTA programme and Nutrinia Ltd (Ramat Gan, Israel) outside the submitted work; the grant from Nutrinia Ltd (2017–18) was for part of his salary to work as an expert advisor on a trial. Jon Dorling was a member of the NIHR HTA General Board (2017-18) and the NIHR HTA Maternity, Newborn and Child Health Panel (2013–18). Manju Chandiramani reports that she undertakes unpaid advisory work for Hologic, Inc., unrelated to the submitted work, and has been supported by Hologic, Inc., to attend a conference in the preceding 12 months. Anna David reports personal fees from Hologic, Inc., outside the submitted work, and salary support from the NIHR UCLH/UCL Biomedical Research Centre. Asma Khalil reports grants and prediction tests from Parsagen Diagnostics, Inc., paid to the institution, during the conduct of the study and declares being a member of the HTA Programme Funding Committee (2018 to present). Andrew Shennan reports grants and prediction tests from Hologic, Inc., for basic science on preterm markers, paid to the institution, and was a member of the HTA Funding Committee (Commissioning) during the conduct of the study (2018 to present). Tina Lavender declares membership of the HTA Obesity Themed Call Board (2013). Ben Mol reports a Practitioner Fellowship from the National Health and Medical Research Council, personal fees from ObsEva SA (Geneva, Switzerland), personal fees and other funding from Merck Sharp & Dohme (Kenilworth, NJ, USA), personal fees from Guerbet (Villepinte, France), travel support to present at meetings from Guerbet, and grants from Merck Sharp & Dohme, outside the submitted work. Richard D Riley reports grants from the NIHR HTA programme outside the submitted work during the conduct of the study. Jane Norman reports grants from the NIHR HTA and the NIHR Global Health programmes and the Medical Research Council, and personal fees from Dilafor AB (Solna, Sweden), outside the submitted work, and was a member of the HTA Maternal, Neonatal and Child Health Panel during the conduct of the study (2013–18); she was a member of the NIHR HTA and Efficacy and Mechanism Evaluation (EME) Editorial Board (2012-14). John Norrie reports grants from the University of Aberdeen and the University of Edinburgh during the conduct of the study, and membership of the following NIHR boards: CPR Decision-Making Committee, HTA Programme Funding Committee (Commissioning), HTA Commissioning Sub-Board (Expression of Interest), HTA Funding Boards Policy Group, HTA Programme Funding Committee (General), HTA Post-board funding teleconference, Clinical Trials Unit Standing Advisory Committee, HTA and EME Editorial Board and Pre-exposure Prophylaxis Impact Review Panel during the conduct of the study.

Published September 2021 DOI: 10.3310/hta25520

^{*}Corresponding author sarah.stock@ed.ac.uk

Plain English summary

The QUIDS meta-analysis and prospective cohort study

Health Technology Assessment 2021; Vol. 25: No. 52

DOI: 10.3310/hta25520

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

Plain English summary

dentifying which women with symptoms of labour will give birth early is challenging, so many women unnecessarily receive therapies aimed at preventing complications in preterm birth.

A test called quantitative fetal fibronectin, which uses vaginal swab samples, may help to improve the diagnosis of preterm labour. Fetal fibronectin is a protein that is released from the fetal membranes that surround the developing baby in the womb. The lower the concentration of fetal fibronectin, the less likely the occurrence of preterm birth.

Our aim was to see if quantitative fetal fibronectin, in combination with some features of pregnancy (e.g. previous pregnancy history and twin pregnancy), can accurately predict preterm birth in women who have symptoms of preterm labour.

We asked women, their partners, doctors and midwives what information would be most useful to them, and how this should be presented. We then analysed previous research data; we used quantitative fetal fibronectin and clinical risk factors together to predict the chance of preterm birth. We explored which features could predict preterm birth most effectively while still being good value to the NHS.

To ensure that this risk predictor worked in UK populations, we undertook a research study across 26 UK hospitals. Women who had symptoms of preterm labour were invited to participate. We collected information from these women (approximately 3000 women), including quantitative fetal fibronectin results.

We found that a risk predictor comprising quantitative fetal fibronectin and four other features performed best at predicting whether or not preterm birth will occur within the next week for women with symptoms of preterm labour, and that this had potential to be clinically useful and cost-effective. The quantitative fetal fibronectin testing process was acceptable to women, and clinicians found the risk predictor useful.

We used our findings to develop a risk calculator to help women and clinicians assess how likely preterm birth is, and decide whether or not to start treatment.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

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 14/32/01. The contractual start date was in December 2015. The draft report began editorial review in May 2019 and was accepted for publication in December 2019. 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.

© Queen's Printer and Controller of HMSO 2021. This work was produced by Stock 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 Professor of Digital Health Care, 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 Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, 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 Emeritus Professor of Wellbeing Research, University of Winchester, 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

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

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