The Arabin pessary to prevent preterm birth in women with a twin pregnancy and a short cervix: the STOPPIT 2 RCT

Jane E Norman,[1*] John Norrie,[2] Graeme MacLennan,[3] David Cooper,[3] Sonia Whyte,[4] Sushila Chowdhry,[5] Sarah Cunningham-Burley,[5] Aileen R Neilson,[5] Xue W Mei,[6] Joel BE Smith,[6] Andrew Shennan,[7] Stephen C Robson,[8] Steven Thornton,[9] Mark D Kilby,[10] Neil Marlow,[11] Sarah J Stock,[5] Philip R Bennett[12] and Jane Denton[13] on behalf of the STOPPIT collaborative group

[1]Faculty of Health Sciences, University of Bristol, Bristol, UK
[2]Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh, UK
[3]Centre for Healthcare Randomised Trials, University of Aberdeen, Aberdeen, UK
[4]Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK
[5]Usher Institute, University of Edinburgh, Edinburgh, UK
[6]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[7]Tommy's London Research Centre, King's College London, London, UK
[8]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[9]Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[10]Fetal Medicine Centre, Birmingham Women's and Children's NHS Foundation Trust and College of Medical and Dental Science, University of Birmingham, Birmingham, UK
[11]Institute for Women's Health, University College London, London, UK
[12]Department of Surgery and Cancer, Imperial College London, London, UK
[13]The Multiple Births Foundation, London, UK

*Corresponding author jane.e.norman@bristol.ac.uk

Declared competing interests of authors: Jane E Norman has received grants from government and charitable bodies for research into understanding the mechanism of term and preterm labour and understanding treatments. Within the last 3 years, Jane E Norman has acted on a Data Safety and Monitoring Board for a study involving a preterm birth therapeutic agent for GlaxoSmithKline plc (GlaxoSmithKline plc, Brentford, UK) and has provided consultancy for a small pharmaceutical company (Dilafor AB, Solna, Sweden) on drugs to alter labour progress. She was on the Health Technology Assessment (HTA) Maternal Neonatal and Child Health Panel (2013–18) and she was a member of the National Institute for Health Research (NIHR) HTA and Efficacy and Mechanism Evaluation (EME) Editorial Board (2012–14). John Norrie reports grants from the University of Edinburgh (Edinburgh, UK)

during the conduct of the study, and declares that he is or has been a member of the following: HTA Commissioning Sub-Board (EOI) (2012–16), NIHR CTU Standing Advisory Committee (2017–present), NIHR HTA and EME Editorial Board (2014–19), Pre-Exposure Prophylaxis Impact Review Panel (2017–present), EME Strategy Advisory Committee (2019–present), EME – Funding Committee Members (2019–present), EME Funding Committee Sub-Group Remit & Comp Check (2019–present), HTA General Committee (2016–19), HTA Funding Committee Policy Group (formerly Clinical Studies Group) (2016–19), HTA Commissioning Committee (2010–16) and was a member of the HTA and EME Editorial Board between 2014 and 2019. Sarah Cunningham-Burley reports personal fees and other from the Wellcome Trust (London, UK), other from the University of Copenhagen (Copenhagen, Denmark), other funding from NIHR Global Health Research, personal fees from the French National Cancer Institute (Paris, France) and personal fees from the Health Research Board (Dublin, Ireland), outside the submitted work. Andrew Shennan is a member of the NIHR HTA Commissioning Committee (2018–22). Stephen C Robson was a member of the NIHR EME Funding Committee (2012–15). Steven Thornton is a trustee of a number of charities, including those that fund related research. He reports personal fees from GlaxoSmithKline plc, during the conduct of the study and outside the submitted work, and personal fees from Johnson & Johnson (Johnson & Johnson, Brunswick, NJ, USA) for consulting services. He holds positions in the Royal College of Obstetricians and Gynaecologists (London, UK) and other organisations. He was a member of the NIHR EME Strategy Advisory Committee (2018–19), EME – Funding Committee Members (2015–19), EME Funding Committee Sub-Group Remit & Comp Check (2018–19) and the Medical Research Council Multimorbidity Board (2020). Neil Marlow reports personal fees from Shire-Takeda (London, UK), Novartis Pharmaceuticals UK Ltd (London, UK) and GlaxoSmithKlein plc, outside the submitted work. Sarah J Stock declares that she is a member of the NIHR HTA General Committee (2016–22). In addition, Sarah J Stock received other research funding from the NIHR (14/32/01 QUIDS), Wellcome Trust (209560/Z/17/Z) and Chief Scientist Office (Edinburgh, UK), during the course of the study. Philip R Bennett reports personal fees and membership of a scientific panel from ObsEva (Plan-les-Ouates, Switzerland), outside the submitted work. In addition, Philip R Bennett has a patent PCT/GB1997/000529 WO1997031631 A1 'COX-2 selective inhibitors for managing labour and uterine contractions' issued, a patent PCT/GB2004/001380 WO2005053705 A1 'Use of a cyclopentenone prostaglandin for delaying the onset and/or preventing the continuation of labour' (priority date 2 December 2003) issued, a patent PCT/GB2016/050618 'Circulating miRNAs predictive of cervical shortening and preterm birth' (pending UK filing 6 March 2015/full international filing completed 7 March 2016) issued, a patent PCT/GB2016/050621 'Rapid evaporative ionisation mass spectroscopy (REIMS) and desorbtion electrospray ionisation mass spectroscopy (DESI-MS) analysis of swabs and biopsy samples' (pending UK filing 6 March 2015/full international filing completed 7 March 2016) pending, a patent PCT/GB2019 'Desorbtion electrospray ionisation mass spectroscopy (DESI-MS) analysis of swabs to predict vaginal microbiota' (pending UK filing March 2019) pending, and a patent PCT/GB2019/ 'Circulating miRNAs predictive of IUGR' (pending UK filing March 2019) pending.

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published July 2021
DOI: 10.3310/hta25440

Scientific summary

The STOPPIT 2 RCT

Health Technology Assessment 2021; Vol. 25: No. 44
DOI: 10.3310/hta25440

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

Scientific summary

Background

Around 16 out of every 1000 women giving birth in England and Wales have a multiple pregnancy. Multiple pregnancies are associated with higher rates of stillbirth, neonatal and infant mortality, and child disability, largely as a direct consequence of higher rates of preterm birth in multiple pregnancies than in singleton pregnancies.

There are no effective strategies for preterm birth prevention in women with multiple pregnancy, but there is increasing interest in the use of the Arabin pessary. The Arabin pessary is a silicone pessary that is placed around the cervix. The pessary is thought to support the utero-vesical angle and keep the cervix closed, preventing preterm birth. Systematic reviews show some evidence of effectiveness in singleton pregnancy. In multiple pregnancy, there is conflicting evidence. The strongest evidence on effectiveness relates to women with a short cervix, who are at the highest risk of preterm birth. STOPPIT 2 was conducted to address the evidence gaps around the effectiveness of the Arabin pessary in women with a short cervix and twin pregnancy.

Objective

STOPPIT 2 was designed to test the hypothesis that the Arabin pessary is effective in preventing preterm birth in women with a short cervix. As the adverse effects of preterm birth relate largely to neonatal outcomes, we had an obstetric and a neonatal primary outcome. The main trial was supplemented with an economic evaluation to consider the cost-effectiveness to the NHS of providing the intervention compared with usual standard care alone. We also conducted a qualitative study to explore the views and experiences of participants and clinicians involved in the study. We preplanned subgroup analyses to determine effectiveness in women with cervical lengths of $\leq$ 25 mm and $\leq$ 28 mm, and in women with a dichorionic pregnancy.

The study was in two phases: (1) screening and (2) treatment. All participants were recruited first into the screening phase. Eligible women had ultrasound measurement of cervical length prior to 20^{+6} weeks' gestation. Those with a cervical length of $\leq$ 35 mm at 18^{+0}–20^{+6} weeks' gestation ($\leq$ 30 mm for the first 6 months of the study) were eligible for randomisation in the treatment phase of the study to either the control group (standard care alone) or the intervention group (Arabin pessary plus standard care).

Methods

STOPPIT 2 was an pragmatic, open-label, multicentre, randomised controlled trial comparing the Arabin pessary and standard care with standard care alone for the prevention of preterm birth in women with twin pregnancy. The randomisation ratio was 1 : 1, carried out by computer accessed through a web-based browser. The allocation sequence employed minimisation with a random element using the variables study centre and chorionicity (mono- or dichorionic).

Participants were recruited from antenatal clinics caring for women with multiple pregnancy in UK NHS hospitals and elsewhere in Europe.

Inclusion criteria for the screening and treatment phases of the study were:

- twin pregnancy (monochorionic or dichorionic)
- known chorionicity (as defined by first-trimester ultrasound screening)
- current gestation of $\leq 20^{+6}$ weeks' gestation (as established by scan at ≤ 16 weeks' gestation, in accordance with National Institute for Health and Care Excellence guidelines)
- age ≥ 16 years
- willingness to participate in both the screening and randomisation phases of the study.

Exclusion for the screening and treatment phase were:

- inability to give written informed consent, known significant congenital structural or chromosomal fetal anomaly at the time of inclusion
- existing or planned cervical cerclage in the current pregnancy
- existing or planned (prior to 20^{+6} weeks' gestation) treatment for twin-to-twin transfusion syndrome in the current pregnancy
- suspected or proven rupture of the fetal membranes at the time of recruitment
- bulging fetal membranes at the time of recruitment
- singleton pregnancy or higher-order multiple pregnancies
- women who have experienced any fetal death (i.e. fetal heartbeat previously detected) in the index pregnancy (prior to randomisation)
- known sensitivity, contraindication or intolerance to silicone
- involvement in a clinical trial of an investigational medicinal product, a phase 1 study or investigation of a treatment for the prevention of preterm birth
- monochorionic, monoamniotic pregnancy
- heavy bleeding due to a low-lying placenta at any time prior to randomisation.

Additional inclusion and exclusion criteria for the treatment phase were:

- inclusion – cervical length of ≤ 35 mm at 18^{+0}–20^{+6} weeks' gestation
- exclusion – cervical length of > 35 mm at 18^{+0}–20^{+6} weeks' gestation, cervical length not measured at 18^{+0}–20^{+6} weeks' gestation, bulging fetal membranes at the time of pessary insertion or suspected or proven rupture of the fetal membranes at the time of pessary insertion.

(Note that the initial cervical length threshold for inclusion for the treatment phase was ≤ 30 mm, which we anticipated to be the 30th centile. This was increased to ≤ 35 mm after 6 months, when it became clear that the population 30th centile was 35 mm.)

All cervical length measurements were conducted transvaginally by an accredited clinician or sonographer.

The co-primary outcomes were (obstetric) all births before 34^{+0} weeks' gestation following the spontaneous onset of labour and (neonatal) a composite of adverse outcomes, including stillbirth or neonatal death, periventricular leukomalacia, early respiratory morbidity, intraventricular haemorrhage, necrotising enterocolitis or proven sepsis. In addition, using questionnaires and focus groups, we explored the experiences of women and clinicians using the Arabin pessary. Resource use data were used to calculate the cost-effectiveness of the pessary.

Results

Fifty-seven centres ($n = 56$ in the UK) participated in the study. A total of 7490 women were assessed for eligibility for the screening phase of the study; 2228 were offered a cervical length scan, of whom 2170 underwent a scan and 523 had a cervical length that conferred eligibility for randomisation. A total of 503 women were subsequently randomised (250 to the intervention and 253 to the control group).

Two hundred and thirty women in the intervention group had an Arabin pessary inserted.

Four women in the intervention group and eight women in the control group were lost to follow-up.

There was no difference in either the primary obstetric or the primary neonatal outcome between the groups. The rate of the primary obstetric outcome was 18.4% (46/250) in the intervention group and 20.6% (52/253) in the control group (adjusted odds ratio 0.87, 95% confidence interval 0.55 to 1.38; $p = 0.54$). For the primary neonatal outcome, rates were 13.4% (67/500) and 15.0% (76/506), respectively (adjusted odds ratio 0.86, 95% confidence interval 0.54 to 1.36; $p = 0.52$). There were no differences in secondary outcomes or safety outcomes between the groups.

Pessary insertion and removal was either painless or only slightly uncomfortable for most participants, with few side effects other than vaginal discharge. Clinicians found insertion and removal 'easy' or 'fairly easy' in the majority of instances.

There was no evidence that the use of the Arabin pessary was more costly than standard care. The findings point to a potential small cost advantage for both maternal and neonatal hospitalisation costs (i.e. £435.16 and £160.59, respectively) for the pessary strategy. The results are, however, surrounded by some uncertainties (e.g. in the price of the pessary and unit costing assignment methods used to value resource use).

Conclusions

Implications for health care

- The Arabin pessary does not prevent spontaneous preterm birth in women with twin pregnancy, and nor does it improve neonatal outcome.
- The Arabin pessary was relatively well tolerated by women with twin pregnancy. The majority of women found insertion and removal painless or only slightly uncomfortable.
- Most insertions and removals of the Arabin pessary were described by clinicians as easy or moderately easy.
- The use of the Arabin pessary is not more costly than standard care.

Future research implications

- Women with twin pregnancies have high rates of preterm birth (19.4%), with 12.1% having at least one serious neonatal outcome. Further work is required to find effective therapies.

Trial registration

This trial is registered as ISRCTN98835694 and ClinicalTrials.gov NCT02235181.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 44. See the NIHR Journals Library website for further project information.

Health Technology Assessment

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 13/04/22. The contractual start date was in November 2014. The draft report began editorial review in September 2020 and was accepted for publication in February 2021. 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).