NIHR | National Institute for Health Research

Journals Library

Check for updates

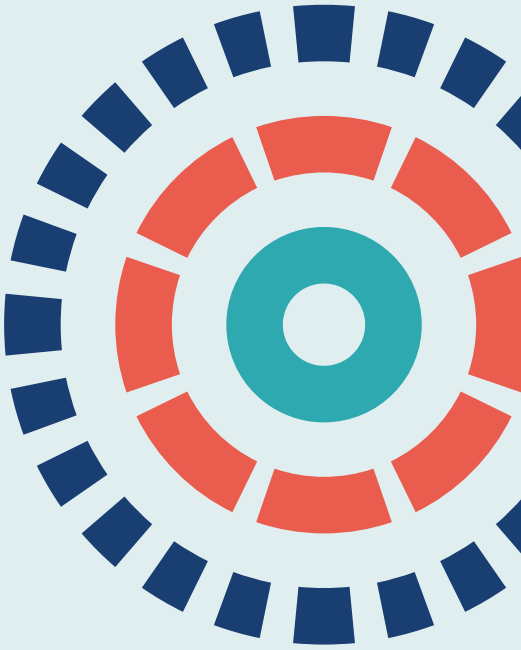
Health Technology Assessment

Volume 24 • Issue 33 • June 2020

ISSN 1366-5278

Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT

Arri Coomarasamy, Hoda M Harb, Adam J Devall, Versha Cheed, Tracy E Roberts, Ilias Goranitis, Chidubem B Ogwulu, Helen M Williams, Ioannis D Gallos, Abey Eapen, Jane P Daniels, Amna Ahmed, Ruth Bender-Atik, Kalsang Bhatia, Cecilia Bottomley, Jane Brewin, Meenakshi Choudhary, Fiona Crosfill, Shilpa Deb, W Colin Duncan, Andrew Ewer, Kim Hinshaw, Thomas Holland, Feras Izzat, Jemma Johns, Mary-Ann Lumsden, Padma Manda, Jane E Norman, Natalie Nunes, Caroline E Overton, Kathiuska Kriedt, Siobhan Quenby, Sandhya Rao, Jackie Ross, Anupama Shahid, Martyn Underwood, Nirmala Vaithilingham, Linda Watkins, Catherine Wykes, Andrew W Horne, Davor Jurkovic and Lee J Middleton



DOI 10.3310/hta24330

Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT

Arri Coomarasamy,[1]* Hoda M Harb,[1] Adam J Devall,[1] Versha Cheed,[2] Tracy E Roberts,[2] Ilias Goranitis,[3] Chidubem B Ogwulu,[2] Helen M Williams,[1] Ioannis D Gallos,[1] Abey Eapen,[4] Jane P Daniels,[5] Amna Ahmed,[6] Ruth Bender-Atik,[7] Kalsang Bhatia,[8] Cecilia Bottomley,[9] Jane Brewin,[10] Meenakshi Choudhary,[11] Fiona Crosfill,[12] Shilpa Deb,[13] W Colin Duncan,[14] Andrew Ewer,[1] Kim Hinshaw,[6] Thomas Holland,[15] Feras Izzat,[16] Jemma Johns,[17] Mary-Ann Lumsden,[18] Padma Manda,[19] Jane E Norman,[14] Natalie Nunes,[20] Caroline E Overton,[21] Kathiuska Kriedt,[9] Siobhan Quenby,[22] Sandhya Rao,[23] Jackie Ross,[17] Anupama Shahid,[24] Martyn Underwood,[25] Nirmala Vaithilingham,[26] Linda Watkins,[27] Catherine Wykes,[28] Andrew W Horne,[14] Davor Jurkovic[9] and Lee J Middleton[2]

[1]Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[2]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[3]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia
[4]Carver College of Medicine, University of Iowa Health Care, Iowa City, IA, USA
[5]Faculty of Medicine and Health Sciences, Queen's Medical Centre, University of Nottingham, Nottingham, UK
[6]Sunderland Royal Hospital, City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK
[7]Miscarriage Association, Wakefield, UK

[8]Burnley General Hospital, East Lancashire Hospitals NHS Trust, Burnley, UK
[9]University College Hospital, University College London Hospitals NHS Foundation Trust, London, UK
[10]Tommy's, London, UK
[11]Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[12]Royal Preston Hospital, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[13]Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK
[14]Medical Research Council Centre for Reproductive Health, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
[15]St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK
[16]University Hospital Coventry, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK
[17]King's College Hospital, King's College Hospital NHS Foundation Trust, London, UK
[18]Reproductive & Maternal Medicine, School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
[19]The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
[20]West Middlesex University Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, Isleworth, UK
[21]St Michael's Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[22]Biomedical Research Unit in Reproductive Health, Warwick Medical School, University of Warwick, Coventry, UK
[23]Whiston Hospital, St Helen's and Knowsley Teaching Hospitals NHS Trust, Prescot, UK
[24]Whipps Cross Hospital, Barts Health NHS Trust, London, UK
[25]Princess Royal Hospital, Shrewsbury and Telford Hospital NHS Trust, Telford, UK
[26]Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, Portsmouth, UK
[27]Liverpool Women's Hospital, Liverpool Women's NHS Foundation Trust, Liverpool, UK
[28]East Surrey Hospital, Surrey and Sussex Healthcare NHS Trust, Redhill, UK

*Corresponding author

Declared competing interests of authors: Jane P Daniels declares membership of the Clinical Trials Unit Standing Advisory Committee. Meenakshi Choudhary declares membership of Health Technology Assessment (HTA) Maternal, Newborn and Child Health (MNCH) Panel and the HTA Prioritisation Committee. Jane E Norman declares membership of the HTA MNCH Panel, that she currently receives funding from the National Institute for Health Research Efficacy and Mechanism Evaluation (EME) programme, that she participates in a Data Monitoring and Ethics Committee for GlaxoSmithKline plc (Brentford, UK) and that she is a paid consultant for Dilafor AB (Solna, Sweden). She was a member of the HTA and EME Editorial Board from 2012 to 2014. Caroline Overton declares that she was a Mylan clinical educator for general practitioner education about hormone replacement therapy and incorporated private practice in April 2017 (now called Bristol Women's Clinic Ltd).

Published June 2020
DOI: 10.3310/hta24330

This report should be referenced as follows:

Coomarasamy A, Harb HM, Devall AJ, Cheed V, Roberts TE, Goranitis I, *et al*. Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT. *Health Technol Assess* 2020;**24**(33).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

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 12/167/26. The contractual start date was in October 2014. The draft report began editorial review in October 2018 and was accepted for publication in May 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.

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

Abstract

Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT

Arri Coomarasamy,[1]* Hoda M Harb,[1] Adam J Devall,[1] Versha Cheed,[2] Tracy E Roberts,[2] Ilias Goranitis,[3] Chidubem B Ogwulu,[2] Helen M Williams,[1] Ioannis D Gallos,[1] Abey Eapen,[4] Jane P Daniels,[5] Amna Ahmed,[6] Ruth Bender-Atik,[7] Kalsang Bhatia,[8] Cecilia Bottomley,[9] Jane Brewin,[10] Meenakshi Choudhary,[11] Fiona Crosfill,[12] Shilpa Deb,[13] W Colin Duncan,[14] Andrew Ewer,[1] Kim Hinshaw,[6] Thomas Holland,[15] Feras Izzat,[16] Jemma Johns,[17] Mary-Ann Lumsden,[18] Padma Manda,[19] Jane E Norman,[14] Natalie Nunes,[20] Caroline E Overton,[21] Kathiuska Kriedt,[9] Siobhan Quenby,[22] Sandhya Rao,[23] Jackie Ross,[17] Anupama Shahid,[24] Martyn Underwood,[25] Nirmala Vaithilingham,[26] Linda Watkins,[27] Catherine Wykes,[28] Andrew W Horne,[14] Davor Jurkovic[9] and Lee J Middleton[2]

[1]Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[2]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[3]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia
[4]Carver College of Medicine, University of Iowa Health Care, Iowa City, IA, USA
[5]Faculty of Medicine and Health Sciences, Queen's Medical Centre, University of Nottingham, Nottingham, UK
[6]Sunderland Royal Hospital, City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK
[7]Miscarriage Association, Wakefield, UK
[8]Burnley General Hospital, East Lancashire Hospitals NHS Trust, Burnley, UK
[9]University College Hospital, University College London Hospitals NHS Foundation Trust, London, UK
[10]Tommy's, London, UK
[11]Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[12]Royal Preston Hospital, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[13]Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK
[14]Medical Research Council Centre for Reproductive Health, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
[15]St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK
[16]University Hospital Coventry, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

[17]King's College Hospital, King's College Hospital NHS Foundation Trust, London, UK
[18]Reproductive & Maternal Medicine, School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
[19]The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
[20]West Middlesex University Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, Isleworth, UK
[21]St Michael's Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[22]Biomedical Research Unit in Reproductive Health, Warwick Medical School, University of Warwick, Coventry, UK
[23]Whiston Hospital, St Helen's and Knowsley Teaching Hospitals NHS Trust, Prescot, UK
[24]Whipps Cross Hospital, Barts Health NHS Trust, London, UK
[25]Princess Royal Hospital, Shrewsbury and Telford Hospital NHS Trust, Telford, UK
[26]Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, Portsmouth, UK
[27]Liverpool Women's Hospital, Liverpool Women's NHS Foundation Trust, Liverpool, UK
[28]East Surrey Hospital, Surrey and Sussex Healthcare NHS Trust, Redhill, UK

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

Background: Progesterone is essential for a healthy pregnancy. Several small trials have suggested that progesterone therapy may rescue a pregnancy in women with early pregnancy bleeding, which is a symptom that is strongly associated with miscarriage.

Objectives: (1) To assess the effects of vaginal micronised progesterone in women with vaginal bleeding in the first 12 weeks of pregnancy. (2) To evaluate the cost-effectiveness of progesterone in women with early pregnancy bleeding.

Design: A multicentre, double-blind, placebo-controlled, randomised trial of progesterone in women with early pregnancy vaginal bleeding.

Setting: A total of 48 hospitals in the UK.

Participants: Women aged 16–39 years with early pregnancy bleeding.

Interventions: Women aged 16–39 years were randomly assigned to receive twice-daily vaginal suppositories containing either 400 mg of progesterone or a matched placebo from presentation to 16 weeks of gestation.

Main outcome measures: The primary outcome was live birth at ≥ 34 weeks. In addition, a within-trial cost-effectiveness analysis was conducted from an NHS and NHS/Personal Social Services perspective.

Results: A total of 4153 women from 48 hospitals in the UK received either progesterone ($n = 2079$) or placebo ($n = 2074$). The follow-up rate for the primary outcome was 97.2% (4038 out of 4153 participants). The live birth rate was 75% (1513 out of 2025 participants) in the progesterone group and 72% (1459 out of 2013 participants) in the placebo group (relative rate 1.03, 95% confidence interval 1.00 to 1.07; $p = 0.08$). A significant subgroup effect (interaction test $p = 0.007$) was identified for prespecified subgroups by the number of previous miscarriages: none (74% in the progesterone group vs. 75% in the placebo group; relative rate 0.99, 95% confidence interval 0.95 to 1.04; $p = 0.72$); one or two (76% in the progesterone group vs. 72% in the placebo group; relative rate 1.05, 95% confidence interval 1.00 to 1.12; $p = 0.07$); and three or more (72% in the progesterone group vs. 57% in the placebo group; relative rate 1.28, 95% confidence interval 1.08 to 1.51; $p = 0.004$). A significant post hoc subgroup effect (interaction test $p = 0.01$) was identified in the subgroup of participants with early pregnancy bleeding and any number of previous miscarriage(s) (75% in the progesterone group vs. 70% in the placebo group; relative rate 1.09, 95% confidence interval 1.03 to 1.15; $p = 0.003$). There were no significant differences in the rate of adverse events between the groups. The results of the health economics analysis show that progesterone was more costly than placebo (£7655 vs. £7572), with a mean cost difference of £83 (adjusted mean difference £76,

95% confidence interval –£559 to £711) between the two arms. Thus, the incremental cost-effectiveness ratio of progesterone compared with placebo was estimated as £3305 per additional live birth at ≥ 34 weeks of gestation.

Conclusions: Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with threatened miscarriage overall, but an important subgroup effect was identified. A conclusion on the cost-effectiveness of the PRISM trial would depend on the amount that society is willing to pay to increase the chances of an additional live birth at ≥ 34 weeks. For future work, we plan to conduct an individual participant data meta-analysis using all existing data sets.

Trial registration: Current Controlled Trials ISRCTN14163439, EudraCT 2014-002348-42 and Integrated Research Application System (IRAS) 158326.

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. 24, No. 33. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
BCa	bias-corrected and accelerated
BMI	body mass index
BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHARM	Charity for Research into Miscarriage
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CRF	case report form
C-section	caesarean section
DAU	day assessment unit
DMEC	Data Monitoring and Ethics Committee
FIGO	International Federation of Gynaecology and Obstetrics
GP	general practitioner
HCHS	Hospital and Community Health Services
HDU	high-dependency unit
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMP	investigational medicinal product
IQR	interquartile range
ITMS	integrated trial management system
ITU	intensive therapy unit
LLETZ	large loop excision of the cervical transformation zone
MID	minimally important difference
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PBAC	pictorial bleeding assessment chart
PI	principal investigator
PRIME	Public and Researchers Involvement in Maternity and Early Pregnancy
PRISM	Progesterone in Spontaneous Miscarriage
PROMISE	Progesterone in Recurrent Miscarriage
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUL	pregnancy of unknown location
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative rate
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TCC	trial co-ordinating centre
TSC	Trial Steering Committee
WTP	willingness to pay

Plain English summary

Miscarriage is a common complication of pregnancy that affects one in five pregnancies. Several small studies have suggested that progesterone, a hormone essential for maintaining a pregnancy, may reduce the risk of miscarriage in women presenting with early pregnancy bleeding.

This research was undertaken to test whether or not progesterone given to pregnant women with early pregnancy bleeding would increase the number of live births when compared with placebo (dummy treatment).

The women participating in the study had an equal chance of receiving progesterone or placebo, as determined by a computer; one group received progesterone (400 mg twice daily as vaginal pessaries) and the other group received placebo with an identical appearance. Treatment began when women presented with vaginal bleeding, were < 12 weeks of gestation and were found to have at least a pregnancy sac on an ultrasound scan. Treatment was stopped at 16 weeks of gestation, or earlier if the pregnancy ended before 16 weeks. Neither the participants nor their health-care professionals knew which treatment was being received.

In total, 23,775 women were screened and 4153 women were randomised to receive either progesterone or placebo pessaries. Altogether, 2972 participants had a live birth after at least 34 weeks of gestation. Overall, the live birth rate in the progesterone group was 75% (1513 out of 2025 participants), compared with 72% (1459 out of 2013 participants) in the placebo group. Although the live birth rate was 3% higher in the progesterone group than in the placebo group, there was statistical uncertainty about this finding. However, it was observed that women with a history of one or more previous miscarriages and vaginal bleeding in their current pregnancy may benefit from progesterone. For women with no previous miscarriages, our analysis showed that the live birth rate was 74% (824 out of 1111 participants) in the progesterone group compared with 75% (840 out of 1127 participants) in the placebo group. For women with one or more previous miscarriages, the live birth rate was 75% (689 out of 914 participants) in the progesterone group compared with 70% (619 out of 886 participants) in the placebo group. The potential benefit appeared to be most strong for women with three or more previous miscarriages, who had a live birth rate of 72% (98 out of 137 participants) in the progesterone group compared with 57% (85 out of 148 participants) in the placebo group. Treatment with progesterone did not appear to have any negative effects.

Scientific summary

Background

Progesterone, produced by the corpus luteum in the ovaries, helps to prepare the endometrium for implantation of the embryo and thus is an essential hormone for a successful pregnancy. Evidence from several controlled clinical trials suggested that there was a benefit from progesterone therapy, but with insufficient certainty owing to the size of the trials and their methodological weaknesses. This prompted the National Institute for Health and Care Excellence (NICE) (Clinical Guideline 154 on 'Ectopic Pregnancy and Miscarriage'; National Collaborating Centre for Women's and Children's Health. *NICE Clinical Guidelines [CG154]. Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management*. London: NICE; 2012) to call for a definitive trial to answer this question.

Objectives

The Progesterone in Spontaneous Miscarriage study was designed to test the hypothesis that, in women with vaginal bleeding in the first 12 weeks of pregnancy, receiving vaginal progesterone (400-mg pessaries, twice daily) as soon as possible after the identification of an intrauterine gestation sac until 16 weeks of gestation increases the rate of live births at $\geq$ 34 completed weeks of pregnancy by at least 5% compared with placebo. In addition, an economic evaluation was conducted alongside the trial to assess the relative cost-effectiveness of progesterone compared with placebo.

Design

The Progesterone in Spontaneous Miscarriage trial was a multicentre, double-blind, placebo-controlled randomised trial, with economic evaluation.

Setting

The study was conducted in hospital settings across the UK (48 sites) between 2015 and 2018.

Participants

Participants were women who presented with early pregnancy bleeding that had started in the preceding 4 days, who were in the first 12 weeks of pregnancy and who had an intrauterine gestation sac visible on ultrasonography. Participants were aged 16–39 years at randomisation and gave informed consent.

Interventions

Each participant in the Progesterone in Spontaneous Miscarriage trial received either progesterone or placebo pessaries at a dose of 400 mg twice daily, which were administered vaginally from the day of randomisation to 16 completed weeks of gestation.

Main outcome measures

The primary outcome measure was live birth at ≥ 34 completed weeks of gestation. The secondary outcome measures included ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital anomalies and resource use.

Methods

Participants were randomised online in a 1 : 1 ratio using a secure internet facility through an integrated trial management system. Minimisation was implemented for age (< 35 or ≥ 35 years), body mass index (< 30 or ≥ 30 kg/m^2), fetal heart activity (present or absent), gestation at presentation by date of last menstrual bleed (≤ 42 or > 42 days) and amount of bleeding (pictorial bleeding assessment chart score of ≤ 2 or ≥ 3). Data were collected at three points of outcome assessment after randomisation, up to 28 days after birth. The primary analysis was by intention to treat. A within-trial cost-effectiveness analysis was conducted from the NHS and NHS/Personal Social Services perspective based on the main clinical outcome of this trial.

Results

A total of 4153 women from 48 hospitals in the UK received either progesterone (2079 participants) or placebo (2074 participants). The follow-up rate for the primary outcome was 97.2% (4038 out of 4153 participants). The live birth rate was 75% (1513 out of 2025 participants) in the progesterone group compared with 72% (1459 out of 2013 participants) in the placebo group (relative rate 1.03, 95% confidence interval 1.00 to 1.07; $p = 0.08$). A significant subgroup effect (interaction test $p = 0.007$) was identified for prespecified subgroups by the number of previous miscarriages: none (74% progesterone vs. 75% placebo; relative rate 0.99, 95% confidence interval 0.95 to 1.04; $p = 0.72$); one or two (76% progesterone vs. 72% placebo; relative rate 1.05, 95% confidence interval 1.00 to 1.12; $p = 0.07$); and three or more (72% progesterone vs. 57% placebo; relative rate 1.28, 95% confidence interval 1.08 to 1.51; $p = 0.004$), thus demonstrating a biological gradient by the increasing number of previous miscarriages. A significant post hoc subgroup effect (interaction test $p = 0.01$) was found when we grouped all participants with any number of previous miscarriage(s) (75% in the progesterone group vs. 70% in the placebo group; relative rate 1.09, 95% confidence interval 1.03 to 1.15; $p = 0.003$). There were no significant differences in the occurrence of adverse events.

For secondary outcomes, there was evidence that progesterone may increase the rate of ongoing pregnancy at 12 weeks (83% in the progesterone group vs. 80% in the placebo group; relative rate 1.04, 95% confidence interval 1.01 to 1.07; $p = 0.01$). There was no evidence of a difference in the safety outcomes.

The results of the health economics analysis show that the average cost per participant was £7655 in the progesterone arm and £7572 in the placebo arm, a mean cost difference of £83 (adjusted mean difference £76, 95% confidence interval –£559 to £711) between the two arms. The incremental cost-effectiveness ratio of progesterone compared with placebo was estimated at £3305 per additional live birth at ≥ 34 weeks of gestation. These results suggest that progesterone is likely to be perceived by decision-makers as cost-effective.

Conclusions

Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with threatened miscarriage overall. However, an increase in live births was observed in the subgroup of women with early pregnancy bleeding and a history of previous miscarriages. A conclusion on the cost-effectiveness of the PRISM trial would depend on the amount that society is willing to pay to increase the chances of an additional live birth at ≥ 34 weeks.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN14163439, EudraCT 2014-002348-42 and Integrated Research Application System (IRAS) 158326.

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. 24, No. 33. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Existing knowledge

Progesterone in pregnancy

Progesterone is an endogenous hormone that is essential to achieve and maintain a healthy pregnancy. Progesterone prepares the lining of the uterus (endometrium) to allow the implantation of the early embryo and stimulates glands in the endometrium to secrete nutrients for the embryo. During the first 8 weeks of pregnancy, progesterone is produced by the corpus luteum; however, between 8 and 12 weeks, the placenta takes over the progesterone-producing role and maintains the pregnancy thereafter.

The physiological importance of progesterone has prompted researchers, physicians and patients to consider progesterone supplementation during early pregnancy to prevent miscarriages. Progesterone supplementation in early pregnancy has been attempted in two contexts: the first is to *prevent* miscarriages in asymptomatic women with a past history of recurrent miscarriages and the second is to *rescue* a pregnancy in women who have started to bleed in early pregnancy.[1] Our Progesterone in Recurrent Miscarriage (PROMISE) study, published in the *New England Journal of Medicine*, addressed the first context.[2] In 2012, the National Institute for Health and Care Excellence (NICE) Clinical Guideline 154[3] called for a large randomised placebo-controlled clinical trial to test whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of threatened miscarriage. In response, the current study was designed to address this question and focuses on the rescue context in women with vaginal bleeding in early pregnancy.

Burden of disease

Miscarriage is the most common complication of early pregnancy; one in five clinically recognised pregnancies end in a miscarriage.[4] This has a substantial impact on physical and psychological well-being: research shows that the level of distress associated with miscarriage can be equivalent to that of a stillbirth of a term baby and can induce post-traumatic stress disorder.[5] An estimated 140,000 women per year miscarry in the UK.[3]

Costs to the NHS

It is estimated that miscarriage costs the NHS > £350M each year.[3] This value includes the costs of diagnosis (blood tests and ultrasonography), management of miscarriages (expectant, medical or surgical), investigations of causes of miscarriages (e.g. antiphospholipid syndrome, parental karyotype and uterine cavity tests) and hospital inpatient costs. There are also the associated costs of complications following treatment of miscarriages (e.g. uterine perforation, infection, bleeding or visceral damage) and any long-term health consequences of miscarriages or miscarriage management (including complications of intrauterine infections and adhesions). Furthermore, the societal costs (including days lost from work and out-of-pocket expenses for patients and partners) can be expected to be far greater.

Progesterone in clinical use for threatened miscarriage

The Progesterone in Spontaneous Miscarriage (PRISM) study was conceived to address the possibility that progesterone therapy in the first trimester of pregnancy may reduce the risk of miscarriage in women presenting with early pregnancy bleeding. We conducted a UK clinician survey ($n = 222$) in October 2012. In the UK, the majority of clinicians (212 out of 222; 95.5%) do not use progesterone to prevent miscarriage in women with early pregnancy bleeding. The key reason for non-use is the lack of robust evidence. Therefore, it is not surprising that the majority of clinicians (201 out of 222; 91%) called for a definitive trial. We also conducted a survey of international practitioners at the International Federation of Gynaecology and Obstetrics (FIGO) 2012 conference in Rome. Surprisingly, this survey found that the majority of clinicians (61 out of 68; 90%) already use progesterone in women with early pregnancy

bleeding, although the vast majority (56 out of 66; 85%) were willing to recruit into a randomised trial, presumably indicating a lack of confidence in the available evidence.

Effectiveness of progesterone in threatened miscarriage

The first trial of progesterone therapy in women with early pregnancy bleeding was published in 1967, and since then six trials have studied this question, which have previously been summarised in a Cochrane systematic review.[1] In 2014, prior to conducting the PRISM trial, we performed a systematic review of trials on the use of progestogens in women with early pregnancy bleeding, and identified seven studies.[6–12] These studies are listed in *Table 1*. The seven studies included a total of 744 women. These studies were small and of poor quality, with none reporting the method of allocation concealment. Only three out of seven studies were placebo controlled and five out of seven studies were not blinded. The modified Jadad quality score varied from 1 out of 6 to 3 out of 6. Outcome data were available for miscarriage rates. Individual studies were too small to show an effect, but a meta-analysis of these seven studies (*Figure 1*) showed a statistically significant reduction in miscarriage rate with progestogen use [relative rate (RR) 0.53, 95% confidence interval (CI) 0.39 to 0.73]. There was no heterogeneity across the studies ($I^2 = 0\%$), suggesting that there was consistency across the studies.

TABLE 1 Randomised trials of progestogens vs. placebo or no treatment

Study	Intervention	Duration of treatment	Comparison	Risk of bias
Ehrenskjöld *et al.*, 1967[6] (*n* = 153)	20 mg of oral dydrogesterone	20 mg then tapering (20 mg after 12 hours/ 20 mg every 8 hours until symptoms ceased/ 10 mg twice daily for 5 days/5 mg twice daily for at least 7 days)	No treatment	Method of randomisation unclear, allocation concealment adequate, blinding of patients and study personnel adequate
El-Zibdeh and Yousef 2009[7] (*n* = 146)	10 mg of oral dydrogesterone twice daily	From enrolment until 1 week after bleeding stopped	No treatment	Quasi-randomised (allocated according to the day of the week), no allocation concealment, no blinding for participants or study personnel
Gerhard *et al.*, 1987[8] (*n* = 34)	25-mg progesterone vaginal suppositories twice daily	Until miscarriage or for 14 days after bleeding stopped	Placebo	Method of randomisation unclear, allocation concealment unclear, no blinding for participants or study personnel
Mistò,1967[9] (*n* = 16)	20 to 40 mg of oral dydrogesterone	Once daily for 6–15 days, sometimes for longer periods and for several cycles	Placebo	Method of randomisation unclear, allocation concealment adequate, blinding of patients and study personnel adequate
Omar *et al.*, 2005[10] (*n* = 154)	Dydrogesterone	40 mg of dydrogesterone followed by 10 mg twice daily until bleeding stopped	No treatment	Method of randomisation unclear, no allocation concealment, no blinding of patients and study personnel
Palagiano *et al.*, 2004[11] (*n* = 50)	90 mg of progesterone (Crinone® 8% Central Pharma Ltd, Bedford, UK) vaginal suppositories	Once daily for 5 days	Placebo	Method of randomisation unclear, allocation concealment adequate, no blinding for participants or study personnel
Pandian, 2009[12] (*n* = 191)	Oral dydrogesterone	40 mg of oral dydrogesterone followed by 10 mg of dydrogesterone twice daily, until 16 weeks of gestation	No treatment	Method of randomisation and allocation concealment adequate, no blinding of participants or study personnel

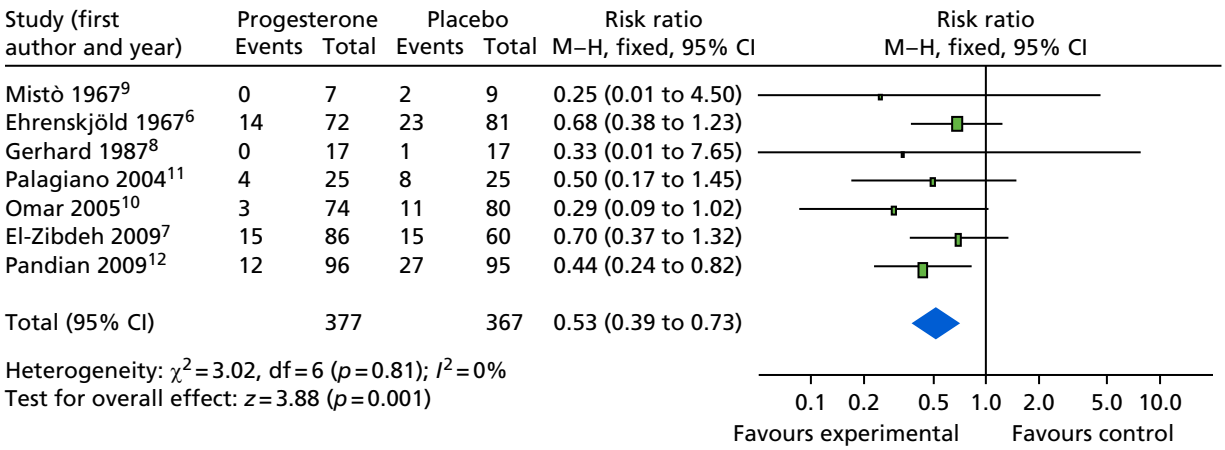


FIGURE 1 Meta-analysis of studies of progesterone in women with early pregnancy bleeding (literature review conducted in 2014). M–H, Mantel–Haenszel.

More recently, a Cochrane review on this question summarised evidence from seven studies (see *Table 1*). The review found that the studies were small with methodological weaknesses (the largest study had a sample size of 191) but the pooled analysis found a significantly lower risk of miscarriages among women who received progesterone than among those who received placebo or no treatment (risk ratio 0.64, 95% CI 0.47 to 0.87).[1]

Safety of progesterone supplementation in pregnancy

Our research group previously conducted the PROMISE trial,[13] and in the lead-up to this study a full literature review was conducted on the safety of progestogen supplementation in pregnancy.[13] This identified one case–control study that suggested an association between hypospadias and progestogen use.[14] The findings from the case–control study represented weaker evidence than the better-quality evidence from larger cohort studies that did not substantiate this association. Moreover, the PROMISE trial did not show any difference in the incidence of hypospadias between the progesterone and the placebo arms.[13]

Rationale

A trial of progesterone therapy in the treatment of threatened miscarriage was required because:

- A guideline by NICE called for a definitive trial to evaluate the research question:

  > *. . . a very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted.*
  >
  > *© NICE [2012] Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management.[3] Available from www.nice.org.uk/guidance/cg154. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication*

- The Association of Early Pregnancy Units, the Royal College of Obstetrics and Gynaecology Early Pregnancy Clinical Studies Group, the Miscarriage Association and a national team of researchers and clinicians from across the UK prioritised this as an urgent research question.
- The existing trials, although small and of poor quality, suggest that there is a benefit in a highly prevalent condition with substantial morbidity and costs. If benefit is confirmed in the PRISM trial, both women and the NHS stand to gain substantially. On the other hand, if progesterone is found to be ineffective (or indeed harmful), treatment with progesterone can be avoided. This is relevant given the common use of progesterone for this indication outside the UK.

- Progesterone treatment is cheap (£0.68 per 400-mg capsule) and safe, and, if benefit is confirmed, we expect the intervention to be taken up rapidly.
- There is support for the study among UK and international clinicians. In a UK survey of 212 practitioners, 91% believed that a clinical trial is needed to investigate whether or not giving progesterone to women with threatened miscarriage can reduce the risk of miscarriage. In the international survey, 56 out of 66 (85%) respondents were willing to recruit into a randomised trial on this question.
- A patient survey supports the study. A patient survey ($n = 79$) showed that 72% of women would consider taking part in this study.
- The study is supported by the Miscarriage Association (a patient support organisation), The Scottish Early Pregnancy Network, INVOLVE (a national advisory group that supports greater public involvement in health research), PRIME (Public and Researchers Involvement in Maternity and Early Pregnancy), CHARM (Charity for Research into Miscarriage) and Tommy's charity.

Specific objectives

Primary objective

- The primary objective of the PRISM trial was to test the hypothesis that in women presenting with vaginal bleeding in the first trimester, receiving progesterone (400 mg vaginal capsules, twice daily) as soon as possible after identification of a visible intrauterine gestation sac with a scan until 16 completed weeks of gestation increases pregnancies with live births at ≥ 34 completed weeks by at least 5% compared with placebo.

Secondary objectives

- To test the hypothesis that progesterone improves other pregnancy and neonatal outcomes, including gestational age at birth and survival at 28 days of neonatal life.
- To test the hypothesis that progesterone, compared with placebo, is not associated with serious adverse effects for the mother or the neonate, including chromosomal anomalies in the newborn.
- To explore differential or subgroup effects of progesterone in prognostic subgroups, including age, fetal heart activity, gestation at presentation, amount of bleeding, body mass index and the number of previous miscarriages.
- To perform a cost-effectiveness analysis, with cost per additional birth over 34 weeks of gestation from an NHS and NHS/Personal Social Services (PSS) perspective. We will also model longer-term outcomes to the extent that the data permit.

Chapter 2 Methods

Design

The PRISM trial was conducted as a multicentre, double-blind, placebo-controlled randomised trial of progesterone in women with early pregnancy vaginal bleeding. The trial had a favourable ethics opinion from the National Research Ethics Service Committee South Central (Oxford C). The final protocol version was v3.0, 20 July 2016.

Participants

The participants in the PRISM trial were recruited in early pregnancy units in secondary or tertiary care NHS hospitals located across the UK if they fulfilled the following eligibility criteria (see *Recruitment* for more details on the recruitment process):

- presented with early pregnancy bleeding that had started in the 4 days prior to screening in the first 12 weeks of pregnancy
- had intrauterine gestation sac visible on ultrasonography (women were still to be offered the trial in the absence of a visible fetal pole)
- were aged 16–39 years at randomisation
- were willing and able to give informed consent.

Participants could not be included if any of the following criteria were applicable:

- had a crown–rump length measuring $\geq$ 7 mm with no visible heartbeat; or had a mean gestational sac of $\geq$ 25 mm with no visible fetal pole on ultrasonography
- had evidence of ectopic pregnancy
- presented with life-threatening bleeding
- currently or had recenly used progesterone supplementation
- had contraindications to progesterone therapy (progestogens should be avoided in patients with a history of liver tumours; they are also contraindicated in those with genital or breast cancer unless progestogens are being used in the management of these conditions, severe arterial disease, acute porphyria or a history during pregnancy of idiopathic jaundice, severe pruritus or pemphigoid gestations)
- were participating in any other blinded, placebo-controlled trials of investigational medicinal products (IMPs) in pregnancy.

Recruitment

Potential participants were identified from dedicated early pregnancy units and approached by clinic doctors, research nurses and midwives, after these professionals had received appropriate training relating to the trial. This training included the development of sensitivity in answering questions about the risks of miscarriage, and the intervention that was being used in the trial.

The participant eligibility pathway to recruitment and randomisation is illustrated in *Figure 2*. Eligible women were given verbal and written explanations about the trial. They were informed clearly that participation in the trial was entirely voluntary, with the option of withdrawing at any stage, and that participation or non-participation would not affect their usual care. They were provided with a participant information sheet. Eligible women were then given the opportunity to decide if they wanted to participate,

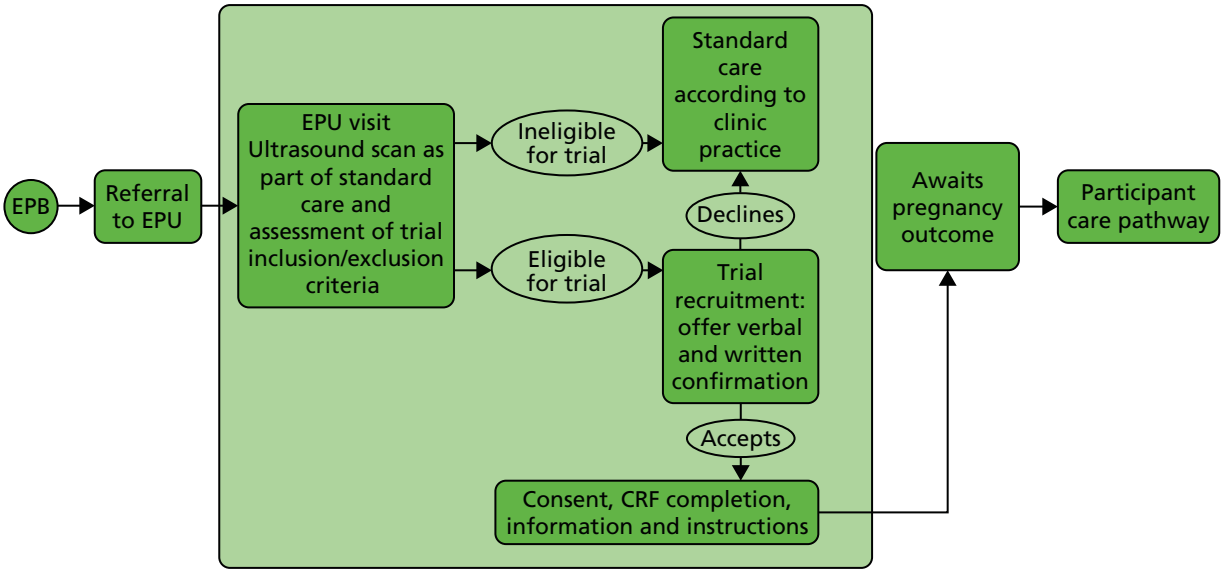


FIGURE 2 Eligibility pathway to recruitment and randomisation. CRF, case report form; EPB, early pregnancy bleeding; EPU, early pregnancy unit.

if they needed more time to consider their decision or if they did not want to participate. In all three scenarios, the decision of the woman was respected. If a woman needed more time to consider her potential involvement, she was asked to call the research nurse or midwife when she had decided. If an undecided woman had not called in 1–2 days, then the research nurse or midwife contacted her. If an initially undecided woman later decided to participate, the research nurse or midwife arranged a mutually convenient opportunity for the woman to be consented, providing she still met the eligibility criteria. A written consent form was provided to each woman who agreed to participate in the trial. The investigator and the participant both signed the consent form. The original copy was kept in the investigator site file, one copy was given to the participant and one copy was retained in the woman's hospital records. Baseline demographic and medical data were collected, anonymised and stored in an electronic integrated trial management system (ITMS). Any identifying information was collected and stored in a password-protected local database on a secure computer with restricted access.

We made provision for translation, if necessary, to communicate with non-English speakers and to accommodate any special communications requirements of potential study participants. Participant information sheets and consent forms were translated from English into Polish, Bengali and Urdu.

Randomisation

Confirmation of eligibility according to inclusion and exclusion criteria was assessed by a medically trained doctor and all of the necessary information was gathered prior to randomisation. Participants were randomised online to receive the trial intervention (either progesterone or placebo) via a purpose-designed ITMS. Each authorised member of the research team was provided with a unique username and password to access the ITMS for this purpose. Online randomisation was available for 24 hours per day, 7 days per week, apart from short periods of scheduled maintenance.

Sequence generation and minimisation

Computer-generated random numbers were used, and participants were randomised online via a secure internet facility. This third-party independent ITMS was designed, developed and delivered by MedSciNet® (MedSciNet UK Ltd, St Thomas' Hospital, London, UK) in accordance with the standards of the International Organisation for Standardisation 27000[15] and the requirements of the US Food and Drug Administration (FDA) CFR21:11.[16,17]

Participants were randomised to receive progesterone or placebo in a 1 : 1 ratio. A 'minimisation' procedure via computer-based algorithm based on the method described by Pocock and Simon[18] was used to avoid chance imbalances in important stratification variables. A random element was incorporated to make the treatment group less predictable.[19] The stratification variables (equally weighted) used for minimisation are listed below:

- age (< 35 or ≥ 35 years)
- body mass index (BMI) (< 30 or ≥ 30 kg/m^2)
- fetal heart activity (present or absent)
- estimated gestational age at presentation (< 42 or ≥ 42 days)
- amount of bleeding [pictorial bleeding assessment chart (PBAC)][20] score of ≤ 2 or ≥ 3).

Allocation

When all of the eligibility criteria and baseline data items were entered online, the ITMS generated a trial number that took into account the minimisation variables recorded for the individual and that was linked to a specific trial intervention pack. The pack number was revealed via e-mail to the local principal investigator (PI), the relevant trial pharmacist (see *Blinding*) and the research nurse or midwife performing the randomisation. The trial intervention pack was dispensed to the patient by the clinical trial pharmacist at the randomising hospital. Each trial intervention pack contained either progesterone or an identical-looking placebo pessary.

Interventions

Each participant in the PRISM trial received either progesterone or placebo pessaries, to be administered vaginally. Both products were supplied by Besins Healthcare International (Besins Healthcare, Montrouge, France), a global pharmaceutical company with a manufacturer's licence for tablets and capsules, in compliance with good manufacturing practice standards,[21] good clinical practice requirements[22] and Medicines for Human Use (Clinical Trials) Regulations 2004.[23] Besins Healthcare also provided qualified person release of the trial drug under the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.[23]

Progesterone pessaries

The IMP was a 400 mg dose of progesterone [i.e. two 200 mg pessaries of Utrogestan® (micronised vaginal progesterone, Utrogestan®, Besins Healthcare, Montrouge, France)] taken vaginally twice daily (every morning and every evening) for the duration of treatment. The product had all of the properties of endogenous progesterone with induction of a full secretory endometrium and, in particular, gestagenic, antiestrogenic, slightly antiandrogenic and antialdosterone effects.

Placebo pessaries

Placebo pessaries were vaginal pessaries, composed of sunflower oil, soybean lecithin, gelatin, glycerol, titanium dioxide and purified water, encapsulated in the same form as the IMP, and identical in colour, shape and weight, for use in the placebo arm of the PRISM trial. The dose, route and timing of administration were also identical to those in the active progesterone arm of the study.

Dose

The biologically effective dosage of progesterone pessaries ranged from 200 mg once daily to 400 mg twice daily according to the summary of product characteristics[24] and the *British National Formulary* (BNF).[25] Our choice of 400 mg twice daily was made after a careful review of the existing literature and an extensive survey of clinicians in the UK (see *Chapter 1*, *Progesterone in clinical use for threatened miscarriage*). We also reviewed other related evidence. For example, progesterone vaginal capsules are commonly used for luteal support in assisted conception at a treatment dose of 400 mg twice daily,

with no specific concerns for safety raised on this dose.[26,27] In addition, the findings from the PROMISE trial, which used the same dose, showed no safety concerns.[13] Therefore, after evaluating the evidence, we considered the dosage of 400 mg vaginal progesterone twice daily to be an acceptable regimen to ensure a clinically effective dose and to minimise the risk of a negative trial result from therapy with a suboptimal dose.

Timing of dose

Treatment commenced as soon as possible after confirmation of an intrauterine pregnancy sac and within 4 days of vaginal bleeding and continued until the gestational age of 16 weeks. Our rationale to discontinue the treatment at 16 weeks was that production of progesterone by the corpus luteum becomes less important when compared with the placental production of progesterone after 16 weeks of gestation. Furthermore, the largest (n = 191) and most recent of the seven previously published trials[12] continued treatment until 16 weeks and found a large and statistically significant reduction in miscarriage risk (risk ratio 0.44, 95% CI 0.24 to 0.82). There was also overwhelming agreement among the clinicians and researchers involved in the preparation of this application that we should continue the progesterone until 16 weeks' gestation.

Route

An immunomodulatory effect of progesterone at the trophoblastic–decidual interface is the key presumed mechanism for preventing miscarriage.[28–31] Our choice to use the vaginal route was, therefore, rational to deliver a greater proportion of the drug to the relevant site (the uterus) using the 'first uterine pass' effect.[32,33] Furthermore, studies that have used vaginal progesterone in the prevention of preterm birth have shown its effectiveness when given via this route.[34–36] For example, 14 out of 36 studies of second and/or third trimester progesterone to prevent preterm birth (identified by a recent systematic review) used vaginal progesterone, with significant improvements being observed for various clinical outcomes, confirming the biological effects of vaginal progesterone.[37]

The acceptability and availability of interventional drugs were also important considerations supporting the vaginal route of drug delivery. Our discussions with consumer representatives confirmed that a vaginal formulation would be more acceptable to women than an intramuscular injection. These findings were further supported by a study in which 12% of participants were unable to tolerate the intramuscular progesterone preparation and declined participation or withdrew from that trial.[38] Of those who did continue, 34% complained of localised soreness around the injection site. Moreover, the Miscarriage Association conducted a survey to identify women's opinions regarding acceptability of administering vaginal or rectal medications. The findings showed that the vaginal route of administration of medicines was acceptable to 100 out of 111 (90%) women, and the rectal route was acceptable to 91 out of 111 (82%) women. The pessary formulation of the PRISM trial is widely available in the UK and worldwide.

Instructions to participants

Each participant commenced the trial intervention on the day it was received and continued administration until it was finished, at 16 completed weeks of gestation, unless the pregnancy had ended before this time. Each participant was given instructions on how to administer the pessaries. In addition, each participant was asked for consent to notify her general practitioner (GP) by letter that she was participating in the trial. Moreover, each participant was given a card with contact details of local PRISM investigators and the central trial co-ordinating centre (TCC), the Birmingham Clinical Trials Unit, to inform any directing clinicians in case of potential drug interactions.

Concomitant non-trial treatments

Concomitant therapy was provided at the discretion of the care-providing clinicians, and all concomitant treatment and medications were documented via the ITMS. Other than identified contraindicated drugs (see *Participants*) and other progestogen preparations, the initiation of treatment for another indication did not necessitate withdrawal from the PRISM trial.

Blinding

Participants, investigators, research nurses, midwives and other attending clinicians remained blind to the trial drug allocation throughout the duration of the trial.

In the case of any serious adverse event (SAE), the general recommendation was to initiate management and care of the participant as though the woman was taking progesterone. Cases that were considered serious, unexpected and possibly, probably or definitely related to the trial intervention were unblinded as appropriate.[39] In any other circumstances, investigators, research nurses and midwives remained blind to drug allocation while the participant remained in the trial. However, if the drug allocation was specifically requested to assist the medical management of a participant, clinicians could contact the trial co-ordinator for this purpose, 24 hours per day, 7 days per week.

Compliance assessment and treatment withdrawal

Compliance monitoring

Our previous experience of research and clinical care for women with miscarriage demonstrated that they would be highly motivated and compliant with therapy advice. However, compliance with the PRISM trial was evaluated by 'pill counting' in the first instance. Participants were asked to return completed, partially used and unused treatment packs to the trial centres. The research nurses and midwives at each study centre documented the pessaries returned by each participant, and the trial pharmacists kept their own accountability logs.

In an effort to improve compliance, women who failed to return their empty or unused blister packs were provided with an envelope to return them to the research team. Finally, if neither of these two approaches was successful, where possible, the patients were contacted directly by the research team via telephone and asked to give an honest assessment of their drug compliance in terms of what percentage of treatment they felt that they took.

Good compliance with the intervention was defined as taking > 80% of trial medicines from the date of allocation up to 16 weeks of gestation.

Participant withdrawal from treatment

Following discussion with the trial management group, participants in the PRISM trial could be withdrawn from the trial treatment if it became medically necessary in the opinion of the investigator(s) or clinician(s) providing patient care. In the event of such premature treatment cessation, study nurses and midwives made every effort to obtain and record information about the reasons for discontinuation and to follow-up all safety and efficacy outcomes as appropriate. Providing that the patient gave their continued consent, the follow-up information for these patients was still collected. Participants in the PRISM trial could also voluntarily decide to cease taking the study treatment at any time. If a woman stopped taking the trial treatment but permitted further data collection, she was followed up and outcome assessments were undertaken for the remainder of the study.

Withdrawal from the trial

Participants could voluntarily withdraw their consent to study participation at any time. If a participant did not return for a scheduled visit, attempts were made to contact her and (where possible) to review compliance and adverse events (AEs). We documented the reason(s) for self-withdrawal where possible.

Each woman could change her mind about withdrawal, and re-consent to participate in the trial, at any time. If a participant explicitly withdrew consent to any further data recording, then this decision was respected and recorded via the ITMS. All communications surrounding the withdrawal were noted in the study records and no further data were collected for such participants.

Outcomes and assessment

Primary outcome

Live births at or beyond 34 completed weeks of gestation (≥ 34 weeks), as a proportion of all women randomised.

Secondary outcomes

Secondary outcomes were as follows (as a proportion of those randomised unless stated):

- Time from conception to pregnancy end (any reason). Conception date was estimated using the date of last menstrual period or, failing that, the date from the ultrasound scan at 9–14 weeks.
- Ongoing pregnancy at 12 weeks of gestation.
- Miscarriage rate (defined as delivery before 24 weeks of gestation).
- Other pregnancy end outcomes – live birth at < 34 weeks' gestation, ectopic pregnancy, termination, stillbirth, molar pregnancy, resolved pregnancy of unknown location (PUL), failed PUL, twin live births, gestational age at miscarriage.
- When there is live birth at ≥ 24 weeks' gestation – time from conception to delivery (gestational age), gestational age < 28/< 32/< 37 weeks' gestation, mode of delivery [unassisted vaginal, instrumental vaginal, elective Caesarean section (C-section), emergency C-section, vaginal breech delivery, other], birthweight adjusted for gestational age and sex, small for gestational age and sex (< 10th centile), arterial and venous cord pH, Apgar scores.
- Antenatal complications – pregnancy-induced hypertension, pre-eclampsia, obstetric cholestasis, cervical cerclarge, preterm (< 37 weeks' gestation) pre-labour rupture of membranes, gestational diabetes mellitus (other complications will be tabulated but not formally analysed).
- Intrapartum complications – chorioamnionitis, intrauterine growth restriction, macrosomia (other complications will be tabulated but not formally analysed).
- Postpartum complications – haemorrhage (other complications will be tabulated but not formally analysed).
- Maternal complications – admission to a high-dependency unit (HDU), admission to an intensive therapy unit (ITU) (other complications will be tabulated but not formally analysed).
- Neonatal complications – discharge to hospital, early infection, retinopathy of prematurity, necrotising enterocolitis, intraventricular haemorrhage, congenital and chromosomal abnormalities, respiratory distress syndrome, ventilation or oxygen support (other complications will be tabulated but not formally analysed).
- Survival at 28 days of neonatal life.
- Maternal unexpected AEs (tabulated but not formally analysed).
- SAEs.

Resource use outcomes

These are detailed in *Chapter 4*.

Future outcomes

Each participant in the PRISM study was asked to consent for the future evaluation of themselves, the child who was born and the health records of both. Although long-term follow-up will remain outside the scope of this trial, we plan to conduct further studies, as discussed in *Chapter 6*, *Recommendations for research*.

Outcome generation

Details of how outcome measures were generated are given in *Table 2*. The ITMS was utilised to capture baseline and outcome data, and to maintain an audit trail. Relevant trial data were transcribed directly into the ITMS. Source data comprised the research clinic notes, hospital notes, hand-held pregnancy notes, laboratory results and self-reports.

First outcome assessment (11–14 weeks of pregnancy)

At the time of randomisation, arrangements for an ultrasound appointment with the woman's routine care providers were made at between 11 and 14 weeks of gestation. The research nurse or midwife assisted with booking an appointment, if necessary, and was responsible for ensuring that the details of the scan were recorded in the ITMS. If the patient did not have a scan for any reason, this was recorded in the ITMS.

Second outcome assessment (end of pregnancy)

The second outcome assessment was conducted at, or after, birth (*Figure 3*). The research nurse or midwife at each study site used the patient's hospital notes to obtain pregnancy outcome data, such as the mode of delivery, gestation, weight and Apgar score at birth. If for any reason the research nurse or midwife was unable to access the hospital records, a telephone call was made to the patient to obtain as much follow-up information as possible.

TABLE 2 Outcome assessment details

	Details			
Outcome assessed	When?	How?	By whom?	PD or SP?
Ongoing pregnancy	11–14 weeks	Ultrasound	Ultrasonographer	SP
• Final pregnancy outcomes including miscarriage • Live birth • Gestation at delivery • Congenital anomalies	At or after the end of pregnancy	From: • Clinical records • Telephonic or face-to-face interview with the participant • Outcome 'post cards'	Research nurse or doctor	Both SP and PD
Neonatal outcomes	Up to 28 days of neonatal life	From: • Neonatal records • Interviews with participants	Research nurse or doctor	Both SP and PD
Resource use outcomes	At any time during the conduct of the trial	From: • Clinical records • Interview with the participant	Research nurse or doctor	PD

PD, protocol driven; SP, standard practice.

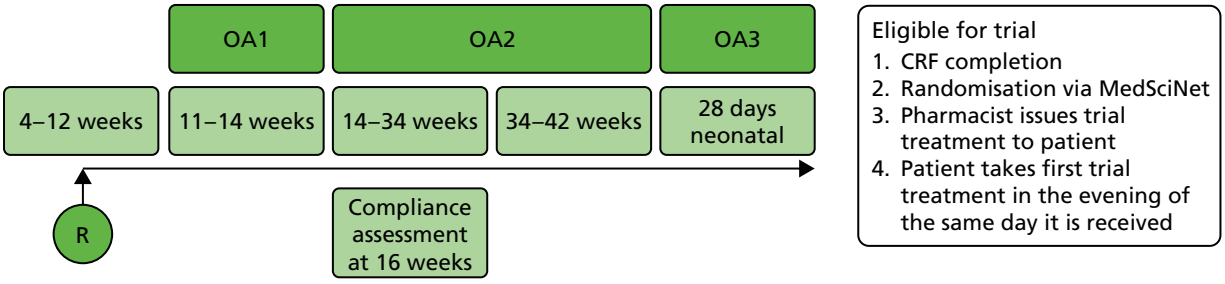


FIGURE 3 Participant care pathway and outcome assessment. OA, outcome assessment points; OA1, ongoing pregnancy beyond 12 weeks (range 11–14 weeks); OA2, live birth at > 34 weeks; OA3, survival at 28 days of neonatal life; R, randomisation.

Third outcome assessment (day 28 post birth)

The third and final outcome assessment was conducted to gather neonatal outcomes at 28 days after birth for those patients who had a successful live birth (see *Figure 3*). The research nurse or midwife at each study site telephoned every participant to ascertain whether or not the baby was still alive at this time point and to enquire about any nights of hospital admission or requirements for ventilation support, and complications (e.g. early infection). Using the full repertoire of evidence-based methods to maximise data collection, the research nurse or midwife also checked birth registers and inpatient records to track hospital admissions and pregnancy outcomes.

Definition of the end of the trial

The observational phase of the trial ceased when the 28-day follow-up had been completed for all surviving babies. The primary analysis was scheduled to occur after all corresponding outcome data had been entered onto the study database and validated as being ready for analysis.

Notes on adverse events and serious adverse events

All of the trial participants were asked to report any hospitalisations, consultations with other medical practitioners, disability, incapacity or any other AEs to their local research team. If the local study nurse or midwife was unavailable for any reason, they were able to report the events to the trial manager or trial co-ordinator via telephone at any time. Moreover, at the time of each outcome assessment, investigators, research nurses and midwives at each study centre proactively asked each participant about any AEs in the preceding weeks. AEs were assessed by clinical investigators, further reported as appropriate and recorded on the ITMS.

Serious adverse events and serious adverse reactions (SARs) were recorded on a purpose-designed SAE form and notified by local investigators to the TCC within 24 hours of the local investigators becoming aware of these events. In addition, local investigators were responsible for reporting SAEs to their host institutions in accordance with local regulations and instituting supplementary investigations as appropriate based on clinical judgement of the causative factors. Any SAE or SAR that was outstanding at the end of the trial treatment period was followed up at least until the final outcome was determined, even if this provision necessitated follow-up beyond 28 days post partum. The TCC reported all SAEs to the Data Monitoring and Ethics Committee (DMEC) approximately every 6 months. The DMEC viewed data blinded to treatment but was able to review unblinded data if requested.

Suspected unexpected serious adverse reactions (SUSARs) were unblinded, as appropriate, reviewed by the trial manager within 24 hours of reporting and further reported to the Medicines and Healthcare products Regulatory Agency and the regional ethics committee by the TCC as soon as possible for any event, within 15 days (or 7 days in the case of fatal or life-threatening SUSARs).

Sample size

The PRISM trial investigators believed that it was important to ensure that the study was large enough to detect reliably moderate but clinically important treatment effects. Our calculations indicated that, to detect a minimally important difference (MID) of 5% in rates of live birth after $\geq$ 34 weeks (from 60% to 65%), for an alpha error rate of 5% (two sided) with 90% power, it would be necessary to randomise 1970 women to the intervention arm and 1970 women to the placebo arm (3940 women in total). However, assuming and adjusting for a worst-case scenario of a loss to follow-up rate of 5%, the total number of participants required would be 4150 (2075 each in the progesterone and placebo arms). The sample size of the study was planned accordingly. The MID of 5% was defined following consultations among health-care practitioners, patients and representatives of patient bodies as well as through a survey of clinicians. The 60% baseline (placebo) event rate was derived from audits from two of the participating units (Imperial College London and the Royal Infirmary of Edinburgh).

Statistical methods

A comprehensive statistical analysis plan (SAP) was drawn up prior to any analysis and provided to the independent DMEC and Trial Steering Committee (TSC) for review. Full details of the statistical analysis can be found in the SAP.[39]

To summarise, categorical baseline data were summarised with frequencies and percentages. Normally distributed continuous variables were summarised as means with standard deviations (SDs), otherwise medians with interquartile ranges (IQRs) were presented. Participants were analysed in the treatment group to which they were randomised in the first instance, irrespective of compliance with the treatment protocol. All estimates of differences between groups are presented with 95%, two-sided CIs. *p*-values from two-sided tests at the 5% significance level are also included.

For the primary outcome (live birth at ≥ 34 weeks' gestation), the population was all randomised participants. A Poisson regression model incorporating robust standard errors was used to generate relative risks along with 95% CIs, adjusting for the minimisation parameters. This method has been shown to be appropriate and less prone to convergence issues compared with other comparable methods.[40] Statistical significance of the treatment group parameter was determined through examination of the associated chi-squared statistic.

Analysis was performed as per the primary outcome for the other binary outcomes. For number of twins, mode of delivery, secondary neonatal outcomes, intrapartum complications, postpartum complications and neonatal complications, the analysis population was those with live births at ≥ 24 weeks' gestation. For secondary neonatal outcomes and neonatal complication rates, twin babies were both counted in the analysis population. For continuous outcomes (e.g. birthweight and birthweight centiles), a linear regression model was used, adjusting for the same minimisation parameters. Here, an *F*-test was used to test the statistical significance of the estimated treatment group parameter generated from the restricted maximum likelihood estimates. The proportion and percentage of patients experiencing any SAE were presented by group. Statistical significance was determined by chi-squared test.

Sensitivity analysis was performed on the primary outcome and the outcome miscarriage at < 24 weeks' gestation to test the impact of any missing data. This assumed that all patients lost to follow-up had a negative outcome (i.e. no live birth ≥ 34 weeks' gestation). An analysis that simulated missing responses using a multiple imputation approach was also performed (Markov chain Monte Carlo method – see SAP for details[39]). We also repeated the primary analysis, prioritising data scan information over last menstrual period dates (the primary analysis prioritised last menstrual period dates).

Pre-planned subgroup analyses (limited to the primary outcome measure and miscarriage rate) were completed in the following: (1) maternal age (< 35 or ≥ 35 years), (2) BMI (< 30 or ≥ 30 kg/m^2), (3) fetal heart activity (present or absent), (4) estimated gestational age at presentation (< 42 or ≥ 42 days), (5) amount of vaginal bleeding (PBAC score[20] of ≤ 2 or ≥ 3), (6) number of previous miscarriages (0, 1/2 or ≥ 3), (7) number of gestational sacs (1 or ≥ 2), (8) ethnicity (white, black, south Asian or other), (9) history of polycystic ovaries (yes or no) and (10) previous cervical excision (yes or no). The effects of these subgroups were examined by adding the subgroup by treatment group interaction parameters to the regression model; a chi-squared test was used to test the statistical significance of this parameter.

Interim analyses of effectiveness and safety end points were performed on behalf of the DMEC on an approximately 6-monthly basis during the period of recruitment. These analyses were performed with the use of the Haybittle–Peto principle[41] and hence no adjustment was made in the final *p*-values to determine significance.

Trial oversight

Study oversight was provided by a TSC (chaired by Professor Siladitya Bhattacharya, University of Aberdeen) and a DMEC (chaired by Professor Andrew Shennan, King's College London).

The TSC provided independent supervision for the trial, providing advice to the chief investigator and co-investigators and the sponsor on all aspects of the trial throughout the study. The DMEC adopted the DAMOCLES (DAta MOnitoring Committees: Lessons, Ethics, Statistics) charter to define its terms of reference and operation in relation to oversight of the PRISM trial.

Chapter 3 Results

This chapter reports the results of the PRISM trial. It commences with a description of the flow of participants through the trial and is followed by demographic information and results of the primary and secondary outcome measures, including the safety outcomes.

Participant flow

Participant flow is illustrated in *Figure 4*. A total of 23,775 participants were screened for eligibility to take part in the PRISM trial. Of these, 10,913 participants were not eligible for randomisation and a further 8709 declined to participate in the trial.

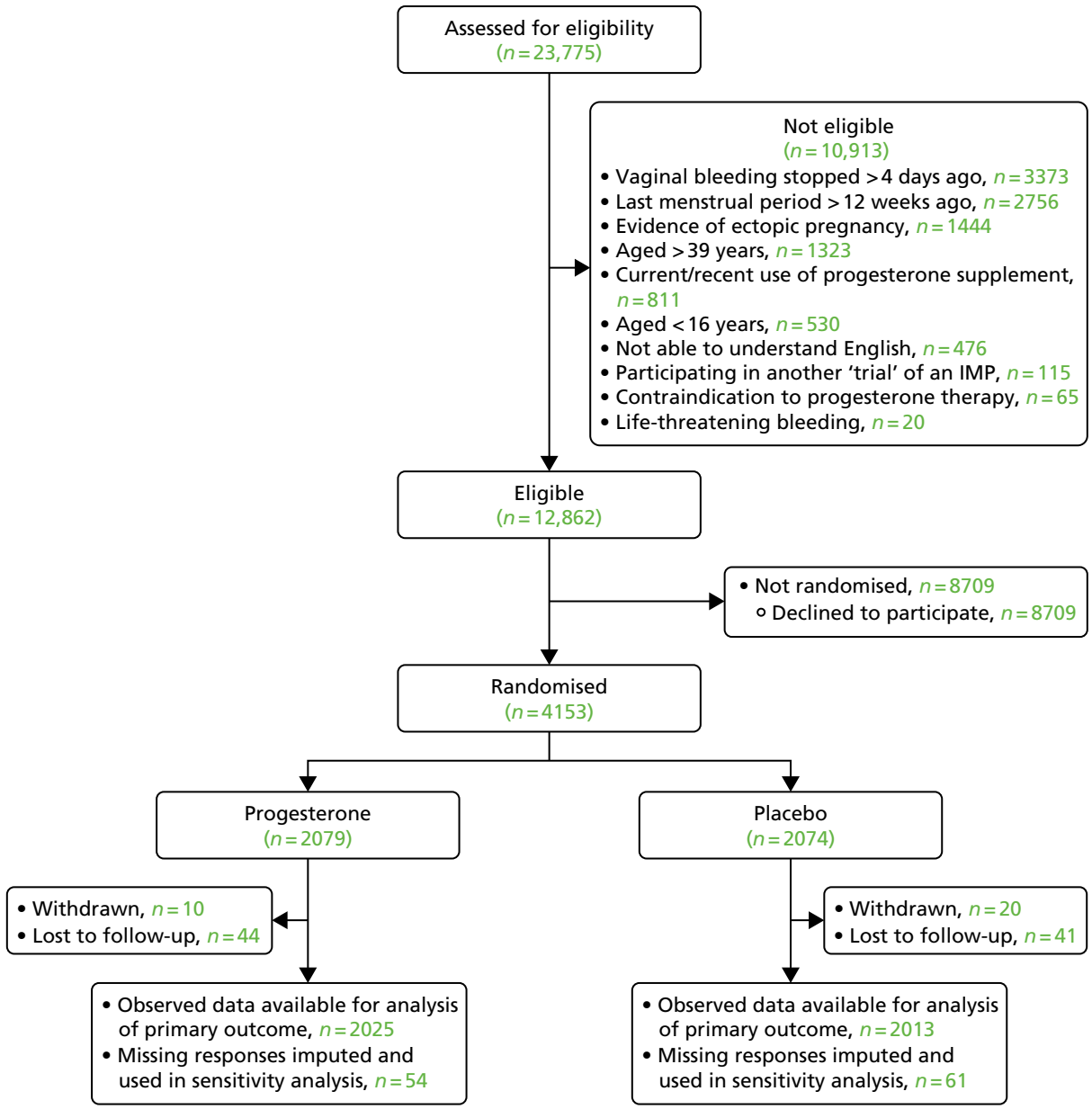


FIGURE 4 The CONSORT flow diagram of participants through the PRISM trial.

A total of 4153 women proceeded to randomisation, with 2079 allocated to progesterone and 2074 allocated to placebo. Thirty participants were withdrawn from the study and a further 85 were lost to follow-up, meaning that 4038 participants (97.2% of those randomised) were available for analysis of the primary outcome.

Recruitment

Recruitment and randomisation took place over 27 months in 48 UK NHS hospitals (*Figure 5*) from May 2015 to July 2017 (*Figure 6*). Two centres, University College London Hospital and St Michael's Hospital, Bristol, contributed > 300 enrolled participants each (*Table 3*).

FIGURE 5 Map of the PRISM trial recruiting centres.

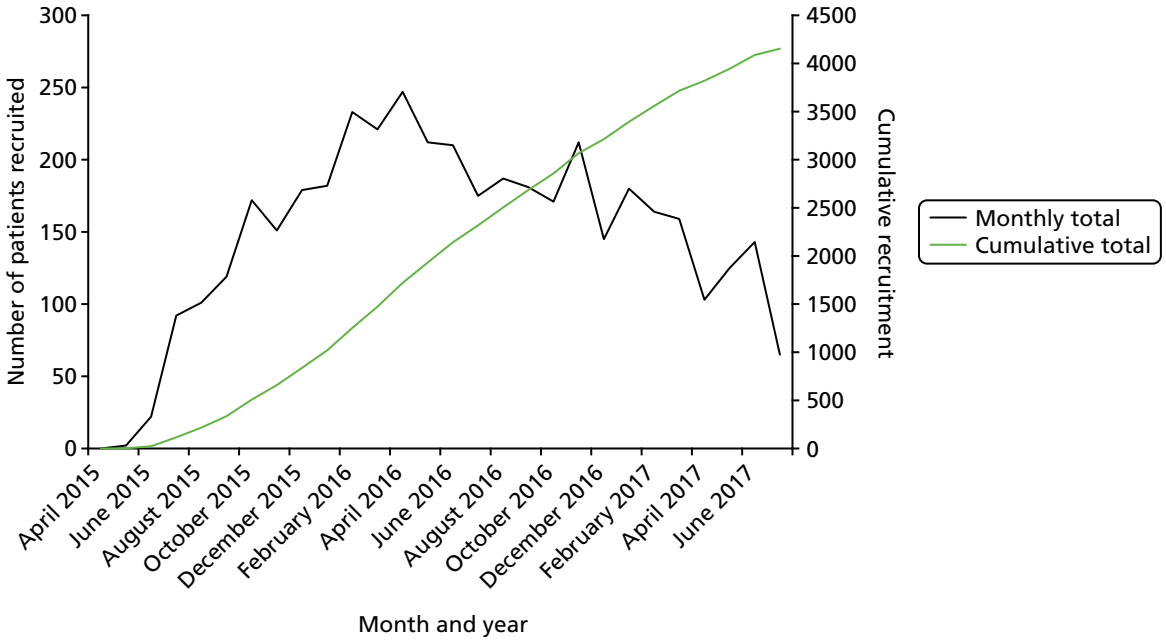


FIGURE 6 Rates of recruitment for the PRISM trial.

TABLE 3 Site-by-site recruitment to the PRISM trial

Hospital	NHS institution	PI	Number randomised, *n* (%)
University College Hospital	University College London Hospitals NHS Foundation Trust	Mr Davor Jurkovic	365 (8.8)
St Michael's Hospital	University Hospitals Bristol NHS Foundation Trust	Mrs Caroline Overton	313 (7.5)
University Hospital Coventry	University Hospitals Coventry and Warwickshire NHS Trust	Mr Feras Izzat	268 (6.5)
Queen's Medical Centre	Nottingham University Hospitals NHS Trust	Dr Shilpa Deb	223 (5.4)
Sunderland Royal Hospital	City Hospitals Sunderland NHS Foundation Trust	Dr Amna Ahmed	210 (5.1)
Royal Infirmary of Edinburgh	Lothian Health Board	Professor Andrew Horne	160 (3.9)
Glasgow Royal Infirmary	NHS Greater Glasgow and Clyde	Professor Mary-Ann Lumsden	156 (3.8)
King's College Hospital	King's College Hospital NHS Foundation Trust	Miss Jemma Johns	152 (3.7)
St Thomas' Hospital	Guy's and St Thomas' NHS Foundation Trust	Dr Thomas Holland	133 (3.2)
Liverpool Women's Hospital	Liverpool Women's NHS Foundation Trust	Dr Linda Watkins	131 (3.2)
Queen Alexandra Hospital	Portsmouth Hospitals NHS Trust	Miss Nime Vaithilingam	130 (3.1)
Birmingham Women's Hospital	Birmingham Women's and Childrens NHS Foundation Trust	Mr Ismail Hassan	129 (3.1)
West Middlesex University Hospital	Chelsea and Westminster Hospital NHS Foundation Trust	Miss Natalie Nunes	125 (3.0)
Princess Royal Hospital	Shrewsbury and Telford NHS Trust	Mr Martyn Underwood	118 (2.8)

continued

TABLE 3 Site-by-site recruitment to the PRISM trial (*continued*)

Hospital	NHS institution	PI	Number randomised, *n* (%)
Birmingham Heartlands Hospital	Heart of England NHS Foundation Trust	Dr Pratima Gupta	117 (2.8)
Royal Preston Hospital	Lancashire Teaching Hospitals NHS Foundation Trust	Dr Fiona Crosfill	110 (2.6)
The James Cook University Hospital	South Tees Hospitals NHS Foundation Trust	Dr Padma Manda	103 (2.5)
East Surrey Hospital	Surrey and Sussex Healthcare NHS Trust	Dr Catherine Wykes	99 (2.4)
Chelsea and Westminster Hospital	Chelsea and Westminster Hospital NHS Foundation Trust	Miss Cecilia Bottomley	91 (2.2)
Burnley General Hospital	East Lancashire Hospitals NHS Trust	Miss Kalsang Bhatia	79 (1.9)
Worcestershire Royal Hospital	Worcestershire Acute Hospitals NHS Trust	Mr Samson Agwu	77 (1.9)
Whiston Hospital	St Helen's and Knowsley NHS Trust	Mrs Sandhy Rao	73 (1.8)
Whipps Cross University Hospital	Barts London NHS Trust	Miss Anupama Shahid	68 (1.6)
Royal Victoria Infirmary	Newcastle Upon Tyne Hospitals NHS Foundation Trust	Dr Meenakshi Choudhary	62 (1.5)
Musgrove Park Hospital, Taunton	Taunton and Somerset NHS Foundation Trust	Dr Hadi Haerizadeh	61 (1.5)
St Peter's Hospital	Ashford and St Peter's Hospitals NHS Foundation Trust	Ms Catey Bass	55 (1.3)
Queen's Hospital, Burton	Burton Hospitals NHS Foundation Trust	Dr Jayasree Srinivasan	50 (1.2)
St Mary's Hospital, Manchester	Central Manchester University Hospitals NHS Foundation Trust	Dr Ursula Winters	50 (1.2)
Royal London Hospital	Barts London NHS Trust	Mrs Anupama Shahid	48 (1.2)
Scunthorpe General Hospital	Northern Lincolnshire and Goole NHS Foundation Trust	Miss Preeti Gandhi	39 (0.9)
Airedale General Hospital	Airedale NHS Foundation Trust	Miss Sumita Bhuiya	38 (0.9)
John Radcliffe Hospital	Oxford University Hospitals NHS Trust	Dr Ingrid Granne	35 (0.8)
Sheffield Royal Hallamshire Hospital	Sheffield Teaching Hospitals NHS Foundation Trust	Mrs Joanne Fletcher	35 (0.8)
Derriford Hospital, Plymouth	Plymouth Hospitals NHS Trust	Dr Rekha Shrestha	34 (0.8)
Cumberland Infirmary	North Cumbria University Hospitals NHS Trust	Dr Laura Hipple	33 (0.8)
North Devon District Hospital	Northern Devon Healthcare NHS Trust	Mr Samuel Eckford	33 (0.8)
St James University Hospital	Leeds Teaching Hospitals NHS Trust	Ms Jayne Shillito	25 (0.6)
Warrington Hospital	Worcestershire Acute Hospitals NHS Trust	Mrs Rita Arya	25 (0.6)
Royal Stoke University Hospital	University Hospitals of North Midlands NHS Trust	Mr Zeiad El-Gizawy	24 (0.6)
Walsall Manor Hospital	Walsall Healthcare NHS Trust	Mr Jonathan Pepper	21 (0.5)
Hinchingbrooke Hospital	North West Anglia Foundation Trust	Miss Hema Nosib	14 (0.3)

TABLE 3 Site-by-site recruitment to the PRISM trial (*continued*)

Hospital	NHS institution	PI	Number randomised, *n* (%)
St Mary's Hospital, London	Imperial College Healthcare NHS Trust	Professor Tom Bourne	13 (0.3)
New Cross Hospital	Royal Wolverhampton Hospitals NHS Trust	Mr Jag Samra	12 (0.3)
Rosie Hospital	Cambridge University Hospitals NHS Foundation Trust	Miss Miriam Baumgarten	5 (0.1)
North Tyneside General Hospital	Northumbria Healthcare NHS Trust	Mr Mamdouh Guirguis	4 (0.1)
Hull Royal Infirmary	Hull and East Yorkshire Hospitals NHS Trust	Mr Piotr Lesny	3 (0.1)
Bradford Royal Infirmary	Bradford Teaching Hospitals NHS Foundation Trust	Professor Derek Tuffnell	2 (0.05)
Royal Devon and Exeter Hospital	Royal Devon and Exeter Hospitals NHS Foundation Trust	Mr James Clark	2 (0.05)

Baseline data

The baseline demographic characteristics of participants in the two groups were comparable, with the minimisation algorithm ensuring balance for the factors indicated in *Table 4*.

The randomised participants had an average age of 30.5 years (SD 5.1 years). The mean BMI was 26.5 kg/m^2 (SD 6.4 kg/m^2) at the time of randomisation. Of those who provided ethnic group data, 3456 (83%) were white, 216 (5%) were South Asian, 163 (4%) were black and 315 (8%) were from other ethnic groups. The majority of the women were non-smokers (3674/4149, 89%).

TABLE 4 Baseline characteristics of included participants by randomised treatment

Characteristic	Progesterone (*N* = 2079)	Placebo (*N* = 2074)
General baseline data		
Maternal age (years)[a]		
< 35, *n* (%)	1604 (77)	1601 (77)
≥ 35, *n* (%)	475 (23)	473 (23)
Mean (SD)	30.6 (5.1)	30.5 (5.1)
BMI (kg/m^2)[a]		
< 30, *n* (%)	1589 (76)	1589 (77)
≥ 30, *n* (%)	490 (24)	485 (23)
Mean (SD)	26.4 (6.2)	26.5 (6.3)
Ethnic group, *n* (%)		
White	1714 (82)	1742 (84)
Black	84 (4)	79 (4)
South Asian	114 (5)	102 (5)
Other	165 (8)	150 (7)
Missing	2 (< 1)	1 (< 1)

continued

TABLE 4 Baseline characteristics of included participants by randomised treatment (*continued*)

Characteristic	Progesterone (*N* = 2079)	Placebo (*N* = 2074)
Pregnancy history		
Nulliparous, *n* (%)	474 (23)	514 (25)
Number of previous miscarriages		
0, *n* (%)	1145 (55)	1157 (56)
1/2, *n* (%)	792 (38)	758 (37)
≥ 3, *n* (%)	142 (7)	159 (8)
Median (IQR)	0 (0–1)	0 (0–1)
Number of previous miscarriages, median (IQR), *n*		
First trimester miscarriages (< 14 weeks) in those with ≥ 1 miscarriages[b]	1 (1–2), 891	1 (1–2), 878
Second trimester miscarriages (≥ 14 weeks and < 24 weeks) in those with ≥ 1 miscarriages[b]	1 (1–1), 74	1 (1–1), 77
Preterm births (≥ 24 weeks and < 34 weeks)	1 (1–2), 83	1 (1–1), 90
Medical history		
Usual length of menstrual cycle (days), median (IQR), *n*	28 (28–30), 1947	28 (28–30), 1928
Polycystic ovaries, *n/N* (%)	226/2077 (11)	227/2072 (11)
Fibroids, *n/N* (%)	100/2077 (5)	78/2072 (4)
Endometriosis, *n/N* (%)	78/2077 (4)	68/2072 (3)
Pelvic inflammatory disease, *n/N* (%)	32/2077 (2)	33/2072 (2)
Uterine abnormalities, *n/N* (%)	48/2077 (2)	53/2072 (3)
History associated with previous gynaecological surgeries, *n/N* (%)		
Previous gynaecological surgeries	580/2077 (28)	564/2072 (27)
LLETZ	110/2077 (5)	103/2072 (5)
Surgical management of miscarriages	118/2077 (6)	144/2072 (7)
Myomectomy	4/2077 (< 1)	2/2072 (< 1)
Division of intrauterine adhesions	3/2077 (< 1)	3/2072 (< 1)
Endometrial surgery	36/2077 (2)	29/2072 (1)
Septum division	2/2077 (< 1)	7/2072 (< 1)
Tubal surgery	35/2077 (2)	29/2072 (1)
Ovarian cystectomy	36/2077 (2)	40/2072 (2)
Other surgeries	286/2077 (14)	270/2072 (13)
Other disorders	37/2077 (2)	44/2072 (2)
Family/social history,* n/N *(%)		
Current smoker	226/2077 (11)	249/2072 (12)
Partner is a current smoker	502/2077 (24)	473/2072 (23)
Current alcohol use	19/2077 (1)	27/2072 (1)
Family history of recurrent miscarriage (≥ 3 miscarriages)	243/2077 (12)	257/2072 (12)
Current medical data,* n/N *(%)		
Currently taking metformin	28/2077 (1)	20/2073 (1)
Current or recent use of aspirin (within 1 week)	73/2077 (4)	66/2073 (3)
Current or recent use of heparin (within 1 week)	7/2077 (< 1)	11/2073 (1)

TABLE 4 Baseline characteristics of included participants by randomised treatment (*continued*)

Characteristic	Progesterone (*N* = 2079)	Placebo (*N* = 2074)
Pregnancy-related information		
Mode of conception, *n* (%)		
Natural	2030 (98)	2036 (98)
Fertility treatment	49 (2)	38 (2)
Number of gestational sacs observed, *n* (%)		
1	2025 (97)	2036 (98)
2	53 (3)	38 (2)
≥ 3	1 (< 1)	0 (–)
Number of fetuses observed, *n* (%)		
0	144 (7)	155 (7)
1	1892 (91)	1887 (91)
2	43 (2)	31 (1)
≥ 3	0 (–)	1 (< 1)
Fetal heart activity, *n* (%)		
Present[a,c]	1710 (82)	1701 (82)
Estimated gestational age at presentation (days)[a]		
< 42, *n* (%)	372 (18)	374 (18)
≥ 42, *n* (%)	1707 (82)	1700 (82)
Median (IQR)	50 (43–61)	51 (43–62)
Amount of bleeding (PBAC score),[a] *n* (%)		
≤ 2	1913 (92)	1907 (92)
≥ 3	166 (8)	167 (8)

LLETZ, large loop excision of the cervical transformation zone.
a Minimisation variable.
b Numbers presented are for those who have provided gestational age at first and second trimester miscarriage.
c If more than one fetus, this is classified as any with heart activity present.

Of the 4153 randomised women, 2302 (55%) had experienced no previous miscarriage and 301 (7%) had experienced three or more previous miscarriages. A total of 124 (3%) women had previously experienced ectopic pregnancy. Cases of comorbidities included 453 (11%) participants with polycystic ovarian syndrome, 178 (4%) with a fibroid uterus, 146 (4%) with endometriosis and 101 (2%) with an arcuate uterus. Furthermore, 213 (19%) women had previously undergone large loop excision of the cervical transformation zone (LLETZ), 65 (7%) women had previously undergone endometriosis surgery, 64 (6%) women had previously undergone tubal surgery and 76 (7%) women had previously undergone ovarian cystectomy. Study records of concurrent medications showed that 48 (1%) of the randomised women were taking metformin at the time of participation and 139 (3%) were taking low-dose aspirin.

Compliance with treatment

Compliance data were reasonably well determined, with data collected for 72% (2920/4038) of participants. Good compliance (≥ 80% of pills taken) with treatment was higher up to 12 weeks' gestation (71%) than up to 16 weeks' gestation (58%), which may reflect an unwillingness of women to take treatment once they felt that their pregnancy was secure following the dating scan at 12–14 weeks (*Tables 5* and *6*). Compliance levels appeared similar in both groups.

TABLE 5 Compliance with treatment allocation up to 16 weeks by group

Compliance	Progesterone (*N* = 1548)	Placebo (*N* = 1469)
≥ 80%, *n* (%)	849 (55)	854 (58)
< 80%, *n* (%)	699 (45)	615 (42)
Missing compliance information, *n*	477	544

TABLE 6 Compliance with treatment allocation up to 12 weeks by group

Compliance	Progesterone (*N* = 1548)	Placebo (*N* = 1469)
≥ 80%, *n* (%)	1087 (70)	1066 (73)
< 80%, *n* (%)	461 (30)	403 (27)
Missing compliance information, *n*	477	544

Results overview

The PRISM trial found no convincing evidence of a difference in the primary outcome (live birth at ≥ 34 weeks) between the two treatment groups. The number of live births was higher in the progesterone group than in the placebo group (75% in the progesterone group vs. 72% in the placebo group; adjusted relative risk 1.03, 95% CI 1.00 to 1.07), but this difference was not statistically significant ($p = 0.08$). There was evidence that the effect was dependent on the number of previous miscarriages, with a significant ($p = 0.007$) treatment by subgroup interaction observed. In women with three or more previous miscarriages, the live birth rate was 72% (98/137) with progesterone, compared with 57% (85/148) in the placebo group (relative risk 1.28, 95% CI 1.08 to 1.51; $p = 0.004$). A post hoc subgroup analysis exploring the effects in the subgroup of women with any number of previous miscarriages found a significant increase in the live birth rate with progesterone (relative risk 1.09, 95% CI 1.03 to 1.15; $p = 0.003$). For secondary outcomes, there was some evidence that progesterone increased the rate of ongoing pregnancy at 12 weeks (83% in the progesterone group vs. 80% in the placebo group; relative risk 1.04, 95% CI 1.01 to 1.07; $p = 0.01$) and reduced the rate of emergency C-sections (15% in the progesterone group vs. 19% in the placebo group; adjusted relative risk 0.80, 95% CI 0.69 to 0.94; $p = 0.006$); there was no evidence of a difference in the other outcomes or in the safety outcomes.

Primary outcome results

Overall, 2972 out of 4038 women (74%) experienced a live birth at ≥ 34 weeks' gestation. The live birth rate in the progesterone group was 75% (1513/2025) and the rate in the placebo group was 72% (1459/2013) (adjusted relative risk 1.03, 95% CI 1.00 to 1.07), a difference that was not statistically significant (absolute risk difference 2.2%, 95% CI –0.4% to 5.0%; $p = 0.08$) (*Table 7*).

Secondary outcome results

Secondary maternal outcome: pregnancy outcomes

There was evidence to suggest that progesterone increased the rate of ongoing pregnancy at 12 weeks: 1672 out of 2025 (83%) women in the progesterone group and 1602 out of 2013 (80%) in the placebo group remained pregnant at 12 weeks (adjusted relative risk 1.04, 95% CI 1.01 to 1.07; $p = 0.01$). However, there was no convincing evidence of a reduction in the number of miscarriages, with 410 out of 2025 (20%) women in the progesterone group and 451 out of 2013 (22%) in the placebo group experiencing a

TABLE 7 Primary and secondary outcome results

Outcome	Progesterone	Placebo	RR[a] or mean difference,[b] 95% CI; *p*-value
Primary outcome			
Live birth at ≥ 34 weeks, *n/N* (%)	1513/2025 (75)	1459/2013 (72)	1.03, 1.00 to 1.07; *p* = 0.08
Secondary maternal outcomes – pregnancy outcomes,[c] n/N (%)			
Ongoing pregnancy at 12 weeks	1672/2025 (83)	1602/2013 (80)	1.04, 1.01 to 1.07; *p* = 0.01
Miscarriage at < 24 weeks[d]	410/2025 (20)	451/2013 (22)	0.91, 0.81 to 1.01; *p* = 0.09
Live birth at < 34 weeks	68/2025 (3)	64/2013 (3)	1.06, 0.76 to 1.49; *p* = 0.73
Ectopic pregnancy	0/2025 (–)	2/2013 (< 1)	–
Stillbirth (interuterine death at ≥ 24 weeks)	5/2025 (< 1)	6/2013 (< 1)	0.82, 0.25 to 2.66; *p* = 0.74
Termination[e]	34/2025 (2)	36/2013 (2)	0.94, 0.59 to 1.50; *p* = 0.81
Secondary maternal outcomes – other outcomes (in live births at ≥ 24 weeks)			
Twins,[f] *n/N* (%)	29/1581 (2)	22/1523 (1)	1.28, 0.74 to 2.22; *p* = 0.38
Mode of delivery, n/N *(%)*			
Unassisted vaginal	845/1577 (53)	794/1515 (52)	1.02,0.96 to 1.10; *p* = 0.39
Instrumental vaginal	224/1577 (14)	199/1515 (13)	1.08, 0.91 to 1.29; *p* = 0.37
Vaginal breech delivery	4/1577 (< 1)	7/1515 (< 1)	0.55, 0.16 to 1.88; *p* = 0.34
Elective C-section	257/1577 (16)	224/1515 (15)	1.10, 0.93 to 1.29; *p* = 0.27
Emergency C-section	241/1577 (15)	286/1515 (19)	0.80, 0.69 to 0.94; *p* = 0.006
Other	6/1577 (< 1)	5/1515 (< 1)	–
Missing	4 (–)	8 (–)	–
Secondary neonatal outcomes (in live births at ≥ 24 weeks)			
Gestation at delivery, weeks [mean (SD), *n*][g]	38 $^{+4}$ (2 $^{+4}$), 1581	38 $^{+4}$ (2 $^{+3}$), 1521	0.11, –0 $^{+1}$ to 0 $^{+2}$; *p* = 0.21
Gestation at delivery			
< 28 weeks, *n/N* (%)	19/1581 (1)	14/1521 (1)	1.33, 0.67 to 2.65; *p* = 0.42
< 32 weeks, *n/N* (%)	42/1581 (3)	36/1521 (2)	1.15, 0.74 to 1.78; *p* = 0.54
< 37 weeks, *n/N* (%)	263/1581 (17)	235/1521 (15)	1.07, 0.91 to 1.25; *p* = 0.42
Birthweight, grams [mean (SD), *n*][h]	3242 (656), 1604	3261 (659), 1539	–21, –67 to 25; *p* = 0.37
Birthweight adjusted for gestational age and sex (using intergrowth[i] standards), centiles [mean (SD), *n*]	61.6 (28.2), 1599	61.6 (28.2), 1537	–0.21, –2.16 to 1.74; *p* = 0.84

continued

TABLE 7 Primary and secondary outcome results (*continued*)

Outcome	Progesterone	Placebo	RR[a] or mean difference,[b] 95% CI; *p*-value
Birthweight adjusted for gestational age, sex, parity, maternal BMI and ethnicity (using GROW[j] standards), centiles [mean (SD), *n*]	45.7 (29.4), 1603	45.5 (29.4), 1539	0.12, –1.91 to 2.15; $p = 0.91$
Small for gestational age and sex (using intergrowth[i] standards; proportion < 10th centile), *n*/*N* (%)	78/1599 (5)	98/1537 (6)	0.77, 0.57 to 1.03; $p = 0.07$
Small for gestational age, sex, parity, maternal BMI and ethnicity (using GROW[j] standards; proportion < 10th centile), *n*/*N* (%)	214/1603 (13)	199/1539 (13)	1.02, 0.85 to 1.22; $p = 0.81$
Large for gestational age and sex (using intergrowth[i] standards; proportion ≥ 90th centile), *n*/*N* (%)	308/1599 (19)	295/1537 (19)	1.01, 0.88 to 1.17; $p = 0.86$
Large for gestational age, sex, parity, maternal BMI and ethnicity (using GROW[i] standards; proportion ≥ 90th centile), *n*/*N* (%)	153/1603 (10)	140/1539 (9)	1.03, 0.83 to 1.28; $p = 0.77$
Apgar score at 1 minute [median (IQR), *n*]	9 (9–9), 1533	9 (9–9), 1477	0.05, –0.06 to 0.15; $p = 0.37$
Apgar score at 5 minutes [median (IQR), *n*]	10 (9–10), 1532	10 (9–10), 1478	0.05, –0.02 to 0.13; $p = 0.15$
Arterial cord pH [mean (SD), *n*]	7.2 (0.1), 474	7.2 (0.1), 464	0.003, –0.01 to 0.02; $p = 0.59$
Venous cord pH [mean (SD), *n*]	7.3 (0.1), 505	7.3 (0.1), 495	0.003, –0.01 to 0.01; $p = 0.55$
Death at 28 days of neonatal life,[k] *n*/*N* (%)	8/1605 (1)	2/1533 (< 1)	3.84, 0.80 to 18.40; $p = 0.09$

GROW, gestation-related optimal weight.
a For binary outcomes, RR < 1 favours the progesterone group apart from live birth at ≥ 34 weeks and ongoing pregnancy at 12 weeks where RR > 1 would favour progesterone.
b For continuous outcomes, mean difference < 0 favours the progesterone group.
c A total of five women on progesterone and three women on placebo had both a live birth ≥ 34 weeks and a miscarriage; one women on placebo had both a termination and a miscarriage; and one women on placebo had both a live birth < 34 weeks and a stillbirth.
d Median gestational age (IQR) in progesterone group, 8 (7–10) weeks; median gestational age (IQR) in placebo group, 8 (7–10) weeks.
e Reasons in progesterone group: social, $n = 13$; medical, $n = 21$. Reasons in placebo group: social, $n = 12$; medical, $n = 24$. Median gestational age (IQR) in progesterone group, 14 (12–19) weeks; median gestational age (IQR) in placebo group, 15 (11–18) weeks.
f Total number of babies, $N = 3155$: progesterone group, $n = 1610$; placebo group, $n = 1545$.
g Unknown gestational age: placebo group, $n = 2$.
h Unknown birthweights: progesterone group, $n = 6$; placebo group, $n = 6$.
i Chatfield *et al.*[42]
j Gardosi *et al.*[43]
k Unknown outcome at 28 days of neonatal life: progesterone group, $n = 5$; placebo group, $n = 12$.

miscarriage (adjusted relative risk 0.91, 95% CI 0.81 to 1.01; $p = 0.09$). The median gestational age at the time of miscarriage was 8 weeks (IQR 7–10 weeks) for both groups. Time from conception to the end of pregnancy for any reason is graphically displayed in *Figure 7*.

Other secondary maternal outcomes

Twenty-nine women in the progesterone group and 22 women in the placebo group gave birth to twins (see *Table 7*). There was evidence to suggest that women in the progesterone group were less likely to deliver via emergency C-section (15% in the progesterone group vs. 19% in the placebo group; adjusted relative risk 0.80, 95% CI 0.69 to 0.94; $p = 0.006$). The results of other secondary maternal outcomes appeared similar in both groups, with no significant differences.

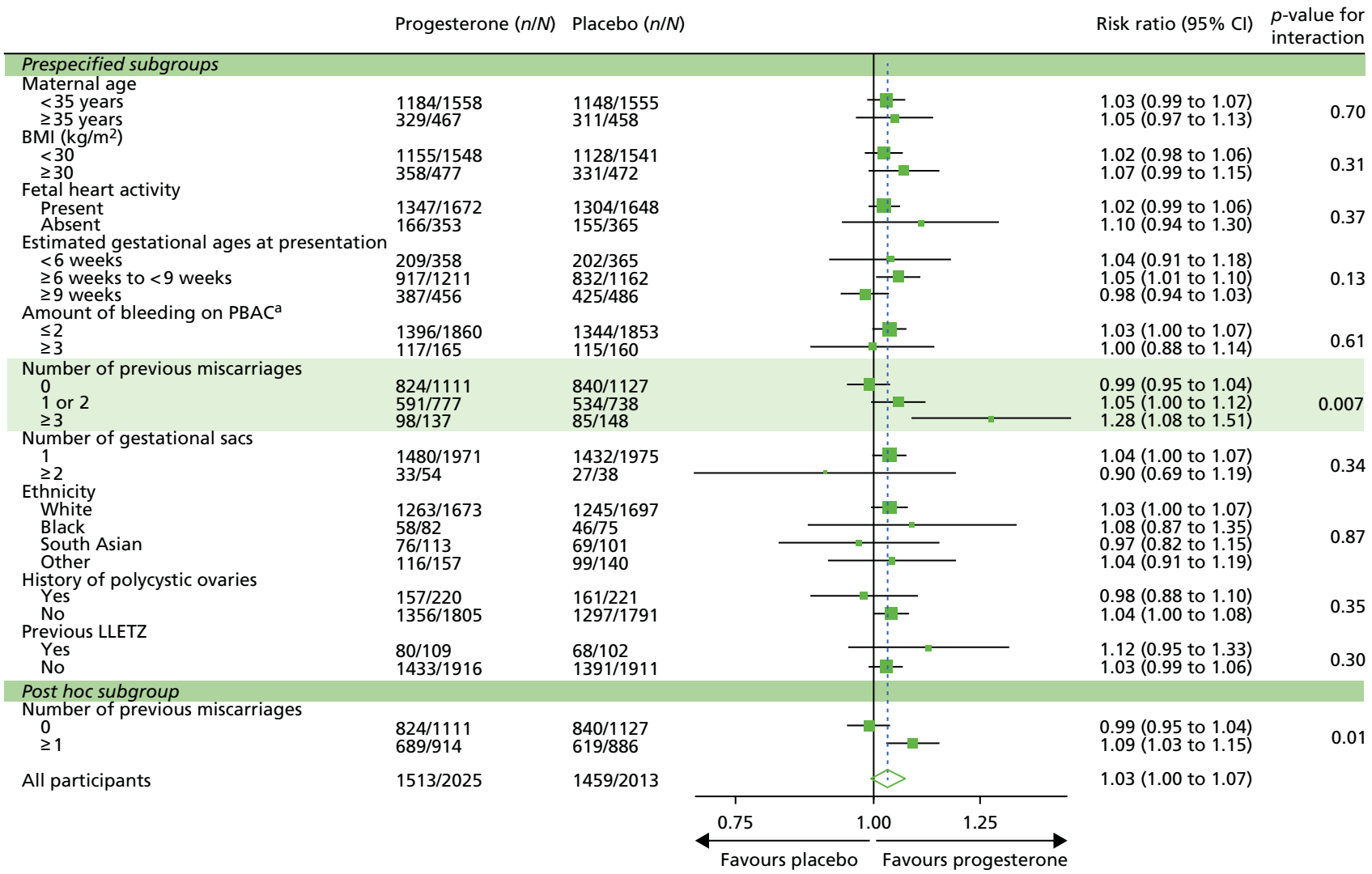


FIGURE 7 Subgroup forest plot. a, PBAC, Pictorial Blood Assessment Chart.[10]

Secondary neonatal outcomes

Overall, the distribution of gestational age at delivery in those women with a live birth was very similar in both groups. Live births were delivered at 38 $^{+4}$ weeks on average in both groups. There were 498 (16%) preterm births (< 37 weeks) observed, but the numbers were very similar in both groups (17% in the progesterone group vs. 15% in the placebo group; adjusted relative risk 1.07, 95% CI 0.91 to 1.25; $p = 0.42$). Birthweights appeared similar across both groups (mean difference –21 g, 95% CI –67 to 25 g; $p = 0.37$), with no evidence of any differences in the numbers of infants being large or small for their gestational age (plus other covariates listed in *Table 7*). No differences were noted in other outcomes. Eight neonatal deaths were observed by 28 days in the progesterone group, compared with two in the placebo group (adjusted relative risk 3.84, 95% CI 0.80 to 18.40; $p = 0.09$).

Pregnancy-related complications

Complication rates of antenatal, intrapartum, postpartum and neonatal complications appeared similar for both groups (*Table 8*). The denominators throughout *Table 8* differ across each outcome as they are based on the number of completed responses for that relevant outcome.

TABLE 8 Complication rates

Type of complication	Progesterone	Placebo	RR,[a] 95% CI; *p*-value
Maternal antenatal complications (all women randomised),* n/N *(%)			
Pregnancy-induced hypertension	46/2019 (2)	56/2005 (3)	0.82, 0.56 to 1.21; $p = 0.31$
Pre-eclampsia	27/2019 (1)	43/2005 (2)	0.63, 0.39 to 1.01; $p = 0.06$
Obstetric cholestasis	24/2019 (1)	27/2005 (1)	0.89, 0.51 to 1.53; $p = 0.67$
Cervical cerclage[b]	10/2019 (< 1)	16/2005 (1)	0.61, 0.28 to 1.34; $p = 0.22$
Preterm (< 37 weeks) pre-labour rupture of membranes	120/2019 (6)	118/2005 (6)	1.02, 0.80 to 1.30; $p = 0.88$
Gestational diabetes mellitus by GTT	114/2019 (6)	103/2005 (5)	1.10, 0.85 to 1.42; $p = 0.48$
Hyperemesis gravidarum	36/2019 (2)	45/2005 (2)	
Uterine artery abnormality[c]	7/206 (3)	11/205 (5)	
Umbilical artery raised resistance[d]	7/600 (1)	9/608 (1)	
Absent umbilical artery end-diastolic flow[d]	2/600 (< 1)	2/608 (< 1)	
Threatened preterm (< 37 weeks) birth requiring tocolysis or steroids	80/2019 (4)	84/2005 (4)	
Antepartum haemorrhage	101/2019 (5)	99/2005 (5)	
Psychological conditions	117/2019 (6)	120/2005 (6)	
Intrapartum complications,* n/N *(%)			
Chorioamnionitis	10/1581 (1)	12/1523 (1)	0.81, 0.35 to 1.89; $p = 0.63$
Intrauterine growth restriction	45/1581 (3)	42/1523 (3)	1.03, 0.68 to 1.56; $p = 0.88$
Macrosomia	16/1581 (1)	9/1523 (1)	1.68, 0.75 to 3.78; $p = 0.21$
Cord prolapse	3/1581 (< 1)	3/1523 (< 1)	
Placenta praevia	7/1581 (< 1)	12/1523 (1)	
Non-reassuring cardiotocography	194/1581 (12)	212/1523 (14)	
Fetal blood sampling	12/1581 (1)	24/1523 (2)	

TABLE 8 Complication rates (*continued*)

Type of complication	Progesterone	Placebo	RR,[a] 95% CI; *p*-value
Suspected abruption	10/1581 (1)	19/1523 (1)	
Failure to progress	125/1581 (8)	116/1523 (8)	
Abnormal presentation	45/1581 (3)	50/1523 (3)	
Hypertension/pre-eclampsia	42/1581 (3)	37/1523 (2)	
Psychosocial problems	7/1581 (< 1)	3/1523 (< 1)	
Failed induction	10/1581 (1)	18/1523 (1)	
Meconium	88/1581 (6)	86/1523 (6)	
Antepartum haemorrhage	33/1581 (2)	42/1523 (3)	
Uterine rupture	0/1581 (–)	0/1523 (–)	
Maternal postpartum complications,* n/N *(%)			
Haemorrhage	180/1574 (11)	186/1512 (12)	0.92, 0.76 to 1.12; $p = 0.42$
Pre-eclampsia/eclampsia/HELLP	11/1574 (1)	10/1512 (1)	
Infection	47/1574 (3)	39/1512 (3)	
Admission to HDU	69/1569 (4)	79/1509 (5)	
Admission to ITU	4/1569 (< 1)	0/1509 (–)	
Neonatal complications,* n/N *(%)			
Discharge to hospital	16/1562 (1)	20/1511 (1)	0.77, 0.39 to 1.52; $p = 0.45$
Early infection	72/1595 (5)	78/1524 (5)	0.83, 0.60 to 1.14; $p = 0.25$
Retinopathy of prematurity	1/1595 (< 1)	2/1525 (< 1)	0.48, 0.04 to 5.27; $p = 0.55$
Necrotising enterocolitis	4/1594 (< 1)	8/1525 (1)	0.48, 0.14 to 1.59; $p = 0.23$
Intraventricular haemorrhage	2/1594 (< 1)	1/1525 (< 1)	1.91, 0.17 to 21.08; $p = 0.60$
Congenital abnormalities	53/1574 (3)	51/1511 (3)	1.00, 0.69 to 1.47; $p = 0.99$
Chromosomal or genetic abnormalities	10/1576 (1)	9/1513 (1)	1.07, 0.43 to 2.62; $p = 0.89$
Respiratory distress syndrome	67/1547 (4)	64/1481 (4)	0.97, 0.68 to 1.37; $p = 0.85$
Ventilation or oxygen support	35/1596 (2)	47/1525 (3)	0.71, 0.46 to 1.10; $p = 0.13$
Severe cranial ultrasound abnormality	4/1595 (< 1)	8/1525 (1)	
Periventricular leukomalacia	1/1594 (< 1)	2/1525 (< 1)	
Bell stage 2 or 3	0/1594 (–)	3/1525 (< 1)	
Septic screening within 48 hours	169/1594 (11)	171/1524 (11)	

GTT, glucose tolerance test; HELLP, haemolysis, elevated liver enzymes and low platelet count.
a RR < 1 favours the progesterone group.
b Number of emergency cerclage: progesterone, $n = 2$; placebo, $n = 3$; number of elective cerclage: progesterone, $n = 8$; placebo, $n = 13$.
c Denominator based on number who had an uterine artery Doppler performed.
d Denominator based on number who had an umbilical artery Doppler performed.

Safety data

The number of SAEs was similar in both groups: 105 out of 2025 (5%) compared with 98 out of 2013 (5%), in the progesterone and placebo groups, respectively (*Table 9*). The SAEs were categorised in body systems as detailed in *Table 10*.

TABLE 9 Serious adverse events: overall numbers

Serious adverse event	Progesterone, *n/N* (%)	Placebo, *n/N* (%)	RR, 95% CI; *p*-value
Total number of participants experiencing a SAE (either maternal or neonatal)	105/2025 (5)	98/2013 (5)	1.07, 0.81 to 0.39; $p = 0.65$
Total number of SAEs	133/2025 (7)	126/2013 (6)	
Maternal	83/2025 (4)	83/2013 (4)	
Neonatal	50/2025 (2)	43/2013 (2)	

TABLE 10 Serious adverse events: clinical conversions

Category	Progesterone, *n*	Placebo, *n*
Maternal		
Bone and joint injuries	2	0
Cardiac disorders	1	2
Congenital, familial and genetic disorders	3	0
Endocrine disorders	1	2
Eye disorders	1	0
Gastrointestinal disorders	0	1
General disorders and administration site conditions	1	6
Infections and infestations	2	4
Metabolism and nutrition disorders	0	1
Nervous system disorders	1	2
Pregnancy, puerperium and perinatal conditions	46	46
Renal and urinary disorders	3	2
Reproductive system and breast disorders	11	9
Respiratory, thoracic and mediastinal disorders	10	7
Skin and subcutaneous tissue	0	1
Vascular disorders	1	0
Total	83	83
Neonatal		
Congenital, familial and genetic disorders	23	22
Gastrointestinal disorders	0	1
General disorders and administration site conditions	1	3

TABLE 10 Serious adverse events: clinical conversions (*continued*)

Category	Progesterone, *n*	Placebo, *n*
Metabolism and nutrition disorders	2	1
Nervous system disorders	0	1
Pregnancy, puerperium and perinatal conditions	17	11
Renal and urinary disorders	1	3
Reproductive system and breast disorders	1	0
Respiratory, thoracic and mediastinal disorders	3	1
Skin and subcutaneous tissue	1	0
Vascular disorders	1	0
Total	50	43

Ancillary analyses

Sensitivity analyses

A sensitivity analysis assuming that all missing responses were treatment failures for live birth at ≥ 34 weeks was statistically significant (adjusted relative risk 1.04; 95% CI 1.00 to 1.08; $p = 0.04$), but not when missing responses were simulated using multiple imputation. An analysis carried out where the dating scan was prioritised over the randomisation scan when calculating gestational age had no effect on the output (*Table 11*).

TABLE 11 Primary outcome and miscarriage rate sensitivity analyses

Outcome	Progesterone	Placebo	RR,[a] 95% CI; *p*-value
Live birth at ≥ 34 weeks*, n/N *(%)			
Sensitivity analysis: assume all missing responses are treatment failures	1513/2079 (73)	1459/2074 (70)	1.04, 1.00 to 1.08; $p = 0.04$
Dating scan prioritised over randomisation scan when calculating gestational age	1517/2025 (75)	1463/2013 (73)	1.03, 1.00 to 1.07; $p = 0.08$
Simulate missing responses using multiple imputation	–	–	1.03, 1.00 to 1.07; $p = 0.07$
Miscarriage at < 24 weeks*, n/N *(%)			
Sensitivity analysis: assume all missing responses are treatment failures	464/2079 (22)	512/2074 (25)	0.90, 0.81 to 1.01; $p = 0.07$
Dating scan prioritised over randomisation scan when calculating gestational age	410/2025 (20)	451/2013 (22)	0.91, 0.81 to 1.01; $p = 0.09$
Simulate missing responses using multiple imputation	–	–	0.90, 0.79 to 1.01; $p = 0.07$

a RR > 1 favours the progesterone group for live birth at ≥ 34 weeks; RR < 1 favours the progesterone group for miscarriage at < 24 weeks.

Subgroup analyses

The output from the subgroup analyses for the primary outcome of live birth at ≥ 34 weeks can be seen in *Table 12* and *Figures 7* and *8*. All tests for subgroup by treatment group interaction were non-significant apart from number of previous miscarriages. Here, there was evidence that the number of live births was higher in the progesterone group than in the placebo group (72% in the progesterone group vs. 57% in the placebo group; relative risk 1.28, 95% CI 1.08 to 1.51; $p = 0.007$) for those who had three or more previous miscarriages. Further post hoc subgroup analysis on the number of previous miscarriages, where the subgroup was split into none compared with ≥ 1 previous miscarriage, suggested that progesterone was effective in those who had ≥ 1 previous miscarriage (75% in the progesterone group vs. 70% in the placebo group; relative risk 1.09; 95% CI 1.03 to 1.15; $p = 0.01$).

TABLE 12 Primary outcome subgroup analyses

Subgroup	Progesterone, *n/N* (%)	Placebo, *n/N* (%)	RR,[a] 95% CI; *p*-value	Interaction *p*-value
Live birth at ≥ 34 weeks				
Maternal age (years)				
< 35	1184/1558 (76)	1148/1555 (74)	1.03, 0.99 to 1.07; $p = 0.16$	$p = 0.70$
≥ 35	329/467 (70)	311/458 (68)	1.05, 0.97 to 1.13; $p = 0.27$	
BMI (kg/m²)				
< 30	1155/1548 (75)	1128/1541 (73)	1.02, 0.98 to 1.06; $p = 0.28$	$p = 0.31$
≥ 30	358/477 (75)	331/472 (70)	1.07, 0.99 to 1.15; $p = 0.09$	
Fetal heart activity				
Present	1347/1672 (81)	1304/1648 (79)	1.02, 0.99 to 1.06; $p = 0.18$	$p = 0.37$
Absent	166/353 (47)	155/365 (42)	1.10, 0.94 to 1.30; $p = 0.23$	
Estimated gestational age at presentation				
< 6 weeks	209/358 (58)	202/365 (55)	1.04, 0.91 to 1.18; $p = 0.59$	$p = 0.13$
≥ 6 weeks to < 9 weeks	917/1211 (76)	832/1162 (72)	1.06, 1.01 to 1.10; $p = 0.02$	
≥ 9 weeks	387/456 (85)	425/486 (87)	0.98, 0.94 to 1.03; $p = 0.53$	
Amount of bleeding on PBAC[20]				
≤ 2	1396/1860 (75)	1344/1853 (73)	1.03, 1.00 to 1.07; $p = 0.06$	$p = 0.61$
≥ 3	117/165 (71)	115/160 (72)	1.00, 0.88 to 1.14; $p = 0.99$	
Number of previous miscarriages				
0	824/1111 (74)	840/1127 (75)	0.99, 0.95 to 1.04; $p = 0.72$	$p = 0.007$
1/2	591/777 (76)	534/738 (72)	1.05, 1.00 to 1.12; $p = 0.07$	
≥ 3	98/137 (72)	85/148 (57)	1.28, 1.08 to 1.51; $p = 0.004$	

TABLE 12 Primary outcome subgroup analyses (*continued*)

Subgroup	Progesterone, *n/N* (%)	Placebo, *n/N* (%)	RR,[a] 95% CI; *p*-value	Interaction *p*-value
Post hoc number of previous miscarriages				
0	824/1111 (74)	840/1127 (75)	0.99, 0.95 to 1.04; $p = 0.72$	$p = 0.01$
≥ 1	689/914 (75)	619/886 (70)	1.09, 1.03 to 1.15; $p = 0.003$	
Number of gestational sacs				
1	1480/1971 (75)	1432/1975 (73)	1.04, 1.00 to 1.07; $p = 0.05$	$p = 0.34$
≥ 2	33/54 (61)	27/38 (71)	0.90, 0.69 to 1.19; $p = 0.47$	
Ethnicity				
White	1263/1673 (75)	1245/1697 (73)	1.03, 1.00 to 1.07; $p = 0.08$	$p = 0.87$
Black	58/82 (71)	46/75 (61)	1.08, 0.87 to 1.35; $p = 0.47$	
South Asian	76/113 (67)	69/101 (68)	0.97, 0.82 to 1.15; $p = 0.74$	
Other	116/157 (74)	99/140 (71)	1.04, 0.91 to 1.19; $p = 0.56$	
History of polycystic ovaries (yes/no)				
Yes	157/220 (71)	161/221 (73)	0.98, 0.88 to 1.10; $p = 0.74$	$p = 0.35$
No	1356/1805 (75)	1297/1791 (72)	1.04, 1.00 to 1.08; $p = 0.04$	
Previous LLETZ				
Yes	80/109 (73)	68/102 (67)	1.12, 0.95 to 1.33; $p = 0.17$	$p = 0.30$
No	1433/1916 (75)	1391/1911 (73)	1.03, 0.99 to 1.06; $p = 0.14$	

a RR < 1 favours the progesterone group.

Subgroup analyses for the outcome of miscarriage (at < 24 weeks) can be seen in *Table 13*. The results were similar to the primary outcome subgroup analyses, with the only evidence of a differential effect observed in the subgroup of number of previous miscarriages. Here, in those with three or more previous miscarriages, there was some evidence that progesterone was effective (23% in the progesterone group vs. 36% in the placebo group; relative risk 0.58, 95% CI 0.40 to 0.83; $p = 0.003$).

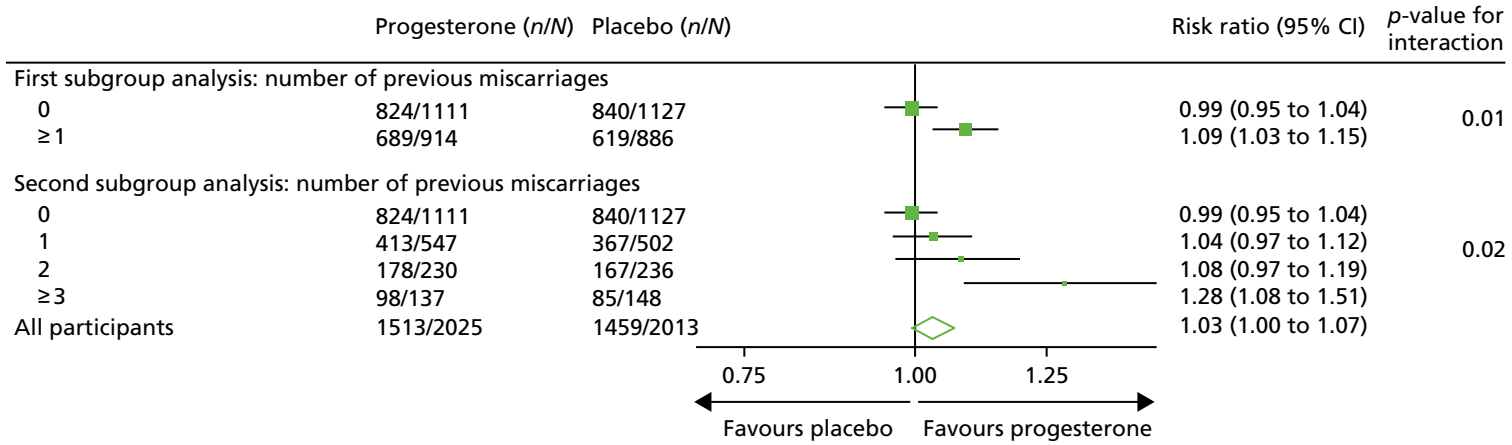


FIGURE 8 Post hoc subgroup analyses. The results are reported as point estimates and 95% CIs. The widths of the CIs have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

TABLE 13 Miscarriage subgroup analyses

Subgroup	Progesterone, *n/N* (%)	Placebo, *n/N* (%)	RR,[a] 95% CI; *p*-value	Interaction *p*-value
Miscarriage at < 24 weeks				
Maternal age (years)				
< 35	297/1558 (19)	329/1555 (21)	0.92, 0.80 to 1.05; $p = 0.19$	$p = 0.80$
≥ 35	113/467 (24)	122/458 (27)	0.89, 0.72 to 1.09; $p = 0.25$	
BMI (kg/m^2)				
< 30	315/1548 (20)	331/1541 (21)	0.95, 0.83 to 1.08; $p = 0.39$	$p = 0.20$
≥ 30	95/477 (20)	120/472 (25)	0.80, 0.64 to 1.00; $p = 0.05$	
Fetal heart activity				
Present	237/1672 (14)	260/1648 (16)	0.88, 0.75 to 1.03; $p = 0.11$	$p = 0.51$
Absent	173/353 (49)	191/365 (52)	0.95, 0.81 to 1.10; $p = 0.48$	
Estimated gestational age at presentation				
< 6 weeks	136/358 (38)	143/365 (39)	1.01, 0.83 to 1.21; $p = 0.96$	$p = 0.18$
≥ 6 weeks to < 9 weeks	237/1211 (20)	274/1162 (24)	0.83, 0.72 to 0.96; $p = 0.01$	
≥ 9 weeks	37/456 (8)	34/486 (7)	1.10, 0.71 to 1.69; $p = 0.68$	
Amount of bleeding on PBAC[20]				
≤ 2	374/1860 (20)	413/1853 (22)	0.91, 0.81 to 1.02; $p = 0.11$	$p = 0.90$
≥ 3	36/165 (22)	38/160 (24)	0.89, 0.61 to 1.28; $p = 0.52$	
Number of previous miscarriages				
0	229/1111 (21)	244/1127 (22)	0.96, 0.82 to 1.11; $p = 0.55$	$p = 0.03$
1/2	150/777 (19)	154/738 (21)	0.95, 0.78 to 1.15; $p = 0.57$	
≥ 3	31/137 (23)	53/148 (36)	0.58, 0.40 to 0.83; $p = 0.003$	
Number of gestational sacs				
1	393/1971 (20)	442/1975 (22)	0.90, 0.80 to 1.01; $p = 0.07$	$p = 0.57$
≥ 2	17/54 (31)	9/38 (24)	1.08, 0.57 to 2.05; $p = 0.81$	
Ethnicity				
White	337/1673 (20)	370/1697 (22)	0.92, 0.81 to 1.04; $p = 0.16$	$p = 0.67$
Black	20/82 (24)	20/75 (27)	1.11, 0.65 to 1.88; $p = 0.71$	
South Asian	26/113 (23)	28/101 (28)	0.89, 0.58 to 1.35; $p = 0.57$	
Other	27/157 (17)	33/140 (24)	0.73, 0.47 to 1.13; $p = 0.16$	
History of polycystic ovaries (yes/no)				
Yes	43/220 (20)	50/221 (23)	0.86, 0.61 to 1.22; $p = 0.40$	$p = 0.76$
No	367/1805 (20)	401/1791 (22)	0.91, 0.81 to 1.03; $p = 0.13$	
Previous LLETZ				
Yes	21/109 (19)	27/102 (26)	0.63, 0.40 to 1.00; $p = 0.05$	$p = 0.12$
No	389/1916 (20)	424/1911 (22)	0.93, 0.83 to 1.04; $p = 0.19$	

a RR < 1 favour the progesterone group for miscarriage.

Chapter 4 Health economic analysis

Introduction

The economic evaluation conducted alongside the PRISM trial is reported in this chapter. The primary objective of the trial was to investigate whether or not progesterone used by women with bleeding in early pregnancy (up to 16 weeks of gestation) can prevent miscarriage and lead to live births at ≥ 34 weeks of pregnancy. The overall aim of the economic evaluation was to assess the relative cost-effectiveness of progesterone compared with placebo in these women.

Methods

A within-trial incremental cost-effectiveness analysis (CEA) was performed from the perspective of the NHS and the NHS/PSS.[44] The CEA results are expressed in terms of cost per additional live birth at ≥ 34 completed weeks of gestation. Given that the duration of the trial was less than 1 year, neither costs nor outcomes were discounted. The health economic analysis was reported following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[45]

Outcomes

The primary outcome of the CEA was live births at ≥ 34 completed weeks of gestation based on the principal outcome of the clinical trial. Gestational age was estimated based on participants' ultrasonography result and 11–14 weeks, when available, or otherwise based on the ultrasonography at randomisation. An additional outcome of the PRISM trial was neonatal survival at 28 days post partum, and this was explored as a secondary outcome in the CEA.

Data

Resource use and costs

Data on all resources consumed in the hospital setting by each woman from randomisation to hospital discharge were collected prospectively using researcher-recorded trial collection forms. The use of other services provided by the community during the same period was captured retrospectively via health services self-completed questionnaires. Unit costs for each resource item (*Table 14*) were identified from established national sources.[47,50] All costs were expressed in 2017–18 Great British pounds. Cost estimates from earlier years were inflated to 2017–18 prices using the Hospital and Community Health Services (HCHS) pay and prices index.[50] Hospital-related unit costs values were obtained from the *NHS Reference Costs 2016/17*[47] where available. Otherwise, these costs were obtained from reference costs for earlier years or from other sources, such as the Personal Social Services Research Unit (PSSRU) costs. In cases where there are different categories associated with a resource use, weighted averages were used (see *Table 14*).

Resource use data within the hospital setting (inpatient and outpatient) focused on the:

- quantity of progesterone administered
- antenatal period
- intrapartum period
- postnatal period (maternal and neonatal).

TABLE 14 Unit costs of resource items (2017–18 prices)

Resource use items	Unit cost (£)[a]	Source[b]
Intervention		
Progesterone (Utrogestan®) 200 mg	4	BNF 2018[46]
Antenatal period		
Antenatal hospital visit	468	*NHS Reference Costs 2016/17*[47] (NZ16Z)
Antenatal DAU	125	*NHS Reference Costs 2016/17*[47] (NZ22Z)
Emergency visit	118	*NHS Reference Costs 2013/14*[48] (NZ23Z)
Inpatient admission (< 24 hours)	303	*NHS Reference Costs 2016/17*[47] (NZ20B)
Night of patient admission	395	PSSRU 2002[49]
Delivery mode		
Unassisted vaginal delivery (without complications)	1840	*NHS Reference Costs 2016/17*[47] (NZ30C)
Unassisted vaginal delivery (with complications)	2187	*NHS Reference Costs 2016/17*[47] (NZ30A NZ30B)
Instrumental vaginal delivery (without complications)	2302	*NHS Reference Costs 2016/17*[47] (NZ40C)
Instrumental vaginal delivery (with complications)	2446	*NHS Reference Costs 2016/17*[47] (NZ40A NZ40B)
Elective C-section (without complications)	3257	*NHS Reference Costs 2016/17*[47] (NZ50C)
Elective C-section (with complications)	4079	*NHS Reference Costs 2016/17*[47] (NZ50A NZ50B)
Emergency C-section (without complications)	4378	*NHS Reference Costs 2016/17*[47] (NZ51C)
Emergency C-section (with complications)	5678	*NHS Reference Costs 2016/17*[47] (NZ51A NZ51B)
Vaginal breech delivery (without complications)	1840	*NHS Reference Costs 2016/17*[47] (NZ30C)
Vaginal breech delivery (with complications)	2187	*NHS Reference Costs 2016/17*[47] (NZ30A NZ30B)
Management		
Spontaneous resolution	619	*NHS Reference Costs 2016/17*[47] (MB08B)
Surgical management	1880	*NHS Reference Costs 2016/17*[47] (MB08A)
Medical management	1880	*NHS Reference Costs 2016/17*[47] (MB08A)
Postnatal period		
Admission to HDU (level 2 care)	965	*NHS Reference Costs 2016/17*[47] (XC06Z)
Admission to ITU (level 3 care)	1586	*NHS Reference Costs 2016/17*[47] (XC01Z to XC05Z)
Hospital visit	145	PSSRU 2002[49]
Day assessment unit	125	*NHS Reference Costs 2016/17*[47] (NZ22Z)
Emergency visit	98	*NHS Reference Costs 2016/17*[47] (VB09Z VB11Z)
Inpatient admissions (< 24 hours)	299	*NHS Reference Costs 2016/17*[47] (NZ26B)
Night of inpatient admissions	395	PSSRU 2002[49]
Neonatal care		
Neonatal intensive care	1318	*NHS Reference Costs 2016/17*[47] (XA01Z)
Neonatal high-dependency care	913	*NHS Reference Costs 2016/17*[47] (XA02Z)
Neonatal special care	514	*NHS Reference Costs 2016/17*[47] (XA03Z to XA04Z)
Primary care services (contacts)		
GP visits	39	PSSRU 2017[50]
Practice/community midwife	30	PSSRU 2015[51]

TABLE 14 Unit costs of resource items (2017–18 prices) (*continued*)

Resource use items	Unit cost (£)[a]	Source[b]
Practice nurse visits	9.5	PSSRU 2017[50]
Psychologist (or counsellor) visits	20	PSSRU 2017[50]
Health visitor visits	22	PSSRU 2015[51]
Social worker visits	20	PSSRU 2017[50]
Number of other community services	21	PSSRU 2017[50]

DAU, day assessment unit.
a Inflated to 2017–18 costs using the UK HCHS pay and prices index.
b Taken from *NHS Reference Costs 2016/17*[47] unless otherwise stated. Where the NHS categories differ from ours, data were extracted from the closest match. Where there are different categories associated with a resource use, weighted averages were used.

Data were collected for primary care resources such as:

- contacts with GPs
- contacts with community midwives.

Progesterone

The quantity of progesterone vaginal pessaries was calculated based on the number of days they were used from randomisation until the end of 16 weeks of gestation (or earlier if miscarriage occurred before 16 weeks). The cost of progesterone was identified from the BNF[46] as £21 for a 21-pessary pack. In the trial, each woman used four pessaries daily, which is equivalent to a cost of £4 per day (see *Table 14*).

Antenatal period

For the antenatal period, resource use data were collected on the number of hospital, day assessment unit (DAU) and emergency visits as well as the number of inpatient day admissions (for a stay of < 24 hours) and nights of inpatient admissions. Based on the descriptions in the trial literature, the costs of antenatal hospital (routine observation) and DAU (antenatal specialised non-routine ultrasound scan) visits were obtained from the *NHS Reference Costs 2016/17*.[47]

For inpatient day admission (< 24 hours), this was described in the trial as a day-case management of an antenatal disorder.[47] Emergency visit (antenatal diagnostic procedures) costs were provided from the *NHS Reference Costs 2013 to 2014*,[48] whereas inpatient night admissions costs were obtained from an earlier PSSRU cost.[49] Because all participants in the trial underwent routine ultrasonography at specified times in the study, the cost of an ultrasound was not included in the analysis.

Intrapartum period

The resource use collected at the end of pregnancy varied depending on whether or not the baby was born alive. Where live births occurred, the onset of labour was recorded as spontaneous, augmented, pre-labour C-section or induced. Information on the mode of delivery included unassisted vaginal deliveries, instrumental vaginal deliveries, elective C-sections, emergency C-sections or vaginal breech deliveries with or without intrapartum complications. Deliveries such as water births and home deliveries were captured as 'others'.

The Healthcare Resource Group (HRG) unit costs[47] for delivery mode are categorised as normal vaginal delivery, assisted vaginal delivery, planned C-section and emergency C-section, corresponding to unassisted

vaginal delivery, instrumental vaginal delivery, elective C-section and emergency C-section on the case report form (CRF), respectively. Each category is grouped further as with or without complications. Weighted averages of the unit costs for the different levels of complications were calculated. As there were no HRG unit costs available for breech delivery or 'other', in consultation with the clinical team, we assumed that the costs were the same as those for a normal vaginal delivery. For labour onset, we assumed that these costs were already accounted for by the delivery mode and, hence, these were not costed separately.

Where babies were not born alive, the outcome was recorded as miscarriage, ectopic pregnancy, termination or stillbirth. The management of such outcomes was recorded as spontaneous resolution, surgical management or medical management. The costs of management were provided in the *NHS Reference Costs* as threatened or spontaneous miscarriage with intervention (medical or surgical management) and without intervention (spontaneous resolution).[47]

Postnatal period

During the postnatal period, data were collected for both maternal and neonatal resource use, from pregnancy end to 28 days post discharge.

Maternal resource use

The unit costs for hospital visits, DAU visits, emergency visits and others that applied to the antenatal period were also relevant to the postnatal period resource use; relevant unit costs are presented in *Table 14*. For postnatal DAU visits and inpatient admissions, the corresponding costs for the antenatal indices were used. The cost of a postnatal emergency visit was obtained using a weighted average of emergency medicine for patients requiring category 0–2 treatment and category 0–1 investigation.[47] Postnatal hospital visit costs were obtained from the PSSRU.[49]

Data collected for immediate maternal postnatal care resource use included admissions to a HDU (level 2 care) or an ITU (level 3 care). Using the UK definitions for level 2 care (patient receiving a single organ support) and level 3 care (patient receiving at least two organ supports),[53] the unit costs for these admissions were obtained from the *NHS Reference Costs 2016/17*.[47] For level 2 care (HDU admissions), 'adult critical care – one organ supported' was used; for level 3 care (ITU admissions), a weighted average was taken across five HRGs [adult critical care (two organs supported) to adult critical care (six or more organs supported)].

Neonatal resource use

The immediate neonatal care resource use included the number of nights receiving intensive care, high-dependency care and special care. Costs for these resources were obtained from the costs schedule.[47]

Serious adverse events

Information on SAEs was collected using SAE forms. In this study, a SAE was defined as an untoward event resulting in maternal death, stillbirth, hospitalisation, persistent or significant disability, congenital anomaly or birth defect. Only clinically specified SAEs deemed to have arisen from the trial intervention were considered to be relevant to the economic analysis. Because there were no SAEs that were clearly related to the use of progesterone, we did not include such costs in the analysis.

Primary care services

Service use questionnaires, completed by a subsample of women, captured data on primary care service resource use in the trial period. These included the number of visits to the GP, practice/community midwife, practice nurse, psychologist (or counsellor), health visitor, social worker and other community services. However, these services were recorded as the number of visits without a specified duration.

The costs for primary care services were obtained from the *Unit Costs of Health and Social Care 2017*.[50] To cost each primary care resource use, we used the recommended average duration of 9.22 minutes for a GP face-to-face visit, 30 minutes for a midwife visit, 15.5 minutes for a GP nurse visit and 20 minutes

for the remaining variables. Because no telephone contacts with the GP or practice nurse were recorded, we did not include these costs.

Primary economic analysis

A within-trial incremental CEA was conducted to estimate the relative costs and benefits of progesterone compared with placebo. The cost-effectiveness of progesterone was expressed in terms of the cost per additional live birth after ≥ 34 complete weeks of gestation. The base-case primary analysis focused on the hospital-related (inpatient and outpatient) costs for the participants incurred in the trial period.

Using study-specific resource use and costs, the total cost over the trial period was calculated by multiplying the resource items used by the corresponding unit cost and adding up all items. The mean total costs and mean total resource use for participants across the trial arms were calculated. Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, we calculated 95% CIs around mean differences through the analyses of 1000 resamples using the bias-corrected and accelerated (BCa) bootstrap method.[54]

To explore heterogeneity in the trial population, multivariate cost analyses were performed using seemingly unrelated regressions.[55,56] Seemingly unrelated regression has been shown to be robust to skewed data and allows for a correlation in the error terms between costs and outcomes.[57] Model covariates included baseline data on age, BMI, the quantity of bleeding and the number of previous miscarriages. The selection of covariates was informed by the prognostic variables used by the clinical team. All results were presented as mean values with SD and, where applicable, as mean differences in costs and effects with 95% CIs.

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in mean total cost between the trial arms by the difference in the number of live births at ≥ 34 weeks. The ICER is a measure that depicts the additional cost ascribed to an additional effect. To calculate ICERs, the formula below was used, with C representing cost and E representing effects:

$$\text{ICER} = \frac{C_{\text{progesterone}} - C_{\text{placebo}}}{E_{\text{progesterone}} - E_{\text{placebo}}}. \quad (1)$$

To quantify the uncertainty that typically occurs as a result of variations in sampling, we used non-parametric bootstrapping to resample the joint distribution in the mean cost and outcome difference.[58] This generated 5000 paired estimates of incremental costs and outcomes, which were plotted in a cost-effectiveness plane as a scatterplot.[59] A cost-effectiveness plane is a four-quadrant plane depicting bootstrap estimates. Based on the location of the scatterplot dots on the quadrant, an intervention may be deemed more effective and less costly (south-east), more effective and more costly (north-east), less effective and more costly (north-west) or less effective and less costly (south-west) than the alternative intervention.

A cost-effectiveness acceptability curve (CEAC) was constructed to show the probability that progesterone is a cost-effective intervention compared with placebo across a range of values, representing the decision-maker's willingness to pay (WTP) for an additional benefit.[44] Currently, there is no standard valuation for an additional live birth.[2,60] In the UK, NICE typically uses a WTP threshold of £20,000–30,000 per quality-adjusted life-year (QALY) in approving a health-care intervention.[44]

Secondary economic analyses

Secondary analyses involving ICER calculations on the primary outcome are based on the following costs.

- Hospital-related costs for resource use for women only: the hospital-related costs for women included antenatal, intrapartum and postnatal care costs. We excluded the neonatal care costs accrued by infants from the total cost for this analysis to examine which aspect of cost had the largest effect on the result – the women's cost or the neonatal care cost.

- Hospital and primary care costs: here we added primary care costs such as GP and practice nurse visits to the hospital costs. This analysis was conducted to explore the perspective of the NHS/PSS.
- Adjusting for missing data: the main base-case analysis was carried out on only individuals for whom there were outcome data. For this analysis, we included participants who were lost to follow-up. We assumed that all women lost to follow-up had a miscarriage and we imputed the costs for this subgroup. Missing costs were imputed using multiple imputations[61] by applying chained equations with predictive mean matching across 60 imputations.[62]
- Hospital-related costs for women with three or more previous miscarriages: preliminary results suggested that there was clinical effectiveness for women with three or more previous miscarriages. Therefore, we conducted a CEA for this subgroup.

We also carried out a secondary incremental CEA based on the final end point using hospital-related costs for participants with complete data. We reported the analysis in terms of cost per additional baby who survived beyond 28 days after birth for each woman.

Sensitivity analysis

Deterministic sensitivity analyses were conducted to explore the inherent uncertainty in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. This involved varying some of the parameters while leaving others at their baseline value. A number of sensitivity analyses were conducted, as detailed below.

- Fixed cost of treatment until 16 weeks of gestation. In the PRISM trial, women in early pregnancy started treatment from randomisation until 16 weeks' gestation. If it is assumed that all women started treatment at approximately 7.4 weeks (52 days) with no miscarriage and continued treatment until 16 weeks (112 days) of gestation, this would translate to 60 days of treatment. Based on the progesterone vaginal pessary cost of £4 per day (as described above for four pessaries) and assuming that on day 1 participants used two pessaries, the expected cost of progesterone is £238 [2 + (59 × 4)]. In a real-life scenario, the intervention would be provided for the expected treatment period (from 6 to 8 weeks) until 16 weeks, and hence we explored the impact of a fixed cost of progesterone until 16 weeks of gestation.
- Unit costs. We explored the impact of alternative cost estimates. For inpatient night of admission for both the antenatal and postnatal periods, we replaced the cost used in the primary analysis with the cost of excess bed-days (£311).[47] The cost of management of miscarriage used in the main analyses was obtained from the *NHS Reference Costs*.[47] However, the NICE guideline on miscarriage management[3,63] provides an estimate of £1522 for medical management and £1827 for surgical management. These values have been used by other studies.[13] For the sensitivity analysis, we replaced the costs of management with these costs.
- Primary care costs. We imputed the missing costs for primary care costs using multiple imputations[61] by applying chained equations with predictive mean matching across 60 imputations.[62] All statistical analyses were performed using Stata version 14 (StataCorp LP, College Station, TX, USA).

Model-based analysis

Preliminary results showed that there was no clinically detectable effect on neonatal outcomes as a result of the PRISM trial that was a result of progesterone. This finding is in keeping with an earlier study in which women were given progesterone.[2,64] In view of this result, modelling costs and outcomes beyond the trial period was not deemed necessary.

Results

A total of 4153 women were recruited to the PRISM trial and randomised to either the progesterone ($n = 2079$) or the placebo ($n = 2074$) arm. Among the 4153 women recruited, 30 women withdrew from the trial and 85 women were lost to follow-up. Hence, the base-case primary analysis was conducted for 4038 participants: 2025 in the progesterone arm and 2013 in the placebo arm.

Outcomes

The details of the major outcomes of the trial are presented in *Table 15*. At the end of pregnancy, 1513 (74.72%) and 1459 (72.48%) women in the progesterone and placebo arms, respectively, had live births after 34 completed weeks of pregnancy. This translates to an effect difference of approximately 2.2% (0.022, 95% CI –0.004 to 0.050). Among women who had live births during the trial period, babies born to 1538 out of 2025 (75.95%) women in the progesterone arm and 1487 out of 2013 (73.87%) women in the placebo arm survived beyond 28 days of birth.

Resource use and costs

A breakdown of the resource use data by trial arm is presented in *Table 16*. Mean health-care costs per participant by trial arm are presented in *Table 17*. During the trial, 2023 women in the intervention arm received progesterone and 2009 women in the non-intervention arm received placebo. Based on the mean number of days that participants utilised progesterone pessaries, the average cost of the intervention was calculated to be £204 (95% CI £200 to £207) per woman (see *Table 17*). The most substantial costs accrued during the trial by participants were from antenatal hospital visits, with a mean cost of £2339 (SD £2672) per woman for the progesterone arm and £2334 (SD £2665) per woman for the placebo arm.

TABLE 15 Outcomes across treatment groups

Outcomes	Progesterone, *n*/*N* (%)	Placebo, *n*/*N* (%)	Bootstrap difference (adjusted effect, 95% CI)
Primary outcome			
Live birth beyond 34 weeks[a]	1513/2025 (74.72)	1459/2013 (72.48)	0.022, –0.004 to 0.050
Secondary outcome			
Alive at 28 days post delivery	1538/2025 (75.95)	1487/2013 (73.87)	0.021, –0.005 to 0.048

a See *Table 7*.

TABLE 16 Mean resource use across treatment groups

Resource items	Progesterone (*N* = 2025), mean (SD), *n*	Placebo (*N* = 2013), mean (SD), *n*	Bootstrap difference (adjusted mean difference, 95% CI)
Days receiving progesterone or placebo	50.40 (21.11), 2023	48.43 (22.01), 2009	2.02, 0.72 to 3.31
Antenatal period			
Antenatal hospital visit	5.00 (5.71), 2020	4.99 (5.69), 2005	0.01, –0.34 to 0.36
Day assessment unit	1.32 (2.50), 2020	1.26 (2.38), 2005	0.06, –0.09 to 0.21
Emergency visit	0.81 (1.51), 2020	0.89 (1.59), 2005	–0.07, –0.16 to 0.02
Inpatient admission (< 24 hours)	0.57 (1.02), 2020	0.59 (1.08), 2005	–0.03, –0.09 to 0.04
Nights of admission (duration, days)	0.86 (2.55), 2020	0.96 (2.99), 2005	–0.09, –0.26 to 0.08

continued

TABLE 16 Mean resource use across treatment groups (*continued*)

Resource items	Progesterone ($N = 2025$), mean (SD), *n*	Placebo ($N = 2013$), mean (SD), *n*	Bootstrap difference (adjusted mean difference, 95% CI)
Mode of delivery			
Unassisted vaginal delivery (without cc)	0.34 (0.48), 695	0.33 (0.47), 673	0.009, –0.023 to 0.042
Unassisted vaginal delivery (with cc)	0.07 (0.26), 150	0.06 (0.24), 122	0.014, 0.000 to 0.03
Instrumental vaginal delivery (without cc)	0.05 (0.22), 101	0.05 (0.21), 93	0.004, –0.01 to 0.02
Instrumental vaginal delivery (with cc)	0.06 (0.24), 123	0.05 (0.22), 107	0.008, –0.007 to 0.02
Elective C-section (without cc)	0.10 (0.30), 204	0.09 (0.28), 172	0.015, –0.004 to 0.03
Elective C-section (with cc)	0.03 (0.16), 53	0.03 (0.16), 52	0.000, –0.01 to 0.01
Emergency C-section (without cc)	0.03 (0.17), 59	0.03 (0.16), 56	0.001, –0.009 to 0.01
Emergency C-section (with cc)	0.09 (0.29), 182	0.11 (0.32), 230	–0.024, –0.043 to –0.006
Vaginal breech delivery (without cc)	0.00 (0.02), 1	0.00 (0.03), 3	0.000, –0.002 to 0.001
Vaginal breech delivery (with cc)	0.00 (0.04), 3	0.00 (0.05), 5	–0.001, –0.004 to 0.002
Other (without cc)	0.00 (0.04), 3	0.00 (0.04), 3	0.00, –0.002 to 0.002
Other (with cc)	0.00 (0.04), 3	0.00 (0.03), 2	0.00, –0.002 to 0.003
Miscarriage management			
Spontaneous resolution	0.10 (0.30), 197	0.12 (0.33), 243	–0.007, –0.022 to 0.007
Surgical	0.06 (0.23), 112	0.06 (0.24), 125	–0.023, –0.043 to –0.004
Medical	0.05 (0.21), 97	0.05 (0.21), 91	0.003, –0.001 to 0.015
Postnatal period			
Admission to HDU (level 2 care)	0.05 (0.30), 2006	0.06 (0.46), 1991	–0.01, –0.035 to 0.012
Admission to ITU (level 3 care)	0.00 (0.04), 2006	0.00 (0.03), 1991	0.00, –0.001 to 0.003
Hospital visit	1.03 (2.98), 1984	1.02 (2.88), 1963	0.01, –0.17 to 0.20
Day assessment unit	0.30 (1.35), 1984	0.27 (1.13), 1963	0.03, –0.04 to 0.11
Emergency visit	0.22 (0.84), 1984	0.22 (0.85), 1963	–0.00, –0.06 to 0.05
Inpatient admission	0.40 (0.59), 1984	0.37 (0.60), 1963	0.03, –0.007 to 0.066
Nights of inpatient admission	1.03 (1.99), 1984	0.96 (1.76), 1963	0.07, –0.04 to 0.19
Neonatal period			
Neonatal intensive care	0.48 (4.76), 1565	0.48 (4.57), 1502	–0.00, –0.34 to 0.32
Neonatal high-dependency care	0.42 (4.02), 1565	0.52 (3.90), 1502	–0.10, –0.38 to 0.18
Neonatal special care	1.02 (5.07), 1565	1.16 (4.95), 1503	–0.15, –0.50 to 0.21
Primary care services			
GP contact	0.64 (1.21), 133	0.77 (1.25), 133	–0.12, –0.40 to 0.15
Practice/community midwife contact	2.69 (3.77), 132	1.95 (3.09), 133	0.79, –0.01 to 1.60

TABLE 16 Mean resource use across treatment groups (*continued*)

Resource items	Progesterone ($N = 2025$), mean (SD), *n*	Placebo ($N = 2013$), mean (SD), *n*	Bootstrap difference (adjusted mean difference, 95% CI)
Practice nurse contact	0.18 (0.61), 136	0.16 (0.47), 136	0.02, –0.12 to 0.15
Psychologist (or counsellor) visit	0.18 (1.05), 136	0.05 (0.52), 136	0.15, –0.07 to 0.37
Health visitor visit	0.39 (0.79), 133	0.29 (0.69), 136	0.10, –0.08 to 0.28
Social worker visit (adult)	0.04 (0.51), 136	0.00 (0.00), 136	0.04, –0.02 to 0.11
Other community services	0.16 (0.78), 134	0.13 (0.45), 133	0.02, –0.13 to 0.17

cc, complications.

Note

The primary care mean values were calculated for only participants with complete primary care data.

TABLE 17 Disaggregated costs by trial arms (2017–18 prices)

Resource items	Progesterone ($n = 2025$), mean cost (SD) (£)	Placebo ($n = 2013$), mean cost (SD) (£)	Bootstrap mean cost difference (adjusted mean, 95% CI) (£)
Intervention	204 (84)	0 (0)	204, 200 to 207
Antenatal services			
Hospital visit	2339 (2672)	2334 (2665)	4, –159 to 166
Day assessment unit	164 (312)	158 (297)	8, –11 to 26
Emergency visit	96 (179)	105 (188)	–9, –20 to 2
Inpatient admission	171 (309)	180 (327)	–8, –28 to 12
Nights of admission	341 (1006)	378 (1182)	–36, –102 to 29
Delivery mode			
Unassisted vaginal delivery (without cc)	632 (874)	615 (868)	18, –36 to 71
Unassisted vaginal delivery (with cc)	162 (573)	132 (513)	30, –3 to 63
Instrumental vaginal delivery (without cc)	115 (501)	106 (483)	8, –23 to 39
Instrumental vaginal delivery (with cc)	149 (584)	130 (549)	19, –15 to 53
Elective C-section (without cc)	328 (981)	278 (911)	48, –11 to 108
Elective C-section (with cc)	107 (651)	105 (647)	1, –40 to 41
Emergency C-section (without cc)	128 (737)	122 (720)	5, –38 to 48
Emergency C-section (with cc)	510 (1624)	649 (1807)	–137, –246 to –28
Vaginal breech delivery (without cc)	1 (41)	2 (58)	–1, –4 to 2

continued

TABLE 17 Disaggregated costs by trial arms (2017–18 prices) (*continued*)

Resource items	Progesterone ($n = 2025$), mean cost (SD) (£)	Placebo ($n = 2013$), mean cost (SD) (£)	Bootstrap mean cost difference (adjusted mean, 95% CI) (£)
Vaginal breech delivery (with cc)	3 (84)	5 (109)	–2, –8 to 4
Other (without cc)	3 (71)	3 (71)	0, –4 to 4
Other (with cc)	3 (84)	2 (69)	1, –4 to 6
Miscarriage management			
Spontaneous resolution	60 (183)	75 (202)	–14, –27 to –2
Surgical	104 (430)	117 (454)	–13, –40 to 13
Medical	90 (402)	85 (391)	5, –20 to 30
Postnatal services			
Admission to HDU (level 2 care)	44 (288)	55 (448)	–11, –34 to 12
Admission to ITU (level 3 care)	3 (71)	2 (50)	2, –2 to 6
Hospital visit	150 (431)	148 (417)	2, –23 to 27
Day assessment unit	38 (169)	34 (141)	4, –5 to 14
Emergency visit	21 (82)	22 (83)	0, –6 to 5
Inpatient admission	118 (175)	110 (180)	9, –3 to 20
Night of inpatient admission	406 (786)	378 (694)	29, –19 to 77
Neonatal services			
Neonatal intensive care	627 (6275)	634 (6017)	–10, –442 to 421
Neonatal high-dependency care	387 (3670)	477 (3560)	–93, –344 to 159
Neonatal special care	523 (2605)	595 (2543)	–76, –260 to 109
Primary care services	$n = 136$	$n = 136$	
GP contacts	25 (47)	30 (49)	–5, –16 to 6
Practice/community midwife	81 (113)	57 (93)	24, –1 to 49
Practice nurse contacts	2 (6)	2 (5)	0.18, –1 to 1
Psychologist (or counsellor) visits	4 (20)	1 (10)	3, –1 to 7
Health visitor visits	9 (17)	6 (15)	2, –2 to 6
Social worker visits (adult)	1 (11)	– (–)	1, –0 to 2
Number of other community services	3 (16)	3 (9)	0.36, –3 to 3

Note
The primary care mean values were calculated for only participants with complete primary care data.

During the antenatal period, women allocated to the progesterone arm had, on average, a higher frequency of antenatal and DAU visits but a smaller number of emergency room visits and hospital admissions than women in the placebo arm. During the postnatal period, women in the progesterone arm utilised similar services more than those in the placebo arm except for emergency hospital visits, which were the same for both arms. However, women in the placebo arm had more admissions to the HDU [mean 0.06 (SD 0.46) for placebo vs. mean 0.05 (SD 0.30) for the progesterone arm]. Similarly, babies born to women in the placebo arm had, on average, a greater number of admissions to the HDU [mean 0.52 (SD 3.90) for placebo vs. mean 0.42 (SD 4.02) for the progesterone arm] and neonatal special care [mean 1.16 (SD 4.95) for placebo vs. mean 1.02 (SD 5.07) for the progesterone arm].

For delivery mode, women in the placebo arm had, on average, more emergency C-sections than women in the intervention arm. On average, women in the placebo arm utilised more neonatal care services than those in the intervention arm.

In keeping with the mean resource use, antenatal care costs for DAU and hospital visits were higher in the intervention arm, whereas emergency visits and hospital admissions costs were higher in the placebo arm.

In terms of cost differences, the greatest mean value for the participants was for emergency C-section with complications, which was greater in the placebo group than in the treatment group (–£137, 95% CI –£246 to –£28). The highest cost difference as a result of the intervention was for elective C-section without complication with a mean difference of £48 (95% CI –£11 to £108) per participant. Neonatal care variables were consistently lower in the progesterone group [ITU, –£10 (95% CI –£442 to £421); HDU, –£93 (95% CI –£344 to £159) and special care unit, –£76 (95% CI –£260 to £109)].

Mean total costs

The mean total costs by trial group for different variables are presented in *Table 18*. The average hospital-related service costs per woman for the trial period was £7452 in the progesterone group and £7572 in the placebo group, generating a mean cost difference of –£127 (BCa mean –£127, 95% CI –£759 to £505). The inclusion of the intervention cost (£204) generated a mean difference of £83 (adjusted mean £76, 95% CI –£559 to £711) per woman, which increased slightly to £78 (95% CI –£563). The differences in cost were not statistically significant.

Primary analysis

The primary (base-case) cost-effectiveness outcome of the PRISM trial was the cost for an additional live birth after ≥ 34 completed weeks of pregnancy. The progesterone intervention appeared to be slightly more effective than placebo, resulting in an additional two live births per 100 women (an effect difference of 0.022, 95% CI –0.004 to 0.050) at ≥ 34 weeks' gestation. The ICER, which combines the differences in costs in both groups, is presented in *Table 19*. The administration of progesterone resulted in an estimated additional cost of £83 per woman (adjusted mean £76, 95% CI –£559 to £711).

TABLE 18 Mean costs per woman (2017–18 prices)

Cost	Progesterone ($n = 2025$), mean (SD) (£)	Placebo ($n = 2013$), mean (SD) (£)	Bootstrapped difference, adjusted mean, 95% CI (£)
Intervention	204 (84)	0 (0)	204, 200 to 207
Hospital-related costs	7452 (9935)	7572 (10,616)	–127, –759 to 505
Mean cost	7655 (9952)	7572 (10,616)	76, –559 to 711
Intervention, hospital and primary care	7663 (9953)	7578 (10,617)	78, –563 to 718

TABLE 19 Point estimate ICER for primary analysis using hospital-related costs

Treatment	Mean cost (£)	Mean effect	Cost difference (£) (95% CI)	Effect difference (95% CI)	ICER (£)
Progesterone	7655	0.747	76, –559 to 711	0.022, –0.004 to 0.0501	3305
Placebo	7572	0.725	–	–	–

Given the differences in costs and effects, the point ICER estimate for progesterone compared with placebo was calculated at £3305 per additional live birth.

Figure 9 shows the results of 5000 bootstrap replications plotted on the cost-effectiveness plane for the primary analysis. Each point on the plane depicts a pair of incremental cost and incremental effectiveness estimates for the comparison between progesterone and placebo. This suggests that progesterone is likely to be more effective, given that the majority of the scatterplots are in the south-east and north-east quadrants. However, it is uncertain whether the progesterone intervention is likely to be more costly (north-east) or less costly (south-east) than no intervention.

The CEAC for the primary analysis (*Figure 10*) shows the probability of progesterone being cost-effective at various values of decision-makers' WTP per additional live birth. *Figure 10* indicates that, for thresholds of WTP per additional live birth of > £15,000, there is > 80% probability that progesterone is cost-effective. For WTP thresholds of > £30,000, the probability of cost-effectiveness exceeds 90%.

Secondary analyses

A series of secondary analyses were conducted to explore the impact of varying costs on the primary outcome.

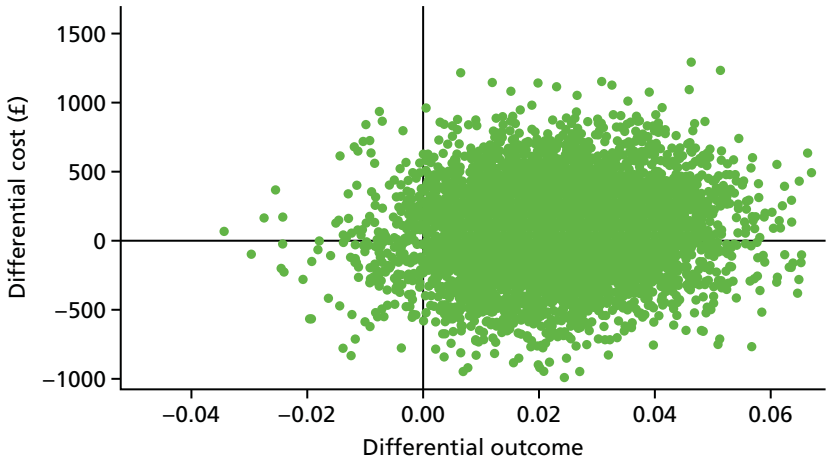


FIGURE 9 Cost-effectiveness plane for the primary analysis using hospital-related costs for the participants. Reproduced from Okeke Ogwulu *et al.*[52] © 2020 The Authors. *BJOG: An International Journal of Obstetrics and Gynaecology* published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

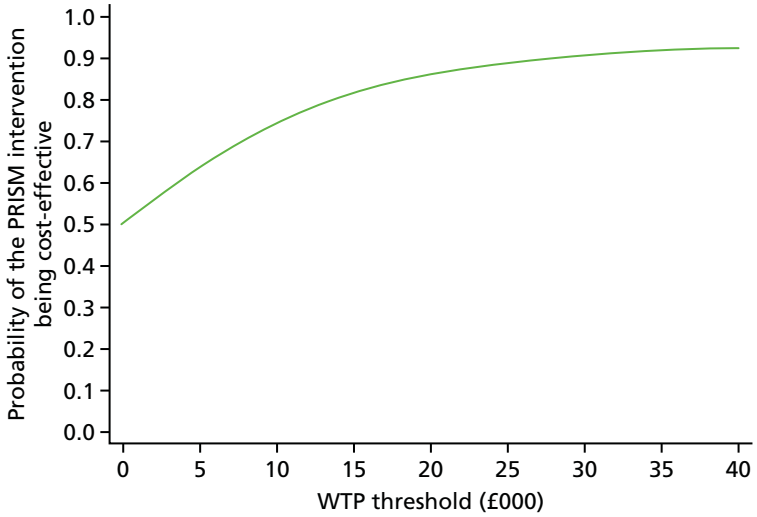


FIGURE 10 The CEAC for the primary analysis using hospital-related costs for the participants. Reproduced from Okeke Ogwulu *et al.*[52] © 2020 The Authors. *BJOG: An International Journal of Obstetrics and Gynaecology* published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Secondary analysis I (hospital-related costs for participants minus neonatal care costs)

For the first secondary analysis, we removed neonatal care costs from the hospital costs. This resulted in an adjusted mean cost difference of £170 (95% CI –£113 to £453) (*Table 20*).

The ICER was calculated as £7370 per additional live birth beyond 34 weeks of gestation. The increased ICER value for this analysis is probably because, on average, women in the placebo arm utilised more neonatal hospital resources than women in the progesterone arm. Hence, the removal of neonatal care costs resulted in a higher cost difference.

The cost-effectiveness plane (*Figure 11*) shows that progesterone is the more effective and more costly intervention, with the majority of the bootstrap replications in the south-east quadrant. The CEAC (*Figure 12*) suggests that, for WTP thresholds of > £12,000 per additional live birth, there is > 95% probability that progesterone is a cost-effective intervention.

Secondary analysis II (hospital and primary care costs for participants)

In another secondary analysis, we included hospital-related costs and primary care costs for the participants. First, we explored the total primary care cost for women with complete primary care service use data; complete data were available for 272 participants. In this subgroup, the mean total cost was £120 for women in the progesterone arm and £98 for women in the placebo arm. For each woman in the progesterone arm, we added £120 to the total hospital-related cost; for each woman in the placebo arm, we added £98 to the total hospital-related cost (*Table 21*). We calculated an additional cost of £106 (adjusted mean £98, 95% CI –£537 to £733) and an ICER of £4264 per additional live birth.

TABLE 20 Point estimate ICER for secondary analysis I (maternal hospital costs)

Treatment	Mean cost (£)	Mean effect	Cost difference (£) (95% CI)	Effect difference	ICER (£)
Progesterone	6467	0.745	170, –113 to 453	0.022	7370
Placebo	6298	0.726	–	–	–

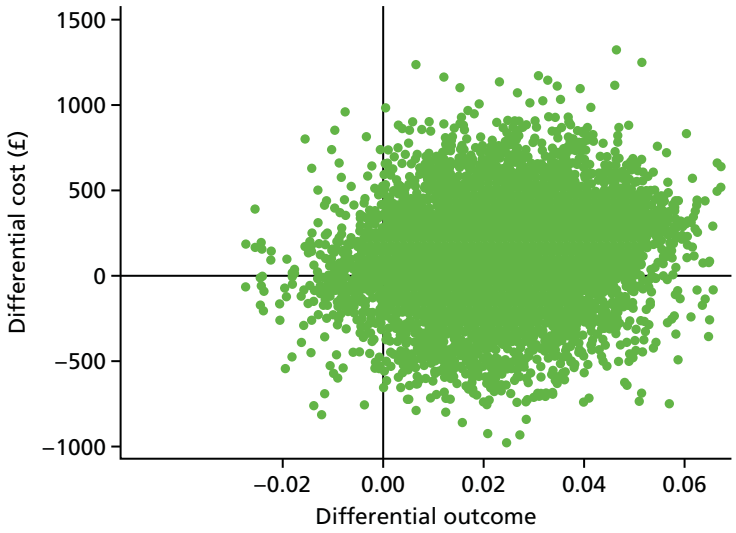


FIGURE 11 Cost-effectiveness plane for secondary analysis I (maternal hospital costs).

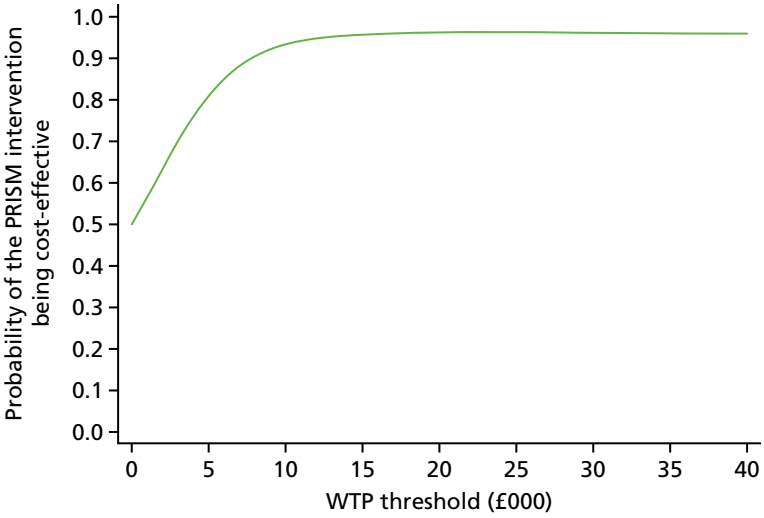


FIGURE 12 The CEAC for secondary analysis I (maternal hospital costs).

TABLE 21 Point estimate ICER for secondary analysis II (hospital and primary care costs)

Treatment	Mean cost (£)	Mean effect	Cost difference (£) (95% CI)	Effect difference	ICER (£)
Progesterone	7776	0.747	98, –537 to 733	0.022	4264
Placebo	7670	0.725	–	–	–

Again, the cost-effectiveness plane (*Figure 13*) clearly suggests that progesterone is more effective. *Figure 14* depicts the CEAC for this analysis. For WTP thresholds of > £15,000, per additional live birth beyond 34 weeks' gestation, the probability of progesterone being more effective than placebo is over 80%. The probability of cost-effectiveness exceeds 90% for WTP thresholds of > £30,000.

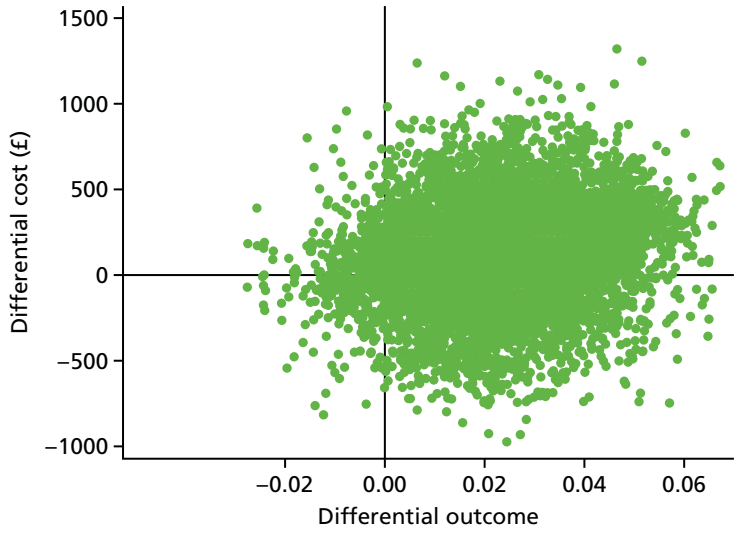


FIGURE 13 Cost-effectiveness plane for secondary analysis II (hospital and primary care costs).

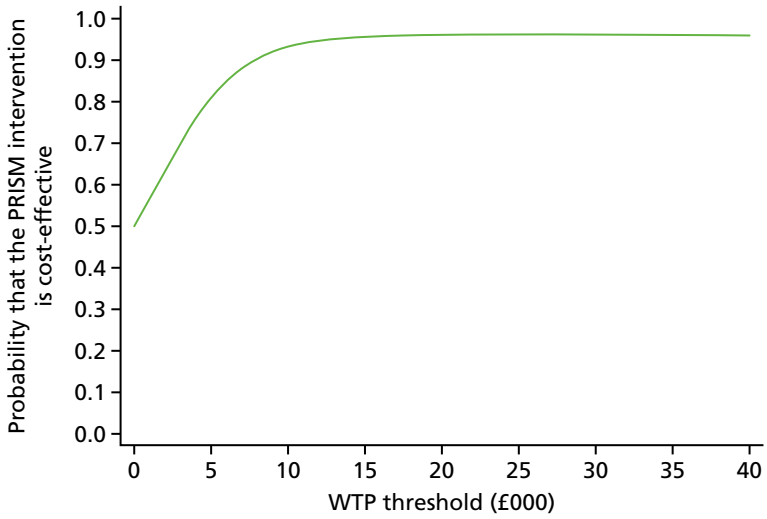


FIGURE 14 The CEAC for secondary analysis II (hospital and primary care costs).

Secondary analysis III (hospital costs for participants including those lost to follow-up)

For this analysis, we included both the women used for the primary base-case analysis and those who were lost to follow-up. We explored a worst-case scenario and assumed that all women lost to follow-up had a miscarriage. We used multiple imputations to impute missing costs and re-ran the primary analysis. This included 2069 participants in the progesterone arm and 2054 participants in the placebo arm.

The results (*Table 22*) showed that progesterone was slightly more costly (cost difference £29, 95% CI –£593 to £651) and more effective than no progesterone for this subgroup, with an ICER of £1378 per additional live birth beyond 34 weeks of gestation.

From the cost-effectiveness plane (*Figure 15*), it is evident that progesterone is more effective; however, it is uncertain which intervention is more costly. The CEAC (*Figure 16*) shows that, for WTP thresholds of > £15,000 per additional live birth beyond 34 weeks of gestation, the probability of progesterone being cost-effective is approximately 85%, and the probability exceeds 90% for WTP thresholds of > £30,000.

TABLE 22 Point estimate ICER for secondary analysis III (hospital costs for participants including those lost to follow-up)

Treatment	Mean cost (£)	Mean effect	Cost difference (£) (95% CI)	Effect difference (95% CI)	ICER (£)
Progesterone	7788	0.731	29, –593 to 651	0.021, –0.007 to 0.049	1378
Placebo	7750	0.710	–	–	–

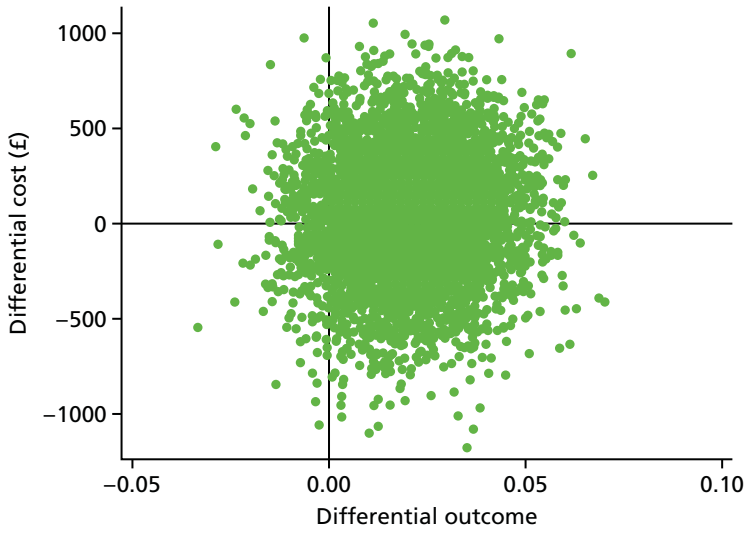


FIGURE 15 Cost-effectiveness plane for secondary analysis III (hospital costs for participants including those lost to follow-up).

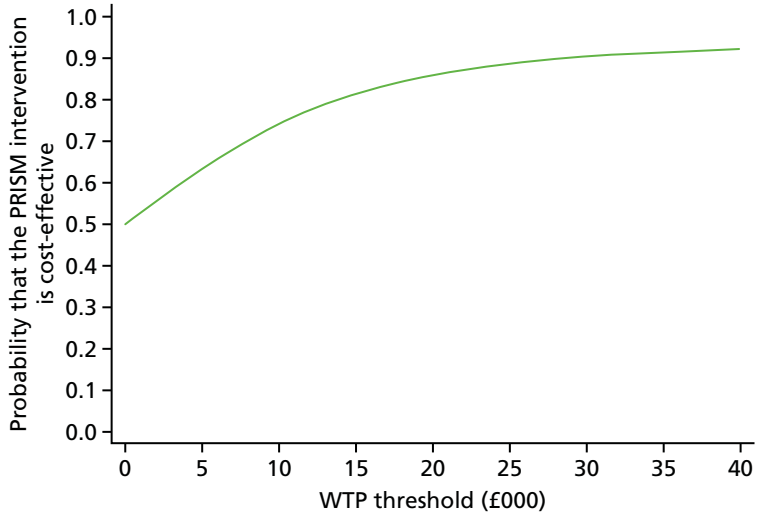


FIGURE 16 The CEAC for secondary analysis III (hospital costs for participants including those lost to follow-up).

Secondary analysis IV (hospital costs for participants with three or more previous miscarriages)

We conducted a subgroup analysis of women with three or more previous miscarriages. This included 137 women in the intervention arm and 148 women in the placebo arm. The intervention was more effective, with an additional gain of 15 live births per 100 women, beyond ≥ 34 weeks' gestation (*Table 23*). An ICER of £11,606 per additional live birth beyond 34 weeks' gestation was calculated for this subgroup.

TABLE 23 Point estimate ICER for participants with three or more previous miscarriages

Treatment	Mean cost (£)	Mean effect	Cost difference (£) (95% CI)	Effect difference (95% CI)	ICER (£)
Progesterone	9304	0.715	1754, –1041 to 4550	0.151, 0.042 to 0.260	11,606
Placebo	7803	0.574	–	–	–

Similarly, the cost-effective plane (*Figure 17*) depicts that progesterone is more effective and more costly with the majority of the bootstrap replications in the south-east quadrant. The CEAC (*Figure 18*) shows over > 90% probability of the intervention being cost-effective for WTP thresholds of > £15,000.

Analyses using secondary outcomes

Incremental CEAs were conducted for the final end point of the PRISM trial (*Table 24*). The analysis was based on the incremental cost of the intervention for an additional baby survival for each woman at 28 days post partum. The effect difference was 0.021 (95% CI –0.005 to 0.048). The ICER for this analysis was £3037 per additional baby who survived beyond 28 days post birth.

Sensitivity analyses

We conducted sensitivity analyses in which we explored different scenarios (*Table 25*). Using alternative cost estimates for nights of hospital admissions and miscarriage management appeared to have a limited effect on the resulting ICER (see *Table 25*).

However, using a fixed cost of progesterone until 16 weeks increased the ICER to £4977 per additional live birth beyond 34 weeks' gestation (see *Table 25*). The cost-effectiveness plane (*Figure 19*) showed dominance in the north-east and south-east quadrants, which indicated that progesterone was more effective and either less costly or more costly. The CEAC (*Figure 20*) shows over 90% probability of the intervention being cost-effective for WTP thresholds of > £25,000. Likewise, the removal of the cost of delivery increased the ICER to £3743 per additional live birth beyond 34 weeks (see *Table 25*).

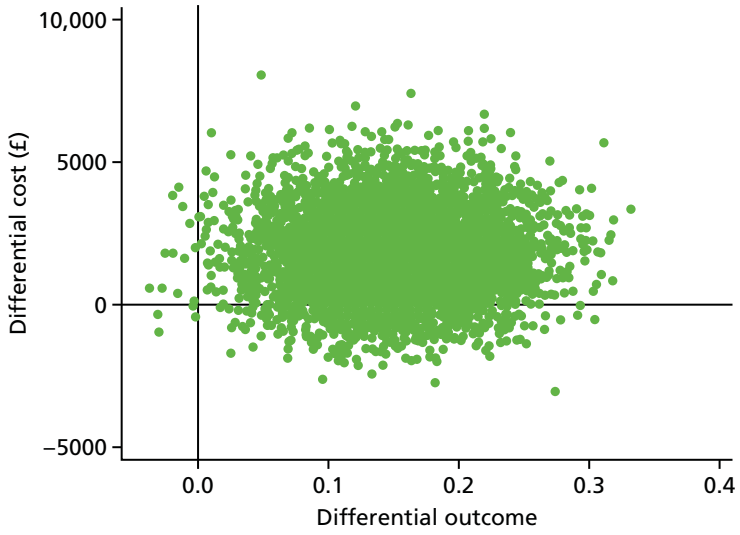


FIGURE 17 Cost-effectiveness plane for participants with three or more previous miscarriages. Reproduced from Okeke Ogwulu *et al.*[52] © 2020 The Authors. *BJOG: An International Journal of Obstetrics and Gynaecology* published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

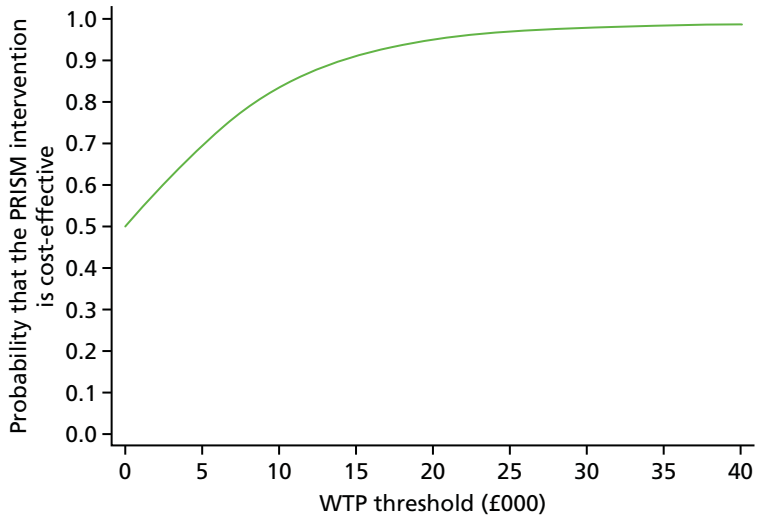


FIGURE 18 The CEAC for participants with three or more previous miscarriages. Reproduced from Okeke Ogwulu *et al.*[52] © 2020 The Authors. *BJOG: An International Journal of Obstetrics and Gynaecology* published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

TABLE 24 Point ICERs for secondary outcomes

Treatment	Progesterone, mean effect	Placebo, mean effect	Effect difference (95% CI)	ICER (£)	Cost-effectiveness plane
Neonatal survival beyond 28 days[a]	0.760	0.739	0.021, –0.005 to 0.048	3037	North-east dominance

a Results based on the number of women for each trial arm.

Reproduced from Okeke Ogwulu *et al.*[52] © 2020 The Authors. *BJOG: An International Journal of Obstetrics and Gynaecology* published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

TABLE 25 Point estimate ICER for the sensitivity analyses

Sensitivity analyses	Mean costs (£)		Cost difference, mean, 95% CI (£)	ICER (£)
	Progesterone	Placebo		
Fixed progesterone cost until 16 weeks	7694	7572	115, –506 to 735	4977
Imputation of primary care costs	7773	7666	100, –532 to 731	4321
Varying cost of inpatient nights of admission	7498	7413	77, –536 to 691	3356
Varying cost of miscarriage management	7635	7552	76, –546 to 697	3282
Removing delivery costs	5515	5421	86, –500 to 672	3743

Reproduced from Okeke Ogwulu *et al.*[52] © 2020 The Authors. *BJOG: An International Journal of Obstetrics and Gynaecology* published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

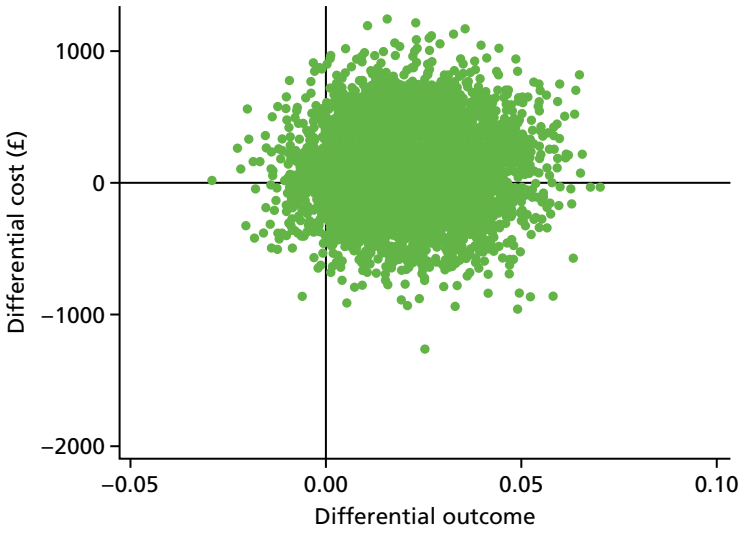


FIGURE 19 Cost-effectiveness plane for a fixed cost of progesterone until 16 weeks' gestation.

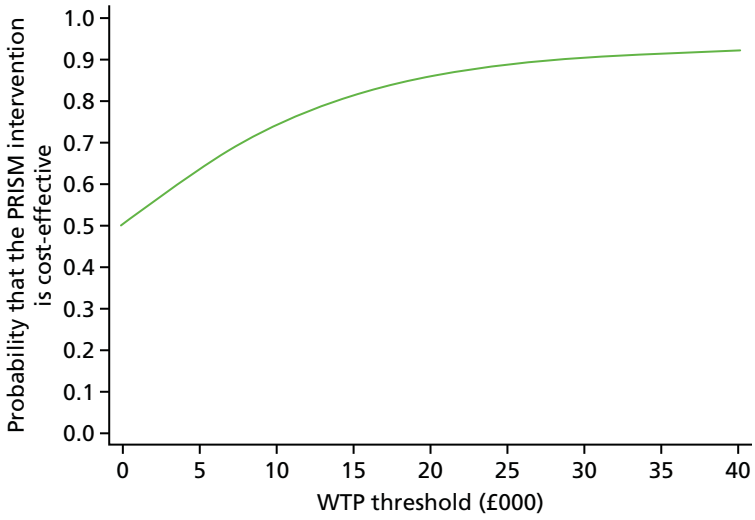


FIGURE 20 The CEAC for a fixed cost of progesterone until 16 weeks' gestation.

In secondary analysis II, we added mean totals of the primary care costs to the total costs for each woman depending on the trial arm. From this, we calculated an ICER of £4264 per additional live birth beyond 34 weeks of gestation (see *Table 21*). The sensitivity analysis in which we imputed costs via multiple imputations did not have much effect on the ICER, with a slight increase to £4321 per additional live birth beyond 34 weeks (see *Table 25*).

Discussion of the health economic findings

Principal findings

We evaluated the cost-effectiveness of progesterone in preventing miscarriage and leading to a live birth at ≥ 34 weeks of pregnancy in women who presented with bleeding in early pregnancy. Our results suggest that progesterone is more effective and slightly more costly than placebo. More specifically, progesterone resulted in an additional two live births per 100 women (0.022, 95% CI –0.004 to 0.050) at ≥ 34 weeks of gestation relative to placebo, with an additional cost of £83 (adjusted mean difference £76, 95% CI –£559 to £711) per woman. The additional cost was mainly attributable to the cost of progesterone administration (mean cost £204). The ICER was estimated at £3305 per live birth at

≥ 34 weeks. A conclusion on the cost-effectiveness of the PRISM trial would depend on the amount that society is willing to pay to increase the chances of an additional live birth at ≥ 34 weeks of pregnancy. For potentially acceptable WTP threshold values for an additional live birth,[44] the probability of progesterone being cost-effective for this population group exceeds 90%.

The National Institute for Health and Care Excellence attached a value to an averted stillbirth of 25 QALYs.[65] This assumes that life lost has a typical life expectancy in good health, but when discounting is applied to the expected years in full health, it yields 25 discounted QALYs. To interpret the primary CEA results in relation to QALYs, we used the NICE value (25 QALYs) as a proxy. If we assume that babies born alive at ≥ 34 weeks live in full health and divide the ICER (£3305 per additional live birth) by 25, then the cost per QALY is likely to be £132. If a baby did live in full health for the anticipated life expectancy, then on the basis of this ICER (£132) the intervention is cost-effective.[44] Furthermore, evidence from the *NHS Reference Costs* schedule[47] indicates that the upper cost quartile of the most expensive delivery is about £15,000, which could go much higher if we allow for the cost of excess bed-days. This further suggests that progesterone intervention is cost-effective.

The ICER for the final end point (secondary outcome) of the trial was £3037 per additional baby surviving beyond 28 days after birth. The intervention was more effective, with a gain of three neonates per 100 women surviving beyond 28 days post partum. A subgroup analysis of women with three or more previous miscarriages led to an increase of 15 live births per 100 women in the intervention group.

Strengths and limitations of the economic analyses

The strength of the CEA is that it was based on a large, robust, multicentre randomised controlled trial involving over 4000 participants, making this the largest study to explore whether or not progesterone provides value for the public health-care resources. The outcome and resource use data were prospectively collected at different points in the trial using CRFs. Unit costs were obtained from established national sources. In cases where HRGs did not clearly depict our variables, we liaised with the clinical team to decide on the most appropriate HRG. The CEA also benefited from the robustness of the main analyses and the sensitivity analyses. However, data on primary care services were available for < 10% of the participants: we accounted for this by imputing missing costs in our analyses. A limitation of this analysis was the failure to explore the wider societal costs to the participants. However, this was beyond the scope of the study and beyond the requested resource.

Comparison with the literature

To our knowledge, this is the first UK study to investigate the cost-effectiveness of progesterone in preventing miscarriage and achieving a live birth beyond 34 weeks of gestation. A similar study investigated the cost-effectiveness of progesterone in preventing miscarriages in women with a history of recurrent miscarriages and leading to a live birth beyond 24 weeks of gestation.[2] The authors reported that the total mean cost of the intervention was £332.17 higher in the progesterone arm than in the placebo arm and an ICER of £18,053 per additional live birth beyond 24 weeks for the base-case analysis, with a cost-effectiveness probability of 50% at this value.

Implications for policy

The results of the CEA suggest that progesterone is likely to be considered a cost-effective intervention by decision-makers for women presenting with early pregnancy bleeding (threatened miscarriage) within 12 weeks of gestation.

Summary of health economic findings

- For the primary analysis, the mean total cost was higher in the progesterone group (£7655) than in the placebo group (£7572), with an additional cost of £83 (1% higher cost than usual care).
- The additional difference in the mean probability of a live birth beyond ≥ 34 completed weeks of gestation was 0.022 (95% CI –0.004 to 0.050), indicating that the progesterone intervention resulted in an additional two live births per 100 women at ≥ 34 weeks.

- For the primary analysis, the ICER per additional live birth beyond 34 weeks of gestation was calculated as £3305.
- There is > 80% confidence that progesterone is cost-effective if decision-makers are prepared to pay £15,000 per additional live birth and > 90% if the WTP threshold is £30,000.
- Currently, in the UK, progesterone is not routinely given to women who are at high risk of miscarriage. The results of the CEA suggest that progesterone is likely to be considered cost-effective, particularly for women (with one or more miscarriages) who present with bleeding in early pregnancy.

Chapter 5 Discussion

Our large multicentre, double-blind, placebo-controlled, randomised trial showed that vaginal progesterone therapy in the first trimester of pregnancy did not result in a significant increase in the rate of live births at ≥ 34 weeks of gestation in women with early pregnancy bleeding. However, the large sample size of our study allowed investigation of prespecified subgroups, and we found that women with early pregnancy bleeding *and* a previous history of miscarriages benefited from progesterone therapy. This subgroup effect showed a biological gradient, with those with no previous miscarriages receiving no benefit, those with one or two previous miscarriages receiving some benefit and those with three or more previous miscarriages receiving a substantial benefit. The biological gradient combined with the overall positive direction of effect in the primary analysis gives us confidence in the effects of progesterone in such high-risk women. The findings of the economic evaluation indicate that progesterone is likely to be considered by decision-makers to be cost-effective for any woman with threatened miscarriage, and particularly for women with a history of a previous miscarriage.

Of the 10 prespecified subgroup analyses, one showed differential effects of progesterone; that is, the effects of progesterone in women with early pregnancy bleeding differed according to the number of previous miscarriages, with a suggestion of benefit in women with ≥ 3 miscarriages. Previous data have indicated a steep and proportionate increase in the loss of chromosomally normal pregnancies (euploid miscarriages) with an increasing number of past miscarriages.[66] Given that the potential benefit of progesterone therapy would be expected to be specific to euploid pregnancies, an increasing level of benefit in women with an increasing number of past miscarriages is consistent with our biological understanding of miscarriage risk. Previous miscarriage history is one of only two stratification or prognostic risk factors (the other being maternal age) stated as useful to identify high-risk patients in the 2017 European Society of Human Reproduction and Embryology guideline on recurrent miscarriage.[67] However, we did not identify this subgroup as of special interest a priori in our SAP, and multiple comparisons were performed (without adjustment for multiplicity); thus, this observation requires further validation.

Study strengths

This study is the largest, multicentre, double-blind, placebo-controlled, randomised clinical trial to report on treatment of early pregnancy bleeding with progesterone. The robust study design – including blinding to treatment allocation of both participants and investigators – ensured internal validity, enabling the results to be interpreted with confidence. Randomisation via computer-generated allocation sequence was effective in achieving balanced groups with respect to important prognostic factors.

The size of the study was driven by a MID, determined following consultations with health-care practitioners, patients and representatives of patient bodies, as well as through a clinician's survey. A consensus of a 5% increase in live birth rates beyond 34 weeks of gestation evolved from this consultation, resulting in a target sample size of 4150 participants with primary outcome data. A total of 4153 women from 48 hospitals in the UK were randomised to receive either progesterone (n = 2079 women) or placebo (n = 2074 women). The follow-up rate for the primary outcome was 97.2% (4038/4153 women).

Our trial design offered a number of other strengths with respect to data collection and analysis. The treatment of participants by a large number of study centres and practitioners allowed intervention impact to be evaluated without confounding by individual variance in clinical practice. The outcome measures selected were routine variables widely used by clinicians who are familiar with early pregnancy care. This ensured that the outcomes were well understood and easy to record. Almost all of the outcome data recorded during the PRISM study were objective outcomes (rather than subjective descriptions) and the study was blinded so there was no risk of incurring assessor bias. The trial intervention was deliverable in the context of customary care without major effects on health service structure. The mode of administration

of IMP was designed to reflect the preferences expressed by patients, and most of our data collection could be performed during routine antenatal and postnatal appointments of the study participants.

Limitations and critique

We consider the trial to have been designed and conducted in order to be methodologically robust. Nevertheless, there were some limitations of our study that should be considered. We studied a vaginal preparation of progesterone, at a dose of 400 mg twice daily, and it is possible that the results with this regimen are not generalisable to patients receiving other doses and preparations. However, this route was chosen to deliver a greater proportion of the drug to the biologically relevant site (i.e. the uterus),[4,32,33] and the dose used (400 mg twice daily) represents a dose at the top end of the therapeutic window.[2,26] We started progesterone treatment only in women who had an intrauterine sac, and thus our study cannot provide evidence on the effects of earlier use of progesterone before a pregnancy sac is visible on an ultrasound. We discontinued progesterone at 16 weeks of gestation but consider it unlikely that therapy beyond this time would have affected aetiology and outcomes related to miscarriage. We found no increase in the risk of congenital anomalies in the offspring of women treated with progesterone, although the study was not powered for such rare outcomes.

The observed primary outcome rate in the placebo group was slightly higher than that assumed in the sample size calculation (72% vs. 60%). However, an assumed higher rate would have required a smaller sample to detect the same 5% absolute difference and, hence, this is unlikely to have had any impact on the conclusions we have drawn from the study.

Findings in the context of existing literature

The pre-existing evidence, summarised in a recent Cochrane review,[1] pooled the results from seven small trials that had substantive methodological limitations; only three of the trials specified the method of concealment of study group assignments, and only four trials used a placebo for comparison. Nevertheless, the pooled analysis did show a benefit in reducing the risk of miscarriages (risk ratio 0.64, 95% CI 0.47 to 0.87).[1] Live birth outcome was not reported in this review.[1]

Interpretation of the principal findings

Although there were more live births in the progesterone group than in the placebo group, the trial did not find a statistically significant difference. However, an important subgroup effect by previous history of miscarriage was observed. This subgroup effect is supported by the fact that the risk of a future miscarriage increases proportionately with increasing number of past miscarriages;[66] there is a steep and proportionate increase in the loss of chromosomally normal pregnancies (euploid miscarriages) with increasing number of past miscarriages.[66] It is euploid miscarriages that are likely to be helped by progesterone therapy, and thus an increasing level of benefit in women with an increasing number of past miscarriages is consistent with our biological understanding of miscarriage risk. We found no increase in the risk of congenital anomalies among offspring of women treated with progesterone, although the study was not powered for such rare outcomes.

Interpretation of the cost-effectiveness findings

The primary CEA found that the mean total cost per woman was higher in the progesterone group (£7655) than in the placebo group (£7572). Hence, the progesterone intervention led to an additional cost of £76 per woman. The ICER per additional live birth beyond 34 weeks of gestation was calculated as £3305.

For potentially acceptable WTP threshold values,[44] the probability of progesterone being cost-effective is over 90%. The likelihood of progesterone being cost-effective increased even further for those women with history of repeated miscarriage.

Patient and public involvement

In the PRISM trial, patient and public involvement was utilised at all stages of the study design, development and monitoring. This included questionnaires for patients to assess the acceptability of the intervention, and engagement in the development of patient-facing literature for participants. The patient and public involvement representative was sent study documentation to review at the design stage and attended design meetings to ensure that it was clear and easy to understand. The TSC included a representative of the Miscarriage Association and a representative of Tommy's charity. We believe that these roles were important to ensure that appropriate communication with study participants and project oversight took place throughout the duration of the research. Dissemination of results will be supported by the international charity Ammalife, the Miscarriage Association and Tommy's charity.

Generalisability

Centres participating in the study were geographically spread across the UK, improving the generalisability of the results for women with early pregnancy bleeding. Women in the trial did not belong to a 'selected population', such as those with a history of previous miscarriage. Therefore, the results of this study are likely to be representative of true unselected 'low-risk' women with no gynaecological or obstetric risk factors. The exclusion criteria were kept to a minimum and the heterogeneity of the population was well reflected by trial participants.

Chapter 6 Conclusions

In conclusion, our trial did not find an overall benefit of progesterone supplementation, but identified a subgroup effect in high-risk women, defined as those with early pregnancy bleeding and a previous history of miscarriages. In women with early pregnancy bleeding and a history of previous miscarriages, the number needed to treat to gain an additional live birth at ≥ 34 weeks' gestation is 18 (95% CI 10 to 71). The results of the economic evaluation, which typically adopts a Bayesian perspective for analysis, suggested that progesterone is likely to be considered cost-effective by decision-makers for women presenting with early pregnancy bleeding, and particularly for women with a history of a previous miscarriage. The final conclusion on the cost-effectiveness of the PRISM trial would depend on the amount that society is willing to pay to increase the chances of an additional live birth at and beyond 34 weeks of pregnancy.

Implications for health care

On the basis of the results of this study, progesterone therapy in the first trimester does not have a significant benefit in women with early pregnancy bleeding overall; however, our study found that women with early pregnancy bleeding *and* a previous history of miscarriages benefited from progesterone therapy. A biological gradient of effect was observed, with those women with no previous miscarriages receiving no benefit, those with one or two miscarriages receiving some benefit and those with three or more miscarriages receiving a substantial benefit. Furthermore, the findings of the economic evaluation suggest that administering progesterone to women with early pregnancy bleeding (< 12 weeks of gestation) is likely to be considered good value for money.

Recommendations for research

Given the large number of data that now exist on this subject, our research group has previously registered to conduct an individual participant data meta-analysis titled 'Vaginal progesterone treatment during the first trimester of pregnancy for the prevention of miscarriage: an individual participant data (IPD) meta-analysis'.[68] This analysis will address two key questions:

1. Is treatment with vaginal progesterone during the first trimester of a naturally conceived pregnancy effective for the prevention of miscarriage?
2. Is treatment with vaginal progesterone during the first trimester of a naturally conceived pregnancy for the prevention of miscarriage effective in women with a history of miscarriage(s)?

Furthermore, each participant in the PRISM study was asked to consent for the future evaluation of themselves, the child who is born and the health records of both. Although long-term follow-up will remain outside the scope of this trial, we plan to conduct further studies on outcomes, such as neurodevelopmental outcomes at 7 years of age using aggregated Standard Attainment Tests results from the National Pupil Database, a parent-reported questionnaire to determine levels of cognition, social responsiveness and behaviour, and face-to-face assessments in a subset of children. The NHS number of each baby was recorded to facilitate future follow-up studies.

Acknowledgements

We thank all of the women who participated in this study. We thank the following investigators for supervising recruitment and randomisation at the study centres: Mr Samson Agwu, Mrs Rita Arya, Miss Miriam Baumgarten, Dr Catey Bass, Miss Sumita Bhuiya, Professor Tom Bourne, Mr James Clark, Mr Samual Eckford, Mr Zeiad El-Gizawy, Mrs Joanne Fletcher, Miss Preeti Gandhi, Dr Mary Gbegaje, Dr Ingrid Granne, Mr Mamdough Guirguis, Dr Pratima Gupta, Dr Hadi Haerizadeh, Dr Laura Hipple, Mr Piotr Lesny, Miss Hema Nosib, Mr Jonathan Pepper, Mr Jag Samra, Ms Jayne Shillito, Dr Rekha Shrestha, Dr Jayasree Srinivasan, Dr Ayman Swidan and Professor Derek Tuffnell. We thank all of the PRISM research nurses who assisted in the collection of data; Leanne Beeson, Mary Nulty and Louisa Edwards for their support in managing and co-ordinating the trial; Professor Siladitya Bhattacharya for chairing the TSC; Professor Andrew Shennan for chairing the DMEC; Dr Javier Zamora and Dr Willem Ankum for participating in the DMEC; and all those not otherwise mentioned above who have contributed to the PRISM study.

Contributions of authors

Arri Coomarasamy (https://orcid.org/0000-0002-3261-9807) (Chief Investigator) was involved with the design, implementation and oversight of the trial, and was the primary author of this manuscript.

Hoda M Harb (https://orcid.org/0000-0002-0813-1318) was involved with the design of, implementation of and recruitment to the trial, and was responsible for co-authoring this manuscript.

Adam J Devall (https://orcid.org/0000-0001-5632-079X) was the trial manager and was involved with the implementation and oversight of the trial and was responsible for co-authoring this manuscript.

Versha Cheed (https://orcid.org/0000-0002-6713-0913) was the trial statistician, was responsible for the analysis of the trial data and was responsible for co-authoring this manuscript.

Tracy E Roberts (https://orcid.org/0000-0002-0624-0537) was the senior health economist, was responsible for the health economic analysis and was responsible for co-authoring this manuscript.

Ilias Goranitis (https://orcid.org/0000-0001-7946-8324) was a health economist for the trial and was responsible for the health economic analysis and for co-authoring this manuscript.

Chidubem B Ogwulu (https://orcid.org/0000-0002-8133-7021) was a health economist for the trial and was responsible for the health economic analysis and for co-authoring this manuscript.

Helen M Williams (https://orcid.org/0000-0003-4417-9404) was responsible for implementation and oversight of the trial and was responsible for the critical review of the paper.

Ioannis D Gallos (https://orcid.org/0000-0002-2766-358X) was involved with recruitment to the trial and was responsible for co-authoring this manuscript.

Abey Eapen (https://orcid.org/0000-0003-1951-758X) was involved with recruitment to the trial and was responsible for the critical review of the paper.

Jane P Daniels (https://orcid.org/0000-0003-3324-6771) contributed to the design and critical review of the manuscript.

Amna Ahmed (https://orcid.org/0000-0003-2960-0731) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Ruth Bender-Atik (https://orcid.org/0000-0002-6751-5901) was a patient public involvement representative for the trial and contributed to the critical review of the manuscript.

Kalsang Bhatia (https://orcid.org/0000-0003-0892-4892) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Cecilia Bottomley (https://orcid.org/0000-0003-1914-2482) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Jane Brewin (https://orcid.org/0000-0002-8411-1802) was a patient and public involvement representative for the trial and contributed to the critical review of the manuscript.

Meenakshi Choudhary (https://orcid.org/0000-0003-0526-8965) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Fiona Crosfill (https://orcid.org/0000-0001-6092-3120) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Shilpa Deb (https://orcid.org/0000-0003-4456-8194) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

W Colin Duncan (https://orcid.org/0000-0002-7170-5740) was a co-applicant for the trial and was responsible for the design and contributed to the critical review of the manuscript.

Andrew Ewer (https://orcid.org/0000-0002-3825-4781) was a co-applicant for the trial and was responsible for the design and contributed to the critical review of the manuscript.

Kim Hinshaw (https://orcid.org/0000-0003-0468-4326) was a co-PI for the trial and contributed to the critical review of the manuscript.

Thomas Holland (https://orcid.org/0000-0001-5727-0659) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Feras Izzat (https://orcid.org/0000-0001-9673-4276) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Jemma Johns (https://orcid.org/0000-0003-1079-9170) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Mary-Ann Lumsden (https://orcid.org/0000-0003-2998-9185) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Padma Manda was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Jane E Norman (https://orcid.org/0000-0001-6031-6953) was a co-applicant for the trial, was responsible for the design and contributed to the critical review of the manuscript.

Natalie Nunes (https://orcid.org/0000-0003-1801-6281) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Caroline E Overton (https://orcid.org/0000-0001-5748-9677) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Kathiuska Kriedt (https://orcid.org/0000-0002-9834-7568) was involved with recruitment to the trial and was responsible for the critical review of the paper.

Siobhan Quenby (https://orcid.org/0000-0003-3221-5471) was a co-applicant for the trial, was responsible for the design and contributed to the critical review of the manuscript.

Sandhya Rao was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Jackie Ross (https://orcid.org/0000-0003-4168-6910) was a co-PI for the trial and contributed to the critical review of the manuscript.

Anupama Shahid was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Martyn Underwood (https://orcid.org/0000-0001-6891-7390) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Nirmala Vaithilingham was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Linda Watkins (https://orcid.org/0000-0002-2031-6577) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Catherine Wykes (https://orcid.org/0000-0002-5589-991X) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Andrew W Horne (https://orcid.org/0000-0002-9656-493X) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Davor Jurkovic (https://orcid.org/0000-0001-6487-5736) was a PI for the trial, overseeing recruitment of patients, and contributed to the critical review of the manuscript.

Lee J Middleton (https://orcid.org/0000-0003-4621-1922) was the senior statistician for the trial, was responsible for the analysis of the trial data and was responsible for co-authoring this manuscript.

Publications

Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, *et al.* A randomised trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med* 2019;**380**:1815–24.

Okeke Ogwulu CB, Goranitis I, Devall AJ, Cheed V, Gallos ID, Middleton LJ, *et al.* The cost-effectiveness of progesterone in preventing miscarriages in women with early pregnancy bleeding: an economic evaluation based on the PRISM trial. *BJOG* 2020;**127**:757–67.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. *Cochrane Database Syst Rev* 2018;**8**:CD005943. https://doi.org/10.1002/14651858.CD005943.pub5
2. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, *et al.* A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med* 2015;**373**:2141–8. https://doi.org/10.1056/NEJMoa1504927
3. National Institute for Health and Care Excellence. *Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management*. NICE Clinical Guidelines 154. London: NICE; 2012.
4. Hemminki E. Treatment of miscarriage: current practice and rationale. *Obstet Gynecol* 1998;**91**:247–53. https://doi.org/10.1016/S0029-7844(97)00606-6
5. Farren J, Jalmbrant M, Ameye L, Joash K, Mitchell-Jones N, Tapp S, *et al.* Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study. *BMJ Open* 2016;**6**:e011864. https://doi.org/10.1136/bmjopen-2016-011864
6. Ehrenskjöld ML, Bondo B, Weile F. [Treatment of threatened abortion with dydrogesterone.] *Ugeskr Laeg* 1967;**129**:1678–9.
7. El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. *Maturitas* 2009;**65**(Suppl. 1):43–6. https://doi.org/10.1016/j.maturitas.2009.11.013
8. Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. Double-blind controlled trial of progesterone substitution in threatened abortion. *Biol Res Pregnancy Perinatol* 1987;**8**:26–34.
9. Mistò A. [Experiences with 6-dehydro-retroprogesterone int the treatment of placental insufficiency.] *Ann Ostet Ginecol Med Perinat* 1967;**89**:102–12.
10. Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. *J Steroid Biochem Mol Biol* 2005;**97**:421–5. https://doi.org/10.1016/j.jsbmb.2005.08.013
11. Palagiano A, Bulletti C, Pace MC, DE Ziegler D, Cicinelli E, Izzo A. Effects of vaginal progesterone on pain and uterine contractility in patients with threatened abortion before twelve weeks of pregnancy. *Ann N Y Acad Sci* 2004;**1034**:200–10. https://doi.org/10.1196/annals.1335.022
12. Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. *Maturitas* 2009;**65**(Suppl. 1):47–50. https://doi.org/10.1016/j.maturitas.2009.11.016
13. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, *et al.* PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages – a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. *Health Technol Assess* 2016;**20**(41). https://doi.org/10.3310/hta20410
14. Carmichael SL, Shaw GM, Laurent C, Croughan MS, Olney RS, Lammer EJ. Maternal progestin intake and risk of hypospadias. *Arch Pediatr Adolesc Med* 2005;**159**:957–62. https://doi.org/10.1001/archpedi.159.10.957
15. International Organisation for Standardisation (ISO). *ISO 27000 – Information technology, Security Techniques, Information Security Management Systems, Overview and Vocabulary*. URL: www.iso.org/obp/ui/#iso:std:iso-iec:27000:ed-5:v1:en (accessed 22 June 2019).
16. e-CFR. *Electronic Code of Federal Regulations*. 2019. URL: https://gov.ecfr.io/cgi-bin/ECFR (accessed 22 August 2019).
17. US Food and Drug Administration. *CFR – Code of Federal Regulations Title 21*. 2018. URL: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11 (accessed 22 June 2019).

18. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;**31**:103–15. https://doi.org/10.2307/2529712

19. White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978;**37**:849–57. https://doi.org/10.1038/bjc.1978.124

20. Bottomley C, Van Belle V, Pexsters A, Papageorghiou AT, Mukri F, Kirk E, *et al.* A model and scoring system to predict outcome of intrauterine pregnancies of uncertain viability. *Ultrasound Obstet Gynecol* 2011;**37**:588–95. https://doi.org/10.1002/uog.9007

21. European Commission. *EudraLex – Volume 4 – Good Manufacturing Practice (GMP) Guidelines*. URL: https://ec.europa.eu/health/documents/eudralex/vol-4_en (accessed 22 June 2019).

22. Official Journal of the European Union. *Commission Directive 2005/28/EC of 8 April 2005 Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products For Human Use, as well as the Requirements for Authorisation of the Manufacturing or Importation of Such Products*. 2005. URL: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf (accessed 22 June 2019).

23. Great Britain. *The Medicines for Human Use (Clinical Trials) Regulations 2004*. London: The Stationery Office; 2004. URL: www.legislation.gov.uk/uksi/2004/1031/contents/made (accessed 22 June 2019).

24. Besins Healthcare (UK) Ltd. *Utrogestan Vaginal 200mg Capsules*. 2019. URL: www.medicines.org.uk/emc/product/3244 (accessed 22 June 2019).

25. National Institute for Health and Care Excellence. *Progesterone*. URL: https://bnf.nice.org.uk/drug/progesterone.html (accessed 22 June 2019).

26. Nosarka S, Kruger T, Siebert I, Grové D. Luteal phase support in in vitro fertilization: meta-analysis of randomized trials. *Gynecol Obstet Invest* 2005;**60**:67–74. https://doi.org/10.1159/000084546

27. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev* 2015;**7**:CD009154. https://doi.org/10.1002/14651858.CD009154.pub3

28. Rai R, Regan L. Recurrent miscarriage. *Lancet* 2006;**368**:601–11. https://doi.org/10.1016/S0140-6736(06)69204-0

29. Li TC, Spuijbroek MD, Tuckerman E, Anstie B, Loxley M, Laird S. Endocrinological and endometrial factors in recurrent miscarriage. *BJOG* 2000;**107**:1471–9. https://doi.org/10.1111/j.1471-0528.2000.tb11670.x

30. Li TC, Tuckerman EM, Laird SM. Endometrial factors in recurrent miscarriage. *Hum Reprod Update* 2002;**8**:43–52. https://doi.org/10.1093/humupd/8.1.43

31. Szekeres-Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage. *Hum Reprod Update* 2008;**14**:27–35. https://doi.org/10.1093/humupd/dmm035

32. Bulletti C, de Ziegler D, Flamigni C, Giacomucci E, Polli V, Bolelli G, Franceschetti F. Targeted drug delivery in gynaecology: the first uterine pass effect. *Hum Reprod* 1997;**12**:1073–9. https://doi.org/10.1093/humrep/12.5.1073

33. Cicinelli E, Cignarelli M, Sabatelli S, Romano F, Schonauer LM, Padovano R, Einer-Jensen N. Plasma concentrations of progesterone are higher in the uterine artery than in the radial artery after vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women. *Fertil Steril* 1998;**69**:471–3. https://doi.org/10.1016/S0015-0282(97)00545-1

34. Coomarasamy A, Thangaratinam S, Gee H, Khan KS. Progesterone for the prevention of preterm birth: a critical evaluation of evidence. *Eur J Obstet Gynecol Reprod Biol* 2006;**129**:111–18. https://doi.org/10.1016/j.ejogrb.2006.05.013

35. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003;**188**:419–24. https://doi.org/10.1067/mob.2003.41

36. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007;**357**:462–9. https://doi.org/10.1056/NEJMoa067815

37. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev* 2013;**7**:CD004947. https://doi.org/10.1002/14651858.CD004947.pub3

38. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, *et al.* Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;**348**:2379–85. https://doi.org/10.1056/NEJMoa035140

39. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, *et al.* A randomised trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med* 2019;**380**:1815–24. https://doi.org/10.1056/NEJMoa1813730

40. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;**159**:702–6. https://doi.org/10.1093/aje/kwh090

41. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;**34**:585–612. https://doi.org/10.1038/bjc.1976.220

42. Chatfield A, Caglia JM, Dhillon S, Hirst J, Cheikh Ismail L, Abawi K, *et al.* Translating research into practice: the introduction of the INTERGROWTH-21st package of clinical standards, tools and guidelines into policies, programmes and services. *BJOG* 2013;**120**(Suppl. 2):139–42. https://doi.org/10.1111/1471-0528.12416

43. Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. *Ultrasound Obstet Gynecol* 1995;**6**:168–74. https://doi.org/10.1046/j.1469-0705.1995.06030168.x

44. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013*. London: National Institute for Health and Care Excellence; 2013.

45. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) – explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 2013;**16**:231–50. https://doi.org/10.1016/j.jval.2013.02.002

46. Joint Formulary Committee. *British National Formulary (Online)*. London: BMJ Group and Pharmaceutical Press; 2018. URL: www.medicinescomplete.com (accessed 22 June 2019).

47. NHS Improvement. *NHS Reference Costs 2016/17*. 2017. London: NHS Improvement; 2017.

48. Department of Health and Social Care. *NHS Reference Costs 2013 to 2014*. London: Department of Health and Social Care; 2014.

49. Curtis L, Netten A. *Unit Costs of Health and Social Care 2002*. Canterbury: PSSRU, University of Kent; 2002.

50. Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury: PSSRU, University of Kent; 2017.

51. Curtis L, Burns A. *Unit Costs of Health and Social Care 2015*. Canterbury: Personal Social Services Research Unit, University of Kent; 2015.

52. Okeke Ogwulu CB, Goranitis I, Devall AJ, Cheed V, Gallos ID, Middleton LJ, *et al.* The cost-effectiveness of progesterone in preventing miscarriages in women with early pregnancy bleeding: an economic evaluation based on the PRISM trial. *BJOG* 2020;**127**:757–67. https://doi.org/10.1111/1471-0528.16068

53. Intensive Care Society. *Levels of Critical Care for Adult Patients*. London: Intensive Care Society; 2009. URL: www.ics.ac.uk/ (accessed 10 May 2018).

54. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000;**19**:3219–36. https://doi.org/10.1002/1097-0258(20001215)19:23<3219::AID-SIM623>3.0.CO;2-P

55. Zellner A. An efficient method of estimating seemingly unrelated regressions and tests for aggregation bias. *J Am Stat Assoc* 1962;**57**:348–68. https://doi.org/10.1080/01621459.1962.10480664

56. Moon HR, Perron B. *Seemingly Unrelated Regressions. The New Palgrave Dictionary of Economics*. London: Palgrave Macmillan; 2008. https://doi.org/10.1057/978-1-349-95121-5_2296-1

57. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004;**13**:461–75. https://doi.org/10.1002/hec.843

58. Glick HA, Briggs AH, Polsky D. Quantifying stochastic uncertainty and presenting results of cost-effectiveness analyses. *Expert Rev Pharmacoecon Outcomes Res* 2001;**1**:25–36. https://doi.org/10.1586/14737167.1.1.25

59. Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis Making* 1990;**10**:212–14. https://doi.org/10.1177/0272989X9001000308

60. Simon J, Petrou S, Gray A. The valuation of prenatal life in economic evaluations of perinatal interventions. *Health Econ* 2009;**18**:487–94. https://doi.org/10.1002/hec.1375

61. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 2004.

62. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. https://doi.org/10.1002/sim.4067

63. Petrou S, Trinder J, Brocklehurst P, Smith L. Economic evaluation of alternative management methods of first-trimester miscarriage based on results from the MIST trial. *BJOG* 2006;**113**:879–89. https://doi.org/10.1111/j.1471-0528.2006.00998.x

64. Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, *et al.* Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM). *Health Technol Assess* 2018;**22**(35). https://doi.org/10.3310/hta22350

65. National Collaborating Centre for Women's and Children's Health (UK). *Diabetes in Pregnancy—Management of Diabetes and its Complications from Preconception to the Postnatal Period*. London: National Institute for Health and Care Excellence; 2015.

66. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. *Fertil Steril* 2000;**73**:300–4. https://doi.org/10.1016/S0015-0282(99)00495-1

67. European Society of Human Reproduction and Embryology. *Recurrent Pregnancy Loss: Guideline of the European Society of Human Reproduction and Embryology*. Grimbergen: European Society of Human Reproduction and Embryology; 2017.

68. Devall AJ, Gallos, ID, Middleton, LJ, Coomarasamy A. Vaginal progesterone treatment during the first trimester of pregnancy for the prevention of miscarriage: an individual participant data (IPD) meta-analysis. PROSPERO 2018:CRD42018064560. URL: www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018064560

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library