



Cervical pessary versus vaginal progesterone in women with a singleton pregnancy, a short cervix, and no history of spontaneous preterm birth at less than 34 weeks' gestation: open label, multicentre, randomised, controlled trial

Charlotte E van Dijk,^{1,2} Annabelle L van Gils,^{1,2} Maud D van Zijl,^{1,2} Bouchra Koullali,^{1,2} Marijke C van der Weide,¹ Eline S van den Akker,³ Brenda J Hermesen,³ Wilhelmina M van Baal,⁴ Henricus Visser,⁵ Joris van Drongelen,⁶ Karlijn C Vollebregt,⁷ Moira Muller,⁷ Flip W van der Made,⁸ Sanne J Gordijn,⁹ Yolanda M de Mooij,¹⁰ Martijn A Oudijk,^{2,11} Marjon A de Boer,^{2,11} Ben WJ Mol,^{12,13} Brenda M Kazemier,¹⁴ Eva Pajkrt^{1,2}

For numbered affiliations see end of the article

Correspondence to: C E van Dijk c.e.vandijk@amsterdamumc.nl (ORCID 0000-0001-9417-4180)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2024;384:e077033

<http://dx.doi.org/10.1136/bmj-2023-077033>

Accepted: 13 February 2024

ABSTRACT

OBJECTIVE

To compare the effectiveness of cervical pessary and vaginal progesterone in the prevention of adverse perinatal outcomes and preterm birth in pregnant women of singletons with no prior spontaneous preterm birth at less than 34 weeks' gestation and who have a short cervix of 35 mm or less.

DESIGN

Open label, multicentre, randomised, controlled trial.

SETTING

20 hospitals and five obstetric ultrasound practices in the Netherlands.

PARTICIPANTS

Women with a healthy singleton pregnancy and an asymptomatic short cervix of 35 mm or less between 18 and 22 weeks' gestation were eligible. Exclusion criteria were prior spontaneous preterm birth at less than 34 weeks, a cerclage in situ, maternal age of younger than 18 years, major congenital abnormalities, prior participation in this trial, vaginal blood loss, contractions, cervical length of less than 2 mm or cervical dilatation of 3 cm or more. Sample size was set at 628 participants.

INTERVENTIONS

1:1 randomisation to an Arabin cervical pessary or vaginal progesterone 200 mg daily up to 36 weeks' of gestation or earlier in case of ruptured membranes, signs of infection, or preterm labour besides routine obstetric care.

MAIN OUTCOME MEASURES

Primary outcome was a composite adverse perinatal outcome. Secondary outcomes were rates of (spontaneous) preterm birth at less than 28, 32, 34, and 37 weeks. A predefined subgroup analysis was planned for cervical length of 25 mm or less.

RESULTS

From 1 July 2014 to 31 March 2022, 635 participants were randomly assigned to pessary (n=315) or to progesterone (n=320). 612 were included in the intention to treat analysis. The composite adverse perinatal outcome occurred in 19 (6%) of 303 participants with a pessary versus 17 (6%) of 309 in the progesterone group (crude relative risk 1.1 (95% confidence interval (CI) 0.60 to 2.2)). The rates of spontaneous preterm birth were not significantly different between groups. In the subgroup of cervical length of 25 mm or less, spontaneous preterm birth at less than 28 weeks occurred more often after pessary than after progesterone (10/62 (16%) v 3/69 (4%), relative risk 3.7 (95% CI 1.1 to 12.9)) and adverse perinatal outcomes seemed more frequent in the pessary group (15/62 (24%) v 8/69 (12%), relative risk 2.1 (0.95 to 4.6)).

CONCLUSIONS

In women with a singleton pregnancy with no prior spontaneous preterm birth at less than 34 weeks' gestation and with a midtrimester short cervix of 35 mm or less, pessary is not better than vaginal progesterone. In the subgroup of a cervical length of 25 mm or less, a pessary seemed less effective in preventing adverse outcomes. Overall, for women with single baby pregnancies, a short cervix, and no prior spontaneous preterm birth less than 34 weeks' gestation, superiority of a cervical pessary compared with vaginal progesterone to prevent preterm birth and consecutive adverse outcomes could not be proven.

TRIAL REGISTRATION

International Clinical Trial Registry Platform (ICTRP, EUCTR2013-002884-24-NL)

WHAT IS ALREADY KNOWN ON THIS TOPIC

In the past two decades, important breakthroughs in the prevention of preterm birth have been established

An individual participant data meta-analysis indicated that vaginal progesterone reduces preterm birth in women with a short cervix of ≤ 25 mm, making it the standard treatment

In women who had singleton births and a short cervix, some studies showed that cervical pessary reduced preterm birth at <34 weeks' gestation too, but other studies could not confirm that reduction

WHAT THIS STUDY ADDS

This trial noted no significant benefit of a cervical pessary over vaginal progesterone in women with singleton pregnancies who had no prior spontaneous preterm birth <34 weeks' gestation and had a midtrimester short cervix of ≤ 35 mm

In a subgroup with a short cervix of ≤ 25 mm, a pessary seemed less effective in preventing adverse outcomes

Even though the study was not powered for the subgroup with a short cervix of ≤ 25 mm, results suggest that a cervical pessary should not be used as preventive treatment in this group

Introduction

Preterm birth is the most important problem in obstetric care and globally the most important cause of neonatal mortality, morbidity, and subsequent neurodevelopmental sequelae.¹⁻⁴ Of all perinatal mortality, 50-70% can be attributed to preterm birth, with higher mortality and morbidity rates at younger gestational ages.⁵⁻⁷

Progesterone is widely understood to reduce preterm birth in pregnant women with a short cervical length.⁸ A second potential preventive treatment is the use of a cervical pessary, which was reported to reduce preterm birth at less than 34 weeks in women with a singleton baby and a cervical length of less than 25 mm.⁹⁻¹¹ However, none of the subsequent trials could confirm the beneficial effect of a cervical pessary¹²⁻¹⁶ and one trial found that a pessary may even cause harm when used for individuals with cervical lengths of less than 20 mm compared with usual care.¹⁷ Some to all participants in both the pessary and non-pessary groups also received progesterone, which makes a direct comparison of their effects unclear. Most importantly, at the start of this trial, most of these results had not yet been published, and no standard intervention was available for women with a short cervix.

In previous studies, a short cervix was commonly defined as cervical length of 25 mm or less. In a Dutch, prospective, observational, cohort study, nulliparous individuals with a cervical length of more than 35 mm had a rate of preterm birth at less than 37 weeks of 6.0%.¹⁸ If cervical length was between 25 mm and 35 mm, the risk doubled to 13.8% and increased even further to 34.2% for a cervical length of at least 25 mm. In women who were multiparous and at low risk, similar trends were reported. In our trial, we chose a cut-off value of 35 mm or less for a short cervix because this population has an increased risk for preterm birth.

Vaginal progesterone is the standard treatment for individuals with a singleton baby and a short cervix, while cervical pessary could potentially be an alternative, despite varying results in different subgroups. Only one randomised controlled trial has directly compared these treatments in women with singleton babies and a cervical length <25 mm, regardless of obstetric history.¹⁶ A direct comparison was not conducted for women of singleton pregnancies with no history of spontaneous preterm birth at less than 34 weeks' gestation and with a cervical length of 25 mm or less, nor with a cervical length <35 mm. Therefore, we compared the effectiveness of cervical pessary and vaginal progesterone in the prevention of preterm birth and adverse perinatal outcomes in women with a singleton pregnancy with no prior spontaneous preterm birth <34 gestation and an asymptomatic midtrimester short cervix ≤35 mm.

Methods

Study design and oversight

We performed a multicentre, open label, randomised controlled trial with a superiority design comparing the effectiveness of cervical pessary and vaginal

progesterone capsules in the reduction of adverse perinatal outcome: the Quadruple P study (pessary or progesterone to prevent preterm delivery in pregnant individuals with short cervical length).¹⁹ Although the protocol was written for both women with a singleton and a multiple pregnancy, we have indicated that we would analyse and publish them separately. This article will focus on the outcomes of singleton pregnancies. The study was done in 20 hospitals and five obstetric ultrasound practices in the Netherlands collaborating within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium). Ethical approval was obtained from the Medical Research Ethics Committee of the Amsterdam University Medical Centre (MEC AMC 2013_019) while the boards of all participating centres approved local execution. This trial was registered at the International Clinical Trial Registry Platform (ICTRP, EUCTR2013-002884-24-NL) and the study protocol has been published previously.¹⁹ This study is reported as per the Consolidated Standards of Reporting Trials (CONSORT) checklist (appendix).²⁰ An independent data safety monitoring committee provided oversight. Assessment for (serious) adverse events was carried out directly after randomisation and up until 30 days after delivery.

Participants

Pregnant women with a healthy singleton pregnancy and an asymptomatic shortened cervical length of 35 mm or less between 18 and 22 weeks of gestation were eligible for participation. Note, although we refer to participants as women throughout our article, we did not ask their gender and therefore we may be including pregnant people who do not identify as women.

Exclusion criteria were prior spontaneous preterm birth <34 weeks' gestation, a cervical cerclage in the current pregnancy, maternal age of less than 18 years, major congenital abnormalities identified in the current pregnancy (defined as conditions of prenatal origin that are present at birth, potentially impacting an infant's health, development and/or survival), prior participation in the Quadruple P study, vaginal blood loss or contractions, cervical length of less than 2 mm, or cervical dilatation of 3 cm or more.

Measurement, randomisation, and masking

In participating centres, pregnant women were offered cervical length measurement during the routine midtrimester structural fetal anomaly scan. Participants had their cervical length measured with transvaginal ultrasound along the endocervical canal between the internal and external os according to the criteria of the Society for Maternal and Fetal Medicine.²¹ All participating ultrasonic operators were trained and qualified according to the national guidelines and the scans were performed on ultrasound systems that met the quality requirement composed by the Institute of Health and Environment.^{22 23}

Eligible women with a short cervix were counselled by nurses (research), midwives, obstetric trainees, or

obstetric specialists trained in Good Clinical Practice and knowledgeable about the aim, methods, and potential hazards of participation in this study. After written informed consent was obtained, women were randomly assigned to either progesterone or cervical pessary through central randomisation using the online computerised randomisation service ALEA in a 1:1 ratio, stratified per centre. Due to the nature of both interventions, participants, study staff, or treating professionals were not blinded to allocation.

Procedures

Gestational age was determined using a first trimester ultrasound according to Dutch national guidelines.²⁴ In participants who were allocated to pessary, an Arabin²⁵ cervical pessary (CE0482, MED/CERT ISO 9003/EN 46003; Arabin GmbH and Company, KG; Witten, Germany) was placed in situ and was removed at 36 weeks' gestation, or earlier in case of ruptured membranes, signs of infection, or preterm labour. Insertion was done by an experienced research midwife or obstetrician, most of whom previously participated in similar trials using pessaries like the ProTwin trial (NTR1858), and the participating hospitals were provided with instructions on pessary placement, but no specialised training was given. Three different pessary sizes were available, namely small (65/25/32 mm), medium (70/25/32 mm), and large (70/25/35 mm). The required size was determined based on physical examination, and subsequently, the accuracy of the selected size was also confirmed through physical examination. Participants were subsequently referred back to their primary obstetric caretaker (obstetrician or midwife). In the initial period after placement, participants were all contacted by the research staff of the participating centre to discuss any complaints. Subsequently, the primary obstetric caretaker continued to check whether any complaints arose during regular antenatal check-ups. During the trial, both participants and the primary obstetric caretakers were instructed to contact the participating centre where the placement had taken place in case of complaints or any adverse symptoms. If necessary, participants were referred back to the participating centre for a vaginal examination. When problems were confirmed, the pessary was either repositioned, removed, or replaced by a different size.

In participants allocated to progesterone, 200 mg vaginal capsules of progesterone (Utrogestan by Besins) were prescribed and were self-administered on a daily basis until 36 weeks' gestational age or earlier in case of ruptured membranes or preterm birth. They were informed by their obstetrician or the research staff on how to insert the vaginal capsules, the preferred time (before sleeping at night) and how to keep track of this schedule in the medication diary. During the regular antenatal check-ups, the obstetric practitioner checked whether the progesterone was still being used and whether there were any complaints or problems regarding its usage, which was noted in the electronic patient file.

Adequate adherence was defined as use of progesterone or pessary during at least 80% of days between randomisation and 36 weeks of gestation or start of labour. Apart from the allocated intervention, participants received routine care according to the local protocol in their own obstetric care centre. In both treatment groups, no behavioural restrictions or physical limitations were given and no standard physical or ultrasound follow-up examination was done. Additionally, no double treatment was given (ie, no additional progesterone with a pessary or vice versa). If an emergency cerclage was indicated, the treated obstetrician made this decision.

Data were collected in electronic case report forms (Open Clinica and Castor EDC v2022.3.2.0). Participants and their offspring were followed up until 10 weeks from the expected due date. Recorded data consisted of maternal characteristics; obstetrical and medical history; current pregnancy, birth, and maternal morbidity and mortality outcomes; and neonatal outcomes.

Outcomes

Outcomes measures align with the core outcomes set for studies on prevention of preterm birth defined by members of GONet and the Core Outcomes in Womens health (CROWN) initiative.²⁶

The primary outcome was a composite adverse perinatal outcome containing specific neonatal syndromes frequently occurring in and associated with preterm infants. The outcome was composed of periventricular leukomalacia of more than grade 1, chronic lung disease (severe respiratory distress syndrome or bronchopulmonary dysplasia), intraventricular haemorrhage grade III or IV, necrotising enterocolitis of more than stage 1, proven sepsis, stillbirth, and death of the baby (both perinatal and neonatal) before discharge from the hospital. Periventricular leukomalacia of more than grade 1 and intraventricular haemorrhage of more than grade 2 was diagnosed by repeated cranial ultrasound according to the guidelines on neuroimaging described by de Vries and colleagues.²⁷ The diagnosis of bronchopulmonary dysplasia was made according to the international consensus guideline as described by Jobe and Bancalari.²⁸ Necrotising enterocolitis of at least stage 2 was diagnosed according to Bell and colleagues.²⁹ Culture proven sepsis is diagnosed on the combination of clinical signs and positive blood cultures. Outcomes were ascertained by qualified neonatologists, who were not masked to randomisation.

Secondary outcomes included time to delivery, rate of preterm birth at less than 24, 28, 32, 34, and 37 weeks (spontaneous, iatrogenic, and total), premature prelabour rupture of the membranes, mode of delivery, placed cerclages, birth weight (in grams), all individual components of the composite neonatal outcome, patent ductus arteriosus, treated seizures, admission days in neonatal intensive care unit, maternal morbidity (thrombo-embolic complications, infections (defined as genital tract infections, urinary

tract infections, and chorioamnionitis treated with antibiotics), pneumonia, endometritis, and eclampsia/haemolysis, elevated liver enzymes, and low platelets), and maternal death.

Serious adverse events were defined as maternal death, life threatening events, events requiring admission to hospital (for complications that were not inherent to pregnancy), events resulting in persistent or significant disability or incapacity, or any other serious or unexpected adverse event.

Sample size

Based on available studies at the time of protocol development, we expected a reduction of adverse perinatal outcome from 5% in the vaginal progesterone group to 1% in the pessary group and therefore a superiority design was chosen. A previous trial in a comparable population in the Netherlands, the Triple P study, showed an adverse perinatal outcome rate of 5% in the vaginal progesterone group.²³ The expected 1% adverse perinatal outcome rate in the pessary group is based on the PECEP trial where a 3% rate of poor neonatal outcomes was reported in the pessary group (compared with 16% in the expectant management group). However, in this study, only participants with a cervix below 25 mm were eligible.¹⁰ Since we included participants with a cervix of 35 mm and shorter, we expect a lower adverse perinatal outcome in our study population. Considering a loss to follow-up rate of 10%, we calculated the sample size to be 628 participants (314 per arm; two sided $\alpha=0.05$, $\beta=80\%$) to detect 1% of adverse perinatal outcome in the pessary group.

Statistical analysis

Analysis was done according a prespecified statistical analysis plan. The primary data were analysed according to the intention to treat principle, with participating centre as a stratification variable. The primary outcome was presented in prevalence rates with relative risks and 95% confidence intervals using a log link binomial model for both crude rates and adjusted rates (with centre as fixed covariate). The secondary outcomes were also calculated with prevalence rates, relative risks, and 95% confidence intervals. Continuous outcomes between both strategies were compared using a random intercept fixed effects linear regression model. For secondary outcomes, time to delivery was evaluated by Kaplan-Meier estimates, taking different durations of gestation at entry into account, and statistical significance was tested with the log rank test. We performed a prespecified subgroup analysis based on cervical length for the subgroups with a cervical length of at least 25 mm and with a cervical length of more than 25 mm and on nulliparous versus multiparous participants.

For the secondary analysis, a per protocol analysis was performed including participants whose allocated treatment was continued up to 36 weeks' gestation or until (threatened) preterm delivery. Participants who

received a cerclage or switched to the other treatment modality were not included in the per protocol analysis. Different cut-off values (60-100%) for treatment adherence were assessed using proportion of days covered as adherence measure.^{30 31}

Patients and public involvement

During the design and conduct phase of this trial, the proposal of the study has been reviewed by the Dutch neonatology patient association Care4Neo, which is affiliated and involved with the European Foundation for the Care of Newborn Infants. They considered the topic of extraordinary importance and therefore strongly supported the study.

Additionally, we agreed on participating in the PROMPT collaboration and the primary and secondary outcomes were chosen to be consistent with the CROWN initiative (Core Outcomes in Women's Health), in particular with the subset chosen to evaluate interventions to prevent preterm birth.²⁶ Within the CROWN initiative, patients extensively participated and were involved in the choice of outcome measures.

Results

From 1 July 2014 to 31 March 2022, 635 participants were randomly assigned to receive either a cervical pessary (n=315) or vaginal progesterone (n=320). Six participants were inappropriately randomised for various reasons, including being screened too early (before 18 weeks) (n=2), too late (after 22 weeks) (n=2), or for not meeting the inclusion criteria in hindsight (n=2). Additionally, 12 participants' written informed consent form was missing after randomisation; as such, confirming whether they had followed the correct informed consent procedure was not possible. Five participants were lost to follow-up (two in the pessary group and three in the progesterone group). Overall, 612 participants were included in the intention to treat analysis (fig 1).

Participants were randomly assigned at a median gestational age of 20.5 weeks in both groups, with a mean cervical length of 28.6 mm (standard deviation (SD) 5.3 mm) in the pessary group versus 28.5 mm (5.3 mm) in the progesterone group (table 1).

The primary outcome, a composite adverse perinatal outcome, occurred in 19 (6%) of 303 participants in the pessary group compared with 17 (6%) of 309 in the progesterone group (corrected relative risk 1.1 (95% confidence interval (CI) 0.59 to 2.1)). A sensitivity analysis with a mixed model using a random effect for participating centre was executed to investigate the possible effect of centre on the outcome (1.1 (0.59 to 2.2), $P=0.70$). No difference was noted between random or fixed effects model on the primary outcome. Given that hardly any difference was also found between the fixed and crude effects model on both the primary and all other outcomes, the specific centre did not have an effect on the outcomes. Thus, the outcomes are generalisable and extrapolation of the outcomes to other centres is justified.

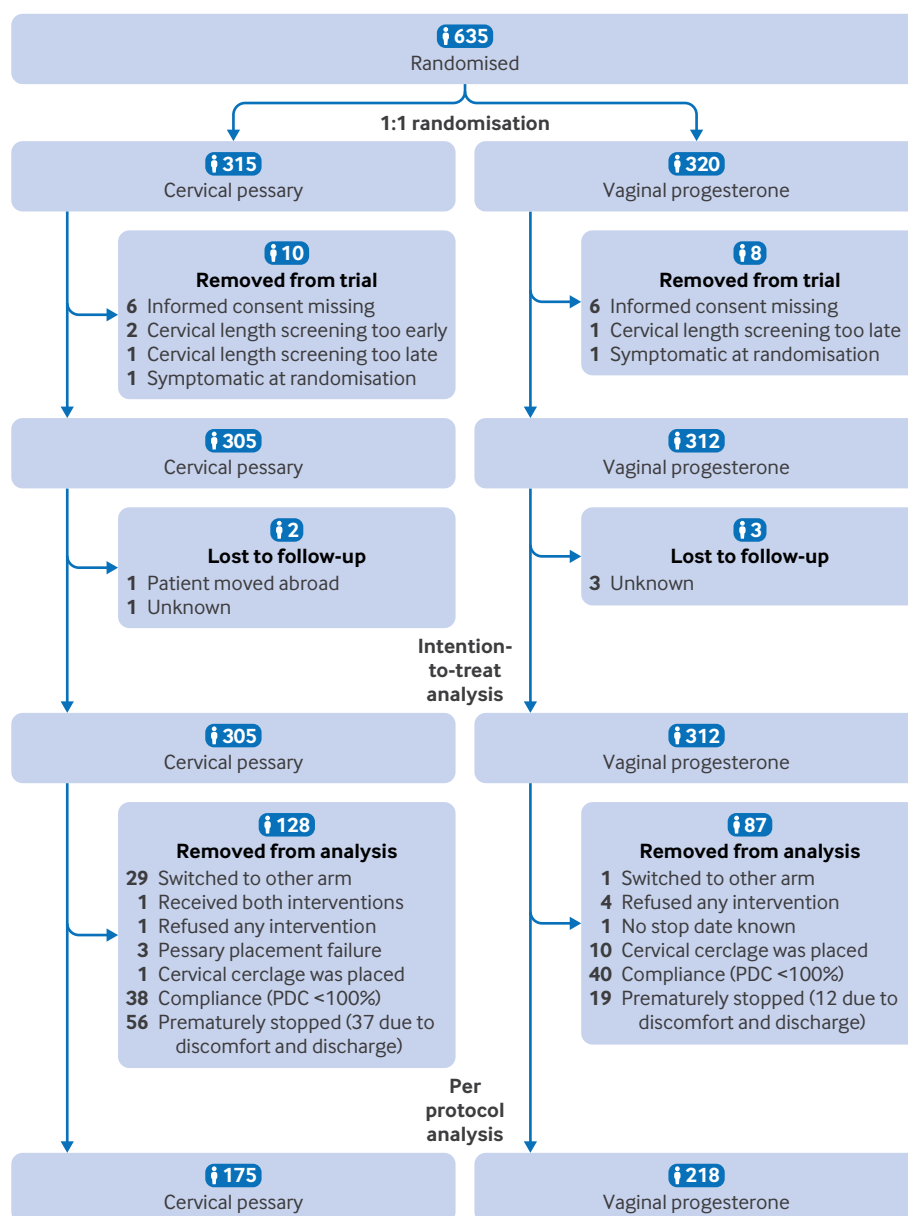


Fig 1 | Flowchart of inclusion, randomisation, and follow-up. PDC=proportion of days covered

The rates of (spontaneous) preterm birth <32, 34, and 37 weeks did not differ significantly between both groups (table 2). Preterm birth rates <28 and 24 weeks of gestation were lower in the progesterone group, but this difference did not reach statistical significance. The Kaplan-Meier curve was not significantly different (fig 2). Mean time to delivery was 121 days (SD 28) and 122 days (24) in the pessary and progesterone group. Neonatal outcomes were not significantly different in both groups, including mean birth weight (3106 g v 3184 g, $P=0.17$), perinatal death (11/303 (4%) v 7/309 (2%), relative risk 1.6 (0.63 to 4.1)) and duration of neonatal intensive care unit admittance (23 days (interquartile range 3-57) v 13 days (6-23); $P=0.89$). Maternal outcomes were similar in both groups, including total infections (56/303 (19%) v

54/309 (18%), relative risk 1.1 (0.75 to 1.5)) and chorioamnionitis (8/303 (3%) v 5/309 (2%), 1.6 (0.54 to 4.9)). Cervical cerclages were placed less often in the pessary group compared with the progesterone group (1/303 (<1%) v 10/309 (3%), 0.10 (0.01 to 0.79)).

Among all randomly assigned participants, serious adverse events occurred in three (1%) women allocated to pessary and two (1%) women in the progesterone group (supplementary table S1). The serious adverse events concerned four admissions for non-obstetric indications (upper respiratory tract infection ($n=2$); inflammation of the shoulder joint; and appendicitis) and one postpartum diagnosis of severe congenital anomaly of the neonate (trisomy 21). None of these serious adverse events was associated with the allocated treatment.

Table 1 | Baseline characteristics; data are numerator (percentage), unless otherwise specified

Characteristics	Pessary (n=303)	Progesterone (n=309)
Maternal age, years (mean, SD)	32.1 (5.4)	32.5 (5.3)
Body mass index, kg/m ² (mean, SD)	24.6 (5.5)	24.8 (5.3)
Education:		
Low*	11 (4)	10 (3)
Middle and high†	118 (39)	122 (39)
Unknown/other	174 (57)	177 (57)
Ethnic group:		
White	172 (57)	183 (59%)
Black	48 (16)	46 (15)
Middle Eastern	30 (10)	20 (7)
Asian	12 (4)	13 (4)
Other	11 (4)	16 (5)
Unknown	25 (8)	27 (9)
Current smoker	17 (6)	18 (6)
Uterus anomaly	9 (3)	10 (3)
Nulliparous	202 (67)	200 (65)
Previous preterm birth (34 ⁺⁰ -36 ⁺⁶)	23 (8)	21 (7)
History of cervical surgery (conisation/LLETZ)	65 (22)	54 (18)
History of curettage	43 (14)	56 (18)
Pregnancy after IVF/ICSI	30 (10)	33 (11)
Gestational age (weeks+days) at randomisation (median, IQR)	20+5 (19+5-21+5)	20+5 (19+6-21+5)
Cervical length at randomisation (mm) (mean, SD)	28.6 (5.3)	28.5 (5.3)
Cervical length, range:		
0-15 mm	11 (4)	11 (4)
16-20 mm	9 (3)	14 (5)
21-25 mm	42 (14)	44 (14)
26-30 mm	116 (39)	102 (33)
31-35 mm	123 (41)	138 (45)
Funnelling	34 (11)	26 (8)

LLETZ=large loop excision of the transformation zone; ICSI=intracytoplasmic sperm injections; IQR=interquartile range; IVF=in vitro fertilisation; SD=standard deviation.

*Primary school, prevocational secondary education (VMBO in Dutch).

†Senior general secondary education (HAVO in Dutch), pre-university secondary education (VWO in Dutch), secondary vocational education (MBO in Dutch), higher professional education (HBO in Dutch), and university education (WO in Dutch).

In the predefined subgroup analysis, effect modification was reported for participants with a cervical length of 25 mm or less compared with more than 25 mm ($P_{\text{interaction}}=0.031$). In participants with a cervical length of 25 mm or more, the composite neonatal outcome occurred more often in the pessary group compared with the progesterone group but did not reach statistical significance (15/62 (24%) v 8/69 (12%), relative risk 2.1 (95% CI 0.95 to 4.6)) (table 3). Extreme spontaneous preterm birth at less than 28 weeks seemed more frequent in the pessary group (10/62 (16%) v 3/69 (4%), 3.7 (1.1 to 12.9)). Supplementary table S2 shows the subgroup analysis on parity and supplementary table S3 shows an exploratory analysis on preterm birth rates for cervical lengths of 0-25, 26-30, and 31-36 mm.

The per protocol analysis, including 393 (64%) of the 612 participants (175 pessary v 218 progesterone), did not show any different insights (supplementary table S4). The lower number of participants in the pessary group primarily results from 29 participants that switched treatment and 37 participants that discontinued due to discomfort or excessive discharge (even after replacement) (supplementary table S5). In the progesterone group, only one participant switched treatment and 12 discontinued due to discomfort or excessive discharge (supplementary

table S5). Progesterone was better tolerated than the pessary. Even with different cut-off values (60-100% proportion of days covered) for treatment adherence, no significant differences were found in the primary outcome (supplementary table S4).

Discussion

Principal findings

In women who had singleton births with no prior spontaneous preterm birth <34 weeks' gestation and with a midtrimester cervical length of 35 mm or less, pessary did not improve perinatal outcome compared with progesterone. In the subgroup of a cervical length of 25 mm or less, differences seemed larger in favour of progesterone, especially for extremely preterm birth at less than 28 weeks.

Strengths and weaknesses of the study

This multicentre, randomised, controlled trial is the first to our knowledge to directly compare the effectiveness of cervical pessary versus vaginal progesterone for preventing preterm birth in women at low risk with a short cervix, of whom had no prior spontaneous preterm birth of less than 34 weeks' gestation and thus had not already been offered standardised preventive interventions. The cut-off value of 35 mm allowed us to assess the effectiveness of these treatments across

Table 2 | Primary and secondary outcomes. Data are numerator (percentage), unless otherwise specified

Outcomes	Pessary (n=303)	Progesterone (n=309)	Relative risk or mean difference (95% CI)	P value
Primary outcome				
Composite adverse neonatal outcome (ITT), crude	19 (6)	17 (6)	1.1 (0.60 to 2.2)	0.69
Composite adverse neonatal outcome (ITT), adjusted for centre	19 (6)	17 (6)	1.1 (0.59 to 2.1)	0.74
Composite adverse neonatal outcome (ITT), adjusted for centre, random	19 (6)	17 (6)	1.1 (0.59 to 2.2)	0.70
Composite adverse neonatal outcome (PP), crude	16 (9)	14 (7)	1.3 (0.68 to 2.7)	0.39
Obstetric outcomes				
PTB <37 weeks	53 (18)	50 (16)	1.1 (0.76 to 1.5)	0.67
sPTB <37 weeks	44 (15)	40 (13)	1.1 (0.75 to 1.7)	0.57
PTB <34 weeks	27 (9)	27 (9)	1.0 (0.61 to 1.7)	0.94
sPTB <34 weeks	23 (8)	23 (7)	1.0 (0.59 to 1.8)	0.95
PTB <32 weeks	24 (8)	24 (8)	1.0 (0.59 to 1.8)	0.94
sPTB <32 weeks	21 (7)	21 (7)	1.0 (0.57 to 1.8)	0.95
PTB <28 weeks	14 (5)	8 (3)	1.8 (0.76 to 4.2)	0.18
sPTB <28 weeks	12 (4)	7 (2)	1.7 (0.70 to 4.4)	0.23
PTB <24 weeks	9 (3)	4 (1)	2.3 (0.71 to 7.4)	0.16
sPTB <24 weeks	8 (3)	4 (1)	2.0 (0.62 to 6.7)	0.24
Time to delivery (days), mean (SD)	121 (28)	122 (24)	1.3 (−2.9 to 5.4)	0.25
Mode of delivery:				
Vaginally	230 (76)	227 (73)	1.1 (0.84 to 1.5)	0.49
Caesarean section	50 (17)	60 (19)	0.97 (0.90 to 1.0)	0.35
PPROM <36 weeks	35 (12)	29 (9)	1.2 (0.78 to 2.0)	0.36
Cerclages after randomisation	1 (<1)	10 (3)	0.10 (0.01 to 0.79)	0.029
Neonatal outcomes				
Birth weight (g), mean (SD)	3106 (810)	3184 (754)	77 (−47 to 202)	0.17
Birth weight <1500 g	21 (7)	17 (6)	1.3 (0.68 to 2.3)	0.47
Birth weight <2500 g	44 (15)	35 (11)	1.3 (0.85 to 1.9)	0.24
Neonatal diagnosis:				
Patent ductus arteriosus	1 (<1)	1 (<1)	1.0 (0.06 to 16.2)	0.99
Treated seizures	2 (1)	1 (<1)	2.0 (0.19 to 22.4)	0.56
Chronic lung disease	2 (1)	5 (2)	0.41 (0.08 to 2.0)	0.28
PVL >grade 1	0 (NA)	0 (NA)	NA	NA
IVH grade III or IV	0 (NA)	0 (NA)	NA	NA
NEC >stage 1	3 (1)	1 (<1)	3.1 (0.32 to 29.2)	0.33
ROP	1 (<1)	0 (NA)	NA	NA
Culture proven sepsis:				
<72 h after birth	1 (<1)	2 (1)	0.51 (0.05 to 5.6)	0.58
>72 h after birth	4 (1)	7 (2)	0.58 (0.17 to 2.0)	0.38
Perinatal death	11 (4)	7 (2)	1.6 (0.63 to 4.1)	0.32
NICU admission (days), median (IQR)	23 (3–57)	13 (6–22.8)	NA	0.89
Congenital abnormalities	6 (2)	7 (2)	0.87 (0.30 to 2.6)	0.81
Maternal outcomes				
Maternal mortality	0 (NA)	0 (NA)	NA	NA
Maternal morbidity:				
Thromboembolic complication	0 (NA)	0 (NA)	NA	NA
Infections during pregnancy*	56 (19)	54 (18)	1.1 (0.75 to 1.5)	0.75
Chorioamnionitis (intrauterine infection)	8 (3)	5 (2)	1.6 (0.54 to 4.9)	0.39
Endometritis	5 (2)	7 (2)	0.71 (0.23 to 2.2)	0.57
Pneumonia	0 (NA)	0 (NA)	NA	NA
Pre-eclampsia/HELLP	5 (2)	10 (3)	0.51 (0.18 to 1.5)	0.21

BPD=bronchopulmonary dysplasia; HELLP=haemolysis, elevated liver enzymes, and low platelets; ITT=intention to treat; IQR=interquartile range; IVH=intraventricular haemorrhage; NA=not available; NEC=necrotising enterocolitis; NICU=neonatal intensive care unit; PP=per protocol; PPRM=premature prelabour rupture of membranes; (s)PTB=(spontaneous) preterm birth; PVL=periventricular leukomalacia; RDS=severe respiratory distress syndrome; ROP=retinopathy of prematurity; SD=standard deviation.

*Genital tract infections, urinary tract infections, chorioamnionitis.

various cervical length thresholds. Therefore, a larger at-risk population could be assessed compared with a cut-off value of 25 mm and the results relate to a larger, general, pregnant population.

We were limited by the fact that masking of treatment groups was not possible due to the nature of interventions, potentially introducing bias. Another limitation is the self-reported medication compliance in the progesterone group, with less than 30% of participants returning their medication diaries. Therefore, obstetric care givers' notes in patient

records and verbal enquiries by research nurses were used to assess adherence. Participants who had no notes, indicating poor adherence or early discontinuation, were assumed to be compliant up until 36 weeks of gestation. This assumption may have led to an overestimation of the actual compliance and an underestimation of the preventive potential of progesterone on preterm birth in the per protocol analysis. Alternatively, the effect of a pessary could have been undervalued because no additional training took place beyond basic placement guidelines.

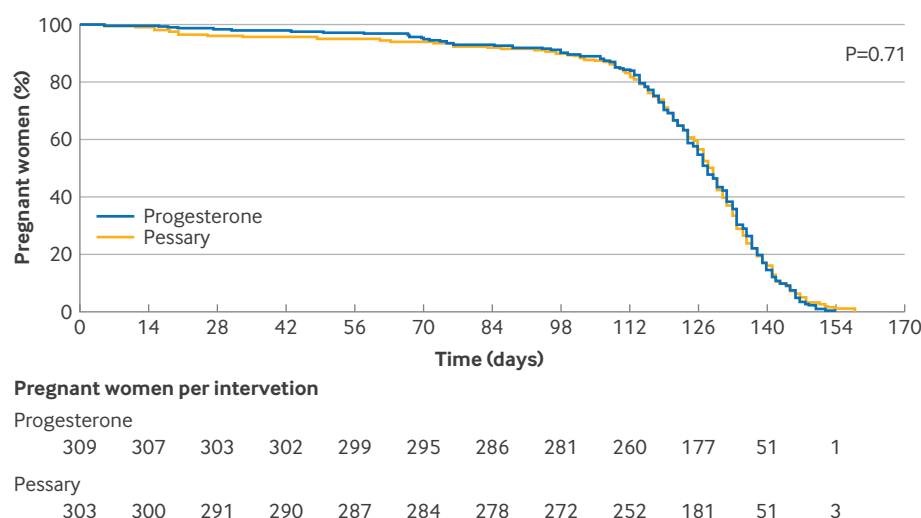


Fig 2 | Kaplan-Meier curve for time to delivery from randomisation

Consequently, less experienced healthcare providers might have inaccurately inserted pessaries. Conversely, our study built on previous studies like the ProTwin trial (NTR1858) in which a positive effect on pessary was reported in women with a twin pregnancy and a short cervix. Our study was performed in the same network of hospitals. Additionally, more cerclages were placed in the progesterone group. We speculate that progesterone may allow for easier monitoring of cervical length and thus lower the threshold to insert an emergency cerclage.

Furthermore, the trial results differed from the planned effect size. We expected to find a reduction in the composite outcome to 1% on the basis of the PECEP trial.¹⁰ The PECEP trial included participants with a cervix of less than 25 mm only. Since our cut-off was 35 mm or less, we expected a lower frequency of adverse perinatal outcomes in our study population with a pessary. Instead, we found a higher percentage compared with the progesterone group (6.3% v 5.5%). Comparing study populations, 11% of the PECEP participants had at least one preterm birth, vaginal and cervical swabs were taken of every participant and treated in case of infection and participants with a history of a cone biopsy were excluded. These differences might have affected the effectiveness of a

pessary in the PECEP population. Nevertheless, these outcomes were unexpected.

By exploring different cut-off values for good adherence, our intention was to include a maximum number of participants displaying some anticipated treatment effect (at least 60%) as well as those showing a pure treatment effect (100%). The accuracy of these cut-off values for determining good or poor adherence is in question, especially considering the lack of clarity as to what the minimum usage requirement should be for reaching a positive outcome with the interventions applied in this context.³⁰⁻³²

Finally, even though many secondary obstetric and maternal outcomes and subgroup analyses show no statistical differences between groups, potentially significant clinical (maternal or obstetric) differences cannot be ruled out due to the wide confidence intervals. Although maternal outcomes are not expected to differ substantially between intervention groups, this study does not have the statistical power to address rare adverse outcomes (such as maternal death). The same applies to the preterm birth rates of less than 28 and 24 weeks' gestation, where a possible reduction in the pessary group cannot be ruled out, given the lack of significant differences with wide confidence intervals. The wide intervals can be

Table 3 | Subgroup analyses on the primary outcome composite adverse perinatal outcome, spontaneous preterm birth (PTB) at <34 weeks' gestation, and spontaneous preterm birth at <28 weeks' gestation, by cervical length.

Subgroup analyses	Pessary, n (%)	Progesterone, n (%)	Relative risk (95% CI)	P value interaction term
Composite adverse perinatal outcome (crude):				
≤25 mm	15/62 (24)	8/69 (12)	2.1 (0.95 to 4.6)	0.031
>25 mm	4/241 (2)	9/240 (4)	0.44 (0.14 to 1.4)	
Spontaneous PTB <34 weeks:				
≤25 mm	15/62 (24)	14/69 (20)	1.2 (0.63 to 2.3)	0.61
>25 mm	8/241 (3)	9/240 (4)	0.89 (0.35 to 2.3)	
Spontaneous PTB <28 weeks:				
≤25 mm	10/62 (16)	3/69 (4)	3.7 (1.1 to 12.9)	0.06
>25 mm	2/241 (1)	4/240 (2)	0.50 (0.1 to 2.7)	

explained by the low incidence of extremely preterm or immature births. Nevertheless, in the subgroup of cervical length of 25 mm or less, progesterone seems to be advantageous over pessary treatment in delivery <28 weeks' gestation.

Strengths and weaknesses in relation to other studies

The effectiveness of progesterone in the prevention of preterm birth has been proven in selected populations in multiple randomised controlled trials and confirmed by an individual participant data meta-analysis and a Cochrane review.^{8 33-35} Goya and colleagues compared a pessary to expectant management in singleton pregnancies with a cervical length of less than 25 mm and found a reduction of preterm birth of less than 34 weeks of 50% in the pessary group.¹⁰ Contradictory, the most recent meta-analysis did not show any benefit of the pessary over expectant management or vaginal progesterone in the reduction of preterm birth or perinatal outcomes in asymptomatic women with a singleton pregnancy with a short cervix.³⁶ Also, two recently published randomised controlled trials comparing a combination of a cervical pessary and progesterone versus progesterone only and a randomised controlled trial comparing cervical pessary versus usual care did not find a reduction of preterm birth in the pessary group.^{13 17} Where Pacagnella and colleagues did not find statistical differences in terms of neonatal morbidity and mortality between both intervention groups, in the study by Hoffman and colleagues, pessary use was associated with a higher rate of fetal or neonatal or infant mortality.^{13 17} Our results are consistent with those from the meta-analysis and the randomised controlled trials, finding no beneficial effect of a pessary over progesterone in the prevention of preterm birth, but alternatively to Hoffman and colleagues also no differences in associated neonatal complications.

In both intervention groups, we report relatively high rates of preterm birth compared with previous trials. In the subgroup of cervical length of 25 mm or less with progesterone use, the rate of preterm birth of less than 28 weeks was 5.8%, which is similar to the rate of 7.6% noted in a meta-analysis of individual patient data on the effectiveness of progesterone.³⁵ However, our rate of preterm birth at less than 28 weeks in the pessary group was 19.4%, which is higher than the placebo group in the meta-analysis (11%). In the interpretation of our preterm birth rates, our preterm birth definition includes 16 weeks as the lower limit of gestational age, whereas Goya and colleagues defined preterm birth as birth from 24 weeks onward.¹⁰ When we only count the preterm births from 24 weeks onward, our preterm birth rates at less than 34 weeks of 30.6% (pessary) and 24.6% (progesterone) become 17.7% and 20.3%, respectively. These rates are still high but emphasise the proportion of extremely preterm births in our preterm birth rates, especially for the pessary group. Additionally, mean gestational age at randomisation in our study is lower compared

with the previously mentioned studies (20.7 weeks v 21.2-23.5 weeks) and therefore, the period to deliver prematurely within the course of this study was longer.^{9 10 12-14} Furthermore, a short cervical length at an earlier gestation is associated with a higher risk of preterm birth.³⁷ Differences in baseline characteristics compared with previous trials may have contributed to the high rates of preterm birth observed, such as a high proportion of nulliparous (66%), previous cervical surgery (20%), and the different distribution of ethnic groups. Specifically, 58% of participants were white, 15% were black, 5% were Middle Eastern, and 4% were Asian. A recent study from the Netherlands confirmed differences in the risk of preterm birth associated with ethnic group: people of South Asian and African ethnic group living in Amsterdam had higher risk.³⁸

In previous studies, cervical and vaginal swabs were taken for bacteriological analysis and 20-27% of patients were treated for abnormal vaginal flora including *Candida*, bacterial vaginosis, *Escherichia coli*, and Group B streptococcus.^{9 10 12 14} Pessary placement was delayed pending treatment. In our study, Nugent-scores or bacteriological swabs were not performed routinely. Whether the presence of abnormal vaginal flora affects the effectiveness of a cervical pessary or vaginal progesterone or whether ruling out an asymptomatic infection before placement is necessary remains unclear. The high rate of preterm birth in the pessary group cannot be attributed to a higher number of symptomatic infections because we noted similar rates of symptomatic maternal infections in both groups (including clinically diagnosed intrauterine and genital tract infections). However, we cannot rule out the possibility of asymptomatic abnormal flora, genital tract infections, or bacterial vaginosis at time of pessary placement.

Unanswered questions and future research

We observed that the differences in preterm birth rates between pessary and progesterone were more pronounced in women with a cervical length of 25 mm or less. This association might suggest that the design of the pessary, which supports the lower segment and shape of the uterus, requires a longer cervical length to be effective in preventing preterm birth. Possibly, this theory could be used as in subsequent studies or post hoc analyses. Our research findings provide an opportunity to update an individual patient data meta-analysis on the efficacy of pessary use in preventing preterm birth. Additionally, the comparison with previous studies raises new questions, such as the added value of performing bacteriological analysis to pessary or progesterone treatment.

Conclusions

To summarise, our study did not find significant differences in the prevention of a composite adverse perinatal outcome between the use of a pessary and progesterone in women with a singleton pregnancy with no prior spontaneous preterm birth at less than 34 weeks' gestation and with a midtrimester short cervix

of 35 mm or less. However, in the subgroup analysis of cervical length of 25 mm or less, a pessary seemed less effective in preventing a composite adverse perinatal outcome and spontaneous preterm birth of less than 28 weeks' gestation. These findings suggest that cervical pessary may be less effective than vaginal progesterone in reducing adverse perinatal outcomes in women with a singleton pregnancy with no prior spontaneous preterm birth of less than 34 weeks' gestation and with a cervical length of 25 mm or less.

AUTHOR AFFILIATIONS

¹Department of Obstetrics and Gynaecology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

²Amsterdam Reproduction and Development Research Institute, Amsterdam, Netherlands

³Department of Obstetrics and Gynaecology, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands

⁴Department of Obstetrics and Gynaecology, Flevoziekenhuis, Almere, Netherlands

⁵Department of Obstetrics and Gynaecology, Ter Gooi Medical Center, Blaricum, Netherlands

⁶Department of Obstetrics and Gynaecology, Radboud University Medical Centre, Radboud University, Nijmegen, Netherlands

⁷Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Haarlem, Netherlands

⁸Department of Obstetrics and Gynaecology, Sint Fransiscus Gasthuis, Rotterdam, Netherlands

⁹Department of Obstetrics, University Medical Centre Groningen, University of Groningen, Groningen, Netherlands

¹⁰Department of Obstetrics and Gynaecology, Zaans Medisch Centrum, Zaandam, Netherlands

¹¹Department of Obstetrics and Gynaecology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

¹²Department of Obstetrics and Gynaecology, Monash University, Clayton, Australia

¹³Aberdeen Centre for Women's Health Research, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK

¹⁴Department of Obstetrics, Wilhelmina's Children Hospital, UMC Utrecht, Utrecht, Netherlands

We thank all women who participated in this study, as well as the staff of the Dutch trial bureau of the Dutch Consortium, all participating hospitals and ultrasound centres and especially all the research nurses and midwives involved in this trial, especially JH Bakker and L Videler-Sinke. We thank the members of the DSMB for their contribution, namely JJ Duvekot, KCB Roes, HJ Wildschut, HW Bruinse, and JH van der Lee. Finally, we also thank the other members of the Quadruple P Research Group, namely the local principal investigators from the hospitals that were initially involved, but withdrew their participation in the trial and stopped recruiting new patients: RH Stigter, Deventer Ziekenhuis, Netherlands; JTJ Brons, Medisch Spectrum Twente, Netherlands; E van Beek, Sint Antonius Ziekenhuis, Netherlands; MN Bekker, University of Utrecht, Wilhelmina's Children Hospital, UMC Utrecht, Netherlands; J Langeveld, Atrium Medisch Centrum Zuyderland, Netherlands; DNN Papatsonis, Amphia Ziekenhuis, Netherlands; EM Tepe, Slingeland Ziekenhuis, Netherlands; ECJ Verheijen, Maasziekenhuis Pantein, Netherlands, and IM Evers, Meander Medisch Centrum, Netherlands.

Contributors: BWJM was the first principal investigator at Amsterdam Medical Center and wrote the first drafts of the protocol and report, and is guarantor for the report. In 2016 EP took over as principal investigator. EP, BMK, BWJM, BK, DJB, CAN, ES, and MDZ represent the QP study group and were involved in conception and design of the study. MDZ, CED, and ALG are involved in the logistics of the study. ESA, BJH, WMB, MAB, HV, JD, FWM, KCV, MAM, SJG, and YMM are local investigators at the participating centres. ALG, CED, BMK, and MCW conducted the analysis with consultation of EP and BWJM. EP, BMK, MAO, ALG, MCW, and CED drafted the manuscript, which follow the SPIRIT check list for reporting randomised trials. All authors read and approved the final draft of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The corresponding author attests that all

listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was supported by Stichting Stoptevroegbevalen, a non-profit research foundation supporting scientific projects in the field of preterm birth. The non-profit research foundation Stichting Stoptevroegbevalen is founded to help finance recruitment of patients. The researchers were (financially) independent from the funder.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest and declare: BWJM declared support by a NHMRC Investigator grant (GNT1176437). BWM reports consultancy, research funding and travel support from Merck. EP and MAO declared participation on the board of the Research foundation 'Stichting Stoptevroegbevalen' that supported this study. EP, MAO and SJG received several grants with the purpose of scientific research in the field of preterm birth and fetal growth restriction. All other authors declare no support from any organisation for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval was obtained from the Medical Research Ethics Committee of the Amsterdam University Medical Centre (MEC AMC 2013_019) while the boards of all participating centres approved local execution.

Data sharing: Individual participant data that underlies the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available. Study protocol and statistical analysis plan are available too. Informed consent form and analytic code can be provided upon request. The data will be available immediately following publication and will have no end date. Data are available for investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for the purpose of individual participant data meta-analysis. Proposals may be submitted to the corresponding author up to 36 months following article publication.

Transparency: I, BWJM, the manuscript's guarantor, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination statement: All participants receive a letter with a plain-language summary of the results. This summary will be assessed by the Dutch neonatology patients' association, Care4Neo, and distributed among their members too. The results will be internally disseminated through the media departments and websites of the authors' institutes. A good clinical practice will be submitted to the Dutch Journal of Obstetrics and Gynaecology and effort will be made to reach a wider audience through press releases and social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

- 1 Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75-84. doi:10.1016/S0140-6736(08)60074-4
- 2 Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. *Semin Perinatol* 2017;41:387-91. doi:10.1053/j.semper.2017.07.009
- 3 UNICEF. Levels & trends in child mortality: report 2019-estimates developed by the UN inter-agency group for child mortality estimation. *Unicef/WHO/WB/UN*. 2019;1-32.
- 4 Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: The EPICure studies. *BMJ* 2012;345:1-13. doi:10.1136/bmj.e7961
- 5 Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. *JAMA* 2000;284:843-9. doi:10.1001/jama.284.7.843
- 6 Potharst ES, Van Wassenar AG, Houtzager BA, Van Hus JWP, Last BF, Kok JH. High incidence of multi-domain disabilities in very preterm children at five years of age. *J Pediatr* 2011;159:79-85. doi:10.1016/j.jpeds.2010.12.055
- 7 Schaaf JM, Mol BWJ, Abu-Hanna A, Ravelli ACJ. Trends in preterm birth: Singleton and multiple pregnancies in the Netherlands, 2000-2007. *BJOG An Int J Obstet Gynaecol*. 2011.

- 8 Stewart LA, Simmonds M, Duley L, et al. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet* 2021;397:1183-94. doi:10.1016/S0140-6736(21)00217-8
- 9 Saccone G, Maruotti GM, Giudicepietro A, et al. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial. *JAMA* 2017;318:2317-24. doi:10.1001/jama.2017.18956
- 10 Goya M, Pratorcorona L, Merced C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): An open-label randomised controlled trial. *Lancet* 2012;379:1800-6. doi:10.1016/S0140-6736(12)60030-0
- 11 Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. *Cochrane Database Syst Rev* 2013;2013.
- 12 Nicolaides KH, Syngelaki A, Poon LC, et al. A randomized trial of a cervical pessary to prevent preterm singleton birth. *N Engl J Med* 2016;374:1044-52. doi:10.1056/NEJMoa1511014
- 13 Pacagnella RC, Silva TV, Cecatti JG, et al. Pessary plus progesterone to prevent preterm birth in women with short cervixes: a randomized controlled trial. *Obstet Gynecol* 2022;139:41-51. doi:10.1097/AOG.0000000000004634
- 14 Hui S, Chor C, Lau T, Lao TLT. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. *Am J Perinatol* 2012;30:283-88. doi:10.1055/s-0032-1322550
- 15 Dugoff L, Berghella V, Sehdev H, Mackeen AD, Goetzl L, Ludmir J. Prevention of preterm birth with pessary in singletons (PoPPS): randomized controlled trial. *Ultrasound Obstet Gynecol* 2018;51:573-9. doi:10.1002/uog.18908
- 16 Cruz-Melguizo S, San-Frutos L, Martínez-Payo C, et al. Cervical pessary compared with vaginal progesterone for preventing early preterm birth: a randomized controlled trial. *Obstet Gynecol* 2018;132:907-15. doi:10.1097/AOG.0000000000002884
- 17 Hoffman MK, Clifton RG, Biggio JR, et al. Cervical pessary for prevention of preterm birth in individuals with a short cervix: the Tops randomized clinical trial. *JAMA* 2023;330:340-348. doi:10.1001/jama.2023.10812
- 18 Van Der Ven J, Van Os MA, Kazemier BM, et al. The capacity of mid-pregnancy cervical length to predict preterm birth in low-risk women: a national cohort study. *Acta Obstet Gynecol Scand* 2015;94:1223-34. doi:10.1111/aogs.12721
- 19 van Zijl MD, Koullali B, Naaktgeboren CA, et al. Pessary or progesterone to prevent preterm delivery in women with short cervical length: the Quadruple P randomised controlled trial. *BMC Pregnancy Childbirth* 2017;17:1-8. doi:10.1186/s12884-017-1454-x
- 20 Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010. doi:10.1136/bmj.c332
- 21 McIntosh J, Feltovich H, Berghella V, Manuck T. The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. *Am J Obstet Gynecol* 2016;215:B2-7. doi:10.1016/j.ajog.2016.04.027
- 22 Rijksinstituut voor Volksgezondheid en Milieu. Kwaliteitseisen tweede trimester SEO (structureel echoscopisch onderzoek). <https://www.pns.nl/documenten/kwaliteitseisen-tweede-trimester-seo>. 2022.
- 23 Rijksinstituut voor Volksgezondheid en Milieu. *Kwaliteitseisen echoapparatuur en beeldopslag voor prenatale screening*. 2020;2020.
- 24 NVOG. Protocol: Datering van de zwangerschap. Versie 2.0. 2018.
- 25 Arabin B, Halbesma JR, Vork F, Hubener M, van Eyck J. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix?. *J Perinat Med* 2003;31:122-33. doi:10.1515/JPM.2003.017
- 26 Van't Hooft J, Duffy JMN, Daly M, et al. A core outcome set for evaluation of interventions to prevent preterm birth. *Obstet Gynecol* 2016;127:49-58. doi:10.1097/AOG.0000000000001195
- 27 de Vries LS, Eken P, Dubowitz LMS. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992;49:1-6. doi:10.1016/S0166-4328(05)80189-5
- 28 Jobe AH, Bancalari E. NICHD / NHLBI / ORD Workshop Summary. *Am J Respir Crit Care Med* 2001;163:1723-9. doi:10.1164/ajrccm.163.7.2011060
- 29 Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978;187:1-7. doi:10.1097/0000658-197801000-00001
- 30 Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify Nonadherence. *Ann Pharmacother* 2009. doi:10.1345/aph.1L496
- 31 Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: Optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;25:2303-10. doi:10.1185/03007990903126833
- 32 Baumgartner PC, Haynes RB, Hersberger KE, Arnet I. A systematic review of medication adherence thresholds dependent of clinical outcomes. *Front Pharmacol* 2018;9. doi:10.3389/fphar.2018.01290
- 33 Da Fonseca EB, Bittar RE, Carvalho MHB, 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. doi:10.1067/mob.2003.41
- 34 Meis PJ, Klebanoff M, Thom E, et al. A for the NI of CH and HDMMUN. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348:2379-85. doi:10.1056/NEJMoa035140
- 35 Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol* 2018;218:161-80. doi:10.1016/j.ajog.2017.11.576
- 36 Conde-Agudelo A, Romero R, Nicolaides KH. Cervical pessary to prevent preterm birth in asymptomatic high-risk women: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2020;223:42-65.e2. doi:10.1016/j.ajog.2019.12.266
- 37 Costantine MM, Ugwu L, Grobman WA, et al. Cervical length distribution and other sonographic ancillary findings of singleton nulliparous patients at midgestation. *Am J Obstet Gynecol* 2021;225:181.e1-11. doi:10.1016/j.ajog.2021.02.017
- 38 Klumper J, Ravelli ACJ, Roos C, Abu-Hanna A, Oudijk MA. Deprived neighborhoods and spontaneous preterm birth: A national cohort study. *Eur J Obstet Gynecol Reprod Biol* 2022;274:88-95. doi:10.1016/j.ejogrb.2022.05.012