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Pessary or progesterone to prevent preterm birth in women with short cervical length: protocol of the 4-6 year follow-up of a randomised controlled trial (Quadruple-P)

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Abstract

Introduction:

Vaginal progesterone and a cervical pessary are both interventions to prevent preterm birth (PTB) in high risk pregnancies. Thus far, beneficial or harmful effects of these interventions on long-term child health and development are described, but the literature is scarce. With this follow-up study, we intent to investigate if progesterone or a pessary is superior for the prevention of PTB considering the child's health on the long term.

Methods and analysis:

This study is a follow-up study of the Quadruple-P trial; a multicentre, randomised clinical trial (NL42926.018.13, Eudractnumber 2013-002884-24) which randomizes women with an asymptomatic midtrimester short cervix to daily progesterone or a pessary for the prevention of PTB. All children born to mothers who participated in the Quadruple-P study (n=628 singletons and n=332 multiples) will be eligible for follow-up at 4-6 years of corrected age. Children will be assessed using parental questionnaires. Main outcomes are child (neuro)development and behavior. Other outcomes include child mortality, growth and general health. A composite of adverse child outcomes will be compared between the progesterone and pessary groups reporting odds ratio and the corresponding 95% Confidence Interval. Analyses will be performed separately for singletons and multiples and using the intention to treat approach.

Ethics and dissemination:

The Medical Research Ethics Committee from Amsterdam UMC confirmed that de Medical Research Involving Human Subjects Act (WMO) did not apply to our study (W20_481 #20.531). Results will be published in a peer-reviewed journal and shared with stakeholders and participants. This protocol is published before analysis of the results.

Registration details:

This follow-up study is registered in the Netherlands Trial Register (NL9646). The original trial is partly funded by Stichting Achmea Gezondheidszorg (SAG), a Dutch health foundation founded by insurance company Achmea (Z475) and partly by "Stop te vroeg bevallen", a foundation that stimulates and supports medical research regarding prevention of preterm birth. This follow-up study is also funded by "Stop te vroeg bevallen".

Key words: follow-up, long-term, pessary, preterm birth, progesterone

Article Summary

- This study will be one of very few studies collecting long-term follow-up data after progesterone and pessary application during pregnancy in context of a randomised controlled trial.
- We will evaluate if a pessary or progesterone is superior for the prevention of preterm birth considering the child's health on the long-term for both singleton and multiple pregnancies.
- We will use two validated questionnaires to assess the child's development and daily functioning on all developmental domains, in combination with questionnaires on behaviour and health.
- In our follow-up population several children will already have passed the age for the validated questionnaires, which could result in detection of children with severe developmental delays, but a few with milder problems might be missed.

Introduction

Background and rationale

Prevention of preterm birth (PTB) is of utmost importance to reduce neonatal mortality and morbidity.[1] Several prenatal interventions to prevent PTB (e.g. progesterone and a pessary) have been investigated with mixed evidence regarding effectiveness in different groups of (high risk) pregnancies.[2-7]

Progesterone promotes uterine quiescence by a range of actions including inhibition of prostaglandin activity, reduction of contraction associated proteins and decreasing oxytocin receptors.[8] In addition, it inhibits cervical ripening by regulating the extracellular matrix metabolism.[9] These range of actions result in its effectiveness to prevent preterm birth. In singletons at risk for PTB (i.e. previous PTB or midtrimester short cervix), vaginal progesterone significantly reduces the risk of birth before 34 weeks (Relative Risk (RR) 0.78, 95% Confidence Interval (CI) 0.68-0.90).[2] In multiples with a midtrimester short cervix, evidence suggests that progesterone decreases the risk of birth before 34 weeks as well (RR 0.68, 95% CI 0.46–0.99).[10] In unselected singleton or multiple pregnancies (i.e. no previous PTB nor midtrimester short cervix), there is no convincing evidence of effect from vaginal progesterone.[2, 11]

Another intervention used for prevention of PTB is a cervical pessary. By altering the axis of the cervical canal and displace the weight of the uterus from the cervix, a pessary may prevent the cervix from shortening and dilation and conserve the mucus plug (a barrier for ascending infections).[12-14] Although several randomised controlled trials (RCTs) have shown a reduction of PTB in singletons with a midtrimester short cervix[15, 16], a recent meta-analysis did not show significant reduction (RR 0.80, 95% CI 0.43-1.49).[17] The ProTWIN trial assessed the effect of a cervical pessary in multiple pregnancies, and in a subgroup with a midtrimester short cervix. They observed a reduction of PTB before 32 weeks of gestation (RR 0.49, 95% CI 0.24-0.97) and improvement of neonatal outcomes with 60% was shown.[5] However, two recent RCTs comparing a cervical pessary (n=250 and n=157) versus no intervention (n=253 and n=158) showed no significant reduction of preterm birth or adverse neonatal outcomes in women with a twin pregnancy and a midtrimester short cervix.[7, 18]

Besides the importance of finding more solid evidence of effectiveness of these obstetric interventions for the prevention of preterm birth, it is necessary to expand the scope beyond immediate neonatal period to the long-term child's health and development. Especially, since previous studies demonstrated that interventions performed during pregnancy can have unexpected harmful long-term effects which may not be apparent at birth.[19, 20] At this moment, only a minority of studies on prenatal exposure to progesterone or pessary have published long term results of the children. To date, there are approximately 150 RCTs on progesterone use for the prevention of

preterm birth. A recently published systematic review identified seven studies (5% of the total amount of studies on progesterone) evaluating long-term effects of prenatal progesterone exposure. This review found no evidence of long-term beneficial or harmful effects, but concluded that the results were based on heterogeneous studies, using different assessments, varying from screening tools to face to face assessments with a follow-up age ranging from 6 months to 8 years.[21] To date, there are approximately 50 RCTs on pessary use for the prevention of preterm birth, of which only two studies (4%) published follow-up information so far.[22, 23] Follow-up of the ProTWIN study showed improvement of child survival without affecting neurodevelopment at three years of corrected age of the children from women with a midtrimester short cervix treated with a pessary compared to no pessary.[22] At four years of corrected age, follow-up data showed no benefits or harmful effects of pessary use regarding child outcome, however, results suggest favourable outcomes for children of women with a midtrimester short cervix .[24] Tran et al[23] performed follow-up of children born to women with a multiple pregnancy and midtrimester short cervix, randomised to vaginal progesterone (n=150) or cervical pessary (n=150), at three years of age. They showed a poor child outcome in 10.5% of the pessary group versus 15.8% in the progesterone group (RR 0.66, 95% CI 0.43-1.01). The data so far is not robust enough to exclude potential harm on long term from pessary or progesterone, or any potential benefit on either one of these interventions. This implies the need for further follow-up research on progesterone and pessary exposure during pregnancy. In 2014, a multicentre randomised trial (Quadruple-P trial) started to evaluate the effectiveness of progesterone versus a pessary in singleton and multiple pregnancies with an asymptomatic midtrimester short cervix for prevention of PTB.[25] This trial allows optimal comparison of the long-term outcomes of exposure to progesterone versus pessary in singleton and multiple pregnancies.

Objectives

We aim to assess the long-term effects of in utero exposure to progesterone versus a pessary on child (neuro)development and behaviour at 4-6 years of corrected age. With this follow-up study, we intent to investigate if progesterone or a pessary is superior for the prevention of PTB considering child's health on the long-term.

Methods and analysis

Study setting

This study will be a follow-up study of a multicentre randomised clinical trial (Quadruple-P trial, NL42926.018.13, Eudractnumber 2013-002884-24) conducted across 21 Dutch hospitals. In the Quadruple-P trial, singletons with an asymptomatic short cervix (≤35mm) at 18-22 weeks of gestation or multiples with an asymptomatic short cervix (<38mm) at 16-22 weeks of gestation are randomised to daily vaginal progesterone versus a pessary continued until 36 weeks of gestation. The Quadruple-P trial has a superiority design and in singletons a pessary is compared with vaginal progesterone as standard care, while in multiples vaginal progesterone is compared with a pessary as standard intervention. Outcomes include adverse perinatal outcomes, PTB rate and maternal morbidity, measured until 10 weeks after expected due date. The Quadruple-P study started in 2014 and finished in the first quartile of 2022 for the singletons. For the multiples recruitment of patients is still ongoing while writing this protocol. Eventually 628 singleton pregnancies and 332 multiple pregnancies will be potentially included in this trial. Long term follow-up of the Quadruple-P study was announced in the original trial protocol.[25]

The follow-up study will be an observational study performed within the Dutch consortium for Healthcare evaluation and Research in Obstetrics and Gynecology and coordinated from the Amsterdam University Medical Centre. Data of this follow-up study will be linked to maternal and neonatal data of the Quadruple-P trial. The study protocol has been developed according to the "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) criteria.

Participants/eligibility criteria

The study population consists of participants of the original Quadruple-P trial and their children. Both singleton- and multiple pregnancies (of whom at least one child is alive) will be eligible for inclusion. Assessment will be performed when children are 4-6 years of corrected age. Only participants who did not refuse to be approached for follow-up research will be approached for this follow-up study. Since the questionnaires in this follow-up study are in Dutch, and the original patient information in both Dutch and English, participants of the original trial who are not able to read Dutch will be excluded from this follow-up study.

Study design

Good clinical practice (GCP) trained research nurses from the local hospital (all involved in the NVOG consortium for research in obstetrics) will verify the medical records of mother and child(ren) for the

possible occurrence of death and to obtain contact details. Using the Dutch Personal Records Database (BRP), a database containing records of all registered citizens of the Netherlands, occurrence of death and up to date contact details will be crosschecked. Thereafter, research nurses will send out information letters and informed consent forms by post. After receiving written informed consent of both parents/caregivers, participants will be contacted by phone to get the opportunity to ask questions, discuss informed consent and to be informed that they can withdraw consent to participate at any time with no reason. Participants will be asked to once fill out four questionnaires when their child is 4-6 years old. Questionnaires will be sent by e-mail and parents/caregivers will be asked to fill out the questionnaires online.

Blinding

No participants or researchers are blinded in the original Quadruple-P trial. In this follow-up study, researchers involved in data entry are blinded for allocation.

Patient involvement

Members of the Parents of preterm children Association (care4neo.nl) have been actively involved by our research team and they have stressed the importance of follow-up research. In 2017, members were asked to fill out an online survey including questions about parents' concerns on their child's development and most important long-term outcomes of complications during pregnancy (e.g. preterm birth). Seventy-five members filled out the online questionnaire of whom 85% percent stated to have concerns on their child's long-term development. In the members' opinion, child's school attainment and cognitive development, behaviour problems or psychological problems, motor skills, respiratory problems, general health, growth, and medication use were the most important outcomes to assess in follow-up research. In 2019, our research team also organised a focus group for women who delivered preterm. This focus group showed comparable outcomes. The results of the questionnaire and focus group have primarily determined our choice in main outcome variables of this follow-up study.

Outcomes

The main outcomes of this follow-up study are child (neuro)development and behaviour disabilities. Other outcomes include child mortality, growth and general health. We will assess all outcomes using parental questionnaires and will report the outcomes as a separate outcome, as well as a composite outcome as described below. We will present data as continuous scores (with mean and Standard Deviation (SD), or median with Interquartile Range IQR) and dichotomised scores (based on the predefined cut-off scores), see table 1. We will document data for singletons and multiples

separately.

Table 1. Overview of the child outcomes and measurements.

Outcome	Method of measurement	Definition	Measurements
Neurodevelopment	Ages and Stages Questionnaire 4th edition (ASQ-4)	Scores of the 5 domains: - communication - gross motor skills - fine motor skills - problem-solving skills - personal-social skills	Mean (SD) Abnormal: ≥2 SD in any domain or multiple domains <1 SD below mean Mildly abnormal: ≥1 and <2 SD in one domain below mean
	Vineland screener	Total adaptive functioning score based on 4 domains: - communication - social skills - daily living skills - motor skills	Mean (SD) Abnormal: ≤10th percentile of the population Mildly abnormal: 11-25th percentile of the population
Behaviour	Strength and Difficulties Questionnaire (SDQ)	Total difficulties score based on 4 subscales: - Conduct problems - Emotional symptoms - Hyperactivity - Peer relationships	Mean (SD) Abnormal: >90th percentile of the population Mildly abnormal: 80-90 percentile of the population
Mortality	Medical records and the Dutch Personal Records Database	Perinatal mortality and death up to 7 years of age.	Number (%)~
General health	General health questionnaire*	Height	Mean (SD) Abnormal: 1.6 SDS above or below target height range
		BMI	Mean (SD) Abnormal: [26, 27] - underweight - overweight - obesity
		Hospital admissions/medication/surgeries	Number (%)

SD: standard deviation. **BMI**: Body Mass Index.

~ The denominator changes into all children born to participants of the original Quadruple-P study.

* This questionnaire was developed by our research team that is specialised in follow-up research of obstetric intervention studies. The questionnaire has been used in multiple follow-up studies.[24, 28-30]

(Neuro)development

- ASQ-4: The Ages and Stages Questionnaire (ASQ) is a screening tool to monitor child development by measuring five domains: communication, gross and fine motor skills, problem-solving skills and personal-social skills. The fourth and thereby newest version of the ASQ will be used for this follow-up study and can be used till 6 years of age. The Dutch version of the ASQ-4 is currently being validated, using a Dutch reference group to identify mean score and SDs.[31]

Interpretation: scores of ≥1 SD below the mean of the ASQ normative data in two or more domains, or ≥2 below the normative mean in at least one domain will be considered abnormal. Results will be considered as mildly abnormal when the scores are ≥1 and <2 SD in one domain below mean. Children >6 years of age with a mildly abnormal score will be considered abnormal.

- Vineland screener: The Vineland screener is a tool to assess adaptive functioning (defined as the collection of conceptual, social and practical skills that have been learned by people in order to function in everyday life) of children from 0 to 6 years. The tool exists of 72 questions concerning everyday behavior and covers four domains: communication, social, motor and daily living skills. The total adaptive functioning score is the sum of these four domains.[32, 33]

Interpretation: A total adaptive functioning score of ≤99 and ≤111 is considered abnormal (≤10th percentile of the population) for children 4-5 years and 5-6 years of age respectively. In children >6 years of age a score ≤115 will be considered abnormal. A total adaptive functioning score of ≤107 and ≤115 will be considered mildly abnormal (11-25th percentile of the population) for children 4-5 years and 5-6 years of age respectively. A mildly abnormal score will not be calculated for children >6 years of age.

Behaviour disabilities

SDQ parent report: The Strengths & Difficulties Questionnaire (SDQ) is a screening tool to identify behavioral problems in children concerning five subscales: emotional problems, conduct problems, hyperactivity, peer problems and prosocial behavior. The validated Dutch translation of the SDQ version 4-17 years will be used. A total difficulties score can be calculated summing the first four subscales, leaving out pro-social behavior.[34, 35]

Interpretation: A Total Difficulty Score of ≥15 is considered abnormal (>90th percentile). A Total Difficulty Score of 11-14 is considered mildly abnormal (80-90th percentile).

Mortality

Child death (i.e. perinatal mortality and death up to 7 years of age). Medical records and the Dutch Personal Records Database will be used to verify the number of deceased children.

General health

General health questionnaire: we used the "general health questionnaire" which is used in several previous obstetric follow-up studies performed by the nationwide obstetric consortium.[24, 36, 37] In the general health questionnaire women will be asked about child growth (i.e. child longitudinal height and weight measurements performed at regular visits at Children's Healthcare Centres at the age of three months, two years and four years) and health related problems (i.e. need for surgery, hospital admissions, medication use and reported medical conditions). Women will also be asked for information about occurrence and outcome of subsequent pregnancies.

Interpretation:

- Growth: Based on Dutch reference values, we will present height as standard deviation scores and dichotomous outcome (normal/abnormal score). An abnormal score is defined as 1.6 SD above or below target height range.[38] We will calculate the body-mass index (BMI) and will report BMI as a continuous value and as a proportion of children who are underweight, overweight or obese based on Dutch reference data.[26, 27]
- Health related problems: we will show the number of child's medical diagnoses, hospital admissions, medication (used) and history of surgery and will classify them per organ system.

Composite outcomes

Composite of adverse child outcome is defined as:

- abnormal: if the score in ASQ-4 or Vineland screener is abnormal for children up to 6 years of age or mildly abnormal for children >6 years, the score in SDQ is abnormal, or the occurrence of child death, as defined above.

- mildly abnormal: if the scores in ASQ-4 or Vineland screener or SDQ questionnaire are mildly abnormal as defined above.

Sample size

In line with the original trial, this follow-up has a superiority design. The original study has included 628 singleton pregnancies (314 participants in each group) and will include 332 multiples (166 participants in each group, i.e. at least 332 children in each group). Although the number of eligible participants for our follow-up study will be fixed, we can calculate the minimum number of participants needed to find significant difference. We considered 0.5 SD as clinically important

difference for the main outcomes (i.e. 6.05 points Vineland screener[31] and 2.41 points SDQ[33]).[38] Therefore, we would need a sample size of 64 participants per study group to achieve a power of 80% and a 2-sided alpha of 0.05 and 86 per study group when we use a conservative alpha of 0.05/3 in view of the three main outcomes as measured by different questionnaires.

Based on prior follow-up studies using questionnaires, we expect to realize a follow-up rate of 30-50%. When only 30% of the participants of the original trial will participate in this follow-up study (n=189 singletons and n=100 multiples, i.e. 200 children), we will still have enough power to detect a clinically important difference of the main outcomes.

Statistical analysis

Analyses will be performed separately for singletons and multiples. Difference in baseline characteristics including sociodemographic background of the families of Quadruple-P follow-up participants in progesterone and pessary group will be measured using unpaired T-test, Mann-Whitney U test, Chi-square test or Fisher's exact test when appropriate. Like so, characteristics of follow-up participants will be compared with those lost to follow-up to detect any attrition bias. A two-sided P-value <0.05 will be considered as statistically significant. We will perform multiple imputation to approach the problem of missing data using maternal characteristics (e.g. ethnicity, age, smoking during pregnancy and education) and neonatal outcomes (e.g. gestational age at birth, birthweight, sex and neonatal sepsis) as predictive variables. We will perform a best and worst-case scenario analysis if the loss to follow-up is substantially high.

For the main outcomes (neurodevelopment) and behaviour, we will report mean scores with SDs and abnormal/mildly abnormal scores of the subscales and total scores of the ASQ-4, Vineland screener and SDQ. For the outcome mortality, the denominator should be changed into all children born to participants of the original Quadruple-P study. In case data of survival is incomplete, multiple imputation can be considered in sensitivity analysis. For the outcome concerning general health, we will mention the outcomes as previously described. Composite of (mildly) abnormal child outcome will be reported for the progesterone and pessary group.

A directed acyclic graph (DAG) analysis will be constructed to assess potential confounders. Identified confounders may be corrected using a linear or logistic regression. In singletons, comparison between progesterone and pessary group will be done using an independent-samples T-test, Mann Whitney U test, Chi-square test or Fisher's exact test, as appropriate. Odds ratio (OR) and the corresponding 95% Confidence Interval (95% CI) for the (mildly) abnormal outcomes will be reported. For multiple pregnancies we will account for multiple children from the

same pregnancy by using generalized linear mixed effects model (GLMM). All analyses will be performed according to the intention-to-treat principle using SPSS or R.

Additional analyses

We will perform sensitivity analysis for the composite of adverse child outcome between progesterone and pessary group (i.e. mortality or abnormal developmental outcome). Analysis will be performed for singletons and multiples separately.

A subgroup analyses will be done comparing children of women with ≥80% compliance versus <80% compliance to progesterone or pessary. Because not all questionnaires are validated for the use up to and including 6 years of age, a subgroup analyse of children <6 years will also be performed.

Data management

All data will be handled confidentially and participants are registered pseudonymised by a 6 digit number. If necessary, investigators have access to the keycode to identify subjects. Procedures of this follow-up study will all be in accordance with the Dutch Personal Data Protection Act.

Discussion

This follow-up study will evaluate long-term child health and development after two frequently used obstetric interventions in pregnancy to prevent preterm birth, vaginal progesterone and cervical pessary. Long-term follow-up is of utmost importance, since short-term success of an intervention does not guarantee beneficial effects for child on the long term and can even have harmful effects.[19, 20, 39] Thus far, only 16% of obstetric randomised controlled trials performed long-term follow-up.[40] To ensure best obstetric care for mother and child, each obstetric intervention study should aim to perform follow-up.

We will perform follow-up during early childhood (4-6 years of age). Early childhood is a very sensitive period for developing cognitive ability, language, social and motor skills. Determining developmental delay or neurodevelopmental disorders at this age will therefore be a reliable predictor for functioning later in life. [41, 42]

In our follow-up study, we will use two different questionnaires to explore child (neuro)development (i.e. ASQ-4 questionnaire and Vineland screener). These questionnaires may complement each other and, therefore, might give better insight in child's functioning. This information could be used in further follow-up research. Thereby, we contribute to the validation of the ASQ 4 questionnaire for the Dutch population. Validation will be completed before the end of the follow-up study. Both questionnaires are suitable for children up to 6 years of age. In our follow-up population several children will already have passed this age before the start of the study. As a result, this may lead to overestimation of the results. However, children with severe developmental delays will still be detected and other questionnaires used (i.e. SDQ and general health questionnaire) are applicable for children beyond 6 years of age. A sub analysis will be performed for only those children who had the appropriate age range for the validated questionnaires.

Ethics and dissemination

This follow-up study is registered at the Dutch Trial Registry (number NL9646, date August 3rd 2021). The Medical Research Ethics Committee from Amsterdam UMC confirmed that de Medical Research Involving Human Subjects Act (WMO) did not apply to our study (W20_481 #20.531). Results will be published in a peer-reviewed journal and shared with stakeholders and participants. This protocol is published before analysis of the results. After analysis and publication, data of this study will be available from the corresponding author upon reasonable request.

Authors' contributions

EvLS, LvdW, EvD, AvB, AL, MvW, MdB, JvH, MO en EP were all involved in conception and design of the study and protocol. The manuscript was drafted by EvLS, LvdW, AL, JvH and EP. The manuscript was reviewed and argued by all authors and all authors approved the final version of the manuscript. The implementation of this follow-up study is made possible in cooperation with the Quadruple-P study group.

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Competing interests statement

No author reported any conflicts of interest.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number:
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Additional file 2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	2, 18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1, 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Pessary or progesterone to prevent preterm birth in women with short cervical length: protocol of the 4-6 year follow-up of a randomised controlled trial (Quadruple-P)

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Pessary or progesterone to prevent preterm birth in women with short cervical length: protocol of the 4-6 year follow-up of a randomised controlled trial (Quadruple-P)

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Abstract

Introduction:

Vaginal progesterone and a cervical pessary are both interventions that are investigated for the prevention of preterm birth (PTB). Thus far, beneficial or harmful effects of these interventions on long-term child health and development are described, but there is no follow-up study comparing these two interventions in a head to head comparison. With this follow-up study, we intent to investigate if progesterone or a pessary is superior for the prevention of PTB considering the child's health at 4-6 years of corrected age.

Methods and analysis:

This study is a follow-up study of the Quadruple-P trial; a multicentre, randomised clinical trial (NL42926.018.13, Eudractnumber 2013-002884-24) which randomizes women with an asymptomatic midtrimester short cervix to daily progesterone or a pessary for the prevention of PTB. All children born to mothers who participated in the Quadruple-P study (n=628 singletons and n=332 multiples) will be eligible for follow-up at 4-6 years of corrected age. Children will be assessed using parental questionnaires. Main outcomes are child (neuro)development and behavior. Other outcomes include child mortality, growth and general health. A composite of adverse child outcomes will be compared between the progesterone and pessary groups reporting odds ratio and the corresponding 95% Confidence Interval. Analyses will be performed separately for singletons and multiples and using the intention to treat approach.

Ethics and dissemination:

The Medical Research Ethics Committee from Amsterdam UMC confirmed that de Medical Research Involving Human Subjects Act (WMO) did not apply to our study (W20_481 #20.531). Results will be published in a peer-reviewed journal and shared with stakeholders and participants. This protocol is published before analysis of the results.

Registration details:

This follow-up study is registered in the Netherlands Trial Register (NL9646). The original trial is partly funded by Stichting Achmea Gezondheidszorg (SAG), a Dutch health foundation founded by insurance company Achmea (Z475) and partly by "Stop te vroeg bevallen", a foundation that stimulates and supports medical research regarding prevention of preterm birth. This follow-up study is also funded by "Stop te vroeg bevallen".

Key words: follow-up, long-term, pessary, preterm birth, progesterone

Article Summary

- This study will be one of very few studies collecting long-term follow-up data after progesterone and pessary application during pregnancy in context of a randomised controlled trial.
- We will evaluate if a pessary or progesterone is superior for the prevention of preterm birth considering the child's health on the long-term for both singleton and multiple pregnancies.
- We will use two validated questionnaires to assess the child's development and daily functioning on all developmental domains, in combination with questionnaires on behaviour and health.
- In our follow-up population several children will already have passed the age for the validated questionnaires, which could result in detection of children with severe developmental delays, but a few with milder problems might be missed.

Introduction

Background and rationale

Prevention of preterm birth (PTB) is of utmost importance to reduce neonatal mortality and morbidity.[1] Several prenatal interventions to prevent PTB (e.g. progesterone and a pessary) have been investigated with mixed evidence regarding effectiveness in different groups of (high risk) pregnancies.[2-7]

Progesterone promotes uterine quiescence by a range of actions including inhibition of prostaglandin activity, reduction of contraction associated proteins and decreasing oxytocin receptors.[8] In addition, it inhibits cervical ripening by regulating the extracellular matrix metabolism.[9] These range of actions result in its effectiveness to prevent preterm birth. In singletons at risk for PTB (i.e. previous PTB or midtrimester short cervix), vaginal progesterone significantly reduces the risk of birth before 34 weeks (Relative Risk (RR) 0.78, 95% Confidence Interval (CI) 0.68-0.90).[2] In multiples with a midtrimester short cervix, evidence suggests that progesterone decreases the risk of birth before 34 weeks as well (RR 0.68, 95% CI 0.46–0.99).[10] In unselected singleton or multiple pregnancies (i.e. no previous PTB nor midtrimester short cervix), there is no convincing evidence of effect from vaginal progesterone.[2, 11]

Another intervention used for prevention of PTB is a cervical pessary. By altering the axis of the cervical canal and displace the weight of the uterus from the cervix, a pessary may prevent the cervix from shortening and dilation and conserve the mucus plug (a barrier for ascending infections).[12-14] Although several randomised controlled trials (RCTs) have shown a reduction of PTB in singletons with a midtrimester short cervix[15, 16], a recent meta-analysis did not show significant reduction (RR 0.80, 95% CI 0.43-1.49).[17] The ProTWIN trial assessed the effect of a cervical pessary in multiple pregnancies, and in a subgroup with a midtrimester short cervix. They observed a reduction of PTB before 32 weeks of gestation (RR 0.49, 95% CI 0.24-0.97) and improvement of neonatal outcomes with 60% was shown.[5] However, two recent RCTs comparing a cervical pessary (n=250 and n=157) versus no intervention (n=253 and n=158) showed no significant reduction of preterm birth or adverse neonatal outcomes in women with a twin pregnancy and a midtrimester short cervix.[7, 18]

Besides the importance of finding more solid evidence of effectiveness of these obstetric interventions for the prevention of preterm birth, it is necessary to expand the scope beyond immediate neonatal period to the long-term child's health and development. Especially, since previous studies demonstrated that interventions performed during pregnancy can have unexpected harmful long-term effects which may not be apparent at birth.[19, 20] At this moment, only a minority of studies on prenatal exposure to progesterone or pessary have published long term

results of the children. To date, there are approximately 150 RCTs on progesterone use for the prevention of preterm birth. A recently published systematic review identified seven studies (5% of the total amount of studies on progesterone) evaluating long-term effects of prenatal progesterone exposure. This review found no evidence of long-term beneficial or harmful effects, but concluded that the results were based on heterogeneous studies, using different assessments, varying from screening tools to face to face assessments with a follow-up age ranging from 6 months to 8 years.[21] To date, there are approximately 50 RCTs on pessary use for the prevention of preterm birth, of which only two studies (4%) published follow-up information so far.[22, 23] Follow-up of the ProTWIN study showed improvement of child survival without affecting neurodevelopment at three years of corrected age of the children from women with a midtrimester short cervix treated with a pessary compared to no pessary.[22] At four years of corrected age, follow-up data showed no benefits or harmful effects of pessary use regarding child outcome, however, results suggest favourable outcomes for children of women with a midtrimester short cervix .[24] Tran et al[23] performed follow-up of children born to women with a multiple pregnancy and midtrimester short cervix, randomised to vaginal progesterone (n=150) or cervical pessary (n=150), at three years of age. They showed a poor child outcome in 10.5% of the pessary group versus 15.8% in the progesterone group (RR 0.66, 95% CI 0.43-1.01). The data so far is not robust enough to exclude potential harm on long term from pessary or progesterone, or any potential benefit on either one of these interventions. This implies the need for further follow-up research on progesterone and pessary exposure during pregnancy. In 2014, a multicentre randomised trial (Quadruple-P trial) started to evaluate the effectiveness of progesterone versus a pessary in singleton and multiple pregnancies with an asymptomatic midtrimester short cervix for prevention of PTB.[25] This trial allows optimal comparison of the long-term outcomes of exposure to progesterone versus pessary in singleton and multiple pregnancies.

Objectives

We aim to assess the long-term effects of in utero exposure to progesterone versus a pessary on child (neuro)development and behaviour at 4-6 years of corrected age. With this follow-up study, we intent to investigate if progesterone or a pessary is superior for the prevention of PTB considering child's health on the long-term.

Methods and analysis

Study setting

This study will be a follow-up study of a multicentre randomised clinical trial (Quadruple-P trial, NL42926.018.13, Eudractnumber 2013-002884-24) conducted across 21 Dutch hospitals. In the Quadruple-P trial, singletons with an asymptomatic short cervix (≤35mm) at 18-22 weeks of gestation or multiples with an asymptomatic short cervix (<38mm) at 16-22 weeks of gestation are randomised to daily vaginal progesterone versus a pessary continued until 36 weeks of gestation. The Quadruple-P trial has a superiority design and in singletons a pessary is compared with vaginal progesterone as standard care, while in multiples vaginal progesterone is compared with a pessary as standard intervention. Outcomes include adverse perinatal outcomes, PTB rate and maternal morbidity, measured until 10 weeks after expected due date. The Quadruple-P study started in 2014 and finished in the first quartile of 2022 for the singletons. For the multiples recruitment of patients is still ongoing while writing this protocol. Eventually 628 singleton pregnancies and 332 multiple pregnancies will be potentially included in this trial. Long term follow-up of the Quadruple-P study was announced in the original trial protocol.[25]

The follow-up study will be an observational study performed within the Dutch consortium for Healthcare evaluation and Research in Obstetrics and Gynecology and coordinated from the Amsterdam University Medical Centre. Data of this follow-up study will be linked to maternal and neonatal data of the Quadruple-P trial. The study protocol has been developed according to the "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) criteria.

Participants/eligibility criteria

The study population consists of participants of the original Quadruple-P trial and their children. In the original Quadruple-P trial participants gave informed consent for follow-up research. Both singleton- and multiple pregnancies (of whom at least one child is alive) will be eligible for inclusion. Assessment will be performed when children are 4-6 years of corrected age. However, some children born to mothers of the Quadruple-P study are already 7 years of corrected age before the start of the follow-up study. We will not exclude these children from the follow-up but will separate this data in sensitivity analysis (see statistical analysis). Since the questionnaires in this follow-up study are in Dutch, and the original patient information in both Dutch and English, participants of the original trial who are not able to read Dutch will be excluded from this follow-up study.

Study design

Good clinical practice (GCP) trained research nurses from the local hospital (all involved in the NVOG consortium for research in obstetrics) will verify the medical records of mother and child(ren) for the possible occurrence of death and to obtain contact details. Using the Dutch Personal Records Database (BRP), a database containing records of all registered citizens of the Netherlands, occurrence of death and up to date contact details will be crosschecked. Thereafter, research nurses will send out information letters and informed consent forms by post or email when child(ren) are 4-6 years of corrected age. After receiving informed consent of parents/caregivers, participants will be contacted by phone to get the opportunity to ask questions, discuss informed consent and to be informed that they can withdraw consent to participate at any time with no reason. If the research team does not receive any response, research nurses of the local hospital will contact women by phone or email to verify if women received the information letter and want to participate in the follow-up. Participants will be asked to fill out four questionnaires once when their child is 4-6 years old. This will take no longer than 40 minutes for all questionnaires. Questionnaires will be sent by e-mail and parents/caregivers will be asked to fill out the questionnaires online. If a questionnaire is incomplete, participants will be kindly asked by phone or email to complete the questionnaire.

Blinding

No participants or researchers are blinded in the original Quadruple-P trial. In this follow-up study, researchers involved in data entry are blinded for allocation.

Patient involvement

Members of the Parents of preterm children Association (care4neo.nl) have been actively involved by our research team and they have stressed the importance of follow-up research. In 2017, members were asked to fill out an online survey including questions about parents' concerns on their child's development and most important long-term outcomes of complications during pregnancy (e.g. preterm birth). Seventy-five members filled out the online questionnaire of whom 85% percent stated to have concerns on their child's long-term development. In the members' opinion, child's school attainment and cognitive development, behaviour problems or psychological problems, motor skills, respiratory problems, general health, growth, and medication use were the most important outcomes to assess in follow-up research. In 2019, our research team also organised a focus group for women who delivered preterm. This focus group showed comparable outcomes. The results of the questionnaire and focus group have primarily determined our choice in main outcome variables of this follow-up study.

Outcomes

The main outcomes of this follow-up study are child (neuro)development and behaviour disabilities. Other outcomes include child mortality, growth and general health. We will assess all outcomes using parental questionnaires and will report the outcomes as a separate outcome, as well as a composite outcome as described below. We will present data as continuous scores (with mean and Standard Deviation (SD), or median with Interquartile Range IQR) and dichotomised scores (based on the predefined cut-off scores), see table 1. We will document data for singletons and multiples separately.

Table 1. Overview of the child outcomes and measurements.

Outcome	Method of measurement	Definition	Measurements
Neurodevelopment	Ages and Stages Questionnaire 4th edition (ASQ-4)	Scores of the 5 domains: - communication - gross motor skills - fine motor skills - problem-solving skills - personal-social skills	Mean (SD) Abnormal: ≥2 SD in any domain or multiple domains <1 SD below mean Mildly abnormal: ≥1 and <2 SD in one domain below mean
	Vineland screener	Total adaptive functioning score based on 4 domains: - communication - social skills - daily living skills - motor skills	Mean (SD) Abnormal: ≤10th percentile of the population Mildly abnormal: 11-25th percentile of the population
Behaviour	Strength and Difficulties Questionnaire (SDQ)	Total difficulties score based on 4 subscales: - Conduct problems - Emotional symptoms - Hyperactivity - Peer relationships	Mean (SD) Abnormal: >90th percentile of the population Mildly abnormal: 80-90 percentile of the population
Mortality	Medical records and the Dutch Personal Records Database	Perinatal mortality and death up to 7 years of age.	Number (%)~
General health	General health questionnaire*	Height	Mean (SD) Abnormal: 1.6 SDS above or below target height range
		BMI	Mean (SD) Abnormal: [26, 27]

			- underweight - overweight - obesity
		Hospital admissions/medication/surgeries	Number (%)

SD: standard deviation. **BMI**: Body Mass Index.

~ The denominator changes into all children born to participants of the original Quadruple-P study.

* This questionnaire was developed by our research team that is specialised in follow-up research of obstetric intervention studies. The questionnaire has been used in multiple follow-up studies.[24, 28-30]

(Neuro)development

- ASQ-4: The Ages and Stages Questionnaire (ASQ) is a screening tool to monitor child development by measuring five domains: communication, gross and fine motor skills, problem-solving skills and personal-social skills. The fourth and thereby newest version of the ASQ will be used for this follow-up study and can be used till 6 years of age. The Dutch version of the ASQ-4 is currently being validated, using a Dutch reference group to identify mean score and SDs.[31]

Interpretation: scores of ≥1 SD below the mean of the ASQ normative data in two or more domains, or ≥2 below the normative mean in at least one domain will be considered abnormal. Results will be considered as mildly abnormal when the scores are ≥1 and <2 SD in one domain below mean. Children >6 years of age with a mildly abnormal score will be considered abnormal.

- Vineland screener: The Vineland screener is a tool to assess adaptive functioning (defined as the collection of conceptual, social and practical skills that have been learned by people in order to function in everyday life) of children from 0 to 6 years. The tool exists of 72 questions concerning everyday behavior and covers four domains: communication, social, motor and daily living skills. The total adaptive functioning score is the sum of these four domains.[32, 33]

Interpretation: A total adaptive functioning score of ≤99 and ≤111 is considered abnormal (≤10th percentile of the population) for children 4-5 years and 5-6 years of age respectively. In children >6 years of age a score ≤115 will be considered abnormal. A total adaptive functioning score of ≤107 and ≤115 will be considered mildly abnormal (11-25th percentile of the population) for children 4-5 years and 5-6 years of age respectively. A mildly abnormal score will not be calculated for children >6 years of age.

Behaviour disabilities

SDQ parent report: The Strengths & Difficulties Questionnaire (SDQ) is a screening tool to identify behavioral problems in children concerning five subscales: emotional problems, conduct problems, hyperactivity, peer problems and prosocial behavior. The validated Dutch translation of the SDQ

version 4-17 years will be used. A total difficulties score can be calculated summing the first four subscales, leaving out pro-social behavior.[34, 35]

Interpretation: A Total Difficulty Score of ≥15 is considered abnormal (>90th percentile). A Total Difficulty Score of 11-14 is considered mildly abnormal (80-90th percentile).

Mortality

Child death (i.e. perinatal mortality and death up to 7 years of age). Medical records and the Dutch Personal Records Database will be used to verify the number of deceased children.

General health

General health questionnaire: we used the "general health questionnaire" which is used in several previous obstetric follow-up studies performed by the nationwide obstetric consortium.[24, 36, 37] In the general health questionnaire women will be asked about child growth (i.e. child's last measured longitudinal height and weight) and health related problems (i.e. need for surgery, hospital admissions, medication use and reported medical conditions). Women will also be asked for information about occurrence and outcome of subsequent pregnancies.

Interpretation:

- Growth: Based on Dutch reference values, we will present height as standard deviation scores and dichotomous outcome (normal/abnormal score). An abnormal score is defined as 1.6 SD above or below target height range.[38] We will calculate the body-mass index (BMI) and will report BMI as a continuous value and as a proportion of children who are underweight, overweight or obese based on Dutch reference data.[26, 27]
- Health related problems: we will show the number of child's medical diagnoses, hospital admissions, medication (used) and history of surgery and will classify them per organ system.

Composite outcomes

Composite of adverse child outcome is defined as:

- abnormal:
    - if the score in ASQ-4 or Vineland screener is abnormal for children up to 6 years of age, as defined above.
    - if the score in ASQ-4 or Vineland screener is mildly abnormal for children >6 years, as defined above.
    - if the score in SDQ is abnormal, as defined above.
    - the occurrence of child death.

- mildly abnormal: if the scores in ASQ-4 or Vineland screener or SDQ questionnaire are mildly abnormal as defined above.

Sample size

In line with the original trial, this follow-up has a superiority design. The original study has included 628 singleton pregnancies (314 participants in each group) and will include 332 multiples (166 participants in each group, i.e. at least 332 children in each group). Although the number of eligible participants for our follow-up study will be fixed, we can calculate the minimum number of participants needed to find significant difference. We considered 0.5 SD as clinically important difference for the main outcomes (0.5 SD difference on ASQ-4, Vineland screener and SDQ). Therefore, we would need a sample size of 64 participants per study group to achieve a power of 80% and a 2-sided alpha of 0.05 and 86 per study group when we use a conservative alpha of 0.05/3 in view of the three main outcomes as measured by different questionnaires.

Based on prior follow-up studies using questionnaires, we expect to realize a follow-up rate of 30-50%. When only 30% of the participants of the original trial will participate in this follow-up study (n=189 singletons and n=100 multiples, i.e. 200 children), we will still have enough power to detect a clinically important difference of the main outcomes.

Statistical analysis

Analyses will be performed separately for singletons and multiples. Difference in baseline characteristics including sociodemographic background of the families of Quadruple-P follow-up participants in progesterone and pessary group will be measured using unpaired T-test, Mann-Whitney U test, Chi-square test or Fisher's exact test when appropriate. Similarly, characteristics of follow-up participants will be compared with those lost to follow-up to detect any attrition bias. A two-sided P-value <0.05 will be considered as statistically significant. We will perform multiple imputation to approach the problem of missing data using maternal characteristics (e.g. ethnicity, age, smoking during pregnancy and education) and neonatal outcomes (e.g. gestational age at birth, birthweight, sex and neonatal sepsis) as predictive variables. We will perform a best and worst-case scenario analysis if the loss to follow-up is more than 20%.[39]

For the main outcomes (neurodevelopment) and behaviour, we will report mean scores with SDs and abnormal/mildly abnormal scores of the subscales and total scores of the ASQ-4, Vineland screener and SDQ. For the outcome mortality, the denominator should be changed into all children born to participants of the original Quadruple-P study. In case data of survival is incomplete, multiple imputation can be considered in sensitivity analysis. For the outcome concerning general

health, we will mention the outcomes as previously described. Composite of (mildly) abnormal child outcome will be reported for the progesterone and pessary group.

A directed acyclic graph (DAG) analysis will be constructed to assess potential confounders. Identified confounders may be corrected using a linear or logistic regression. In singletons, comparison between progesterone and pessary group will be done using an independent-samples T-test, Mann Whitney U test, Chi-square test or Fisher's exact test, as appropriate. Odds ratio (OR) and the corresponding 95% Confidence Interval (95% CI) for the (mildly) abnormal outcomes will be reported. For multiple pregnancies we will account for multiple children from the same pregnancy by using generalized linear mixed effects model (GLMM). All analyses will be performed according to the intention-to-treat principle using SPSS or R.

Additional analyses

We will perform sensitivity analysis for the composite of adverse child outcome between progesterone and pessary group (i.e. mortality or abnormal developmental outcome). Analysis will be performed for singletons and multiples separately.

A subgroup analyses will be done comparing children of women with ≥80% compliance versus <80% compliance to progesterone or pessary. Because not all questionnaires are validated for the use up to and including 6 years of age, a subgroup analyse of children <6 years will also be performed.

Data management

All data will be handled confidentially and participants are registered pseudonymised by a 6 digit number. If necessary, investigators have access to the keycode to identify subjects. Procedures of this follow-up study will all be in accordance with the Dutch Personal Data Protection Act.

Discussion

This follow-up study will evaluate long-term child health and development after two frequently used obstetric interventions in pregnancy to prevent preterm birth, vaginal progesterone and cervical pessary. Long-term follow-up is of utmost importance, since short-term success of an intervention does not guarantee beneficial effects for child on the long term and can even have harmful effects.[19, 20, 40] Thus far, only 16% of obstetric randomised controlled trials performed long-term follow-up.[41] To ensure best obstetric care for mother and child, each obstetric intervention study should aim to perform follow-up.

We will perform follow-up during early childhood (4-6 years of age). Early childhood is a very sensitive period for developing cognitive ability, language, social and motor skills. Determining developmental delay or neurodevelopmental disorders at this age will therefore be a reliable predictor for functioning later in life. [42, 43]

In our follow-up study, we will use two different questionnaires to explore child (neuro)development (i.e. ASQ-4 questionnaire and Vineland screener). These questionnaires may complement each other and, therefore, might give better insight in child's functioning. This information could be used in further follow-up research. Thereby, we contribute to the validation of the ASQ 4 questionnaire for the Dutch population. Validation will be completed before the end of the follow-up study. Both questionnaires are suitable for children up to 6 years of age. In our follow-up population several children will already have passed this age before the start of the study. As a result, this may lead to overestimation of the results. However, children with severe developmental delays will still be detected and other questionnaires used (i.e. SDQ and general health questionnaire) are applicable for children beyond 6 years of age. A sub analysis will be performed for only those children who had the appropriate age range for the validated questionnaires.

Ethics and dissemination

This follow-up study is registered at the Dutch Trial Registry (number NL9646, date August 3rd 2021). The Medical Research Ethics Committee from Amsterdam UMC confirmed that de Medical Research Involving Human Subjects Act (WMO) did not apply to our study (W20_481 #20.531). If outcomes indicate abnormal child development, this will be discussed with a neonatologist and/or (neuro)psychologist from our research team. If applicable, parents will be contacted by email or phone about the results of their child(ren) and will be referred to their general practitioner for further assistance.

Results will be published in a peer-reviewed journal and shared with stakeholders and participants. This protocol is published before analysis of the results. After analysis and publication, data of this study will be available from the corresponding author upon reasonable request.

Authors' contributions

EvLS, LvdW, EvD, AvB, AL, MvW, MdB, JvH, MO, EP and Quadruple-P study group were all involved in conception and design of the study and protocol. The manuscript was drafted by EvLS, LvdW, AL, JvH and EP and the Quadruple-P study group was involved planning the follow-up. The manuscript was reviewed and argued by EvLS, LvdW, EvD, AvB, AL, MvW, MdB, JvH, MO and EP and all approved the final version of the manuscript. The implementation of this follow-up study is made possible in cooperation with the Quadruple-P study group.

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Competing interests statement

No author reported any conflicts of interest.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number:
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Additional file 2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	2, 18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1, 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.