

BMJ Open 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 evidence is not robust enough to draw firm conclusions. 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 randomises 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 behaviour. 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 OR and the corresponding 95% CI. 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.

Trial registration number Dutch Trial Register (NL9646).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ 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 (eg, 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 PTB. In singletons at risk for PTB (ie, previous PTB or midtrimester short cervix), vaginal

progesterone significantly reduces the risk of birth before 34 weeks (relative risk (RR) 0.78, 95% CI 0.68 to 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 to 0.99).¹⁰ In unselected singleton or multiple pregnancies (ie, 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 to 1.49).⁶ 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 to 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 PTB or adverse neonatal outcomes in women with a twin pregnancy and a midtrimester short cervix.^{7 17}

Besides the importance of finding more solid evidence of effectiveness of these obstetric interventions for the prevention of PTB, 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.^{18 19} 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 PTB. 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.²⁰ To date, there are approximately 50 RCTs on pessary use for the prevention of PTB, of which only two studies (4%) published follow-up information so far.^{21 22} Follow-up of the ProTWIN study showed improvement of child survival without affecting neurodevelopment at 3 years of corrected age of the children from women with a midtrimester short cervix treated with a pessary compared with no pessary.²¹ At 4 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.²³ Tran *et al*²² performed a 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 3 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 to 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.²⁴ 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 (≤ 35 mm) at 18–22 weeks of gestation or multiples with an asymptomatic short cervix (< 38 mm) 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.²⁴

The follow-up study will be an observational study performed within the Dutch consortium for Health-care 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' 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 the Statistical analysis section). 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, 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 min for all questionnaires. Questionnaires will be sent by email 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 (eg, PTB). Seventy-five members filled out the online questionnaire of whom 85% 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 SD, or median with IQR) and dichotomised scores (based on the predefined cut-off scores), see [table 1](#). We will document data for singletons and multiples separately.

(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.²⁵

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

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 five domains: <ul style="list-style-type: none"> ▶ 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 four domains: <ul style="list-style-type: none"> ▶ Communication ▶ Social skills ▶ Daily living skills ▶ Motor skills 	Mean (SD) Abnormal: ≤ 10 th percentile of the population Mildly abnormal: 11–25th percentile of the population
Behaviour	Strength and Difficulties Questionnaire (SDQ)	Total difficulties score based on four subscales: <ul style="list-style-type: none"> ▶ Conduct problems ▶ Emotional symptoms ▶ Hyperactivity ▶ Peer relationships 	Mean (SD) Abnormal: > 90 th 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: <ul style="list-style-type: none"> ▶ Underweight ▶ Overweight ▶ Obesity
		Hospital admissions/ medication/surgeries	Number (%)

*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.^{23 40–42}
BMI, body mass index; SDS, Standard Deviation Score.

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 learnt by people in order to function in everyday life) of children from 0 to 6 years. The tool exists of 72 questions concerning everyday behaviour and covers four domains: communication, social, motor and daily living skills. The total adaptive functioning score is the sum of these four domains.^{26 27}

Interpretation

A total adaptive functioning score of ≤ 99 and ≤ 111 is considered abnormal (≤ 10 th 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

Strengths and Difficulties Questionnaire parent report

The Strengths and Difficulties Questionnaire (SDQ) is a screening tool to identify behavioural problems in children concerning five subscales: emotional problems, conduct problems, hyperactivity, peer problems and prosocial behaviour. 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 behaviour.^{28 29}

Interpretation

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

Mortality

Child death (ie, 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.^{23 30 31} In the General Health Questionnaire women will be asked about child growth (ie, child’s last measured longitudinal height and weight) and health-related problems (ie, 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 mean with SD and dichotomous outcome (normal/abnormal score). An abnormal score is defined as 1.6 Standard Deviation Score above or below target height range.³² 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.^{33 34}
- ▶ 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 included 628 singleton pregnancies (314 participants in each group) and will

include 332 multiples (166 participants in each group, that is, 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 two-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 realise 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, ie, 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, χ^2 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 (eg, ethnicity, age, smoking during pregnancy and education) and neonatal outcomes (eg, gestational age at birth, birth weight, 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%.³⁵

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 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, χ^2 test or Fisher’s exact test, as appropriate. OR and the corresponding 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 generalised linear mixed effects model. All analyses will be performed according to the intention-to-treat principle using the latest version of SPSS or R.

Additional analyses

We will perform sensitivity analysis for the composite of adverse child outcome between progesterone and pessary group (ie, 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 $\geq 80\%$ 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 six-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 PTB, 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.^{18 19 36} Thus far, only 16% of obstetric RCTs performed long-term follow-up.³⁷ 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.^{38 39}

In our follow-up study, we will use two different questionnaires to explore child (neuro)development (ie, 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 (ie, SDQ and General Health Questionnaire) are applicable for children beyond 6 years of age. A subanalysis will be performed for only those children who had the appropriate age range for the validated questionnaires.

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Contributors EVJvLS, LlvdW, CEvD, ALvB, AGL, MvW, MAdB, JvH, MAO, EP were all involved in conception and design of the study and protocol. The manuscript was drafted by EVJvLS, LlvdW, AGL, JvH and EP and the Quadruple-P study group was involved planning the follow-up. The manuscript was reviewed and argued by EVJvLS, LlvdW, CEvD, ALvB, AGL, MvW, MAdB, JvH, MAO 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 None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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REFERENCES

- Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. *The Lancet* 2008;371:75–84.
- EPPIIC Group. Evaluating progestogens for preventing preterm birth international collaborative (EPPIIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet* 2021;397:1183–94.
- DoddJM, JonesL, FlenadyV. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev* 2013;7.
- 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.
- Liem S, Schuit E, Hegeman M, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet* 2013;382:1341–9.
- 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.
- Norman JE, Norrie J, MacLennan G, et al. The Arabin pessary to prevent preterm birth in women with a twin pregnancy and a short cervix: the STOPPIT 2 RCT. *Health Technol Assess* 2021;25:1–66.
- Di Renzo GC, Tosto V, Tsbizova V, et al. Prevention of preterm birth with progesterone. *J Clin Med* 2021;10. doi:10.3390/jcm10194511. [Epub ahead of print: 29 09 2021].
- Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science* 2014;345:760–5.
- Romero R, Conde-Agudelo A, Rehal A, et al. Vaginal progesterone for the prevention of preterm birth and adverse perinatal outcomes in twin gestations with a short cervix: an updated individual patient data meta-analysis. *Ultrasound Obstet Gynecol* 2022;59:263–6.
- Brizot ML, Hernandez W, Liao AW, et al. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2015;213:82. e1–82.e9.
- Vitsky M. Simple treatment of the incompetent cervical os. *Am J Obstet Gynecol* 1961;81:1194–7.
- Becher N, Adams Waldorf K, Hein M, et al. The cervical mucus plug: structured review of the literature. *Acta Obstet Gynecol Scand* 2009;88:502–13.
- Hein M, Helmig RB, Schönheyder HC, et al. An in vitro study of antibacterial properties of the cervical mucus plug in pregnancy. *Am J Obstet Gynecol* 2001;185:586–92.
- Goya M, Pratcorona 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.
- 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.
- Grossolles M, Winer N, Sentilhes L, et al. Arabin pessary to prevent adverse perinatal outcomes in twin pregnancies with a short cervix: a multicenter randomized controlled trial (PESSARONE). *Am J Obstet Gynecol* 2022;227:271.e1–271.e13 <http://bmjopen.bmj.com/site/about/guidelines.xhtml> BMJ Open
- Kenyon S, Pike K, Jones DR, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *The Lancet* 2008;372:1319–27.
- van der Heyden JL, Willekes C, van Baar AL, et al. Behavioural and neurodevelopmental outcome of 2-year-old children after preterm premature rupture of membranes: follow-up of a randomised clinical trial comparing induction of labour and expectant management. *Eur J Obstet Gynecol Reprod Biol* 2015;194:17–23.
- Simons NE, Leeuw M, Van't Hooft J, et al. The long-term effect of prenatal progesterone treatment on child development, behaviour and health: a systematic review. *BJOG* 2021;128:964–74.
- van 't Hooft J, van der Lee JH, Opmeer BC, et al. Pessary for prevention of preterm birth in twin pregnancy with short cervix: 3-year follow-up study. *Ultrasound Obstet Gynecol* 2018;51:621–8.
- Tran VTT, Nguyen NA, Nguyen NT, et al. 15 long-term development of children born to women with twin pregnancies treated with pessary or progesterone. *Am J Obstet Gynecol* 2021;224:S10.
- Simons NE, van de Beek C, van der Lee JH, et al. Child outcomes after placement of a cervical pessary in women with a multiple pregnancy: a 4-year follow-up of the ProTWIN trial. *Acta Obstet Gynecol Scand* 2019;98:1292–300.
- 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;17:284.
- Voorop O, 2020. Available: <https://www.ontwikkelingvoorop.nl/> [Accessed 1 February 2022].
- van Duijn G, Dijkhoorn Y, Noens I, et al. Vineland screener 0-12 years research version (nl). constructing a screening instrument to assess adaptive behaviour. *Int J Methods Psychiatr Res* 2009;18:110–7.
- Sparrow SS, Carter AS, Cicchetti DV. Nederlandse bewerking door Evert Scholte, Gijs van Duijn, Yvette Dijkhoorn, Ilse Noens en Ina van Berckelaer-Onnes. In: Scholte EM, van Nbewerking, eds. *Vineland screener 0-6 jaar*. The Netherlands.: Handleiding, 2019.
- Maurice-Stam H, Haverman L, Splinter A, et al. Dutch norms for the Strengths and Difficulties Questionnaire (SDQ) - parent form for children aged 2-18 years. *Health Qual Life Outcomes* 2018;16:123.
- Grieken van A, Mieloo C, Theunissen MHCWd, M. *Handleiding, voor vhgvdSbdJV, het signalering van psychosociale problemen bij 3-17 jarigen*. Tno L, 2016. <http://bmjopen.bmj.com/site/about/guidelines.xhtml> BMJ Open
- de Ruigh AA, Simons NE, van 't Hooft J, et al. Child outcomes after amniocentesis compared with no intervention in women with second-trimester rupture of membranes: a long-term follow-up study of the PROMEXIL-III trial. *BJOG* 2021;128:292–301.
- Cuijpers CJJ, Van't Hooft J, Schneeberger C, et al. Progesterone for prevention of preterm birth in women with short cervical length: 2-year infant outcomes. *Ultrasound Obstet Gynecol* 2021;57:431–9.
- Netherlands Organisation for applied scientific research (TNO). JGZ-Richtlijn Lengtegroei [Dutch], 2019. Available: <https://www.ncj.nl/richtlijnen/allierichtlijnen/richtlijn/lengtegroei-2019> [Accessed 10 Aug 2021].
- Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320:1240–3.
- Cole TJ, Flegal KM, Nicholls D, et al. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007;335:194.
- Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002;359:781–5.
- Thorp JA, O'Connor M, Jones AM, et al. Does perinatal phenobarbital exposure affect developmental outcome at age 2? *Am J Perinatol* 1999;16:51–60.
- Teune MJ, van Wassenaer AG, Malin GL, et al. Long-Term child follow-up after large obstetric randomised controlled trials for the evaluation of perinatal interventions: a systematic review of the literature. *BJOG* 2013;120:15–22.
- Currie J, Stabile M, Manivong P, Roos LL, et al. Child health and young adult outcomes. *J Hum Resour* 2010;45:517–48.
- Boyle CA, Decouflé P, Yeargin-Allsopp M. Prevalence and health impact of developmental disabilities in US children. *Pediatrics* 1994;93:399–403.
- van Winden T, Klumper J, Kleinrouweler CE, et al. Effects of tocolysis with nifedipine or atosiban on child outcome: follow-up of the APOSTEL III trial. *BJOG* 2020;127:1129–37.
- de Ruigh AA, Simons NE, Van 't Hooft J, et al. Child outcomes after induction of labour or expectant management in women with preterm prelabour rupture of membranes between 34 and 37 weeks of gestation: study protocol of the PPROMEXIL follow-up trial. A long-term follow-up study of the randomised controlled trials PPROMEXIL and PPROMEXIL-2. *BMJ Open* 2021;11:e046046.
- Simons NE, van Limburg Stirum EVJ, van Wassenaer-Leemhuis AG, et al. Long-Term follow-up of children exposed in-utero to progesterone treatment for prevention of preterm birth: study protocol of the AMPHIA follow-up. *BMJ Open* 2021;11:e053066.