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Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies

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[Progesteron, cerclage, pessar eller acetylsalicylsyra för att förebygga förtidsbörd hos enkel- och flerbördsgraviditeter]

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1. Abstract

Background

Preterm birth is the leading cause of child mortality and morbidity, both short-term complications and long-term neurodevelopmental impairment, globally. Preterm birth is defined as follows: extremely preterm (<28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks). Any preterm birth comprises spontaneous (approximately 2/3) and indicated preterm birth (1/3), the latter due to maternal or fetal complications. Spontaneous preterm birth has a multifactorial aetiology. Risk factors include previous spontaneous preterm birth, late miscarriage, cervical surgery, short cervical length, and multifetal pregnancy. The preterm birth rate <37 weeks in Sweden during 2020 was 5.3%. There is presently no national guideline in Sweden concerning screening and prevention of preterm birth.

Question at issue

Will the interventions progesterone, cerclage, pessary, or acetylsalicylic acid (ASA), alone or in combinations, decrease the risk of preterm birth and neonatal and maternal mortality/morbidity, and long-term child morbidity in asymptomatic women with a singleton pregnancy at risk of preterm birth or in asymptomatic women with a multifetal pregnancy with or without additional risk factor(s), in comparison with no or any of the above-mentioned interventions?

Methods

Two authors performed searches during January 2021 with an update in February 2022 in six databases, selected studies, independently assessed abstracts, and made a first selection of full-text articles from randomised controlled trials (RCTs). These articles were sent to all authors and inclusion was decided in consensus. The trials were critically appraised. Data were extracted and pooled in meta-analyses using RevMan 5.4, stratified for high and low risk of bias trials. Certainty of evidence was assessed using the GRADE approach.

Results

The search identified 2309 unique articles of which 87 were included in the assessment. There were 71 original RCTs and 16 secondary publications, including six systematic reviews and one HTA report which contributed with outcome data. Conclusions were based solely on trials with low risk of bias (n=50).

Progesterone

Conclusions were based on 29 trials. In singleton pregnancies, progesterone compared with placebo reduces the risk of any preterm birth, assessed down to <28 weeks, for <37 weeks: 26.8% vs 30.2% (RR 0.82 [95% CI 0.71 to 0.95]) (high certainty of evidence). In subgroup analyses, vaginal administration in women with short cervical length reduces preterm birth <34 weeks. Neonatal mortality <28 days and respiratory distress syndrome are probably reduced by progesterone (moderate certainty of evidence). There were no significant differences in long-term child outcomes or maternal morbidity (low to high certainty of evidence).

In multifetal pregnancies, progesterone compared with placebo did not significantly reduce preterm births (low to high certainty of evidence).

Cerclage

Conclusions were based on five open trials. In singleton pregnancies, cerclage probably reduces the risk of any preterm birth, assessed down to <28 weeks, for <37 weeks: 29.0% vs 37.6% (RR 0.78 [95% CI 0.69 to 0.88]) (moderate certainty of evidence).

Perinatal mortality may be significantly reduced by cerclage (low certainty of evidence). Other neonatal, or maternal outcomes did not display any differences (very low to low certainty of evidence).
The effect of cerclage in twin pregnancies for preterm birth was uncertain. In an extreme high-risk population, cerclage may reduce the risk of perinatal mortality (low certainty of evidence).

Pessary
Conclusions were based on 12 open trials. All trials on singletons had short cervical length as risk factor. In singleton pregnancies, pessary may not reduce the risk of any preterm birth from <37 to <28 gestational weeks (low to moderate certainty of evidence). For spontaneous preterm birth there may be no difference between groups, except for spontaneous preterm birth <28 weeks (RR 0.45 [95% CI 0.22 to 0.93]) (all low certainty of evidence). There may be no significant differences neither in perinatal or neonatal mortality, nor in neonatal or maternal morbidity outcomes (all low certainty of evidence), except for increased vaginal discharge (moderate certainty of evidence).
In multifetal pregnancies, pessary did not significantly affect preterm births or perinatal, neonatal, and severe maternal outcomes (very low to moderate certainty of evidence).

ASA
In one trial on women with a history of spontaneous preterm birth, ASA compared with placebo in singleton pregnancies did neither affect preterm birth <37, <34, and <28 weeks (low certainty of evidence), nor perinatal mortality, neonatal morbidity, or maternal outcomes (very low to low certainty of evidence).

Organisational and economical aspects
Preventive treatment for preterm birth would require screening to identify women at risk. Some history factors are easily identified, but short cervical length would require screening with transvaginal ultrasound. The cost for ultrasound screening in Region Västra Götaland (assuming 20,000 pregnancies beyond 18 gestational weeks) would be approx. 11 million SEK/year. The treatment associated cost is considerably lower, from 1250 SEK per woman with a singleton pregnancy for vaginal progesterone to 20,000 SEK for cerclage, excluding cost for physician visit. Screening and treatment with vaginal progesterone can be considered cost-effective, while cerclage cannot.

Concluding remarks
Progesterone compared with placebo in singleton pregnancies with increased risk of preterm birth, reduces the risk of any preterm birth, thereby reducing neonatal mortality and respiratory distress syndrome. In multifetal pregnancies the effect of progesterone is very limited, if any. Cerclage in singleton pregnancies probably reduces the risk of any preterm birth and perinatal mortality. Pessary did not demonstrate any overall effect. ASA in singleton pregnancies did not affect any outcome. Prevention of preterm birth would require screening programmes to identify women at risk of preterm birth.

2. Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Bakgrund

Att födas för tidigt är den viktigaste orsaken till komplikationer under nyföddhetsperioden och till långtidseffekter på den motoriska och kognitiva utvecklingen. Förtidsbörd avser alla förlossningar mellan 22 och 37 fulla graviditetsveckor. Frekvensen förtidsbörd i Sverige 2020 var 5,3%. Det finns ett starkt samband mellan graviditetslängd vid förlossningen och överlevnad för barnet. Av levande födda barn som föds i enkelbörd före 33 fulla graviditetsveckor dör cirka 75 per 1000 barn under första levnadsmånaden, motsvarande siffra för barn födda mellan 33 och 37 graviditetsveckor är 5 per 1000 födda barn.

Förtidsbörd kan delas in i spontan och inducerad. Spontan förtidsbörd börjar antingen med värkar eller vattenavgång och utgör cirka två tredjedelar av all förtidsbörd. Kända riskfaktorer är tidigare förtidsbörd eller sent missfall, flerbördsgraviditet, genomgången operation i livmoderhalsen och kort livmoderhals vid ultraljudsundersökning. Ungefär en tredjedel av all förtidsbörd är inducerad och orsakas av medicinska graviditetskomplikationer, såsom havandeskapsförgiftning eller tillväxthämning och där man i förtid avslutar graviditeten. Det finns inga nationella riktlinjer avseende förebyggande behandling av förtidsbörd.

Vi har utvärderat fyra metoder avseende effekt att minska andel förtidsbörd samt att minska död och sjuklighet hos barn och mödrar: två utgörs av läkemedel, det kvinnliga könshormonet progesteron samt acetylsalicylsyra (ASA), medan två är av mekanisk karaktär. Cerclage är en grov sutur runt livmoderhalsen och ett pessar är en silikonring som placeras runt livmoderhalsen.

Metod

Med hjälp av etablerade metoder identifierades vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågeställningen. Endast s.k. randomiserade studier inkluderades, dvs där det var en slumpmässig fördelning av de behandlingsmetoder som jämfördes. De enskilda studiernas kvalitet granskades och tillförlitligheten i de sammanlagda resultaten bedömdes.

Resultat

Denna rapport baseras på 71 originalstudier med 23 886 kvinnor och 32 893 nyfödda barn, samt 16 sekundärpublikationer, inklusive sju systematiska litteraturöversikter med data. Slutsatser baseras endast på studier av hög kvalitet (n=50).

Progesteron jämfördes med placebo i 29 studier. Risken vid enkelbörd att föda före 37 veckor minskar med progesteron (26,8% vs 30,2%). Riskkvoten var 0,82 (95% konfidensintervall [KI] 0,71; 0,95), och resultatet bedömdes ha hög tillförlitlighet. Liknande resultat förelåg även vid kortare graviditetslängd, ned till före 28 veckor. Vaginalt progesteron hos kvinnor med kort livmoderhals kan minska risken för förtidsbörd före 34 veckor. Risken hos nyfödda att dö före en månads ålder eller att få andningsstörningar minskar troligen av progesteron (måttlig tillförlitlighet). Ingen skillnad sågs vid långtidsuppföljning av barnen eller avseende komplikationer hos mamman (låg till stark tillförlitlighet). Ingen påverkan av progesteron sågs heller vid flerbörd (låg till stark tillförlitlighet).

Cerclage utvärderades i fem studier. Förtidsbörd före 37 veckor vid enkelbörd minskar sannolikt med cerclage (29,0% vs 37,6%). Riskkvoten var 0,78 (95% KI 0,69; 0,88) och resultatet bedömdes ha måttlig tillförlitlighet. Liknande resultat förelåg även vid kortare graviditetslängd. Cerclage kan minska risken för det nyfödda barnet att dö i anslutning till eller inom en vecka efter förlossningen (låg tillförlitlighet). Effekten vid tvillinggraviditeter är osäker, men cerclage kan minska risken för det nyfödda barnet att dö före en månads ålder, vid mycket hög risk för förtidsbörd (låg tillförlitlighet).

Pessar utvärderades i 12 studier, där samtliga kvinnor med enkelbörd hade kort livmoderhals. Varken förtidsbörd eller sjuklighet hos barnet påverkades (låg tillförlitlighet). Enda biverkan som sågs hos mamman var ökade flytningar (måttlig tillförlitlighet).

ASA jämfördes med placebo i en studie på kvinnor med tidigare förtidsbörd. Ingen effekt av ASA noterades avseende förtidsbörd (låg tillförlitlighet) eller påverkan på barn och mamma (mycket låg tillförlitlighet).

Kostnader

Förebyggande behandling av förtidsbörd skulle kräva ett screeningprogram för att urskilja kvinnor med ökad risk att föda för tidigt. Screening med vaginalt ultraljud skulle kunna identifiera kvinnor med förkortad livmoderhals, till en kostnad av ca 11 miljoner SEK per år i Region Västra Götaland. Behandlingskostnaden är 1250 SEK för vaginalt progesteron och 20 000 SEK för cerclage, exklusive läkarbesök, per kvinna. Screening och behandling med vaginalt progesteron bedöms vara kostnadseffektivt, men inte med cerclage.

Etiska aspekter

Det saknas nationella riktlinjer avseende screening och förebyggande behandling av förtidsbörd, vilket innebär att kvinnor kan behandlas olika. Det är oklart hur effektivt screening för att hitta kvinnor med ökad risk för förtidsbörd och förebyggande behandling skulle vara i Sverige. Screening kan å ena sidan innebära ökad oro och behandling i onödan, och å andra sidan att behandlingen inte når dem som skulle behöva den mest, beroende på utformningen av ett screeningprogram. Det finns en risk för undanträngningseffekter, eftersom tillgången till ultraljuds-barnmorskor är begränsad. Trots stöd för att behandling med progesteron eller cerclage troligen minskar risken för förtidsbörd samt komplikationer och död i nyföddhetsperioden, har en effekt på barnens utveckling på lång sikt inte kunnat styrkas.

Slutsatser

Screening och behandling med vaginalt progesteron bedöms vara kostnadseffektivt genom att förebygga förtidsbörd, och därmed död och allvarlig sjuklighet hos det nyfödda barnet. Cerclage är sannolikt effektivt för vissa riskgrupper. Svårigheten är att urskilja de kvinnor som har nytta av en förebyggande behandling. Ingen effekt sågs vid behandling med pessar eller ASA.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA (excluding members* who were authors of the report). The abstract is a concise summary of the results of the systematic review. The plain language summary in Swedish is intended for decision makers.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, June 28th, 2022.

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Abbreviations/Acronyms

17-OHPC 17-alpha-hydroxyprogesterone caproate
ART assisted reproductive technology
ASA acetylsalicylic acid
ASQ ages and stages questionnaire
BPD bronchopulmonary dysplasia
CDI child developmental inventory
CI confidence interval
CL cervical length
cm centimetre
d days
g gram
GDM gestational diabetes mellitus
HDP hypertensive disorders in pregnancy
HTA health technology assessment
ICP intrahepatic cholestasis in pregnancy
ICTRP International Clinical Trials Registry Platform
im intramuscular injection
IVF in vitro fertilization
IVH intraventricular haemorrhage
IQR interquartile range
LY life year
MD mean difference
mg milligram
mm millimetre
NEC necrotizing enterocolitis
NICU neonatal intensive care unit
PPROM preterm prelabour rupture of membranes
PROSPERO the international prospective register of systematic reviews
PTB preterm birth
RCT randomised controlled trial
RD risk difference
RDS respiratory distress syndrome
ROP retinopathy of prematurity
RR relative risk/risk ratio
SBU Swedish agency for health technology assessment and assessment of social service
SD standard deviation
SEK Swedish krona
SoF summary of findings
sPTB spontaneous preterm birth
SR systematic review
TVS transvaginal sonography
UK United Kingdom
US United States
VGR Region Västra Götaland
WHO World Health Organization

4. Background

Disease/disorder of interest and its degree of severity

Preterm birth is the leading cause of child mortality and morbidity globally. About 15 million children worldwide are born preterm each year, and one million of these will die due to preterm birth complications. Sixty percent of all children born preterm are born in Asia and sub-Saharan Africa (Blencowe et al., 2012). Preterm birth is the most common cause of death in children under five (Perin et al., 2022) and 35% of neonatal deaths are associated with preterm birth complications (Perin et al., 2022, World Health Organization [WHO], 2012) Furthermore, there is an increased risk of many short-term complications such as respiratory distress syndrome, bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, intraventricular haemorrhage, and retinopathy of prematurity compared with children born at term. These short-term complications can cause permanent illness or damage (Manuck et al., 2016). Preterm birth is associated with an increased risk of long-term neurodevelopmental impairment where learning difficulties, cognitive and developmental delay, cerebral palsy, and hearing and visual impairment are the most common. Almost 40% of children born preterm suffer from at least one sequela later in life, potentially reducing their quality of life and increasing healthcare costs (Mwaniki et al., 2012). There is a strong correlation between gestational age at birth and survival without short-and long-term morbidity. To prevent or delay preterm birth is therefore of great importance.

Preterm birth is defined by WHO as a liveborn child before 37 gestational weeks are completed. There are subgroups of preterm birth based on gestational age; extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks) (WHO, 2012). According to the Swedish Neonatal Quality Register (SNQ)[1], around 45% of children born preterm in Sweden survive in gestational week 22, 82% below 28 weeks, 97% between 28 and 31 weeks, and 99% between 32 and 37 weeks.

Preterm birth (herein described as any preterm birth) is either physician indicated or spontaneous preterm birth. One third are physician indicated preterm delivery due to maternal or fetal complications such as preeclampsia or intrauterine growth restriction. Spontaneous preterm birth accounts for two thirds of all preterm births. A spontaneous birth starts with contractions or spontaneous preterm prelabour rupture of membranes (PPROM). The underlying causes of spontaneous preterm birth are multifactorial, including infection, inflammation, vascular disease, or distention of the uterus, but the cause often remains elusive (Goldenberg et al., 2008, Jacobsson et al., 2019a, Vogel et al., 2018).

Several different risk factors for spontaneous preterm birth have been identified. Risk factors include previous spontaneous preterm birth or late miscarriage, cervical surgery, or multifetal pregnancy (Cobo et al., 2020). A short cervix measured by transvaginal ultrasound in the mid-trimester is a predictor of spontaneous preterm birth (Iams et al., 1996, Kuusela et al., 2021). However, Ferrero et al. showed that nulliparity is the strongest risk factor for preterm birth at a population level (2016). Identification of women with short cervix would require either universal or targeted screening. Socioeconomic status, country of birth, ethnicity, assisted reproductive technology, smoking and other lifestyle choices are also associated with elevated risk of preterm birth (Blencowe et al., 2012, D'Angelo et al., 2011, Goldenberg et al., 2008, Pinborg et al., 2013).

[1] Stellan Håkansson, associate director, SNQ, data from 2017-2021. Personal communication 2022-05-20.

Multifetal pregnancy is a known risk factor for both physician indicated and spontaneous preterm birth. The risk of adverse outcomes for both mother and child are higher compared with singleton pregnancies mainly due to the higher rate of preeclampsia and preterm birth. Fetal growth restriction, complications associated with chorionicity, in addition to all the multifactorial causes mentioned above affect gestational length at birth.
A monochorionic (MC) twin pregnancy is at higher risk compared with a dichorionic (DC) twin pregnancy, while a monochorionic monoamniotic twin (MCMA) pregnancy is at the highest risk (Farmer et al., 2021, Kalikkot Thekkeveedu et al., 2021).

Prevalence and incidence

In Sweden, during 2020, 5.3% of all live births occurred before 37 completed gestational weeks, 4.2% of all live singleton and 42.7% of all live multifetal births, according to the Swedish official statistical records. Also, 1.4% of all births during 2020 were multifetal. In Region Västra Götaland, 5.5% (1065/19173) of all newborns (including stillborns) were born before 37 gestational weeks in 2020 (Socialstyrelsen, 2020). Furthermore, preterm birth is more prevalent among nulliparous (6.5%) than multiparous women (4.7%) (Socialstyrelsen, 2020).

Present treatment and the typical pathway through the healthcare system and current wait time for medical assessment/treatment

There is no universal screening programme in Sweden for prevention of preterm birth. However, pregnant women, especially women with known risk factors for preterm birth or women with multifetal pregnancies are given information at the antenatal clinics on signs of preterm birth and where to have an assessment if needed. In mid-trimester, planned transvaginal cervical length measurements may be used for pregnant women with one or several risk factors for preterm birth. Cerclage could be an option if cervix is short as measured with transvaginal ultrasound. Cerclage may also be placed without prior ultrasound assessment in high-risk women with a history of repeated late miscarriages or early preterm births if cervical incompetence is suspected. Cerclage is administered in an operating theatre under regional or general anaesthesia. Neither pessary nor pharmacological treatment such as progesterone or acetylsalicylic acid (ASA) as a prophylactic regimen for the prevention of preterm birth has widespread use in Sweden (Jacobsson et al., 2019b). Currently, there is no waiting time in Sweden for women that need a medical assessment or treatment during pregnancy.

Number of patients per year who undergo current treatment regimen

In a global comparison, Sweden has a low frequency of preterm birth and a low frequency of intervention to prevent preterm birth. Statistics from the Swedish Pregnancy Register between 2014 and 2022 showed that the rate of procedure codes for cerclage during pregnancy varied between regions (between <0.01% and 0.08%), however, there may be uncertainty due to underreporting to the Pregnancy Register[2]. In a recent, large Swedish study, it was found that 0.2% of women pregnant after 18 gestational week used vaginal progesterone (Wikström et al., 2021). The other two interventions studied in this report, ASA and pessary, are thought to be used to a lesser extent for the prevention of preterm birth in Sweden and there is no available statistics for these interventions (Jacobsson et al., 2019b).

Present recommendations from medical societies or health authorities The Danish Society of Obstetrics and Gynecology (Dansk Selskab for Obstetrik og Gynækologi, DSOG), the American College of Obstetricians and Gynecologists (ACOG), the International Federation of Gynecology and Obstetrics (FIGO), the Royal Australian and New Zealand College of Obstetricians and

[2] Mikalea Granfors, director Pregnancy Register, data from 2014-2022. Personal communication 2022-05-09.

Gynaecologists (RANZCOG), Society of Obstetricians and Gynaecologists of Canada (SOGC) and the National Institute for Health and Care Excellence (NICE) all recommend vaginal progesterone for selected groups of women at risk of preterm birth (ACOG, 2021, DSOG, 2013, Jain et al., 2020, NICE, 2015, RANZCOG, 2017, Shennan et al., 2021a).
In addition, some also recommend considering cerclage (DSOG, FIGO, SOGC and NICE) or pessary (DSOG) if certain criteria are met (Brown et al., 2019, DSOG, 2018, NICE, 2019, Shennan et al., 2021b).
Furthermore, ACOG recommends screening of cervical length with a transvaginal ultrasound during specified gestational weeks for women with prior spontaneous preterm birth (ACOG, 2021), and RANZCOG supports cervical length screening with transabdominal ultrasound for all women with low risk of preterm birth with a singleton pregnancy (RANZCOG, 2021). FIGO recommends against the use of pessary as an intervention to prevent preterm birth after appraising the scientific evidence (Grobman et al., 2021).
Putora et al. published a compilation of ten international guidelines of the prevention of preterm birth and concluded that a short cervix and/or a history of preterm birth respectively are relevant factors when recommending progesterone and/or cerclage (2022). In the case of multifetal pregnancy most guidelines advise against prophylactic treatment.
The Swedish Association for Obstetrics and Gynecology (Svensk Förening för Obstetrik och Gynekologi, SFOG) has no written guideline on prevention of preterm birth. In addition, there are no national guidelines from the Swedish National Board of Health and Welfare for the prevention of preterm birth, although it is presently under consideration.

5. Health technology at issue: Progesterone, pessary, cerclage and ASA

Several treatments have been suggested to prevent preterm birth. In this report four interventions have been studied— two pharmacological (progesterone and ASA) and two mechanical interventions (cerclage and pessary).

Progesterone is an essential hormone to maintain a pregnancy until term. In addition to its endocrine properties critical for implantation and development in early pregnancy, it also modulates immune response (Raghupathy and Szekeres-Bartho, 2022). Progesterone is also suggested to reduce the production of prostaglandins, thereby inhibiting the myometrial contractions (Sfakianaki and Norwitz, 2006). Administration of progesterone has shown reduced rates of preterm birth in selected groups (Kuon et al., 2019, Romero et al., 2022, EPPPIC, 2021). Different administration routes are possible; vaginal, oral, or intramuscular (im) injection. The studied dosage and treatment interval differ. However, im injections of progesterone are not approved in Sweden as an intervention for the prevention of preterm birth. However, no gold standard of progesterone treatment has been identified.

Cervical cerclage offers mechanical support to the cervix by placing a stitch around the cervix by a vaginal (most common) or transabdominal approach. The purpose is to prevent late miscarriage and preterm birth (Berghella et al., 2017, Kuusela et al., 2019). Eligible patients for a prophylactic cerclage are women with a history of cervical surgery or prior cervical insufficiency resulting in pregnancy loss (history-indicated), or a short cervical length measured by transvaginal ultrasound with or without a history of previous pregnancy loss (ultrasound-indicated). Cerclage may also be used as an emergency intervention to close the cervical os if presenting with a threatening late miscarriage or preterm birth (rescue cerclage) (Suhag and Berghella, 2014).
Complications associated with the procedure are iatrogenic rupture of the membranes, vaginal bleeding and intraamniotic infection.

There are two well described methods for vaginal placement: McDonald and Shirodkar. In the McDonald technique, stitches are inserted lateral of the cervical canal in a purse-string fashion and tied anteriorly. In the Shirodkar technique, the vaginal epithelium in the anterior and posterior fornices is dissected to allow upward displacement of the rectum and bladder. Next, a mersilene tape is placed and tied posteriorly (Issah et al., 2021). The stitch can be placed under general or regional anaesthesia in an operating theatre and is commonly removed during a gynaecological examination at 37 weeks of gestation, or at delivery, if labour starts earlier, with no need of an operating theatre or anaesthesia. The transabdominal approach is mostly used after a previous failed vaginal cerclage or in women who have undergone a trachelectomy (radical surgery after cervical cancer).

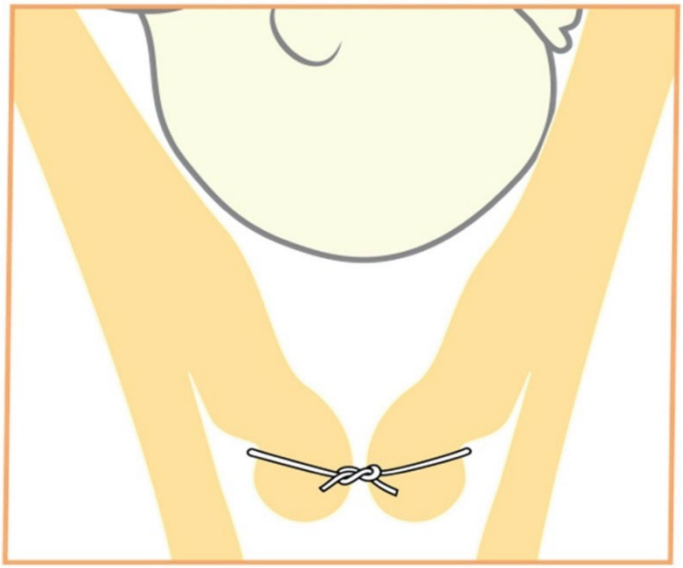
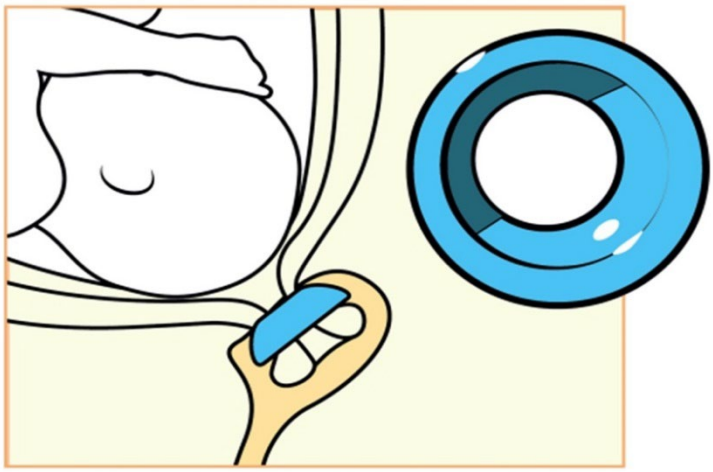


Figure 1. Cerclage placed around cervix, frontal view (Illustration courtesy of Bo Jacobsson)

The cervical pessary, a round concave silicon ring with a hole in the middle, is suggested to change the position of the cervix to a more posterior angle and thus change the weight of the pregnancy towards the anterior lower segment of the uterus. In addition, the pessary can prevent the cervix from dilating and prevent the amnion and chorion from dissociation from the uterine wall. It is placed into the correct position by a gynaecologist or a midwife during an outpatient visit and removed during an outpatient visit around gestational week 37 or earlier, if delivery occurs earlier (Arabin and Alfirevic, 2013). The intervention is thus less invasive and requires less resources compared with cerclage.

Figure 2. Pessary placed around cervix, sagittal view (Illustration courtesy of Bo Jacobsson)



ASA has an anti-inflammatory effect and an effect on preterm birth might be due to decreasing uterine contractility through inhibition of cyclooxygenase (COX)-dependent prostaglandin synthesis (Abramovici et al., 2012). It is an established treatment to prevent preeclampsia even though the exact mechanism behind its effect is yet to be uncovered. Even so, ASA treatment reduces the incidence of preterm births in women at risk of preeclampsia (Duley et al., 2019). It has been suggested that low-dose ASA potentially could reduce spontaneous preterm birth rates in groups at risk, but with conflicting results (Andrikopoulou et al., 2018, Hoffman et al., 2020, Landman et al., 2022). The proposed dosage is one tablet, 75-150 mg daily starting in the first or second trimester and terminating the intervention at around 37 weeks of gestation or earlier if delivery occurs earlier. Advantages of ASA treatment are the low price and accessibility globally, possible disadvantages are complications such as increased risk of bleeding due to ASA's anti-platelet aggregation properties.

6. Focused question

Will the interventions progesterone, cerclage, pessary, or acetylsalicylic acid (ASA), alone or in combinations, decrease the risk of preterm birth and neonatal and maternal mortality/morbidity, and long-term child morbidity in asymptomatic* women with a singleton pregnancy at risk of preterm delivery** or in asymptomatic women with a multifetal pregnancy with or without additional risk factor(s)?

*Without symptoms indicating risk of preterm delivery
**Previous preterm delivery, previous spontaneous late miscarriage between 16 and 22 gestational weeks, short cervix, previous cervical surgical treatment for cervical intraepithelial neoplasia or other risk factors defined by the authors.

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P
Asymptomatic (without symptoms indicating risk of preterm delivery) women with a singleton pregnancy at increased risk of preterm delivery <37+0 gestational weeks.
Asymptomatic women with a multi-fetal pregnancy, irrespective of other risk factors.

I
Progesterone, any type, initiated in the second trimester, alone or in combination with the other specified interventions in the PICO. Comparisons between different dosage and administration routes are not included.
Cerclage, any type applied before pregnancy, in first or second trimester, alone or in combination with the other specified interventions in the PICO.
Pessary, any type applied in first or second trimester, alone or in combination with the other specified interventions in the PICO.
Acetylsalicylic acid (ASA), initiated before pregnancy, in first or second trimester, alone or in combination with the other specified interventions in the PICO.

C
No intervention, placebo or other intervention (progesterone, cerclage, pessary, ASA).

O
Critical for decision making:
Any preterm birth <37, <35, <34, <33, <32, <28 gestational weeks
Spontaneous preterm birth <37, <35, <34, <33, <32, <28 gestational weeks
Perinatal mortality (intrauterine fetal death and neonatal mortality <7 or <28 days)
Neonatal mortality <7, <28 days
Serious neonatal morbidity (such as bronchopulmonary dysplasia, severe intraventricular haemorrhage, necrotizing enterocolitis, confirmed sepsis, retinopathy of prematurity), individually or as a composite outcome with or without peri/neonatal mortality.
Long-term morbidity (such as cerebral palsy, epilepsy, visual impairment, hearing impairment, intellectual impairment, developmental delay)
Maternal mortality
Maternal morbidity (adverse effects such as infections, surgical complications, cancer)
Important for decision making:
Gestational length
Low birth weight (<2500g), very low birth weight (<1500g)

Comments to O:
Spontaneous preterm birth is the most prioritised outcome since it may be preventable. However, it is not reported as often as *any* preterm birth, likely due to indistinguishable conditions in the clinical setting. Established definitions are: preterm birth (<37 gestational weeks), very preterm birth (<32), extreme preterm birth (<28). A cut-off for active treatment to delay delivery <34 weeks is common, to allow for corticosteroid treatment to accelerate fetal lung maturation.
The most critical clinical outcomes are peri/neonatal and maternal mortality and long-term child outcome.

Study design:
Systematic reviews including RCTs
RCT

In a separate search, addressing the intervention progesterone and the outcome cancer in the woman, cohort studies with any number of participants will be included, to support the discussion of long-term risk.

Prespecified subgroup analyses for all interventions
For the population group with singleton pregnancies:
Short cervical length
Previous preterm birth
Cervical surgical treatment for cervical intraepithelial neoplasia

Exploratory subgroup analyses
For the population group with singleton and multifetal pregnancies:
Administration route of progesterone
For the population group with multifetal pregnancies:
Short cervical length
Previous preterm birth

7. Methods

Systematic literature search (Appendix 1)

During January 2021, with an update in February 2022, two authors (AL, ACE) performed systematic searches in PubMed, Embase, Medline and the Cochrane Library. The websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Service (SBU) and Folkehelseinstituttet were searched, and reference lists of relevant articles were scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1a. The above-mentioned authors independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion. The selected articles were sent to all authors, who independently read the articles. In a consensus meeting, the authors decided which articles to include in the HTA. Any disagreements were resolved in consensus. The excluded studies, including reasons for exclusions, are presented in Appendix 3.
A separate search was done in November 2021, addressing the intervention progesterone and the outcome cancer in the woman, including cohort studies of any size for assessment of long-term risk. Two authors (AL, ACE) performed systematic searches in PubMed, Embase, Medline and the Cochrane Library. The websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Service (SBU) and Folkehelseinstituttet were searched. Reference lists of relevant articles were scrutinised for additional references.
Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1b. The above-mentioned authors independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. No further references where found.
The review was registered in PROSPERO March 26th, 2021(registration ID: CRD42021234946) prior to data extraction.

Critical appraisal and certainty of evidence

With the exception mentioned above, only randomised controlled trials (RCTs) were eligible for inclusion. Characteristics of the included trials are presented in Appendix 2. The excluded trials and the reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using a checklist for assessment of randomised controlled trials, modified from the SBU by HTA-centrum (Checklist, 2021).

The results and the assessed quality of each article have been summarised per outcome in Appendix 4. Data were extracted by at least two authors per outcome. A detailed risk of bias assessment of the trial and its primary outcome was conducted using the Cochrane risk-of-bias tool (Cochrane, 2022). When possible, data were pooled in meta-analyses using a random effects model in RevMan 5.4 and presented as forest plots with an associated risk-of-bias graph. Point estimates are presented as risk ration (RR) with 95% confidence interval (CI) and as pooled weighted risk differences (RD) with 95% CI. Continuous data presented with median and interquartile range (IQR), was transformed to mean and standard deviation (SD), assuming normal distribution.
Stratified analyses were conducted based on the risk of bias. Studies classified as having high risk of bias included those that in an overall assessment had major problems with risk of bias (-). In the detailed risk of bias assessment, random sequence generation and allocation concealment had to be evaluated as 'no or minor problems' (+) to be classified as low risk of bias. If one of these domains was evaluated as 'some problems' (?), at least three of the remaining domains (detection, performance, attrition bias, selective reporting and other/conflict of interest) had to be classified as 'no or minor problems' (+). If both random sequence generation and allocation concealment was evaluated as 'some problems' (?), at least four of the remaining domains had to be classified as 'no or minor problems' (+). The risk of bias assessment of original trials was applied to all outcomes in subsequent publications. Conclusions are based solely on trials with low risk of bias. The two strata are referred to as trials with low and high risk of bias. Stata (version 17) was used to construct graphs with several pooled estimates.
A summary result per outcome and the associated certainty of evidence are presented in Summary-of-findings tables (pages 22-29). The certainty of evidence was defined according to the GRADE system (Atkins et al., 2004; GRADE Working group).
Pre-specified subgroup analyses according to risk factor (short cervix or history of preterm birth) in women with singleton pregnancies among trials with low risk of bias were conducted. Subgroup analyses according to administration route of progesterone (vaginal, intramuscular injection (im) of 17-alpha-hydroxyprogesterone caproate [17-OHPC], or oral progesterone) were conducted as exploratory analyses comprising trials with low risk of bias. Subgroup analyses in women with multifetal pregnancies according to additional risk factors were exploratory.

Singleton and multifetal pregnancies are presented separately. Trials with mixed populations without separate reporting, were included in meta-analyses of singleton pregnancies, if twins constitute ≤2% of the study population. Trials with >2% and <10% multifetal pregnancies were also included in meta-analyses of singleton pregnancies, followed by a sensitivity analysis with exclusion of the mixed population trial. Trials with ≥10% multifetal pregnancies were not included in any meta-analyses.

Ongoing research

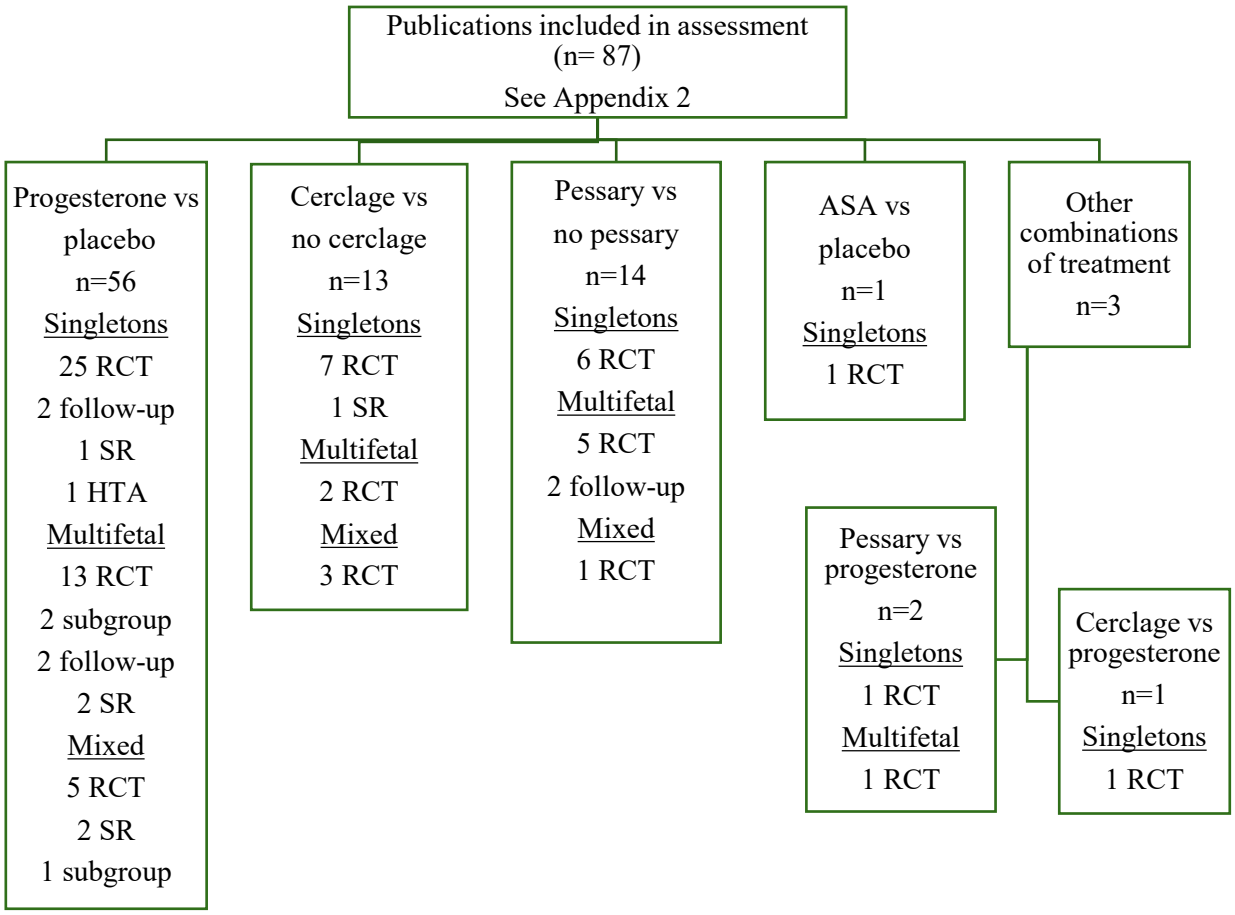
A search in Clinicaltrials.gov and WHO ICTRP database (2021-05-12) and an updated search in Clinicaltrials.gov (2022-04-13) were done. The following search terms were used: (Preterm OR Preterm birth OR Preterm delivery OR premature OR prematurity) AND (progesterone OR hydroxyprogesterone OR 17-hydroxyprogesterone OR 17-OHPC OR 17OHPC OR progestin OR progestagen OR progestogen OR desogestrel OR gestagen OR Algestone OR Dydrogesterone OR gestrinone OR progestative OR medroxyprogesterone acetate OR Pessary OR vaginal pessary OR Arabin OR Arabin Pessary OR cerclage OR Cervical stitch OR Suture of cervix OR cervical ligation OR Shirodkar's OR McDonald OR McDonald's OR McDonalds OR MacDonald OR MacDonald's OR MacDonalds OR Aspirin OR Aspirins OR Acetylsalicylic OR Acetylsalicylic acid OR Acetylsalicylic acids).

8. Results

Search results and study selection (Appendix 1a)

The literature search identified 2309 articles after removal of duplicates. After reading the abstracts 1961 articles were excluded. Another 95 articles were excluded by two authors (AL, ACE) after reading the articles in full text. The remaining 253 articles were sent to all participants of the project group, and 87 articles were finally included in the assessment (Appendix 2) (Fig. 3). In addition, four health economy studies were commented upon.

Figure 3. Included publications (71 RCTs, six follow-up studies, three secondary subgroup analyses, six systematic reviews (SR) and one HTA-report) according to intervention.



Literature search (Appendix 1b)

A separate search was done, by two authors (AL, ACE) addressing the intervention progesterone and the outcome cancer in the woman. The search identified 369 references. After reading the abstracts, 365 articles were excluded, the remaining four articles were excluded after full text reading. No further references were found.

Result resumé for the comparison progesterone vs placebo and other interventions vs progesterone

(Complete results and outcome tables are presented in the separate result section 8.1)

Progesterone vs placebo in singleton pregnancies

Low risk of bias trials showed an overall effect of progesterone to reduce the risk of preterm birth, assessed from <37 down to <28 gestational weeks. A reduction of preterm birth was demonstrated for <37 and <34 gestational weeks for any administration route, (high certainty of evidence). A reduction of preterm birth <35 and <28 gestational weeks for any administration route, and <33 weeks for vaginal progesterone to women with short cervical length was demonstrated (moderate certainty of evidence). Prespecified subgroup analysis of trials with women with previous spontaneous preterm birth as a risk factor demonstrated an effect of progesterone on preterm birth <37 and <34 weeks. Exploring the effect of different administration routes, women with a short cervical length given vaginal progesterone experienced a reduced risk of preterm birth <34 weeks.

Spontaneous preterm birth was less frequently reported, and thus yielded imprecise estimates for a reduction (low to moderate certainty of evidence).

The reduced risk of preterm birth was reflected in neonatal outcomes, above all in reduced mortality within 28 days (moderate certainty of evidence). All neonatal morbidity outcomes were assessed with risk ratios <1.0 (low certainty of evidence), but only respiratory distress syndrome expressed a significant reduction (moderate certainty of evidence).

Maternal morbidity outcomes were not significantly affected by progesterone (low to high certainty of evidence).

Progesterone vs placebo in multifetal pregnancies

Low risk of bias trials demonstrated no effect of progesterone (any administration route) on the risk of preterm birth, assessed from <37 down to <28 gestational weeks (high certainty of evidence for all gestational weeks except <37 and <33 weeks).

Neonatal mortality within 28 days, respiratory distress syndrome and admittance to NICU was not affected by progesterone (moderate certainty of evidence). Neither were the other neonatal morbidity outcomes (low certainty of evidence).

Maternal morbidity outcomes were not significantly affected by progesterone (low to high certainty of evidence).

Other interventions vs progesterone

Cerclage vs 17-OHPC in singleton pregnancies

No difference was reported in spontaneous preterm birth <35 weeks comparing the two methods in women with short cervical length (very low certainty of evidence).

Pessary vs vaginal progesterone in singleton pregnancies

No difference was reported in spontaneous preterm birth <34 weeks comparing the two methods in women with short cervical length (low certainty of evidence).

Pessary vs vaginal progesterone in twin pregnancies

No difference was reported in spontaneous preterm birth <34 weeks comparing the two methods in women with short cervical length (low certainty of evidence).

Result resumé for the comparison cerclage vs no cerclage

(Complete results and outcome tables are presented in the separate result section 8.2)

Cerclage vs no cerclage in singleton pregnancies

Low risk of bias trials showed an overall effect of cerclage to reduce the risk of any preterm birth, assessed from <37 down to <28 gestational weeks, reaching significance for <37 and <34 weeks (moderate certainty of evidence). The certainty of evidence was low for a reduced risk of preterm birth <35 weeks and <33 weeks and very low for <32 weeks. In pre-specified subgroup analyses of a risk factor, women with a short cervical length, cerclage significantly reduced the risk of preterm birth <37 weeks, as well as <34 weeks (Figures 8-9 in result section 8.2).

Spontaneous preterm birth was not reported.

The risk of perinatal mortality was significantly reduced with cerclage (low certainty of evidence).

Composite adverse neonatal outcome was not significantly affected by cerclage (low certainty of evidence).

Maternal morbidity outcomes were not significantly affected by cerclage (very low to low certainty of evidence).

Cerclage vs no cerclage in multifetal pregnancies

Any effect on preterm birth below any gestational week was uncertain (very low certainty of evidence).

Peri/neonatal mortality may be reduced by cerclage in a high-risk group of women with a twin pregnancy, dilated cervix and visible membranes (low certainty of evidence). Neonatal morbidity outcomes were not significantly affected by cerclage (very low to low certainty of evidence).

Maternal morbidity outcomes were not significantly affected by cerclage (very low certainty of evidence).

Result resumé for the comparison pessary vs no pessary

(Complete results and outcome tables are presented in the separate result section 8.3)

Pessary vs no pessary in singleton pregnancies

All women with a singleton pregnancy had a short cervical length. Low risk of bias trials demonstrated no effect of pessary on the risk of preterm birth, for all assessed gestational weeks, with the exception of spontaneous preterm birth <28 weeks, where a reduced risk with pessary was shown (low to moderate certainty of evidence).

Peri/neonatal mortality and neonatal morbidity was not affected by pessary (low certainty of evidence).

Maternal morbidity was not affected by pessary (low certainty of evidence), except for an increase in vaginal discharge (moderate certainty of evidence).

Pessary vs no pessary in multifetal pregnancies

Low risk of bias trials demonstrated no effect of pessary on the risk of preterm birth, assessed from <37 down to <28 gestational weeks (low to moderate certainty of evidence) for all gestational weeks.

Subgroup-analyses of women with short cervical length did not affect the results for any preterm birth <37 or <34 gestational weeks (Figures 36-37 in result section 8.3).

No effect on peri/neonatal mortality, and composite adverse neonatal outcome was demonstrated with pessary (moderate certainty of evidence).

Maternal morbidity (very low to low certainty of evidence) was not affected by pessary, except for an increased risk of vaginal discharge (moderate certainty of evidence).

Result resumé for the comparison acetylsalicylic acid vs placebo

(Complete results and outcome tables are presented in the separate result section 8.4)

Only one trial examined the effect of ASA on preterm birth in women with previous spontaneous preterm birth. No difference between groups was demonstrated below any gestational week, reported from <37 down to <28 weeks (low certainty of evidence).
Any assessment of neonatal morbidity and mortality was uncertain (very low certainty of evidence), except for no difference in admittance to neonatal intensive care unit (NICU) (low certainty of evidence).
The assessments of maternal morbidity and mortality were uncertain (very low certainty of evidence), except for no differences in gestational diabetes mellitus and PPROM (low certainty of evidence).

9. Summary of findings (SoF) for critical outcomes
(based on trials with low risk of bias)

SoF Table 1. Progesterone (any administration route and dosage unless otherwise stated) vs placebo in women with a singleton pregnancy and any risk factor(s) for preterm birth.

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE[1]
Preterm birth (PTB)				
Any PTB <37 weeks	14 (6303)	**0.82 (0.71 to 0.95)**	**26.8 vs 30.2**	⊕⊕⊕⊕
Spontaneous PTB <37 weeks	6 (3698)	0.87 (0.67 to 1.13)	17.7 vs 17.4	⊕⊕⊕◯[2]
Any PTB <35 weeks	5 (3872)	**0.80 (0.68 to 0.93)**	**14.5 vs 18.8**	⊕⊕⊕◯[3]
Spontaneous PTB <35 weeks (17-OHPC)	1 (1687)	0.94 (0.68 to 1.30)	8.6 vs 8.9	⊕⊕⊕◯[4]
Any PTB <34 weeks	16 (7581)	**0.78 (0.68 to 0.89)**	**11.7 vs 15.2**	⊕⊕⊕⊕
Spontaneous PTB <34 weeks	2 (330)	**0.57 (0.38 to 0.86)**	**16.3 vs 28.6**	⊕⊕◯◯[5]
Any PTB <33 weeks (vaginal prog)	5 (974)	**0.63 (0.48 to 0.83)**	**14.0 vs 22.5**	⊕⊕⊕◯[6]
Any PTB <32 weeks	6 (3645)	0.71 (0.50 to 1.01)	7.0 vs 10.1	⊕⊕◯◯[7]
Spontaneous PTB <32 weeks	2 (1770)	0.84 (0.51 to 1.39)	3.4 vs 4.1	⊕⊕◯◯[8]
Any PTB <28 weeks	6 (2793)	**0.64 (0.44 to 0.95)**	**2.6 vs 4.5**	⊕⊕⊕◯[4]
Neonatal mortality and morbidity				
Neonatal mortality <28 days	12 (7169)	**0.60 (0.39 to 0.92)**	**1.3 vs 2.4**	⊕⊕⊕◯[4]
Composite adverse neonatal outcome	5 (4742)	0.83 (0.66 to 1.06)	11.2 vs 14.3	⊕⊕◯◯[9]
Respiratory distress syndrome	9 (4636)	**0.70 (0.57 to 0.87)**	**6.8 vs 10.0**	⊕⊕⊕◯[10]
Bronchopulmonary dysplasia	7 (5233)	0.89 (0.58 to 1.37)	1.5 vs 1.9	⊕⊕◯◯[11]
Intraventricular haemorrhage	10 (6310)	0.67 (0.45 to 1.02)	1.1 vs 1.8	⊕⊕◯◯[11]
Necrotizing enterocolitis	11 (6406)	0.80 (0.51 to 1.23)	1.0 vs 1.6	⊕⊕◯◯[12]
Neonatal sepsis	9 (5563)	0.70 (0.39 to 1.24)	2.2 vs 3.1	⊕⊕◯◯[13]
Retinopathy of prematurity	5 (3812)	0.71 (0.34 to 1.45)	1.1 vs 1.5	⊕⊕◯◯[14]
Admittance NICU	10 (5772)	0.77 (0.60 to 1.00)	14.4 vs 17.7	⊕⊕◯◯[15]
Maternal morbidity				
Hypertensive disorder in pregnancy	5 (4665)	0.97 (0.74 to 1.27)	4.1 vs 4.0	⊕⊕⊕◯[4]
Gestational diabetes mellitus	4 (3519)	0.83 (0.60 to 1.15)	3.8 vs 4.8	⊕⊕◯◯[16]
Intrahepatic cholestasis	2 (1369)	0.66 (0.19 to 2.33)	0.6 vs 0.9	⊕⊕◯◯[8]
Chorioamnionitis	6 (4021)	1.16 (0.75 to 1.80)	2.1 vs 2.0	⊕⊕◯◯[12]
Preterm prelabour rupture of membranes	6 (3648)	0.93 (0.78 to 1.11)	10.7 vs 11.4	⊕⊕⊕⊕

[1] Certainty of evidence	
High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Reasons for downgrading:

[2] One level based on inconsistency (I^2 68%) and uncertain precision.
[3] One level based on serious indirectness (ethnicity discrepancies).
[4] One level based on serious imprecision.
[5] Two levels based on serious indirectness (cervical length with different cut-offs, 10% twins included) and serious imprecision.
[6] One level due to study limitations (3 of 5 trials include subgroups of original trials).
[7] Two levels based on some inconsistency (I^2 51%), uncertainty in directness (high PTB rate in controls) and serious imprecision (crossing unity).
[8] Two levels based on very serious imprecision.
[9] Two levels based on some variation in the definition of the composite outcome, some inconsistency (I^2 49%) and serious imprecision (crossing unity).
[10] One level based on various definitions of the outcome.
[11] Two levels based on some study limitations, uncertain directness and serious imprecision.
[12] Two levels based on various definitions of the outcome and serious imprecision.
[13] Two levels based on various definitions of the outcome, some inconsistency (I^2 44%) and serious imprecision.
[14] Two levels based on some study limitations, inconsistency (I^2 27%), indirectness and serious imprecision.
[15] Two levels based on serious inconsistency (I^2 72%), and indirectness (high PTB rate).
[16] Two levels based on serious imprecision and no definition of GDM in three trials.

SoF Table 2. Progesterone (any administration route and dosage unless otherwise stated) vs placebo in women with a multifetal pregnancy with or without additional risk factor(s).

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE
Preterm birth (PTB)				
Any PTB <37 weeks	10 (4517)	1.01 (0.95 to 1.08)	58.3 vs 57.2	⊕⊕⊕◯[1]
Spontaneous PTB <37 weeks (vaginal prog)	3 (1189)	1.08 (0.94 to 1.24)	41.6 vs 37.0	⊕⊕⊕◯[2]
Any PTB <35 weeks	4 (954)	1.00 (0.90 to 1.11)	50.6 vs 46.0	⊕⊕⊕⊕
Spontaneous PTB <35 weeks (17-OHPC)	2 (788)	1.17 (0.96 to 1.44)	32.4 vs 28.8	⊕⊕⊕◯[3]
Any PTB <34 weeks	15 (5257)	1.02 (0.92 to 1.12)	22.4 vs 21.6	⊕⊕⊕⊕
Spontaneous PTB <34 weeks	4 (2372)	1.05 (0.82 to 1.35)	12.2 vs 11.7	⊕⊕⊕⊕
Any PTB <33 weeks (vaginal prog)	6 (95)	0.70 (0.43 to 1.16)	35.7 vs 55.8	⊕⊕◯◯[4]
Any PTB <32 weeks	10 (4581)	1.00 (0.81 to 1.01)	12.0 vs 11.8	⊕⊕⊕⊕
Spontaneous PTB <32 weeks (vaginal prog)	1 (1100)	1.03 (0.59 to 1.77)	4.5 vs 4.4	⊕⊕◯◯[4]
Any PTB <28 weeks	10 (4578)	0.99 (0.76 to 1.29)	4.8 vs 4.9	⊕⊕⊕⊕
Spontaneous PTB <28 weeks (vaginal prog)	1 (1126)	1.13 (0.41 to 3.09)	1.4 vs 1.2	⊕⊕◯◯[4]
Neonatal mortality and morbidity				
Neonatal mortality <28 days	10 (6869)	0.96 (0.60 to 1.53)	1.5 vs 1.7	⊕⊕⊕◯[5]
Composite adverse neonatal outcome	8 (4504)	0.98 (0.80 to 1.21)	18.7 vs 18.2	⊕⊕◯◯[6]
Respiratory distress syndrome	8 (5142)	0.97 (0.77 to 1.22)	15.0 vs 13.8	⊕⊕⊕◯[7]
Bronchopulmonary dysplasia	6 (3175)	0.87 (0.50 to 1.51)	3.5 vs 3.7	⊕⊕◯◯[8]
Intraventricular haemorrhage	7 (4559)	1.38 (0.76 to 2.51)	1.2 vs 0.8	⊕⊕◯◯[9]
Necrotizing enterocolitis	8 (5137)	0.73 (0.41 to 1.30)	0.9 vs1.1	⊕⊕◯◯[9]
Neonatal sepsis	7 (4968)	1.02 (0.53 to 1.95)	3.6 vs 3.5	⊕⊕◯◯[10]
Retinopathy of prematurity	6 (3565)	0.61 (0.29 to 1.28)	1.0 vs 1.5	⊕⊕◯◯[11]
Admittance NICU	5 (4968)	1.00 (0.79 to 1.27)	29.4 vs 31.0	⊕⊕⊕◯[12]
Maternal morbidity				
Hypertensive disorder in pregnancy	10 (4502)	1.02 (0.84 to 1.25)	11.2 vs 10.3	⊕⊕⊕⊕
Gestational diabetes mellitus	8 (3268)	1.02 (0.77 to 1.35)	6.1 vs 5.5	⊕⊕⊕◯[13]
Intrahepatic cholestasis (vaginal prog)	4 (2535)	0.63 (0.22 to 1.86)	1.4 vs 2.3	⊕⊕◯◯[13]
Infection	5 (1773)	1.29 (0.77 to 2.15)	3.7 vs 2.8	⊕⊕◯◯[13]
Preterm prelabour rupture of membranes	4 (1279)	1.09 (0.73 to 1.63)	7.0 vs 7.3	⊕⊕⊕◯[5]

Reasons for downgrading:

[1] One level based on some inconsistency (I^2 38%) and some indirectness (high proportion IVF pregnancies).
[2] One level based on serious indirectness (34-95% IVF pregnancies).
[3] One level based on uncertain directness (unclear selection process) and uncertain precision.
[4] Two levels based on very serious imprecision.
[5] One level based on serious imprecision.
[6] Two levels based on some variation in the definition of the composite outcome, and serious inconsistency (I^2 61%).
[7] One level based on various definitions of the outcome and serious inconsistency (I^2 64%).
[8] Two levels based on some study limitations and inconsistency (I^2 48%) and serious imprecision.
[9] Two levels based on some study limitations and serious imprecision.
[10] Two levels based on various definitions of the outcome, serious inconsistency (I^2 75%) and uncertain precision.
[11] Two levels based on some study limitations, inconsistency (I^2 29%), and serious imprecision.
[12] One level based on serious inconsistency (I^2 84%).
[13] One level based on some imprecision and no definition of GDM in most trials.
[14] Two levels based on various definitions of the outcome and serious imprecision.

SoF Table 3. Cerclage vs no cerclage in women with a singleton pregnancy and any risk factor(s) for preterm birth.

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE
Preterm birth (PTB)				
Any PTB <37 weeks	4 (1919)	**0.78 (0.69 to 0.88)**	**29.0 vs 37.6**	⊕⊕⊕◯[1]
Any PTB <35 weeks	1 (301)	0.76 (0.56 to 1.03)	31.8 vs 41.8	⊕⊕◯◯[2]
Any PTB <34 weeks	4 (1919)	**0.79 (0.66 to 0.94)**	**20.0 vs 22.3**	⊕⊕⊕◯[1]
Any PTB <33 weeks	2 (1517)	**0.79 (0.63 to 0.99)**	**14.4 vs 18.3**	⊕⊕◯◯[3]
Any PTB <32 weeks	1 (101)	0.85 (0.27 to 2.70)	10.3 vs 12.1	⊕◯◯◯[4]
Any PTB <28 weeks	4 (1915)	0.77 (0.60 to 1.00)	9.1 vs 12.2	⊕⊕⊕◯[1]
Neonatal mortality and morbidity				
Perinatal mortality	3 (1818)	**0.72 (0.54 to 0.97)**	**8.0 vs 11.1**	⊕⊕◯◯[5]
Neonatal mortality <28 days	3 (1674)	0.62 (0.31 to 1.25)	1.5 vs 2.4	⊕⊕◯◯[6]
Composite adverse neonatal outcome	2 (554)	1.02 (0.60 to 1.72)	9.1 vs 9.0	⊕⊕◯◯[7]
Respiratory distress syndrome	1 (300)	1.03 (0.49 to 2.14)	8.8 vs 8.6	⊕◯◯◯[8]
Bronchopulmonary dysplasia	1 (244)	0.98 (0.25 to 3.84)	3.3 vs 3.3	⊕◯◯◯[8]
Intraventricular haemorrhage	2 (544)	0.35 (0.05 to 2.29)	0.4 vs 1.5	⊕◯◯◯[8]
Necrotizing enterocolitis	1 (300)	1.03 (0.15 to 7.20)	1.4 vs 1.3	⊕◯◯◯[8]
Neonatal sepsis	1 (244)	2.46 (0.49 to 12.43)	1.6 vs 1.7	⊕◯◯◯[8]
Retinopathy of prematurity	2 (544)	0.47 (0.13 to 1.67)	1.1 vs 2.9	⊕◯◯◯[8]
Maternal morbidity				
Fever antepartum (To, 2004) Fever postpartum (Macnaughton, 1993)	1 (253) 1 (798)	4.96 (0.59 to 41.86) 2.01 (0.99 to 4.07)	3.9 vs 0.8 5.7 vs 2.8	⊕◯◯◯[9] ⊕◯◯◯[9]
Preterm prelabour rupture of membranes	2 (1517)	1.57 (0.45 to 5.50)	3.4 vs 2.5	⊕⊕◯◯[10]

Reasons for downgrading:

[1] One level based on some study limitations (open trials), and some indirectness (one old trial and ethnicity discrepancies).

[2] Two levels based on some study limitations (open trial), and some indirectness (ethnicity discrepancies), and serious imprecision (few events, crossing unity).

[3] Two levels based on some study limitations (open trials), some indirectness (one old trial and ethnicity discrepancies), and non-robust result after sensitivity analysis.

[4] Three levels based on some study limitations (open trial), some indirectness (ethnicity discrepancies) and serious imprecision (very few events).

[5] Two levels based on some study limitations (open trials), and some indirectness (including miscarriages in Macnaughton, 1993, but no major change after exclusion of that trial) and some imprecision.

[6] Two levels based on some study limitations (open trials), and some indirectness (including miscarriages and 2% twins in Macnaughton, 1993), and serious imprecision (few events and crossing unity).

[7] Two levels based on some study limitations (open trials), and some indirectness (ethnicity discrepancies), and serious imprecision (few events, crossing unity).

[8] Three levels based on some study limitations (open trials), and some indirectness (ethnicity discrepancies), and very serious imprecision (few events, crossing unity).

[9] Three levels based on some study limitations (open trials, reporting bias), and some indirectness (one old trial and ethnicity discrepancies, including miscarriages in Macnaughton, 1993), and very serious imprecision (few events).

[10] Two levels based on serious study limitations (open trials and reporting bias regarding the reported number of PPROM), and some indirectness (one old trial and ethnicity discrepancies, including miscarriages and 2% twins in Macnaughton, 1993), and serious imprecision (few events and wide CI).

SoF Table 4. Cerclage vs no cerclage in women with a multifetal (twin) pregnancy with or without additional risk factor(s).

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE
Preterm birth (PTB)				
Any PTB <37 weeks	1 (28)	1.33 (0.71 to 2.51)	66.7 vs 50.0	⊕◯◯◯[1]
Spontaneous PTB <34 weeks	1 (30)	**0.72 (0.52 to 0.99)**	**70.6 vs 100**	⊕◯◯◯[2]
Any PTB <33 weeks	1 (28)	0.27 (0.04 to 1.99)	8.3 vs 31.3	⊕◯◯◯[1]
Spontaneous PTB <32 weeks	1 (30)	**0.66 (0.46 to 0.95)**	**64.7 vs 100**	⊕◯◯◯[2]
Spontaneous PTB <28 weeks	1 (30)	**0.49 (0.26 to 0.90)**	**41.2 vs 84.6**	⊕◯◯◯[2]
Neonatal mortality and morbidity				
Perinatal mortality (Macnaughton, 1993) Perinatal mortality (Roman, 2020)	1 (56) 1 (60)	1.33 (0.20 to 8.80) **0.23 (0.11 to 0.49)**	8.3 vs 6.3 **17.6 vs 76.9**	⊕◯◯◯[1] ⊕⊕◯◯[3]
Neonatal mortality <28 days	1 (60)	**0.23 (0.11 to 0.49)**	**17.6 vs 76.9**	⊕⊕◯◯[3]
Composite adverse neonatal outcome	1 (36)	0.93 (0.38 to 2.27)	46.7 vs 50.0	⊕◯◯◯[2]
Respiratory distress syndrome	1 (36)	1.40 (0.42 to 4.62)	46.7 vs 33.3	⊕◯◯◯[2]
Intraventricular haemorrhage	1 (36))	0.80 (0.11 to 5.96)	13.3 vs 16.7	⊕◯◯◯[2]
Necrotizing enterocolitis	1 (36)	-	0 vs 0	⊕◯◯◯[2]
Neonatal sepsis	1 (36)	0.40 (0.04 to 3.74)	6.7 vs 16.7	⊕◯◯◯[2]
Retinopathy of prematurity	1 (36)	1.00 (0.14 to 7.10)	16.7 vs 16.7	⊕◯◯◯[2]
Admittance NICU	1 (36)	0.78 (0.58 to 1.05)	73.3 vs 100	⊕⊕◯◯[3]
Maternal morbidity				
Chorioamnionitis	1 (30)	0.51 (0.10 to 2.62)	11.8 vs 23.1	⊕◯◯◯[2]
Preterm prelabour rupture of membranes	1 (30)	1.68 (0.78 to 3.64)	64.7 vs 38.5	⊕◯◯◯[2]

Reasons for downgrading:
[1] Three levels based on some study limitations (open trial), and some indirectness (old trial, ethnicity discrepancies), and very serious imprecision (few events, crossing unity).
[2] Three levels based on some study limitations (open trial), and some indirectness (high risk population with dilated cervix and bulging membranes, Roman 2020), and very serious imprecision (few events).
[3] Two levels based on some study limitations (open trial), some indirectness (high risk population with dilated cervix and bulging membranes, Roman 2020) and serious imprecision (few events).

SoF Table 5. Pessary vs no pessary in women with a singleton pregnancy and short cervical length.

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE
Preterm birth (PTB)				
Any PTB <37 weeks	5 (1531)	0.87 (0.73 to 1.03)	24.4 vs 28.3	⊕⊕⊕◯[1]
Spontaneous PTB <37 weeks	4 (1694)	0.67 (0.41 to 1.09)	19.5 vs 31.8	⊕⊕◯◯[2]
Any PTB <34 weeks	7 (2843)	0.78 (0.49 to 1.23)	11.0 vs 14.8	⊕⊕◯◯[3]
Spontaneous PTB <34 weeks	6 (2726)	0.71 (0.41 to 1.21)	9.5 vs 13.5	⊕⊕◯◯[2]
Any PTB <32 weeks	4 (2239)	0.87 (0.56 to 1.34)	7.5 vs 8.2	⊕⊕◯◯[4]
Spontaneous PTB <32 weeks	1 (300)	0.71 (0.33 to 1.56)	6.7 vs 9.3	⊕⊕◯◯[5]
Any PTB <28 weeks	5 (2319)	0.86 (0.52 to 1.42)	4.7 vs 5.1	⊕⊕◯◯[4]
Spontaneous PTB <28 weeks	4 (1694)	**0.45 (0.22 to 0.93)**	2.9 vs 6.6	⊕⊕◯◯[5]
Perinatal mortality, neonatal mortality and morbidity				
Perinatal mortality	4 (2353)	0.73 (0.36 to 1.46)	2.8 vs 4.1	⊕⊕◯◯[4]
Neonatal mortality <28 days	7 (2931)	0.66 (0.39 to 1.10)	1.6 vs 2.4	⊕⊕◯◯[5]
Composite adverse neonatal outcome	5 (2668)	0.67 (0.40 to 1.13)	12.3 vs 16.3	⊕⊕◯◯[3]
Respiratory distress syndrome	6 (2761)	0.77 (0.48 to 1.23)	10.9 vs 13.0	⊕⊕◯◯[4]
Bronchopulmonary dysplasia	3 (1365)	0.75 (0.43 to 1.30)	3.0 vs 4.1	⊕⊕◯◯[5]
Intraventricular haemorrhage	5 (1812)	1.17 (0.48 to 2.81)	1.9 vs 1.5	⊕⊕◯◯[4]
Necrotizing enterocolitis	5 (2651)	1.00 (0.47 to 2.15)	1.0 vs 1.1	⊕⊕◯◯[6]
Neonatal sepsis	6 (2759)	0.89 (0.55 to 1.43)	4.1 vs 4.6	⊕⊕◯◯[4]
Retinopathy of prematurity	4 (1704)	0.51 (0.10 to 2.60)	0.9 vs 1.9	⊕⊕◯◯[4]
Admittance NICU	5 (2428)	1.04 (0.78 to 1.38)	15.0 vs 14.2	⊕⊕◯◯[4]
Maternal morbidity				
Chorioamnionitis	4 (942)	1.04 (0.54 to 2.00)	3.8 vs 3.6	⊕⊕◯◯[6]
Genitourinary infection	3 (1165)	0.94 (0.70 to 1.26)	12.4 vs 13.3	⊕⊕◯◯[5]
Vaginal discharge	3 (798)	**1.91 (1.60 to 2.28)**	91.0 vs 46.2	⊕⊕⊕◯[7]
Preterm prelabour rupture of membranes	5 (1838)	0.83 (0.44 to 1.56)	6.0 vs 6.7	⊕⊕◯◯[4]

Reasons for downgrading:
[1] One level based on lack of blinding, uncertain directness regarding populations, uncertain precision
[2] Two levels based on lack of blinding, uncertain directness regarding populations, uncertain precision, serious inconsistency
[3] Two levels based on serious inconsistency and imprecision
[4] Two levels based on lack of blinding, some inconsistency, uncertain directness regarding populations, serious imprecision
[5]Two levels based on lack of blinding, uncertain directness regarding populations, serious imprecision
[6]Two levels based on very serious imprecision
[7] One level based on lack of blinding and subjective outcome

SoF Table 6. Pessary vs no pessary in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth.

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE
Preterm birth (PTB)				
Any PTB <37 weeks	4 (1428)	0.97 (0.89 to 1.04)	60.4 vs 61.6	⊕⊕⊕◯[1]
Spontaneous PTB <37 weeks	3 (683)	0.93 (0.78 to 1.10)	33.7 vs 36.8	⊕⊕⊕◯[1]
Any PTB <34 weeks	5 (1931)	0.86 (0.65 to 1.15)	20.1 vs 21.4	⊕⊕◯◯[2]
Spontaneous PTB <34 weeks	4 (1860)	0.80 (0.54 to 1.17)	14.5 vs 16.6	⊕⊕◯◯[3]
Any PTB <32 weeks	4 (2559)	0.85 (0.67 to 1.09)	10.4 vs 11.9	⊕⊕⊕◯[1]
Spontaneous PTB <32 weeks	1 (503)	0.82 (0.51 to 1.33)	10.4 vs 12.6	⊕⊕◯◯[4]
Any PTB <28 weeks	5 (2605)	0.79 (0.52 to 1.22)	4.4 vs 5.5	⊕⊕◯◯[2]
Spontaneous PTB <28 weeks	3 (683)	0.67 (0.39 to 1.13)	6.2 vs 9.4	⊕⊕◯◯[4]
Perinatal mortality, neonatal mortality and morbidity				
Perinatal mortality	2 (2183)	0.81 (0.48 to 1.38)	2.2 vs 2.7	⊕⊕◯◯[4]
Neonatal mortality <28 days	4 (4346)	0.99 (0.65 to 1.49)	2.0 vs 2.1	⊕⊕◯◯[4]
Composite adverse neonatal outcome	5 (5291)	1.01 (0.84 to 1.21)	12.5 vs 12.8	⊕⊕⊕◯[1]
Respiratory distress syndrome	4 (4285)	1.13 (0.91 to 1.40)	7.7 vs 6.8	⊕⊕⊕◯[1]
Bronchopulmonary dysplasia	3 (2732)	0.74 (0.23 to 2.43)	0.9 vs 1.2	⊕⊕◯◯[5]
Intraventricular haemorrhage	5 (5291)	1.20 (0.74 to 1.93)	1.4 vs 1.2	⊕⊕◯◯[6]
Necrotizing enterocolitis	5 (5291)	0.78 (0.33 to 1.86)	0.7 vs 0.9	⊕⊕◯◯[2]
Neonatal sepsis	5 (5291)	1.00 (0.73 to 1.37)	3.9 vs 3.9	⊕⊕⊕◯[1]
Retinopathy of prematurity	3 (2651)	**3.84 (1.19 to 12.42)**	1.0 vs 0.2	⊕◯◯◯[7]
Admittance NICU	2 (2640)	0.90 (0.74 to 1.09)	13.3 vs 14.7	⊕⊕⊕◯[8]
Maternal mortality and morbidity				
Hypertensive disorder in pregnancy	1 (808)	1.24 (0.89 to 1.74)	16.2 vs 13.0	⊕⊕◯◯[4]
Chorioamnionitis	3 (988)	1.05 (0.53 to 2.06)	3.7 vs 3.2	⊕⊕◯◯[9]
Genitourinary infection	2 (854)	4.24 (0.74 to 24.39)	1.6 vs 0.2	⊕◯◯◯[10]
Vaginal discharge	2 (180)	**1.88 (1.53 to 2.31)**	95.6 vs 50.6	⊕⊕⊕◯[11]
Preterm prelabour rupture of membranes	4 (1491)	0.99 (0.44 to 2.21)	7.0 vs 6.7	⊕⊕◯◯[4]

Reasons for downgrading:

[1] One level based on lack of blinding and uncertain precision

[2] Two levels based on lack of blinding, some inconsistency, serious imprecision

[3] Two levels based on lack of blinding, some inconsistency, uncertain precision

[4] Two levels based on lack of blinding, serious imprecision

[5] Two levels based on serious inconsistency and imprecision

[6] Two levels based on lack of blinding, different outcome definitions, serious imprecision

[7] Three levels based on lack of blinding, lack of classification of outcome, very serious imprecision

[8] One level based on lack of blinding, possible different routines regarding admittance to NICU, uncertain precision

[9] Two levels based on very serious imprecision

[10] Three levels based on lack of blinding, poorly defined outcome, very serious imprecision

[11] One level based on lack of blinding and subjective outcome

SoF Table 7. Acetylsalicylic acid (ASA) vs placebo in women with a singleton pregnancy and the risk factor previous preterm birth.

Outcomes	Number of RCTs (patients)	Relative effect RR (95% CI) In bold if difference is statistically significant	Absolute effect (%)	Certainty of evidence GRADE
Preterm birth (PTB)				
Any PTB <37 weeks	1 (387)	0.83 (0.58 to 1.20)	21.2 vs 25.4	⊕⊕◯◯[1]
Spontaneous PTB <37 weeks	1 (387)	0.84 (0.58 to 1.23)	20.1 vs 23.8	⊕⊕◯◯[1]
Any PTB <34 weeks	1 (387)	1.05 (0.56 to 1.98)	9.3 vs 8.8	⊕⊕◯◯[1]
Spontaneous PTB <34 weeks	1 (387)	1.12 (0.59 to 2.13)	9.3 vs 8.3	⊕⊕◯◯[1]
Any PTB <28 weeks	1 (387)	1.39 (0.45 to 4.31)	3.6 vs 2.6	⊕⊕◯◯[1]
Spontaneous PTB <28 weeks	1 (387)	1.39 (0.45 to 4.31)	3.6 vs 2.6	⊕⊕◯◯[1]
Neonatal outcomes				
Perinatal mortality	1 (387)	2.99 (0.61 to 14.60)	3.1 vs 1.0	⊕◯◯◯[2]
Composite adverse neonatal outcome	1 (387)	1.79 (0.61 to 5.25)	4.6 vs 2.6	⊕◯◯◯[2]
Bronchopulmonary dysplasia	1 (387)	0.33 (0.04 to 3.16)	0.5 vs 1.6	⊕◯◯◯[3]
Intraventricular haemorrhage	1 (387)	0.22 (0.01 to 5.05)	0.5 vs 0	⊕◯◯◯[3]
Necrotizing enterocolitis	1 (387)	0.22 (0.01 to 5.05)	0.5 vs 0	⊕◯◯◯[3]
Neonatal sepsis	1 (387)	1.99 (0.37 to 10.74)	2.1 vs 1.0	⊕◯◯◯[3]
Retinopathy of prematurity	1 (387)	0.50 (0.05 to 5.44)	0.5 vs 1.0	⊕◯◯◯[3]
Admittance NICU	1 (387)	1.18 (0.54 to 2.56)	6.7 vs 5.7	⊕⊕◯◯[1]
Maternal outcomes				
Maternal mortality	1 (387)	-	0 vs 0	⊕◯◯◯[3]
Hypertensive disorder in pregnancy	1 (387)	0.80 (0.22 to 2.92)	2.1 vs 2.6	⊕◯◯◯[3]
Gestational diabetes mellitus	1 (387)	1.00 (0.50 to 1.98)	7.7 vs 7.8	⊕⊕◯◯[1]
Any genital infection	1 (387)	0.40 (0.16 to 1.00)	3.1 vs 7.8	⊕◯◯◯[4]
Vaginal bleeding Other bleeding	1 (222)	0.78 (0.26 to 2.39) 1.54 (0.77 to 3.01)	4.7 vs 6.0 16.0 vs 10.4	⊕◯◯◯[5]
Preterm prelabour rupture of membranes	1 (387)	0.50 (0.23 to 1.08)	4.6 vs 9.3	⊕⊕◯◯[1]

Reasons for downgrading:
[1] Two levels based on very serious imprecision.
[2] Three levels based on very serious imprecision and uncertainty about directness (the outcome included fetal deaths (≥16 weeks).
[3] Three levels based on extremely serious imprecision.
[4] Three levels based on very serious imprecision and study limitation (cointervention with cerclage in the ASA group).
[5] Three levels based on very serious imprecision and study limitation (self-reported/subjective outcome).

10. Organisational aspects

Pre-requisites for the putative introduction of "screen and treat" preterm birth

Interventions for preventing preterm birth such as vaginal progesterone and cerclage are already available, although not used in a standardised way in clinical practice in VGR/Sweden. ASA is available but used for other indications such as the prevention of preeclampsia. Pessary is so far not used in VGR/Sweden. Standardised use of any method to prevent preterm birth would require the introduction of a screening program to identify women at risk.

In Sweden, the antenatal clinics in primary health care have a task to identify the pregnant women at risk, including the risk of preterm birth. Cervical length measurement is already applied to a limited extent for some women at high risk, but universal screening of cervical length is not performed in a standardised way neither in VGR nor elsewhere in Sweden. Moreover, the consultation in specialised health care and advise for preventive alternatives may differ for women at high risk of preterm birth, partly due to the lack of national or regional guidelines. If such a routine transvaginal ultrasound programme of measurement of the cervical length is introduced, the sonographers (usually midwives) need to be certified after theoretical and practical training on the standardised measurement method (Kagan and Sonek, 2015). An educational and examination committee should be established on a national or regional level. The educational efforts will take between 6 to 12 months to organise, and then continuous surveillance is needed to ensure the quality of the ultrasound measurements. Financial support is required to create the standard educational material (online), hands-on training, and support the digital image transfer and storage system.

The cervical measurement takes about an additional 15 minutes if it is combined with the routine fetal ultrasound examination between 18 and 21 gestational weeks. The diagnostic performance is better between 21 and 23 gestational weeks (Kuusela et al., 2021), but an extra visit would require 30 minutes for the examination. All clinics in VGR provide routine fetal ultrasound examinations and indicated cervical measurements in the second trimester and thus have the necessary equipment, i.e., ultrasound devices and vaginal probes. However, if universal screening is recommended, the existing equipment may not suffice.

Time needed to implement a new guideline for the prevention of preterm birth is depending on the wideness of the screening program and cannot be estimated.

Present use of preventive interventions in other hospitals in Region Västra Götaland

Universal screening for the prevention of preterm birth is not offered to women in VGR/Sweden today. No guidelines were found in VGR, the Swedish Society of Obstetrics and Gynaecology, or the Swedish National Board of Health and Welfare for screening or prevention of preterm birth in asymptomatic women.

Cerclage is used for high-risk women at all hospitals in VGR based on individual consultations, especially if cervical insufficiency is suspected based on medical history or on ultrasound findings. Ten women received a cerclage during 2020 in VGR, six of these at Sahlgrenska University Hospital.

Consequences of the new health technology for personnel

A new guideline for preventing preterm birth will implement up-to-date knowledge and improve equal treatment for all women in VGR. In addition, sonographers (usually midwives) need to be educated on how to measure cervical length if a transvaginal ultrasound measurement of cervical length is included in the risk assessment. In case of a short cervix, obstetricians will then decide upon and handle the preventive treatment, resulting in an increased workload. This educational effort to teach and train the midwives/sonographers/doctors how to perform cervical length measurement will increase the overall competence.

Both screening based on history and sonographically cervical length screening may imply referral to specialised regional consultation. The cervical cerclage procedure is of rare occurrence and the annual experience for a senior obstetrician in VGR can be estimated to one or two insertions. The establishment of regional preterm birth prevention clinics can be considered. A centralisation would improve the consistency of indications, and equality and performance skills.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Since both screening and treatment would be handled by the primary health care and the specialised health care, other clinics would not primarily be affected if a screening programme is introduced. If the prevention of preterm birth succeeds and neonatal morbidity is reduced, the number of admitted newborn to neonatal intensive care units (NICU) will decrease.

11. Economic aspects

Present costs of currently used technologies

The care as usual (control) is no intervention, represented by the cost of a current birth (including costs of potential NICU etc.). From Wikström et al. (2022), the expected health-care cost of the current care as usual is about 53,000 to 55,000 Swedish kronor (SEK) per singleton delivery.

Expected costs of the new health technology

The costs of the four interventions are listed in the table below. The cost of vaginal progesterone is based on the drug cost for 16 weeks of treatment (200 mg daily). The cost of cerclage is based on the VGR regional health care registry (code MAB00). The cost of a pessary is based on product cost. The cost of ASA is based on the drug cost for 28 weeks of treatment. For all interventions it is assumed that one physician visit would be required to initiate treatment (cost 1700 SEK).

Intervention	Cost for treatment (including physician visit)
Vaginal progesterone	2,950 SEK
Cerclage	21,700 SEK
Pessary	1,850 SEK
ASA	1,800 SEK

Total change in costs

Scenario 1: Treatment based on transvaginal sonography for cervical length screening

Transvaginal sonography for cervical length (TVS CL) screening is used to identify pregnant women with a short cervix for the potential treatment with vaginal progesterone, cerclage, or pessary.
The screening would be performed on the day of the routine fetal ultrasound examination (between 18+0 and 20+6 weeks). Potential ASA treatment would not require TVS CL screening and would only be implemented among a group of high-risk women based on patient history (3.6% of women).

For an assumed population of pregnant women (18+ weeks) of 20,000 per year, TVS CL screening and a short cervix (cut-off ≤25mm) prevalence of 3.98% (Wikström et al., 2022), the annual screening cost in VGR would amount to about 11 million SEK.

Intervention	The total increase in annual health care costs due to screening and treatment (for a cohort of 20,000)
Screening + Vaginal progesterone	13 million SEK
Screening + Cerclage	28 million SEK
Screening + Pessary	12 million SEK
ASA	1.3 million SEK

Scenario 2: Treating high-risk women without TVS CL screening (treatment based on history)
No TVS CL screening is performed. Any of the interventions are only implemented in the group of high-risk women based on patient history (previous late miscarriage or spontaneous preterm birth) assumed to be 3.6% of women (Wikström et al., 2022).

Intervention	The total increase in annual health care costs (for a cohort of 20,000)
Vaginal progesterone	2.1 million SEK
Cerclage	15.6 million SEK
Pessary	1.3 million SEK
ASA	1.3 million SEK

Expected cost-effectiveness of the health technologies

To model the total change in costs over a lifetime perspective, we rely on a cost-effectiveness model from a previously published paper (see Wikström et al., 2022 for details on the model framework). In short, the model includes costs for screening, treatment, cost of delivery, potential NICU costs, etc. The health outcome in the model is the reduction in preterm births and the associated gain in life-years (each reduced death is assumed to lead to a child born with average life expectancy).

The cost-effectiveness analyses are only carried out for vaginal progesterone and cerclage since the results did not show any evidence in favor of preventing preterm birth from ASA or pessary. For the vaginal progesterone intervention, we assume a reduction in preterm births by 0.15 (week 34+0 to 37+0) and 0.23 (week <34+0), respectively. For the cerclage intervention, we assume a risk reduction of 0.2. The reduction estimates are derived from this HTA-report.

Scenario 1: Treatment based on TVS CL screening
The table shows the cost per gained life-year compared with care as usual (control).

Intervention	Costs per each life-year (LY) gained
Screening + Vaginal progesterone	430,000 SEK per LY
Screening + Cerclage	1.6 million SEK per LY

Based on thresholds used by the Swedish National Board of Health and Welfare, the cost per gained LY with vaginal progesterone can be seen as modest, while the cost of cerclage can be seen as very high.

Scenario 2: Treating high-risk women without TVS CL screening (treatment based on history)
The table shows the cost per gained life-year compared with care as usual (control). The risk reduction from vaginal progesterone is based on studies identifying women with short cervix from screening, and not based on treatment initiation by history – therefore, the results for vaginal progesterone under Scenario 2 should be seen as tentative.

Intervention	Costs per each life-year (LY) gained
Vaginal progesterone	Lower costs and gained LYs (“dominant”)
Cerclage	1.2 million SEK per LY

The model results for vaginal progesterone intervention indicates that it would reduce total health care costs over a life-time perspective while increasing healthy life-years (a so-called dominant intervention). The cost per gained life-year with cerclage is very high based on thresholds used by the Swedish National Board of Health and Welfare.

Possibility to adopt and use the new technology within the present budget

Only considering the initial intervention year, it would not be able to implement any of the four different interventions within the current health care budget. If total health care budget funds are assumed fixed, implementing any of the interventions would thus displace other health care services. If considering a life-time perspective, treating high-risk women without TVS CL screening with vaginal progesterone may reduce total health care costs.

Available economic evaluations or cost advantages/disadvantages

A health economic evaluation alongside the CERVIX-study compared a no-screening strategy (reflecting the current situation in Sweden) with different second trimester screening strategies, followed by vaginal progesterone prophylaxis to women considered at increased risk of spontaneous preterm delivery (Wikström et al., 2022). Another strategy included in the Wikström study that can be considered in this context is screening of nulliparous women and treatment of parous women at risk. Conclusions were that any screening strategy compared with no screening resulted in better health outcome and could be cost-effective in a Swedish setting.

An additional four economic evaluation studies were identified in the literature search.

Two of the studies concerned the cost-effectiveness of prescribing vaginal progesterone gel. Eddama et al. (2010) conducted a cost-effectiveness analysis alongside an RCT in a UK health care setting (STOPPIT trial) comparing vaginal progesterone gel to placebo gel to prevent preterm birth in twins. The results indicated a very low likelihood for vaginal progesterone gel to be a cost-effective intervention, primarily because the intervention did not reduce preterm births. Pizzi et al. (2014) assessed the cost consequences and cost-effectiveness of vaginal progesterone gel among women with a short cervix in a US setting using a decision-analytic model informed by a trial (PREGNANT trial). The results from the model showed that the intervention reduced costs and resulted in a slight reduction in preterm births in singleton pregnancies. However, this was based on assuming that all women are screened for a short cervix, irrespective of offered treatment. The control arm in the study is thus not representative of care as usual in Sweden, where there is no universal screening for a short cervix, which implies that it is not likely that the cost reductions from the intervention translate to a Swedish context.

Two of the identified studies concern using pessary to prevent preterm birth. Liem et al. (2014) evaluated the cost consequences and cost-effectiveness of using pessary (vs. no pessary) in women with a twin pregnancy based on the ProTWIN trial. In the full sample, costs and the likelihood of preterm birth were similar in both groups. In a pre-specified sub-group analysis of women with a cervix length <38 mm, the results indicated that using a cervical pessary reduced costs and preterm births. Again, as in the studies reported above, this assumed that screening for cervix length was conducted in both groups. Finally, Le et al. (2020) conducted a cost-effectiveness analysis alongside an RCT (Dang et al., 2019) on using a pessary compared with vaginal progesterone among women with a twin pregnancy and a cervix <38 mm. The results showed that the use of a pessary led to lower costs and better health outcomes in terms of the number of morbidity-free neonates.

12. Ethical aspects

Preterm birth is the primary cause of neonatal mortality and morbidity. Therefore, increasing gestational length and thereby reduction of preterm birth is probably of great importance. Another important outcome would be the child's long-term follow-up regarding morbidity related to preterm birth. Still, available studies have failed to show a difference regarding progesterone in both singleton and multifetal pregnancies. For pessary, no difference has been shown in long-term follow up for multifetal pregnancies and studies for singleton pregnancies are lacking. For cerclage and ASA, there are no long-term follow-up data on the offspring.
The treatment effect is documented for women with singleton pregnancies with an increased risk of preterm birth. It is unknown how large the reduction of preterm birth rate would be in Sweden. The lack of RCTs in a Swedish setting with a low incidence of preterm birth, involving both screening and subsequent treatment of women found to be at high risk, explains the uncertainty regarding the value of screening.

With a low sensitivity of a prediction test (i.e., screening), the population attributable fraction would be small, and the interventions might not reach the women in most need. Resources directed towards a screening program would require extra midwife resources. If access to midwives is limited, this could potentially lead to displacement effects. If the specificity is poor, many women might screen falsely positive, and they would not profit from an intervention. This might also lead to unnecessary worries and potential risks of side effects from the treatments without any benefit. A positive screening result may increase the concern about pregnancy complications. There is always a risk that the women and her family will choose active treatment rather than refrain from treatment when it is available. However, there is also a risk that pregnant women are reluctant to receive medication during pregnancy due to fear of adverse effects on the fetus. Compliance is also probably greater if the woman perceives that she is genuinely at increased risk of the outcome. Therefore, it is of utmost importance that the treatment is considered safe, efficient in the target population, and well tolerated before being offered to patients on a larger scale.

In a Swedish setting, progesterone will most likely be offered as a vaginal treatment, usually well tolerated and with moderate side effects. Cerclage is an invasive procedure, performed under general or regional anaesthesia, but is usually well tolerated. However, the pregnant women will be more exposed during placement and removal of the cerclage. The use of pessary will expose the woman to two additional vaginal examinations at placement and removal.

In current practice, women are treated differently depending on which antenatal clinic they attend. Thus, this report can help guide the development of a national guideline, provide equal care for preventing preterm birth throughout Sweden, and reduce inequities in health care for women at increased risk of preterm birth.

13. Discussion

Summary of main results

Progesterone has a protective effect against preterm birth and cerclage probably has a protective effect against preterm birth in women with a singleton pregnancy who are asymptomatic but at high risk of preterm birth. In multifetal pregnancies the effect of treatment is very limited if any. For multifetal pregnancies, most estimates were close to no effect or were very uncertain. In most trials on multifetal pregnancies the only risk factor was twin or triplet pregnancy. However, in a highly selected risk group of asymptomatic women with dilated cervix and visible membranes in the second

trimester (one trial), cerclage versus no cerclage may reduce neonatal mortality. Pessary does not seem to have a convincing protective effect against preterm birth neither in singleton nor in multifetal pregnancies. For ASA there is only one small RCT showing no significant effect. There is little evidence regarding combined interventions.
In a Swedish context, vaginal progesterone appears to be the best prevention for preterm birth <34 gestational weeks in asymptomatic women with a singleton pregnancy at overall risk of preterm birth. The use of 17-OHPC and oral progesterone is not approved by the Swedish Medical Products Agency for the prevention of preterm birth and in addition, our subgroup analysis displayed that 17-OHPC in comparison with placebo did not decrease the risk of preterm birth.
Trials on oral progesterone were small but showed a protective effect. The strongest evidence for vaginal progesterone was within the group of women with a sonographic short cervix, with or without risk factors. There were fewer trials on cerclage. The largest trial was an old trial including women with heterogeneous risk factors and no cervical length screening. Only two trials used universal cervical screening to identify women at high risk of preterm birth. Thus, the target population for treatment may differ between progesterone and cerclage. For cerclage, there is uncertainty in what group of women the cerclage would be most useful. Cerclage is an invasive procedure, and considerably more costly than progesterone. No trial reported clear harm with progesterone or cerclage, which is an important result for the woman and the caregiver. We did not find any trials comparing vaginal progesterone with cerclage. Pessary is not used in Sweden, and as the evidence for a benefit of pessary is lacking, results from ongoing trials must be added before any conclusions can be made for the use of pessary as prophylaxis.
Multifetal pregnancies carry a much higher risk of preterm birth than singleton pregnancies with an approximately 50% risk of preterm birth in twins. Unfortunately, there is no evidence to support the use of progesterone, cerclage, or pessary in unselected multifetal pregnancies to prevent preterm birth or to improve neonatal outcome.
As a consequence of this HTA report, national evidence-based guidelines should be established to support clinicians in decision-making. Such guidelines already exist in many countries (Putora et al., 2022). The initiative for developing national guidelines can be initiated by The Swedish National Board of Health and Welfare or “the National system for knowledge-driven management within Swedish healthcare” (Nationella Programområden, NPO).

Overall completeness and applicability of evidence

In this comprehensive report including 23,886 women and 32,893 offspring, all 71 trials fulfilling inclusion criteria were included in the assessment, but for the benefit of reliability, conclusions were based on 50 original trials with low risk of bias and their secondary publications, the vast majority being trials on progesterone versus placebo (n=29). We acknowledge a few limitations. Many of our meta-analyses included a small number of trials, with sparse data, yielding low precision with wide CIs and uncertainty of results. Long-term children follow up data was sparse, and meta-analyses were not feasible due to heterogeneity of data. Some early trials were not registered, or were registered after trial completion, and some trials did not report the predefined primary outcome. These trials may be biased by selective outcome reporting (so called p-hacking) and distortion of results (Prior et al., 2017).
We identified several trials registered many years ago, but still unpublished, as ongoing research and publication bias can therefore not be excluded (Appendix 6). Finally, we did not compare the different interventions with each other, apart from including trials with direct comparisons. A network meta-analysis was discussed but not considered feasible within this report.

Agreements and disagreements with other studies and reviews

In the literature search process, a total of 34 recent systematic reviews, relevant for our PICO and published between 2017 and 2022, were identified and are presented in Appendix 5. Our results are generally consistent with previous systematic reviews with some exceptions.

A recent systematic review with a network meta-analysis including progesterone, cerclage, and pessary in singletons, concluded that vaginal progesterone should be the choice in women with a prior preterm birth or short cervical length (Care et al., 2022). A similar systematic review with a network meta-analysis on twins found no significant effect on the rate of preterm birth or neonatal morbidity for any of the interventions (D'Antonio et al., 2021). Conflicting results and conclusions, compared with ours, regarding vaginal progesterone in women with a twin pregnancy and short cervix were reached by Romero et al. (2022), solely based on different effect models. We believe that the results are more robust with random effect models compared to fixed effect models used by Romero et al.

Applicability of evidence

All interventions for preterm birth prevention imply identification of women being at high risk of preterm birth. Traditionally this is based on accurate history of maternal and gestational risk factors. Unfortunately, available risk scoring systems have a low detection rate and a high false-positive rate (Honest et al., 2004). An alternative strategy may be screening with transvaginal ultrasound in the second trimester to identify women with a short cervical length. Though, a recent Swedish blinded prospective observational study comprising more than 11,000 women showed that the diagnostic performance of transvaginal ultrasound screening in the second trimester was at best moderate (Kuusela et al., 2021). The prevalence of short cervical length (≤25 mm) in the second trimester was 4.0% and out of these, 3.9% had a spontaneous preterm delivery <33 gestational weeks. Regarding risk factors for preterm birth (late miscarriage or previous spontaneous preterm birth), the prevalence was 3.6% out of which 1.5% had a spontaneous preterm delivery <33 gestational weeks (Wikström et al., 2021). Assuming a 30% relative reduction of spontaneous preterm birth with progesterone or cerclage in any of the screened groups, the potential effect would be larger by universal screening for short cervix compared with screening for risk factors.

If screening of cervical length would be offered to all women, the numbers needed to screen to detect one spontaneous preterm birth <33 gestational weeks would be about five times higher compared with screening only women with risk factors for preterm birth. The number of false positive test results per one true positive test will be higher, though potentially a larger detection rate (Wikström et al., 2021). Thus, the potential benefit of screening must be balanced against the potential negative effects for the woman of false positive screening results i.e., unnecessary progesterone treatment, anxiety, extra visits, sick leave etc. Also, the workload caused by screening and a possible displacement effect must be considered.

Implications for research

There are multiple areas of debate and with lack of evidence. Most trials used any preterm birth as the primary outcome. Spontaneous preterm birth is a more clinically relevant outcome than any preterm birth because it may be possible to identify women at risk (either with a history of a prior spontaneous preterm birth or a short cervical length) with subsequent treatment and prevention. Still, few trials reported on spontaneous preterm birth.

Preterm birth or spontaneous preterm birth may be considered as a surrogate outcome, and for the offspring; a more important outcome is neonatal mortality and short- and long-term sequelae of preterm birth. Intrauterine infection or inflammation is associated with spontaneous preterm birth and may also cause neonatal lung disease and brain injury, therefore prolongation of a pregnancy in an inflammatory environment may be harmful for the offspring (Kenyon et al., 2008).

Neonatal mortality and severe adverse neonatal morbidity are rare events, and the definitions of diagnoses and reporting were heterogenous across trials. Researchers should be encouraged to harmonize reporting of outcome data and use the recommended core outcome set that has been recommended for evaluations of interventions to prevent preterm birth (van't Hooft et al., 2016). This will facilitate future individual patient data analyses and allow adequately powered subgroup analyses.

Importantly, long-term neurodevelopment, an important knowledge gap, is now included as a key clinical outcome.

14. Future perspectives

The organisation of preterm birth prevention – specialised preterm birth prevention clinics

Recently, there have been initiatives to establish regional preterm birth prevention clinics in some countries and regions due to the complexity of counselling and treating women with an increased risk of preterm birth. Also, the growing body of knowledge of risk factors and predictive abilities of women at high risk of preterm birth has led to the establishment of these clinics. Similar specialist clinics exist for some gynaecological conditions, but they are also relevant for complex obstetrical syndromes. A preterm birth prevention clinic aims to prolong pregnancy and reduce the rate of preterm birth and the associated perinatal morbidity and morbidity. Preterm birth prevention clinics have two main rationales: consistent indications for different prevention strategies and equal and individualised high-quality care. In addition, recent studies have shown that pregnancy-related anxiety related to the perception of being identified as high risk of preterm birth can be reduced by attending a preterm birth prevention clinic (Dawes et al., 2022).

Some studies provide support for preterm birth prevention clinics improving different pregnancy outcomes, but further adequately designed and powered randomised controlled trials are needed to guide their organisation and importance (Whitworth et al., 2011; Dodd et al., 2015; Malouf and Redshaw, 2017; Dawes et al., 2020). Furthermore, consistency in practice offered to these women at such clinics may be improved by developing Swedish national guidelines for preventing preterm birth.

Scientific knowledge gaps

Progesterone

The effect of vaginal progesterone against preterm birth is best documented in women with a short cervix (≤25 mm) detected on ultrasound screening. The best cut-off for short cervical length has been debated, and a recent Swedish study has shown it to be 29 mm in 18-20 gestational weeks and 27 mm in 21-23 gestational weeks (Kuusela et al., 2021). However, there is uncertainty regarding the effect of vaginal progesterone in asymptomatic women with an ultrasound screened cervical length between 25-30 mm. The EPPPIC trial concluded that progesterone also works when the cervical length is between 25 and 30 mm, but the number of included women is small (EPPPIC Group, 2021). Therefore, there is a need for trials to clarify this. A Swedish or Nordic study would be feasible to investigate the effect of vaginal progesterone (RCT, treatment vs. placebo) in asymptomatic women with an ultrasound screened cervical length between 25-30 mm.

Other aspects that need to be clarified in future research are if vaginal progesterone and weekly 17-OHPC injections are equally effective (Saccone et al., 2017d; Boelig et al., 2022), the dosage of vaginal progesterone, if oral progesterone is effective, and whether progesterone should be offered to subgroups of women carrying a multifetal pregnancy with concomitant risk factors for preterm birth such as short cervix or previous preterm birth.

There is also some unclarity regarding if women with a previous preterm birth and normal cervical length should be offered progesterone. A recent systematic review showed no benefit of vaginal progesterone to women at risk if they had a cervical length >25 mm in the second trimester; however, the meta-analyses included only 1127 women (Phung et al., 2021). It is also unclear whether progesterone works for other risk factors of preterm birth, e.g., cervical conisation. Further studies are needed to clarify these issues.

We did not include cancer in the offspring as an outcome. A recent cohort study by Murphy et al found a possible link between 17-OHPC exposure in early pregnancy and cancer in the offspring (Murphy et al., 2022). Further studies are needed.

Cerclage
Included studies were heterogenous regarding risk factors for preterm birth in the population. Additional studies are needed to clarify the proper indications for cerclage and its relation to preterm birth prevention by investigating specific subgroups of women at risk to target the population that would profit the most from the intervention. This is a challenging area of research since it has been a common practice in many clinics for several decades (Shennan et al., 2021).
A recent study comparing vaginal and abdominal cerclage for previously failed cerclage indicates an advantage for the latter (Shennan et al., 2020) but further studies are needed to verify these findings.

Additional knowledge gaps
Regarding pessary, the results from different research groups are conflicting (Goya et al., 2012; Nicolaides et al., 2016b). Thus, further research is needed to identify which women, if any, might profit from pessary as an intervention for preterm birth prevention (Grobman et al., 2021).
A large trial performed in low- and middle-income countries including nulliparous women with singleton pregnancies and no other specified risk factors, found that ASA initiated in the first trimester reduced the risk of any preterm birth <37 weeks and perinatal mortality (Hoffman et al., 2020). Further studies are needed to clarify if ASA provides benefit for preterm birth in other populations, outside the area of preeclampsia prevention.
Further studies are also needed regarding different combinations of prevention strategies for preterm birth.

Ongoing research

The search (2021-12-05) in Clinicaltrials.gov and WHO ICTRP database identified 507 ongoing clinical trials, and the updated search in Clinicaltrials.gov (2022-04-13) identified 28 additional trials. Fourteen trials (including the published article by Groussolles et al., 2022) are relevant according to the PICO of this report and are listed in Appendix 6.
There were 11 additional trials with unknown status, passed completion date more than two years ago, not identified from our systematic literature search (Jan 2021, Feb 2022), and not found in PubMed (April 2022) which are also shown in Appendix 6.

Among the 14 relevant registered (ongoing or completed) trials, nine included singletons and five included multifetal pregnancies. Among RCTs on singleton pregnancies, one trial included oral progesterone versus placebo (NCT03428685), one cerclage versus no cerclage (ChiCTR2000033510), and one cerclage and progesterone versus progesterone only (NCT02746900, NCT03251729). Five trials included pessary in the intervention group; three of them compared pessary versus no pessary (NCT04147117, NCT03418012, NCT02901626), one pessary versus progesterone (NCT04300322), and one trial compared pessary versus cerclage (NCT02405455). One trial included ASA and progesterone versus progesterone (NCT05319834). Target sample size varied between 60 and 1714 women. Inclusion criteria were a history of previous late miscarriage or preterm birth or a sonographic short cervical length (cut off ≤20, ≤25, or <25 mm).

The trials on multifetal pregnancies included only twins. One trial (PESSARONE) was published a few days after our updated systematic search and therefore not included (NCT02328989, Groussolles et al., 2022). The trial was conducted in France and included 315 women with a twin pregnancy with a sonographic cervical length of <35 mm at 16-24 gestational weeks and compared pessary versus no pessary. The primary outcome, a composite of perinatal mortality and severe neonatal morbidity occurred in 16.8% in the pessary group and in 22.5% in the no pessary group (RR 0.69; 95% CI 0.39

to 1.23, p=0.21). The rate of any preterm birth or spontaneous preterm birth did not differ significantly between groups. Further trials on twins compared cerclage versus progesterone (NCT03340688), and pessary versus progesterone (NCT04342585).
Trials on twins with multiple arms included a three-armed trial comparing progesterone versus pessary versus placebo (NCT02518594), and one trial with four arms: cerclage versus pessary versus cerclage and progesterone versus pessary and progesterone (NCT03863613). Target sample size varied between 200 and 630 women. Inclusion criteria were a twin pregnancy with sonographic short cervical length (cut off ≤15, ≤28, ≤30, or <30 mm).

15. Participants in the project

The question was nominated by

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Patient representative

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Declaration of interests

Among authors:
BJ declares having been leading a working group within FIGO (International Federation of Gynecology and Obstetrics) on preterm birth and is now the FIGO Division Director of Maternal and Newborn Health. He has conducted diagnostic clinical trials for different companies: Ariosa, Natera, Vanadis, Hologic, and has ongoing probiotic studies in cooperation with BioGaia and FucoPharma.
BJ, UBW and PK declare being co-investigators in the OPPTIMUM trial, an included article in this HTA.
LB, EL and AM have nothing to declare.

Among authors from HTA-centrum:
AS, PS, CHV, AL, ACE, MS, and MP have nothing to declare.

Among external reviewers:
MH and MS have nothing to declare.
AH declares having received lecture honoraria from Ferring AB.
MS has nothing to declare.
Patient representative PR (also project coordinator) declares being the founder of "Prematurföreningen Mirakel".

Any published statement herein does not automatically imply a conflict of interest but contributes to transparency. All individual declarations of interests have been evaluated by HTA-centrum if there is any relevant association with the present HTA topic.

Project time

The HTA was accomplished during the period of 14th January 2021 – 28th June 2022.
Literature searches were made January 25th, 2021, with an update February 1st, 2022.

Appendix 1a: PICO, study selection, search strategies, and references

Question(s) at issue:

Will the interventions progesterone, cerclage, pessary, or acetylsalicylic acid (ASA), alone or in combinations, decrease the risk of preterm birth and neonatal and maternal mortality/morbidity, and long-term child morbidity in asymptomatic* women with a singleton pregnancy at risk of preterm delivery** or in asymptomatic women with a multifetal pregnancy with or without additional risk factor(s)?

*Without symptoms indicating risk of preterm delivery
**Previous preterm delivery, previous spontaneous late miscarriage between 16 and 22 gestational weeks, short cervix, previous cervical surgical treatment for cervical intraepithelial neoplasia or other risk factors defined by the authors

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

	PICO
P	Asymptomatic (without symptoms indicating risk of preterm delivery) women with a singleton pregnancy at increased risk of preterm delivery < 37+0 gestational weeks. Asymptomatic women with a multi-fetal pregnancy, irrespective of other risk factors
I	Progesterone, any type, initiated in the second trimester, alone or in combination with the other specified interventions in the PICO. Comparisons between different dosage and administration routes are not included. Cerclage, any type applied before pregnancy, in first or second trimester, alone or in combination with the other specified interventions in the PICO. Pessary, any type applied in first or second trimester, alone or in combination with the other specified interventions in the PICO. Acetylsalicylic acid (ASA), initiated before pregnancy, in first or second trimester, alone or in combination with the other specified interventions in the PICO.
C	No intervention, placebo or other intervention (progesterone, cerclage, pessary, ASA).
O	*Critical for decision making:* Any preterm birth <37, <35, <34, <33, <32, <28 gestational weeks Spontaneous preterm birth <37, <35, <34, <33, <32, <28 gestational weeks Perinatal mortality (intrauterine fetal death and neonatal mortality <7 or <28 days) Neonatal mortality <7, <28 days Serious neonatal morbidity (such as bronchopulmonary dysplasia, severe intraventricular haemorrhage, necrotizing enterocolitis, confirmed sepsis, retinopathy of prematurity), individually or as a composite outcome with or without peri/neonatal mortality. Long-term morbidity (such as cerebral palsy, epilepsy, visual impairment, hearing impairment, intellectual impairment, developmental delay) Maternal mortality Maternal morbidity (adverse effects such as infections, surgical complications, cancer) *Important for decision making:* Gestational length Low birth weight (<2500g), very low birth weight (<1500g)

	Comments to O: *Spontaneous* preterm birth is the most prioritised outcome since it may be preventable. However, it is not reported as often as *any* preterm birth, likely due to indistinguishable conditions in the clinical setting. Established definitions are: preterm birth (<37 gestational weeks), very preterm birth (<32), extreme preterm birth (< 28). A cut-off for active treatment to delay delivery <34 weeks is common, to allow for corticosteroid treatment to accelerate fetal lung maturation. The most critical clinical outcomes are peri/neonatal and maternal mortality and long-term child outcome.

Eligibility criteria

Study design:
Systematic reviews including RCTs
Randomised controlled trials
In a separate search, addressing the intervention progesterone and the outcome cancer, cohort studies of any size will be included, to support the discussion of long-term risk.

Prespecified subgroup analyses for all interventions
For the population group with singleton pregnancies:
Short cervical length
Previous preterm birth
Cervical surgical treatment for cervical intraepithelial neoplasia
According to authors' definition of high risk.

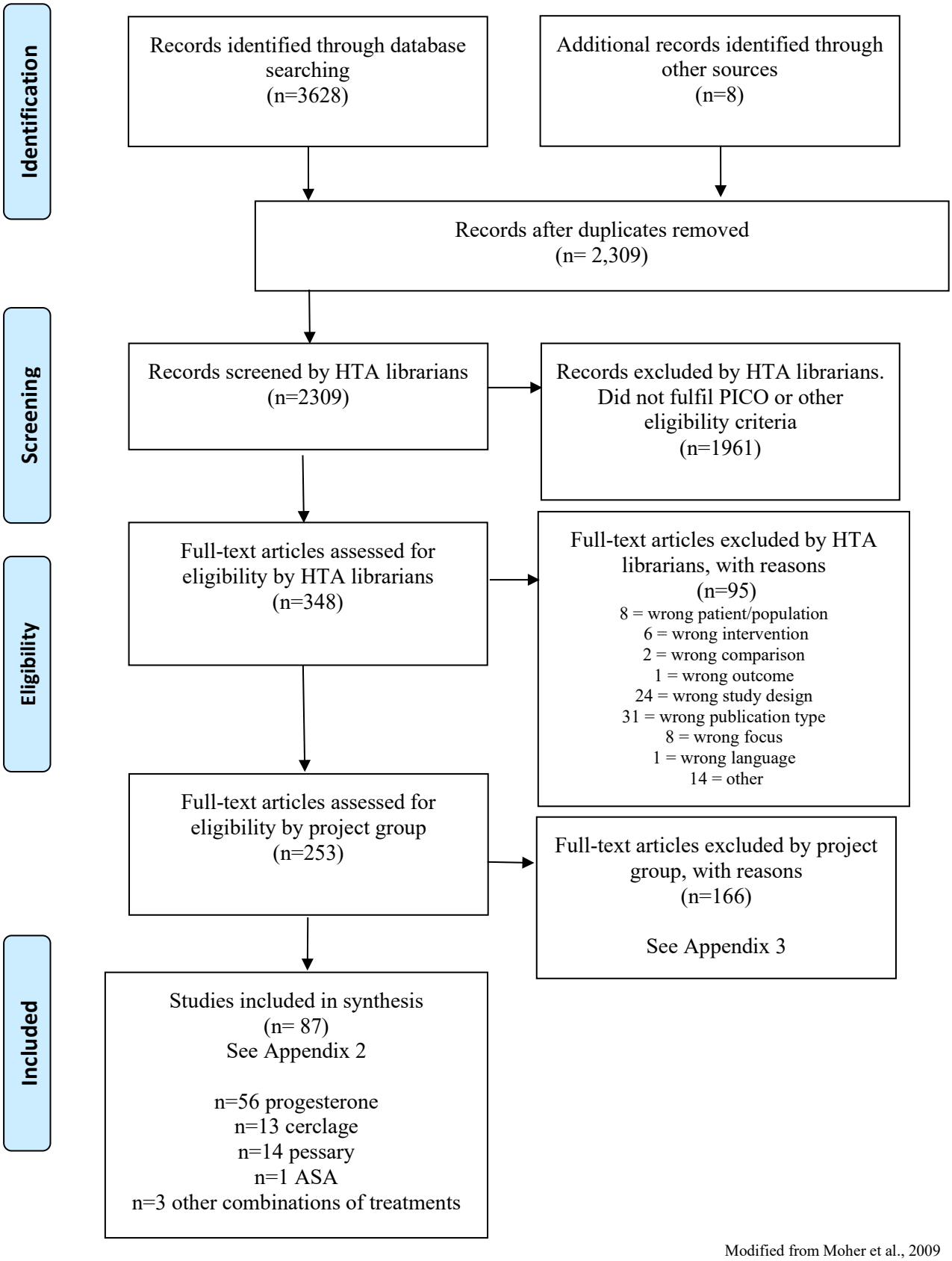
Exploratory subgroup analyses
For the population group with singleton and multifetal pregnancies:
Administration route of progesterone

For the population group with multifetal pregnancies:
Short cervical length
Previous preterm birth

Language: English, Swedish, Norwegian, Danish

Publication date: 1960

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: PubMed
Date: 25 Jan 2021
No. of results: 47
Search updated: 1 Feb 2022, 12 results

Search	Query	Results
#24	**Search: #16 and #19 Filters: Danish, English, Norwegian, Swedish Sort by: First Author**	**47**
#20	Search: #16 and #19 Sort by: First Author	47
#19	Search: #17 or #18 Sort by: First Author	3,641,306
#18	Search: review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev" OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] Sort by: First Author	2,301,833
#17	Search: Randomized controlled trial[pt] OR Randomized controlled trials as topic[mh] OR Controlled Clinical Trial[Mesh] OR Controlled Clinical Trials as Topic[Mesh] OR Random allocation [mh] OR Double-blind method[mh] OR Single-blind method[mh] OR Control Groups[Mesh] OR Random*[tw] OR "Placebos"[Mesh] OR Placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (Mask*[tw] OR blind*[tw] OR dumm*[tw])) Sort by: First Author	1,552,603
#16	Search: #14 and #15 Sort by: First Author	112
#15	Search: pubmednotmedline[sb] Sort by: First Author	3,599,407
#14	Search: #3 and #6 and #13 Sort by: First Author	1,824
#13	Search: #7 or #8 or #9 or #10 or #11 or #12 Sort by: First Author	116,681
#12	Search: Aspirin*[tw] or Acetylsalicylic*[tw] Sort by: First Author	72,574
#11	Search: Shirodkar*[tiab] or McDonald*[tiab] or MacDonald*[tiab] Sort by: First Author	3,072
#10	Search: ((cervi*[tiab]) AND (stitch*[tiab] or sutur*[tiab] or ligat*[tiab])) Sort by: First Author	3,024
#9	Search: Progestin*[tw] or Progestagen*[tw] or Progestogen*[tw] or gestagen*[tw] or 20 alpha dihydroprogesteron*[tw] or algeston*[tw] or allylestrenol*[tw] or desogestrel*[tw] or dydrogesteron*[tw] or flurogestone acetate*[tw] or gestrinon*[tw] or progestative*[tw] or medroxyprogesteron* acetate*[tw] Sort by: First Author	30,237
#8	Search: Progestron*[tw] or hydroxyprogesteron*[tw] or 17-alphahydroxyprogesteron*[tw] or 17-hydroxyprogesteron*[tw] or 17-OHPC[tw] or 17OHPC[tw] or 17Pc[tw] or Progestin*[tw] or Progestagen*[tw] or Progestogen*[tw] Sort by: First Author	33,262
#7	Search: Pessar*[tiab] or Arabin[tiab] Sort by: First Author	1,825
#6	Search: #4 or #5 Sort by: First Author	208,707
#5	Search: Prematur*[tiab] or pre-matur*[tiab] Sort by: First Author	153,177
#4	Search: ((preterm*[tiab] or pre-term*[tiab]) AND (birth*[tiab] or deliver*[tiab] or rupture*[tiab] or interruption*[tiab] or labo?r[tiab] or labo?rs[tiab] or labo?ring[tiab] or infant*[tiab] or baby[tiab] or babies[tiab] or child*[tiab] or neonate*[tiab])) Sort by: First Author	74,945
#3	Search: #1 or #2 Sort by: First Author	2,467,999
#2	Search: ((Asymptomatic*[tiab] or risk*[tiab] or Twin*[tiab] or Triplet*[tiab] or Quadruplet*[tiab] or Quintuplet*[tiab] or multiple*[tiab] or spontaneous*[tiab]) AND (wom?n*[tiab] or patient*[tiab])) Sort by: First Author	1,727,007
#1	Search: Pregnan*[tiab] or Gestation*[tiab] or Trimester*[tiab] or Postpartum*[tiab] or Maternal*[tiab] or singleton*[tiab] Sort by: First Author	807,579

Database: Medline (OVID) 1946 to January 22, 2021
Date: 25 Jan 2021
No. of results: 885
Search updated: 1 Feb 2022, 97 results

#	Searches	Results
1	exp Pregnancy/ or exp Pregnancy Trimesters/ or Pregnant Women/ or Postpartum Period/ or exp Multiple Birth Offspring/	928506
2	(Pregnan* or Gestation* or Trimester* or Postpartum* or Maternal* or singleton*).ab,kf,ti.	808169
3	((Asymptomatic* or risk* or Twin* or Triplet* or Quadruplet* or Quintuplet* or multiple* or spontaneous*) adj6 (wom?n* or patient*)).ab,kf,ti.	651689
4	1 or 2 or 3	1809082
5	exp Obstetric Labor, Premature/	27217
6	exp Infant, Premature/	57056
7	((preterm* or pre-term*) adj6 (birth* or deliver* or rupture* or interruption* or labo?r or labo?rs or labo?ring or infant* or baby or babies or child* or neonate*)).ab,kf,ti.	73975
8	(Prematur* or pre-matur*).ab,kf,ti.	153931
9	5 or 6 or 7 or 8	227593
10	Pessaries/	1495
11	(Pessar* or Arabin).ab,kf,ti.	1837
12	exp Progesterone/	70544
13	(Progestron* or hydroxyprogesteron* or 17-alphahydroxyprogesteron* or 17-hydroxyprogesteron* or 17-OHPC or 17OHPC or 17Pc or Progestin* or Progestagen* or Progestogen*).mp.	33319
14	exp Progestins/ or Desogestrel/	68862
15	(Progestin* or Progestagen* or Progestogen* or gestagen* or 20 alpha dihydroprogesteron* or algeston* or allylestrenol* or desogestrel* or dydrogesteron* or flurogestone acetate* or gestrinon* or progestative* or medroxyprogesteron* acetate*).mp.	34665
16	Cerclage, Cervical/	900
17	(cervi* adj10 (stitch* or sutur* or ligat*)).ab,kf,ti.	1097
18	(Shirodkar* or McDonald* or MacDonald*).ab,kf,ti.	3069
19	exp Aspirin/	45504
20	(Aspirin* or Acetylsalicylic*).mp.	72719
21	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	173991
22	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	614165
23	exp Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or Placebos/ or Control Groups/	864509
24	(random* or sham or placebo*).ti,ab,hw,kf.	1564177
25	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	243463
26	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	1125
27	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.	1032733
28	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	46307
29	allocated.ti,ab,hw.	69497
30	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.	36706
31	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	9160

32	(pragmatic study or pragmatic studies).ti,ab,hw,kf.	441
33	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.	5730
34	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.	8661
35	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.	29647
36	or/22-35	2246945
37	Meta-Analysis.pt.	125413
38	Meta-analysis/ or Systematic review/ or exp Meta-analysis as topic/ or Systematic Reviews as Topic/ or exp Technology assessment, biomedical/	239513
39	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ab,kf,ti.	215751
40	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ab,kf,ti.	11828
41	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ab,kf,ti.	29332
42	(data synthes* or data extraction* or data abstraction*).ab,kf,ti.	29754
43	(handsearch* or hand search*).ab,kf,ti.	9682
44	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ab,kf,ti.	28201
45	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ab,kf,ti.	9959
46	(meta regression* or metaregression*).ab,kf,ti.	10004
47	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	338259
48	(medline or cochrane or pubmed or medlars or embase or cinahl).ab,hw,ti.	244677
49	(cochrane or (health adj2 technology assessment) or evidence report).jw.	20032
50	(comparative adj3 (efficacy or effectiveness)).ab,kf,ti.	14298
51	(outcomes research or relative effectiveness).ab,kf,ti.	9835
52	((indirect or indirect treatment or mixed-treatment) adj comparison*).ab,kf,ti.	2295
53	or/37-52	511050
54	36 or 53	2567627
55	4 and 9 and 21 and 54	1037
56	(animals not (animals and humans)).sh.	4746268
57	55 not 56	963
58	(comment or editorial or letter).pt.	1928598
59	57 not 58	929
60	limit 59 to (danish or english or norwegian or swedish)	885
61	limit 60 to yr="1960 -Current"	885

Database: Embase (OVID) 1974 to 2021 January 21
Date: 25 Jan 2021
No. of results: 1,668
Search updated: 1 Feb 2022, 190 results

#	Searches	Results
1	exp pregnancy/ or exp high risk pregnancy/ or pregnant woman/ or puerperium/ or exp multiple birth offspring/	772481
2	(Pregnan* or Gestation* or Trimester* or Postpartum* or Maternal* or singleton*).ab,kw,ti.	986629
3	((Asymptomatic* or risk* or Twin* or Triplet* or Quadruplet* or Quintuplet* or multiple* or spontaneous*) adj6 (wom?n* or patient*)).ab,kw,ti.	1040625
4	1 or 2 or 3	2180162
5	exp premature labor/	47074
6	exp prematurity/	106098
7	((preterm* or pre-term*) adj6 (birth* or deliver* or rupture* or interruption* or labo?r or labo?rs or labo?ring or infant* or baby or babies or child* or neonate*)).ab,kw,ti.	103937
8	(Prematur* or pre-matur*).ab,kw,ti.	203169
9	5 or 6 or 7 or 8	309477
10	exp vagina pessary/	2843
11	(Pessar* or Arabin).ab,kw,ti.	2761
12	progesterone/ or hydroxyprogesterone/ or hydroxyprogesterone caproate/	95237
13	(Progestron* or hydroxyprogesteron* or 17-alphahydroxyprogesteron* or 17-hydroxyprogesteron* or 17-OHPC or 17OHPC or 17Pc or Progestin* or Progestagen* or Progestogen*).mp.	33096
14	exp gestagen/ or 20-alpha-dihydroprogesterone/ or desogestrel/ or medroxyprogesterone acetate/	167659
15	(Progestin* or Progestagen* or Progestogen* or gestagen* or 20 alpha dihydroprogesteron* or algeston* or allylestrenol* or desogestrel* or dydrogesteron* or flurogestone acetate* or gestrinon* or progestative* or medroxyprogesteron* acetate*).mp.	54458
16	exp cerclage/	2158
17	Cerclage*.ab,kw,ti.	4696
18	(cervi* adj10 (stitch* or sutur* or ligat*)).ab,ti,kw.	1562
19	(Shirodkar* or McDonald* or MacDonald*).ab,ti,kw.	5525
20	exp acetylsalicylic acid/	214928
21	(Aspirin* or Acetylsalicylic*).mp.	227712
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	412362
23	exp randomized controlled trial/ or "randomized controlled trial (topic)"/ or controlled clinical trial/ or "controlled clinical trial (topic)"/ or exp randomization/ or double blind procedure/ or single blind procedure/ or placebo/ or control group/	1423893
24	(random* or sham or placebo*).ti,ab,hw,kw.	2145687
25	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	316802
26	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	1484

27	(control* adj3 (study or studies or trial* or group*)).ti,ab,kw.	1438186
28	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw.	58043
29	allocated.ti,ab,hw.	89619
30	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw.	67366
31	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw.	13374
32	(pragmatic study or pragmatic studies).ti,ab,hw,kw.	648
33	((pragmatic or practical) adj3 trial*).ti,ab,hw,kw.	6017
34	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw.	13674
35	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kw.	96974
36	or/23-35	3193950
37	exp meta analysis/ or "systematic review"/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or biomedical technology assessment/	444709
38	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ab,kw,ti.	267467
39	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ab,kw,ti.	14006
40	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ab,kw,ti.	41581
41	(data synthes* or data extraction* or data abstraction*).ab,kw,ti.	36563
42	(handsearch* or hand search*).ab,kw,ti.	11720
43	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ab,kw,ti.	37006
44	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ab,kw,ti.	16117
45	(meta regression* or metaregression*).ab,kw,ti.	12396
46	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	535571
47	(medline or cochrane or pubmed or medlars or embase or cinahl).ab,hw,ti.	320867
48	(cochrane or (health adj2 technology assessment) or evidence report).jx.	27490
49	(comparative adj3 (efficacy or effectiveness)).ab,kw,ti.	20811
50	(outcomes research or relative effectiveness).ab,kw,ti.	14094
51	((indirect or indirect treatment or mixed-treatment) adj comparison*).ab,kw,ti.	4321
52	or/37-51	741825
53	36 or 52	3642344
54	4 and 9 and 22 and 53	2534
55	limit 54 to (article or article in press or conference paper or "review")	1795
56	limit 55 to (danish or english or norwegian or swedish)	1694
57	(animal not (animal and human)).sh.	1100804
58	**56 not 57**	**1668**

Appendix 1a. PICO, study selection, search strategies, and references for the main study question

Database: The Cochrane Library
Date: 25 Jan 2021
No of results: 664
Cochrane reviews: 31
Cochrane protocols: 1
Trials: 630
Clinical answers: 2

Search updated: 1 Feb 2022, 65 results
Cochrane reviews: 2
Trials: 63

ID	Search	Hits
#1	MeSH descriptor: [Pregnancy] explode all trees	22051
#2	MeSH descriptor: [Pregnancy Trimesters] explode all trees	1735
#3	MeSH descriptor: [Pregnant Women] this term only	274
#4	MeSH descriptor: [Postpartum Period] this term only	1188
#5	MeSH descriptor: [Multiple Birth Offspring] explode all trees	191
#6	(Pregnan* or Gestation* or Trimester* or Postpartum* or Maternal* or singleton*):ti,ab,kw (Word variations have been searched)	84049
#7	((Asymptomatic* or risk* or Twin* or Triplet* or Quadruplet* or Quintuplet* or multiple* or spontaneous*) NEAR/6 (wom?n* or patient*)):ti,ab,kw (Word variations have been searched)	85626
#8	{OR #1-#7}	162396
#9	MeSH descriptor: [Obstetric Labor, Premature] explode all trees	2175
#10	MeSH descriptor: [Infant, Premature] explode all trees	3785
#11	((preterm* or pre-term*) NEAR/6 (birth* or deliver* or rupture* or interruption* or labo?r or labo?rs or labo?ring or infant* or baby or babies or child* or neonate*).):ti,ab,kw (Word variations have been searched)	13242
#12	(Prematur* or pre-matur*):ti,ab,kw (Word variations have been searched)	23704
#13	{OR #9-#12}	27970
#14	MeSH descriptor: [Pessaries] this term only	183
#15	(Pessar* or Arabin):ti,ab,kw (Word variations have been searched)	739
#16	MeSH descriptor: [Progesterone] explode all trees	3162
#17	(Progestron* or hydroxyprogesteron* or "17 alphahydroxyprogesteron*" or "17 hydroxyprogesteron*" or "17 OHPC" or 17OHPC or 17Pc or Progestin* or Progestagen* or Progestogen*):ti,ab,kw (Word variations have been searched)	3456
#18	MeSH descriptor: [Progestins] explode all trees	537
#19	MeSH descriptor: [Desogestrel] this term only	452
#20	(Progestin* or Progestagen* or Progestogen* or gestagen* or "20 alpha dihydroprogesteron*" or algeston* or allylestrenol* or desogestrel* or dydrogesteron* or "flurogestone acetate*" or gestrinon* or progestative* or "medroxyprogesteron* acetate*"):ti,ab,kw (Word variations have been searched)	5465
#21	MeSH descriptor: [Cerclage, Cervical] this term only	56
#22	((cervi*) NEAR/10 (stitch* or sutur* or ligat*)):ti,ab,kw (Word variations have been searched)	125
#23	(Shirodkar* or McDonald* or MacDonald*):ti,ab,kw (Word variations have been searched)	681
#24	MeSH descriptor: [Aspirin] explode all trees	5935
#25	(Aspirin* or Acetylsalicylic*):ti,ab,kw (Word variations have been searched)	16547
#26	{OR #14-#25}	25414
#27	#8 AND #13 AND #26	913
#28	(CINAHL):an (Word variations have been searched)	18849
#29	#27 NOT #28	908
#30	(clinicaltrials or trialsearch):so	352906
#31	#29 NOT #30	664

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
25 Jan 2021
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 8 new records

Reference lists

Included studies:

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Appendix 1b: PICO, study selection, and search strategies

Question(s) at issue:
Will the intervention progesterone during pregnancy, alone or in combination with other interventions, affect the risk of any cancer in the woman?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

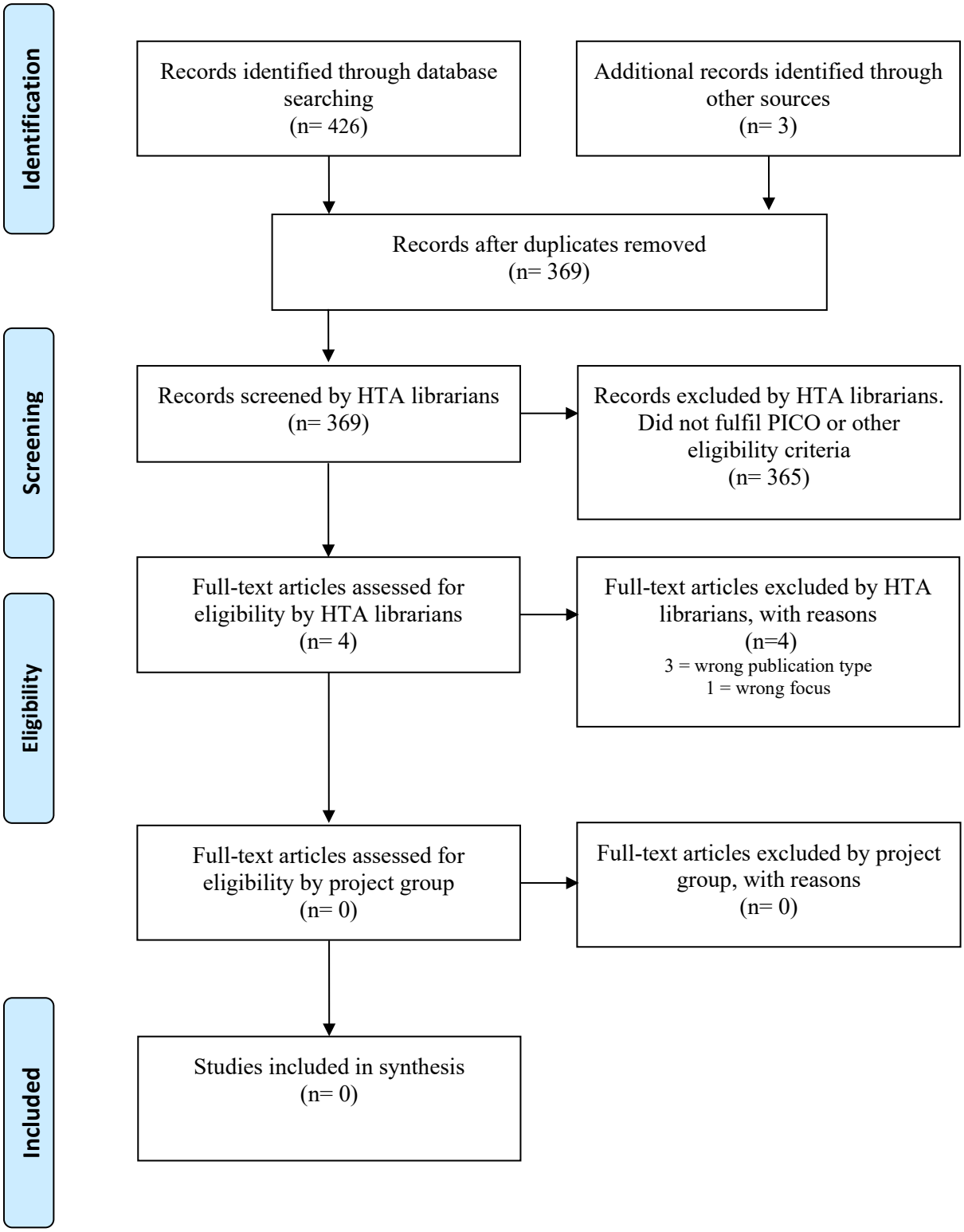
P1	Pregnant women
I	Progesterone, any type, initiated during pregnancy, alone or in combination with other interventions for prevention of preterm birth
C	No intervention, placebo or other interventions for prevention of preterm birth (such as cerclage, pessary, ASA)
O	Any cancer in the woman

Eligibility criteria
Study design:
Randomised controlled trials
Non-randomised controlled studies

Language:
English, Swedish, Norwegian, Danish

Publication date: 1960-

Selection process – flow diagram



Modified from Moher et al., 2009

Appendix 1b.
PICO, study selection, and search strategies for the study question on progesterone and cancer in the woman

Database: PubMed
Date: 30 Nov 2021
No. of results: 7

Search	Query	Results
#13	Search: #11 AND #12 Sort by: First Author	7
#12	Search: (pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb]) Sort by: First Author	4,659,948
#11	Search: #3 AND #6 AND #9 AND #10 Sort by: First Author	35
#10	Search: cancer*[tiab] or tumo?r*[tiab] or malignan*[tiab] or neoplas*[tiab] or carcino*[tiab] or oncolog*[tiab] or oncogen*[tiab] Sort by: First Author	3,100,087
#9	Search: #7 OR #8 Sort by: First Author	37,190
#8	Search: Progestin*[tw] or Progestagen*[tw] or Progestogen*[tw] or gestagen*[tw] or 20 alpha dihydroprogesteron*[tw] or algeston*[tw] or allylestrenol*[tw] or desogestrel*[tw] or dydrogesteron*[tw] or flurogestone acetate*[tw] or gestrinon*[tw] or progestative*[tw] or medroxyprogesteron* acetate*[tw] Sort by: First Author	30,789
#7	Search: Progestron*[tw] or hydroxyprogesteron*[tw] or 17-alphahydroxyprogesteron*[tw] or 17-hydroxyprogesteron*[tw] or 17-OHPC[tw] or 17OHPC[tw] or 17Pc[tw] or Progestin*[tw] or Progestagen*[tw] or Progestogen*[tw] Sort by: First Author	33,833
#6	Search: #4 OR #5 Sort by: First Author	220,117
#5	Search: Prematur*[tiab] or pre-matur*[tiab] Sort by: First Author	160,450
#4	Search: ((preterm*[tiab] or pre-term*[tiab]) AND (birth*[tiab] or deliver*[tiab] or rupture*[tiab] or interruption*[tiab] or labo?r[tiab] or labo?rs[tiab] or labo?ring[tiab] or infant*[tiab] or baby[tiab] or babies[tiab] or child*[tiab] or neonate*[tiab])) Sort by: First Author	80,585
#3	Search: #1 OR #2 Sort by: First Author	2,636,683
#2	Search: ((Asymptomatic*[tiab] or risk*[tiab] or Twin*[tiab] or Triplet*[tiab] or Quadruplet*[tiab] or Quintuplet*[tiab] or multiple*[tiab] or spontaneous*[tiab]) AND (wom?n*[tiab] or patient*[tiab])) Sort by: First Author	1,862,176
#1	Search: Pregnan*[tiab] or Gestation*[tiab] or Trimester*[tiab] or Postpartum*[tiab] or Maternal*[tiab] or singleton*[tiab] Sort by: First Author	845,363

Database: Ovid MEDLINE(R) ALL
Date: 30 Nov 2021
No. of results: 100

#	Searches	Results
1	exp Pregnancy/ or exp Pregnancy Trimesters/ or Pregnant Women/ or Postpartum Period/ or exp Multiple Birth Offspring/	968497
2	(Pregnan* or Gestation* or Trimester* or Postpartum* or Maternal* or singleton*).ab,kf,ti.	842596
3	((Asymptomatic* or risk* or Twin* or Triplet* or Quadruplet* or Quintuplet* or multiple* or spontaneous*) adj6 (wom?n* or patient*)).ab,kf,ti.	694817
4	1 or 2 or 3	1892283
5	exp Obstetric Labor, Premature/	29699
6	exp Infant, Premature/	60390
7	((preterm* or pre-term*) adj6 (birth* or deliver* or rupture* or interruption* or labo?r or labo?rs or labo?ring or infant* or baby or babies or child* or neonate*)).ab,kf,ti.	78930
8	(Prematur* or pre-matur*).ab,kf,ti.	160595
9	5 or 6 or 7 or 8	238395

Appendix 1b.
PICO, study selection, and search strategies for the study question on progesterone and cancer in the woman

10	exp Progesterone/	71649
11	(Progestron* or hydroxyprogesteron* or 17-alphahydroxyprogesteron* or 17-hydroxyprogesteron* or 17-OHPC or 17OHPC or 17Pc or Progestin* or Progestagen* or Progestogen*).mp.	33870
12	exp Progestins/ or Desogestrel/	70056
13	(Progestin* or Progestagen* or Progestogen* or gestagen* or 20 alpha dihydroprogesteron* or algeston* or allylestrenol* or desogestrel* or dydrogesteron* or flurogestone acetate* or gestrinon* or progestative* or medroxyprogesteron* acetate*).mp.	35257
14	10 or 11 or 12 or 13	96144
15	exp Neoplasms/	3579896
16	(cancer* or tumo?r* or malignan* or neoplas* or carcino* or oncolog* or oncogen*).ab,kf,ti.	3766887
17	15 or 16	4746186
18	4 and 9 and 14 and 17	115
19	(animals not (animals and humans)).sh.	4889136
20	18 not 19	108
21	(comment or editorial or letter).pt.	2016291
22	20 not 21	107
23	limit 22 to (yr="1960 -Current" and (danish or english or norwegian or swedish))	100

Database: Embase (OVID) 1974 to 2021 November 29
Date: 30 Nov 2021
No. of results: 301

#	Searches	Results
1	exp pregnancy/ or exp high risk pregnancy/ or pregnant woman/ or puerperium/ or exp multiple birth offspring/	802167
2	(Pregnan* or Gestation* or Trimester* or Postpartum* or Maternal* or singleton*).ab,kf,ti.	1033178
3	((Asymptomatic* or risk* or Twin* or Triplet* or Quadruplet* or Quintuplet* or multiple* or spontaneous*) adj6 (wom?n* or patient*)).ab,kf,ti.	1116274
4	1 or 2 or 3	2301027
5	exp premature labor/	49984
6	exp prematurity/	112093
7	((preterm* or pre-term*) adj6 (birth* or deliver* or rupture* or interruption* or labo?r or labo?rs or labo?ring or infant* or baby or babies or child* or neonate*)).ab,kf,ti.	110735
8	(Prematur* or pre-matur*).ab,kf,ti.	212680
9	5 or 6 or 7 or 8	325869
10	progesterone/ or hydroxyprogesterone/ or hydroxyprogesterone caproate/	97987
11	(Progestron* or hydroxyprogesteron* or 17-alphahydroxyprogesteron* or 17-hydroxyprogesteron* or 17-OHPC or 17OHPC or 17Pc or Progestin* or Progestagen* or Progestogen*).mp.	33836
12	exp gestagen/ or 20-alpha-dihydroprogesterone/ or desogestrel/ or medroxyprogesterone acetate/	172010

Appendix 1b.
PICO, study selection, and search strategies for the study question on progesterone and cancer in the woman

13	(Progestin* or Progestagen* or Progestogen* or gestagen* or 20 alpha dihydroprogesteron* or algeston* or allylestrenol* or desogestrel* or dydrogesteron* or flurogestone acetate* or gestrinon* or progestative* or medroxyprogesteron* acetate*).mp.	55647
14	10 or 11 or 12 or 13	177682
15	exp neoplasm/	4857623
16	(cancer* or tumo?r* or malignan* or neoplas* or carcino* or oncolog* or oncogen*).ab,kf,ti.	4949646
17	cancer risk/	185312
18	15 or 16 or 17	6081329
19	4 and 9 and 14 and 18	435
20	(animal not (animal and human)).sh.	1125235
21	19 not 20	435
22	limit 21 to (article or article in press or conference paper or note or "review")	327
23	**limit 22 to ((danish or english or norwegian or swedish) and yr="1960 -Current")**	**301**

Database: The Cochrane Library
Date: 30 Nov 2021
No of results: 18
Cochrane reviews: 3
Trials: 15

ID	Search	Hits
#1	MeSH descriptor: [Pregnancy] explode all trees	23560
#2	MeSH descriptor: [Pregnancy Trimesters] explode all trees	1813
#3	MeSH descriptor: [Pregnant Women] this term only	395
#4	MeSH descriptor: [Postpartum Period] this term only	1297
#5	MeSH descriptor: [Multiple Birth Offspring] explode all trees	200
#6	(Pregnan* or Gestation* or Trimester* or Postpartum* or Maternal* or singleton*):ti,ab,kw (Word variations have been searched)	90285
#7	((Asymptomatic* or risk* or Twin* or Triplet* or Quadruplet* or Quintuplet* or multiple* or spontaneous*) NEAR/6 (wom?n* or patient*)):ti,ab,kw (Word variations have been searched)	92752
#8	{OR #1-#7}	175112
#9	MeSH descriptor: [Obstetric Labor, Premature] explode all trees	2323
#10	MeSH descriptor: [Infant, Premature] explode all trees	4047
#11	((preterm* or pre-term*) NEAR/6 (birth* or deliver* or rupture* or interruption* or labo?r or labo?rs or labo?ring or infant* or baby or babies or child* or neonate*).):ti,ab,kw (Word variations have been searched)	14130
#12	(Prematur* or pre-matur*):ti,ab,kw (Word variations have been searched)	25286
#13	{OR #9-#12}	29768
#14	MeSH descriptor: [Progesterone] explode all trees	3269
#15	(Progestron* or hydroxyprogesteron* or "17 alphahydroxyprogesteron*" or "17 hydroxyprogesteron*" or "17 OHPC" or 17OHPC or 17Pc or Progestin* or Progestagen* or Progestogen*):ti,ab,kw (Word variations have been searched)	3639
#16	MeSH descriptor: [Progestins] explode all trees	570
#17	MeSH descriptor: [Desogestrel] this term only	477

Appendix 1b.
PICO, study selection, and search strategies for the study question on progesterone and cancer in the woman

#18	(Progestin* or Progestagen* or Progestogen* or gestagen* or "20 alpha dihydroprogesteron*" or algeston* or allylestrenol* or desogestrel* or dydrogesteron* or "flurogestone acetate*" or gestrinon* or progestative* or "medroxyprogesteron* acetate*"):ti,ab,kw (Word variations have been searched)	5720
#19	{OR #14-#18}	7760
#20	MeSH descriptor: [Neoplasms] explode all trees	84994
#21	(cancer* or tumo?r* or malignan* or neoplas* or carcino* or oncolog* or oncogen*):ti,ab,kw (Word variations have been searched)	239209
#22	#20 or #21	248390
#23	#8 AND #13 AND #19 AND #22	26
#24	(CINAHL):an (Word variations have been searched)	20362
#25	#23 NOT #24	26
#26	(clinicaltrials or trialsearch):so	382098
#27	**#25 NOT #26**	**18**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
30 Nov 2021
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 0 new records

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Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Progesterone												
Aboulghar 2012 Egypt (single centre)	ISRCTN 69810120 Funding NR	August 2008 to March 2010	Singletons 215/306 (70.3%) Twins (DC) 91/306 (29.7%)	ART	NR	GA between 18-24 w	I: 400 mg vag prog/d (Prontogest) C: Placebo Randomised 1:1 Until 36+6	None	410 invited, 313 women randomised I: 161 C: 152	I: 30.2 (4.6) C: 31.4 (4)	I: 161 (112 singletons, 49 sets of twins) C: 145 (103 singletons, 42 set of twins)	PTB <37 w (PO) PTB <34 w (PO) LBW, VLBW PNM, NNM NICU admission
Aflatoonian 2013 Iran (single centre)	IRCT 20121016 1132 Funding NR	October 2010 to October 2011	Singleton	ART	NR	GA between 16 w	I: 250 mg 17-OHPC im/w (Femolife) C: Placebo Randomised 1:1 Until 36+6	None	106 invited, 99 women randomised I: 52 C: 47	I: 30.3 (4.5) C: 29.1 (4.9)	I: 52 C: 47	PTB, sPTB <37 w PTB <34 w LBW PNM NICU admission Maternal morbidity
Ali 2020 Egypt (single centre)	NCT 02846909 Funding NR	April 2017 to March 2019	Singleton	Indication for cerclage: previous second trimester loss, sPTD (<34 w) or short cervix (<25 mm)	I: 23.8 (5.3) C: 23.9 (5.6)	GA between 12-14 w	I: 400 mg prog vag (pessary)/d (Prontogest) C: Placebo Randomised 1:1 Until 36+6	Cerclage	250 invited, 242 women randomised I: 121 C: 121	I: 28.5 (4.7) C: 29.1 (4.4)	I: 121 C: 121 Lost to follow up I: 6 C: 9	PTB <37 w PTB <34 w GA at delivery PNM NICU admission
Ashoush 2017 Egypt (single centre)	NCT 2571296 Funding NR	June 2015 to December 2016	Singleton	Previous sPTB <37 weeks	I: 25.7 (8.3 C: 23.9 (9.7)	GA between 14-18 w	I: 100 mg prog oral/d (Utrocare) C: Placebo Randomised 1:1 Until 36+6	TVS CL-screening and cerclage for short cervix	326 invited, 212 women randomised I: 106 C: 106	I: 29.2 (4.5) C: 29.5 (3.5)	I: 96 C: 91	PTB <37 w GA at delivery LBW PNM, NNM Neonatal and maternal morbidity NICU admission

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Awwad 2015 Libanon (single centre)	PROGES-TWIN NCT 00141908 Funding NR	September 2006 to December 2011	Twins	ART 75% MC 17%	NR	GA between 16-20 w	I: 250mg 17-OHPC im/w (Proloton Depot) C: Placebo (castor oil) Until 36+6	None	344 invited, 293 women randomised 2:1 I: 197 C: 96	I: 30.5 (5.6) C: 30.7 (5.0)	I: 194 C: 94	PTB <37 w (PO) PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal and maternal morbidity NICU admission
Azargoon 2016 Iran (single centre)	IRCT 20101227 3386N2. Funding NR	November 2010 to April 2012	Singleton	Previous PTB <37 w, uterine anomaly,	NR	GA between 16-22 w	I: 400 mg prog vag supp/d (Aboryhan) C: Placebo Randomised 1:1 Until 36+6	Cerclage if uterine anomaly, previous PTB or TVS CL < 28mm	106 invited, 103 women randomised I: 51 C: 52	I: 25.4 (4.8) C: 24.6 (4.9)	I: 50 C: 50	PTB <37 w (PO) PTB <34 w GA at delivery LBW, VLBW NNM Neonatal morbidity NICU admission
Blackwell 2020 USA (9 countries, 93 centres. USA (41), outside USA (52))	PRO-LONG NCT 01004029 Funding reported	November 2009 to October 2018	Singleton	Previous singleton sPTB	NR (TVS was not prescribed in study protocol) but TVS CL <25 mm before intervention started: I: 10/833 (1.2%) C: 8/420 (1.9%)	GA between 16+0-20+6 w based on ultrasound at 14+0-20+3 w	I: 17-OHPC 250 mg im/w (Makena), C: Placebo Between 16+0-36+6 Randomised 2:1	None	1877 assessed, 1740 eligible, 1708 I: 1130 C: 578	I: 30+0 (5.2) C: 29+9 (5.2)	Women I: 1130 C: 578 Children I: 1093 C: 559	PTB, sPTB <37 w PTB <35 w (PO) sPTB <35 w PTB, sPTB <32 w PNM, NNM Neonatal and maternal morbidity NICU admission Infant follow up at 23-25 months, ongoing.

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Briery 2009 USA (single centre)	NCT 00811057 Funding NR	NR	Twins	1/3 previous PTB	NR	GA between 20-30 w	I: 250 mg 17-OHPC im/w C: Placebo Until 34+6	None	I: 16 C: 14	I: 23.3 (5.8) C: 25.4 (5.0)	I: 16 C: 14	PTB <37w PTB <35w (PO) PTB <34w GA at delivery NNM Neonatal and maternal morbidity NICU admission
Brizot 2015 Brazil (single centre)	NCT 01031017 Funding NR	June 2007 to October 2013	Twins (DA)	MC I: 25% C: 19%	I: 37.8 (9.7) C: 38.2 (8.0)	GA between 18-21 w	I: 200 mg natural prog vag/d C: Placebo Randomised 1:1 Until 34+6	None	390 women randomised I: 195 C: 195	I: 28.1 (6.0) C: 28.4 (6.2)	I: 189 C: 191	PTB <37 w PTB, sPTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal and maternal morbidity NICU admission
Caritis 2009 USA (14 centres)	STTARS NCT 00099164 Funding reported	April 2004 to September 2006	Triplets	DC 30% ART 70%	NR	GA between 16-20 w	I: 250 mg 17-OHPC im/w C: Placebo Randomised 1:1 Until 35w	None	241 invited, 134 women randomised I: 71 C: 63	I: 30 (20-35) C: 32 (28-35) median (IQR)	Women I: 71 C: 63 Children I: 212 C: 183	PTB or fetal loss <35 w (PO) PTB or fetal loss <32 w PTB or fetal loss <28 w sPTB <35 w GA at delivery LBW, VLBW PNM, NNM Neonatal and maternal morbidity
Cetingoz 2011 Turkey (single centre)	Registra-tion and funding NR	December 2004 to February 2007	Singleton I: 51.3% C: 60% Twins I: 48.7% C: 40.0%	Twin pregnancy, ≥1 previous sPTB, uterine anomaly	I: 34.6 (6.8) C: 34.3 (6.1)	GA 24 w	I: 100 mg prog vag/d C: Placebo Randomised 1:1 Until 36+6	None	170 invited, 160 women randomised I: 84 C: 76	NR	I: 80 C: 70	PTB <37 w (PO?) PTB <34 w GA at delivery NNM NICU admission Maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Combs 2010 USA (14 centres)	NCT 00163020 Funding reported	November 2004 to August 2008	Triplets (TCTA)	TCTA ART I: 90% C: 84%	NR	GA between 18-22 w	I: 250mg 17-OHPC im/w C: Placebo Randomised 2:1 Until 34+0	None	248 assessed 81 women randomised I: 56 C: 25	I: 33.4 (5.0) C: 33.6 (5.4)	I: 56 C: 25	PTB <35 w PTB <32 w PTB <28 w GA at delivery PNM, NNM Composite adverse neonatal outcome (PO) Maternal morbidity NICU admission
Combs 2011 USA (14 centres)	NCT 00163020 Funding reported	November 2004 to August 2009	Twins (DCDA)	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	NR	GA between 16-24 w	I: 250mg 17-OHPC (in 1 mL castor oil) im/w C: Placebo (1 mL castor oil) Until 34+0	None	1450 assessed 240 women randomised 2:1 I: 160 C: 80	I: 34.0 (5.8) C: 34.5 (6.6)	I: 160 C: 78	PTB <37 w PTB, sPTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Composite adverse neonatal outcome (PO) Maternal morbidity
Crowther 2017 Australia (39 centres, Australia (33), New Zealand (4), Canada (2))	PRO-GRESS ISRCTN 20269066 Funding reported	February 2006 to September 2012	Singleton (98.5%) Twins (1.5%)	Previous sPTB	NR	GA between 20+0- 23+6 w I: 20.6 w (19.3-22.1) C: 20.4 w (19.3-22.0) median (IQR)	I: 100 mg prog vag/d (Cyclogest) C: Placebo Until 34 w, max 98 days	None	1919 eligible, 787 randomised I: 398: 390 singletons, 8 twin pregnancies C: 389: 385 singletons, 4 twin pregnancies	I: 30.0 (5.5) C: 30.3 (5.6)	Women I: 398 C: 393 Children I: 406 C: 393	PTB <37 w PNM, NNM Neonatal morbidity (PO) Maternal morbidity NICU admission

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Cuijpers 2021 The Netherlands Long term follow-up of Van Os 2015 (TRIPLE P study)	Registra-tion NR Funding reported	November 2009 to August 2012	Singleton	Short TVS CL ≤30 mm at 18-22 w	NR	NR	I: 200 mg micronized prog vag/d C: Placebo	None	Randomised I: 41 C: 39	I: 31 (26–34) C: 31 (29–34) median (IQR)	Follow up at 2 years I: 29 C: 30	Long-term child outcome: Bayley III cognitive and motor score ASQ CBCL, Death or abnormal development
Da Fonseca 2003 Brazil (single centre)	Registra-tion and funding NR	February 1996 to March 2001	Singleton	Previous sPTB, prophylactic cerclage, uterine anomaly	NR	I: 26.5 w C: 25.2 w	I: 100 mg vag prog/d C: Placebo 24-34 w	Antibiotics if positive cervico-vaginal culture. Home monitoring of contractions	157 randomised I: 81 C: 76	I: 26.8 C: 27.6	I: 72 C: 70	PTB <37 w PTB <34 w GA at delivery
Fonseca 2007 UK (multicentre UK (5), Chile, Brazil, Greece)	NCT 00422526 Funding reported	September 2003 to May 2006	Singleton (90%) and twins (DA) (10%)	TVS CL ≤15 mm	I: 11.0 (9-14) C: 12.0 (9-14) median (IQR)	Screening at GA 20-25 w (median 22 w) Randomised at I: 165 days (159-168) C: 164 days (160-169) median (IQR)	I: 200 mg vag prog/d (Utrogestan) C: Placebo Between 24+0 to 33+6 w	None	24 620 assessed 413 TVS CL ≤15 mm, 250 randomised I: 125 (11 twins, 8 DC, 3 MC) C: 125 (13 twins, 9 DC, 4 MC)	I: 29 (24-34) C: 29 (24-34) median (IQR)	Women I: 125 C: 125 Children I: 136 C:138	PTB <34 w sPTB <34 w (PO) LBW, VLBW PNM, NNM Neonatal morbidity NICU admission
Glover 2011 USA (single centre)	NCT 01180296 Funding reported	November 2006 to January 2009	Singleton	Previous singleton sPTB	NR	GA <20 w	I: 400 mg oral micronised progesterone/ d C: Placebo	Cerclage if TVS CL <5 mm (none)	I: 20 C: 16	I: 29.3 (4.7) C: 27.2 (4.9)	I: 19 C: 14	sPTB <37 w (PO) GA at delivery NICU admission

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Grobman 2012 USA (14 centres)	NCT 00439374 Funding reported	April 2007 to May 2011	Singleton	Nulliparous TVS CL <30mm	I: 23.9 (5.6) C: 23.8 (5.7)	GA between 16+0-22+3 w I: 21.4 w (1.2) C: 21.3 w (1.3)	I: 250 mg 17-OHPC im/w C: placebo im weekly (castor oil) Until 36+6 w	None	15 435 assessed 657 randomised I: 327 C: 330	I: 22.8 (5.3) C: 21.6 (4.4)	I: 327 C: 330	PTB <37 w (PO) sPTB <37 w PTB <35 w PTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal morbidity NICU admission
Gyamfi 2009 Secondary analysis of Meis 2003 (singleton) and Rouse 2007 (twins), USA	Meis 2003: Registra-tion NR Rouse 2007: SSTARS NCT 00099164 Funding reported	Meis 2003: April 1998 to February 2002 Rouse 2007: April 2004 to February 2006	Singleton Meis 2003) and twins (Rouse, 2007)	Singleton: Women with previous sPTB Twins with or without additional risk factors	NA	GA between 16+0-20+6 w	I: 250 mg 17-OHPC im/w C: placebo im weekly (castor oil) Until 36+6 w (singletons) or 34+6 w (twins)	None	Singleton (Meis 2003): I: 310 C: 153 Twins (Rouse 2009): I: 325 C: 330	Singleton I: 25.9 (5.6) C: 26.4 (5.4) Twins: I: 29.7 (7.0) C: 29.6 (6.8)	Singleton I: 293 C: 148 Twins: I: 323 C: 330	GDM
Hassan 2011 USA (10 countries, 44 centres)	PREG-NANT NCT 00615550 Funding reported	March 2008 to November 2010	Singleton	TVS CL 10-20 mm (all), Previous PTB 16% (16%) between 20-35 w	I: 17 (2.5) C: 17 (2.8)	GA between 20+0-23+6 w	I: 90 mg vag prog gel/d (Prochive 8%/ Crinone 8%) C: Placebo Until 36+6 w	None	32091 assessed 733 eligible with TVS CL 10-20 mm, 465 randomised I: 236 C: 229	I: 26.5 (5.8) C: 26.2 (5.1)	I: 235 C: 223	PTB <37 w PTB <35 w PTB <33 w (PO) PTB <28 w LBW, VLBW PNM, NNM Neonatal morbidity
Hauth 1983 Texas, USA (single centre)	Registra-tion and funding NR	July 1977 to March 1981	Singleton	Women in active duty – military population	NR	GA between 16-20 w	I: 17-OHPC C: Placebo (castor oil)	None	Women I: 80 C:88 Children I: 80 C: 88	NR	Women I: 80 C:88 Children I: 80 C: 88	PTB <37 w LBW PNM NNM Maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Hayashi 2021 Japan (12 centres)	TROPI-CAL UMIN000 013518 Funding NR	April 2014 to March 2018	Singleton	TVS CL 25 - < 30 mm Previous PTB I: 11.9% C: 16.7%	I: 27.8 (25-29.9) C: 28 (25-29.8) median (range)	GA between I: 22 w (17.1-24.1) C: 21.9 w (16.4 -23.9) median(range)	I: 200 mg vag prog/d C: Placebo Between 16 and 34 w	If TVS CL < 20 mm before 34 w, treatment was stopped, "other treatment" was provided	132 enrolled and randomised I: 65 C: 67	I: 33 (21-43) C: 34 (22-41) median (range)	I: 59 C: 60	PTB <37 w PTB <34 w PTB <28 w GA at delivery NNM
Ibrahim 2010 Egypt (single centre)	Registra-tion and funding NR	August 2006 to November 2008	Singleton	Previous PTB	NR	NR	I: 250 mg 17-OHPC im/w C: Placebo (saline)	NR	I: 25 C: 25	I: 25.3 (4.2) C: 25.6 (3.9)	I: 25 C: 25	PTB <37 w GA at delivery LBW NNM NICU admission
Jabeen, 2012 Pakistan (single centre)	Registra-tion and funding NR	January 2011 to December 2011	Singleton	Previous sPTB	NR	GA between 16-20 w	I: 250 mg 17-OHPC im/w C: Placebo (inert oil)	NR	60 women I: 30 C: 30	I: 29 C: 28	I: 30 C: 30	PTB <37 w (PO) PTB <35 w PTB <32 w LBW PNM NICU admission
Jafarpour 2020 Iran (single centre)	IRCT 20190309 042978N2 Funding NR	March 2015 to March 2015	Singleton	Previous PTB.	NR	NR	I: 250 mg 17 OHPC im/w C: Routine prenatal care Between 16-37 w	NR	100 enrolled I: 50 C: 50	I: 24.2 (2.6) C: 25 (2.38)	I: 50 C: 50	PTB < 37 w GA at delivery LBW

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Johnson 1975 USA (single centre)	Registra-tion and funding NR	NR	Singleton and twins Twin n=1	Two spontaneous abortions immediately before this pregnancy or, one PTB and one spontaneous abortion immediately before this pregnancy or, two PTB at any point.	NR	GA determined by last menstruation < 24 w	I: 250 mg 17-OHCP im/w C: Placebo injection once a week	Cerclage if suspicion of cervical incompeten ce, also, 100 mg prog injected every six hours for 24-36 hours after procedure I: 4 C: 3 If PTL; iv isoxsuprine	50 randomised 43/50 analysed, 37 included in final analysis I: 18 C: 25	NR	Per protocol analysis (43/50) I: 21 C: 22	LBW PNM
Klein 2011 Denmark and Austria Secondary analysis of Rode 2011 (PREDICT study)	EudraCT 2006-000503-41 and NCT 00329914 Funding reported	June 2006 to October 2008	Twins	TVS CL ≤30 mm (≤10th percentile) Previous sPTB <34 w or late miscarriage >12 w	NR	GA between 21.9 w (20.6-22.9) median (IQR)	I: 200 mg prog vag (pessary)/d (Utrogestan), micronized progesterone C: Placebo	NR	TVS CL ≤30 mm I: 17 C: 30 Previous sPTB or late miscarriage: I: 10 C: 18	TVS CL ≤30 mm: I: 30.8 (4.7) C: 31.8(4.3) Previous PTB or late miscarriage: I: 33.6 (4.1) C: 33.3(5.2)	TVS CL ≤30 mm I: 17 C: 30 Previous sPTB or late mis-carriage: I: 10 C: 18	PTB<34 w (PO)
Lim 2011 the Netherlands (55 centres)	ISRCTN 40512715 Funding reported	August 2006 to July 2009	Multifetal pregnancy (all chorio-nicity, twins, triplets, quads)	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	TVS CL measured in 542 women (81%): 2.4% had CL <25mm (I: n=9 C: n=4) and, 11.3% had CL<35mm (I: n=37 C: n=24)	GA between I: 16.7±1.5 w C: 16.8±1.6 w	I: 250 mg 17-OHPC im/w C: Placebo	None	I: 336 C: 335	I: 32.7 (4.4) C: 32.8 (4.7)	Women I: 336 C: 332 Children I: 681 C: 674	PTB < 37w PTB < 32w PTB < 28w GA at delivery LBW, VLBW NNM Composite adverse neonatal outcome (PO) NICU admission Maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Majhi 2009 India (single centre)	Registra-tion and funding NR	December 2004 to February 2006	Singleton	Previous sPTB	NR	GA between I: 20.8±2.1 w C: 20.5±2.4 w	I: 100mg vag prog /d (Utrogestan), C: No placebo	If infection was diagnosed, antibiotics was given.	I: 50 C: 50	I: 26.56 (3.5) C: 26.42 (3.2)	I: 50 C: 50	PTB <37 w (PO) PTB < 34 w (PO) Neonatal morbidity NICU admission
McNamara 2015 UK Long term follow-up of Norman 2009 (STOPPIT study)	ISRCTN 35782581 Funding reported	After STOPPIT 2008, linkage March 2013, questionn aires mailed 2011 and 2012	Twins	MC twins I: 46/247 C: 45/247 No MA twins	NR	GA 24+0	I: 90 mg vag prog/d C: Placebo	NR	I: 247/494 C: 247494	NR	Children I: 386 C: 395	Long-term child outcome: Effect of in utero progesterone exposure assessed with Health Utilities Index CDI score
Megli, 2020 USA Secondary analysis with IPD MA of Rouse 2007 (MFMU SSTARS trial) and Combs 2011 (Obstetrix trial)	Registra-tion NR Funding reported from AMAG Pharma-ceutical	Rouse (2007) April 2004 to February 2006 Combs (2011) November 2004 to August 2009	2 RCTs with twins	Twin pregnancy (DCDA) with history of PTB	I: 35.5 (1.8) C: 36.8 (1.6)	GA between I: 19.3 w (0.4) C: 18.6 w (0.3)	I: 250 mg/w im 17-OHPC C: Placebo	NR	Women I: 34 C: 32 Children I: 68 C: 64	I: 31.1 (1.1) C: 33.2 (1.0)	Women I: 34 C: 32 Children I: 68 C: 64	PTB < 34
Meis 2003 USA (19 centres)	Registra-tion NR Funding reported	April 1998 to February 2002	Singleton	Previous sPTB	NR	GA between 15-20+6 w I: 18.4 w (1.4) C: 18.4 w (1.4) (SD)	I: 250 mg 17-OHPC im/w C: Placebo (castor oil) Until 36 w	None	2980 assessed 1039 eligible 463 Randomised 2:1 I: 310 C: 153	I: 26.0 (5.6) C: 26.5 (5.4)	I: 306 C: 153	PTB <37 w (PO) sPTB <37 w PTB <35 w PTB <32 w LBW, VLBW PNM, NNM Neonatal and maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Norman 2009 UK (9 hospitals)	STOPPIT ISRCTN 35782581 Funding reported	December 2004 to April 2008	Twins	Twins (MC) I: 46/247 C: 45/247 No MA twins	NR	GA 24+0 w	I: 90 mg vag prog/d (Crinone) C: Placebo	NR	1483 assessed 500 randomised I: 247 C: 247	I: 33 (5) C: 33 (6)	Women I: 247 C: 247 Children I: 494 C: 494	PTB or IUFD <34 w (one or both twins) (PO) GA at delivery PNM, NNM NICU admission Maternal morbidity
Norman 2016 UK (66 hospitals, UK (65), Sweden (1))	OPPTI-MUM ISRCTN 14568373 Funding reported	February 2009 to April 2013	Singleton	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I:28.2 (10.6) C:28.8 (11.1)	GA between 22-24 w	I: 200 mg vag prog/d C: Placebo Until 34 w	None	15132 assessed 1228 randomised I: 618 C: 610	I: 31.5 (5.6) C: 31.4 (5.8)	Mater-nal I: 600 C: 597 Neona-tal I: 589 C: 587 Child-hood I: 430 C: 439	IUFD or PTB <34 w (PO) PNM, NNM Neonatal morbidity (PO) NICU admission Long-term child outcome: Bayley III cognitive score (PO) Maternal morbidity
Northen 2007 USA Follow-up of Meis 2003	Funding reported from NICHD.	November 2004 to November 2005	Singleton	Previous PTB	NR	NR	I: 250 mg 17-OHPC im/w C: Placebo	None	463 women in original study, I: 310 C: 153 348 children were potentially eligible for follow-up I: 194 C: 84	I: 26.4 (5.8) C: 26.1 (5.5)	Children I: 194 C: 84	Long-term child outcomes: ASQ score Preschool Activities Inventory

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
O'Brien 2007 USA (5 countries, 53 centres)	Registra- tion NR Funding reported	April 2004 to January 2007	Singleton	Previous sPTB, I: 23.6% C: 25.5%	I: 37 (7) C: 37 (7)	GA between 18+0-22+6 w I: 19.9 w (2.1) C 20.1 w (3.3) mean (SD)	I: 90 mg vag prog/d (Crinone 8%) C: Placebo Until 37 v	None	711 consented 669 enrolled 659 randomised I: 332 C: 327	I: 27.1 (5.8) C: 27.3 (5.6)	I: 309 C: 302	PTB < 37 w PTB ≤35 w PTB ≤32 w (PO) PTB ≤28 w GA at delivery PNM, NNM Neonatal and maternal morbidity NICU admission
Price 2021 USA (2 centres in Zambia)	IPOP NCT 03297216 Funding; Bill and Melinda Gates Founda- tion and US NIH	February 2018 to January 2020	Singleton	HIV positive receiving or intending to start anti- retroviral therapy Previous sPTB excluded.	I: 41 (35-46) C: 40 (36-46) median IQR)	GA between I: 19.3 w (16.9-21.6) C: 18.7 w (16.7-21.3) median (IQR)	I: 250 mg 17-OHPC im/w C: Placebo Until 37 w	NR	1042 assessed 800 enrolled and randomised I: 399 C: 401	I: 29 (25-33) C: 30 (25-34) median (IQR)	I: 399 C: 401	PTB, sPTB <37 w PTB <34 w PTB <28 w LBW, VLBW PNM, NNM, NICU admission Maternal mortality morbidity
Rai 2009 India (single centre)	Registra- tion and funding NR	January 2005 to December 2006	Singleton	Previous sPTB	NR	GA between I: 20.69 w (2.83) C: 20.73 w (1.78) mean (SD)	I: 200 micronized oral prog/d C: Placebo	Tocolysis given I: 20.3% C: 27%	I: 75 C: 75	I: 26.07 (3.24) C: 25.72 (3.42)	I: 74 C: 74	Delivery ≥37 w (PO) PTB 34-<37 w PTB 32-<34 w PTB 29-<32 w PTB <28 w GA at delivery NNM NICU admission

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Rehal 2021 (6 countries, 22 hospitals)	EudraCT 2015-005180-16 and ISRCTN 66445401 Funding reported.	May 2017 to April 2019	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 34.4 (31.0-38.0) C: 34.0 (30.0-37.6) median (IQR)	GA between I: 13.2 w (12.7-13.6) I C: 12.2 w (12.7-13.7) median (IQR)	I: 600mg vag prog/d C: Placebo 11-14 w until 34 w	NR	I: 582 C: 587	I: 34.1 (30.3-37.7) C: 34.0 (30.0-37.6) median (IQR)	Women I: 582 C: 587 Children I: 1125 C: 1113	sPTB 24 w-<34 w (PO) sPTB between 24 and <28 w, <37 w PTB between 24 and <28 w, <32, <34, <37 w PTB between randomization and <28, <32, <34, <37w VLBW PNM Maternal morbidity
Rode 2011 Denmark and Austria (17 centres, Denmark (13) Austria (4))	PREDICT EudraCT 2006-000503-41 and NCT 00329914 Funding reported.	June 2006 to October 2008	Twins	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	NR	GA between I: 146.0 days (139–157) C: 146.5 days (139–158) median (IQR)	I: 200 mg prog vag/d (pessary) (Utrogesta) C: Placebo pessary	NR	I: 334 C: 343	I: 32.0 (4.5) C: 31.9 (4.4)	I: 334 C: 341	PTB <37 w PTB <34 w (PO) sPTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal and maternal morbidity NICU admission Long-term child outcome: ASQ

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Rouse 2007 USA (14 centres)	SSTARS NCT 00099164 Funding reported.	April 2004 to February 2006	Twins (DCDA 82%, MCDA 18%)	Twins (MC) I: 18% C: 17.1%	NR	GA between 16+0-20+6 w Randomised at I: 19.2 w (1.5) C: 19.2 w (1.4) mean (SD)	I: 250 mg 17-OHPC im/w C: Placebo Until 34 w	Cerclage I: 1.9% C: 1.2%	1526 eligible 699 consented 661 random. I: 327 C: 334	I: 29.7 (7.0) C: 29.6 (6.8)	I: 325 C: 330	PTB or IUFD <37 w PTB or IUFD <35 w (PO) PTB or IUFD <32 w PTB or IUFD <28 w sPTB or IUFD <35 w GA at delivery LBW, VLBW PNM Maternal morbidity
Saghafi 2011 Iran (single centre)	Registration and funding NR	2007 to 2008	NR handled as singleton	Previous PTB	NR	Randomised at GA 16 w	I: 250 mg 17-OHPC im/w Between 16-37 w C: No placebo	NR	I: 50 C: 50	I: 29.98 (5.36) C: 29.32 (5.69)	I: 50 C: 50	PTB <37 w PTB <34 w GA at delivery
Serra 2013 Spain (5 university clinics)	EudraCT 2004-004136-31, NCT 00480402 and EF489-2004/1 Funding reported	December 2005 to January 2008	Twins (DCDA)	ART I1: 92/96 (95.8%) I2: 94/97 (96.9%) C:96/97 (99.0%)	I 1: 42.1 (7.7) I:2: 42.4 (7.9) C: 43.5 (7.6) TVS CL <25 mm I1: 2.1% I2: 2.1% C: 1.0%	Randomised at GA 20 w	I 1: vag I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d C: Placebo Treatment from 20 to 34 weeks	None	I1: 98 I2: 98 C: 98	I1: 33.5 (4.6) I2: 33.5 (4.0) C: 33.3 (5.2)	Women I1:96 I2: 97 C: 96 Children I1: 194 I2:191 C:190	PTB <37 w (PO?) sPTB <37 w PTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal and maternal morbidity NICU admission
Shadab 2018 Pakistan (single centre)	Registration and funding NR	NR	Singleton	Previous sPTB	NR	GA between 16-20 w	I: 250 mg 17-OHPC im/w C: Placebo (Vitamin B) Until 37 w	None	I: 66 C: 66	I: 26.75 (3.76) C: 29.99 (1.43)	I: 66 C: 66	PTB <37 w GA at delivery

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Shahgheibi 2016 Iran (single centre)	IRCT 20141010 19222N2 Funding reported	2013 to 2014	Singleton	Previous sPTB or uterine anomaly	NR	GA between 24-34 w	I: 250 mg 17-OHPC im/w C: Placebo	None	I: 50 C: 50	I: 25.4 (2.58) C: 27.4 (2.21)	I: 50 C: 50	PTB <37 w
Van Os 2015 the Netherlands (7 university hospitals, 23 general hospitals)	TRIPLE P Registra-tion NR Funding reported	November 2009 to August 2012	Singleton	TVS CL <30 mm, no previous PTB	I: 26 (23-29) C: 27 (25-28) median (IQR)	GA between I: 21.7 w (20.7-22.6) C: 21.6 w (20.9-22.7) median (IQR)	I: 200 mg micronized prog/d C: Placebo	Standard care	I: 41 C: 39	I: 31 (5) C: 30 (5)	I: 41 C: 39	PTB, sPTB <37 w PTB, sPTB <34 w PTB, sPTB <32 w LBW, VLBW PNM, NNM Neonatal and maternal morbidity NICU admission
Vedel 2016 Denmark Follow-up of Rode 2011 (PREDICT study)	EudraCT 2006-000503-41 and NCT 00329914 Funding reported	June 2006 to October 2008. questionn aire February 2012 to July 2013. Register data April 2014 to November 2014.	Twins (DA)	ART I: 50.0% C: 47.2%	NR	GA between I: 144 days (138-158) C: 145 days (137-158) median (IQR)	I: 200 mg micronised vag prog (pessary) C: Placebo	None	I: 114 C: 106 women (ASQ)	I: 32.2 (4.1) C: 32.2 (4.2) From PREDICT I: 248 C: 250 median (IQR)	Women: I: 114 C: 106 Children I: 492 C: 497 (register-data) I: 225 C: 212 (ASQ)	Long-term child outcome: ASQ Medical history up to 8 years.
Wood 2012 Canada (2 centres)	NCT 00343265 Funding reported	June 2006 to October 2010	Twins and triplets	ART I: 55% C: 60% Selective reduction: 5% vs 0% Triplets: I: 2 (5%) C: 1 (2%)	NR	GA between 16+0-20+6 w I: 19+2 w (1-3) C: 19+6 w (1-3) median (IQR)	I: 90 mg, 8% /d vag prog gel C: Placebo Until 35+6 w	None	Women I: 42 C: 42 Children I: 86 C: 85	I: 34 (19-43) C: 34 (22-44 median (range)	Women I: 42 C: 42 Children I: 86 C: 85	PTB, sPTB <37 w PTB <35 w GA at delivery PNM, NNM Neonatal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

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Yemini 1985 Israel	Registra-tion and funding NR	NR	Singleton	Previous ≥2 PTB or ≥2 spontaneous miscarriages	NR	GA between I: 12.2 w (3.3) C: 12.2 w (3.)	I: 250 mg 17-OHPC im/w C: Placebo Until 37 w	All had cerclage	I: 39 C: 40	I: 27.8 (4.6) C: 28.3 (5.2)	I: 39 C: 40	PBT <37 w Neonatal morbidity
Systematic reviews with individual patient data meta-analysis and unique study data												
EPPPIC group 2021	EPPPIC study PROS-PERO, CRD 42017068 299 Funding; PCORI award PPA-1608-35702	1946 April 2017, updated July 2019	31 RCTs with singleton or multifetal pregnanci es	Asympto-matic women at increased risk of PTB	TVS CL ≤25 mm Singletons Vag. prog. 26.6% 17-OHPC 14.3% Multifetal pregnancy Vag. prog. 3.5% 17-OHPC 10.0%	GA between 14-25 w	I: vag prog (14 RCTs), 17-OHPC im (13 RCTs) oral prog (2 RCTs), C: Placebo, standard care, or other forms of prog (2 RCTs compared vag prog vs 17-OHPC im) Treatment until 34-37 w	NR	11644 women, 16185 children	Singletons Vag prog 29.2 (5.9) 17-OHPC 27.6 (6.1) Multifetal pregnancies Vag. prog. 31.3 (5.4) 17-OHPC 31.2 (5.9)	Singletons Vag prog I: 1904 C: 1865 17-OHPC I: 1889 C: 1164 Oral prog I: 93 C: 88 Multifetal pregnanci es Vag prog I: 1073 C: 973 17-OHPC I: 1240	PTB <34 w (PO, only outcome with unique study data)

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Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Norman 2018 UK HTA-report	OPPTI-MUM ISRCTN 14568373	January 2013 to June 2016	One RCT with singleton pregnancies	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 28.2 (10.6) C: 28.8 (11.1)	GA between 22-24 w	I: 200 mg vag prog/d C: Placebo Until 34 w	Cerclage recorded; other interventions not prohibited but not recorded	15132 assessed 1228 randomised I: 618 C: 610	I: 31.5 (5.6) C: 31.4 (5.8)	Maternal I: 600 C: 597 Neonatal I: 589 C: 587 Child-hood I: 430 C: 439 Children with Bailey score at 2 years I: 410 C: 423	Long-term child outcome: Bayley-III cognitive composite score (PO, only outcome with unique study data)
Romero 2017	PROS-PERO CRD 42016039682 Funding reported	From inception to December 2016	6 RCTs with twin pregnancies	Asympto-matic women with short 2nd trimester TVS CL ≤25 mm and a twin pregnancy	All TVS CL ≤25 mm	GA between I: 21.7 (20.6-23.1) w C: 22.1 (21.1-23.3) w median (IQR)	I: 90-200 mg vag prog/d C: Placebo or standard care Treatment until 34-36 w	NR	303 women, 606 children	I: 27 (25-30) C: 28 (25-31) median (IQR)	Women I: 159 C: 144 Children I: 318 C: 288	PTB <33 w (only outcome with unique study data)
Romero 2018	PROS-PERO CRD 42017057155 Funding reported	From inception to September 2017	5 RCTs with singleton pregnancies	Asympto-matic women with singleton pregnancies and short 2nd trimester TVS CL ≤25 mm	All TVS CL ≤25 mm	GA between I: 22.6 (21.4–23.6) w C: 22.6 (21.4–23.4) w median (IQR)	I: 90-200mg vagl prog/d C: Placebo Treatment until 34-36 w	NR	974 women	I: 28.0 (23.6-33.0) C: 27.5 (23.5-32.8) median (IQR)	I: 498 C: 476	PTB <33 w (only outcome with unique study data)

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Romero 2022 Update IPD MA of Romero 2017	Funding reported	From inception to November 2021	6 RCTs with twin pregnancies	Asympto-matic women with short 2nd trimester TVS CL ≤25 mm and a twin pregnancy	All TVS CL ≤25 mm	NR	I: 100-600 mg vag prog/d C: Placebo	NR	95 women 190 children	NR	I: 52 C: 43	PTB <33 w (only outcome with unique study data)
Simons 2021	PROSPERO CRD 42019142422 Funding NR	From inception to May 2020	7 RCTs (based on 5 RCTs) with singleton (3) and multifetal pregnancies (4)	Children born to women who received progesterone treatment for any indication during pregnancy	NR	NR	I: Prog treatment C: Placebo or another intervention	NR	4222 children aged 6 m to 8 years	NR	Children 2580 Singleton: 1206 Multiples: 1374	Long-term child outcome: Composite Bailey score
Cerclage												
Althuisius 2001 The Netherlands	CIPRACT Registra-tion NR Funding reported	July 1995 to July 2000	Singleton	Previous PTB <34w, PPROM <32w or, cold knife conization and TVS CL <25 mm at <27 w or, uterine anomaly.	I: 19.9 (2.9) C: 19.6 (4.3) Before 27 w.	GA between I: 20.9 w (3.0) C: 20.4 w (3.3) median (IQR)	I: Cerklage (McDonald) and bed rest C: No cerclage, bed rest	NR?	36 women randomised I: 19 C: 16	I: 30.5 (4.6) C: 34.5(4.9)	<27 w I: 19 C: 16	PTB <34 w (PO) PNM (PO) Neonatal morbidity (PO)

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Berghella 2004 USA (2 centres)	Registra-tion and funding NR	February 1998 to June 2003	Singleton and twins (4/61, 7%)	≥1 of high-risk factors for preterm birth (≥1 preterm birth <35 w, ≥2 curettages, diethyl-stilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregnancy) and/or TVS CL < 25 mm or significant funnelling	I: 15.7 (9.2) C: 16.7 (8.0)	GA between 14-23 w	I: Cerclage (McDonald) and bed rest C: No cerclage, bed rest Randomised 1:1	Bed rest	451 invited, 61 women randomised (6 lost to follow-up) I: 31 C: 30	I: 27.8 (6.4) C: 29.9 (6.9)	I: 14/31 C: 14/30 <35 w	PTB <35 w (PO), PTB <34 w PTB <32 w PTB <28 w GA at delivery NNM Neonatal and maternal morbidity NICU admission
Dor 1982 Israel (single centre)	Registra-tion and funding NR	1975 to 1979	Twins	Twin pregnancy	NR	GA 13 w	I: Cerclage (McDonald) C: No cerclage	None	45/90	I: 28.1 C: 30.4	Women I: 22 C: 23 Children I: 44 C: 46	PTB <37 w PTB <33 w PTB <28 w NNM Maternal morbidity
Ezechi, 2004 Nigeria	Registra-tion and funding NR	June 2000 to June 2002	NR handled as singleton	Previous PTB	NR	GA 14 w	I: Cerclage (McDonald) C: No cerclage	None	I: 38 C: 43	I: 24.6 (4.4) C: 24.4 (4.5)	I: 38 C: 43	PTB, not defined in text but seems to be <37w GA at delivery LBW PNM NICU admission

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Lazar 1984 France (four centres)	Registra-tion and funding NR	NR	Singleton	Composite score of a combination of: Previous PTB 29-36 w, history of previous miscarriage, prior threatening PTL treated by hospitalisation, uterine malformation, previous forced cervical dilatation, low lying placenta with bleeding, CL <2 cm, cervix open for inner os	NR	NR	I: Cerclage (McDonald) C: No cerclage	Hospitali-sation after cerclage 1-2 days	I: 268 C: 238	I: 26.6 C: 26.4	I: 268 C: 238	PTB <37 w PTB <35 w PTB <32 w PNM

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Macnaughton 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	MRC/ RCOG Registration NR Funding reported	1981 to 1988	Singleton (98%) and twins (2%)	Included if physician was uncertain if to place a cerclage or not for at risk patients with risk factors: previous PTB, previous 2nd trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, twin pregnancy, uterine anomaly	NR	GA between I: 15.6 w (5.1) C: 14.9 w (5.1) mean (SD)	I: Cerclage (type not prespecified) C: No cerclage	Bedrest, hospital admission, tocolysis	1318 enrolled 1292 randomised I:647 C:645	I: 27.7 (5.1) C: 27.2 (5.0)	Women I: 647 C: 645 Children I: 659 C: 661	PTB <37 w PTB <33 w (PO) LBW, VLBW PNM, NNM
Otsuki 2016 Japan (60 centres)	UMIN000001870 Funding reported	2004 to 2009	Singleton	General population screening; TVS CL <25 mm History of PTB: 11-15%, History of previous abortion: 20%	I1:18.3 (5.0) I2: 16.9 (4.5) C: 16.4 (5.9)	GA between I1: 24.6 w (2.8) I2: 24.6 w (2.9) C: 24.0 w (3.2) mean (SD)	I1: Cerclage (Shirodkar) I2: Cerclage (McDonald) C: Bedrest Cerclage removed at 37 w	All were screened for infection or inflammation of the LGT, exclusion if LGTI was diagnosed	I1: 35 I2: 36 C: 35	I1: 33.4 (4.5) I2: 33.2 (4.9) C: 33.9 (3.6)	I1: 34 I2: 34 C: 30	PTB < 37 w PTB < 34 w PTB < 32 w PTB < 28 w NNM

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Owen 2009 USA (15 centres)	Registra-tion NR Funding reported	January 2003 to November 2007	Singleton	History of sPTB + TVS CL <25 mm	At randomi-sation I: 19.5 (5.3) C: 18.6 (6.3)	GA at randomisation I: 19.5 w (2.0) C:19.4 w (1.9) mean (SD)	I: Cerclage (McDonald) C: standard care Cerclage removed at 37 w	Antibiotics if positive culture	8770 assessed 1044 with prior SPTB screened with TVS CL: 318 TVS CL <25 mm 302 randomised I: 149 C: 153	I: 26.6 (5.1) C: 26.4 (5.5)	I: 148 C: 153	PTB <37 w PTB <35 w (PO) PNM Neonatal morbidity
Roman 2020 (8 centres, Italy, USA, Spain, Poland, Denmark, Switzerland	NCT 02490384 External funding NR	July 2015 to July 2019	Twins (DA)	Asymptoma tic women with twin pregnancy, with dilated cervix 1-5 cm by pelvic examination and/or speculum examination and/or TVS	I: 10/14 had CL<25mm C: 10/10 had CL<25mm	GA between I: 20.7 w (1.7) C: 19.4 w (1.5) mean (SD)	I: Cerclage McDonald) C: No cerclage	I: Indomethasi n and antibiotics	I: 17 C: 13	I: 31.6 (4.4) C: 28.2 (5.1)	I: 17 C: 13	sPTB <34 w (PO) sPTB <32 w sPTB <28 w VLBW PNM, NNM Neonatal and maternal morbidity NICU admission
Rush 1984 South Africa (single centre)	Registra-tion and funding NR	January 1979 to April 1982	Singleton	History of previous late miscarriage or PTB out of ≥1 between 14-36 w, total ≥2 pregnancies ending <37 w	NR	GA between I: 124.1 days (12.9) C: 126.2 days (14.0)	I: Cerclage McDonald) C: No cerclage	None	I: 96 C: 98	I: 26.16 (4.40) C: 25.79 (4.09)	I: 96 C: 98	PTB <37 w LBW Neonatal and maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Rust 2000 USA (single centre)	Registra-tion and funding NR	May 1998 to June 1999	Singleton (88,5%) and twins (11,5%)	(1) width of dilatation of the internal os, (2) depth of membrane prolapse into the endo-cervical canal, (3) distal CL, and (4) total CL	I: 39 (12) C: 36 (12)	GA between 16-24 w	I: Cerclage (McDonald) C: Modified bedrest	I: Bedrest 48-72 h, clindamycin and indo-methasin	I: 31 C: 30	NR	I: 31 C: 30	PTB <37 w PTB <34 w PTB <28 w GA at delivery NNM Neonatal and maternal morbidity
To 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Registra-tion and funding NR	January 1998 to May 2002	Singleton	TVS CL ≤15 mm. Previous cervical surgery: I: 6% C: 7%	I: 9.6 (2-15) C: 9.3 (2-15) mean (range)	GA between 22-24 w I: 23.5 w (22.3-25.9) C: 23.6 w (22.3-25.3) mean (range)	I: Cerclage (Shirodkar) C: Standard care Cerclage removed at 37 w	Steroids at 26-28 w for fetal lung maturation for all	47123 assessed 470 eligible 253 randomised I: 127 C: 126	I: 29.8 (14.7-43.0) C: 29.3 (13.9-41.2) mean (range)	I: 127 C: 125	PTB <33 w (PO) GA at delivery PNM, NNM Neonatal and maternal morbidity
Systematic reviews with individual patient data meta-analysis and unique study data												
Alfirevic 2017	Cochrane review Registra-tion and funding NR	From inception to June 2016	15 RCTs of singleton pregnanci es	History of PTB or short TVS CL	NR	NR	I: Cerclage C: No cerclage, other intervention	Bedrest in some studies	3490 women	NR	Women 3490	PTB <37 w PTB <34 PTB <28 w PNM (PO) Neonatal and maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Pessary												
Berghella 2017a USA (3 centres)	PoPPT NCT 02056639 Funding NR	April 2014 to June 2016	Twins	TVS CL <30 mm DCDA 78% MCDA22% Previous PTB 0% vs 13%	I: 16.7 (10.7-27.8) C: 22.9 (15.9-25.6) median (IQR)	GA between 18+0-27+6 w I: 21.0 w (20.1-24.3) C: 21.2 w (21.1-24.3) median (IQR)	I: Pessary (Bioteque cup™) C: No pessary Pessary removed at 36 w	Progesterone I: 1 C: 2	421 assessed 85 TVS CL ≤30 mm 46 randomised I: 23 C: 23	I: 27.0 (23.4-33.0) C: 32.9 (26.2-36.8) median (IQR)	Women I: 23 C: 23 Children I: 46 C: 46	PTB, sPTB <37 w PTB, sPTB <34 w PTB, sPTB <28 w GA at delivery NNM Neonatal and maternal morbidity
Dugoff 2018 USA (5 centres)	PoPPS NCT 02056652 Funding reported	March 2014 to July 2016	Singleton	TVS CL ≤25 mm	I: 17.6 (10.9-22.0) C: 19.0 (11.2-22.9) median (IQR)	GA between 18+0-23+6 w I: 20.9 w (20.1-21.9) C: 20.7 w (20.1-22.1) median (IQR)	I: Pessary (Biotech™ cup) C: No pessary Pessary removed at 37 w	Vag prog if TVS CL ≤20 mm I: 84% C: 91% Cerclage I: 2 (3.3%) C: 3 (5.2%)	17383 assessed 391 met inclusion criteria, 122 agreed to randomisation I: 61 C: 61	I: 27.7 (23.0-32.3) C: 29.5 (23.0-34.8) median (IQR)	I: 60 C: 58	PTB <37 w (PO) sPTB <37 w PTB, sPTB <34 w PTB, sPTB <28 w GA at delivery NNM Neonatal and maternal morbidity
Goya 2012 Spain (5 centres)	PECEP NCT 00706264 Funding reported	June 2007 to June 2010	Singleton	TVS CL ≤25 mm Previous PTB: 11% in both groups	I: 19.0 (4.6) C: 19.0 (4.9)	GA between I: 22.2 w (0.9) C: 22.4 w (0.9)	I: Pessary (Arabin) C: Standard care Pessary removed at 37 w	None	18235 eligible, 6360 declined, 11875 assessed, 726 TVS CL ≤25 mm 385 randomised I:192 C:193	I: 30.3 (5.1) C: 29.6 (5.4)	I: 190 C: 190	sPTB <37 w PTB <34 w sPTB < 34 w (PO) sPTB < 28 w GA at delivery LBW, VLBW NNM Neonatal and maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 2 – Characteristics of included publications, RCTs and SRs were included

Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Goya 2016 Spain (5 centres)	PECEP-twins NCT 01242410 Funding NR	January 2011 to July 2014	Twins	TVS CL ≤25 mm. Previous PTB: I: 16.7% C: 17.6% Twins (MC) I: 19.1% C: 17.6%	I: 19.2 (3.5) C: 19.6 (3.6)	GA between 18-22 w I: 22.1 (0.8) C: 22.5 (0.7)	I: Pessary (Arabin) C: Standard care Pessary removed at 37 w	None	2931 eligible, 2287 assessed, 154 TVS CL ≤25 mm, 137 randomised I: 68 C: 66	I: 35.4 (3.6) C: 35.9 (5.6)	Women I: 68 C: 65 Children I: 136 C: 130	sPTB <37 w PTB <34 w sPTB < 34 w (PO) sPTB <28 w GA at delivery LBW, VLBW NNM Neonatal and maternal morbidity
Hui 2013 China (single centre)	ISRCTN 18185477 Funding reported	October 2008 to February 2011	Singleton	TVS CL ≤25 mm	I: 19.6 (0.5) C: 20.5 (0.4)	GA between 20-24 w	I: Pessary (Arabin) C: Digital examination at entry to simulate pessary insertion. Pessary removed at 37 w	Dexa-methasone if TVS CL <10 mm	4438 assessed, 203 TVS CL <25 mm, 17 not eligible, 78 declined, 108 consented, I: 53 C: 55	I: 31.6 (4.7) C: 31.8 (5.3)	I: 53 C: 55	PTB <37 w PTB < 34 w (PO) sPTB <34 w PTB <28 w GA at delivery NNM Neonatal and maternal morbidity NICU admission
Karbasian, 2016 Iran (single centre)	Registra-tion NR Funding reported	August 2014 to December 2015	Singleton	TVS CL <25 mm	I: 22 (1.8) C: 22 (1.6)	GA between 18-22 w	I: Pessary (Arabin) +400 mg/d vag prog C: 400 mg/d vag prog	Progesteron e	I: 71 C: 73	I: 28.8 (5.3) C: 27.9 (5.4)	I: 71 C: 73	PTB <37 w (PO) PTB <34 w PTB <32 w GA at delivery LBW PNM, NNM NICU admission Maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Liem 2013a the Netherlands (40 hospitals)	ProTWIN NTR 1858 Funding reported	September 2009 to March 2012	Twins (98%) Triplets (2%)	Triplets: I: 2% (n=9) C: 2% (n=9) Twins (MC): I: 22% C: 24% Previous PTB I: 7% C: 6%	CL measured at GA 16-22 w I: 43.6 (8.1) C: 44.2 (8.5)	GA between 16-20 w I: 18.4 (1.7) C: 18.6 (2.3)	I: Pessary (Arabin) C: Standard care Pessary removed at 36 w	Cerclage I: 5 C: 0	1242 assessed 813 randomised I: 403 C: 410	I: 33.1 (4.6) C: 32.7 (4.5)	Women I: 401 C: 407 Children I: 811 C: 823	PTB <37 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW NNM Composite adverse neonatal outcome (PO) Neonatal morbidity (PO) NICU admission (PO) Maternal mortality and morbidity
Nicolaides 2016a UK (12 countries, 23 centres)	ISRCTN 01096902 Funding reported	August 2008 to May 2011	Twins	Twins (MC): I: 18.8% C: 18.8% Previous PTB: I: 8.8% C: 14.3%	I: 32.0 (27.0-36.0) C: 32.0 (27.0-37.0) median (IQR)	GA between 20+0-24+6 w I: 22+6 w (21.4-23.9) C: 22.7 w (21.4-23.9) median (IQR)	I: Pessary (Arabin) C: Standard care Pessary removed at 37 w	Steroids if TVS CL <10 mm after 26 w Vag prog I:0 C:2	2107 eligible 1180 randomised I:590 C: 590	I: 33.1 (29.5-36.7) C: 33.2 (29.1-36.6) median (IQR)	Women I: 588 C: 589 Children I: 1176 C: 1178	sPTB <34 w (PO) PTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal morbidity
Nicolaides 2016b UK (9 countries, 16 centres)	ISRCTN 01096902 Funding reported	September 2008 to January 2013	Singleton	Short TVS CL ≤25 mm Previous PTB I: 15.1% C: 18%	I: 20 (14-22) C: 20 (15-22) median (IQR)	GA between 20+0-24+6 w I: 23.4 w (22.6-24.3) C: 23.6 w (22.7-24.4) median (IQR)	I: Pessary (Arabin) C: Standard care Pessary removed at 37 w	Vag prog if TVS CL ≤15 mm I: 204 (43.9%) C: 219 (46.9%) Antibiotics: I: 156 C: 111 Cerclage I: 2 C: 5	1829 eligible 935 randomised I: 466 C: 469	I: 30.1 (26.0-34.2) C: 29.5 (25.4-34.1) median (IQR)	I: 460 C: 464	sPTB <34 w (PO) PTB <34 w PTB <32 w PTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal morbidity NICU admission

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Norman 2021	STOPPIT-2 NCT 02235181 Funding reported	April 2015 to February 2019	Twins	TVS CL <35 mm MCDA 20% DCDA 80%	I: 28.8 (5.8) C: 29.5 (5.1)	GA between 18+0–21+6 w	I: Pessary (Arabin) C: Standard care Pessary removed at 37 w	None	503 randomised I: 250 C: 253	I: 32.4 (17.51) C: 32.7 (17.50)	Women I: 246 C:245 Children I: 492 C: 490	PTB, sPTB <37 w (PO) PTB, sPTB <34 w (PO) PTB, sPTB <32 w (PO) PTB, sPTB <28 w (PO) GA at delivery PNM Composite adverse neonatal outcome (PO) Neonatal morbidity (PO) NICU admission (PO) Maternal morbidity
Pacagnella 2022 Brazil	ReBec U1111-1164-2636 Funding reported	July 2015 to March 2019	Singleton (92.4%) Twins (7.6%)	TVS CL <30 mm Twin pregnancy (all DA)	I: 25 (20.7-27.0) C: 25.0 (21.1-27.0) median (IQR)	Within 72h after randomisation GA at randomisation I: 21.2 w (20.0-22.3) C: 21.1 w (20.0-22.1) median (IQR)	I: Pessary (Ingamed) and vag prog C: vag prog Pessary removed at 36 w	None	936 randomised I: 475 C: 461	I: 26.5 (7.0) C: 26.3 (6.6)	Women I: 463 C:436 Children I: 509 C: 468	PTB <37 w sPTB <37 w (PO) PTB, sPTB <34 w (PO) PTB, sPTB <32 w (PO) PTB <28 w sPTB <28 w (PO) GA at delivery PNM, NNM Neonatal morbidity (PO) NICU admission (PO) Maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables
Saccone 2017c Italy (single centre)	NCT 02716909 Funding NR	March 2016 to May 2017	Singleton	TVS-CL ≤25 mm Prior cervical surgery: I: 7 (4.7%) C: 5 (3.3%)	I: 11.5 (5.7) C: 12.5 (5.9)	GA between 18+0-23+6 w	I: Pessary (Arabin) C: Standard care Pessary removed at 37 w	If TVS CL ≤ 20mm, vag prog 200 mg/d in both groups: I: 133 (88.7%) C: 125 (83.3%)	503 women eligible 300 women randomised I: 150 C: 150	I: 28.5 (6.2) C: 28.9 (6.5)	I: 150 C: 150	PTB, sPTB <37 w PTB <34 w sPTB <34 w (PO) PTB, sPTB <32 w PTB, sPTB <28 w GA at delivery LBW, VLBW PNM, NNM Neonatal and maternal morbidity NICU admission
Simons 2019 the Netherlands Planned secondary analysis of Liem 2013 (ProTWIN trial)	Funding reported	Liem: September 2009 to March 2012	Twins Triplets	Twins (MC) 24.4% Triplets 2.7%	CL measured at 16-22 w I: 43.6 (8.1) C: 44.2 (8.5)	GA between 16 -20 w	I: Pessary (Arabin) C: No pessary	None	I: 140 C: 118 Eligible for follow up: Unselected: I: 392/781 C: 395/788 Approached I: 311/621 C: 268/531	I: 32 (29-36) N=140 C: 33 (30-37) N=118 median (IQR)	Women I: 140 C: 118 Children I: 281 C: 233	Long-term child outcome: 4-year follow ASQ SDQ Physical problem Abnormal child outcome
Van't Hooft 2018 the Netherlands Planned secondary analysis of Liem 2013 (ProTWIN trial)	ProTWIN Kids Funding reported	Liem: September 2009 to March 2012	Twins Triplets	Twins (MC) 27% Triplets 1.1%	CL<38 mm	GA between 16 -20 w	I: Pessary (Arabin) C: Standard care		I: 58 C: 31	I: 32 (29-36) C: 30 (28-34) median (IQR)	Surving children 241 Response rate 83% n=200 children I: 120 C: 80	Long term child outcome: 3-year follow-up

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Aspirin												
Landman 2022 The Netherlands (34 centres)	NL5553 Funding reported	May 2016 to June 2019	Singleton	History of sPTB	NR	GA between 8-16 w	I: ASA 80 mg/d oral C: Placebo Until 36+0 w or delivery	Progesterone, cerclage, pessary at physicians discretion	406 women randomised (19 excluded) I: 194 C: 193	I: 32.8 (3.9) C: 32.3 (3.6)	I: 194 C: 193	PTB <37 w (PO) sPTB <37 w PTB, sPTB <34 w PTB, sPTB <28 w GA at delivery PNM Neonatal morbidity NICU admission Maternal mortality and morbidity
Other combinations of treatment												
Cruz-Melguizo 2018 Spain (27 centres)	NCT 01643980 Funding reported	August 2012 to April 2016	Singleton	Short CL <25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 20.8 (4.2) C: 20.9 (4.1)	GA between 20-23 w	I: Cervical pessary C: 200 mg prog vag/d Randomised 1:1 Until 36+6	None	254 women randomised (11 excluded) I: 125 C: 118	I: 32.5 (5.3) C: 33.1 (5.5)	I: 125 C: 118	sPTB <37w sPTB < 34 w (PO) sPTB <28 w GA at delivery LBW, VLBW PNM Neonatal and maternal morbidity NICU admission

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Dang 2019 Vietnam (single centre)	NCT 02623881 Funding reported	March 2016 to June 2017	Twins	Short TVS-CL <38 mm	I: 30.9 (4.5) C: 31.7 (4.1)	GA between I: 17.5 w (1.5) C: 18.0 w (1.8)	I: Pessary (Arabin) C: 400 mg/day vag prog/d (Cyklogest) Interventions until 36+0 w	None	1113 assessed 444 TVS CL< 38 mm 300 randomised I: 150 C: 150	I: 31.7 (5.2) C: 32.1 (4.9)	Women I: 148 C: 149 Children I: 296 C: 298	PTB <34 w (PO) PTB < 37 w PTB < 28 w GA at delivery LBW, VLBW PNM, NNM Neonatal morbidity NICU admission Maternal mortality and morbidity
Keeler 2009a USA (single centre)	Registra-tion NR Funding reported	November 2003 to December 2006	Singleton	TVS CL ≤25 mm in women with risk factors for PTB (history of sPTB, 2nd trimester pregnancy loss, previous cervical surgery or, uterine anomaly)	I: 16.8 (5.1) C: 14.5 (6.6)	GA between 16-24 w	I: Cerclage (MacDonald) C: 250 mg 17-OHPC im/w	Indomethacin, antibiotics before randomisation	I: 42 C: 37	I: 27.6 (6.58) C: 29.6 (7.15)	I: 42 C: 37	PTB, sPTB <37 w PTB <35 w sPTB <35 w (PO) PTB, sPTB <32 w PTB, sPTB <28 w GA at delivery PNM Neonatal and maternal morbidity

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
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Author Year Country/ Setting	Trial registration Funding	Study period	Singleton/ Twin/ Triplet	Risk factors for PTB	Cervical length at study entry mean (SD) mm	Gestational age/interval for start of intervention	Study Groups; Intervention vs control/other intervention	Concomitant intervention	Women/ children (n)	Maternal mean age (years) mean (SD)	Women/ children in outcomes	Outcome variables

17-OHPC; 17-α-hydroxyprogesterone caproate, AMAG; Advanced Magnetics Inc , ART; assisted reproductive technology, ASA; acetylsalicylic acid, ASQ Age and Stages Questionnaire, BPD; bronchopulmary dysplasia, C; control, CBCL; Child Behavior Checklist, CDI; child development inventory score categorization, CHI; Community Health Index, CIPRACT; Cervical incompetence prevention randomized cerclage trial, CL; cervical length, CRD; Centre for Reviews and Dissemination, DCHIA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, EPPIC; Evaluating Progestogens for Preventing Preterm birth International Collaborative, EudraCT; European Union Drug Regulating Authorities Clinical Trials Database, FFN; fetal fibronectin, GA; gestational age, GDM; gestational diabetes mellitus, HIV; human immunodeficiency virus, I; intervention, im; intramuscular, IPD MA; Individual Participant Data Meta-Analysis, IPOP; The Improving Pregnancy Outcomes with Progesterone, IRCT; Iranian Clinical Trial registry, ISRCTN; International Standard Randomized Controlled Trial Number, IUFD; intrauterine foster death, IQR; interquartile range, IV; intra venous, LBW; low birth weight (<2500g), LGT; lower genital tract, LGTI; lower tract genital infection, MC; monochorionic, MCDA; monochorionic diamniotic, MFMU; Maternal-Fetal Medicine Units, MRC/RCOG; Medical Research Council/Royal College of Obstetrics and Gynaecology, n; number, neg; negative, NICHD; National Institute of Child Health and Human Development, NICU; neonatal intensive care unit, NCT; National Clinical Trial, NNM; neonatal mortality, NR; not reported, NTR; the Netherlands trial registration, OPPTIMUM; dOes Progesterone Prophylaxis To prevent preterm labour IMprove oUtcoMe, PCORI; Patient-Centered Outcomes Research Institute, PECEP; Pesario Cervical para Evitar Prematuridad, PECEP-twins; Pesario Cervical para Evitar Prematuridad-twins, PNM; perinatal mortality, PO; primary outcome, PoPPS; Prevention of preterm birth with pessary in singletons, PoPPT; Prevention of Preterm birth with Pessary in Twins, pos; positive, PPA; Public and Professional Abstract, PREGNANT; Vaginal Progesterone Bioadhesive Gel (Prochieve)® Extending Gestation A New Therapy, PTB; preterm birth, PTD; preterm delivery, PTL; preterm labor, PPROM; preterm prelabour rupture of membranes, Prog; progesterone, PROLONG; Progestin's Role in Optimizing Neonatal Gestation, RCT; randomised controlled trial, ReBec; Brazilian Clinical Trial Registry, SD; standard deviation, SDQ; Strength and Difficulties Questionnaire, sPTB spontaneous preterm birth, SR; systematic review, STOPPIT; STudy Of Progesterone for the Prevention of Preterm Birth In Twins, TCTA; trichorionic triamniotic, TRIPLE P; Preventing preterm birth with progesterone: costs and effects of screening low risk women with a singleton pregnancy for short cervical length, the Triple P study, TROPICAL; TRial Of Progesterone vaginal tab In prevention of preterm delivery evaluated by CervicAl Length, TVS; transvaginal scan, UK; United Kingdom, UMIN; University Hospital Medical Information Network, USA; United States of America, US NIH; the United States National Institutes of Health, Vag; vaginal, VLBW; very low birth weight <1500g.

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 3 Excluded publications

Author, year	Reason for exclusion
Abdel 2021	Wrong intervention: Comparing different dosages, no placebo.
Abdi 2020	Wrong population: Women with a previous history of preeclampsia (PE).
Abramovici 2015	Wrong population: Women with low or high risk of PE.
Agra 2019	Wrong outcome: Women with cervical shortening.
Allshouse 2016	Wrong population: Women with high risk of PE.
Althuisius 2000	Preliminary results. Double publication, Althuisius 2001.
Althuisius 2002	Wrong outcome: Cervical length.
Andrikopoulou 2018	Wrong population: Nulliparous women without any specific risk factors. Secondary analysis of Sibai 1993.
Atallah 1996	Wrong population: Women with high risk of PE.
Ayala 2013	Wrong population: Women with high risk of PE.
Bakhtii 2011	Wrong population: Nulliparous women without any specific risk factors.
Berghella 2010a	Wrong study design: No RCT.
Beroyz 1994	Wrong population: Women with high risk of PE or intra uterine growth restriction (IUGR).
Buchbinder 2002	Wrong population: Women with a previous history of PE.
Caritis 1998	Wrong population: Women with high risk of PE.
Caritis 2012	Wrong intervention: Concentration of 17-hydroxyprogesteron caproate (17-OHPC) in blood.
Caritis 2014	Wrong intervention: Concentration of 17-OHPC in blood.
Connealy 2014	Wrong population: Women with a previous history of PE.
Corrado 2002	Wrong population: Women who underwent midtrimester amniocentesis.
De Franco 2007	Double publication, O´Brien 2007.
Durnwald 2010	Secondary analysis of Rouse, 2007.
Ebrashy 2005	Wrong population: Women with high risk of PE or IUGR.
Eddama 2010	Wrong study design: Cost effectiveness article.
El Refaie 2016	Retracted article.
Farinelli 2012	Wrong intervention: Association between body mass index and pregnancy outcome.
Fratto 2016	Wrong population: Women with low or high risk of PE.
Gu 2020	Wrong population: Women with risk of PE.
Hajizadeh 2020	Wrong design: Pseudorandomisation. Wrong intervention: Unclear gestational age at start of intervention.
Hamid 1994	Wrong population: Women with raised alpha-fetoprotein in blood and abnormal doppler waveform pattern.
Hartikainen-Sorri 1980	Wrong intervention: 17-OHPC in third trimester.

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 3 Excluded publications

Author, year	Reason for exclusion
Heyborne 2016	Secondary analysis of PTB and smoking, Meis 2003.
Heyborne 2015	Secondary analysis of PTB and obese women, Meis 2003.
Hezelgrave 2016	Wrong study design: Study protocol.
Hoffman 2020	Wrong population: Nulliparous women without any specific risk factor
Huai 2021	Wrong population: Women with high risk of PE.
Jessani 2021	Wrong outcome: Haemoglobin level. Secondary analysis of Hoffman 2020.
Keeler 2009b	Double publication to Rust 2001, Roman 2003, Rust 2007.
Khazardoost 2014	Wrong population: Women with raised alfa-fetoprotein in blood.
Kumar 2014	Wrong intervention: Oral progesterone in first trimester.
Kumar 2020	Wrong population: Women with high risk of PE.
Lambers 2009	Wrong outcome: Hypertensive disorders in pregnancy.
Le 2020	Wrong study design: Cost effectiveness article.
Leslie 1995	Wrong population: Women with high risk of PE.
Liem 2014	Wrong study design: Cost effectiveness article.
Liem 2016	Double publication, Liem 2013, per protocol analysis.
Mancuso 2010	Wrong population: Women with different type of cervical funnelling.
Manuck 2011	Wrong intervention: Receptor polymorphisms and response to 17-alpha-hydroxyprogesterone caproate.
Marat 2019	Wrong study design: No RCT.
Macnaughton 1988	Wrong study design: Interim report.
Meis 2005	Wrong outcome: Secondary analysis on different risk factors, Meis 2003.
Mendoza 2017	Wrong outcome: Cervical length. Secondary analysis, Goya 2012.
Mourad 2019	Double publication with Mourad 2021 (same article first published on-line)
Mourad 2021	Secondary publication analysing the effect of GDM on hypertensive disorder of pregnancy
Moussa 2015	Wrong population: Women with high risk of PE.
Odibo 2015	Wrong population: Women with high risk of PE.
Pizzi 2014	Wrong study design: Cost effectiveness article.
Poon 2017	Wrong population: Women with high risk of PE.
Rode 2012	Wrong outcome: Secondary analysis of Rode 2011, inflammatory markers and PTB.
Rust 2001	Wrong outcome: Secondary analysis of Rust 2000, PTB and different risk factors.
Rust 2003	Wrong outcome: Gestational age (GA) in relationship with location of cerclage.

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 3 Excluded publications

Author, year	Reason for exclusion
Schisterman 2014	Wrong outcome: Preconception initiated ASA and live birth.
Senat 2013	Wrong intervention: Intervention (progesterone) starts too late in pregnancy.
Shabaan 2018	Wrong intervention: Intervention (progesterone) starts too late in pregnancy (third trimester).
Sharma 2018	Wrong population: Women with high risk of PE.
Short 2021	Wrong outcome: Safety of ASA. Secondary analysis of Hoffman 2020.
Sibai 2000	Wrong intervention: Comparing singleton and twin pregnancies. Secondary analysis of Sibai 1993 (ASA)
Silver 2015	Wrong population: Secondary analysis of Schisterman 2014 (EAGER trial).
Spong 2005	Wrong outcome: GA compared to GA of last delivery. Secondary analysis of Meis 2003.
Szychowski 2012	Secondary analysis of Owen 2009. Additional effect of cerclage in women randomised to 17-OHPC
Szychowski 2016	Wrong outcome: Cervical length. Secondary analysis of Owen 2009.
Talari 2014	Wrong population: Women with high risk of PE. Wrong outcome: Incidence of PE.
Tewari 1997	Wrong population: Women with high risk of PE.
Tolcher 2020	Wrong population: Women with high risk of PE.
Van Limburg 2021	Wrong outcome: Pessary effect on subsequent pregnancy. Secondary analysis of Liem 2013.
van Os 2017	Wrong outcome: Cervical length cut off values. Secondary analysis of van der Veen 2015.
Winer 2015	Wrong intervention: Intervention (progesterone) starts too late in pregnancy.
Wing 2010	Wrong study design: Secondary analysis, Owen 2009. Observational study on risk factors for PTB (gestational age at prior PTB).
Wright 2019	Wrong population: Women with high risk vs low risk of PE.
Wright 2017	Wrong population: Women with high risk of PE.
Yu 2003	Wrong population: Women with abnormal uterine artery Doppler at 23 weeks

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 3 Excluded publications

Author, year	Reason for exclusion
Systemic reviews not included in the HTA report (without unique study data). See Appendix 5 for more information on systematic reviews relevant for our PICO published after 2017.	
Abdel-Aleem 2013	Old = before 2017
Ahn 2017	Progesterone, singletons and multifetal, outcome mortality. Appendix 5
Almutairi 2021	17-OHPC, singletons previous PTB. Appendix 5
Bachmann 2003	Old = before 2017
Baradwan 2021	17-OHPC, singletons previous PTB. Appendix 5
Belej Rak 2003	Old = before 2017
Berghella 2010b	Old = before 2017
Berghella 2011	Old = before 2017
Berghella 2017b	Cerclage, singletons, previous PTB. Appendix 5
Boelig 2019	Vaginal progesterone vs intramuscular progesterone, singletons previous PTB. Appendix 5
Bujold 2010	Old = before 2017
Chaemsaithong 2020	ASA PE excluded
Chaman Ara 2016	Old = before 2017
Combs 2016	Old = before 2017
Conde Agudelo 2018	Cerclage vs vaginal progesterone, singletons, previous PTB, short cervix. Appendix 5
Conde Agudelo 2020	Pessary, singletons and multifetal vs no pessary or other interventions. Appendix 5
Coomarasamy 2003	Old = before 2017
Coomarasamy 2006	Old = before 2017
Correa 2019	Pessary, singletons. Appendix 5
Cui 2018	ASA, PE excluded
D´Antonio 2021	NW MA all interventions twins. Appendix 5
De Jong 2014	Old = before 2017
Dodd 2006	Old = before 2017
Dodd 2008	Old = before 2017
Dodd 2019	Progesterone, multifetal, Cochrane. Appendix 5
Dodd 2013	Old = before 2017
Dodd 2005	Old = before 2017
Drakeley 2003a	Old = before 2017

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 3 Excluded publications

Author, year	Reason for exclusion
Drakeley 2003b	Old = before 2017
Duley 2019	ASA, PE excluded
Eke 2019b	17-OHPC, outcome GDM. Appendix 5
Eke 2019a	Adjuvant 17-OHPC to cerclage. Appendix 5
Fernandez-Macias 2019	17-OHPC, prior PTB, singletons. Appendix 5
Ghazanfarpour 2020	ASA, excluded
Goldstein 1989	Old = before 2017
Grabovac 2019	Previous conisation. All interventions, singletons. Appendix 5
Groeneveld 2013	Old = before 2017
Haas 2019	Outcome miscarriage, progesterone, excluded
Henderson 2014a	Old = before 2017
Henderson 2014b	Old = before 2017
Jarde 2017a	The more the better, different combinations of treatment. Appendix 5
Jarde 2017b	Twins NW MA. Appendix 5
Jarde 2017c	Singletons NW MA. Appendix 5
Jarde 2019	Singletons updated NW MA. Appendix 5
Jin 2017	Pessary singletons. Appendix 5
Jin 2019	Pessary singletons and multifetal. Appendix 5
Jorgensen 2007	Old = before 2017
Kozer 2003	Old = before 2017
Li 2019	Twins, cerclage. Appendix 5
Liem 2013b	Old = before 2017
Likis 2012a	Old = before 2017
Likis 2012b	Old = before 2017
Liu 2019	Vaginal progesterone + pessary, singletons. Appendix 5
Liu 2013	Old = before 2017
Mackenzie 2006	Old = before 2017
Man 2021	Wrong population: ASA in nulliparous women without any specific risk factor
Meher 2017	ASA, PE excluded
Meher 2006	Old = before 2017

Project: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies
Appendix 3 Excluded publications

Author, year	Reason for exclusion
Odibo 2003	Old = before 2017
Perez-Lopez 2019	Pessary, short cervix, singletons. Appendix 5
Phung 2021	Vaginal progesterone normal cervix, previous PTB, singletons. Appendix 5
Prior 2017	P-hacking, excluded
Rafael 2014	Old = before 2017
Roberge 2016	Old = before 2017
Roberge 2012	Old = before 2017
Rode 2009	Old = before 2017
Romero 2012	Old = before 2017
Romero 2016	Old = before 2017
Rossi 2011	Old = before 2017
Saccone 2015	Old = before 2017
Saccone 2017a	Pessary twins short cervical length. Appendix 5
Saccone 2017b	Pessary singletons short cervical length. Appendix 5
Sanchez-Ramos 2005	Old = before 2017
Schuit 2015	Old = before 2017
Simons 2020	Same article as Simons 2021, Appendix 5
Sotiriadis 2012	Old = before 2017
Thangatorai 2018	Pessary twins, Appendix 5
Trivedi 2011	Old = before 2017
Turner 2020	ASA, excluded
van Vliet 2017	ASA, excluded
Velez Edwards 2013	Old = before 2017
Villa 2013	Old = before 2017
Xiong 2020	Pessary singletons and twins. Appendix 5
Xu 2015	Old = before 2017
Yan 2020	Progesterone miscarriage, excluded.
Zheng 2019	Pessary, singletons and twins. Appendix 5

17-OHPC; 17-hydroxyprogesteron caproate, ASA; acetylic salicylic acid, GA; gestational age, GDM; gestational diabetes mellitus, IUGR; intrauterine growth restriction, NW MA; network meta-analysis, PE; preeclampsia, PTB; preterm birth, RCT; randomised controlled trial

Appendix 5. Systematic reviews relevant for our PICO and published between 2017 and 2022 (n=34). Significant results are marked in bold.

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
Almutairi, 2021	MA June 2021	Singletons with previous PTB	I: 17-OHPC C: placebo	6/2439	PTB <37, 35, 32 w	<37 w 0.68 (0.46-1.00) <35 w 0.60 (0.10-3.67) <32 w 0.61 (0.13-2.77)	
Ahn, 2017	MA Nov 2015	Singletons and multifetal pregnancies	I1: Vaginal progesterone C1: placebo I1: 17-OHPC C2: placebo	22/11 188 offspring	Neonatal mortality	Singletons I1: 0.69 (0.31-1.54) I2: 0.6 (0.33-1.09) Multiples I1: 0.96 (0.51-1.8) I2: 0.96 (0.49-1.9)	
Baradwan, 2021	MA April 2021	Singletons with previous PTB	I: 17-OHPC C: placebo	6/2573	PTB <35 w	**0.77** **(0.63-0.93)**	
Eke, 2019a	MA Published before June 2018	Singletons with history (previous sPTB) indicated cerclage	I: Cerclage + 17-OHPC C: Cerclage	5/546 (RCTs and cohort studies included)	PTB <24 w	0.86 (0.45-1.65)	
Eke, 2019b	MA Published before October 2018	Singletons previous PTB	I: 17-OHPC C: Placebo	6/6053 (RCTs and cohort studies included)	Gestational diabetes	All studies 1.77 (1.22–2.55) Only RCTs 1.21 (0.63–2.36)	
Fernandez-Macias, 2019	MA Aug 2018	Singletons Previous sPTB	I: 17-OHPC C: placebo	4/761	PTB <37, 35, 32 w	**<37 w** **0.71 (0.53-0.96)** **p=0.001** **<35 w** **0.74 (0.58-0.96) p=0.021** **<32 w** **0.60 (0.42-0.85) p=0.004**	
Liu, 2019	MA February 2019	Singletons TVS CL ≤25 mm	I: Vaginal progesterone+ pessary C: Pessary	3/820	PTB <34 w	0.91 (0.47-1.77)	No additional effect of vaginal progesterone

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
Norman, 2018	HTA report July 2016	Singletons at risk (Previous sPTB, TVS CL ≤25 mm, positive FFN and other risk factors)	I: 200 mg vaginal progesterone C: Placebo	1 /1228 (Norman OPPTIMUM, 2016)	1. Fetal death or PTB 34+0 w, 2. neonatal (a composite of death, brain injury on ultrasound scan and BPD, and 3. childhood cognitive score (the Bayley-III cognitive composite score) at 22–26 months of age	C vs I 1: 0.86 (0.61 - 1.22) 2: 0.62, (0.38–1.03) 3: 97.3 (SD 17.9) *vs* 97.7 (17.5); difference in means –0.48, 95% CI –2.77 to 1.81)	Data from Norman 2018 included in our HTA report Control vs intervention, adjusted OR
Phung, 2021	MA Dec 2020	Singletons at high-risk and TVS CL >25 mm	I: Vaginal progesterone C: placebo	3/1127	sPTB <37 w	0.76 (0.37-1.55) p=0.45	
Romero, 2017	IPD MA Dec 2016	Twin pregnancies TVS CL ≤25 mm	I: Vaginal progesterone C: placebo	6/303 (606 fetuses/infants)	PTB <33 w	**0.69*** **(0.51-0.93)** **p=0.01**	Moderate *Fixed model effect Data from Romero 2017 included in our HTA report
Romero, 2018	IPD MA Sept 2017	Singletons TVS CL ≤25 mm	I: Vaginal progesterone C: placebo	5/974 I: 498 C: 476	PTB <33 w	**0.62** **(0.47-0.91)** **p=0.006**	Data from Romero 2018 included in our HTA report
Romero, 2022	IPD MA Nov 2021	Twin pregnancies TVS CL ≤25 mm	I: Vaginal progesterone C: placebo	6/95 (190 fetuses/infants)	PTB <33 w	**0.60*** **(0.38-0.95)** **p=0.03**	Moderate *Fixed model effect Data from Romero 2022 included in our HTA report
Saccone, 2017d	MA Jan 2016	Singletons with history of sPTB	I: Vaginal progesterone C: 17-OHPC	3/680	sPTB <34 w	**0.71 (0.53-0.95)** **p=0.02**	Low

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
Simons, 2021	MA	Singletons and multiples	I: Progesterone C: Placebo/other intervention	7 (based on 5 RCTs)/4222	Long term child development 6-8 years	MA (two studies, n=890 children) no difference in neurodevelopment as assessed by the Bayley-III Cognitive Composite score at 2 years between children exposed to progesterone versus placebo (Standardised Mean Difference 0.04 (-0.26 -0.19), Other long-term outcomes showed no differences.	Data from Simons 2021 included in our HTA report No evidence of benefit or harm in offspring prenatally exposed to progesterone
EPPPIC Group, 2021	IPD MA July 2019 with targeted update 2020 (including the PROLONG trial, Blackwell 2020)	Singleton at risk for preterm birth (previous PTB or short TVS CL) Multifetal pregnancies	I: Progesterone (im, vaginal, oral) C: Placebo	31/11644 (16 185)	PTB <37, <34, <28 w Maternal complications Perinatal death Serious neonatal morbidity	Singletons: PTB <37 w Vaginal progesterone 0.92 (0.84-1.00) 17-OHPC 0.94 (0.78-1.13) < 34 w Vaginal progesterone **0.78 (0.68-0.90)** 17-OHPC 0.83 (0.68-1.01) Multifetal pregnancies: NS for all main outcomes for vaginal progesterone and 17-OHPC	Data from EPPPIC 2021 included in our HTA report. NS for <28 w, maternal complications perinatal death and serious neonatal morbidity. Insufficient evidence for oral progesterone.

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
Alfirevic, 2017	MA June 2016	Singletons at risk	I: Cerclage C: No cerclage	15/3490	1. Perinatal loss: all losses including miscarriages, stillbirth and neonatal deaths. 2. Serious neonatal morbidity. 3. Baby discharged home healthy.	Perinatal loss 0.82 (0.65 to 1.04) p=0.11 Neonatal morbidity 0.80 (0.55 to 1.18) p=0.39 Baby discharged home healthy. 1.02 (0.97 to 1.06) p=0.49	1. Moderate 2. Low 3. Moderate Data from Alfirevic 2017 included in our HTA report
Berghella, 2017b	MA Febr 2017	Singletons with TVS CL <25mm, no prior sPTB	I: Cerclage C: No cerclage	5/419	PTB <35 weeks	0.88 (0.63-1.23) p=0.46	Low
Li, 2019	MA July 2018	Twin pregnancies	I: Cerclage C: No cerclage	16/1211 (RCTs and cohort studies included) Ultrasound indicated 3 RCTs/49	PTB 37, 34, 32, <28 w	<37 w 1.18 (0.91-1.53) p=0.2 <34 w 2.42 (1.12-5.21) p=0.02 <32 w 2.48 (0.96-6.37) p=0.06 < 28 w 2.62 (0.72-9.51) p=0.14	Effect in twins with TVS CL <15 mm
Conde-Agudelo 2020	MA October 2019	Singletons with TVS CL ≤25 mm Unselected twin pregnancies Twin pregnancies with TVS CL <38 mm Twin pregnancies with ≤25 mm	I1: Pessary C1: No pessary or I2: Pessary C2: Progesterone	12 /4687 (7167 offspring)	sPTB <34 w	1. Singletons 0.80 (0.43-1.49) p=0.48 2. Unselected twins 1.05 (0.79-1.41) p=0.72 3. Twins with TVS CL <38 mm 0.75 (0.41-1.36) p=0.34 4.Twins with TVS CL ≤25 mm 0.72 (0.25-2.06) p=0.54 I2: No significant differences for sPTB in any group	1. Low 2. Moderate 3. Low 4. Low

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
Correa, 2019	MA Between 2010 and 2018	Singletons Inclusion criteria not stated	I: Pessary C: No pessary or I: Pessary with progesterone C: progesterone	5 /1856	PTB <37, <34 w	<37 w 0.63 (0.38-1.06) p=0.08 <34 w 0.74 (0.35-1.57) p=0.43	
Jin, 2017	MA Nov 2016	Singletons with TVS CL ≤25 mm	I: Pessary C: No pessary	3 /1412	sPTB <34 w	0.71 (0.21-2.43) p=0.59	
Jin, 2019	MA Dec 2016	Singletons and twins combined, results also presented separately for singletons and twins. Most studies with TVS CL <25 mm	I: Pessary C: No pessary	7/3679 (RCTs and cohort studies included)	PTB <37, 34, 32, 28 w	<28 w 0.78 (0.46-1.31) p=0.34 <32 w 0.92 (0.67-1.28) p=0.50 <34 w 0.74 (0.49-1.13) p=0.17 <37 w 0.79 (0.54-1.15) p=0.17	28 w: Low 32 w: High 34 w: Moderate 37 w: Moderate
Perez-Lopez, 2019	MA July 2018	Singletons with TVS CL ≤25 mm	I: Pessary C: No pessary	3/1612	sPTB <34 w	0.51 (0.19-1.38) p=0.19	Included RCTs: Goya, Saccone, Nicolaides
Saccone, 2017a	MA February 2016	Twins with TVS CL ≤25	I: Pessary C: No pessary	3/481	sPTB <34 w	0.73 (0.27-2.01) p=0.55	≤25 mm (Goya, Nicolaides), ≤38 mm (Liem)
Saccone, 2017b	MA February 2016	Singletons with TVS CL ≤25 mm	I: Pessary C: No pessary	3/1420	sPTB <34 w	0.72 (0.21-2.49) p=0.55	Included RCTs: Goya, Hui, Nicolaides
Thangatorai, 2018	MA Nov 2016	Multifetal pregnancies with TVS CL <25 mm	I: Pessary C: No pessary	2/348	sPTB <34 w	0.72 (0.25-2.06) p=0.56	

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
Xiong 2020	Updated MA March 2019	Singletons with TVS CL <25 mm and twins with or without short TVS CL	I: Pessary C: No pessary	Singletons 6/1982 Twins 5/511	PTB <34 w	Singletons 0.73 (0.42-1.28) Twins 0.81 (0.49-1.35)	
Zheng, 2019	MA July 2016	Singletons with short TVS CL and twin pregnancies with or without short TVS CL	I: Pessary C: No pessary	11 (6 RCTs, 5 cohort studies) /3911 women	sPTB <34 w	**All** **0.65** **(0.44–0.96)** Singletons 0.71 (0.21-2.42) **Twin pregnancies** **0.65 (0.44-0.96)**	
Care, 2022	NW MA Aug 2021	Singletons at risk overall (previous PTB, short TVS CL, or other factors as defined by authors	I: Progesterone (vaginal, oral, im), cerclage, pessary C: Other intervention or no intervention	61/17 273	PTB < 37, <34, < 28 w, sPTB <34 w, PPROM, maternal infection, PNM, NNM, gestational age, neonatal morbidy	PTB < 34 w* Vaginal progesterone **0.50 (0.34-0.70)** 17-OHPC 0.68 (0.43-1.02) Oral progesterone 0.42 (0.12-1.40) McDonald cerclage 0.66 (0.21-2.03) Shirodkar cerclage **0.06 (0.00-0.84)** Pessary 0.65 (0.39-1.08) Perinatal death* Vaginal progesterone **0.66 (0.44-0.97)** 17-OHPC 0.78 (0.50-1.21) Oral progesterone Insufficient data McDonald cerclage 0.59 (0.33-1.03) Shirodkar cerclage Insufficient data Pessary 0.90 (0.52-1.54)	Several other interventions were also included as bedrest, fish oils, nutritional supplements, antibiotics etc *Reported as OR with 95% credible interval. Only vaginal progesterone clear evidence of benefit, with high quality of evidence for PTB <34 w, moderate for PNM

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
D'Antonio, 2021	NW MA March 2021	Twins	I: Progesterone, cerclage, pessary alone, or any combinations of these C: Placebo or standard care	26/8518 women	PTB <34 w	Vaginal progesterone 1.04 (0.84-1.30) p=0.7 17-OHPC 1.09 (0.74-1.60) p=0.7 Pessary 1.07 (0.82-1.38) p=0.6 No data for cerclage	Conclusions: no effect of progesterone, cerclage or pessary in unselected twin pregnancies or in twin pregnancies with a short cervix
Grabovac, 2019	MA May 2017	Women with previous conisation	I: Progesterone, cerclage or pessary C: No treatment	9/196 (RCTs and cohort studies included)	PTB <34 w (cerclage)	Singletons Cerclage vs no cerclage 2.10 (0.87–5.05)	Very low. No effect in singletons. Very scarce data on twins
Jarde, 2017a	MA July2016	Singletons and multifetal pregnancies	Combinations of treatment Singletons and twins: I1: Pessary + progesterone C1: Pessary alone or progesterone alone I2: Cerclage + progesterone C2: Cerclage alone or progesterone alone	7 (6 on singletons 1 in twins)/1656 (RCTs and cohort studies included)	PTB <37, <34 w Neonatal death	Singletons <34 w I1: Pessary + progesterone vs pessary alone 1.30 (0.70-2.42) or vs progesterone alone 1.16 (0.79-1.72) < 37 w I2: Cerclage + progesterone vs cerclage alone 1.04 (0.56-1.93) or vs progesterone alone 0.82 (0.57-1.19) Pessary + progesterone vs pessary alone 1.04 (0.62-1.74) No data on neonatal death Twins: <34 w Neonatal death No data on PTB < 37 Twins: Pessary + progesterone vs progesterone PTB < 34 w	Scarce information on combinations of treatment

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
						0.54 (0.24-1.21) NND 0.32 (0.17-1.17)	
Jarde, 2017b	NW MA January 2016	Twins	I: Progesterone, cerclage, or pessary alone, or any combinations of these C: Placebo or standard care	23/6626 women	PTB <37, <34 w NND	<37 w Any progesterone 1.01 (0.95–1.08) Vaginal 0.94 (0.83–1.07) im 17-OHPC 1.04 (0.98–1. Cerclage 1.11 (0.75–1.65) Pessary 0.96 (0.86–1.07) <34 w Any progesterone 0.91 (0.70–1.18 Vaginal 0.82 (0.64–1.05) im 17-OHPC 1.18 (0.66–2.12) Cerclage 1.21 (0.34–4.31) Pessary 0.71 (0.29–1.71) NND Progesterone 1.16 (0.76–1.79) Vaginal 1.38 (0.78–2.45) im 17-OHPC 1.03 (0.51–2.11) Cerclage 5.57 (0.44–70.55) Pessary 0.89 (0.57–1.38)	Vaginal progesterone improved some secondary neonatal outcomes
Jarde, 2019	NW MA	Singletons	I: Progesterone (vaginal, oral, im),	40/11 311	PTB <37, <34 w	At risk overall: Vaginal progesterone	Vaginal progesterone the

Author, year of publication	Design/Search date	Inclusion criteria	Intervention/control	Number of trials/women (offspring)	Primary outcome	Results RR (95% CI)	Comments/ Quality of evidence (according to author)
		at risk overall (previous PTB, short TVS CL, or other factors as defined by authors	cerclage, pessary C: Other intervention or no intervention		sPTB <37 w, <34 w	PTB<37 w 0.51 (0.34-0.74)* PTB<34 w 0.43 (0.21-0.78)* Previous PTB: Vaginal progesterone PTB <37 w 0.51 (0.34-0.74)* PTB <34 w 0.43 (0.21-0.78)* 17-OHPC** PTB <37 w 0.53 (0.27-0.95)* TVS CL ≤25 mm PTB <34 w Vaginal progesterone** 0.45 (0.24-0.84)*	only intervention with consistent evidence for preventing PTB in singletons at risk overall and in those with a previous PTB *OR (95% Credibility intervals) ** Moderate, the other low-very low

17-OHPC; 17a-hydroxyprogesterone caproate, BPD; bronchopulmonary dysplasia, CL; cervical length, FFN; fetal fibronectin, im; intramuscular, IPD; individual patient data, MA; meta-analysis, NND; neonatal death, NW; network, OR; odds ratio, PNM; perinatal mortality, PPROM, preterm prelabour rupture of the membranes, PTB, preterm birth, RR; relative risk, sPTB; spontaneous preterm birth, TVS; transvaginal scan

Appendix 6. Ongoing research identified from a search (2021-12-05) in Clinicaltrials.gov and WHO ICTRP database and an updated search in Clinicaltrials.gov (2022-04-13) and relevant to the PICO of this report.

Registration/ Country/ Author/ Acronym	Registration date/Estimated completion date/ Recruitment status	Study design/ Inclusion criteria	Study groups	Estimated patients	Outcomes
Singletons (n=9)					
NCT03428685 Hongkong PI Cheung SINPRO study Published protocol in Trials 2020	Jan 2019 Estimated completion date Jan 2023. Recruiting.	RCT Singletons	I: Early (from 12 w-14 w) oral progesterone 10 mg x 3/d C: Placebo Both groups: Universal screening with TVS CL 18-24 w and progesterone if short cervix (<25 mm)	1714	PO PTB <37 w
NCT02746900 NCT03251729 USA and Italy PI Berghella/Saccone) COLORS Cerclage on low risk singletons	Sept 2017. Estimated completion date Dec 2025. Recruiting.	RCT Singletons with TVS CL ≤25 mm and no previous sPTB	I: Cerclage + vaginal progesterone, 90 mg gel or 200 mg supp/d C: vaginal progesterone, 90 mg gel or 200 mg supp/d	206	PO PTB <35 w
ChiCTR2000033510 China PI Xiang	Jan 2021. Estimated completion date Dec 2023.	RCT Singletons with previous history of single midtrimester loss	I: Cerclage C: No cerclage	433	PO PTB <34 w
NCT04147117 Spain PI Martinez	Oct 2017. Estimated completion date Dec 2020. Still recruiting.	RCT Singletons with previous history of sPTB, late miscarriage, or cervical surgery	I: Pessary C: No pessary	214	PO sPTB <37 w
NCT03418012 Australia, Germany, Greece, Spain PI Kyvernitakis/BW Mol	Sept 2020. Estimated completion date Oct 2024. Recruitment not started	RCT Singletons with previous history of sPTB <34 w or cervical surgery	I: Early pessary (12-16 w) C: No pessary	310	PO Neurodevelopment at 3 years
NCT02901626 USA PI Clifton TOPS	Febr 2017. Estimated completion date May 2022. Recruitment not started.	RCT Singletons with TVS CL ≤20 mm	I: Pessary C: No pessary (with progesterone in both groups if standard care)	544	PO Delivery <37 w or fetal demise

Registration/ Country/ Author/ Acronym	Registration date/Estimated completion date/ Recruitment status	Study design/ Inclusion criteria	Study groups	Estimated patients	Outcomes
NCT04300322 Vietnam PI Dang	March 2020. Estimated completion date Dec 2022 Recruiting.	RCT Singletons with TVS CL ≤25 mm	I: Pessary C: 200 mg vaginal progesterone/d	804	PO PTB <37 w
NCT02405455 Spain PI Goya CEPEIC Cerclage or Cervical Pessary in women with Cervical Insufficiency	June 2015. Completed. March 2021 Not in PubMed April 2022	RCT Singletons with previous PTB based on cervical insufficiency (<16 w) (primary intervention), or a previous PTB and a short cx (<24 w) (secondary intervention)	I: Pessary C: Cerclage	60	PO sPTB <34 w
NCT05319834 Egypt PI Maher	April 2022. Not started recruiting yet.	RCT Singletons with previous PTB	I: Vaginal progesterone 200 mg x2/d + 100 mg ASA/d C: Vaginal progesterone 200 mg x2/d	254	PO PTB <34 w
Multifetal pregnancies (n=5)					
NCT02328989 France PESSARONE PI Vayssière	Completed. Published AJOG Febr 2022	RCT Twins with TVS CL <35 mm	I: Pessary C: No pessary	315	PO Composite adverse neonatal outcome NS between groups
NCT02518594 USA PI Clifton PROSPECT A Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation With a Short Cervix	Aug 2015. Estimated completion date Febr 2025. Recruiting.	RCT Twins with TVS CL <30 mm	I1: 200 mg vaginal progesterone/d I:2 Arabin pessary C: Placebo (identical with progesterone)	630	PO PTB <35 w or fetal loss
NCT03863613 Vietnam PI Dang PCP-twins	March 2019. Estimated completion date Dec 2022. Recruiting	RCT Twins with TVS CL ≤28 mm Two by two factorial RCT 1:1:1:1	I:1 Cerclage I:2 Pessary I:3 Cerclage + 400 mg vaginal progesterone/d I:4 Pessary+ 400 mg vaginal progesterone/d	340	PO PTB <34 w

Appendix 6. Ongoing research

Registration/ Country/ Author/ Acronym	Registration date/Estimated completion date/ Recruitment status	Study design/ Inclusion criteria	Study groups	Estimated patients	Outcomes
NCT03340688 USA, Italy, Spain, Egypt PI Roman TWIN-UIC	June 2017. Estimated completion date June 2025. Recruiting.	RCT Twins (DA) with TVS CL ≤15 mm	I: Cerclage + 400 mg vaginal progesterone/d C: 400 mg vaginal progesterone/d	200	PO PTB <34 w
NCT04342585 Malaysia PI Latif	April 2020. Last update March 2022 Study start Jan 2023 Not yet recruiting	RCT Twins with TVS CL ≤30 mm	I: Pessary C: 200 mg vaginal progesterone/d	310	PO sPTB <37 w
Trials with passed completion date, status not verified in more than two years and not found in PubMed, Apr 1 2022 (n=11)					
Singletons (n=7)					
NCT01180296 USA PI McKenna	Aug 2010. Completed Febr 2019.	RCT Singletons with prior sPTB	I: 400 mg oral progesterone/d C: placebo	36	sPTB <37 v Maternal serum progesterone levels
NCT02571296 Egypt PI Abdel-Aziz	Oct 2015. Estimated completion date June 2016. Unknown status.	RCT Singletons with previous sPTB	I: 100 mg oral progesterone x2/d C: Placebo	212	PO PTB <37 w
ISRCTN11186205 UK PI Cornforth	No longer recruiting. Completed in March 2016.	RCT Singletons with history of PTB and TVS CL <3rd centile or history of cervical surgery	I1: MacDonald cerclage I2: Arabin pessary I3: progesterone	NA	Feasibility study, before a planned large scale trial planned
ISRCTN13364447 UK PI/Hezelgrave/Shennan (SuPPoRT) Protocol published BMC Pregnancy and Childbirth 2016	No longer recruiting. Completed without results, published according to ISRCTN? Date assigned 2015, no more data in register.	RCT Singletons with TVS CL <25 mm	I1: Cerclage I2: Pessary I3: 200 mg vaginal progesteron/d	510	PTB <37 w
ISRCTN18185477 China PI Hui	Completed 2012, published according to ISRCTN? Date assigned 2012, no more data in register.	RCT Singletons with TVS CL <25 mm	I: Pessary C: No pessary	4000	PO sPTB <34 w
NTR4415 PC study The Netherlands PI Koullali Protocol published BMC Pregnancy and Childbirth 2017	2014 Completed 2018?	RCT Singletons with TVS CL ≤25 mm and a history of PTB <34 w	I: Pessary C: Cerclage	440	PO PTB <32 w

Appendix 6. Ongoing research

Registration/ Country/ Author/ Acronym	Registration date/Estimated completion date/ Recruitment status	Study design/ Inclusion criteria	Study groups	Estimated patients	Outcomes
NCT02746900 USA PI Saccone	Apr 2016. Estimated completion date Apr 2019. Unknown status.	RCT Singletons with TVS CL ≤25 mm and no previous PTB	I: McDonald cerclage C: No cerclage	587	PO sPTB <35 w
Multifetal pregnancies (n=3)					
NCT03058536 Brazil PRECEPT PI Burlacchini de Carvalho	Started in Febr 2017. Estimated to be completed 2019. Unknown status.	RCT Twins with TVS CL ≤30 mm at 16+0-22+0 w or ≤25 mm at 22+1-24+0 w or ≤20 mm at 24+0-27+6 w)	I1: 400 mg vaginal progesterone/d +pessary I2: 400 mg vaginal progesterone/d I3: Pessary C: no intervention	312	PO sPTB < 34 w
NCT02697331 Egypt PI Abdelhafeez	March 2016. Completed in Sept 2018.	RCT Twins (DCDA) with TVS CL 10-25 mm	I: 200 mg vaginal progesterone pessary x 2/d C: Placebo	144	PO PTB <37 w
NCT01927029 Chile PI Yamamoto	Aug 2013. Estimated completion date Dec 2014. Unknown status.	RCT Twins (DC or MC)	I: 180 mg vaginal progesterone C: Placebo	213	PO PTB <34 w
Singletons and twins (n=1)					
NTR4414 The Netherlands PI Van Zilj Email: quadruplep@studies-obsgyn.nl Also in EUCTR2013-002884-24-NL, there classified as ongoing Protocol published	Jan 2014. Estimated completion date June 2018.	RCT Singletons and twins with TVS CL ≤35 and ≤38 mm, respectively	I: 200 mg vaginal progesterone/d C: Pessary	1020	PO Composite adverse neonatal outcome (mortality and morbidity)

AJOG; American Journal of Obstetrics and Gynecology, ASA; acetylsalicylic acid, C; control, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, I; intervention, MC; monochorionic, PI; principal investigator, PO; primary outcome, PTB; preterm birth, RCT; randomised controlled trial, sPTB; spontaneous preterm birth, TVS; transvaginal

Appendix 6. Ongoing research

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