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Cervical length screening followed by progesterone with or without additional treatment for short cervix to prevent preterm birth

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[Screening av cervixlängd och behandling med progesteron med eller utan tilläggsbehandling vid kort cervix för att förebygga förtidsbörd]

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1 Abstract

Background: Preterm birth (PTB) is the leading cause of perinatal mortality and is associated with physical and mental impairments that may be lifelong. Prevention of PTB is therefore a high priority. Measurement of cervical length by vaginal ultrasound during the second trimester of pregnancy can be used for risk stratification since short cervical length is associated with an increased risk for PTB. Treatment with vaginal progesterone can reduce the risk for PTB and is a logical choice of treatment of asymptomatic women identified with short cervical length in a screening situation due to low invasiveness, high tolerability, low cost and evidence for efficacy. However, it is unclear if universal screening of pregnant women for short cervical length and subsequent treatment with vaginal progesterone, with or without additional treatment, is effective to prevent PTB.

Question at issue: Is universal cervical length screening during the second trimester using vaginal ultrasound in women with singleton pregnancies, followed by vaginal or oral progesterone, with or without additional treatment, when short cervix length is demonstrated, effective in preventing any or spontaneous PTB and does it affect perinatal outcomes?

Methods: Systematic literature searches were conducted in Medline, Embase, and the Cochrane Library. Titles, abstracts, and subsequently full text articles were independently screened by at least two authors. Final inclusion was decided in consensus amongst all authors. Included studies were critically appraised using checklists. The results of each study were summarised per outcome and, when possible, data were pooled in meta-analyses. The certainty of evidence was assessed using the GRADE approach.

Results: Two RCTs and four retrospective cohort studies with a total of 1,634 and 425,735 individuals, respectively, were included. The main problems in the two RCTs were imprecision due to low statistical power. In addition, one of the RCTs had problems with directness due to an unclear selection process and the study being performed in a health care setting that is substantially different from Sweden (India). Three cohort studies compared rates of PTB and perinatal outcomes before and after introduction of a screening program either in a geographical area or in a defined group of hospitals. One cohort study used a propensity score matched comparison of one institution that introduced screening with another that continued without screening. The high number of participants was a major strength of the cohort studies. Risk of bias, related to non-randomised study design and use of historical controls, was the most important reason for reducing the level of certainty of evidence.

Meta-analyses of the RCTs did not show any statistically significant association between cervical length screening and the rate of any or spontaneous PTB at any studied cut-off for gestational length.

Meta-analyses of cohort studies showed a significant reduction of the risk for any and spontaneous PTB at <37 weeks; any PTB adjusted odds ratio 0.87 (95% confidence interval (CI) 0.78 to 0.98) and spontaneous PTB risk ratio (RR) 0.82 (95% CI 0.70 to 0.96), at <34 weeks; any PTB RR 0.85 (95% CI 0.74 to 0.97) and spontaneous PTB RR 0.77 (95% CI 0.66 to 0.90), and at <32 weeks; any PTB RR 0.84 (95% CI 0.74 to 0.99) and spontaneous PTB RR 0.68 (95% CI 0.49 to 0.95), but no statistically significant associations for any or spontaneous PTB at <30, <28 or <24 weeks.

For perinatal mortality and morbidity, information was available in the RCTs only. No association between cervical length screening and perinatal mortality or morbidity was observed.

Ethical aspects: Due to low precision and very low certainty of evidence, it was not possible to establish the risk-benefit ratio of screening with transvaginal ultrasound and treatment with progesterone for women with short cervix. The potential benefit of screening lies in the possibility to prevent neonatal morbidity and mortality through prevention of preterm birth. However, our analysis shows that it is not possible to definitively establish that screening has this effect. Examination with vaginal ultrasound is not associated with serious risks for the mother or the foetus and treatment with progesterone has a low risk of side effects. On an organizational level, screening would require substantial economic and personnel resources with a subsequent risk for displacement of other needs within healthcare.

Economic aspects: In Region Västra Götaland, with about 17,000 births per year, the costs of a universal screening program with measurement of cervical length with transvaginal ultrasound, followed by progesterone with or without additional treatment, for women with short cervix, with singleton pregnancies, were estimated to 13.7 million SEK per year. This estimate includes costs for implementation spread over a ten-year period. Calculation of the costs for one prevented PTB was not possible since no clear benefit of cervical screening could be defined.

Conclusion: Based on very low certainty of evidence, it is uncertain whether universal cervical length screening with vaginal ultrasound, followed by progesterone, with or without additional treatment, for women with short cervix and a singleton pregnancy, reduces the rate of any or spontaneous PTB, or affect perinatal outcomes, compared with no screening (GRADE ⊕OOO). This conclusion is based on the absence of significant findings in severely underpowered RCTs. Although, meta-analyses of cohort studies showed statistically significant associations between cervical length screening, followed by treatment, to women with short cervix, and reduction of spontaneous PTB rates at <37, <34 and <32 weeks, this did not change the general conclusion due to concerns related to directness and risk of bias in these studies.

2 Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Frågeställning: I denna rapport utvärderades om förlossning som äger rum innan den 37:e graviditetsveckan (förtidsbörd), samt dödlighet och sjuklighet i nyföddhetsperioden kan förebyggas genom allmän screening av gravida kvinnor med enkelbörd med vaginalt ultraljud och mätning av livmoderhalsens längd i andra tredjedelen av graviditeten följt av läkemedelsbehandling med progesteron, med eller utan tilläggsbehandling, vid fynd av kort livmoderhals.

Bakgrund: Förtidsbörd är den främsta orsaken till att barn dör i nyföddhetsperioden och för ökad risk för fysisk- och/eller mental funktionsnedsättning hos barnet. Mätning av livmoderhalsens längd med vaginalt ultraljud kan identifiera kvinnor med kort livmoderhals som ger ökad risk för förtidsbörd, och det finns vetenskapligt stöd för att vaginal progesteronbehandling kan minska risken för förtidsbörd hos kvinnor med enkelbörd och kort livmoderhals. Det är dock oklart om allmän screening med vaginalt ultraljud och efterföljande behandling med vaginalt progesteron när kort livmoderhals påvisats, är effektivt för att förebygga förtidsbörd hos gravida kvinnor utan symptom eller kända riskfaktorer för förtidsbörd.

Metod: Vetenskapliga studier om frågeställningen identifierades genom en systematisk litteratursökning. De enskilda studierna kvalitetsgranskades och resultatens tillförlitlighet bedömdes sammantaget.

Resultat: Totalt sex studier identifierades, två med den design som är bäst lämpad för att besvara frågeställningen (randomiserade kontrollerade studier) och fyra med en design som ger resultat med något lägre tillförlitlighet (kohortstudier). Sammantagen analys av de randomiserade kontrollerade studierna kunde inte påvisa att screening med vaginalt ultraljud och medicinering med progesteron till gravida kvinnor med kort livmoderhals gav någon positiv effekt på förtidsbörd, dödlighet eller sjuklighet i nyföddhetsperioden. Antalet patienter i dessa studier var dock mycket litet, vilket innebär att en klinisk relevant effekt inte kan uteslutas. Sammantagen analys av kohortstudierna visade en minskning av förekomsten av förtidsbörd i områden där screening tillämpades jämfört med områden utan screening eller inom områden där frekvensen förtidsbörd jämfördes före och efter införande av allmän screening. Det är dock inte uteslutet att andra faktorer som också påverkar risken för förtidsbörd kan ha skiljt sig mellan de områden som undersökts, varför det inte är möjligt att säkert fastslå att det var screeningen och behandling med progesteron som ledde till den minskade förekomsten av förtidsbörd i dessa studier.

Etiska aspekter: Det vetenskapliga underlaget är mycket osäkert för bedömning avseende risk-nyttabalans av ett eventuellt införande av screening av gravida med vaginalt ultraljud för kort livmoderhals och behandling med progesteron i syfte att förebygga förtidsbörd. Potentiell nytta med screening för individ och samhälle består i att risk för död och sjuklighet i nyföddhetsperioden skulle kunna förebyggas om screening leder till minskad förekomst av förtidsbörd. Vår analys visar dock att det inte går att fastställa att screening har denna effekt. Undersökning med vaginalt ultraljud är inte förknippat med några betydande risker för vare sig mor eller barn och behandling med progesteron har låg risk för biverkningar. Allmän screening skulle dock ta stora

ekonomiska och personella resurser i anspråk med risk för undanträngning av andra behov inom sjukvården.

Kostnader: I Västra Götaland sker cirka 17 000 förlossningar per år. Kostnaden för att implementera ett allmänt screeningsprogram i Västra Götaland där livmoderhalsens längd mäts med vaginalt ultraljud på alla gravida kvinnor med enkelbörd och behandling ges till dem med kort livmoderhals uppskattades till 13,7 miljoner kronor per år. Mot bakgrund av att effekten av screeningen är osäker var det inte möjligt att beräkna kostnad för att förebygga enstaka fall av förtidsbörd.

Slutsats: Den samlade slutsatsen i denna HTA-rapport är att det är osäkert om allmän screening med vaginalt ultraljud, följt av förebyggande läkemedelsbehandling med progesteron, med eller utan tilläggsbehandling, till kvinnor med kort livmoderhals och enkelbörd, minskar förekomsten av förtidsbörd och risken för dödlighet och sjuklighet i nyföddhetsperioden.

The above summaries were written by representatives from HTA-centrum. The HTA report was approved by the regional board for quality assurance of activity-based HTA.

Ylva Carlsson
Head of HTA-centrum of Region Västra Götaland, Sweden, 2025-06-02

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MD Medical doctor
PhD Doctor of Philosophy
RN Registered Nurse
RNRM Registered Nurse Registered Midwifery

3 Summary of findings

Outcomes	Number of studies RCT and cohort studies Number of patients	Relative effect RR (95% CI)	Absolute effect %	Certainty of evidence* Grade
Any PTB <37 weeks	1 RCT n=1,257 2 cohort n=400,810	0.86 (0.59-1.25), n.s. 0.96 (0.93-0.98) p value 0.0005 AOR 0.87 (0.78-0.98) p=0.017	7.5 vs 8.7 5.6 vs 6.0	Very low (GRADE ⊕OOO)[1]
Any PTB <34 weeks	1 RCT n=1,257 1 cohort n=64,207	0.97 (0.46-2.01), n.s. 0.85 (0.74-0.97) p=0.01	2.2 vs 2.3 1.7 vs 2.0	Very low (GRADE ⊕OOO)[2]
Any PTB <32 weeks	1 RCT n=1,257 1 cohort n=64,207	0.87 (0.36-2.13), n.s. 0.84 (0.70-0.99) p=0.04	1.4 vs 1.6 1.0 vs 1.1	Very low (GRADE ⊕OOO)[2]
Any PTB <30 weeks	1 RCT n=1,257	0.83 (0.28-2.45), n.s.	0.9 vs 1.1	Very low (GRADE ⊕OOO)[2]
Any PTB <28 weeks	1 RCT n=1,257	0.58 (0.14-2.42), n.s.	0.5 vs 0.8	Very low (GRADE ⊕OOO)[2]
Any PTB <24 weeks	1 RCT n=1,257	0.19 (0.01-4.02), n.s.	0.0 vs 0.3	Very low (GRADE ⊕OOO)[2]
Spontaneous PTB <37 weeks	2 RCT n=1,553 3 cohort n=401,703	0.98 (0.67-1.42), n.s. 0.82 (0.70-0.96) p=0.02	6.5 vs 6.7 2.0 vs 2.6	Very low (GRADE ⊕OOO)[1]

Spontaneous PTB <35 weeks	1 cohort n=893	0.63 (0.46-0.85) p=0.003	12.2 vs 19.5	Very low (GRADE ⊕OOO)[3]
Spontaneous PTB <34 weeks	1 RCT n= 1,257 2 cohort n=65,100	0.73 (0.31-1.71), n.s. 0.77 (0.66-0.90) p=0.001	1.4 vs 1.9 1.2 vs 1.4	Very low (GRADE ⊕OOO)[1]
Spontaneous PTB <32 weeks	2 RCT n=1,553 3 cohort n=71,306	0.87 (0.34-2.23), n.s. 0.68 (0.49-0.95) p=0.03	1.0 vs 1.2 0.6 vs 0.7	Very low (GRADE ⊕OOO)[1]
Spontaneous PTB <30 weeks	1 RCT n= 1,257	0.77 (0.21-2.87), n.s.	0.6 vs 0.8	Very low (GRADE ⊕OOO)[2]
Spontaneous PTB <28 weeks	1 RCT n= 1,257 1 cohort n=893	0.64 (0.11-3.85), n.s. 1.13 (0.25-5.03), n.s.	0.3 vs 0.5 0.8 vs 0.7	Very low (GRADE ⊕OOO)[4]
Spontaneous PTB <24 weeks	1 RCT n=1,257 1 cohort n=6,206	0.32 (0.01-7.90), n.s. 0.14 (0.01-2.16), n.s.	0.0 vs 0.2 0.0 vs 0.1	Very low (GRADE ⊕OOO)[5]
Spontaneous PTB 32-37 weeks	1 RCT n=296	1.20 (0.55-2.59), n.s.	8.8 vs 7.4	Very low (GRADE ⊕OOO)[1]
Perinatal mortality*	2 RCT n=1,553	0.56 (0.17-1.84), n.s.	0.5 vs 0.9	Very low (GRADE ⊕OOO)[1]
Composite neonatal morbidity**	2 RCT n=1,553	0.94 (0.62-1.43), n.s.	5.1 vs 5.5	Very low (GRADE ⊕OOO)[1]
Respiratory distress syndrome	2 RCT n=1,553	0.74 (0.39-1.41), n.s.	2.0 vs 2.7	Very low (GRADE ⊕OOO)[1]

Intraventricular haemorrhage	2 RCT n=1,553	0.51 (0.10-2.52), n.s.	0.3 vs 0.5	Very low (GRADE ⊕OOO)[6]

AOR: adjusted odds ratio, C: comparison, I: intervention, n: number, PTB: preterm birth, RCT: randomised controlled trial, RR: relative risk

*__Perinatal mortality__: intrauterine foetal death and neonatal mortality <7 or <28 days

**__Neonatal morbidity__: A composite outcome of neonatal morbidity (at least one of bronchopulmonary dysplasia, severe intraventricular haemorrhage, necrotising enterocolitis, confirmed sepsis, retinopathy of prematurity) with or without perinatal mortality.

[1] Downgraded one level for some study limitations, some inconsistency and some indirectness, two levels for very serious imprecision

[2] Downgraded one level for some study limitations and some inconsistency, two levels for very serious imprecision

[3] Downgraded one level for serious study limitations, one level for serious indirectness, one level for serious imprecision

[4] Downgraded one level for serious study limitations and serious indirectness, two levels for very serious imprecision

[5] Downgraded one level for serious study limitations, two levels for very serious imprecision

[6] Downgraded one level for some study limitations and some indirectness, two levels for very serious imprecision

* **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 ⊕⊕⊕O	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 to the estimate of the effect
Low certainty ⊕⊕OO	Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low certainty ⊕OOO	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

4 Abbreviations

ACOG	American College of Obstetricians and Gynaecologists
ADHD	Attention deficit hyperactivity disorder
AOR	Adjusted odds ratio
ART	Assisted reproductive technology
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CP	Cerebral palsy
FIGO	The International Federation of Gynaecology and Obstetrics
HTA	Health technology assessment
ICTRP	International Clinical Trials Registry Platform
ISUOG	International Society of Ultrasound in Obstetrics and Gynaecology
IVH	Intraventricular haemorrhage
MBR	Swedish Medical Birth Register
mm	Millimetre
NICE	National Institute for Health and Care Excellence
PROSPERO	The international prospective register of systematic reviews
PTB	Preterm birth
RANZCOG	The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RDS	Respiratory distress syndrome
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SBU	Statens beredning för medicinsk och social utvärdering
SEK	Swedish krona
SFOG	Svensk Förening för Obstetrik och Gynekologi
SoF	Summary of findings
sPTB	Spontaneous preterm birth
SNQ	Swedish Neonatal Quality Register
SR	Systematic review
USD	United States dollars
VGR	Region Västra Götaland
WHO	World Health Organization

5 Background

Disease/disorder of interest and its degree of severity

Preterm birth (PTB) complications are the leading causes of death among children under the age of five (Perin et al. 2022). An estimated 13.4 million babies were born preterm (before a gestational age of 37+0 weeks) in the world in 2020 (Ohuma et al. 2023). This corresponds to 10% of all newborns ranging from 4-16%, with the highest numbers in southern Asia and sub-Saharan Africa. The corresponding number for Sweden in 2023 was 5.6% of all newborns (National Medical Birth Register, MBR). The global PTB rate is not declining. Programs aiming to reduce the incidence of PTB has the potential to save millions of children globally every year from early death or lifelong disability, under the assumption that interventions that prevent PTB also prevent PTB-related morbidity and mortality (World Health Organisation [WHO] 2023). The risk of death or illness is increased for children born preterm compared to those born at term, with each week of shortened pregnancy further raising the risk. There are subgroups of PTB based on gestational age; extremely preterm (less than 28+0 weeks), very preterm (28+0 to 31+6 weeks) and moderate to late preterm (32+0 to 36+6 weeks) (WHO 2012). According to Swedish register data, most PTBs occur after 32+0 weeks (78.5%). Of all PTBs, 16% occur before 32+0 weeks and 5.5% before 28+0 weeks (Swedish Neonatal Quality Register [SNQ] 2023).

Today, the majority of children born preterm in Sweden survive the neonatal period (first 28 days). The survival rate for preterm neonates in Sweden is 99.6 % between 32+0 and 36+0 and 96.9% between 28+0 and 31+0. Survival rate decreases by gestational week; in extreme preterm birth (defined as birth <28 weeks gestation) the survival rate is 90% between 25+0 and 27+0 weeks, 71% in week 24, 66% in week 23, and 45% in week 22 (SNQ). As many as 45% of preterm neonates experience complications during the neonatal period, of which 7.9% is major morbidity including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), severe intraventricular haemorrhage (IVH), necrotizing enterocolitis, confirmed sepsis, and retinopathy of prematurity (ROP) (Mitha et al. 2021; Manuck et al. 2016). This increased burden of disease in earlier weeks persists into childhood, when a majority of children born preterm are diagnosed with conditions leading to permanent disabilities. The risk of moderate or severe neurological disability is approximately 60% for those born at 22+0 to 23+6 weeks decreasing to 25% at 26+0 to 26+6 weeks (Serenius et al. 2016). The children born 32+0 to 36+6 weeks also suffer from increased risk of delays in neurological development compared to children born at term and this difference persists into school-age (Mitha et al. 2024, Cheong et al. 2024).

PTB is classified as either spontaneous or induced. The majority of PTBs are spontaneous, starting with either contractions or preterm prelabour rupture of membranes. Spontaneous PTB is associated with inflammatory and infectious processes, as well as cervical shortening, but full insight into its underlying mechanisms remain poorly understood (Romero et al. 2014; Jacobsson et al. 2019). Approximately one third of all cases are medically induced due to maternal or foetal complications, such as preeclampsia or foetal growth restriction (Goldenberg et al. 2008). Induced PTB can be reduced by a restrictive approach to early birth and/or prevention of preeclampsia and

other conditions necessitating early birth (Valencia et. al. 2022). There are several risk factors associated with spontaneous PTB that can be assessed through the patient history and a basic physical examination; previous spontaneous PTB shows the strongest correlation to PTB. However, 50% of women giving birth preterm have no retrospectively identifiable risk factor (Goldenberg et al. 2008) and 28% of preterm neonates are firstborn by mothers without known risk factors (Ferrero et al. 2016). This demonstrates a need for additional methods and refined models to identify women at risk of PTB (Meertens et al. 2018). Transvaginal cervical ultrasound during mid-trimester can be used to detect short cervical length and this finding has been demonstrated to be associated with an increased risk of spontaneous PTB (Campbell, 2018; Iams et al. 1996; Kuusela et al. 2021).

Finding individuals at risk of PTB is important since treatments that may prevent PTB exist. Most national and international organisations for obstetrics and gynaecology today recommend treatment with vaginal progesterone to women at risk (Ramachandran et.al, 2024). This treatment is reserved for women pregnant with singletons without symptoms of labour (contractions, bleeding or preterm prelabour rupture of membranes as described above).

Prevalence and incidence

In Region Västra Götaland during 2023, 5.4% of all live newborns (singletons and multiples) were born preterm (before 37+0 weeks); 0.9% were born before 32+0 weeks (161 neonates) and 4.5% between 32+0 and 36+6 weeks (772 neonates). The corresponding percentage of preterm births in Sweden the same year was 5.6%; 1% were born before 32+0 weeks (954 neonates) and 4.6% between 32+0 and 36+6 weeks (4568 neonates). In total, 4.3% of live singletons births (4196 neonates) and 44.3% of live multifoetal births (1151 neonates) were born preterm (MBR).

Present treatment

Currently, universal screening with transvaginal ultrasound of asymptomatic women without a history of spontaneous PTB or late miscarriage is not performed in Sweden. Transvaginal ultrasound can be performed on clinical indication during pregnancy and treatment with vaginal progesterone is offered if cervix length is ≤25 mm. Cerclage; a temporary closure of the cervix with a suture, is an alternative in high-risk patients with more than three late miscarriages or PTBs (Jacobsson et al. 2023). During 2023, 0.3% of women with a singleton pregnancy in Region Västra Götaland redeemed prescribed vaginal progesterone after 18 weeks.

Present recommendations from medical societies or health authorities

Most national organisations recommend screening for short cervix of high-risk groups. SFOG (Svensk Förening för Obstetrik och Gynekologi) published the first national guideline for prevention of PTB in 2023. This guideline states that women with singleton pregnancies and a history of spontaneous PTB or spontaneous late miscarriage can be

offered a transvaginal ultrasound to measure cervical length at 16+0 to 23+6 weeks. If the cervical length is ≤25 mm, treatment with vaginal progesterone is recommended until 34+0 weeks (Jacobsson et al. 2023). This is consistent with guidelines from the American College of Obstetricians and Gynaecologists (ACOG 2021, updated 2023) and the National Institute for Health and Care Excellence (NICE 2015, updated 2022). Other international organisations recommend vaginal progesterone to women with a singleton pregnancy and a prior PTB or a short cervix (<25 mm) on transvaginal ultrasound (Shennan 2021; Royal Australian and New Zealand College of Obstetricians and Gynaecologists [RANZCOG] 2017, updated 2023). There are some international and national organisations in obstetrics and gynaecology that recommend universal screening. ISUOG (The International Society of Ultrasound in Obstetrics and Gynaecology) recommend screening of asymptomatic low risk singleton pregnancies with transvaginal ultrasound as part of the second trimester (typically between 18+0 and 22+0 weeks) anatomy scan (ISUOG 2022). In Australia, screening is implemented according to this recommendation.

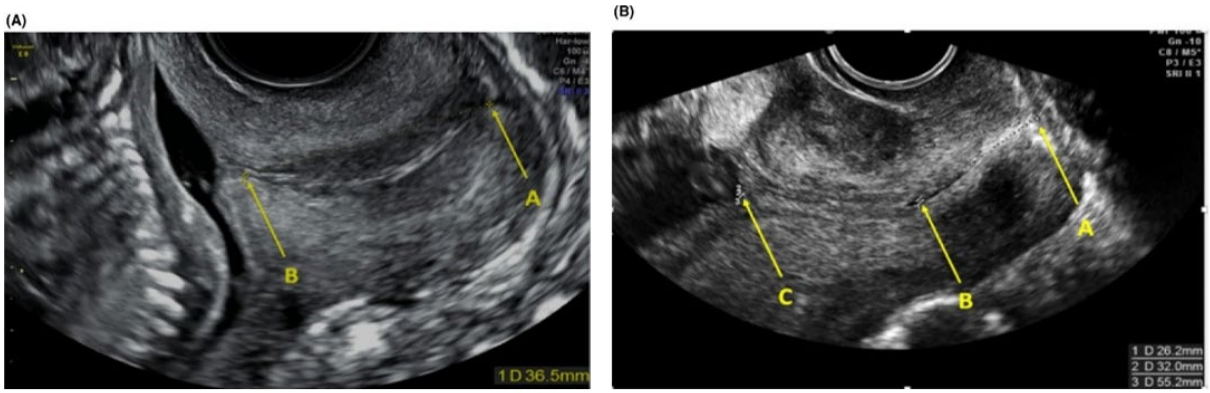
6 Health Technology at issue: Transvaginal ultrasound for cervical length measurement and progesterone with or without additional treatment to prevent PTB in women with short cervix

Transvaginal ultrasound measurement of the cervix

Cervical measurement via transvaginal ultrasound has been utilised since the 1990s to evaluate the risk of PTB (Campbell, 2013). The procedure follows the criteria established by Iams (1996), Heath (1998) and Kagan (2015). There are several organisations that certify examiners, one of them is the Fetal Medicine Foundation (FMF). During a cervical length examination, the patient is lying in a lithotomy position in a gynaecological chair and a transvaginal ultrasound probe is inserted onto the anterior fornix to get a sagittal view of the cervix (Figure 1). The distance between the internal and external os (opening) is measured three times over a period of about 3 minutes and the shortest measurement of the cervical length is recorded. Accurate measurements require measuring after bladder voiding. The efficacy of this method has been studied in various settings, and it is not without limitations; reproducibility varies significantly depending on the examiner (Kuusela et al. 2020). The protocol for a correct image includes distinguishing between the cervical canal and isthmus, enlarging the image, avoiding pressure on the cervix with the probe, and allowing sufficient time for measurement (FMF, Kuusela et al. 2021). Despite technical challenges, transvaginal ultrasound screening for short cervical length during pregnancy has consistently been shown to identify women at risk of giving birth preterm (Campbell, 2018; Iams et al. 1996; Kuusela et al. 2021). In a general Swedish population, second-trimester screening with transvaginal ultrasound identified 4.4% of pregnant women as having a short cervix

(≤25 mm). However, these women constituted only 27% of all women who gave birth before 33+0 weeks (Kuusela et al. 2021).

Figure 1. Measurement of cervical length by vaginal ultrasound.



Measurement of cervical length when isthmus is absent (A) or present (B). A denotes the external os, B denotes the internal os. C is the innermost end of the juxtaposed anterior and posterior isthmus. Reprinted with permission from John Wiley and Sons, Wikström T et al. Cost-effectiveness of cervical length screening and progesterone treatment to prevent spontaneous preterm birth in Sweden. Ultrasound Obstet Gynecol. 2022

Progesterone treatment for the prevention of PTB

Progesterone can be used to prevent PTB. It can be administered intramuscularly, vaginally, or orally, but vaginal administration is shown to have best preventive effect for PTB (Ljungström et al. 2022, Wennerholm et al. 2023). In Sweden, natural micronised progesterone for vaginal administration is the only available treatment for this indication, in the dosage of 100 to 200 mg every night until 34+0 weeks (Jacobsson et al. 2023). It is a relatively low-cost, well-tolerated medication with no known adverse effects on the child up to two years of age (OPPTIMUM, Norman et al. 2016). Adverse maternal effects for vaginal administration include itching, burning sensation, vaginal discharge and/or bleeding (FASS Vårdpersonal). No difference in maternal morbidity was seen in the progesterone treated vs placebo group in the above-mentioned systematic review (Ljungström et al. 2022, Wennerholm et al. 2023). Compliance for vaginal progesterone ranges from 69-88.5% in different studies (OPPTIMUM, Norman et al. 2016, Hassan et al. 2011). Meta-analyses have shown that vaginal progesterone treatment reduces the rate of any PTB in asymptomatic women at high risk of PTB with the most robust results for PTB before 33 weeks resulting in a 22-38% reduction (Ljungström et al. 2022, Wennerholm et al. 2023, Romero et.al. 2018, Stewart et al. EPPPIC Group 2021).

7 Focused question

The focused research question investigated in this report is as follows: Is universal cervical length screening with transvaginal ultrasound in women with singleton pregnancies followed by vaginal or oral progesterone, with or without additional treatment, when short cervix length is demonstrated, effective in preventing any or spontaneous PTB and does it affect perinatal outcomes?

PICO	
P= patient	Women with singleton pregnancies in the first or second trimester
I= Intervention	Screening with transvaginal ultrasound and measurement of cervical length followed by vaginal or oral progesterone, with or without additional treatment, if short cervical length* is demonstrated
C= Comparison	No screening with transvaginal ultrasound
O= Outcome	Critical for decision making: • Any PTB, any cut off below 37+0 weeks, defined by the authors • Spontaneous PTB, any cut off below 37+0 weeks, defined by the authors • Perinatal mortality (intrauterine foetal death and neonatal mortality <7 or <28 days) • Neonatal mortality (<7 or <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
Study design	Randomised controlled studies (RCT), non-randomised controlled studies with at least 1000 screened women, systematic reviews (SR)
Publication year	In general, RCT and non-randomised controlled studies 1980-, SR 2020-
Language	Danish, English, Norwegian, Swedish
Prespecified subgroup analyses for all interventions**	• Different cut-offs for cervical length • Women with previous PTB • Women without previous PTB • First trimester vs second trimester screening • Exclusion of studies where the intervention includes more than only progesterone

*As defined by the authors, ** Only RCT

8 Method

Systematic literature search (Appendix 1)

During October 2024 two authors (AL, ACE) performed systematic searches in Medline, Embase, and in the Cochrane Library. Websites of Scandinavian national and regional HTA-organisations were visited. Reference lists of relevant reports were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted literature searches, and independently of one another screened the obtained abstracts to decide eligibility for full-text retrieval. All abstracts were screened using the Rayyan tool, a systematic review software (Ouzzani et al. 2016). Any disagreements were resolved in consensus. All full-text reports were independently assessed by at least two authors,

after which a consensus meeting with all authors took place to decide on inclusion or exclusion according to PICO. Reasons for exclusion of excluded articles are presented in Appendix 3.

The review was registered in PROSPERO on the 7th of November 2024 (registration ID: CRD42024605203) prior to data extraction.

Critical appraisal and certainty of evidence

Included studies were critically appraised using an adjusted checklist from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) for assessment of RCTs and for assessment of non-randomised controlled studies. Data was extracted by at least two authors and summarised for each outcome in Appendix 4. When possible, data was pooled in meta-analysis (RevMan 5.4 and Stata 18) using the random and fixed effects model and mainly risk ratio (RR) as point estimate with 95% CI. When available adjusted odds ratio (AOR) was used. RCTs and cohort studies were handled separately in meta-analyses. In case of zero events in one or both arms, Peto OR was used. The certainty of evidence for each outcome was assessed using the GRADE approach separately for RCTs and cohort studies (Atkins et al. 2004; GRADE Working group). Summary of the results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (Chapter 3).

Ongoing research

A search in Clinicaltrials.gov (13 Dec 2024) using the search terms (Length* OR Measurement* OR Short* OR Assessment*) AND (Echotomograph* OR Echograph* OR Sonograph* OR Ultrasound* OR Ultrason* OR Screening* OR Scan*) AND (Cervix OR Cervical) AND (Prematur* OR Pre-matur* OR Preterm* OR Pre-term*) AND (Progesterone OR Hydroxyprogesterone OR Progestin OR Progestagen OR Progestogen OR Desogestrel OR Gestagen OR Algestone OR Dydrogesterone OR Gestrinone OR Progestative OR Medroxyprogesterone acetate) identified 54 trials.

A search in WHO International Clinical Trials Registry Platform (ICTRP) (13 Dec 2024) using the search terms (Length* OR Measurement* OR Short* OR Assessment*) AND (Echotomograph* OR Echograph* OR Sonograph* OR Ultrasound* OR Ultrason* OR Screening* OR Scan*) AND (Cervix OR Cervical) AND (Prematur* OR Pre-matur* OR Preterm* OR Pre-term*) AND (Progesterone OR Hydroxyprogesterone OR Progestin OR Progestagen OR Progestogen OR Desogestrel OR Gestagen OR Algestone OR Dydrogesterone OR Gestrinone OR Progestative OR Medroxyprogesterone acetate) identified 18 trials.

9 Results

Search results and study selection (Appendix 1)

The literature search identified a total of 2,295 records after removal of duplicates. DedupEndNote (Lobbestael, 2023) was used for deduplication. After reading the abstracts, 2,238 records were excluded, and 59 articles were sought for retrieval. A total

of 31 of these publications were excluded by two authors after reading them in full text. The remaining 28 publications were sent to all participants of the project group. Of these, 22 publications were excluded after full-text reading and discussion in the project's consensus meetings (Appendix 3). Six publications were finally included in the assessment. In addition, one systematic review (SR) was commented upon (Appendix 2).

Included studies

Six articles were included: two RCTs (Mishra et al. 2018, Saccone et al. 2024) and four retrospective cohort studies (Figarella et al. 2023, Melchor et al. 2023, Son et al. 2016, and Souka et al. 2024). Three of the cohort studies had a before and after design and one was carried out in parallel, with the intervention and control groups from two different hospitals. The RCTs were from one tertiary centre in India (Mishra et al. 2018) and from two hospitals in Italy (Saccone et al. 2024), respectively. One of the cohort studies was regional including 41 maternity centres in France (Figarella et al. 2023), and one study was carried out at two private hospitals in Greece (Souka et al. 2024). The studies by Melchor (2023) and Son (2016) were conducted at one hospital in Spain and the United States, respectively. One study included all women with a singleton pregnancy and a birth after 24 weeks (Figarella et al. 2023). The other studies excluded high risk patients: four studies excluded women with previous spontaneous PTB (Mishra et al. 2018, Saccone et al. 2024, Melchor et al. 2023 and Souka et al. 2024), and one study excluded any PTB (Son et al. 2016). Three studies also excluded previous second trimester abortion (Mishra et al. 2018, Son et al. 2016, and Souka et al. 2024). Souka et al. (2024) also excluded women with previous cervical surgery.

Intervention

One study used a different cut-off for cervical length: ≤15 mm (Souka et al. 2024) instead of ≤25 mm used by Mishra et al. (2018), Saccone et al. (2024), Figarella et al. (2023), and Son et al. (2016). Melchor et al. (2023) used <25 mm as cut-off. Son et al. (2016) prescribed treatment when cervix was ≤20 mm. Rates of short cervix (</≤25) were 0.9-6.6% in the included studies. The treatment rate of vaginal progesterone was a few percent in the intervention groups. In the RCTs 2/147 (1.4%) and 15/675 (2.2%) participants received treatment. Treatment rate with progesterone in the cohort studies were in Figarella et al. (2023) only noted for a subgroup (a prospective cohort that was included in the before-after cohort) 25/3,468 (0.7%), 32/483 (6.6%) in Melchor et al. (2023), 43/17,609 (0.2%) in Son et al. (2016), and 31/3,103 (1.0%) in Souka et al. (2024). Five studies combined treatments in different ways. The only study with exclusive vaginal progesterone treatment was Mishra et al. (2018). In Figarella et al. (2023) the choice of treatment was left to the physician: either vaginal progesterone, cerclage, or pessary. Saccone et al. (2024) treated all with short cervix with both vaginal progesterone and pessary -and cerclage if cervix was <5 mm or dilated ≥15 mm. Melchor et al. (2023) added cerclage if cervix was <10 mm or progressive shortening. Souka et al. (2024) added cerclage if progressive cervical shortening despite progesterone treatment. Son et al. (2016) added cerclage in case of cervical dilation before 24 weeks.

Directness, study limitations and precision

The RCTs had serious imprecision (underpowered with few events and wide CI) and some risk of bias (not blinded assessments, missing information). Mishra et al. (2018) had some problems with indirectness (unclear clinical setting and selection process, high level of high-risk patients).

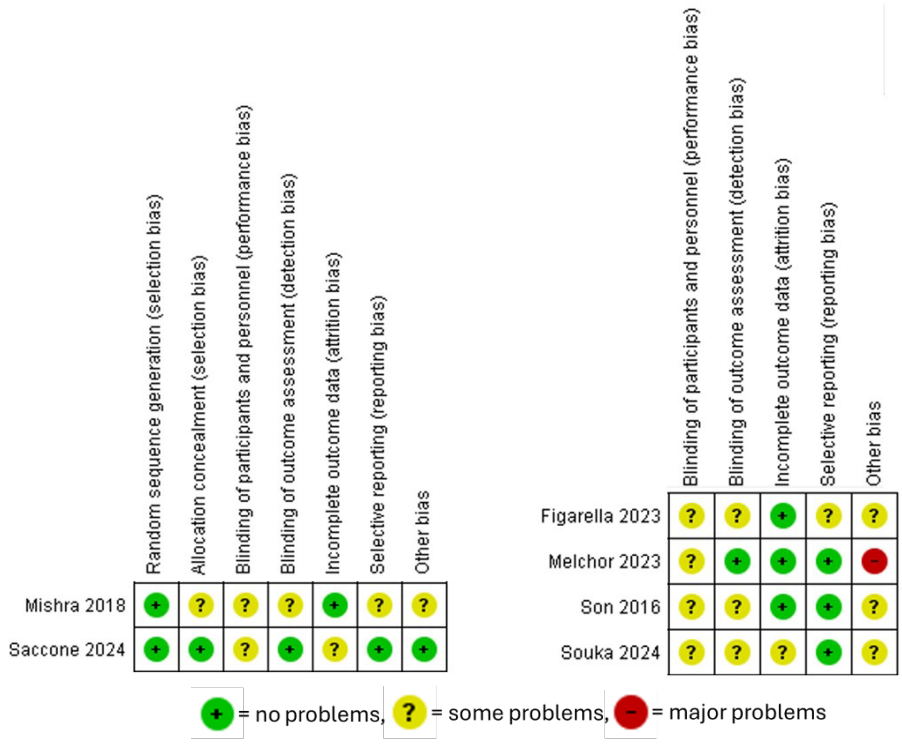
Three cohort studies had problems with indirectness: Souka et al. (2024) had some problems (unclear study population and intervention) and Melchor et al. (2023) had major problems (no information on baseline population), Figarella et.al. (2023) had some problems (28.9% of the participants in the control group were screened and unclear intervention regarding progesterone). All cohort studies had some or major problems with risk of bias (unblinded assessments, missing data, and unclarities). Two cohort studies had problems with imprecision: Melchor et al. (2023) had some problems (no power calculation, primary outcome preterm labour instead of PTB), while Souka et al. (2024) had major problems (no power calculations, few events). For more details see Table 1, Figure 2, and Appendix 5.

Table 1. Summary of critical appraisal for each study

Author, year	**Study design**	**Directness**	**Risk of bias**	**Precision**
Mishra, 2018	RCT	?/-	?	-
Saccone, 2024	RCT	+	?	-
Figarella, 2023	Cohort (before-after)	?	?/-	+
Melchor, 2023	Cohort (before-after)	-	-	?
Son, 2016	Cohort (before-after)	+	?	+
Souka, 2024	Cohort (propensity score matched)	?	-	-

Green=no problems, yellow=some problems, red=major problems, RCT= randomised controlled study

Figure 2. Details of risk of bias for each study, RCTs and cohort studies respectively



The planned subgroup analyses i.e. different cut-offs for cervical length, women with or without previous PTB, first trimester vs second trimester screening, and exclusion of studies where the intervention included more than only progesterone were not made due to insufficient data (only two underpowered RCTs).

The GRADE assessment resulted in the same rating for both RCTs and cohort studies and is therefore reported together for each outcome. For more details see Table 2 and Appendix 5.

Table 2. Result from GRADE assessment per outcome

Outcome	**Risk of bias**		**Consistency**		**Directness**		**Precision**	
	RCT	Cohort	RCT	Cohort	RCT	Cohort	RCT	Cohort
Any PTB <37								
Any PTB <34								
Any PTB <32								
Any PTB <30		-		-		-		-
Any PTB <28		-		-		-		-
Any PTB <24		-		-		-		-
Spontaneous PTB <37								
Spontaneous PTB <35	-		-		-		-	
Spontaneous PTB <34								
Spontaneous PTB <32								

Spontaneous PTB <30		-		-		-		-
Spontaneous PTB <28								
Spontaneous PTB <24								
Spontaneous PTB <32-37		-		-		-		-
Perinatal mortality		-		-		-		-
Composite neonatal morbidity		-		-		-		-
Respiratory distress syndrome		-		-		-		-
Intraventricular haemorrhage		-		-		-		-

Green=no problems, yellow=some problems, red=major problems

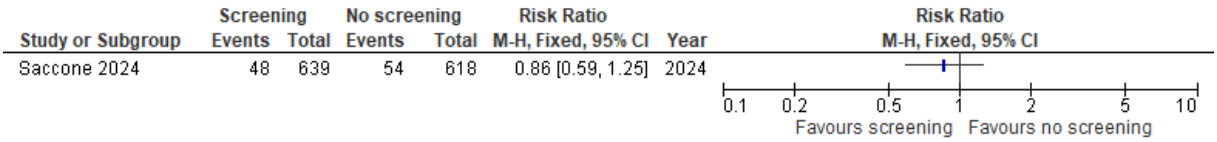
Results per outcome

Outcomes critical for decision-making

Any PTB before 37+0 weeks (Appendix 4.1)

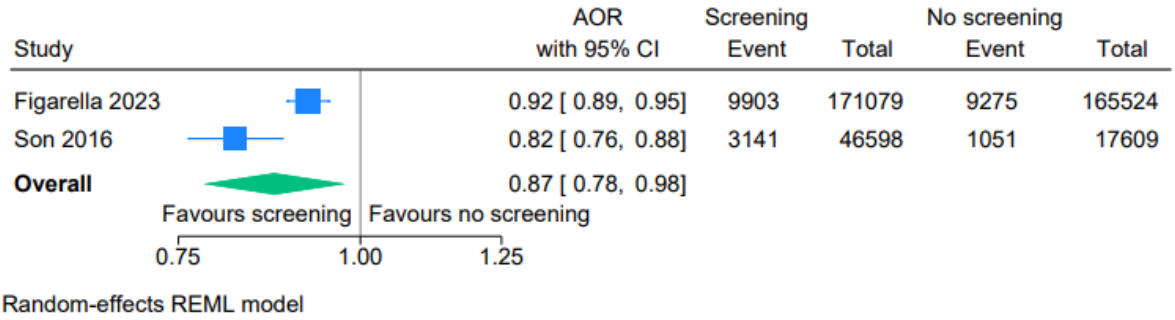
Any PTB before 37+0 weeks was reported in one RCT (n=1,257) There was no reduction in the rate of any PTB before 37+0 weeks (RR: 0.86, 95% CI 0.59-1.25, p=0.43) (Figure 3a). The GRADE was based on some risk of bias and inconsistency (only one study), and very serious imprecision (Table 2, Appendix 5).

Figure 3a. Any PTB before 37+0 weeks from RCT. RR for screening compared with no screening.



Any PTB before 37+0 weeks was reported in two cohort studies (n=400,810). There was a significant reduction in the rate of any PTB before 37+0 weeks (RR: 0.96, 95% CI 0.93-0.98, p= 0.0005; AOR 0.87, 95% CI 0.78-0.98, p=0.017) (Figure 3b). The GRADE was based on some risk of bias and indirectness (Table 2, Appendix 5).

Figure 3b. Any PTB before 37+0 weeks from cohort studies. AOR for screening compared with no screening.



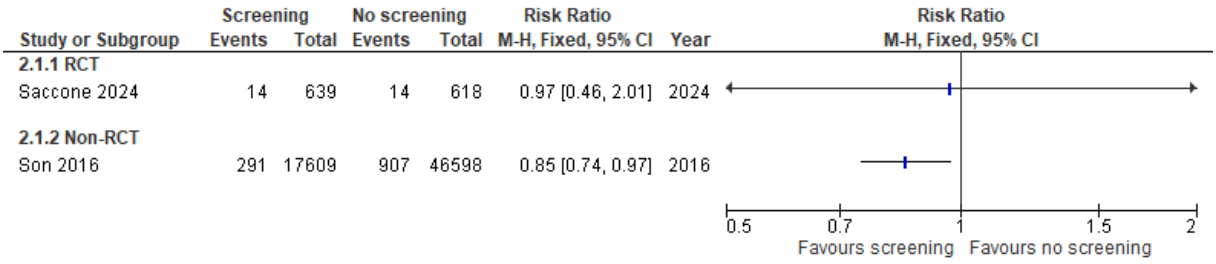
Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of any PTB before 37+0 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Any PTB before 34+0 weeks (Appendix 4.1)

Any PTB before 34+0 weeks was reported in one RCT (n=1,257). The RCT showed no reduction in the rate of any PTB before 34+0 weeks (RR 0.97, 95% CI 0.46-2.01, p=0.93, Figure 4). The GRADE was based on some risk of bias and inconsistency (only one study), and very serious imprecision (Table 2, Appendix 5).

Any PTB before 34+0 weeks was reported in one cohort study (n=64,207). The study showed a reduction in the rate of any PTB before 34+0 weeks (RR 0.85, 95% CI 0.74-0.97, p=0.01, Figure 4). The GRADE was based on some risk of bias and inconsistency (Table 2, Appendix 5).

Figure 4. Any PTB before 34+0 weeks. RR for screening compared with no screening



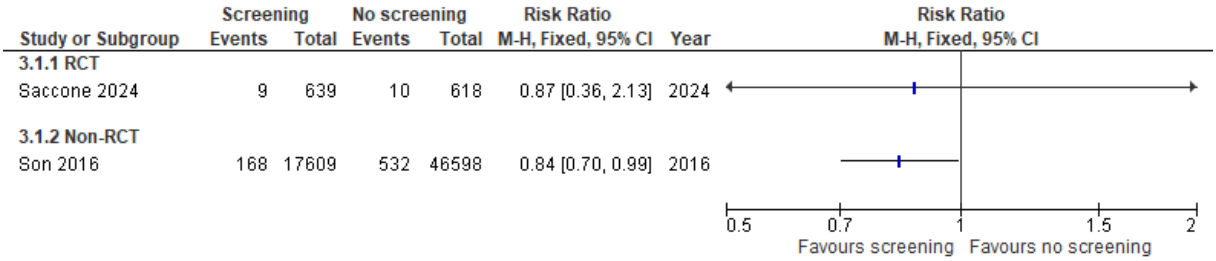
Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of any PTB before 34+0 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Any PTB before 32+0 weeks (Appendix 4.1)

Any PTB before 32+0 weeks were reported in one RCT (n=1,257). The RCT showed no reduction in the rate of any PTB before 32+0 weeks (RR: 0.87, 95% CI 0.36-2.13, p=0.76, Figure 5). The GRADE was based on some risk of bias and inconsistency (only one study), and very serious imprecision (Table 2, Appendix 5).

Any PTB before 32+0 weeks were reported in one cohort study (n=64,207). The cohort study showed a reduction in the rate of any PTB before 32+0 weeks (RR 0.84, 95% CI 0.70-0.99, p=0.04, Figure 5). The GRADE was based on some risk of bias and inconsistency (Table 2, Appendix 5).

Figure 5. Any PTB before 32+0 weeks. RR for screening compared with no screening

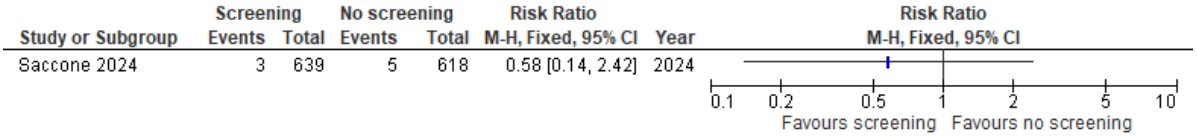


Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of any PTB before 32+0 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Any PTB before 28+0 weeks (Appendix 4.1)

Any PTB before 28+0 weeks was reported in one RCT (n=1,257). The study showed no reduction in the rate of any PTB before 28+0 weeks (RR: 0.58, 95% CI 0.14-2.42, p=0.45, Figure 6). The GRADE was based on some risk of bias and inconsistency (only one study), and very serious imprecision (Table 2, Appendix 5).

Figure 6. Any PTB before 28+0 weeks. RR for screening compared with no screening.



Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of any PTB before 28 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Any PTB before 30+0 and 24+0 weeks (Appendix 4.1 and 6)

Any PTB before 30+0 and before 24+0 weeks were reported in one RCT (Saccone et al. 2024, n=1,257). The GRADE was based on some problems with risk of bias and inconsistency (only one study), and very serious imprecision (Table 2, Appendix 5).

Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of any PTB before 30 and 24 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

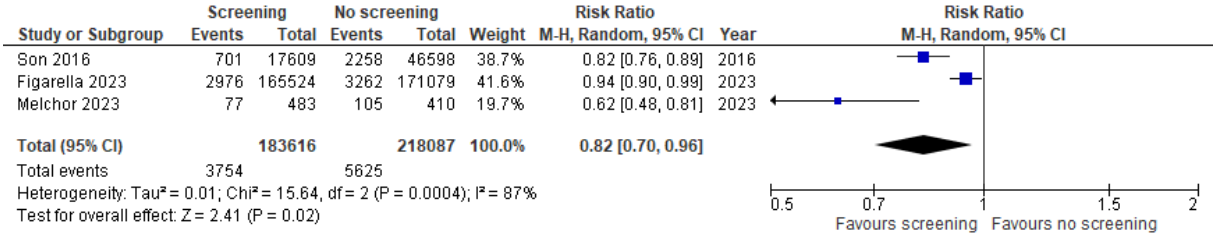
Spontaneous PTB before 37+0 weeks (Appendix 4.2)

This outcome was reported in two RCTs (n=1,553). The RCTs showed no reduction in the rate of spontaneous PTB before 37+0 weeks (RR: 0.98, 95% CI 0.67-1.42, p=0.91, Figure 7a). The GRADE was based on some risk of bias and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 7a. Spontaneous PTB before 37+0 weeks from RCTs. RR for screening compared with no screening.

This outcome was reported three cohort studies (n=401,703). The cohort studies showed a reduction in the rate of spontaneous PTB before 37+0 weeks (RR: 0.82, 95% CI 0.70-0.96, p=0.02, Figure 7b). The GRADE was based on some risk of bias, inconsistency, and indirectness (Table 2, Appendix 5).

Figure 7b. Spontaneous PTB before 37+0 weeks from cohort studies. RR for screening compared with no screening.

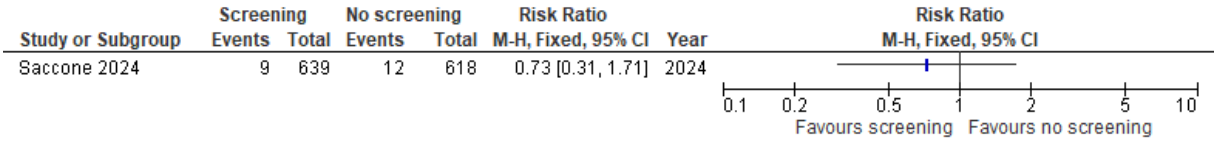


Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of spontaneous PTB before 37 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Spontaneous PTB before 34+0 weeks (Appendix 4.2)

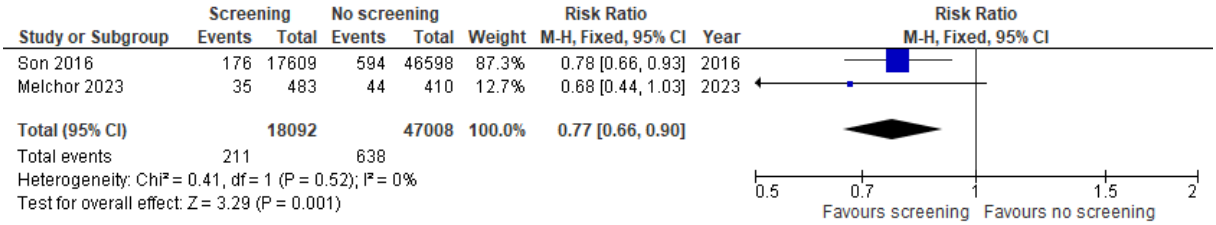
Spontaneous PTB before 34+0 was reported in one RCT (n=1,257). The RCT showed no reduction in the rate of spontaneous PTB before 34 weeks (RR: 0.73, 95% CI 0.31-1.71, p=0.46) (Figure 8a). The GRADE was based on some risk of bias and inconsistency (only one study), and very serious imprecision (Table 2, Appendix 5).

Figure 8a. Spontaneous PTB before 34+0 weeks from RCT. RR for screening compared with no screening.



Spontaneous PTB before 34+0 was reported in two cohort studies (n=65,100). The cohort studies showed a reduction in the rate of spontaneous PTB before 34+0 weeks (RR: 0.77, 95% CI 0.66-0.90, p=0.001, Figure 8b). The GRADE was based on some risk of bias and indirectness (Table 2, Appendix 5).

Figure 8b. Spontaneous PTB before 34+0 weeks from cohort studies. RR for screening compared with no screening.

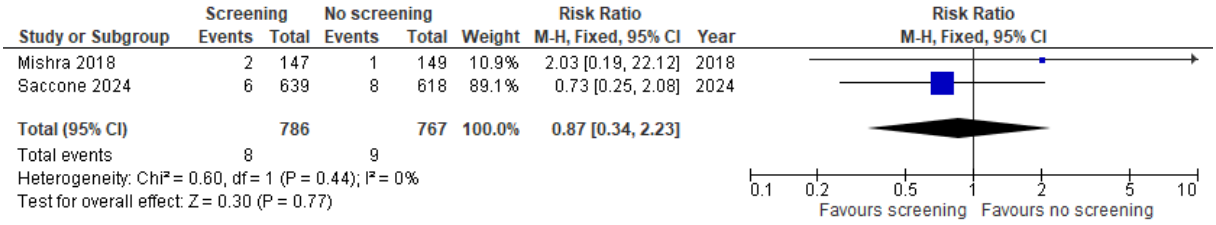


Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of spontaneous PTB before 34 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Spontaneous PTB before 32+0 weeks (Appendix 4.2)

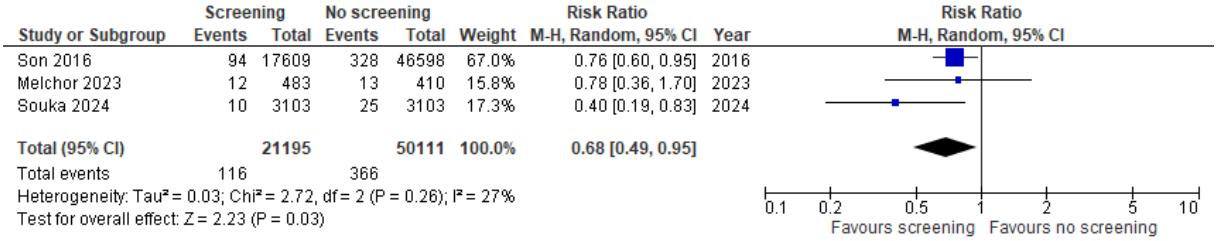
Spontaneous PTB before 32+0 was reported in two RCTs (n=1,553). The RCTs showed no reduction in the rate of spontaneous PTB before 32 weeks (RR: 0.87, 95% CI 0.3-2.23, p=0.77, Figure 9a). The GRADE was based on some risk of bias, inconsistency, and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 9a. Spontaneous PTB before 32+0 weeks from RCTs. RR for screening compared with no screening.



Spontaneous PTB before 32+0 was reported in three cohort studies (n=71,306). The cohort studies showed a reduction in the rate of spontaneous PTB before 32 weeks (RR: 0.68, 95% CI 0.49-0.95, p=0.03, Figure 9b). The GRADE was based on some risk of bias, inconsistency, and indirectness (Table 2, Appendix 5).

Figure 9b. Spontaneous PTB before 32+0 weeks from cohort studies. RR for screening compared with no screening. RCT and cohort studies separately.



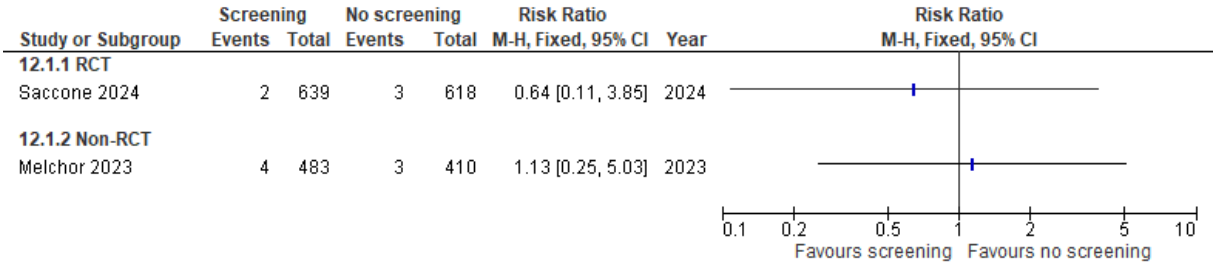
Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of spontaneous PTB before 32 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Spontaneous PTB before 28+0 weeks (Appendix 4.2)

Spontaneous PTB before 28+0 weeks were reported in one RCT (n=1,257). The RCT showed no reduction in the rate of spontaneous PTB before 28+0 weeks (RR: 0.64, 95% CI 0.11-3.85, p=0.63, Figure 10). The GRADE was based on some risk of bias, inconsistency and indirectness, and very serious imprecision (Table 2, Appendix 5).

Spontaneous PTB before 28+0 weeks were reported in one cohort study (n=893). The cohort study showed no reduction in the rate of spontaneous PTB before 28+0 weeks (RR: 1.13, 95% CI 0.25-5.03, p=0.87, Figure 10). The GRADE was based on some inconsistency, serious risk of bias and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 10. Spontaneous PTB before 28+0 weeks. RR for screening compared with no screening



Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of spontaneous PTB before 28+0 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Spontaneous PTB before 35+0, 30+0, 24+0, and between 32+0 to 36+6 weeks (Appendix 4.2 and 6)

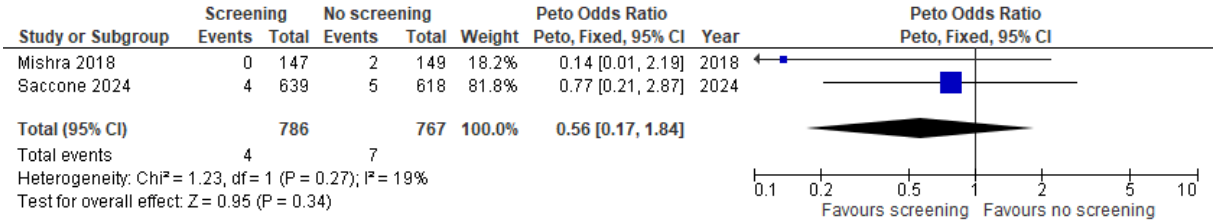
Spontaneous PTB before 35+0 (Melchor et al. 2023, n=893), before 30+0 and before 24+0 (Saccone et al. 2024, n=1,257, Souka et al. 2024, n=6,206), and between 32+0 to 36+6 weeks (Mishra et al. 2018, n=296) were reported in two RCTs and in two cohort studies. The GRADE was based on moderate to serious risk of bias, some inconsistency (only one study), no to serious indirectness, and moderate to very serious imprecision (Table 2, Appendix 5).

Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of spontaneous PTB before 35+0, 30+0, 24+0, and 32+0 to 36+6 weeks, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Perinatal mortality: intrauterine foetal death and neonatal mortality (Appendix 4.3)

This outcome was reported in two RCTs (Mishra et al. 2018; Saccone et al. 2024, n=1,553). The RCTs showed no reduction in the rate of perinatal mortality (Peto OR: 0.56, 95% CI 0.17-1.84, p=0.34, Figure 11). The GRADE was based on some risk of bias, inconsistency, and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 11. Perinatal mortality. Peto OR for screening compared with no screening



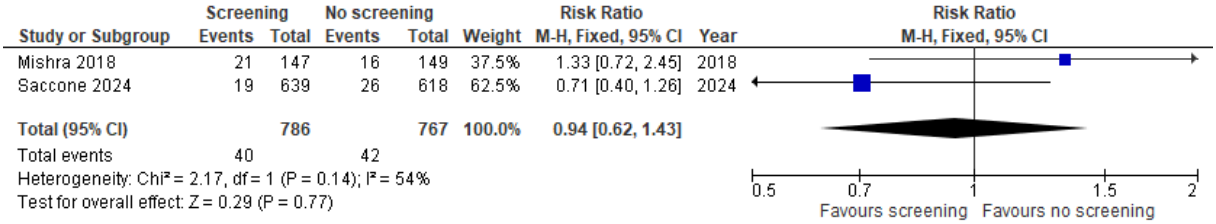
Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of perinatal mortality, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Serious neonatal morbidity: composite neonatal morbidity (Appendix 4.4)

This outcome was reported in two RCTs (Mishra et al. 2018; Saccone et al. 2024, n=1,553). Serious neonatal morbidity is reported as a composite outcome and as the individual components bronchopulmonary dysplasia (BPD), severe IVH, necrotizing enterocolitis (NEC), confirmed sepsis and retinopathy of prematurity (ROP), or neonatal mortality in one trial (Saccone et al. 2024) and as neonatal jaundice, RDS, and IVH in one trial (Mishra et al. 2018).

A meta-analysis showed no reduction in the rate of serious composite neonatal morbidity (RR: 0.94, 95% CI 0.62-1.43, p=0.77, Figure 12). The GRADE was based on some risk of bias, inconsistency, and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 12. Composite neonatal morbidity. RR for screening compared with no screening

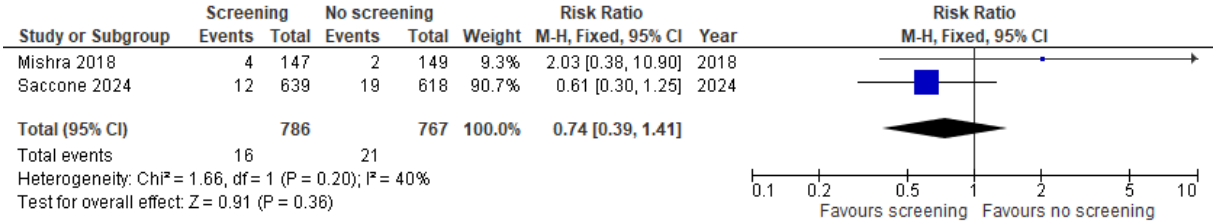


Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of serious neonatal morbidity, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Serious neonatal morbidity: Respiratory distress syndrome (RDS) (Appendix 4.4)

This outcome was reported in two RCTs (n=1,553). The RCTs showed no reduction in the rate of RDS (RR: 0.74, 95% CI 0.39-1.41, p=0.36, Figure 13). The GRADE was based on some risk of bias, inconsistency, and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 13. RDS. RR for screening compared with no screening

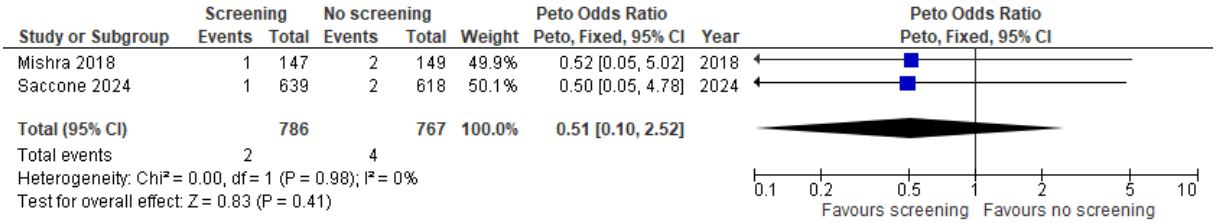


Conclusion: It is uncertain whether universal cervical length screening with transvaginal

ultrasound, followed by progesterone treatment, reduces the rate of RDS, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Serious neonatal morbidity: Intraventricular haemorrhage (IVH) (Appendix 4.4)
This outcome was reported in two RCTs (n=1,553). The RCTs showed no reduction in the rate of IVH (RR: 0.51, 95% CI 0.10-2.52, p=0.41, Figure 14). The GRADE was based on some risk of bias and indirectness, and very serious imprecision (Table 2, Appendix 5).

Figure 14. IVH. RR for screening compared with no screening



Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of IVH, compared with no screening. Very low certainty of evidence (GRADE ⊕OOO).

Serious neonatal morbidity: BPD, NEC, sepsis, and ROP (Appendix 4.4)
BPD, NEC, proven sepsis, and ROP were reported in one RCT (Saccone et al. 2024, n=1,257). The RCT had very serious imprecision due to few events. The RCT showed no reduction in BPD, NEC, sepsis, or ROP. The GRADE was based on some risk of bias, inconsistency, and indirectness, and very serious imprecision (Table 2, Appendix 5).

Conclusion: It is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone treatment, reduces the rate of BPD, NEC, proven sepsis, or ROP, compared with no screening. Very low certainty evidence (GRADE ⊕OOO).

10 Ethical aspects

Cervical length screening with subsequent progesterone treatment if short cervix is demonstrated, is recommended in Sweden for women with singleton pregnancies and high risk for PTB (Jacobsson et al. 2023). However, interventions that are restricted to women with high risk will only have modest effect on the overall PTB rate since two-thirds of all PTBs occur in low-risk pregnancies (Goodfellow et al. 2021). This argues for universal screening, i.e. screening of all women with a singleton pregnancy.

Minimum requirements and standards for screening programs have been defined by the WHO (2020) and the Swedish National Board of Health and Welfare (2019). Universal screening for PTB meets many of these requirements; PTB is the leading cause of neonatal mortality and morbidity and extension of the duration of pregnancy has the potential to significantly reduce perinatal morbidity and disability. Transvaginal ultrasound is a relatively simple and well tolerated procedure with very limited risk of complications and has the ability to detect short cervical length. Furthermore, there is evidence indicating that short cervical length has the characteristics of a condition that is suitable for screening; it is associated with the outcome of interest PTB, it is in many cases asymptomatic, and there is an existing potential treatment with very few serious side effects.

However, a fundamental requirement for implementation of any medical intervention is that a clear benefit that outweighs harms can be demonstrated. This is particularly important for screening programs since the vast majority of subjects that are investigated in the program are without symptoms and will not benefit from the intervention themselves. In this report we find that it is uncertain whether universal cervical length screening with vaginal ultrasound, followed by progesterone, with or without additional treatment, for women with short cervix and a singleton pregnancy, reduces the rate of PTB. This means that for the time being, this intervention fails to meet minimal requirements for screening procedures that are related to the evidence of effect on clinically relevant outcomes and a clear and positive risk-benefit ratio, and that cost-effectiveness cannot be established. A screening program would require significant midwife and financial resources with a non-negligible risk of displacement of other pregnancy related care. Other potential negative effects of screening include the anxiety that a false positive test result could cause and the risks and costs of unnecessary subsequent treatment.

11 Organisational aspects

Time frame for the putative introduction of the new health technology

If screening is implemented, it will probably be incorporated into the routine foetal anatomy scan, offered to all pregnant women around 18–20 weeks. This approach would extend the total scanning time by 15 minutes, and 30 minutes if it is performed as a separate examination (Wikström et al. 2021). This would require full-time training for midwives of at least 2 weeks per midwife (Romosan et al. 2020), who predominantly, and often exclusively, use abdominal ultrasound for routine foetal anatomy scanning and are thus not familiar with transvaginal ultrasound. Furthermore, an additional 15 minutes to a 30-minute routine foetal anatomy scan mean that 50% more time will be needed, approximately 50% more midwives, approximately 50% more examination rooms, and 50% more ultrasound machines. Pregnant women identified with a short cervix would require a consultation with a physician (30 minutes) for information and prescription of progesterone. The number of women requiring such appointments would depend on the chosen cut-off for defining a short cervix. The widely used threshold of ≤25 mm would identify approximately 680 women per year in Region Västra Götaland (estimated 17,000 women screened every year, 4% with short cervix). In summary, education and quality control of examiners would be the most time-consuming and costly post in the implementation process (Wikström et al. 2021).

Present use of the technology in other hospitals in Region Västra Götaland

Universal screening of cervical length is currently not practised in Region Västra Götaland.

Consequences of the new health technology for personnel

Midwife resources are limited. If a screening program of cervical length is implemented, this would require additional midwife and administrative resources and could therefore potentially cause displacement effects.

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

There are four hospitals with obstetric care in VGR and several ultrasound clinics, all employing specially trained midwives that perform all routine foetal anatomy scans. Women with a singleton pregnancy will ideally be asked during a maternal health visit whether they wish to undergo transvaginal ultrasound screening for a short cervix. Screening is preferably integrated with the routine foetal anatomy scan at the ultrasound clinic.

12 Economic aspects

Economic aspect of this report consists of a budget impact analysis, describing the imposed financial burden on VGR if to introduce universal cervical length screening followed by progesterone treatment to those at risk. The budget impact analysis is based on 17,000 women, i.e. the number of women with a singleton pregnancy in VGR per year. Actions required for implementation and running of a screening program in a Swedish setting has been investigated in a recent study, including costs in United States dollars (UDS) in 2021 year's price index (Wikström et al. 2022). These estimates were applied to the population of VGR, converted to Swedish krona (SEK) (USD=8.5842 SEK in 2021) and updated to 2024 year's price index by adjusting for inflation (SCB, 2025). Items included in the budget impact analysis were teaching and training of 40 midwife sonographers, development of an online database and its operation, quality control of the screening program, costs for ultrasound examinations, physician visits and vaginal progesterone.

Few of these inputs are considered as capital items (e.g. training of midwives, online database, ultrasound machines), meaning that the economic investment effects of them sustain longer than a one-year period and therefore the costs of them need to be split into its one-year equivalent amount (Drummond et. al. 2015). It should be noted that 40 midwives would be trained with a cost of 72,320 SEK each. We assumed that the median time a trained midwife sonographer stays in the program is 10 years. The cost of the online database was estimated to 90,000 SEK and the database was assumed to be usable over 10 years. A total of 6 ultrasound machines needs to be purchased at a price of 1,796,550 SEK per machine. We assumed the lifetime of the ultrasound machine is 7 years. For considering the time differential, a discounting rate of 3% was applied

(Drummond et. al. 2015). The annual cost of training and the online database has been estimated to approximately 400,000 SEK and 12,400 SEK respectively.

Table 3. Annual costs (SEK) of universal screening of cervical length screening and progesterone treatment, 2024

Inputs	Costs in SEK, 2024	Share of total costs
Training of midwives	398,214	2.91%
Online database	12,389	0.09%
Operation of online database	70,454	0.52%
Quality control of screening program	81,301	0.59%
Investment in ultrasound equipment	1,730,141	12.66%
Ultrasound examinations	9,596,087	70.22%
Physician visits	1,199,511	8.78%
Vaginal progesterone	577,320	4.22%
Total costs	**13,665,417**	**100.00%**
Cost per women screened	**804**	

All other listed inputs are recurrent in nature as they are consumed instantly within a one-year period. The operating cost of online database and the quality control of the screening program is estimated to 70,500 and 81,300 SEK per year. Six ultrasound machines with an estimated lifespan of 7 years cost 1.7 million SEK annually. A total of 17,000 women per year would go through vaginal ultrasound screening which would generate a cost of 481 SEK each in year 2021, resulting in a total sum of 9,6 million SEK in 2024 after adjusting for inflation. Based on the CERVIX study (Kuusela et al., 2021), we assumed that a short (<25 mm) cervix would be found in 4% (680/17,000) of the screening examinations. We postulated that the finding of a short cervix would require a follow-up visit with a physician visit and progesterone treatment. The cost of a visit to a physician was estimated to 1,500 SEK (1.2 million SEK for 680 women). The 2024 updated cost for vaginal progesterone treatment is 849 SEK per pregnancy (577 thousand SEK for 680 pregnancies).

In sum, a total cost of almost 13.7 million SEK per year or 804 SEK per woman would be needed for operating the universal screening of cervical length screening and progesterone treatment in VGR, where the largest cost burden will be related to the ultrasound examinations (70.2%), followed by the costs of ultrasound machines (12.7%) (Table 3). It was not possible to calculate the cost for one prevented PTB since no clear benefit of cervical screening could be defined.

13 Discussion

Summary of main results

The conclusion of this report is that it is uncertain whether universal cervical length screening with transvaginal ultrasound, followed by progesterone, with or without additional treatment, for women with short cervix, reduces the rate of PTB or adverse neonatal outcomes, compared with no screening. This conclusion is based on meta-analysis of RCTs and cohort studies and applies to all outcomes: any PTB, spontaneous PTB for all gestational weeks and adverse neonatal outcomes. Meta-analyses of cohort studies showed statistically significant associations between cervical length screening, followed by progesterone treatment when short cervix, and spontaneous PTB at <37, <34 and <32 weeks. However, these findings did not change the overall conclusion since the certainty of evidence for these estimates was very low due to concerns related to directness and risk of bias.

The main methodological shortcoming of the two included RCTs (Mishra et at. 2018 and Saccone et al. 2024) was the low number of participants (300 and 1,334 participants), rendering these studies severely underpowered to show any difference in PTB (any or spontaneous). Sample size calculation in the study by Saccone et al. was based on a predicted rate of any PTB of 6.7% and an assumed 50% reduction of any PTB in the intervention arm. The actual rates of any PTB in the study were 8.7% in the control arm and 7.5% in the intervention arm and this difference was not statistically significant. In the discussion of this finding, the authors speculated that if this was the true effect size of screening, a study including 16,228 participants would be needed to achieve sufficient statistical power to demonstrate this difference. Sample size calculation in the study by Mishra et al. was based on the assumption of a very high spontaneous PTB rate (15%) in the control arm and very high effect of progesterone with a reduction of PTB to 5% in the intervention arm. However, the actual rate of spontaneous PTB was 8.1% in the control arm and 10.2% in the intervention arm. Hence, overestimation of the underlying PTB-rate and the effect of progesterone treatment explain why the sample-size calculation gave relatively low number of required patients in this study. It is noteworthy that the rate of progesterone treatment in the RCTs was low; only 2 participants in the study by Mishra et al. and 15 in the study by Saccone et al. Furthermore, interventions other than vaginal progesterone were frequent in both RCTs and cohort studies. In the study by Saccone et al. 11 of the 15 patients with short cervix were treated with pessary and two received cervical cerclage in addition to vaginal progesterone. In the study by Mishra et al. only two patients were identified with short cervix, one received vaginal progesterone alone and one received cerclage in combination with progesterone.

In the meta-analyses of the cohort studies (425,735 participants) there were statistically significant effects with narrow confidence intervals that favours universal screening for any and spontaneous PTB before 37, 34 and 32 weeks. Two of the cohort studies included a large number of participants (Figarella et al. 2023: 336,603 participants and Son et al. 2016: 81,816 participants), even so the magnitude of effect in the meta-analyses were not large enough (RR>2) to upgrade the strength of evidence. The baseline differences among study subjects also affected the grading negatively.

Overall completeness and applicability of evidence

This report includes six studies and 427,369 pregnant women with singleton pregnancies. There are apparent limitations reflected in the low grading. The RCTs had some risk of bias, and the cohort studies had some or major risk of bias. All included studies apart from Figarella et al. 2023 (336,603 participants) excluded high risk patients, i.e. previous PTB or spontaneous PTB, which make the results difficult to apply to universal screening. The compliance to progesterone treatment is only reported in Melchor et al. 2023, making the results difficult to relate to progesterone effect. Progesterone treatment alone to prolong a pregnancy with a short cervix is also difficult to evaluate since several studies combined progesterone treatment with cerclage or pessary. In addition, important baseline characteristics, for example description of high-risk patients, were missing in the cohort studies (Mishra et at. 2018, Figarella et al. 2023, Melchor et al. 2023 and Souka et al. 2024). Some studies reported a high baseline rate of PTB compared to Sweden i.e Melchor et al. (2023) reported 25%. Finally, in most studies, the description of the process for certification of ultra sonographers, the measurement technique and quality analysis of scans is not complete. There are some positive aspects: there seems to be consensus regarding the cut-off for short cervix and first line treatment for short cervix making the results homogenous. All included studies used a 25 mm cut-off for short cervix apart from Souka et al. that used ≤15 mm. Most studies prescribed vaginal progesterone (with or without additional treatment) if the cervix was short. One study included treatment with vaginal progesterone and/or cerclage and/or pessary (Figarella et al. 2023).

Agreements and disagreements with other studies and reviews

A recent systematic review evaluated the risk of spontaneous PTB with or without universal transvaginal ultrasound screening (Hessami et al. 2024). The meta-analysis included eight studies, five of these are also included in this report. Importantly, one of the two RCTs in our report (Saccone et al.) was published after the systematic review by Hessami et al. was conducted. In contrast to our report, Hessami et al. concluded that universal screening in women without prior spontaneous PTB significantly decreases spontaneous PTB before 37 weeks. The main reason for this discrepancy is that the conclusion by Hessami et al. is based on a combined meta-analysis of RCTs and cohort studies. Hessami et al. also used a different tool for evaluation of certainty of evidence (the Newcastle-Ottawa Scale and the Risk of Bias 2 tool). The consequence of analysing RCTs and cohort studies together is that cohort studies with considerably higher total number of participants will dominate the result of the meta-analysis. This is problematic since cohort studies are susceptible to biases that are difficult to eliminate. In our current report results from RCTs and cohort studies were analysed separately. Furthermore, the main conclusion of our report is based on meta-analysis of RCTs and not cohort studies due to concerns related to risk of bias in the latter study design. This is in accordance with the GRADE methodology for evaluation of certainty of evidence (Higgins et al. 2024). A separate analysis of RCTs was also more meaningful in our current report since one more RCT was available.

14 Future perspectives

Scientific knowledge gaps

There is need for more robust evidence concerning the effect of cervical length screening followed by progesterone, with or without additional treatment, on PTB rates in the general population. We conclude in this report that it is uncertain whether universal cervical length screening with vaginal ultrasound, followed by progesterone treatment for women with short cervix reduces the rate of PTB, and neonatal morbidity and mortality. However, given the low certainty of evidence, a clinically relevant effect of this screening strategy is nevertheless excluded. Point estimates in the direction of a positive effect of screening on PTB (although not statistically significant) for almost all outcomes in RCTs and statistically significant reduction of PTB in screening groups in cohort studies are interesting signals that prompt further investigation.

RCTs with considerably more participants than those included in this systematic review would be necessary to investigate this issue with a statistical power that is sufficient to detect a clinically relevant effect. It is also important to keep in mind that the real aim of a screening program is to reduce perinatal mortality and morbidity rather than PTB *per se* and even larger studies would be required to demonstrate effect on those outcomes. A pragmatic alternative to a study randomised on the individual level could be a national stepped wedge cluster randomised trial (Hemming et al. 2015). Introducing cervical length screening to one group/cluster at a time in a randomised fashion would make investigation of screening more feasible with reasonable control over potential biases.

There is also data suggesting that other cut-off levels for cervical length and screening later in the pregnancy could be more accurate to prevent spontaneous PTB. A cervix <29 mm at routine ultrasound scan (week 18-20) identified 14.8% of women delivering spontaneously before 33 weeks versus 8% if measuring between 21-23 weeks and using the best cut-off of 27 mm (Kuusela et al. 2021). Hence, further studies may shed new light on optimal cervical length cut-off and optimal gestational week for examination.

Ongoing research

ClinicalTrials.gov and WHO ICTRP were searched resulting in 54 and 18 matches respectively. None of the ongoing studies found were relevant for this report.

15 Participants in the project

The question was nominated by

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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 PTB and is now the FIGO Division Director of Maternal and Newborn Health.

LB declares membership in FIGO (International Federation of Gynecology and Obstetrics) on longterm maternal health within the division of maternal and newborn health.

ACE, AL, BL, CHV, JK, MP, MZ, PK, PS, TW, UBW have no conflicts of interest related to the content of this HTA.

Among external reviewers:

OA and OB have no conflicts of interest related to the content of this HTA.

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 2024-09-05 to 2025-05-09.
Literature searches were conducted 2024-10-24.

Components of this Health Technology Assessment

- ✓ Description of methods
- ✓ PICO
- ✓ Full literature search
- ✓ Flowchart
- ✓ Selection based on relevance
- ✓ Quality assessment
- ✓ Data tabulation
- ✓ Evidence synthesis
- ✓ Meta-analysis
- ✓ Certainty of evidence by GRADE
- ✓ Summary
- ✓ Economical aspects
- ✓ Organisational aspects
- ✓ Ethical aspects
- ✓ Ongoing studies
- ✓ Excluded articles
- ✓ Participation of experts
- ✓ External review
- ✓ Knowledge gaps identified
- ✓ Conflict of interest reported

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

Question(s) at issue: Is universal cervical length screening with transvaginal ultrasound in women with singleton pregnancies followed by treatment with vaginal or oral progesterone, with or without additional therapy, when short cervix length is demonstrated, effective in preventing any or spontaneous PTB and does it affect perinatal outcomes?

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

P	Women with singleton pregnancies in the first or second trimester.
I	Screening with transvaginal ultrasound and measurement of cervical length followed by treatment with vaginal or oral progesterone, with or without additional therapy, if short cervical length* is demonstrated
C	No screening with transvaginal ultrasound
O	Critical for decision making: • Any preterm birth, any cut off below 37+0 weeks, defined by the authors • Spontaneous preterm birth, any cut off below 37+0 weeks, defined by the authors • 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.

*As defined by the authors

<u>Eligibility criteria</u>

Study design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled studies with at least 1,000 screened women

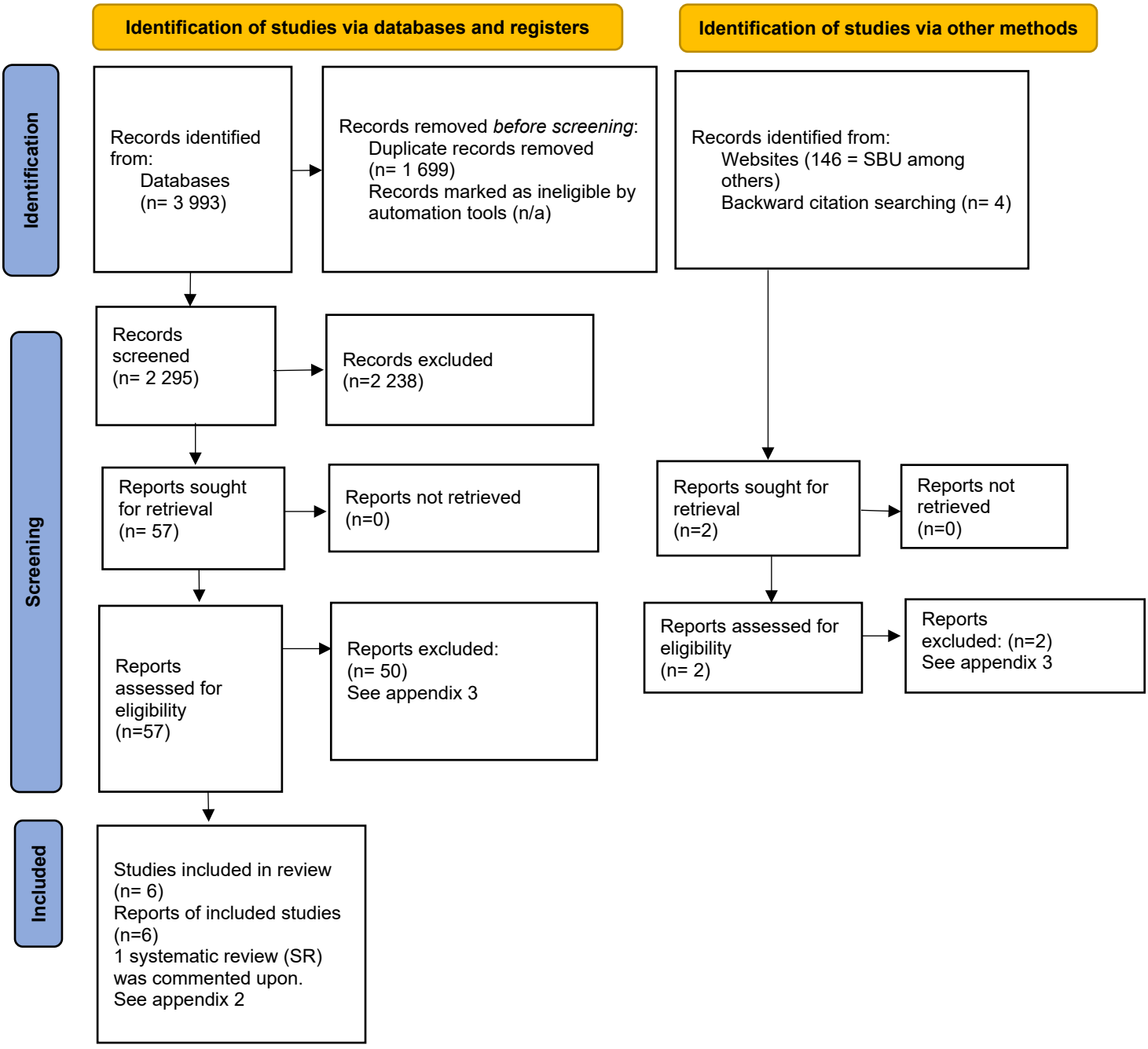
Language:
English, Swedish, Norwegian, Danish

Publication date:
1980-
Time limit SR: 2020-

Planned subgroup analyses
Different cut-offs for cervical length
Women with previous PTB
Women without previous PTB
First trimester vs second trimester screening
Exclusion of studies where the intervention includes more than only progesterone

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



Database: Medline ALL (OvidSP)
Date: 24 Oct 2024
No. of results: 1,686

Search	Query	Items found
1	exp Ultrasonography/	501868
2	exp Mass Screening/	148254
3	Cervix Uteri/di, dg	2071
4	(Echotomograph* or Echograph* or Sonograph* or Ultrasound* or Ultrason* or screening* or scan*).ab,kf,ti.	1941569
5	1 or 2 or 3 or 4	2222554
6	exp Cervical Length Measurement/	930
7	(Cervi* adj4 (length* or measurement* or short* or assessment*)).ab,kf,ti.	6964
8	6 or 7	7025
9	Premature Birth/	23547
10	exp Infant, Premature/	67969
11	(Prematur* or Pre-matur* or Preterm* or Pre-term*).ab,kf,ti.	264757
12	9 or 10 or 11	280103
13	5 and 8 and 12	1882
14	(comment or editorial or letter).pt.	2288402
15	13 not 14	1800
16	limit 15 to (danish or english or norwegian or swedish)	1686
17	limit 16 to yr="1980 -Current"	**1686**

exp/ = term from the Medline controlled vocabulary, including terms found below this term in the MeSH hierarchy
/ = term from the Medline controlled vocabulary, does not include terms found below this term in the MeSH hierarchy
/di = diagnosis a subheading to pinpoint a specific aspect of a subject heading concept.
/dg = diagnostic imaging a subheading to pinpoint a specific aspect of a subject heading concept.
adj4 = next to each other, in any order, up to 3 word(s) in between
.ab,kf,ti. = abstract, author keyword and title
.pt. = publication type
***** at end of word = truncation of word for alternate endings

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Database: Embase 1974 to 2024 October 14 (OvidSP)
Date: 24 Oct 2024
No. of results: 2,065

#	Searches	Results
1	exp echography/	1081466
2	exp mass screening/	336071
3	uterine cervix/di [Diagnosis]	2
4	(Echotomograph* or Echograph* or Sonograph* or Ultrasound* or Ultrason* or screening* or scan*).ab,kf,ti.	2725310
5	1 or 2 or 3 or 4	3493414
6	cervical length measurement/	2791
7	(Cervi* adj4 (length* or measurement* or short* or assessment*)).ab,kf,ti.	10427
8	6 or 7	10789
9	exp prematurity/	138090
10	(Prematur* or Pre-matur* or Preterm* or Pre-term*).ab,kf,ti.	361886
11	9 or 10	385929

12	5 and 8 and 11	3518
13	limit 12 to (article or article in press or conference paper or note or "review")	2250
14	limit 13 to (danish or english or norwegian or swedish)	2073
15	**limit 14 to yr="1980 -Current"**	**2065**

exp/ = term from the Embase controlled vocabulary, including terms found below this term in the Emtree hierarchy
/ = term from the Embase controlled vocabulary, does not include terms found below this term in the Emtree hierarchy
/di = diagnosis a subheading to pinpoint a specific aspect of a subject heading concept.
adj4 = next to each other, in any order, up to 3 word(s) in between
.ab,kf,ti. = abstract, author keyword and title
***** at end of word = truncation of word for alternate endings

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Database: The Cochrane Library
Date: 24 Oct 2024
No of results: 242 ref
Cochrane reviews: 10
Cochrane protocols: 0
Trials: 232
Editorials: 0
Special collections: 0
Clinical answers: 0

#	Searches	Results
#1	MeSH descriptor: [Ultrasonography] explode all trees	19578
#2	MeSH descriptor: [Mass Screening] explode all trees	6079
#3	MeSH descriptor: [Cervix Uteri] this term only and with qualifier(s): [diagnostic imaging - DG]	132
#4	(Echotomograph* or Echograph* or Sonograph* or Ultrasound* or Ultrason* or screening* or scan*):ti,ab,kw (Word variations have been searched)	180968
#5	#1 or #2 or #3 or #4	186683
#6	MeSH descriptor: [Cervical Length Measurement] explode all trees	119
#7	((Cervi* NEAR/3 (length* or measurement* or short* or assessment*))):ti,ab,kw (Word variations have been searched)	1398
#8	#6 or #7	1398
#9	MeSH descriptor: [Premature Birth] this term only	2548
#10	MeSH descriptor: [Infant, Premature] explode all trees	5924
#11	(Prematur* or Pre-matur* or Preterm* or Pre-term*):ti,ab,kw (Word variations have been searched)	36114
#12	#9 or #10 or #11	36114
#13	#5 AND #8 AND #12	419
#14	(clinicaltrials OR trialsearch):so	535215
#15	#13 NOT #14	295
#16	(conference proceeding):pt	248848
#17	#15 NOT #16	**242**

MeSH descriptor: [] explode all trees = term from the MeSH controlled vocabulary, including terms found below this term in the hierarchy
NEAR/3 = Next to each other, in any order, up to 3 words in between
:ti,ab,kw = title, abstract and author keywords
:pt = publication type
***** = truncation of word for alternate endings

The websites listed below were visited 14 Oct 2024.
Nothing relevant to the question at issue was found/

Source	Search terms / Browsing	No. of results	No. of relevant results
SBU www.sbu.se "Visa även träffar äldre än 5 år"	Cervix	4	1 relevant: SBU. Kartläggning av metoder för diagnostik och behandling av graviditetskomplikationen hotande spontan förtidsbörd – Identifiering av evidens och vetenskapliga kunskapsluckor utifrån systematiska översikter. Stockholm: Statens beredning för medicinsk och social utvärdering (SBU); 2021. SBU Kartlägger 320_2. [accessed Jan 18 2022]. Available from: https://www.sbu.se/320_2.
	Förtidsbörd	6	2 relevant varav en dubblett: Ljungström E, Möller AC, Bergman L, Ekelund A-C, Hongslo Vala C, Jacobsson B, Kuusela P, Liljegren A, Petzold M, Sjögren P, Svensson M, Wennerholm U-B, Strandell A Titel: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies. [Progesteron, cerclage, pessar eller acetylsalicylsyra för att förebygga förtidsbörd hos enkel- och flerbördsgraviditeter]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum: 2022. Regional activity-based HTA 2022:127 – 130
	Preterm	14	2 relevanta = dubbletter
	Premature	9	0 relevanta
	Pre-term	71	2 relevanta = 2 dubbletter
	Ultraljud	42	1 relevant = dubblett
Folkehelseinstituttet (Norge) https://www.fhi.no/ku/metodevurdering/	Browsat kategori Metodevurdering – Rapporter	0	0 relevanta
Behandlingsrådet (Danmark) https://behandlingsraadet.dk/	Browsat	0	0 relevanta
Nationale Kliniske Anbefalinger og Retningslinjer (Danmark) https://www.sst.dk/da/Fagperson/Retningslinjer-og-procedurer/NKA-og-NKR/NKR-og-NKA-efter-omraade	Browsat Övrige emner	0	0 relevanta
CAMTÖ	Browsat från 2020:39 t.o.m. 2024:72	0	0 relevanta

https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/			
HTA Region Stockholm https://www.chis.regionstockholm.se/hta/rapporter/	Browsat 2020:53-2024:03	0	0 relevanta
Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/	Browsat 2020-2021 (finns inga senare rapporter)	0	0 relevanta
HTA Syd https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365	Browsat 2020-2024:1	0	0 relevanta
Medicinska rådet, Region Dalarna https://www.regiondalarna.se/plus/vard/utveckling-och-utbildning/kunskapsstyrning/vetenskapliga-radet/#:~:text=Vetenskapliga%20r%C3%A5det%20inr%C3%A4ttades%202024.,beslut%20i%20%C3%B6vergripande%20medicinska%20fr%C3%A5gor.	Browsat. Publicerade rapporter saknas **241015 info. På webbsidan:** Vetenskapliga rådet inrättades 2024 och ersätter Medicinska rådet och Omvårdnadsrådet, som tidigare var de som drev Region Dalarnas arbete med Health Technology Assessment (HTA). *Rapporter från det tidigare medicinska rådet* *Kontakta Vetenskapliga rådet om du önskar få tag i någon av rapporterna.*	-	-

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Reference lists

A comprehensive review of reference lists brought four new records.

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Project: Cervixscreening

Appendix 2 Included articles

Author Year Country	Trial registration Funding	Study design	Study period	Timing of TVU	High risk patients included?	Cervical length cut-off	Interventions for prevention PTB	Concomitant intervention	Number of participants	Outcome variables Primary outcome in bold text
Mishra 2018 India, one tertiary centre	CTRI/ 2016/01/ 010438 No conflicts of interest reported	RCT	July 2014 to Dec 2015	16-24 w	No prior second trimester abortion or singleton sPTB (>16 to < 37 w), >2 first trimester abortions, multifetal pregnancy, fetal malformations, medical disorders	≤25 mm	I: Vaginal progesterone 200 mg daily until 37 w C: Routine care	I+C: If PTL or PPROM: iv fluid, tocolysis, betamethasone, if PPROM also antibiotics and vaginal progesterone were stopped	I: 150 (screened) C: 150 (not screened)	**sPTB <37 w (PO)** 32-36+6 w, 28-31+6 w, <28 w BW NNM Composite: RDS, IVH, NICU admission, jaundice, or death The components NICU admission RDS, IVH reported also reported.
Saccone 2024 Italy, 2 centres	NCT 0292830 2	RCT	July 2018 to Dec. 2022	18+0-23+6 w	No multifetal pregnancy, previous sPTB. At randomisation: PPROM, bleeding, symptoms of PTL, major malformations, cerclage or pessary in situ	≤25 mm	CL ≤25 mm: I: Vaginal progesterone 200 mg daily and pessary until 36w CL 25.1 to 29.9 mm: TVU within 1 week, if ≤25 mm, 200 mg progesterone daily and pessary, if > 25 mm no further exam C: Routine care	CL ≤25 mm: I: Pessary until 36w If CL ≤5 mm speculum exam and if dilation ≥15 mm or visible membranes: physical examination-indicated cerclage and progesterone	I: 675 (screened) C: 659 (not screened)	**PTB <37 w (PO)** PTB < 34, <32, <30, <28, <24 w sPTB <37, 34, 32, 30, 28, 24 w (sPTB in supplementary file) BW NICU admission NNM <28 d Stillbirth and NNM Composite neonatal adverse outcome (at least one): NNM, IVH ≥ grade 3, NEC, RDS, BPD, proven sepsis
Figarella 2023 France	NCT 0259832 3	Cohort before-after	Before (period A)	At the time of	All women with a singleton pregnancy and delivery after	≤25 mm	Vaginal progesterone 200 mg daily		Period A (C) 171,079	**PTB <37 w (PO)** induced PTB, length of hospital stay for PTL

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Appendix 2 Included articles

Author Year Country	Trial registration Funding	Study design	Study period	Timing of TVU	High risk patients included?	Cervical length cut-off	Interventions for prevention PTB	Concomitant intervention	Number of participants	Outcome variables Primary outcome in bold text
multi-center, 41 maternities	No conflicts of interest reported		Jan 1 2012 to Dec 3 2014 After (period B) May 1 2015 to April 30 2018	the second trimester anatomy scan	24 w were included		or cerclage or pessary		(not screened group), (49,504, (28.9%) were screened) <u>Period B (I)</u> 165,524 (screened group) (87,546 (52.9%) were screened	(with TVU, with/without treatment for PTB prevention), no of hospital admissions, NICU days, neonatal resuscitation, stillbirths
Melchor Corco-stegui 2023 Spain University Hospital of Vizcaya	NA No conflicts of interest reported	Cohort before-after	Jan 1 2011 to Dec 31 2011 (not screened) and Jan 1 2018 to Dec 31 2018 (screened)	19+0-22+6 w	Excluded if prior sPTB	<25 mm	Vaginal progesterone 200 mg daily until 36+6 w	Cerclage if CL<10 mm or progressive cervical shortening in women with CL <25 mm	Women included in analysis/ all women presenting with tPTL: I: 483/628 (screened) C: 410/482 (not screened)	tPTL, PTL, length of hospital stay, sPTB<37, <35, <34, <32 <28 w

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Appendix 2 Included articles

Author Year Country	Trial registration Funding	Study design	Study period	Timing of TVU	High risk patients included?	Cervical length cut-off	Interventions for prevention PTB	Concomitant intervention	Number of participants	Outcome variables Primary outcome in bold text
Son 2016 US North-western Memorial Hospital Chicago	NA No conflicts of interest reported	Cohort before-after	Jan 2007 to Jan 2014	18-24 w	Excluded if <18 y, multifetal pregnancy, previous PTB <37w, also, if spontaneous miscarriage loss at <20 w or if terminating pregnancy <24 w	≤25 mm	≤20 mm: vaginal progesterone 200 mg daily >20-≤25 mm follow up at <24 w	≤25 mm also digital cervical examination and cerclage if cervical dilation <24 w	I: 17,609 (screened) C: 46,598 (not screened)	**PTB <37 w** (PO) PTB <34, <32 w sPTB <37, 34, 32 w
Souka 2024 Greece 2 private fetal medicine units	NA No conflicts of interest reported	Cohort propensity score matched	Jan 2006 to Dec 2015	20-24 w	Excluded if previous spontaneous preterm birth, second trimester abortion history of cervical surgery or congenital uterine malformations, singletons from embryo reduction, intrauterine death of one twin	≤15 mm	Vaginal progesterone 200 mg daily or cerclage or pessary, at the discretion of the obstetrician. Progesterone in the majority of cases.	Cerclage or pessary added if persistent cervical shortening, despite progesterone	I: 3,103 (screened) C:3,103 (not screened) Original sample 10,133 (6,913 screened, 3,220 not screened)	sPTD32: sPTB between 24 and 31+6 w sPTD20-32: sPTB <32 w or spontaneous miscarriage between 20 and 23 w (No PO)

BPD: bronchopulmonary dysplasia, BW: birth weight, C: control, CL: cervical length, CTRI: Clinical Trials Registry India, I: intervention, IVH: intraventricular haemorrhage, NA: not available, NEC: necrotising enterocolitis, NICU: neonatal intensive care unit, NNM: neonatal mortality, PO: primary outcome, PTL: preterm labour, PPROM: preterm prelabour rupture of the membranes, PTB: preterm birth, RCT: randomised controlled study, RDS: respiratory distress syndrome, sPTB: spontaneous preterm birth, sPTD: spontaneous preterm delivery, tPTL: threatening preterm labour, TVU: transvaginal ultrasound, US: Unites States, w: weeks

Project: Cervix screening
Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Boelig, 2021	Wrong comparison (comparison with no screening is missing)
Brown, 2023	Wrong comparison (comparison with no screening is missing)
Cahill, 2010	Wrong study design (decision-analysis model)
Crosby, 2016	Wrong study design (decision-analysis model)
Einerson, 2016	Wrong study design (decision-analysis model)
Erasmus, 2005	Wrong comparison (comparison with no screening is missing)
Facco, 2013	Wrong comparison (comparison with no screening is missing)
Granese, 2017	Wrong comparison (comparison with no screening is missing)
Gudicha, 2021	Wrong comparison (comparison with no screening is missing)
Heath, 1998	Wrong comparison (comparison with no screening is missing)
Hebbar, 2006a	Wrong comparison (comparison with no screening is missing)
Hebbar, 2006b	Wrong comparison (comparison with no screening is missing)
Hutcheon, 2012	Wrong publication type (commentary)
Iams, 1996	Wrong comparison (comparison with no screening is missing)
Jain, 2016	Wrong study design (decision-analysis model)
Kuusela, 2015	Wrong intervention
Kuusela, 2020	Wrong focus (estimate inter- and intraobserver agreement and reliability)
Kuusela, 2021	No intervention
Leshno, 2024	Wrong study design (decision-analysis model)
Liu, 2021	Wrong population (third trimester included)
Maerdan, 2017	Wrong comparison (comparison with no screening is missing)
Marotta, 2017	Wrong population (twins)
Maymon, 2023	Wrong intervention (primary screening with transabdominal ultrasound)
McCurdy, 2020	Wrong study design (decision-analysis model)
Miller, 2015	Wrong comparison (comparison with no screening is missing)
Navathe, 2019	Wrong outcome (preterm labour not birth)
Newnham, 2017	Wrong intervention (primary screening with transabdominal ultrasound)
Orzechowski, 2014a	Wrong control group (subjects declining screening)
Orzechowski, 2014b	Wrong focus (evaluation of implementation and acceptability of universal screening)
Orzechowski, 2015	Wrong comparison (comparison with no screening is missing)
Romero, 2021	Wrong publication type (opinion)
Rosenbloom, 2020	Wrong comparison (comparison with no screening is missing)

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Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Sandager, 2003	Wrong study design (review, not systematic)
Schlembach, 2017	Wrong language (German)
Serrvalli, 2023	Wrong comparison (comparison with no screening is missing)
Shainker, 2016	Wrong intervention (cerclage without progesterone)
Silva, 2023	Wrong study design (decision-analysis model)
Slager, 2012	Wrong publication type (summery)
Son, 2017	Wrong study design (review, not systematic)
Soto-Torres, 2023	Wrong comparison (comparison with no screening is missing)
Souka, 2019	Duplicate publication (Souka 2024)
Stratulat, 2024	Wrong control (screening with transabdominal ultrasound)
Taipale, 1998	Wrong comparison (comparison with no screening is missing)
Temming, 2016a	Wrong control group (subjects declining screening)
Temming, 2016b	Wrong study design (review, not systematic)
Werner, 2011	Wrong study design (decision-analysis model)
Werner, 2015	Wrong study design (decision-analysis model)
Wikstrom, 2021	Wrong comparison (comparison with no screening is missing)
Wikström, 2022	Wrong study design (decision-analysis model)
Williams, 2004	Wrong intervention (cerclage without progesterone)
Wu, 2024	Wrong comparison (comparison with no screening is missing)
Wulff, 2018	Wrong control group (subjects declining screening)

Project: Cervixscreening

* + No or minor problems
? Some problems
- Major problems

Appendix 4.1
Outcome variable: Any preterm birth

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)	Difference				
Saccone 2024 Italy	RCT	n=1.334 I=675 C=659	I=36 C=41 Eligible: 1487 Excluded before enrolment: 153 (including declined 69)	< 37w: 48/639 (7.5) < 34w: 14/639 (2.2) < 32w: 9/639 (1.4) < 30w: 6/639 (0.9) < 28w: 3/639 (0.5) < 24w: 0/639	< 37w: 54/618 (8.7) < 34w: 14/618 (2.3) < 32w: 10/618 (1.6) < 30w: 7/618 (1.1) < 28w: 5/618 (0.8) < 24w: 2/618 (0.3)	**RR (CI 95%), p value** 0.86 (0.59-1.25), 0.43 0.97 (0.46-2.01), 0.93 0.87 (0.36-2.13), 0.76 0.83 (0.28-2.45), 0.72 0.58 (0.14-2.42), 0.45 0.19 (0.01-4.02), 0.29	-	+	?	?
Figarella 2023 France	Cohort before-after	n=336,603 Period A C=171,079 (not screened) Period B I=165,524 (screened)	-	Period B < 37w: 9275/ 165,524 (5.60)	Period A < 37w: 9903/ 171,079 (5.79)	**aOR (95% CI), p value** 0.92 (0.89-0.95), <0.0001	Study with 2 parts, prospective cohort (ECHOCOL) not included in analysis. Variables used in adjusted analysis not shown, only described as "variables that had clinical relevance"	?	?/-	+
Son 2016 US	Cohort before-after	n=64,214 I=17,616 (screened) C=46,598 (not screened)	I: 7 terminated their pregnancies after screening, excluded from analysis. 19 declined screening, included in analysis.	< 37w: 1051/17,609 (6.0), p<0.001 < 34w: 291/17,609 (1.7), p=0.014 < 32w: 168/17,609 (1.0), p=0.41	< 37w: 3141/46,598 (6.7) < 34w: 907/46,598 (1.9) < 32w: 532/46,598 (1.1)	**OR (95% CI)** **aOR (95% CI)** 0.88 (0.82-0.94) 0.82 (0.76-0.88) 0.85 (0.74-0.97) 0.74 (0.64-0.85) 0.84 (0.70-0.99) 0.74 (0.62-0.90)	Adjusted for race/ethnicity, BMI, history of cervical excision, smoking, chronic hypertension and pregestational diabetes	+	?	+

aOR: adjusted odds ratio, BMI: body mass index, C: control, CI: confidence interval, I: intervention, n: number, OR: odds ratio, RCT: randomized controlled trial, RR: risk ratio, US: United States, w: weeks

Project: Cervixscreening

*	+	No or minor problems
	?	Some problems
	-	Major problems

Appendix 4.2
Outcome variable: Spontaneous preterm birth

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)	Difference				
Mishra 2018 India	RCT	n=300 I=150 C=150	I=3 (2 induced PTB, 1 lost to follow up) C=1 (induced PTB) Eligible: 1113 Excluded before enrolment: 813 (no decliners)	<37w: 15/147 (10.2) Subgroups (secondary outcome): 36+6 –32+0w: 13/147 (8.84) <32w: 2/147 (1.36) <28: 0/147	<37w: 12/149 (8.1) Subgroups (secondary outcome: 36+6 –32+0w: 11/149 (7.3) <32w: 1/149 (0.7) <28: 0/149	**p value** 0.433 0.370	73% excluded before enrolment.	?/-	?	-
Saccone 2024 Italy	RCT	n=1.334 I=675 C=659	I=36 C=41 Eligible: 1.487 Excluded before enrolment: 153 (including declined 69)	< 37w: 36/639 (5.6) < 34w: 9/639 (1.4) < 32w: 6/639 (0.9) < 30w: 4/639 (0.6) < 28w: 2/639 (0.3) < 24w: 0/639	< 37w: 39/618 (6.3) < 34w: 12/618 (1.9) < 32w: 8/618 (1.3) < 30w: 5/618 (0.8) < 28w: 3/618 (0.5) < 24w: 1/618 (0.2)	**RR (CI 95%), p value** 0.89 (0.58-1.39), 0.61 0.73 (0.31-1.71), 0.46 0.73 (0.25-2.08), 0.55 0.77 (0.21-2.87), 0.70 0.64 (0.11-3.85), 0.63 0.32 (0.01-7.90), 0.49		+	?	?
Figarella 2023 France	Cohort before-after	n=336, 603 Period A C=171, 079 before screening Period B I=165, 524 after screening	-	**Period B** <37w: 2976/165,524 (1.8)	**Period A** <37w**:** 3262/171,079 (1.9)	**OR 95% CI, p value** 0.94 (0.88-0.99), 0.02	During period A 49,504/171,079 (28.9%) were screened During period B 87.546/165.524 (52.9%) were screened	?	?/-	+

Project: Cervixscreening

* + No or minor problems
? Some problems
- Major problems

Appendix 4.2
Outcome variable: Spontaneous preterm birth

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)	Difference				
Melchor Corcostegui 2023 Spain	Cohort before-after	n=1110 I=628 screened C=482 not screened	I=145 C=72 Eligible: 1110 Excluded before enrolment: 128 (I: 103 C: 25) Excluded after enrolment: 89 (I: 42 C: 47), abandon or repeated visits	<37w: 77/483 (15.94) ≤35w: 59/483 (12.21) ≤34w: 35/483 (7.24) ≤32w: 12/483 (2.48) ≤28w: 4/483 (0.82)	<37w: 105/410 (25.60) ≤35w: 80/410 (19.51) ≤34w: 44/410 (10.73) ≤32w: 13/410 (3.17) ≤28w: 3/410 (0.73)	**p value** 0.0004 0.0027 0.0673 0.5334 0.8789		-	-	?
Son 2016 US	Cohort before-after	n=81,816 I=17,609 C=64,207	I: 7 terminated their pregnancies after screening, not included in analysis. 19 declined screening, included in analysis	<37w: 701/17,609 (4.0) p<0.001 <34w: 176/17,609 (1.0) p=0.004 <32w: 94/17,609 (0.5) p=0.017	<37w: 2258/46,598 (4.8) <34w: 594/46,598 (1.3) <32w: 328/46,598 (0.7)	**OR (95% CI)** **aOR (95% CI)** 0.81 (0.75-0.89) 0.79 (0.72-0.86) 0.78 (0.66-0.93) 0.72 (0.60-0.86) 0.76 (0.60-0.95) 0.70 (0.55-0.89)	Adjusted for race/ethnicity, BMI, history of cervical excision, smoking, chronic hypertension and pregestational diabetes	+	?	+
Souka 2024 Greece	Cohort propensity score matched	n= 6206 I=3103 screened C=3103 not screened	Eligible: 10,133 (I: 6913, C: 3220) Excluded: 3927 after propensity score matching	24-32w: 10/3103 (0.3) 20-32w: 10/3103 (0.3)	24-32w: 25/3103 (0.8) 20-32w: 27/3103 (0.9)	**HR (95% CI), p value** 0.39 (0.19-0.82), 0.013 0.36 (0.18-0.75), 0.006		?	-	?

aOR: adjusted odds ratio, C: comparison, CI: confidence interval, HR hazard ratio, I: intervention, n: number, OR: odds ratio, PTB: preterm birth, RCT: randomised controlled study, RR: risk ratio, US: United States, w: weeks

Project: Cervixscreening

* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Intrauterine fetal death, neonatal mortality

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Intervention	Control	Difference				
Mishra 2018 India, one tertiary centre	RCT	I: 150 screened C: 150 not screened	I: 3 (one lost to follow up, two iatrogenic PTBs) C: 1 (one iatrogenic PTB)	NNM 0/147 p=0.552	NNM 2/149	-	NNM not defined	?/-	?	-
Saccone 2024 Italy, 2 centres	RCT	I: 675 screened C: 659 not screened	-	IUFD 1/639 (0.2%) RR 0.97 (95% CI 0.06-15.43) p=0.98 NNM 3/639 (0.5%) 0.73 (95% CI 0.16-3.23) p=0.67	IUFD 1/618 (0.2%) NNM 4/618 (0.6%)	-	NNM (<28 days)	+	?	?

C: control, CI: confidence interval, I: intervention, IUFD: intrauterine fetal death, NNM: neonatal mortality, PTB: preterm birth, RCT: randomised controlled study, RR: risk ratio

Project: Cervixscreening

* + No or minor problems
? Some problems
- Major problems

Appendix 4.4
Outcome variable: Serious neonatal morbidity

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Intervention	Control	Difference				
Mishra 2018 India, one tertiary centre	RCT	I: 150 screened C: 150 not screened	I:3 (one lost to follow up, two iatrogenic PTBs) C: 1 (one iatrogenic PTB)	Neonates with complications* 21/147 (14.3%) p=0.187 Neonates with complications including NNM* 21/147 (14.3%) RDS 4*/147 (2.7%) p=0.554 IVH 1*/147 (0.7%) p=0.552	Neonates with complications* 16/149 (10.7%) Neonates with complications including NNM* 18/149 (12.1%) RDS 2/149 (1.3%) IVH 2/149 (1.3%)	-	*Neonates with complications include at least one of neonatal jaundice, RDS, IVH or neonatal jaundice without or with NNM. Neonatal complications calculated from table 3. **One neonate had RDS and IVH	?/-	?	-
Saccone 2024 Italy, 2 centres	RCT	I: 675 screened C: 659 not screened	I: 36 C: 41	Composite perinatal outcome including NNM* 19/639 (3.0%) RR 0.71 (95% CI 0.40-1.26) p=0.24 NEC 0/639 RR 0.32 (95% CI 0.01-7.90) p=0.49 IVH 3-4 1/639 (0.2%) RR 0.48 (95% CI 0.04-5.32) p=0.55	Composite perinatal outcome including NNM* 26/618 (4.2%) NEC 1/618 (0.2%) IVH 3-4 2/618 (0.3%)	-	*Composite perinatal outcome includes at least one of NEC, IVH 3-4, RDS, BPD, ROP, proven sepsis, or NNM	+	?	?

Project: Cervixscreening

* + No or minor problems
? Some problems
\- Major problems

Appendix 4.4
Outcome variable: Serious neonatal morbidity

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Intervention	Control	Difference				
				RDS 12/639 (1.9%) RR 0.61 (95% CI 0.30-1.25) p=0.18 BPD 1/639 (0.2%) RR 0.32 (95% CI 0.03-3.09) p=0.33 ROP 0/639 RR 0.14 (95% CI 0.01-2.67) p=0.19 Sepsis 6/639 (0.9%) RR 0.64 (95% CI 0.23-1.80) p=0.40	RDS 19/618 (3.1%) BPD 3/618 (0.5%) ROP 3/618 (0.5%) Sepsis 9/618 (1.4%)					

BPD: bronchopulmonary dysplasia, C: control, CI: confidence interval, I: intervention, IVH: intraventricular haemorrhage, IUFD: intrauterine fetal death, NEC: necrotizing enterocolitis, NNM: neonatal mortality, RCT: randomised controlled study, RDS: respiratory distress syndrome, ROP: retinopathy of prematurity; RR: risk ratio

Project: Cervixscreening

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author Year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**					
		Directness		**Study limitations**		**Precision**	
Mishra et al. 2018 India	RCT	?/-	Ethnicity High level of high-risk patients Unclear clinical setting/context Unclear selection process	?	Unclear if the allocation is concealed Unclear where the finance of the study comes from. Not blinded assessments No certification for ultrasound staff Important variables are missing (e.g. smoking, BMI) Unclear if the patient groups have been treated equally Protocol maybe registered after publication and not easily available Side effects not reported	-	Few events Power calculation not reasonable Power does not match the result at all
Saccone et al. 2024 Italy	RCT	+		?	Not blinded assessments Compliance and reasons for lost to follow-up not reported	-	Few events Power calculation too optimistic (50% reduction of PTB) Power does not match the results
Figarella et al. 2023 France	Cohort before-after	?	Unclear ethnicity Difficult to evaluate the effect with so many screened in the comparison group (28.9%) - however relevant in a transition phase in Sweden Unclear number of women treated with progesterone	?/-	Not blinded assessments Baseline differences No statistical handling of group imbalances Important variables are missing Unclear compliance Not adjusted for any variables Side effects not reported	+	
Melchor et al. 2023 Spain	Cohort before-after	-	Unclear study population (high-risk patients not reported, no info on base population, only demographics for the small preterm labour group)	-	Not blinded assessments Confounders and finance not reported	?	Power calculations not reported Primary outcome not our outcome

Project: Cervixscreening

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author Year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**					
		Directness		**Study limitations**		**Precision**	
Son et al. 2016 US	Cohort before-after	+		?	Not blinded assessments Baseline differences Finance not reported Low treatment rate with progesterone	+	
Souka et al. 2024 Greece	Cohort propensity score matched	?	Private hospitals Unclear study population (high-risk patients not reported, missing important info) Unclear intervention (obstetrician decides treatment, limited cut-off to 15mm)	-	Not blinded assessments Risk of selection bias when choosing the control group Large dropout in the screening group Compliance not reported Unclear if the correct statistical methods were used (Hazard ratio)	-	Power calculations not reported Few events

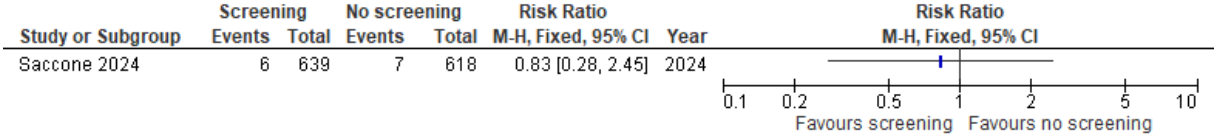
BMI: Body mass index, PTB: preterm birth, RCT: randomised controlled trial, US: United States

Appendix 6. Results

Any PTB before 30+0 weeks

Any PTB before 30+0 weeks were reported in one RCT (Saccone et al. 2024, n=1257). The RCT showed no reduction in the rate of any preterm birth before 30+0 weeks (RR 0.83, 95% CI 0.28-2.45, p value 0.73)

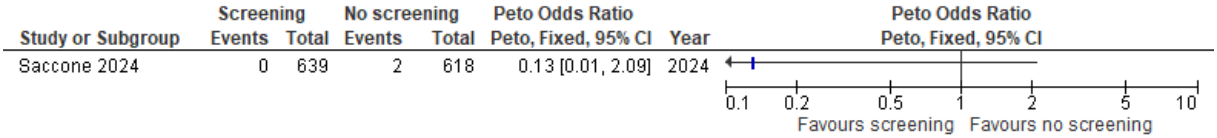
Figure 1 Any PTB before 30+0 weeks. RR for screening compared with no screening



Any PTB before 24+0 weeks

Any PTB before 24+0 weeks were reported in one RCT (Saccone et al. 2024, n=1257). The RCT showed no reduction in the rate of any preterm birth before 24+0 weeks (RR 0.13, 95% CI 0.01-2.09, p value 0.15).

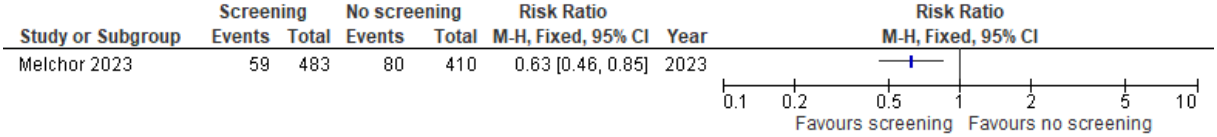
Figure 2 Any PTB before 24+0 weeks. RR for screening compared with no screening



Spontaneous PTB before 35+0 weeks (Appendix 4.2)

Spontaneous PTB before 35+0 weeks was reported in one cohort study (Melchor et al. 2023, n=893). The cohort study showed a reduction in the rate of spontaneous PTB before 35 weeks (RR 0.63, 95% CI 0.46-0.85, p value 0.003).

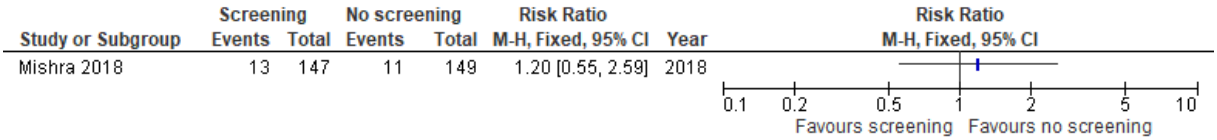
Figure 3 Spontaneous PTB before 35+0 weeks. RR for screening compared with no screening



Spontaneous PTB between 32+0 and 36+6 weeks (Appendix 4.2)

Spontaneous PTB 32+0 to 36+6 weeks were reported in one RCT (Mishra et al. 2018, n=296). The RCT showed no reduction in the rate of spontaneous preterm birth 32+0-36+6 weeks (RR 1.20, 95% CI 0.55-2.59, p value 0.65).

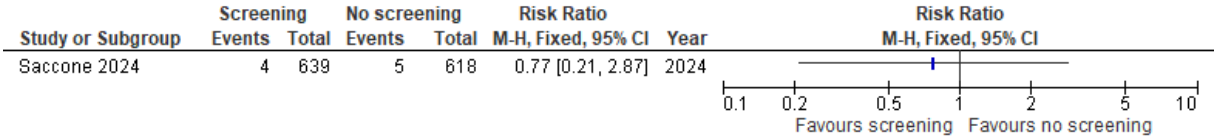
Figure 4 Spontaneous PTB between 32+0 and 36+6 weeks. RR for screening compared with no screening



Spontaneous PTB before 30+0 weeks (Appendix 4.2)

Spontaneous PTB before 30+0 weeks was reported in one RCT (Saccone et.al. 2024, n=1257). The RCT showed no reduction in the rate of spontaneous preterm birth before 30+0 weeks (RR 0.77, 95% CI 0.21-2.87, p value 0.70).

Figure 5 Spontaneous PTB before 30+0 weeks. RR for screening compared with no screening



Spontaneous PTB before 24+0 weeks (Appendix 4.2)

Spontaneous PTB before 24+0 weeks were reported in one RCT (Saccone et al. 2024, n=1257) and in one cohort study (Souka et al., 2024, n=6206). The RCT showed no reduction in the rate of spontaneous preterm birth before 24+0 weeks (Peto odds ratio 0.13, 95% CI 0.00-6.60, p value 0.31. The cohort study showed no reduction in the rate of spontaneous preterm birth before 24+0 weeks (Peto odds ratio 0.14, 95% CI 0.01-2.16, p-value 0.16).

Figure 6. Spontaneous PTB before 24+0 weeks. Peto odds ratio for screening compared with no screening