Evidence evaluation report — Cervical length measurement

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Contents

Key messages

- Evidence from systematic reviews of observational studies and subsequent observational studies suggests that cervical length measurement at the 18-20 week ultrasound using a threshold of 25 mm has the potential to predict preterm birth but is more accurate when combined with an assessment of relevant maternal factors. No evidence on harms associated with cervical length measurement was identified.
- Observational and cost-effectiveness studies suggest that universal measurement of cervical length and treatment with vaginal progesterone for women with a short cervix (≤25 mm) at 18-25 weeks reduces the risk of preterm birth and is cost-effective (in the United States and the United Kingdom). No Australian cost-effectiveness studies were identified.
- Evidence from observational studies suggests that initial transabdominal measurement of cervical length may represent a useful strategy for detecting women with short cervix on transvaginal ultrasound. However, the evidence is inconsistent in terms of gestational age and cut-offs and a cost-effectiveness study found that universal transvaginal ultrasound was more cost-effective than including an initial transabdominal measurement.
- Evidence from observational studies suggests that cervical length measurement earlier than 20 weeks may predict cervical shortening and risk of early preterm birth in women at high risk of preterm birth. However, a cervical length >25 mm does not preclude preterm birth in this group of women.
- Evidence from systematic reviews of RCTs and subsequent RCTs suggest that vaginal progesterone reduces the risk of preterm birth (<35 weeks) in women with a short cervix identified on ultrasound at 18-25 weeks (moderate quality evidence).
- No studies on the additional needs of Aboriginal and Torres Strait Islander women or migrant and refugee were identified or on women who require an interpreter to explain the transvaginal approach. However, issues of access to ultrasound services (eg due to remote location or language barriers) and availability of accredited trained professionals in some areas may limit the availability of cervical measurement for some women.

1 Process of the review

1.1 Research questions

1.1.1 Harms and benefits

Q1 What are the harms and benefits of measuring women's cervical length at the 20 week ultrasound?

Q2 Should measuring of cervical length be restricted to women with risk factors for preterm birth?

Q3 Should women's cervical length be measured via transabdominal or transvaginal ultrasound?

Q4 At what point/s in pregnancy should cervical length measuring/screening be undertaken in women who are at risk of preterm birth due to the presence of risk factors?

1.1.2 Interventions

Q5 What is the efficacy of progesterone in preventing preterm birth in women who are at risk of preterm birth due to short cervical length?

1.1.3 Additional considerations

Q6 What are the additional needs of Aboriginal and Torres Strait Islander women?

Q7 What are the additional considerations for migrant and refugee women?

1.1.4 PICO criteria used to inform the literature search

Population	Intervention	Comparator	Outcomes
Pregnant women	Cervical length measurement	No cervical measurement	Preterm birth <37 weeks Preterm birth <34 weeks
	Transvaginal ultrasound	Transabdominal ultrasound	Perinatal mortality Low birth weight (<2,500 g)
	Progesterone	Placebo/no treatment	Respiratory distress syndrome

1.2 Search strategy

To be included.

1.3 Exclusion criteria

Full texts of 319 papers were reviewed and the exclusion criteria outlined below applied.

- Background information (20 studies)
- Duplicate (4 studies)
- Not specific to target population (eg specific to multiple pregnancy) (70 studies)
- Does not answer research question (117 studies)
- Included in systematic review (10 studies)
- Overlap with included systematic review (6 studies)
- Narrative review or opinion paper (editorial, letter, comment)(24 studies).

The excluded studies are listed in Section 5.

Following application of the exclusion criteria, 68 studies were included in the analysis.

PRISMA diagram to be included.

1.4 Assigning level of evidence

Levels of evidence were assigned using the NHMRC levels and the study design definitions given in Section 1.5.

Level	Intervention	Aetiology
I	Systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study
III-1	Pseudo-randomised trial	All or none
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with control group	A retrospective cohort study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without parallel control	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross-sectional study or case series

1.5 Study design definitions

- **Case series** – a single group of people exposed to the intervention (factor under study). **Post-test** – only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made. **Pre-test/post-test** – measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared (also known as a 'before- and-after study').
- **Case-control study** – people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study.
- **Cross-sectional study** – a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time ie proportion of people with asthma in October 2004. This type of study is useful for hypothesis-generation, to identify whether a risk factor is associated with a certain type of outcome, but more often than not (except when the exposure and outcome are stable eg genetic mutation and certain clinical symptoms) the causal link cannot be proven unless a time dimension is included.
- **Historical control study** – outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (ie. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention.
- **Non-randomised, experimental trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared. This can include:
  - **a controlled before-and-after study**, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group.
  - **an adjusted indirect comparison**, where two randomised controlled trials compare different interventions to the same comparator ie. the placebo or control condition. The outcomes from the two interventions are then compared indirectly.
- **Prospective cohort study** – where groups of people (cohorts) are observed at a point in time to be *exposed or not exposed* to an intervention (or the factor under study) and then are followed prospectively with further outcomes recorded as they happen.

- **Pseudo-randomised controlled trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared.
- **Randomised controlled trial** — the unit of experimentation (eg. people, or a cluster of people4) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared.
- **Retrospective cohort study** — where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes, eg. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis.
- **Systematic literature review** — systematic location, appraisal and synthesis of evidence from scientific studies.
- **Two or more single arm study** - the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared.

Source: NHMRC (2009) *NHMRC levels of evidence and grades of recommendations for developers of guidelines.*

1.6 Selection of outcomes for GRADE analysis

Outcomes were selected on the basis of clinical impact.

Outcome	Importance	Inclusion
Perinatal mortality	9	☑
Preterm birth <37 weeks	9	☑
Preterm birth <34 weeks	9	☑
Birth weight <2,500 g	9	☑
Respiratory distress syndrome	9	☑

Key: 1 - 3 less important; 4 - 6 important but not critical for making a decision; 7 - 9 critical for making a decision

1.7 Quality assessment

Quality of included studies was assessed using adapted NHMRC criteria for quality assessment of systematic reviews and GRADE criteria for quality assessment of randomised controlled trials and observational studies.

Assessment of quality of systematic literature reviews

Considerations in assessing quality of systematic reviews
Questions and methods clearly stated
Search procedure sufficiently rigorous to identify all relevant studies
Review includes all the potential benefits and harms of the intervention
Review only includes randomised controlled trials
Methodological quality of primary studies assessed
Data summarised to give a point estimate of effect and confidence intervals
Differences in individual study results are adequately explained
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included
Reviewers' conclusions are supported by data cited
Sources of heterogeneity are explored

Source: Adapted from (NHMRC 2000a; NHMRC 2000b; SIGN 2004).

Assessment of limitations of randomised controlled trials

Study limitation	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (a major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial).
Incomplete accounting of patients and outcome events	Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available. The significance of particular rates of loss to follow-up, however, varies widely and is dependent on the relation between loss to follow-up and number of events. The higher the proportion lost to follow-up in relation to intervention and control group event rates, and differences between intervention and control groups, the greater the threat of bias.
Selective outcome reporting	Incomplete or absent reporting of some outcomes and not others on the basis of the results.
Other limitations	Stopping trial early for benefit. Substantial overestimates are likely in trials with fewer than 500 events and large overestimates are likely in trials with fewer than 200 events. Empirical evidence suggests that formal stopping rules do not reduce this bias. Use of unvalidated outcome measures (e.g. patient-reported outcomes) Carryover effects in crossover trial Recruitment bias in cluster-randomised trials

Source: (Schünemann et al 2013).

Assessment of limitations of observational studies

Study limitation	Explanation
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	Under- or over-matching in case-control studies Selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	Differences in measurement of exposure (e.g. recall bias in case-control studies) Differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	Failure of accurate measurement of all known prognostic factors Failure to match for prognostic factors and/or adjustment in statistical analysis
Incomplete or inadequately short follow-up	Especially within prospective cohort studies, both groups should be followed for the same amount of time.

Source: (Schünemann et al 2013).

Quality criteria of diagnostic accuracy studies derived from QUADAS-2

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 X 2 table Describe the interval and any interventions between index tests and the reference standard

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Signaling questions	Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?

Source: (Schünemann et al 2013).

1.8 Assessing clinical utility of tests

- *Risks*: what is the extent of the risks associated with the condition?
- *Diagnostic accuracy*: how does the test compare to a reference test?
- *Prevalence*: at what prevalence does testing make a difference?
- *Treatment*: is effective treatment available and does it improve maternal/fetal outcomes?
- *Cost-effectiveness*: is the test cost-effective for the target population in the Australian context?

1.9 Grading of the certainty of the body of evidence

Assessing the certainty of a body of evidence using GRADE involves consideration of the following five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

For an evidence base drawn from RCTs, the grading of the certainty of the body of evidence starts at 'high'. An evidence base drawn from observational studies starts as 'low'. In both cases, the evidence can be downgraded for each of the five domains depending on whether the limitation is considered serious (downgrade one level) or very serious (downgrade two levels). Evidence can also be upgraded when the effect is large (upgrade one level) or very large (upgrade two levels), where confounders would reduce the effect or where there is a dose-response effect.

Diagnostic accuracy studies start as high quality evidence. However, these studies are vulnerable to limitations and often lead to low quality evidence, mostly owing to indirectness of evidence associated with diagnostic accuracy being only a surrogate for patient outcomes.

2 Harms and benefits of cervical length measurement

2.1 Q1: What are the harms and benefits of measuring women's cervical length at the 20 week ultrasound?

2.1.1 Background information

Factors associated with increased risk of short cervical length at mid trimester include:

- previous spontaneous (Cho et al 2017) (Palma-Dias et al 2004) or induced (Miller et al 2015) preterm birth
- previous cervical excisional procedure (Miller et al 2015; Cho et al 2017)
- non-Caucasian ethnicity (Miller et al 2015; van der Ven et al 2015; Buck et al 2016).

Studies were inconsistent in their results on the impact of BMI and cervical length, finding:

- no significant association with maternal weight (Cho et al 2017)
- shortest mean cervical lengths among underweight women (Palma-Dias et al 2004; Kandil et al 2017)
- shorter cervical length at 18-22 weeks associated with higher maternal weight (van der Ven et al 2015).

Studies were also inconsistent in regard to maternal age:

- maternal age was not significantly associated with women having a short cervix (Miller et al 2015)
- shorter mid-trimester cervical length was associated with younger maternal age (van der Ven et al 2015)
- there was no difference in mean cervical length or incidence of cervical length ≤25 mm between women younger than 19 years and women aged 20-24 years (Buck et al 2018)
- women having their first baby who were younger than 16 years had shorter cervices than older women, and a higher percentage had cervices shorter than 25 mm (D'Agostini et al 2013).

Studies were consistent in finding no significant association between short cervical length and maternal height (van der Ven et al 2015; Cho et al 2017) or assisted conception (Aboulghar et al 2009; Miller et al 2015).

2.1.2 Accuracy of cervical length measurement

Systematic reviews of observational studies were heterogeneous in populations and cut-off thresholds but suggest that cervical length is more accurate in predicting preterm birth when conducted before 20 weeks with a cut-off <25 mm.

Preterm birth	Population	Cut-off	Timing	Positive likelihood ratio (95%CI)	Reference
<34 wk	Low risk	<15 mm	14-20 wk	142.86 (3.58 to 5,709.07)	(Honest et al 2012)
		<20 mm		35.36 (4.32 to 289.68)	
		<25 mm		13.38 (6.90 to 25.96)	
		<30 mm		2.48 (1.19 to 5.19)	
	Low risk	<20 mm	20-24 wk	7.64 (5.21 to 11.20)	
		<22 mm		4.51 (1.16 to 17.64)	
		<25 mm		4.68 (3.64 to 6.03)	
		<30 mm		2.28 (1.91 to 2.71)	
<35 wk	Mixed risk	≤20 mm	14-24 wk	12.4	(Domin et al 2010)
		≤25 mm		6.30	
	High-risk	<25 mm	<20 wk	4.31 (3.08 to 6.01)	(Crane & Hutchens 2008)
			20-24 wk	2.78 (2.22 to 3.49)	
			>24 wk	4.01 (2.53 to 6.34)	
<37 wk	Low risk	<32.5 mm	20-24 wk	3.99 (2.84 to 5.62)	(Honest et al 2012)
	Mixed risk	<33.15 mm	14-24 wk	4.9	(Domin et al 2010)

Findings from observational studies suggest that short cervical length is a stronger predictor of preterm birth <34 weeks than preterm birth <37 weeks.

Preterm birth	Population	Cut-off	Timing	Effect	Reference
<34 weeks	Low risk	26 mm	18-24 wk	LR* 0.8 (0.4-1.8)	(Matijevic et al 2010)
		28 mm	18-22 wk	OR 28.7 (14.54-41.73)	(Barber et al 2010)
			16-23 wk	LR+ 6.62 (1.68 to 26.10)	(Kuusela et al 2015)
		29 mm	18-22 wk	OR 20.5 (11.51-25.05)	(Barber et al 2010)
		30 mm	18-22 wk	OR 10.3 (5.44-10.5)	
		31 mm	16-23 wk	LR+ 4.29 (1.94 to 9.47)	(Kuusela et al 2015)
		33 mm	16-23 wk	LR+ 2.08 (1.12 to 3.87)	
<37 weeks	Low risk	25 mm	20-24 wk	PPV 100; NPV 88.4	(Arora et al 2012)
	High risk	25 mm	14-24 wk	RR 3.3 (1.4 to 7.4)	(Visintine et al 2008)
	Low risk	26 mm	18-24 wk	LR* 2.7 (1.1 to 6.7)	(Matijevic et al 2010)
		28 mm	18-22 wk	OR 25.47 (15.5 to 41.73)	(Barber et al 2010)
			16-23 wk	LR+ 2.52 (0.78 to 8.15)	(Kuusela et al 2015)
		29 mm	18-22 wk	OR 16.98 (11.51 to 25.05)	(Barber et al 2010)
		30 mm	18-22 wk	OR 7.55 (5.44 to 10.5)	
		31 mm	16-23 wk	LR+ 2.20 (1.19 to 4.07)	(Kuusela et al 2015)
		33 mm	16-23 wk	LR+ 1.44 (0.95 to 2.17)	

* Weighted for prevalence

2.1.3 Cervical length measurement combined with other factors in women at low or mixed risk

In studies that investigated the combination of other factors and short cervical length in women of low or mixed risk:

- in women without a history of preterm birth, assessment of other risk factors for preterm birth does not add to prediction of preterm birth provided by cervical length alone (Mella et al 2013)
- detection rate of early preterm birth, at a fixed false-positive rate of 10%, was 38% for maternal factors (maternal characteristics and gestational age for previous preterm birth), 55% for cervical length and 69% for combined testing (To et al 2006)
- combined cervical length and obstetric history (nulliparity, gestational age for previous births) provides a better prediction of spontaneous preterm birth than either factor alone and the sensitivity of screening improves for increasing degrees of prematurity (Celik et al 2008)
- the magnitude of risk of preterm birth associated with short cervical length increases with a history of first- and second-trimester vaginal bleeding (Ramaeker & Simhan 2012)
- in low-risk women with singleton pregnancies, combined fetal fibronectin and cervical length had low predictive accuracy for spontaneous preterm birth (Jwala et al 2016; Esplin et al 2017).

2.1.4 Evidence summary

Evidence from systematic reviews of observational studies and subsequent observational studies suggests cervical length measurement at the 18-20 week ultrasound using a threshold of 25 mm has the potential to predict preterm birth but is more accurate when combined with an assessment of relevant maternal factors. No evidence on harms of cervical length measurement was identified.

2.1.5 Advice to the Expert Working Group

Include the above information in the narrative.

2.1.6 Evidence table: Maternal factors associated with short cervical length

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Cho et al 2017)	Retrospective cohort	III-2	3,296	**Aim**: to determine the maternal characteristics (demographics, an obstetric history, and prior cervical excisional procedure) associated with a short mid-trimester cervical length (CL, defined as a CL of ≤25 mm) and whether having a short cervix explains the association between these maternal characteristics and spontaneous preterm birth < 34 weeks. **Population**: women with a singleton pregnancy who underwent routine CL measurement between 20 and 24 weeks. **Methods**: Data were collected on maternal age, weight, height, parity, obstetric history (nulliparity; a history of at least 1 SPTD; and at least 1 term birth and no preterm birth [low-risk history group]), and prior cervical excisional procedure.	In the multivariate regression analysis, an obstetric history, prior cervical excisional procedure, and gestational age at measurement were the variables significantly associated with short CL. In contrast, maternal weight, height, age, and parity were not significantly associated with short CL. By using the likelihood of SPTD as an outcome variable, logistic regression indicated that short CL and obstetric history, but not prior cervical excisional procedure, were significantly associated with SPTD after adjustment for potential confounders. A history of SPTD and prior cervical excisional procedure were associated with an increased risk of a short mid-trimester CL. A history of SPTD, but not prior cervical excisional procedure, is associated with an increased risk of SPTD, independent of a short CL.	
(Kandil et al 2017)	Prospective cohort	II	100	**Aim**: to evaluate the effects of different body mass indices on the length of the cervix. **Population**: Low risk women with singleton pregnancies. **Methods**: Participants were allocated into four groups according to their body mass indices (underweight, normal weight, overweight, obese). Vaginal ultrasound was performed at 20-22 weeks to measure cervical length. The shortest cervical measurement was recorded.	Mean cervical lengths were significantly longer in overweight (35.96 mm) and obese (40.36 mm) groups than women in the normal weight group (31.16 mm) ($p<0.001$). Underweight women had the shortest mean cervical length (mean 27.4 mm). The incidence of preterm delivery was the highest in underweight women (RR; 1.5). The incidence of post-term delivery was 10% in total in overweight and obese women.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(van der Ven et al 2015)	Prospective cohort	II	5,092	**Aim**: to assess possible associations between CL and maternal characteristics. **Population**: women at low risk with a singleton pregnancy **Methods** A nationwide screening study was performed in which CL was measured during the standard anomaly scan at 18+0 to 22+6 weeks. Data on maternal height, pre-pregnancy weight, ethnicity, parity and gestational age at the time of the CL measurement were collected. Univariable and multivariable linear regression analyses were performed to assess the relationship between CL and maternal characteristics.	The mean CL was 44.3mm. No association was found between CL and maternal height or gestational age of the measurement. Maternal weight was associated with CL (p=0.007, adjusted R(2) 0.03). Separate analysis for BMI did not change these results. Ethnicity, known in 2702 out of 5092 women, was associated with CL (mean CL in Caucasian women 45.0mm, Asian 43.9mm, Mediterranean 43.1mm, and African 41.8mm, p=0.003), as well as parity (mean CL multiparous 45.3mm, nulliparous 43.5mm, p<0.0001). Shorter mid-trimester cervical length is associated with higher maternal weight, younger maternal age, nulliparity and non-Caucasian ethnicity, but not with maternal height.	
(Palma-Dias et al 2004)	Cross-section	IV	1,131	**Aim**: to determine the distribution of cervical length and to examine which variables of demographic characteristics and obstetric history increase the risk of a short cervix (15 mm or less). **Population**: women at 22-24 weeks of pregnancy. **Methods**: The distribution of maternal demographic and obstetric history characteristics among patients with cervical length ≤15 mm was analysed and compared to the findings for the general population. Risk ratios (RR) between subgroups were generated from this comparison.	Median cervical length was 37 mm and in 1.5% of cases it was 15 mm or less. The proportion of women with a short cervix (≤15 mm) was significantly higher among patients with a low body mass index (RR = 3.5) and in those with previous fetal losses between 16-23 weeks (RR = 33.1) or spontaneous preterm deliveries between 24-32 weeks (RR = 14.1). There are specific variables of demographic characteristics and obstetric history which increase the risk of short cervix at 22-24 weeks.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Miller et al 2015)	Retrospective cohort	III-2	18,250	**Aim**: To estimate whether there are demographic or clinical characteristics that are associated with the likelihood of having a short cervix and whether these characteristics can be used to optimise cervical length screening. **Population**: women with a singleton gestation without a history of spontaneous preterm birth who underwent routine transvaginal second-trimester (18+0 to 23+6 weeks) cervical length screening. **Methods**: Seven risk factors for preterm birth were compared by cervical length status. A multivariable logistic regression was performed to identify independent risk factors for a short cervix (cervical length 2.5 cm or less). Different prediction models for a short cervix, based on the number of risk factors present, were developed and test characteristics for cervical length assessment for different risk-based screening approaches were calculated.	Of the women screened, 164 (0.9%) had a short cervix. Maternal age and conception by in vitro fertilisation were not significantly associated with a short cervix. However, African American (aOR 3.77, 95%CI 2.42 to 5.87) and Hispanic (aOR 1.73, 95%CI 1.10 to 2.74) ethnicity, current tobacco use (aOR 3.67, 95%CI 1.56 to 8.62), prior induced preterm birth (aOR 2.26, 95%CI 1.26 to 4.05), and prior cervical excisional procedure (aOR 2.96, 95%CI 1.86 to 4.70) were independent risk factors for a short cervix.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Buck et al 2018)	Retrospective cohort	III-2	341	**Aim**: to evaluate whether adolescent women have a higher incidence of short CL compared to their 20-24 year old counterparts. **Population**: nulliparous singleton gestations undergoing universal second trimester transvaginal ultrasound between 18 0/7 and 23 6/7 weeks. **Methods**: Adolescent women ≤19 years of age (n=105) were compared to women 20-24 years of age (n=236). Primary outcomes were mean CL and incidence of CL ≤25 mm. Secondary outcomes were incidence of PTB <37 weeks, delivery mode, birth weight, and NICU admission.	There was no difference in mean CL (40.6 mm vs. 40.6 mm, p = 0.51) or incidence of CL ≤25 mm (1.0% vs. 1.7%; OR 0.56 [0.06-5.1]). After controlling for maternal differences, there still was no significant correlation between maternal age and CL. There was no significant difference in PTB, birth weight, or NICU admission between the groups. CL measurements did not significantly differ across all maternal ages (14-42 years).	
(D'Agostini et al 2013)	Cross-section	IV	80	**Aim**: To compare cervical lengths of adolescents and adults in mid-gestation. **Population**: Primigravidae adolescents under the age of 16 and adults over age 20 (n=40/group) . **Methods**: Cervical measurements were performed between 21 and 24 weeks of gestation through transvaginal ultrasonography using a previously validated method. Mean cervical length (Mann-Whitney test) and percentage of cervices below 25 mm (Fisher exact test).	For adolescents and adults, average uterine cervix lengths were 28 +/- 6.6 mm 33 +/- 4.1 mm (P<0.0001), respectively, and the proportion of cervixes below 25 mm were 27.5% and 7.5% (P<0.02), respectively. In addition, adolescents had significantly lower gynecologic age, education, and family income than adults.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Buck et al 2016)	Retrospective cohort	III-2	1,751	**Aim**: to evaluate whether there are racial discrepancies in the incidence of second trimester short cervical length (25 mm). **Population**: women with singleton pregnancies without prior sPTB undergoing second trimester (18+0 to 23+6 weeks) transvaginal CL screening. **Methods**: African American women (n=1,092) were compared to non-Hispanic caucasian women (n=659). Our primary outcome was the incidence of CL 25 mm. Secondary outcomes were incidence of PTB 37 weeks, delivery mode, birth weight and neonatal intensive care unit (NICU) admission.	African American women differed from non-Hispanic white women with respect to maternal age (26.0 vs 30.7 years), gravidity (3.1 vs 2.1), prepregnancy BMI (29.6 vs 25.0 kg/m_2), and smoking status (9.8% vs 16%), respectively ($p<0.001$). African American women had higher incidence of CL 25mm (1.9% vs 0.6%; OR: 3.21 [1.1–9.4]), rates of sPTB (8.5% vs 4.4%; aOR: 1.95 [1.1–3.4]), incidence of low birthweight infants (<2,500 g, 8.3% vs 5.6%; aOR 1.80 [1.1–3.0]) and were more likely to have their infants admitted to the NICU (16% vs 11%; OR: 1.52 [1.0–2.3]).	
(Aboulghar et al 2009)	Prospective cohort	III-2	395	**Aim**: to measure cervical length in singleton and twin ICSI pregnancies at midtrimester (20 weeks) and compare it to a control group with naturally conceived pregnancies. **Population**: Women with twin intracytoplasmic sperm injection (ICSI) pregnancies (n=222), singleton ICSI pregnancies (n=122) and spontaneous singleton pregnancies (n=51). **Methods**: transvaginal ultrasound measurement of cervical length was compared. Preterm birth was defined as ≤34 weeks. Full data were obtained for 193 twin pregnancies (group A), 102 singleton pregnancies (group B) and 51 spontaneous singleton pregnancies (group C).	Cervical length at midterm was not statistically different between the three groups: group A, 37.6±7.1 mm; group B, 37.2±7.2 mm; and group C, 39.2±5.4 mm. The incidence of preterm birth was statistically different between groups: 30.5% in group A; 17.6% in group B; and 3.9% in group C (P=0.011). The ROC curve for optimum cut-off of cervical length in prediction of preterm birth for group A was 38.05 mm, sensitivity 67%, specificity 50%, positive predictive value (PPV) 37.7, and negative predictive value (NPV) 78.1. For group B the data were 33.05 mm, sensitivity 50%, specificity 70%, PPV 34.6, and NPV 88.1.	

2.1.7 Evidence table: Accuracy of cervical length as a measure of risk of preterm birth in women at low or mixed risk

Systematic reviews

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Domin et al 2010)	SLR	IV	23 observational studies	**Aim**: To determine whether routine second trimester transvaginal cervical length screening can identify which women would benefit from interventions to prevent preterm delivery. **Methods**: A systematic review was conducted, 957 abstracts were screened, 234 articles underwent full-text review, and 23 studies were included in the final analysis including 26,792 women. Data from relevant studies were pooled to produce summary estimates of sensitivity, specificity, and likelihood ratios using a random effects model. The ideal criteria of transvaginal cervical length measurements to predict preterm delivery were assessed.	Among women of mixed risk, CL measurement by TVU had a positive likelihood ratio for predicting preterm birth at <35 weeks of 6.30 with a cut-off threshold of ≤25 mm and 12.4 with a threshold of ≤20 mm. When stratified on gestational age, the test was more sensitive (58%) when performed more than 20 weeks (compared with 28.2% at <20 weeks), yet more specific (98.5%) when performed less than 20 weeks (compared with 82.0% at >20 weeks).	Timing of cervical length ranged from 14 to 24 weeks

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Honest et al 2012)	SLR	IV	321 observational studies	**Aim**: To examine the accuracy of tests to predict preterm birth. **Method**: A search as conducted of MEDLINE, EMBASE, the Cochrane Library, and MEDION databases from inception to 22 September 2006 inclusive, targeting all tests used in the prediction of spontaneous preterm birth.	Positive likelihood ratios for predicting preterm birth at <34 weeks in low-risk women at 14-20 weeks were: • CL 15 mm: 142.86 (3.58 to 5709.07) • CL 20 mm: 35.36 (4.32 to 289.68) • CL 25 mm: 13.38 (6.90 to 25.96) • CL 30 mm: 2.48 (1.19 to 5.19). Positive likelihood ratios for predicting preterm birth at <34 weeks in low-risk women at 20-24 weeks were: • CL 20 mm: 7.64 (5.21 to 11.20) • CL 22 mm: 4.51 (1.16 to 17.64) • CL 25 mm: 4.68 (3.64 to 6.03) • CL 30 mm: 2.28 (1.91 to 2.71). Positive likelihood ratio for predicting preterm birth at <37 weeks in asymptomatic women at 20-24 weeks was 3.99 (2.84 to 5.62) with a CL of 32.5 mm.	Not clear how many studies were relevant to CL and whether there is overlap with other systematic reviews.

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Honest et al 2003)	SLR	IV	33 studies	**Aim**: To investigate the accuracy with which transvaginal cervical sonography predicts spontaneous preterm birth. **Methods**: Published studies were identified without language restrictions through nine databases and manual searching of bibliographies of known primary and review articles. Studies were selected if they undertook antenatal transvaginal sonographic cervical assessment among a population of pregnant women with known gestational age of delivery. Accuracy data were used to form 2 x 2 contingency tables for various cervical length measurements with birth before 32, 34 and 37 weeks' gestation as the reference standards.	Pooled positive and negative likelihood ratios for preterm birth <34 weeks among asymptomatic singleton pregnancies of 20–24 weeks gestation were: • CL 16 mm: 4.65 (1.51 to 14.29) and 0.75 (0.55 to 1.03) • CL 20 mm: 7.64 (5.21 to 11.20) and 0.79 (0.72 to 0.87) • CL 22 mm: 4.51 (1.15 to 17.64) and 0.74 (0.51 to 1.08) • CL 25 mm: 4.40 (3.53 to 5.49) and 0.67 (0.59 to 0.76) • CL 30 mm: 2.28 (1.90 to 2.59) and 0.44 (0.32 to 0.61)	Unclear overlap with (Honest et al 2012)

Observational studies

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Barber et al 2010)	Prospective cohort	II	2,351	**Aim**: To study the relationship between cervical length measured by ultrasound and risk of preterm birth. **Population**: women with singleton pregnancies. **Methods**: We measured cervical length between the 18th and 22nd week of pregnancy. Preterm birth was categorised as before 37 weeks, before 34 weeks, and before 30 weeks.	Odds ratios (95%CI) of preterm birth <37 weeks were: • CL 28 mm: 25.47 (15.5 to 41.73) • CL 29 mm: 16.98 (11.51 to 25.05) • CL 30 mm: 7.55 (5.44 to 10.5). ORs (95%CI) for preterm birth <34 weeks were: • CL 28 mm: 28.7 (14.54-41.73) • CL 29 mm: 20.5 (11.51-25.05) • CL 30 mm: 10.3 (5.44-10.5) ORs (95%CI) for preterm birth <30 weeks were: • CL 28 mm: 29.8 (15.54-41.73) • CL 29 mm: 23.1 (11.51-25.05) • CL 30 mm: 19.1 (7.44-31.5) In predicting preterm delivery, the sensitivity, specificity, positive predictive value, and negative predictive value of cervical length were 26%, 98%, 63.6%, and 93.57% for CL 28 mm; 34%, 97%, 51%, and 94% for CL 29 mm; and 39%, 92%, 31%, and 94% for CL 30 mm.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Kuusela et al 2015)	Prospective cohort	II	2,122	**Aim**: To evaluate cervical length in the second trimester by means of transvaginal ultrasonography, and to examine the relation between cervical length and spontaneous preterm delivery. **Population**: women with singleton pregnancies without fetal anomalies. **Methods**: Cervical length was measured between 16 and 23 weeks. Data were analysed using logistic regression analysis.	Eleven women had a cervical length of ≤25 mm (0.5%) and 73 women had a cervical length of ≤30 mm (3.4%). Spontaneous preterm delivery at <34 weeks occurred in 22/2061 women (1.1%) and at <37 weeks in 87/2061 women (4.2%). LR+ for preterm birth <34 weeks: • 28 mm: 6.62 (1.68 to 26.10) • 31 mm: 4.29 (1.94 to 9.47) • 33 mm: 2.08 (1.12 to 3.87) LR+ for preterm birth <34 weeks: • 28 mm: 2.52 (0.78 to 8.15) • 31 mm: 2.20 (1.19 to 4.07) • 33 mm: 1.44 (0.95 to 2.17) There was a significant association between cervical length and spontaneous preterm delivery at <34 weeks (OR 1.78; 95%CI 1.19 to 2.65 for a decrease of cervical length by 5 mm) but no significant association at <37 weeks (OR 1.19; 95%CI 0.99–1.42 for a decrease of cervical length by 5 mm, p = 0.059).	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Boelig et al 2016)	Prospective cohort	II	2,071	**Aim**: To evaluate differences in risk factors and outcomes among women with short (≤25 mm) versus normal (>25 mm) cervical length (CL). **Population**: singleton gestations between 18 0/7 and 23 6/7 weeks, without prior sPTB, undergoing universal transvaginal CL screening. Only women with sPTB (<37 0/7 weeks) were included in the analysis. **Methods**: Demographic characteristics, risk factors for sPTB, birth outcomes and presentation of PTB were collected. The primary outcome was mean number of risk factors.	145 (7%) women had PTB and 84 (4%) had sPTB. Sixty-nine (82%) women with sPTB had a CL >25 mm and 15 (18%) had a CL ≤25 mm. Women with a short CL did not differ from women with normal CL with respect to demographic variables or mean number of risk factors (4.20±2.11 versus 3.52±1.97, p=0.23), but they did deliver at a significantly earlier gestational age (25.0±1.1 versus 34.6±3.1 weeks, p<0.01). The distribution of the presentation of sPTB was different in women with a short versus normal CL (p<0.01).	
(Matijevic et al 2010)	Prospective cohort	II	316	**Aim**: To assess the accuracy of a sign of bacterial vaginosis and a sign of cervical insufficiency in predicting preterm labour (PTL <37 weeks) and early PTL (<34 weeks). **Population**: low-risk pregnant women. **Methods**: Vaginal pH was assessed using test gloves and cervical length (CL) was measured by transvaginal ultrasound at 18 to 24 weeks. A pH value less than 5.0 (the 95th percentile threshold) and a CL greater than 26 mm (the 5th percentile threshold) were considered normal.	A shortened CL was significantly correlated with PTL (likelihood ratio [LR] weighted by prevalence; 2.7; 95% CI, 1.1 to 6.7) but not with early PTL (LR, 0.8; 95% CI, 0.4-1.8). An elevated vaginal pH was a better predictor of PTL (LR, 3.7; 95% CI, 1.3-10.4) and early PTL (LR, 1.7; 95% CI, 1.1-3.1).	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Arora et al 2012)	Prospective cohort	II	200	**Aim**: To study the relationship between midtrimester cervical length measurement on transvaginal ultrasonography and timing and mode of delivery. **Population**: Low-risk pregnant women at 20 to 24 weeks. **Methods**: Cervical assessment with transvaginal ultrasound was performed using a 5 MHz transvaginal probe. Findings of cervical assessment were then correlated with the timing and mode of delivery. Chisquare test and odd's ratios with 95% confidence intervals were used.	A cervical length of ≤30 mm had good specificity and NPV. At the cut-off value of 25 mm or less, sensitivity was 31.3%, specificity was 100%, PPV was also 100% and NPV was 88.4%. Increased cervical length on TVS (>40 mm) was associated with higher rate of ceasarean section as compared to <40 mm (66% vs 34%) and this observation was statistically significant.	
(Szymusik et al 2011)	Prospective cohort	II	451	**Aim**: To verify the relation between pregnancy duration and cervical length (CL) at 22-24 wks and to assess its predictive value for preterm delivery (<37 wks). **Population**: women with spontaneous (n=344) and IVF (n=107) singleton gestations. **Methods**: CL was measured at 22-24 wks. The results of CL in both groups were divided into subgroups: ≤29 mm, 30-34 mm; 35-39 mm; 40-44 mm; 45-49 mm and ≥50 mm. They were subsequently correlated with mean durations of gestation within subgroups and parameters of accuracy were calculated. Correlation and regression analysis was performed.	The average age of women in both groups was 28.1 y.o. (SD=4.2 years) and 33.4 y.o. (SD=4.1 years), respectively. The mean gestation age at delivery was 38.9 wks (SD=2.1 wks) vs. 37.9 wks (SD=2.3 wks) and the rate of prematurity equaled 7% vs. 15%, respectively. Regardless of the method of conception, there is a positive correlation between the CL and the duration of gestation. The regression analysis showed that the significant increase in pregnancy duration was correlated with CL ≥35 mm (correlation coefficient greater for spontaneous vs. IVF: rxy=0.418 vs rxy=0.341; p<0.001). All CL parameters of accuracy were better for spontaneous in comparison to IVF pregnancies.	

2.1.8 Evidence table: Accuracy of cervical length measurement combined with other factors in women at low or mixed risk

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Mella et al 2013)	Prospective cohort	II	539	**Aim**: To evaluate for the presence of risk factors (RFs) for preterm birth (PTB) in women without prior PTB having second trimester cervical length (CL) screening, and to estimate the utility of risk factor screening. **Population**: "Low-risk" singleton pregnancies. **Methods**: Women were prospectively screened with midtrimester transvaginal ultrasound CL. Women were analysed based on second trimester CL (<25 mm versus ≥25 mm) and the presence of RFs for PTB. A p-value of < 0.05 was considered significant.	CL was <25 mm in 8% of women. Risk factors for preterm birth were present in 98% of women with CL <25 mm and 95% of women with CL ≥25 mm. Preterm birth occurred in 5% of women with a CL ≥25 mm compared to 18% with CL <25 mm (p<0.01). When data were analysed by CL, the presence of additional RFs did not add to the prediction of PTB <37 weeks. Over 95% of singleton gestations without prior PTB have ≥1 other RF for PTB. In women without prior PTB, assessment of other PTB RFs does not add to prediction of PTB provided by CL alone.	
(To et al 2006)	Prospective cohort	II	40,995	**Aim**: To develop a model for calculating the patient-specific risk of spontaneous early preterm delivery by combining maternal factors and the transvaginal sonographic measurement of cervical length at 22+0 to 24+6 weeks. **Population**: unselected women with singleton pregnancies attending for routine hospital antenatal care. **Methods**: Complete follow-up was obtained from 39,284 (95.8%) cases. The main outcomes were detection rate, false-positive rate and accuracy of predicting spontaneous delivery before 32 weeks' gestation.	Spontaneous birth before 32 weeks occurred in 235 (0.6%) women. The detection rate of screening for early preterm birth, at a fixed false-positive rate of 10%, was 38% for maternal factors, 55% for cervical length and 69% for combined testing. There was good agreement between the model estimates and the observed probabilities of preterm birth.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Celik et al 2008)	Prospective cohort	II	58,807	**Aim**: To evaluate the ability of combinations of cervical length and maternal history to assess the risk of spontaneous preterm birth, and to provide a simple procedure for the optimal estimation of risk. **Population**: Women with singleton pregnancies at 20+0 to 24+6 weeks of gestation. **Methods**: Transvaginal sonographic measurement of cervical length was carried out. The outcome measure was spontaneous extreme (< 28 weeks), early (28-30 weeks), moderate (31-33 weeks) and mild (34-36 weeks) preterm birth. Logistic regression analysis was used to derive models for the prediction of spontaneous preterm birth from the maternal obstetric history, demographic characteristics and cervical length.	The rates of extreme, early, moderate and mild spontaneous preterm birth were 0.23%, 0.24%, 0.57% and 2.93%, respectively. The best prediction of spontaneous preterm birth was provided by cervical length (area under the receiver-operating characteristics curve (AUC), extreme 0.903, early 0.816, moderate 0.784 and mild 0.617) and this was improved by adding obstetric history (AUC, extreme 0.919, early 0.836, moderate 0.819 and mild 0.650). Addition of other parameters was without material effect. For a 10% screen-positive rate, models using cervical length and obstetric history had a sensitivity of 80.6%, 58.5%, 53.0% and 28.6% for extreme, early, moderate and mild spontaneous preterm birth, respectively. These models were expressed as tables of adjusted likelihood ratios to allow simple estimation of the risk of spontaneous preterm birth.	
(Ramaeker & Simhan 2012)	Prospective cohort	II	2,988	**Aim**: to evaluate the contributions of vaginal bleeding and cervical length to the risk of preterm birth. **Population**: women with singleton gestations. **Methods**: This was a secondary analysis of a cohort study designed to study predictors of preterm birth. Women underwent midtrimester (20.8 to 28 weeks) transvaginal ultrasound assessment of cervical length and were queried regarding first- and second-trimester vaginal bleeding.	There was a significant interaction between cervical length and vaginal bleeding (P=0.015). After accounting for cervical length and interaction, the adjusted odds ratio for vaginal bleeding and preterm birth was 4.8 (95%CI 1.89 to 12.4; P=0.001).	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Esplin et al 2017)	Prospective cohort	II	9,410	**Aim**: To assess the accuracy of universal screening to predict spontaneous preterm birth in nulliparous women using serial measurements of vaginal fetal fibronectin levels and cervical length. **Population**: nulliparous women with singleton pregnancies. Methods: Women and clinicians were blinded to results unless cervical shortening less than 15 mm was identified. Exposures: Transvaginal cervical length and quantitative vaginal fetal fibronectin levels were reviewed at 2 study visits 4 or more weeks apart.	Among women with spontaneous preterm birth, cervical length of 25 mm or less occurred in 35 of 439 (8.0%) at 16 to 22 weeks' gestation and in 94 of 403 (23.3%) at 22 to 30 weeks' gestation. Fetal fibronectin levels of 50 ng/mL or greater at 16 to 22 weeks identified 30 of 410 women (7.3%) with spontaneous preterm birth and 31 of 384 (8.1%) at 22 to 30 weeks. The area under the receiver operating characteristic curve for screening between 22 and 30 weeks for fetal fibronectin level alone was 0.59 (95% CI, 0.56-0.62), for transvaginal cervical length alone was 0.67 (95% CI, 0.64-0.70), and for the combination as continuous variables was 0.67 (95% CI, 0.64-0.70).	
(Jwala et al 2016)	Prospective cohort	II	528	**Aim**: to evaluate the possible additive effect of quantitative fetal fibronectin to transvaginal ultrasound cervical length measurement between 18(0/7) and 23(6/7) weeks for prediction of spontaneous preterm birth at <37(0/7) weeks. **Population**: asymptomatic low-risk with singleton gestations between 18(0/7) and 23(6/7) weeks and no prior spontaneous preterm birth. **Methods**: Physicians were blinded to the quantitative fetal fibronectin levels, but the cervical length measurements were made available. The primary outcome was spontaneous preterm birth at <37(0/7) weeks.	36 (6.82%) had spontaneous preterm birth at <37(0/7) weeks. Using the receiver-operating characteristic curve, fetal fibronectin value of ≥5 ng/mL was identified as the optimal cut-off for predicting spontaneous preterm birth at <37(0/7) weeks. As compared with cervical length ≥20 mm alone, with the use of cervical length ≤20 mm or quantitative fetal fibronectin ≥5 ng/mL as screening criteria for prediction of spontaneous preterm birth at <37(0/7) weeks; sensitivity improved from 11.11 to 61.11%, specificity decreased from 99.59 to 55.08%, positive predictive value decreased from 66.67 to 9.05%, negative predictive value marginally improved from 93.87 to 95.09% and predictive accuracy decreased from 93.56 to 55.49%.	

2.1.9 Evidence table: Accuracy of cervical length as a measure of risk of preterm birth in women at high risk

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Crane & Hutchens 2008)	SLR	IV	14 cohort studies	**Aim**: To estimate the ability of cervical length (CL) measured by transvaginal ultrasonography (TVU) to predict spontaneous preterm birth. **Population**: asymptomatic high-risk women. **Methods**: MEDLINE, PubMed, EMBASE and the Cochrane Library were searched, identifying cohort studies evaluating transvaginal cervical length measurement in predicting preterm birth in asymptomatic women who were at increased risk (because of a history of spontaneous preterm birth, uterine anomalies or excisional cervical procedures), with intact membranes and singleton gestations. The primary analysis included all studies meeting the inclusion criteria. Secondary analyses were also performed specifically for (1) women with a history of spontaneous preterm birth; (2) those who had undergone an excisional cervical procedure; and (3) those with uterine anomalies.	CL measured by TVU predicted spontaneous preterm birth. The shorter the CL cut-off the higher the positive likelihood ratio (LR). The most common CL cut-off was <25 mm. Using this cut-off to predict spontaneous preterm birth at <35 weeks, TVU at <20 weeks had LR+ 4.31 (95%CI 3.08 to 6.01); at 20–24 weeks, LR+ 2.78 (95%CI 2.22 to 3.49); and at >24 weeks, LR+ 4.01 (95%CI 2.53 to 6.34). In women with a history of preterm birth (6 studies; n=663) CL at <20 weeks revealed LR+ 11.30 (95%CI 3.59 to 35.57) and at 20–24 weeks LR+ 2.86 (95%CI 2.12 to 3.87), data on the use of CL at >24 weeks was limited in this group (1 study, n=42). In women who had had excisional cervical procedures, two studies presented data on CL (one at <24 weeks and one at >24 weeks), finding CL at <24 weeks to be predictive of spontaneous preterm birth at <35 weeks (LR+ = 2.91, 95% CI, 1.69–5.01). One study (n=64 women) evaluated cervical length in women with uterine anomalies, finding it predictive of spontaneous preterm birth at <35 weeks (LR+ = 8.14, 95% CI, 3.12–21.25).	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Visintine et al 2008)	Retrospective cohort	III-2	65	**Aim**: To determine whether transvaginal sonographic cervical length predicts preterm birth. **Population**: women with multiple prior induced abortions. **Methods**: This was a retrospective cohort study using the Thomas Jefferson University Prematurity Database. Patients with a singleton pregnancy and a history of more than one induced abortion were identified. Exclusion criteria were cerclage and induced preterm birth. Subjects were followed with transvaginal ultrasound measurement of the cervix between 14 and 24 weeks' gestation and grouped into those with and those without a short cervix; a cervical length of <25 mm was considered short. The primary outcome was spontaneous preterm birth at < 35 weeks.	Fifteen of the 65 (23%) women with more than one induced abortion included in the study had a short cervix. The demographics and risk factors were similar between those with and those without a short cervix. The overall incidence of preterm birth was 21.5% (14/65); in women with a short cervix the incidence was 47% (7/15) and in women without a short cervix it was 14% (7/50). The sensitivity, specificity and positive and negative predictive values of a short cervix in the prediction of preterm birth were 50%, 84%, 47% and 86%, respectively. The relative risk of a short cervix for spontaneous preterm birth was 3.3 (95%CI 1.4-7.4).	

2.2 Q2: Should measuring of cervical length be restricted to women with risk factors for preterm birth?

2.2.1 Universal versus targeted cervical length screening

In settings where universal screening of women's cervical length has been implemented:

- there has been a reduction in preterm births <37 weeks (aOR 0.82; 95%CI 0.76 to 0.88), <34 weeks (aOR 0.74; 95%CI 0.64 to 0.85) and <32 weeks (aOR 0.74; 95%CI 0.62 to 0.90), with similar effect sizes in nulliparous and multiparous women with previous term births (Son et al 2016)
- after 6 months of implementation, there was no change in rates of acceptance of cervical length screening and rates of spontaneous preterm birth <28 weeks were higher in those who declined screening (aOR 2.01; 95%CI 1.33 to 3.02) (Temming et al 2016).

A study that calculated the number of women needed to screen (NNS) to prevent one preterm birth <34 weeks based on a 40% risk reduction with use of vaginal progesterone found that, at a cut-off of ≤15 mm, the NNS in low-risk women would be 1,075 compared to 344 among nulliparous women and 167 among women with a previous preterm birth. At a cut-off of ≤20 mm, NNSs were 802, 221 and 97, respectively (Facco & Simhan 2013).

Another study identified independent risk factors for preterm birth (African American and Hispanic ethnicity, current tobacco use, prior induced preterm birth and prior cervical excisional procedure) (Miller et al 2015). It found that, if only women with any of these variables present were offered transvaginal cervical length screening, the specificity increases from 62.8% for universal screening to 96.5% with a risk-based approach. The sensitivity with one variable present was 60.4% and with two factors 14.6%. However, this strategy results in nearly 40% of women with a short cervix not being ascertained.

Transvaginal sonography to measure cervical length did not have a statistically significant impact on the amount of time for completion of the entire ultrasound examination and there were no differences in attitudes regarding discomfort or embarrassment between women who underwent no cervical length screening or transvaginal or transabdominal screening (Romero et al 2014).

2.2.2 Cost effectiveness of universal cervical length measurement

Five studies (of which four were conducted in the United States and one in the United Kingdom) analysed the cost-effectiveness of universally screening women for cervical length and found:

- universal transvaginal cervical length screening and treatment with vaginal progesterone for women with a cervical length ≤15 mm was more cost-effective than targeted screening plus progesterone treatment, risk-based treatment with 17 α-hydroxyprogesterone Caproate without screening and no screening or treatment (Cahill et al 2010)
- universal transvaginal cervical length ultrasound screening appears to be a cost-effective strategy under a wide range of clinical circumstances (varied preterm birth rates, predictive values of a shortened cervix and costs) (Werner et al 2011)
- the health benefits of universal screening result in that strategy being more cost-effective than risk-based screening, with an incremental cost-effectiveness ratio of $21,144 per quality-adjusted life-year (Einerson et al 2016)
- universal cervical length screening and vaginal progesterone for women with a cervical length of ≤15 mm would reduce the rate of preterm birth <34 weeks by 27.7% at an annual cost of €109,249 (Crosby et al 2016)
- cervical length screening and treatment with progesterone is a not a dominant, cost-effective strategy unless progesterone is more effective than has been suggested by available US data (Jain et al 2016).

There are a number of barriers that may prevent or restrict the implementation of a universal cervical length screening program — cost, availability of vaginal progesterone and other treatment options, reluctance of women to undergo transvaginal ultrasound and the perceptions and beliefs of medical practitioners (Pedretti et al 2017).

2.2.3 Evidence summary

Observational and cost-effectiveness studies suggest universal measurement of cervical length and treatment with vaginal progesterone for women with a short cervix (≤15 mm) at 17-24 weeks reduces the risk of preterm birth and is cost-effective (in the United States and the United Kingdom). No Australian cost-effectiveness studies were identified.

2.2.4 Advice to the Expert Working Group

Include the above information in the narrative.

2.2.5 Evidence table: Universal versus targeted cervical length screening

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Son et al 2016)	Retrospective cohort	III-2	64,207	**Aim**: to examine whether the introduction of a universal transvaginal cervical length screening program is associated with a reduction in the preterm birth rate. **Population**: women with singleton gestations and without any previous preterm births who underwent an obstetric sonogram at 18-24 weeks of gestation. **Methods**: Preterm birth rates were compared before and after the implementation of universal screening at 18-24 weeks of gestation. Multivariable analysis was used to identify whether the program was associated independently with the frequency of preterm birth.	The introduction of the cervical length program was associated with a significant decrease in the frequency of preterm birth <37 weeks (6.7% vs 6.0%; aOR 0.82 [95%CI 0.76 to 0.88]), <34 weeks (1.9% vs 1.7%; aOR, 0.74 [95%CI 0.64 to 0.85]), and <32 weeks (1.1% vs 1.0%; aOR, 0.74 (95%CI 0.62 to 0.90]). This reduction in frequency of preterm birth primarily was due to a change in spontaneous (and not induced) preterm births. The effect size for the reduction in preterm birth was similar in nulliparous and multiparous women with previous term births.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Temming et al 2016)	Retrospective cohort	III-2	10,871	**Aim**: to evaluate the acceptability of a universal CL screening program. **Population**: women with singleton, viable pregnancies, without current or planned cerclage **Methods**: Institutional protocol recommended transvaginal CL measurement at the time of anatomic survey between 17-23 weeks. Women with CL ≤20 mm were considered to have clinically significant cervical shortening and were offered treatment. We assessed acceptance rate, risk factors for declining CL screening, and the trend of acceptance of CL screening over time. We also calculated the prevalence of CL ≤25, ≤20, and ≤15 mm, and estimated the association between CL screening and spontaneous preterm birth.	Of 12,740 women undergoing anatomic survey during the study period, 10,871 (85.3%; 95% confidence interval [CI], 84.7-85.9%) underwent CL screening. Of those, 215 (2.0%) had a CL </=25 mm and 131 (1.2%) had a CL </=20 mm. After the first 6 months of implementation, there was no change in rates of acceptance of CL screening over time (P for trend=0.15). Women were more likely to decline CL screening if they were African American (aOR 2.17; 95%CI 1.93 to 2.44), obese (aOR 1.18; 95%CI 1.06 to 1.31), multiparous (aOR 1.45; 95%CI 1.29 to 1.64), age <35 years (aOR 1.24; 95%CI 1.08 to 1.43), or smokers (aOR 1.42; 95%CI 1.20 to 1.68). Rates of spontaneous preterm birth <28 weeks were higher in those who declined CL screening (aOR 2.01; 95%CI 1.33 to 3.02).	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Facco & Simhan 2013)	Prospective cohort	II	2,998	**Aim**: To understand the relationship between cervical length and the risk of prematurity. **Population**: Singleton pregnancies. **Methods**: Data from women enrolled in a multicenter, observational cohort study were analysed. The population was sub-grouped into the following categories: those with history of at least one spontaneous preterm birth (n=467); nulliparous (n=1,237); and parous with a history of at least one term birth and no previous preterm birth (low-risk history group, n=1,284). The relationship between cervical length (measured at 22-24 6/7 weeks) and preterm birth was examined using logistic regression [corrected]. Assuming a 40% risk reduction with the use of vaginal progesterone, the number needed to screen to prevent one preterm birth was calculated.	An inverse relationship between cervical length and risk of preterm birth was demonstrated for each subgroup. A short cervix (15 mm or less) was identified in only 0.93% of the low-risk group participants compared with 3.4% of the previous preterm birth group participants and 2.1% of nulliparous women. The overall rate of preterm birth was lowest (10.5%) in the low-risk history group; however, the rate of preterm birth for these women with a short cervix was 25%. For a cervical length cutoff of ≤15 mm, preventing one spontaneous birth <34 weeks would require screening 167 (95%CI 112 to 317) women with a previous preterm birth, 344 (95%CI 249 to 555) nulliparous women, and 1,075 (95%CI 667 to 2,500) women at low risk. For a cervical length cutoff of ≤20 mm, preventing one spontaneous birth <34 weeks would require screening 97 (95%CI 72 to 153) women with a previous preterm birth, 221 (95%CI 179 to 294) nulliparous women, and 802 (95%CI 583 to 1,250) women at low risk.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Miller et al 2015)	Retrospective cohort	III-2	18,250	**Aim**: To estimate whether there are demographic or clinical characteristics that are associated with the likelihood of having a short cervix and whether these characteristics can be used to optimise cervical length screening. **Population**: women with a singleton gestation without a history of spontaneous preterm birth who underwent routine transvaginal second-trimester cervical length screening. **Methods**: Seven risk factors for preterm birth were compared by cervical length status. A multivariable logistic regression was performed to identify independent risk factors for a short cervix (cervical length 2.5 cm or less). Different prediction models for a short cervix, based on the number of risk factors present, were developed and test characteristics for cervical length assessment for different risk-based screening approaches were calculated.	Of the women screened, 164 (0.9%) had a short cervix. Maternal age and conception by in vitro fertilisation were not significantly associated with a short cervix. However, African American (aOR 3.77, 95%CI 2.42 to 5.87) and Hispanic (aOR 1.73, 95%CI 1.10 to 2.74) race-ethnicity, current tobacco use (aOR 3.67, 95%CI 1.56 to 8.62), prior induced preterm birth (aOR 2.26, 95%CI 1.26 to 4.05), and having a prior cervical excisional procedure (aOR 2.96, 95%CI 1.86 to 4.70) were independent risk factors for a short cervix. If only women with any of these variables present were offered transvaginal cervical length screening, the specificity increased from 62.8% for universal screening to 96.5% with a risk-based approach. The sensitivity with one variable present was 60.4% and with two factors 14.6%. However, this strategy results in nearly 40% of women with a short cervix not being ascertained.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Romero et al 2014)	Prospective cohort	II	60	**Aim**: to quantify the time required for transvaginal cervical length measurements during a second-trimester anatomy scan and to evaluate patient attitudes regarding cervical length assessment. **Population:** Women at mixed risk of preterm birth. **Methods**: Women were randomly assigned to: (1) standard arm-cervix visualised, no prespecified cervical length measurement; (2) sequential arm-3 transabdominal cervical length measurements obtained, transvaginal sonography performed if images were inadequate or if any measurement was 3 cm or less; and (3) screening transvaginal sonography arm-3 transvaginal cervical length measurements obtained. Times were recorded for the entire examination and cervical length evaluation. Participants completed a questionnaire at the end of their visits.	Demographic characteristics were similar across groups except for body mass index, which was greater in the sequential arm than the screening arm (mean ±SD, 28.5±7.75 versus 24.7±3.89 kg/m(2); P=0.03). There were no differences in total examination times between the 3 arms (24.8 ±8.59 versus 27.8 ±8.75 versus 28.5±7.78 minutes; P=0.39). There were no differences across groups in participant attitudes regarding examination discomfort or embarrassment.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Einerson et al 2016)	Decision analysis model	—	—	**Aim**: to evaluate the cost-effectiveness of risk-based screening compared to universal cervical length screening or no screening for preterm birth prevention in low-risk women. **Methods**: A decision analytic model compared the cost and effectiveness of 3 cervical length screening strategies in a population of women with no prior preterm birth. Risk-based screening, universal screening, and no screening were compared using cost, probability, and utility estimates derived from the existing literature and the incremental cost-effectiveness ratios for each strategy were calculated.	In the base-case analysis, risk-based screening and universal screening were more effective and less costly than no screening. In comparison to the risk-based strategy, universal screening of the United States population of women without a prior preterm birth (n=3.5 million annually) would result in 2.19 million more transvaginal ultrasounds, 11,027 more women treated with vaginal progesterone, 913 fewer preterm births <35 weeks gestational age, and 63 fewer neonatal deaths at an additional cost of $51,936,699 annually. Despite costing more, the additional health benefits of universal screening resulted in that strategy being more cost-effective than risk-based screening, with an incremental cost-effectiveness ratio of $21,144 per quality-adjusted life-year.	In women without a prior spontaneous preterm birth, universal cervical length screening is cost-effective in comparison to both risk-based screening and no screening.

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Werner et al 2011)	Decision-analysis model	—	—	**Aim**: To determine whether routine measurement of second-trimester transvaginal cervical length in low-risk singleton pregnancies is a cost-effective strategy. **Population**: women with history of at least one spontaneous preterm birth (n=467); nulliparous women (n=1,237); and parous women with a history of at least one term birth and no previous preterm birth (low-risk history group, n=1,284) **Methods**: We developed a decision analysis model to compare the cost-effectiveness of two strategies for identifying pregnancies at risk for preterm birth: (1) no routine cervical length screening and (2) a single routine transvaginal cervical length measurement at 18-24 weeks' gestation. In our model, women identified as being at increased risk (cervical length < 1.5 cm) for preterm birth would be offered daily vaginal progesterone supplementation. We assumed that vaginal progesterone reduces preterm birth at < 34 weeks' gestation by 45%. We also assumed that a decreased cervical length could result in additional costs (ultrasound scans, inpatient admission) without significantly improved neonatal outcomes. The main outcome measure was incremental cost-effectiveness ratio.	Our model predicts that routine cervical-length screening is a dominant strategy when compared to routine care. For every 100,000 women screened, $12,119,947 can be potentially saved (in 2010 US dollars) and 423.9 quality-adjusted life-years could be gained. Additionally, we estimate that 22 cases of neonatal death or long-term neurologic deficits could be prevented per 100,000 women screened. Screening remained cost-effective but was no longer the dominant strategy when cervical-length ultrasound measurement costs exceeded $187 or when vaginal progesterone reduced delivery risk at < 34 weeks by less than 20%.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Jain et al 2016)	Decision analysis model	—	—	**Aim**: To evaluate the cost-effectiveness of universal cervical length screening. **Population**: women without a history of spontaneous PTB, assuming that all women with shortened cervical length receive progesterone to reduce the likelihood of PTB. **Methods**: A decision analysis model was developed to compare universal screening and no-screening strategies. The primary outcome was the cost-effectiveness ratio of both the strategies, defined as the estimated patient cost per quality-adjusted life-year (QALY) realized by the children. One-way sensitivity analyses were performed by varying progesterone efficacy to prevent PTB. A probabilistic sensitivity analysis was performed to address uncertainties in model parameter estimates.	In our base-case analysis, assuming that progesterone reduces the likelihood of PTB by 11%, the incremental cost-effectiveness ratio for screening was $158,000/QALY. Sensitivity analyses show that these results are highly sensitive to the presumed efficacy of progesterone to prevent PTB. In a 1-way sensitivity analysis, screening results in cost-saving if progesterone can reduce PTB by 36%. Additionally, for screening to be cost-effective at WTP=$60,000 in three clinical scenarios, progesterone therapy has to reduce PTB by 60%, 34% and 93%. Screening is never cost-saving in the worst-case scenario or when serial ultrasounds are employed, but could be cost-saving with a two-day hospitalization only if progesterone were 64% effective.	
(Cahill et al 2010)	Decision analysis model	—	—	**Aim**: To estimate which strategy is the most cost-effective for prevention of preterm birth and associated morbidity. **Methods**: We used decision-analytic and cost-effectiveness analyses to estimate which of 4 strategies was superior based on quality-adjusted life-years (QALYs), cost in US dollars ($), and number of preterm births prevented.	Universal sonographic screening for cervical length and treatment with vaginal progesterone for women with cervical length ≤15 mm was the most cost-effective strategy and dominant over three alternatives: cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone; risk-based treatment with 17 α -hydroxyprogesterone Caproate (17-OHP-C) without screening; no screening or treatment. Universal screening represented savings of $1,339 ($8,325 vs. $9,664) when compared to treatment with 17-OHP-C, and led to a reduction of 95,920 preterm births annually in the US.	

Study ref	Design	LoE	N	Aim/methods	Results	Comments
(Crosby et al 2016)	Retrospective cohort	III-2	94,646 singleton births	**Aim**: to investigate whether routine measurement of the cervical length performed in conjunction with the anomaly scan is justifiable in a population where the risk of preterm birth is low. **Population**: Low risk women **Methods**: We reviewed 12 years of obstetric data. Relative risks of adverse outcomes from the randomised controlled trial were applied and we extrapolated the possible numbers of women requiring intervention. We then used published neonatal data to estimate the cost of neonatal care and estimated the costs of providing the service.	Among singleton births, 1,776 occurred before 34 weeks. Spontaneous onset occurred in 882 (49.7%) of this group. These 882 births were studied. If we apply the figures from a randomised controlled trial, 1,609 women (1.7% from our total population) would be expected to have a cervical length 15 mm. If we gave vaginal progesterone to all women with a sonographically short cervix, we would reduce the rate of preterm birth <34 weeks by 27.7%. The annual costs of providing the service were estimated to be €109,249 based on 8,800 births per year and the total saved on immediate neonatal care was estimated to be €380,514, resulting in annual savings of €271,265.	

2.3 Q3: Should women's cervical length be measured via transabdominal or transvaginal ultrasound?

2.3.1 Accuracy of transabdominal cervical length measurement

Some studies have found high sensitivities for transabdominal ultrasound in prediction of short cervical length on transvaginal ultrasound at a range of gestational ages and cut-offs (Saul et al 2008; Friedman et al 2013a; Friedman et al 2013b; Cho & Roh 2016; Kongwattanakul et al 2016). However, the evidence on the accuracy of transabdominal cervical length as a predictor of transvaginal length or preterm birth is inconsistent (see table below).

A limitation of transabdominal ultrasound is that the cervix may not be adequately visualised in as many as 60% of women (Friedman et al 2013a; Friedman et al 2013b).

Characteristics and findings of observational studies on transabdominal cervical length measurement

Study	Gestational age	N	Bladder status	Main findings
(Friedman et al 2013b)	18-24 wk	1,217	Prevoid	TA ≤36 mm 96% sensitive for TV ≤25 mm
(Friedman et al 2013a)	18-24 wk	703	Prevoid	TA ≤36 mm 96% sensitive for TV ≤25 mm
(Stone et al 2010)	20 wks	203	Postvoid	TA ≤33 mm correlated to TV ≤36 mm
(Saul et al 2008)	14-34 wk	191	Postvoid	TA ≤30 mm 100% sensitive for TV ≤25 mm
(Peng et al 2015)	20-24 wk	174	Postvoid	TA 29 mm correlated to TV <25 mm
(Hernandez-Andrade et al 2012)	6.3-39 wk	220	Prevoid	TA ≤25 mm 43% sensitive for TV ≤25 mm
(Kongwattanakul et al 2016)	18-23 wk	307	Postvoid	TA ≤25 mm 100% for TV ≤25 mm
(Marren et al 2014)	18-20 wk	198	Prevoid	TA ≤25 mm 33% sensitive for TV ≤25 mm
			Postvoid	TA ≤25 mm 15% sensitive for TV ≤25 mm
(Cho & Roh 2016)	20-29 wk	771	–	TA <20 mm 100% sensitive for TV <20 mm
(Puttanavijarn & Phupong 2017)	16-24 wk	160	Postvoid	TA ≤30 mm 21.4% sensitive for preterm birth TA ≤35 mm 50% sensitive for pretem birth
(Chaudhury et al 2013)	18-26 wk	127	Postvoid	TV ≤32 mm; TA mean 2.88 mm shorter TV >32 mm; TA longer
(Roh et al 2013)	20-29 wk	255	–	Transabdominal cervical measurements were consistently shorter than transvaginal measurements in the cases with discrepancies

2.3.2 Cost-effectiveness of transabdominal cervical length measurement

A cost-effectiveness study found that universal transvaginal ultrasound was more cost-effective than an initial transabdominal screen but that optimising testing characteristics or applying a transabdominal screening strategy in lower risk populations may lead to an initial screening approach being cost-effective (Miller & Grobman 2013).

2.3.3 Evidence summary

Evidence from observational studies suggests initial transabdominal measurement of cervical length may represent a useful strategy for detecting women with short cervix on transvaginal ultrasound. However, a cost effectiveness study found that universal transvaginal ultrasound was more cost-effective than including an initial transabdominal measurement.

2.3.4 Advice to the Expert Working Group

Include the above information in the narrative.

2.3.5 Evidence table: Transvaginal versus transabdominal cervical length measurement

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Friedman et al 2013b)	Prospective cohort	II	1,217	**Aim**: To determine a threshold cervical length measured by transabdominal ultrasound above which risk for short transvaginal cervical length is extremely low. **Population**: Women with a singleton pregnancy at 18+0 to 23+6 weeks. **Methods**: This prospective cohort study evaluated a consecutive series of women offered universal transvaginal cervical length screening during anatomy ultrasound. Transabdominal measurement of the cervix-obtained before and after voiding for each patient-was performed before transvaginal ultrasound. The study was powered to detect a transabdominal cervical length cutoff with 95% sensitivity (95% confidence interval, 90-99%) for transvaginal cervical length of ≤25 mm.	Prevoid transabdominal cervical length ≤36 mm detects 96% of transvaginal cervical lengths ≤25 mm with 39% specificity. A prevoid transabdominal cervical length ≤35 mm detects 100% of transvaginal cervical lengths ≤20 mm with 41% specificity. Transabdominal images of the cervix could not be obtained in 6.2% of women prevoid and 17.9% of women postvoid. Transabdominal cervical length screening successfully identifies women at very low risk for short transvaginal cervical length. Transabdominal screening may significantly reduce the burden of universal cervical length screening by allowing approximately 40% of women to avoid transvaginal ultrasound. To ensure high sensitivity of transabdominal screening, approximately 60% of patients will still require a transvaginal study	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Friedman et al 2013a)	Retrospective cohort	III-2	703	**Aim**: To determine whether transabdominal cervical length screening could identify women at high risk for having a short cervix on transvaginal ultrasound. **Population**: Women with a singleton pregnancy at 18 to 23(+6) weeks of gestation who underwent transabdominal and transvaginal cervical length assessment during anatomy ultrasound at a single institution. **Methods**: Electronic medical records were reviewed to identify women who met the study criteria. The primary outcome was the number of women with a short transabdominal cervical length (defined as ≤30 mm) who needed to undergo transvaginal ultrasound to detect one woman with a short transvaginal cervical length of ≤20 mm.	Prevoid TA ultrasound was 96.1% sensitive at a cutoff of 36 mm for detecting short cervix on TV ultrasound of 25 mm (95%CI 90.0 to 99.2%) with a specificity of 39.4% (95% CI 36.7 to 42.2%) Prevoid TA ultrasound was 100% sensitive at a cutoff of 35 mm for detecting short cervix on TV ultrasound 20 mm (95% CI, 89.1 to 100.0%). Specificity was 40.8% (95% CI 38.0–43.7%) at this cutoff. In our cohort, using 35 mm as a prevoid TA cutoff would result in 39.8% of patients avoiding TV ultrasound. The 60.2% of patients would still require TV ultrasound either because their TA length was 35mm or because their cervix could not be viewed transabdominally.	
(Stone et al 2010)	Prospective cohort	II	203	**Aims**: To investigate the relationship between transabdominal (TA) and transvaginal (TV) ultrasound measurements of the cervix at 20 weeks' gestation. **Population**: Healthy nulliparous women at 20 weeks gestation. **Methods**: TA and TV cervical length was measured and measurements were correlated and examined for variance.	The shortest cervical length on TV scanning was 22 mm, the longest was 59 mm, with TA equivalents of 21 mm and 56 mm respectively. The mean TV cervical length was 39.1 (SD 6.2) mm and mean TA 36.6 (SD 5.8) mm. The average difference between the measurements was 2.6 (SD 5.2) mm, the TA length being the shorter of the two. A TA on the 25th percentile (33 mm) was associated with a 25th percentile TV length of 36 mm. The intraclass correlation coefficient between TV and TA measurements was 0.77, but the actual difference between the two measurements was not constant.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Saul et al 2008)	Prospective cohort	II	191	**Aim**: to assess the correlation and agreement between transvaginal and transabdominal cervical length measurement after bladder emptying as well as the feasibility of transabdominal sonography in cervical length screening. **Population**: Women at 14 to 34 weeks gestation. **Methods**: After voiding, transabdominal and transvaginal cervical length measurements were obtained. The optimal trans-abdominal technique was established during an unblinded series of transabdominal and transvaginal cervical length measurements (n=96). The same measurements were obtained in 191 participants under a blinded 2-sonographer protocol. The transabdominal cervical length cutoff to ensure 100% sensitivity in detecting a short cervix (<or=2.5 cm) was determined.	There was no difference between mean transabdominal and transvaginal cervical lengths ±SD (3.57±0.74 vs 3.61±0.74 cm; P=0.20). The Pearson correlation coefficient was 0.824. The 95% tolerance interval for any paired observation (transabdominal minus transvaginal) was -0.92 to 0.84 cm. All transvaginal cervical lengths of ≤25 mm were associated with paired transabdominal cervical lengths ≤30 mm. With an optimal sonographic technique, postvoid transabdominal cervical measurement shows a close correlation and agreement with transvaginal assessment and is useful for cervical length screening.	
(Hernandez-Andrade et al 2012)	Prospective cohort	II	220	**Aim**: To assess the diagnostic performance of transabdominal sonographic measurement of cervical length in identifying patients with a short cervix. **Population**: Pregnant women with singleton pregnancy at 6 2/7 to 39 weeks. **Methods**: Cervical length was measured transabdominal and transvaginal ultrasound (US). Reproducibility and agreement between and within both methods were assessed. The diagnostic accuracy of transabdominal US for identifying cases with a cervical length <25 mm was evaluated.	Twenty-one out of 220 cases (9.5%) had a cervical length <25 mm by transvaginal US. Only 43% (n=9) of patients with a short cervix were correctly identified by transabdominal US. In patients with a cervical length of <25 mm by transvaginal US, transabdominal measurement of the cervix overestimated this parameter by an average of 8 mm (95% LOAs, -26.4 to 10.5 mm). Among women without a short cervix, transabdominal US underestimated cervical length on average (LOA) by 1.1 mm (95% LOAs, -11.0 to 13.2 mm). Transvaginal US was also more reproducible (intra-class correlation coefficient: (ICC) (0.96; 95% CI, 0.94 to 0.97) based on comparisons between 2D images and immediately acquired 3D volume datasets relative to transabdominal US (ICC: 0.71; 95% CI, 0.57 to 0.84).	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Chaudhury et al 2013)	Prospective cohort	II	127	**Aim**: to assess the correlation between transabdominal and transvaginal ultrasound measurements of the cervix in pregnancy. **Population**: Women between 18 and 26 weeks of pregnancy **Methods**: Cervical length was measured by transabdominal and transvaginal ultrasound scan after bladder emptying. Transabdominal and transvaginal measurements were compared and correlated.	In women with transvaginal ultrasound scan (TVS) cervical length ≤32 mm, cervical length was shorter (mean 2.88 mm) than by transabdominal ultrasound scan (TAS). Most of these women needed >3 cm of vertical pocket of urine in the bladder for adequate visualisation of the cervix. In women with TVS cervical length >32 mm, the TVS measurement of the cervix was longer than the TAS measurement of the cervix. In these women, the cervix could be seen by TAS when there was either ≤3 cm vertical pocket of urine in the bladder or an empty bladder.	
(Kongwattanakul et al 2016)	Prospective cohort	II	307	**Aim**: to evaluate the diagnostic properties of transabdominal sonography with the postvoid technique for cervical length measurement. **Population**: pregnant women aged 18–40 years with gestational age of 18–23 weeks. **Methods**: Transabdominal sonography with vertical bladder depth of less than 5 cm and transvaginal cervical length measurements were carried out by a single experienced sonographer.	The mean cervical lengths obtained through transabdominal (TA) and transvaginal (TV) measurement were 3.33 and 3.47 cm, respectively. Ten patients (3.3 %) were identified as having a short cervix using transvaginal sonography, and 12 patients (3.9 %) were identified using transabdominal sonography. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for TA ≤25 mm for TV ≤25 mm were 100%, 99.3%, 142.9, 0, and 0.99, respectively. The 95%CI confidence intervals for sensitivity and specificity were 69.2 to 100% and 97.6 to 99.9%, respectively.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Puttanavijarn & Phupong 2017)	Prospective cohort	II	160	**Aim**: to assess the relationship between transabdominal and transvaginal ultrasonography for the cervical length assessment and to evaluate the predictive value of the transabdominal ultrasonography cervical length assessment for predicting preterm birth. **Population**: Women between 16 and 23 (+) (6) weeks of gestation. **Methods**: Transabdominal and transvaginal ultrasonography cervical length assessments were performed.	Transabdominal ultrasonography cervical length assessment was positively correlated with the transvaginal ultrasonography cervical length assessment. Mean ± standard deviation of the cervical length was significantly different between transabdominal and transvaginal ultrasonography (36.4±5.4 vs 41.2±5.4 mm, p<0.001). Transabdominal cervical length was shorter than the transvaginal cervical length with a mean difference of 4.8 mm. The sensitivity, specificity, positive predictive value and negative predictive value for predicting preterm birth: TA ≤35 mm: 50%, 52.1%, 9.1%, and 91.6% TA ≤30mm were 21.4%, 92.5%, 21.4% and 92.5%.	
(Roh et al 2013)	Retrospective cohort	III-2	255	**Aim**: to investigate the relationship and discrepancies between cervical lengths measured by transabdominal and transvaginal sonography in midpregnancy. **Population**: pregnant women between 20 and 29 weeks **Methods**: The discrepancies in cervical lengths between the two methods were analysed for the following maternal and fetal conditions: (1) vertex versus breech fetal presentation, (2) whether the fetal presenting part overlay the cervical internal os, (3) whether both the internal os and external os were visible or only the internal os was clearly visible, (4) maternal bladder filling status, (5) maternal age, (6) parity, and (7) gestational age.	The mean cervical lengths were not significantly different (mean ±SD, 3.88±0.73 cm on transabdominal sonography and 3.93±0.72 cm on transvaginal sonography; P=0.129; Pearson r=0.75). The 5th-percentile transabdominal cervical length was 26.0 mm, and the transvaginal length was 27.8 mm. There were significant discrepancies between the two methods in the cases in which a fetal presenting part overlay the internal os, in the cases in which the external os was not clearly visible, and in primiparous women. Transabdominal cervical measurements were consistently shorter than transvaginal measurements in the cases with discrepancies.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Cho & Roh 2016)	Prospective cohort	II	771	**Aim**: to determine whether transabdominal sonography could identify those women who should undergo transvaginal sonography for prediction of preterm birth. **Population**: Women of mixed risk with singleton pregnancy. **Methods**: Women underwent cervical length measurements by transabdominal and transvaginal sonography between 20 and 29 gestational weeks and were followed until birth. We assessed whether short cervical lengths on transabdominal sonography could predict short cervical lengths on transvaginal sonography and whether these measurements could predict preterm births (<34 gestational weeks).	The mean cervical lengths were not significantly different between the techniques (mean +/- SD, 3.78±0.82 and 3.82±0.77 cm on transabdominal and transvaginal sonography, respectively; P=0.09). The sensitivity of short cervical lengths (<20 mm) on transabdominal sonography for prediction of short cervical lengths (<20 mm) on transvaginal sonography was 100%. The sensitivity, specificity, positive predictive value, negative predictive value, and relative risk of short cervical lengths (<2 cm) for predicting preterm birth were 21.4%, 98.68%, 50.00%, 95.32%, and 13.22 when using transabdominal sonography and 28.57%, 94.94%, 66.6%, 95.74%, and 17.78 when using transvaginal sonography, respectively. In an analysis that included cases with transabdominal sonography, the sensitivity of short cervical lengths for predicting preterm birth was increased.	
(Marren et al 2014)	Prospective cohort	II	198	**Aim**: To determine whether a policy of reverting to transvaginal cervical assessment only if the cervix appears short (≤25 mm) on transabdominal assessment affects the efficiency of screening. **Population**: Women with a singleton pregnancy at 18-20 weeks. **Methods**: Women had their cervical length assessed transabdominally, initially with the maternal bladder full (TABF) and then empty (TABE). Cervical length was then assessed transvaginally (TV).	Identification of the internal and external cervical os was possible during TABF, TABE and TV sonography in 97.0, 82.8 and 100%, respectively. Compared with TV sonography, TABF overestimates cervical length (6.1 mm difference in median values; P<0.01). There was no significant difference between TV and TABE. However, TABE assessment was not possible in one in six women. If TABF sonography was to be used as a screening tool using ≤25 mm as the cut-off, the sensitivity and specificity were 15.4 and 93.2%, respectively.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Peng et al 2015)	Prospective cohort	II	174	**Aim**: To determine the correlation between transabdominal (TA) and transvaginal (TV) cervical length measurement. **Population**: Women with a singleton pregnancy between 20 weeks and 24 weeks of gestation. **Methods**: Women underwent postvoid TA and TV cervical length measurements. Differences between the measurements obtained using the two methods were evaluated.	The mean TA cervical length was 36.0±4.9 mm and the mean TV cervical length was 37.6±5.4 mm. The mean TA cervical length was shorter than the mean TV cervical length by 1.6 mm. The 5th percentile of TA and TV cervical length was 29 mm and 29.1 mm, respectively. The discrepancies between the two methods were not significantly correlated with maternal body mass index. All women with TV cervical length <25 mm had a corresponding TA cervical length <29 mm.	
(Miller & Grobman 2013)	Decision analysis model	—	—	**Aim**: to identify whether and under what circumstances transabdominal ultrasound (TAUS) would be cost-effective. **Population**: a hypothetical cohort of women with a singleton pregnancy **Methods**: This is a decision analytic model designed to compare an initial TAUS CL screening approach with universal transvaginal (TV) screening. Cost, probability, and utility estimates were derived from the existing literature.	Under baseline assumptions, universal TV was the dominant strategy. In comparison to TAUS, universal TV CL screening reduced preterm birth by 0.03%, reduced costs by $1.2 million and increased quality-adjusted life years by 70 per 100,000 women. Although robust to many changes in many estimates, the model was sensitive to the cost of a TV ultrasound, the prevalence of a short cervix and the test characteristics (ie, sensitivity and specificity) of a TAUS screening examination for short CL. Compared with an initial TAUS screen, universal TV ultrasound was a more cost-effective strategy under most assumptions. Optimising TAUS testing characteristics or applying a transabdominal screening strategy in lower risk populations may yield an initial TAUS to be cost-effective.	

2.4 Q4: At what point/s in pregnancy should cervical length measuring/screening be undertaken in women who are at risk of preterm birth due to the presence of risk factors?

2.4.1 Timing of cervical length screening in women at high risk of preterm birth

Among women at risk of spontaneous preterm birth, risk increases as the length of the cervix declines and as the gestational age decreases (Berghella et al 2007).

Observational studies suggest that short cervix at mid trimester can be predicted by cervical length at 16 weeks (Banicevic et al 2014) or at the 11-14 week scan, with repeat measurement at 17 weeks improving prediction (Souka et al 2011). The average gestational age at which a short cervix was detected in women at high risk of preterm birth was 18.7±2.9 weeks (Berghella et al 2003).

Women with a cervical length ≤15 mm before 20 weeks had a significantly higher risk of preterm birth <28 weeks (P<0.001) and preterm birth <32 weeks (P=0.004) than women diagnosed at 20-24 weeks (Vaisbuch et al 2010). Women who had a cervical length ≤30 mm before 22 weeks were more likely to experience a mid-trimester than later preterm birth than women whose cervix shortened to ≤30 mm at 22-24 weeks (Owen et al 2004).

Among high-risk women with a cervical length <30 mm at 20-28 weeks, further cervical length shortening (identified by follow-up cervical length measurement within 3 weeks of the initial screen) independently predicted preterm birth <35 weeks and perinatal morbidity (Crane & Hutchens 2011).

Among women with a previous preterm birth, cervical length >25 mm at mid-trimester did not preclude preterm birth:

- repeat cervical length measurement at 26±1 weeks did not improve prediction of preterm birth <37 weeks and 16.5% of women with cervical length >25 mm at 26±1 weeks had preterm birth <37 weeks (Caradeux et al 2017)
- 20.9% of women experienced preterm birth or premature rupture of the membranes before 37 weeks (Care et al 2014)
- 16% of women experienced preterm birth <35 weeks (Owen et al 2010).

Women with a prior spontaneous preterm birth at <24 weeks are at a higher risk of cervical shortening, and do so at a higher rate and at an earlier gestational age, than do women with a later preterm birth history (Szychowski et al 2009).

2.4.2 Evidence summary

Evidence from observational studies suggests cervical length measurement earlier than 20 weeks may predict cervical shortening and risk of early preterm birth in women at high risk of preterm birth. However, a cervical length >25 mm does not preclude preterm birth in these women.

2.4.3 Advice to the Expert Working Group

Include the above information in the narrative.

2.4.4 Evidence table

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Owen et al 2004)	Analysis of prospective cohort	II	183	**Aim**: To test the hypothesis that shortened midtrimester cervical length is more predictive of early (<26 weeks) than later (26-34 weeks) spontaneous preterm birth. **Population**: Women with a prior preterm birth. **Methods**: Vaginal sonography was begun at 16 to18 weeks' gestation and scheduled every 2 weeks (maximum 4 scans per patient). Cervical length and any observed dynamic shortening were recorded at each visit to determine the shortest observed cervical length from 16 to 24 weeks' gestation. The shortest cervical length measurements were categorised as <25 mm, 25 to 29 mm and ≥30 mm. The initial cervical length was also compared with the shortest cervical length to categorise women on the basis of the timing of cervical shortening to ≤30 mm. Contingency table, linear regression, and survival analysis were used to analyse the relationship between cervical length groups and spontaneous preterm birth.	In both the <25 mm and 25-29 mm groups, the incidence of spontaneous midtrimester birth (<26 weeks) was higher than the incidence of later (26-34 weeks) preterm birth (<25 mm group: 37% vs 19%; 25-29 mm group: 16% vs 3%, respectively) as compared with women with a shortest cervical length ≥30 mm, who had rates of 1% and 9% respectively (P<0.0001). Women who had an initial cervical length ≤30 mm and those whose cervix shortened to ≤30 mm before 22 weeks were also more likely to experience a mid-trimester than later preterm birth, whereas women whose cervix shortened to ≤30 mm later (22-24 weeks) or who maintained a cervical length ≥30 mm had lower rates of mid-trimester than later preterm birth (P<0.0001).	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Berghella et al 2003)	Prospective cohort	II	183	**Aim**: To determine whether high-risk women manifest cervical length <25 mm on transvaginal ultrasound before 14 weeks of gestation, and if this finding is predictive of preterm delivery. **Population**: Asymptomatic pregnancies at high risk for preterm birth. **Methods**: Women were followed prospectively from 10+0 weeks to 13+6 weeks with transvaginal sonographic measurement of the cervix. A cervical length <25 mm was considered a short cervix at this gestational age and at the follow-up ultrasound examinations, performed between 14 and 24 weeks. The primary outcome was preterm birth at <35 weeks of gestation.	Only 10 (5%) patients had a cervix <25 mm before 14 weeks. The sensitivity, specificity and positive and negative predictive values of a short cervix were 14%, 97%, 50%, and 82%, respectively (relative risk, 2.8; 95%CI 1.4 to 5.6). The mean transvaginal sonographic cervical length before 14 weeks of gestation was 33.7±6.9 mm in pregnancies which delivered preterm (n=36), and 35.0±6.8 mm in those delivering at term (n=147) (P=0.3). Follow-up transvaginal ultrasound examination of the cervix to 24 weeks revealed that the average gestational age at which a short cervix was detected was 18.7±2.9 weeks.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Crane & Hutchens 2011)	Retrospective cohort	III-2	70	**Aim**: To determine whether further cervical length shortening by transvaginal ultrasonography in asymptomatic high-risk women with a short cervical length adds additional predictive value for spontaneous preterm birth and perinatal morbidity. **Population**: Women with a history of spontaneous preterm birth, loop electrosurgical excision procedure, cone biopsy or uterine anomaly, who were pregnant with singleton gestations and were found by transvaginal ultrasonography to have a cervical length <30 mm at 20 to 28 weeks' gestation, and who underwent a follow-up cervical length within 3 weeks. **Methods**: Women were evaluated, comparing those with further cervical length shortening (>10%) to those without further shortening. Primary outcomes were spontaneous preterm birth <35 weeks' gestation and perinatal morbidity. Secondary outcomes included spontaneous preterm birth <37 weeks, <34 weeks, <32 weeks, birth weight <2500 g, maternal and other neonatal outcomes.	Compared with women without further cervical shortening, those with further shortening were found by univariate analyses to have higher rates of spontaneous preterm birth <35 weeks (34.8 versus 8.5%, P=0.014), <37 weeks (56.5 versus 21.3%, P=0.003), <34 weeks (30.4 versus 2.1%, P=0.001), <32 weeks (21.7 versus 0%, P=0.003), birth weight <2500 g (60.9 versus 17.0%, P<0.0001), neonatal intensive care unit admission (47.8 versus 17.0%, P=0.006) and composite perinatal morbidity (43.5 versus 14.9%, P=0.009). Logistic regression revealed the only independent predictors of spontaneous preterm birth <35 weeks were further cervical length shortening (aOR 5.73; 95%CI 1.31 to 24.43) and gestational age at short cervical length (aOR 0.95; 95% CI 0.91 to 0.99).	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Banicevic et al 2014)	Prospective cohort	II	200	**Aim**: To follow up the cervical length in pregnant women from 16(th) to 37(th) week, as well as to do a microbiological analysis of the vaginal and cervical flora and to identify relation between the cervical shortening and microbiological flora as well as with a preterm birth. **Population**: High-risk women (n=100) and low-risk women (n=100). **Methods**: At 16 weeks, all women received classic gynecological examination, transvaginal ultrasound examination with measurement of cervical length, cervical smear, and fetal biometry with routine laboratory tests as defined by the protocol.	In the high risk group at 16 weeks, 8% of women had cervical length <15mm, 30% cervical length 15-25m and 62% cervical length >25mm. In the low risk group, no women had cervical length <15mm, 95% had cervical length >25mm and 5% had cervical length 15-25 mm. Incidence of preterm birth (<36.6 weeks) was 50% in women with cervical length <15mm (of which half were <34.6 weeks). In women with cervical length up to 25mm all births occurred after 36 weeks.	
(Souka et al 2011)	Prospective cohort	II	800	**Aim**: To develop a model for the prediction of short cervix (≤15 mm) at 20-24 weeks by combining maternal history and transvaginal ultrasonographic measurement of cervical length at 11-14 weeks. To explore the value of an additional ultrasound examination of the cervix at about 17 weeks. **Population**: unselected pregnant women presenting for first-trimester ultrasound assessment by nuchal translucency and serum biochemistry. **Methods**: Cervical length was evaluated transvaginally between 11 weeks and 13 weeks and 6 days (cx1), at 16-19 weeks (cx2) and 20-24 weeks (cx3). Backward multiple logistic regression analysis with cx3 ≤15 mm as the dependent variable was used to identify the predictors of a short cervix at 20-24 weeks.	Cx1 and history of preterm delivery were significant independent contributors of a short cervix at 20-24 weeks [area under the curve (AUC 0.808, p < 0.001, Model) 1]. Furthermore, the cx1/cx2 ratio was a significant independent predictor of a short cervix at 20-24 weeks (odds ratio = 58.325 p = 0.012). The addition of the cx1/cx2 ratio improved the model (AUC = 0.878, p < 0.001, Model 2).	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Caradeux et al 2017)	Retrospective cohort	III-2	131	**Aim**: To evaluate whether CL measurement at 26±1 weeks in asymptomatic high-risk patients improves the prediction of preterm birth recurrence. **Population**: Women with previous preterm birth, a CL ≥25 mm at 20±1 weeks and subsequent CL measurement at 26±1 weeks. **Methods**: The association and predictive performance of CL at 26±1 weeks for sPTB was studied.	Among women, who had repeat CL measurement at 26±1 weeks, 19% and 4.6% presented sPTB before 37 and 34 weeks, respectively. The rate of sPTB <37 weeks was higher in women with a CL <25 mm (37.5 vs 16.5%, RR 2.3 [1.07 to 4.8], p=0.045). The detection rate of CL at 26±1 weeks to predict sPTB before 37 weeks was 24% (95% CI 10 to 46%). The performance did not improve regardless of the selected cutoff.	
(Care et al 2014)	Retrospective cohort	III-2	134	**Aim**: To identify risk factors predicting spontaneous preterm birth or preterm prelabor rupture of membranes (PPROM). **Population**: women with a history of spontaneous preterm birth and a cervical length (CL) of ≥25 mm at 20-24 weeks' gestation. **Methods**: Maternal characteristics, obstetric history, shortest cervical length and gestational age at shortest cervical length of women who delivered preterm (<37 weeks) were compared with those who delivered at or after 37 weeks in the index pregnancy. Multiple regression analysis was planned to identify significant clinical predictors of spontaneous preterm birth.	Of 134 women with a normal CL at 20-24 weeks, 28 (20.9%) delivered spontaneously or had PPROM before 37 weeks; of these 12 (9.0%) delivered before 34 weeks. None of the selected explanatory variables was predictive of recurrent preterm birth in this cohort. No correlation between absolute cervical length and gestational age at birth was found (R=0.01). In high-risk women with a cervical length of ≥25 mm at 20-24 weeks' gestation, maternal characteristics and absolute cervical length are not useful in predicting subsequent spontaneous preterm birth.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Owen et al 2010)	Analysis of RCT	II	1,014	**Aim**: to assess pregnancy outcome along a continuum of cervical lengths (CLs) ≥25 mm. **Population:** women with prior spontaneous preterm birth 17(0)-34(6/7) weeks with Cl measured at 16(0/7)-22(6/7) weeks. **Methods**: We conducted secondary analysis of a randomised cerclage trial. Outcomes of women who maintained CLs ≥25 mm were analysed. Women with CLs <25 mm randomised to no cerclage comprised an internal comparison group.	Of 1014 screened, 153 had CL <25 mm, and 672 had CL ≥25 mm. Birth <35 weeks occurred in 16% of the ≥25 mm cohort. The relationship between CLs ≥25 mm and birth gestational age was null (P=0.15). In the <25 mm group, progressively shorter CLs predicted birth <35 weeks (P<0.001); this relationship was null in the ≥25 mm group (P=0.17). The continuum of CLs ≥25 mm measured between 16(0/7)-22(6/7) weeks does not predict gestational length in women with prior spontaneous preterm birth.	
(Berghella et al 2007)	Prospective cohort	II	705	**Aim**: To estimate the risk of spontaneous preterm birth based on transvaginal ultrasound cervical length and gestational age at which cervical length was measured. **Population**: Women at high risk for spontaneous preterm birth and with transvaginal ultrasound cervical length measurements between weeks 12 and 32. Inclusion criteria for women at high risk were prior spontaneous preterm birth at 14 to 35 weeks, cone biopsy, mullerian anomaly, or two or more dilation and evacuations. Women with multiple gestations, cerclage, induced preterm birth, or fetal anomalies were excluded. **Methods**: Logistic regression was used to estimate the spontaneous preterm birth risk before 35, 32, and 28 weeks.	The incidences of spontaneous preterm birth before 35, 32, and 28 weeks were 17.7, 10.6, and 6.7%, respectively. The risk of spontaneous preterm birth before 35 weeks decreased by approximately 6% for each additional millimeter of cervical length (OR 0.94, 95%CI 0.92 to 0.95, P=.001) and by approximately 5% for each additional week of pregnancy at which the cervical length was measured (OR 0.95, 95%CI 0.92 to 0.98, P=.004). Similar results were obtained for spontaneous preterm birth before 32 and 28 weeks. Gestational age at which transvaginal ultrasound cervical length is measured significantly affects the calculation of risk of spontaneous preterm birth. The spontaneous preterm birth risk increases as the length of the cervix declines and as the gestational age decreases.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Vaisbuch et al 2010)	Retrospective cohort	III-2	109	**Aim**: To determine whether the risk of early spontaneous preterm delivery (PTD) in asymptomatic women with a sonographic cervical length of ≤15 mm in the mid-trimester changes as a function of gestational age at diagnosis. **Population**: Asymptomatic women with a sonographic cervical length of ≤15 mm diagnosed at 14-24 weeks of gestation. Women with a multifetal gestation, cerclage and a cervical dilatation of >2 cm were excluded. **Methods**: The study population was stratified by gestational age at diagnosis (<20 weeks vs 20-24 weeks) and by cervical length (≤10 mm vs. 11-15 mm). The primary outcome variables were PTD at <28 and <32 weeks of gestation and the diagnosis-to-birth interval.	The median gestational age at diagnosis of a short cervix before 20 weeks and at 20-24 weeks was 18.9 and 22.7 weeks, respectively. Women diagnosed before 20 weeks had a higher rate of PTD at <28 weeks (76.9% vs 30.9%; P<0.001) and at <32 weeks (80.8% vs 48.1%; P=0.004), and a shorter median diagnosis-to-birth interval (21 vs 61.5 days, P=0.003) than those diagnosed at 20-24 weeks.	

Study ref	Design	LoE	N	Aim/population/method/outcomes	Results	Comments
(Szychowski et al 2009)	Retrospective cohort	III-2	1,014	**Aim**: To examine the natural history of cervical length shortening in high-risk women. **Population**: women who had experienced at least one prior spontaneous preterm birth at between 17+0 and 33+6 weeks' gestation. **Methods**: This was an analysis of prerandomisation data from the multicentre Vaginal Ultrasound Cerclage Trial. Serial cervical length was measured by transvaginal sonography in 1014 high-risk women at 16+0 to 22+6 weeks. We performed survival analyses in which the outcome was cervical length shortening <25 mm and data were censored if this did not occur before 22+6 weeks' gestation. The incidence of cervical length shortening and the time to shortening were compared for women whose earliest prior preterm birth was in the mid-trimester, defined as <24 weeks, vs. those at weeks 24-33. Similar comparisons were performed based on each patient's most recent birth history.	Time to cervical length shortening by survival analysis was significantly shorter (hazard ratio (HR)=2.2, P<0.0001) and the relative risk (RR) of shortening significantly higher (RR=1.8, P<0.0001) for women whose earliest prior spontaneous preterm birth was at <24 weeks. A larger effect was observed for women whose most recent birth was at <24 weeks (HR=2.8, P<0.0001; RR=2.1, P<0.0001). The observed hazard ratios remained significant after adjusting for confounders in a multivariable Cox proportional hazards model. Women with a prior spontaneous preterm birth at <24 weeks are at a higher risk of cervical shortening, and do so at a higher rate and at an earlier gestational age, than do women with a later preterm birth history.	

3 Interventions

3.1 Q5: What is the efficacy of progesterone in preventing preterm birth in women who are at risk of preterm birth due to short cervical length?

3.1.1 Effectiveness of progesterone in preventing preterm birth in women with a short cervix

One systematic review analysed the effectiveness of progesterone compared to placebo in women with short cervical length (without other risk factors for preterm birth or premature onset of labour). It found that, while preterm birth <34 weeks, <37 weeks and neonatal deaths were reduced in women overall, there was only a reduction of preterm birth <34 weeks in women with a short cervix (Jarde et al 2017).

When studies specific to vaginal progesterone treatment in women with a short cervix were analysed separately, there were statistically significant effects on preterm birth <35 weeks (RR 0.62; 95%CI 0.42 to 0.92; 1 RCT, moderate quality), preterm birth <34 weeks (RR 0.60; 95%CI 0.41 to 0.89; 2 RCTs, moderate quality), preterm birth <28 weeks (RR 0.55; 95%CI 0.25 to 0.97; 1 RCT; moderate quality) and respiratory distress syndrome (RR 0.51; 95%CI 0.31 to 0.86; 3 RCTs; moderate quality) (see Summary of Findings Table 1). There were no statistically significant effects on preterm birth associated with intramuscular progesterone in women with a short cervix (1 RCT; low quality) (see Summary of Findings Table 2).

A small trial that compared vaginal progesterone with bed rest found lower rates of preterm birth <33 weeks in women with a cervix length of 10–20 mm (9.5% vs 45.5%; p=0.02) but not in women with a cervical length of 20–25 mm (5.3 vs 3.2% (Maerdan et al 2017). However, a cohort study (not included in this review) found that, among women at high risk of preterm birth, activity restriction was associated with increased risk of preterm birth (Levin et al 2017).

Characteristics of randomised controlled trials of progesterone treatment for women with a short cervix

Study	Population	Cervical length	Gestation at ultrasound	Intervention
Vaginal progesterone				
Fonseca 2007	Singleton or twin pregnancies	<15 mm	20 to 25 weeks	200 mg each night from 24 to 33+6 weeks
Hassan 2011	Singleton pregnancies	10–20 mm	19+0 to 23+6 weeks	90 mg each morning from 20+0 to 23+6 weeks to 36+6 weeks, rupture of membranes or birth, whichever occurred first
Van Os 2015	Singleton pregnancies	≤30 mm	18 to 22 weeks	200 mg daily from 22 to 34 weeks
Intramuscular progesterone				
Grobman 2012	Nulliparous with singleton pregnancy	<30 mm	16+0 to 22+3 weeks	Weekly IM injections of 250 mg alpha-hydroxyprogesterone caproate until 36+6 weeks or birth, whichever occurred first

Randomised controlled trials found no evidence of a statistical difference in outcomes among asymptomatic women with cervical length ≤25 mm between:

- vaginal progesterone and intramuscular progesterone (1 RCT; low quality; see Summary of Findings Table 3) (Pirjani et al 2017)
- vaginal progesterone and vaginal progesterone plus cervical pessary (1 RCT; low quality; see Summary of Findings Table 4) (Karbasian et al 2016)
- vaginal progesterone and cerclage (Pustotina 2018).

A modelling study in the United Kingdom found that universal cervical length screening and vaginal progesterone for women with a cervical length of ≤15 mm would reduce the rate of preterm birth <34 weeks by 27.7% at an annual cost of €109,249 for additional ultrasound services and progesterone in a hospital with 8,800 births per year. Annual savings of €271,265 due to reduced neonatal care costs were predicted (Crosby et al 2016).

3.1.2 Evidence summary

Evidence from systematic reviews of RCTs and subsequent RCTs suggest that vaginal progesterone reduces the risk of early preterm birth in women with a short cervix identified on ultrasound at 18-25 weeks (moderate quality evidence).

3.1.3 Advice to the Expert Working Group

Include the above information in the narrative.

Summary of findings 1: Vaginal progesterone compared to placebo for prevention of preterm birth in women with a short cervix identified on ultrasound

Patient or population: Women with a short cervix identified on ultrasound

Setting: Multinational

Intervention: Vaginal progesterone

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Vaginal progesterone**				
Preterm birth <37 weeks	317 per 1,000	**288 per 1,000** (225 to 374)	**RR 0.91** (0.71 to 1.18)	538 (2 RCTs)	⨁⨁◯◯ LOW [a, b]	(Hassan et al 2011; van Os et al 2015)
Preterm birth <35 weeks	233 per 1,000	**146 per 1,000** (94 to 215)	**RR 0.62** (0.42 to 0.92)	458 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	(Hassan et al 2011)
Preterm birth <34 weeks	311 per 1,000	**187 per 1,000** (128 to 277)	**RR 0.60** (0.41 to 0.89)	330 (2 RCTs)	⨁⨁⨁◯ MODERATE [b]	(Fonseca et al 2007; van Os et al 2015)
Preterm birth <28 weeks	103 per 1,000	**51 per 1,000** (26 to 99)	**RR 0.50** (0.25 to 0.97)	458 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	(Hassan et al 2011)
Perinatal mortality	54 per 1,000	**30 per 1,000** (15 to 60)	**RR 0.55** (0.27 to 1.11)	788 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	(Fonseca et al 2007; Hassan et al 2011; van Os et al 2015)
Birthweight <2,500 g	352 per 1,000	**316 per 1,000** (260 to 383)	**RR 0.90** (0.74 to 1.09)	784 (3 RCTs)	⨁⨁◯◯ LOW [a, b]	(Fonseca et al 2007; Hassan et al 2011; van Os et al 2015)
Respiratory distress syndrome	98 per 1,000	**50 per 1,000** (30 to 84)	**RR 0.51** (0.31 to 0.86)	788 (3 RCTs)	⨁⨁⨁◯ MODERATE [b]	(Fonseca et al 2007; Hassan et al 2011; van Os et al 2015)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Confidence interval crosses line of no effect

b. Small number of events

Summary of findings 2: Intramuscular progesterone compared to placebo for prevention of preterm birth in women with a short cervix identified on ultrasound

Patient or population: Women with a short cervix identified on ultrasound

Setting: United States

Intervention: IM progesterone

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with IM progesterone**				
Preterm birth <28 weeks	67 per 1,000	**46 per 1,000** (24 to 86)	**OR 0.67** (0.34 to 1.32)	657 (1 RCT)	⨁⨁◯◯ LOW [a,b]	(Grobman et al 2012)
Preterm birth <37 weeks	242 per 1,000	**251 per 1,000** (189 to 323)	**OR 1.05** (0.73 to 1.49)	657 (1 RCT)	⨁⨁◯◯ LOW [a,b]	(Grobman et al 2012)
Preterm birth <35 weeks	161 per 1,000	**134 per 1,000** (92 to 193)	**OR 0.81** (0.53 to 1.25)	657 (1 RCT)	⨁⨁◯◯ LOW [a,b]	(Grobman et al 2012)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Small number of events

b. Confidence interval crosses line of no effect

Summary of findings 3: Vaginal progesterone compared to IM progesterone for prevention of preterm birth in women with a short cervix identified on ultrasound

Patient or population: Asymptomatic pregnant women with a sonographically short cervix

Setting: Iran

Intervention: Vaginal progesterone

Comparison: IM progesterone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IM progesterone	**Risk with Vaginal progesterone**				
Preterm birth <34 weeks	47 per 1,000	**48 per 1,000** (17 to 133)	**RR 1.02** (0.37 to 2.84)	297 (1 RCT)	⨁⨁◯◯ LOW [a]	(Pirjani et al 2017)
Preterm birth 34-36 weeks	93 per 1,000	**62 per 1,000** (27 to 137)	**RR 0.66** (0.29 to 1.47)	297 (1 RCT)	⨁⨁◯◯ LOW [a]	(Pirjani et al 2017)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Wide confidence interval crosses line of no effect and small number of events

Summary of findings 4: Vaginal progesterone compared to vaginal progesterone plus cervical pessary for prevention of preterm birth in women with a short cervix identified on ultrasound

Patient or population: Pregnant women with singleton pregnancy who had a cervical length ≤25 mm, at 18-22 gestational weeks

Setting: Iran

Intervention: Vaginal progesterone

Comparison: Vaginal progesterone plus cervical pessary

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vaginal progesterone plus cervical pessary	**Risk with vaginal progesterone**				
Preterm birth <37 weeks	197 per 1,000	**164 per 1,000** (81 to 331)	**RR 0.83** (0.41 to 1.68)	144 (1 RCT)	⨁⨁◯◯ LOW [a]	(Karbasian et al 2016)
Preterm birth < 34 weeks	141 per 1,000	**96 per 1,000** (37 to 228)	**RR 0.68** (0.26 to 1.62)	144 (1 RCT)	⨁⨁◯◯ LOW [a]	(Karbasian et al 2016)
Low birth weight <2,500 g	239 per 1,000	**177 per 1,000** (93 to 340)	**RR 0.74** (0.39 to 1.42)	144 (1 RCT)	⨁⨁◯◯ LOW [a]	(Karbasian et al 2016)
Perinatal mortality	28 per 1,000	**14 per 1,000** (1 to 148)	**RR 0.49** (0.05 to 5.24)	144 (1 RCT)	⨁⨁◯◯ LOW [a]	(Karbasian et al 2016)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Wide confidence interval crosses line of no effect and small number of events

3.1.4 Evidence table: Progesterone vs control in women with a short cervix

Study ref	Design	LoE	N	Aim/setting/population/intervention/outcomes	Results	Comments
(Jarde et al 2017)	SLR	I	17 RCTs	**Aim**: To compare progesterone, cerclage and pessary, determine their relative effects and rank them. **Methods**: We searched Medline, EMBASE, CINAHL, Cochrane CENTRAL and Web of Science (to April 2016), without restrictions, and screened references of previous reviews. We included randomised trials of progesterone, cerclage or pessary for preventing PTB in women with singleton pregnancies at risk as defined by each study. We extracted data by duplicate using a piloted form and performed Bayesian random-effects network meta-analyses and pairwise meta-analyses. We rated evidence quality using GRADE, ranked interventions using SUCRA and calculated numbers needed to treat (NNT).	Progesterone reduced PTB < 34 weeks (OR 0.44; 95% credible interval (CrI) 0.22-0.79; NNT 9; low quality), <37 weeks (OR 0.58; 95% CrI 0.41-0.79; NNT 9; moderate quality), and neonatal death (OR 0.50; 95% CrI 0.28-0.85; NNT 35; high quality), compared with control, in women overall at risk. We found similar results in the subgroup with previous PTB, but only a reduction of PTB < 34 weeks in women with a short cervix.	Only 4 studies (Fonseca et al 2007; Hassan et al 2011; Grobman et al 2012; van Os et al 2015) included women based on cervical length.
(Maerdan et al 2017)	Cohort	III-2	85	**Aim**: To evaluate the efficacy of micronized progesterone for prolonging gestation in nulliparous patients with a short cervix (≤25 mm). **Setting**: China **Population**: Asymptomatic women with singleton pregnancies **Intervention**: The therapies prescribed include vaginal micronized progesterone capsules (200 mg each night) or bed rest from 20 to 34 weeks of gestation. **Outcomes**: The primary outcome was spontaneous delivery before 33 weeks.	Progesterone use in cervical length 10-20 mm was associated with a statistically significant reduction in preterm birth <33 weeks (9.5% versus 45.5%, p = 0.02) compared with bed rest. There were no significant differences in cervical length 20-25 mm in rates of preterm delivery <33 (5.3% vs 3.2%, p=0.72), <37 (33.3% vs 54.5%, p=0.25), or <35 weeks (14.3% vs 45.5, p=0.06) between vaginal progesterone and bed rest.	

Study ref	Design	LoE	N	Aim/setting/population/intervention/outcomes	Results	Comments
(Crosby et al 2016)	Cohort	III-2	94,646 singleton births	**Aim**: to investigate whether routine measurement of the cervical length performed in conjunction with the anomaly scan is justifiable in a population where the risk of preterm birth is low. **Population**: Low risk women **Methods**: We reviewed 12 years of obstetric data. Relative risks of adverse outcomes from the randomised controlled trial were applied and we extrapolated the possible numbers of women requiring intervention. We then used published neonatal data to estimate the cost of neonatal care and estimated the costs of providing the service.	Among singleton births, 1,776 occurred before 34 weeks. Spontaneous onset occurred in 882 (49.7%) of this group. These 882 births were studied. If we apply the figures from a randomised controlled trial, 1,609 women (1.7% from our total population) would be expected to have a cervical length 15 mm. If we gave vaginal progesterone to all women with a sonographically short cervix, we would reduce the rate of preterm birth <34 weeks by 27.7%. The annual costs of providing the service were estimated to be €109,249 and the cost of immediate neonatal care was estimated to be €380,514.	

3.1.5 Evidence table: Vaginal progesterone vs intramuscular progesterone in women with a short cervix

Study ref	Design	LoE	N	Aim/setting/population/intervention/outcomes	Results	Comments
(Pirjani et al 2017)	RCT	II	304	**Aim:** To compare 17-alpha-hydroxyprogesterone caproate (17OHP-C) with vaginal progesterone for the prevention of preterm birth in women with a short cervix and to evaluate the changes of the cervical length (CL) over time. **Setting**: Iran **Population**: Asymptomatic pregnant women with a sonographically short cervix ≤25 mm. **Methods**: Participants received 400 mg vaginal progesterone daily (n=147) or IM 250 mg 17OHP-C (n=150) weekly. Transvaginal sonography was repeated every 3 weeks until 36 weeks or the occurrence of preterm labour. **Outcomes**: primary outcome was spontaneous preterm birth <37 weeks; secondary outcomes were preterm birth <34 weeks and changes in CL.	The rates of preterm birth were 10.4% in the progesterone group and 14% in the 17OHP-C group: a difference that was not statistically significant (P=0.416). Moreover, 264 participants underwent ultrasound examination five times and CL changes were studied for 15 weeks. The results showed that the CL changes over 15 weeks were statistically significant (P < 0.001), but the method of intervention (progesterone/17OHP-C) had no significant effect on CL change (P=0.64).	Low risk of bias.

3.1.6 Evidence table: Vaginal progesterone vs vaginal progesterone plus cervical pessary in women with a short cervix

Study ref	Design	LoE	N	Aim/setting/population/intervention/outcomes	Results	Comments
(Karbasian et al 2016)	RCT	II	144	**Aim**: To compare cervical pessary plus vaginal progesterone with vaginal progesterone alone in decreasing the rate of preterm birth in women with short cervix in the second trimester. **Setting**: Iran **Population**: women with singleton pregnancy with cervical length ≤25 mm, at 18-22 weeks. **Methods**: Women were assigned to receive 400 mg vaginal progesterone daily (Group A, n=73) or cervical pessary plus 400 mg vaginal progesterone daily (Group B, n=71), until 37 weeks. **Outcomes**: Preterm birth, low birth weight, premature rupture of the membranes, chorioamnionitis, neonatal intensive care admission and perinatal mortality.	The rates of preterm birth were 16.4% in group A and 19.7% in group B, which was not statistically different (P=0.6). There were no statistically significant differences in the rates of preterm birth at <37, <34, <32, and ≤26 weeks groups (P=0.55). Rates of low-birthweight were 17.8% in group A, and 23.9% in group B, which was not statistically different (P=0.36). The rates of other outcomes were similar between the two groups.	Low risk of bias.

3.1.7 Evidence table: Vaginal progesterone or other progesterone drugs vs cerclage in women with a short cervix

Study ref	Design	LoE	N	Aim/setting/population/intervention/outcomes	Results	Comments
(Pustotina 2018)	RCT	II	35 asymptomatic women	**Aim:** To compare the efficacy of dydrogesterone, 17-OH progesterone (17OHP) and oral or vaginal progesterone with cerclage for the prevention of preterm birth in women with a short cervix. **Setting**: Russian Federation **Population**: Subgroup of symptomatic women with singleton gestation and cervical length (CL) ≤25 mm. **Methods**: Women were randomised to receive dydrogesterone, 17OHP or oral progesterone (OP) (n=6) or vaginal progesterone (n=17); after one week of therapy some women underwent cerclage (n=12). **Outcomes**: Gestational age at birth, preterm birth, latency to delivery, birth weight.	In asymptomatic women, there were no significant differences in any outcomes between vaginal progesterone and cerclage, with the exception of side effects (p=0.001). Women from the dydrogesterone, 17OHP and OP groups, had a significantly lower gestational age at birth (23.3 ± 3.7 vs 34 ± 5.2 weeks) was observed. Latency to delivery (14.5 ± 3.9 vs 18.7 ± 2.8 weeks) and birth weight (2506.7 ± 479.2 vs 3320 ± 340 g) were also lower. The rate of low birth weight, preterm birth < 37 or < 32 weeks were significantly increased (RR 8.0, 21.0, and 8.0, respectively).	High risk of bias and small sample size.

3.1.8 Evaluation of quality of systematic reviews

(Jarde et al 2017)	Comment
Questions and methods clearly stated	The review question is implicit in the title and objective of the review. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	Medline, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and ISI Web of Science without language restrictions. Reference lists of systematic reviews were screened. Search terms are described.
Review includes all the potential benefits and harms of the intervention	Primary outcomes were PTB at <34 and <37 weeks of gestation, overall and stratified into spontaneous PTB. Infant secondary outcomes included: mortality (neonatal death [NND], perinatal death, miscarriage and stillbirth), PTB (<24, <28, <30 and <32 weeks of gestation), gestational age at birth, low birthweight (<2500 g), different definitions of small-for-gestational-age (<10th, <5th and <3rd percentile for gestational age and sex), birthweight, admission and length of stay in the neonatal intensive or special care unit (NICU), morbidities related to prematurity (respiratory problems, intraventricular haemorrhage, periventricular leucomalacia, necrotising enterocolitis, retinopathy of prematurity, sepsis), congenital anomalies, masculinisation of female fetuses, umbilical cord pH <7.1, and low Apgar score (<7) at 5 minutes. Shortly after data collection started we decided to also record very low birthweight (<1500 g) and any other definition of PTB. Induced PTB was considered not relevant in this context and was not studied, although it was initially included in the protocol. Maternal secondary outcomes were: mortality, preterm premature rupture of membranes (PPROM), intervention side effects, length of inpatient antepartum stay, number of outpatient visits and caesarean section.
Review only includes randomised controlled trials	Review included only randomised controlled trials.
Methodological quality of primary studies assessed	Two reviewers (AJ and either OL or CP) used a piloted data collection form to independently extract data on study characteristics, potential effect modifiers, outcomes and risk of bias (using the Cochrane Risk of Bias tool).
Data summarised to give a point estimate of effect and confidence intervals	Odds ratios reported for all outcomes.
Differences in individual study results are adequately explained	No significant differences in study results.
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included	Not applicable
Reviewers' conclusions are supported by data cited	Reviewers' conclusions are supported by data cited.
Sources of heterogeneity are explored	Heterogeneity was explored though comparison of the results of network meta-analyses with pairwise meta-analyses.

3.1.9 Evaluation of quality of randomised controlled trials

Study limitation	Judgement	Support for judgement
(Pirjani et al 2017)		
Random sequence generation	Low risk	The participants were divided into two groups using permutated-randomized blocks (e.g. AABB) in which the sonologist was blinded to the labels A and B. The person who performed randomisation was not involved in the screening process.
Allocation concealment	Low risk	The person who measured the CL was unaware of the type of intervention; and the person who followed up the pregnant women for prenatal care was also blinded to the CL.
Blinding	HIgh risk	The participants in group 1 received vaginal progesterone suppositories at a dose of 400 mg daily while women in group 2 received an i.m. dose of 250 mg 17OHP-C once a week until 36 GW or until the occurrence of preterm labour.
Incomplete outcome data	Low risk	Two women were lost to follow-up in the vaginal group and three discontinued the intervention (reasons given). Two women from the IM group discontinued the intervention (reasons given). Analysis does not include women lost to follow-up.
Selective reporting	Low risk	Pre-specified outcomes reported.
Other limitations	Low risk	No significant differences between baseline characteristics of groups

Study limitation	Judgement	Support for judgement
(Karbasian et al 2016)		
Random sequence generation	Low risk	Simple randomization using a computerized random-number generator for sequence generation.
Allocation concealment	Low risk	S. H. performed the allocation concealment using consecutive opaque envelopes. The envelopes were opened sequentially only after the participant's name and other details had been written on the appropriate envelope.
Blinding	High risk	Open label
Incomplete outcome data	Low risk	Two women were lost to follow-up in the vaginal plus cervical pessary group. Analysis does not include women lost to follow-up.
Selective reporting	Low risk	Pre-specified outcomes reported.
Other limitations	Low risk	No significant differences between baseline characteristics of groups

Study limitation	Judgement	Support for judgement
(Pustotina 2018)		
Random sequence generation	High risk	Not described.
Allocation concealment	High risk	Not described.
Blinding	High risk	Open label.
Incomplete outcome data	High risk	Not described.
Selective reporting	Low risk	Pre-specified outcomes reported.
Other limitations	Low risk	No significant differences between baseline characteristics of groups

4 Additional considerations

4.1 Q6: What are the additional needs of Aboriginal and Torres Strait Islander women?

No studies were identified to answer this question.

4.2 Q7: What are the additional considerations for migrant and refugee women?

No studies were identified to answer this question.

5 Excluded studies

5.1 Background information

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5.7 Narrative review or opinion piece

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