



*UK National
Screening Committee*

Screening for Preterm Labour in asymptomatic, low-risk women

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: 6

Bazian

August 2014

This analysis has been produced by Bazian Ltd for the UK National Screening Committee. Bazian Ltd has taken care in the preparation of this report, but makes no warranty as to its accuracy and will not be liable to any person relying on or using it for any purpose.

The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at <http://www.screening.nhs.uk/policies> and the policy review process is described in detail at <http://www.screening.nhs.uk/policyreview>

Template v1.2, June 2010

Introduction

This update review concentrates on screening for preterm birth in asymptomatic, low risk women using cervical length measurement as the screening test. This is the main focus of the review. However, it also reviews the evidence for screening for bacterial vaginosis and other risk factors for preterm birth.

The National Institute for Health and Care Excellence (NICE) is currently producing a guideline on symptomatic and “high risk” preterm labour and birth.¹ It will cover:

- Pregnant women who are considered to be at high risk of preterm labour and birth because they have a history of:
 - Spontaneous preterm birth
 - Preterm prelabour rupture of membranes (PPROM)
 - Mid-trimester loss
 - Cervical trauma (including surgery)
- Pregnant women who are considered to be at risk of preterm labour and birth because they have a short cervix that has been identified on ultrasound scan and/or bulging membranes in the current pregnancy
- Pregnant women with PPRM
- Pregnant women clinically suspected to be in preterm labour
- Women diagnosed to be in spontaneous preterm labour
- Women having a planned preterm birth

It will not cover women with multiple pregnancy.

This review concentrates on screening for preterm birth in asymptomatic, low risk women. Therefore, women with multiple pregnancies, history of preterm birth, PPRM or fetal loss in the second trimester, uterine anomalies or cervical surgery were considered to be at high risk of preterm labour and outside the scope of this review. Women with signs and symptoms of preterm labour were also excluded.

Preterm birth is defined as delivery before 37 weeks’ gestation.

Preterm birth can be spontaneous or iatrogenic. Iatrogenic preterm delivery follows induction of labour or caesarean delivery.¹ These interventions may be required to reduce the risk to the mother or baby from complications of pregnancy, for example hypertensive diseases of pregnancy, intra-uterine growth restriction, placental abruption or non-reassuring fetal surveillance.

The consequences of preterm delivery include death, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, developmental problems and long-term neurological impairment.² The risk of adverse outcomes is inversely proportional to the length of gestation. Therefore, infants born extremely preterm (before 28 weeks) have significantly worse outcomes than those born moderately preterm.¹

Screening for preterm labour aims to identify women at risk in early pregnancy so that they can be targeted for preventative interventions.

Currently, screening for preterm labour is not recommended by the UKNSC or supported by recommendations from NICE.³ In the NICE guideline on Antenatal Care (2008) the diagnostic value of screening methods in identifying women at risk of preterm labour was assessed. It was concluded that the evidence does not justify the routine screening of low-risk women for preterm labour with clinical examination, asymptomatic bacteriuria, vaginal swabs or ultrasound to assess cervical change. It was recommended that future research investigated the value of tests that are cheap and easy to perform such as maternal serum human chorionic gonadotrophin (MSHCG), serum C-reactive protein (CRP) and cervico-vaginal fetal fibronectin levels. In addition, the diagnostic accuracy and cost-effectiveness of transvaginal ultrasound to measure cervical length and funnelling to identify women at risk of preterm labour should be investigated.

The UKNSC recommendation is informed by an HTA by Honest et al. (2009) which systematically reviewed the accuracy of tests for the prediction of spontaneous preterm birth and the effectiveness of interventions to reduce spontaneous preterm birth in asymptomatic women in early pregnancy carrying a singleton gestation.² The HTA used likelihood ratios to guide the interpretation of test accuracy. They considered tests with a positive likelihood ratio (LR+) above five and a negative likelihood ratio (LR-) of less than 0.2 to be useful. The review found that few tests in asymptomatic women had a positive likelihood ratio of greater than five. These were ultrasonographic cervical length and funnelling measurement, and cervicovaginal fetal fibronectin screening. Only two tests in asymptomatic women had a negative likelihood ratio of less than 0.2. These were detection of uterine contractions (by home uterine monitoring device) and amniotic fluid CRP measurement. No test had both positive and negative likelihood ratios in the useful range. The review of interventions to reduce spontaneous preterm birth found that antibiotic treatment for bacterial vaginosis in women with intermediate flora and smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising primary prevention interventions.

The review concluded that primary prevention approaches (without prior testing) were likely to be more cost effective than any screen-and-treat approach.² The candidates for primary prevention interventions were periodontal care, fish oil, progesterone, and antibiotics active against asymptomatic bacteriuria.

This review summarises the evidence published between January 2007 and May 2013 related to screening for preterm labour in asymptomatic, low risk women. It will concentrate on cervical length measurement using transvaginal ultrasound as a screening test, and the treatment of women identified as having a short cervix.

Of the promising screening tests identified by the HTA review (cervical length measurement, cervicovaginal fetal fibronectin, detection of uterine contraction [by home uterine monitoring device] and amniotic fluid CRP measurement), only studies reporting on cervical length screening were identified in the update search. Therefore cervical length was chosen as the primary candidate for a screening test for this review, with the recommendation that further research is undertaken on the other three mentioned

In the updated search, studies were also identified for cervical volume, serum relaxin and abnormal flora and bacterial vaginosis. Although these risk factors were not considered useful in

the HTA review, the included studies on each have been assessed against the relevant UKNSC criteria, separately, in Appendix 3.

Executive summary - Cervical length

The condition

Preterm birth is an important health problem, with both short- and long-term consequences including death, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, developmental problems and long-term neurological impairment. In England in 2011-12, 6.3% (34,925) of live singleton births were born prematurely at between 24 and 36 weeks' gestation, although it is unclear how many of these premature births were to low-risk women (without history of preterm birth, preterm prelabour rupture of membranes [PPROM] or fetal loss in the second trimester, uterine anomalies or cervical surgery).

The risk of adverse outcomes increases with increasing prematurity. Although preterm birth is defined as birth <37 weeks' gestation, it remains to be determined whether a screening programme should aim to prevent preterm births <37 weeks or to prevent earlier preterm births. A Health Technology Assessment (HTA) reported that complications of prematurity are significantly reduced after 32–34 weeks' gestation, and assessed the accuracy of tests to predict preterm birth and interventions to prevent preterm birth <34 weeks in addition to <37 weeks.

The decision of what a screening programme would aim to prevent is important as it may affect whether a test is judged to be accurate and whether a treatment is judged to prevent preterm birth.

The test

This evidence review concentrated on cervical length measurement, using transvaginal ultrasound, as a screening test.

Screening typically involves the use of a diagnostic test after a screening test. However, there is no diagnostic test for preterm birth. As such the HTA review suggested that a sufficient degree of test reliability was required.

Using the HTA criteria to demonstrate the utility of test as a reference point, the studies included in this review suggest that the accuracy of cervical length screening in the first trimester is unsatisfactory. The evidence relating to test accuracy in the second trimester has limitations because the majority of studies reported accuracy outcomes that did not meet the HTA criteria.

A systematic review and ten primary studies of transvaginal ultrasound measurement for predicting preterm birth were identified in the update search. These studies assessed cervical length in different populations, at different gestational ages, using different cut-offs, and aimed to predict preterm birth at different gestational ages.

The systematic review found that cervical length screening performed best (according to ROC curves) when the cervical length cut-off was ≤ 20 mm for the prediction of preterm delivery at <35 weeks. They calculated the sensitivity to be 22.1%, the specificity to be 98.2%, the LR+ to be 12.4 and the LR- to be 0.74, and the AUC to be 0.89.

The ten primary studies, not included in the systematic review, measured cervical length between 10 weeks and 28 weeks' gestation, and assessed the accuracy of predicting preterm birth <30 weeks to <37 weeks' gestation. There was a large variation in reported accuracy and just two studies fulfilled the HTA criteria for a useful test (LR+ >5 and LR- <0.2). A cut-off of ≤ 27 mm at 20-

24 weeks for predicting preterm birth <35 weeks had a LR+ of 116.00 and a LR- of 0.19 in mixed risk women in one study and a cut-off of ≤ 26 mm at 18-24 weeks for predicting preterm birth <34 weeks had a LR+ of 33.7 and a LR- of 0.13 in low risk women in the other study. The positive predictive value was generally reported to be low raising the possibility that many women who test positive could be exposed to preventative treatments without any benefit to them.

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) consider women with a cervical length ≤ 20 mm at ≤ 24 weeks' gestation to have a short cervix. However, the SMFM state that <25mm was traditionally considered as short in the US. However, as illustrated in the review, the optimal cervical length cut-off and the gestational age at which screening should be performed remains to be determined. The uncertainty regarding cervical length cut-offs is complicated further by the discovery that it is important to differentiate between the endocervix and the isthmus, especially if the measurement is taken in the first trimester.

The treatment

Vaginal progesterone and cervical pessary were found to significantly reduce the risk of preterm birth (as defined by each study) compared to placebo or expectant management. Intramuscular progesterone and cerclage were not found to significantly reduce the risk of preterm delivery.

The evidence for the effectiveness of vaginal progesterone comes from two RCTs. One found that 14 women with a cervical length between 10 and 20mm would need to be treated to prevent one preterm birth <33 weeks. Based on the frequency of a cervical length between 10 and 20mm seen in this study, 604 women would have to be screened to prevent one preterm birth <33 weeks. This is equivalent to preventing approximately 17 preterm births <33 weeks for every 10,000 women screened. The other RCT found that seven women with a cervical length ≤ 15 mm would need to be treated to prevent one spontaneous preterm birth <34 weeks. Based on the frequency of a cervical length ≤ 15 mm seen in this study, 387 women would have to be screened to prevent one spontaneous preterm birth <34 weeks. This is equivalent to preventing approximately 26 spontaneous preterm births <34 weeks for every 10,000 women screened. Despite the positive outcomes for preterm births at <34 and <33 weeks, there was no evidence that vaginal progesterone reduces the risk of preterm birth <37 weeks.

In some studies, vaginal progesterone also significantly decreased the risk of some other adverse outcomes. For example, vaginal progesterone was found to reduce the risk of respiratory distress syndrome, composite measures of neonatal morbidity and mortality, admission to neonatal intensive care and neonatal death; however the evidence for this was not consistent.

The optimal cervical length cut-off, treatment protocol (when to start/frequency of application/finish treatment) and formulation of vaginal progesterone to use remains uncertain. The two RCTs had different cervical length inclusion criteria (between 10 and 20mm at 19+0 to 23+6 weeks' gestation or ≤ 15 mm at 20 to 25 weeks' gestation), used different formulations and doses of vaginal progesterone (bioadhesive gel with 90mg or capsules containing 200mg, both daily) and started and finished treatment at different gestational ages (between 20 to 23+6 and 36 weeks' gestation or between 24 and 34 weeks' gestation). It should also be noted that the US Food and Drug Administration (FDA) did not approve vaginal progesterone gel for the prevention of preterm labour.

These trials also included women outside the scope of this review, for example women with twin gestations, or prior preterm birth.

A RCT of intramuscular progesterone did not reduce the risk of preterm birth vs. placebo. The difference in the result of this RCT compared to the RCTs of vaginal progesterone may be due to difference in the characteristics of women included in the trials, the form and dose of progesterone used and how it was delivered.

One RCT reported evidence for cervical pessary. It found that five women with a cervical length ≤ 25 mm would need to be treated to prevent one spontaneous preterm birth < 34 weeks. Based on the frequency of a cervical length ≤ 25 mm seen in this study, 78 women would have to be screened to prevent one spontaneous preterm birth < 34 weeks. This is equivalent to preventing approximately 128 spontaneous preterm births < 34 weeks for every 10,000 women screened.

In this trial, cervical pessary also reduced the risk of preterm birth < 37 weeks, and the risk of other adverse outcomes (birthweight $< 1,500$ g or $< 2,500$ g, respiratory distress syndrome, treatment for sepsis, and a composite measure of adverse outcomes).

The screening programme

No RCTs assessing the effectiveness of screening asymptomatic low-risk women for short cervix were identified.

Despite this, two cost-effectiveness analyses have been performed. Both of cost-effectiveness studies were done from a US perspective and based on the results of one of the RCTs that assessed vaginal progesterone for preventing preterm birth in women with a cervical length ≤ 15 mm. In both cost-effectiveness studies cervical length screening and treatment with progesterone was found to be the dominant strategy. It is unclear how applicable the results of these analyses would be to the UK.

It is also unclear whether an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be more cost-effective.

Estimating the effectiveness of a universal screening programme from the results of an RCT of treatment is problematic. There could be differences in population, logistical differences in screening methods, stretching of eligibility and management criteria (scope creep), and unintended consequences.

The RCTs which found a benefit of vaginal progesterone or pessary were all performed in populations of pregnant women at mixed risk: for example some women had a prior preterm birth, and in one study twin gestations were included. The number needed to screen and number needed to treat could be higher in exclusively low risk populations.

As the optimal cervical length cut-off and the gestational age at which screening should be performed remains to be determined, it is difficult to know whether the cervical length cut-offs used in the treatment RCTs were appropriate. However, in one RCT, less than one third of the scanned women who had spontaneous preterm delivery had a cervical length of ≤ 15 mm (cut-off applied in this study). In another, more than two thirds of the scanned women who had a spontaneous preterm delivery < 34 weeks' gestation had a cervical length ≤ 25 mm (cut-off applied in this study). It should be noted that these analyses included women who participated in the trials. The other treatment RCTs did not report this information.

Other authorities, notably the ACOG and SMFM, in the US and NICE in the UK have not recommended universal screening. This is due to concerns over quality assurance, availability,

the potential for women to receive unnecessary or unproven interventions as well as the absence of a RCT comparing screening with no screening and the problems of trying to estimate the results of universal screening from RCTs of treatment.

Implications for research

Future research should address:

- What a screening program would aim to prevent
- The optimal cut-off and gestational age for cervical length screening, and whether it fulfils the HTA criteria for the useful test
- The optimal treatment strategy
- Whether a screen-and-treat strategy reduces preterm birth
- Logistic consequences and population acceptability issues arising from screening.
- Large studies evaluating the use of cervicovaginal fetal fibronectin, amniotic fluid CRP measurement and uterine contractions (by home uterine monitoring device) test for screening in asymptomatic women

Executive summary - Other tests to predict preterm labour and treatments to prevent preterm labour (including testing and treatment for bacterial vaginosis)

The test

Screening for preterm birth using vaginal flora, cervical volume or serum relaxin did not meet the HTA's criteria for a useful test.

Screening for bacterial vaginosis using vaginal pH as an indicator fulfilled the HTA's criteria for a useful test in one study of 316 low risk women. The HTA review by Honest et al. (2009) concluded that screening for bacterial vaginosis did not have potential. However, included studies used Amsel or Nugent criteria to diagnose bacterial vaginosis. The potential of vaginal pH as a screening test should be examined further.

The treatment

Antibiotic treatment of asymptomatic bacteriuria, probiotics for bacterial vaginosis, and specialised antenatal treatments for women at high risk of preterm birth were not found to significantly alter the risk of preterm birth. COX inhibitors increased the risk of preterm birth based on the results of one RCT.

Systematic reviews of antibiotic treatment of bacterial vaginosis/abnormal flora or in women with other risk factors for preterm birth, for example a positive fetal fibronectin result, have found conflicting results, with some studies finding that antibiotic treatment had no effect, some finding that antibiotic treatment reduced the risk of preterm birth, and some studies finding that antibiotic treatment increased the risk of preterm birth. The results may differ due to the inclusion/exclusion criteria of the different studies, the antibiotic used, the indication or the gestational period in which treatment was given.

Future research should aim to determine the cause of the conflicting results, and whether treatment of bacterial vaginosis/abnormal flora or the administration of antibiotics to women with other risk factors for preterm birth reduces the risk of preterm birth.

The screening programme

The studies included in the review found conflicting outcomes of the efficacy for a prospective bacterial vaginosis/abnormal flora screening programme. A RCT performed in a European country has found that screening for asymptomatic vaginal infection significantly reduced the risk of preterm birth. A follow-up cohort study with a historical control group confirmed this finding. In addition, a US cohort study has also found that women with bacterial vaginosis identified by screening who were treated also had a reduced risk of preterm delivery compared to women with bacterial vaginosis were not treated. However, a RCT of screening and treatment in Indonesia did not find any evidence of benefit, but this may have been due to limitations in the screening programme. Larger studies would be needed to explore the effectiveness of screening and treatment further.

No cost-effectiveness analyses were identified.

Appraisal against UK NSC Criteria

These criteria are available online at <http://www.screening.nhs.uk/criteria>.

1. The condition should be an important health problem

Preterm birth is defined as delivery before 37 weeks' gestation.

Preterm birth can be spontaneous or iatrogenic. Iatrogenic preterm delivery follows induction of labour or caesarean delivery.¹ These interventions may be required to reduce the risk to the mother or baby from complications of pregnancy, for example hypertensive diseases of pregnancy, intra-uterine growth restriction, placental abruption or non-reassuring fetal surveillance.

The HTA review by Honest et al. (2009) concluded that:

*"Because of the magnitude of the burden of spontaneous preterm birth on the society, it represents an important public-health issue such that if screening and/or testing were possible then such a screening programme would be desirable provided certain conditions are met."*²

The HTA review by Honest et al. (2009) also reported that:

*"Preterm delivery, particularly that before 34 weeks' gestation, accounts for three-quarters of neonatal mortality and one-half of long-term neurological impairment in children. Many of the surviving infants also suffer from other serious short-term and long-term morbidity, such as respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasia [retinopathy of prematurity] and developmental problems. Even those premature infants that are classified as developmentally 'normal' or as having 'mild' developmental problems, in the longer term have higher rates of multiple problems that affect their lives. Although complications of prematurity are significantly reduced after 32–34 weeks' gestation, minor morbidities, which often lengthen hospitalisation, remain for neonates born between 34 and 37 weeks' gestation."*²

The complications of preterm birth are associated with infants having immature organ systems that are not yet prepared to support life outside the womb.⁴ In addition, preterm birth may also be a marker of other problems, including fetal infection or systemic inflammation.⁴ Outcomes after preterm birth are influenced by the cause of the preterm birth; maternal and family risk factors; and the environment, including the neonatal intensive care unit, the home and the community.⁴

A report on global preterm births and stillbirths reported that complications of preterm birth are the leading direct cause of neonatal mortality (responsible for 27% of deaths) and is a risk factor for many neonatal deaths due to other causes.⁴

A recent review described neonatal problems in infants born between 32 and 36 weeks' gestation.⁵ It reported that:

- There is a continuous relationship between neonatal morbidity/mortality and gestational age between 32 and 36 weeks' gestation
- Infants born at 32 to 36 weeks are more likely than term infants to experience respiratory distress syndrome, transient tachypnea of the newborn, pneumonia and pulmonary hypertension of the newborn. Each week of gestation up to 39 weeks' gestation reduces the risk of respiratory morbidity and improves prognosis

- Hypothermia and cold stress threaten babies born between 32 and 36 weeks' gestation during the first days of life
- Hypoglycaemia affects between 8% and 16% of infants born between 32 and 36 weeks' gestation. The causes of hypoglycaemia include limited enteral intake, poor suck-swallow coordination, delayed or ineffective oral feeding, associated pathologies (cold stress, sepsis) and limited compensatory mechanisms
- Infants born between 32 and 36 weeks' gestation are more likely than term infants to present feeding intolerance
- Infants born between 32 and 36 weeks' gestation are at increased risk of jaundice and hyperbilirubinaemia-induced neurological injury. This is due to exaggerated bilirubin production, hepatic immaturity in the uptake and conjugation of bilirubin, and excessive re-uptake due to intestinal immaturity and delayed enteral feeding
- Infants born between 32 and 36 weeks' gestation are more likely to develop severe infections such as sepsis, meningitis and pneumonia than term infants
- Infants born between 32 and 36 weeks' gestation are at moderately increased risk of necrotising enterocolitis, low grade intraventricular haemorrhage, chronic lung disease and apnoea of prematurity
- Infants born between 32 and 36 weeks' show a reduction in drug clearance and prolonged half-lives.

Criterion 1 met: Preterm birth is an important health problem. The consequences of preterm birth can be both short and long-term. The risk of adverse outcomes is inversely proportional to the length of gestation, with babies born severely preterm most at risk. Although preterm birth is defined as birth <37 weeks' gestation, it remains to be determined whether a screening programme would aim to prevent preterm births <37 weeks or to prevent earlier preterm births.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Epidemiology

The HTA review by Honest et al. (2009) reported that:

*"Spontaneous preterm birth before 37 weeks' gestation occurs in 7–12% of pregnancies and it occurs in about 4% of pregnancies before 34 weeks' gestation. Advances in perinatal health care have not reduced the rate of spontaneous preterm birth. Extrapolation from live births data in England and Wales (2004), shows that an estimated 76,000 and 26,000 spontaneous preterm births occur before 37 weeks' and 34 weeks' gestation, respectively."*²

No data exclusively on low risk women was identified (i.e. that excluded women with multiple pregnancies, history of preterm birth, PPRM or fetal loss in the second trimester, uterine anomalies or cervical surgery).

Beck et al. (2010) systematically reviewed published and unpublished data, such as national registries and information sources provided by governments and international agencies, on

maternal morbidity.⁶ It estimated that in 2005 9.6% of all births worldwide were preterm, with the rate in Europe being 6.2%.

In England, 6.3% (34,925) of live singleton births were born prematurely between 24 and 36 weeks' gestation in 2011-12 (6.5% in 2010-11).⁷ Live singleton births by gestation are shown in Table 1. In 2011-12 in England, preterm birth was spontaneous in 69.7% of deliveries \leq 31 weeks' gestation and 52.3% of deliveries between 32 and 36 weeks' gestation.⁸ Birth occurred <31 weeks in 3.1% of all spontaneous deliveries and between 32 and 36 weeks in 4.3% of all spontaneous deliveries.⁸

Table 1: Liveborn singleton deliveries by gestation in NHS Hospitals, England, 2011-2012. NHS Maternity Statistics- England, April 2011 to March 2012: NHS Maternity Statistics tables.⁸

Gestation (weeks)	Liveborn singleton deliveries (%)
Under 20	0.5%
20-23	0.1%
24-27	0.7%
28-31	1.0%
32-36	4.6%
37-41	88.8%
42-47	4.3%
48 or over	0.0%

Aetiology and risk factors

The HTA report by Honest et al. (2009) stated that spontaneous preterm births “are probably the results of covert or subclinical infective/inflammatory processes, cervical dysfunction, idiopathic (unknown cases), multiple gestations and possible social, nutritional and environmental interactions.”²

Preterm birth is a complex multifactorial disorder, and several risk factors for preterm birth have been identified. The HTA report performed a systematic review of predictive tests for preterm birth. For asymptomatic women they considered previous history of spontaneous preterm birth, fetal fibronectin, serum glycoproteins (α -fetoprotein, human chorionic gonadotrophin), serum inflammatory markers (interleukins), bacterial vaginosis, periodontal screening, midstream urine culture, uterine activity monitoring, and measurement of cervical length.² The ability of these tests to identify women who go onto have a preterm birth will be discussed in Criterion 5. However, as preterm birth is a multifactorial disorder, it is unlikely that measurement of one risk factor will identify all women at risk of preterm birth.

Criterion 2 partially met: In England in 2011-12 6.3% (34,925) of live singleton births were born prematurely at between 24 and 36 weeks' gestation. Preterm birth is a multifactorial disorder. Several risk factors for preterm birth have been identified, but it is unlikely that measurement of one risk factor will identify all women at risk of preterm birth.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

This criterion assesses:

- What are the cost-effective primary prevention interventions
- Have they been implemented as far as practicable?

Systematic reviews of preventative interventions that could be used without prior testing were identified in the update search, and the results of these are summarised here.

The HTA report by Honest et al. (2009) concluded that *“an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach to reducing spontaneous preterm births among asymptomatic antenatal women in early pregnancy for primary prevention.”*²

In the cost-effectiveness analysis, the most cost effective options with respect to prevention of threatened preterm birth for asymptomatic women up to 34 weeks’ gestation were fish oil or progestational agents for all women (no prior testing), and fish oil for women with a history of preterm birth. For up to 37 weeks’ gestation, the most cost-effective options were antibiotics active against asymptomatic bacteriuria and periodontal therapy for all women (no prior testing).

The report concluded that it is likely that an effective intervention applied to all asymptomatic women without preceding testing will be the most cost-effective approach to reducing spontaneous preterm birth. Candidates for the intervention are:

- Periodontal care
- Fish oil
- Progesterone
- Antibiotics for asymptomatic bacteriuria

However, they go onto state that *“it is premature to suggest implementation of a treat-all strategy of simple interventions such as fish oil for asymptomatic women.”*²

The results of systematic reviews for the prevention of preterm birth are reported in Table 2. They assessed smoking cessation, antibiotics, probiotics, nutritional advice, energy and protein supplementation, long-chain n-3 fatty acid supplements and micronutrient supplementation.

- Smoking cessation programmes,⁹ nutritional advice,¹⁰ long chain n-3 fatty acid supplementation¹¹ and zinc supplementation¹² were all found to significantly lower the risk of preterm birth <37 weeks’ gestation.
- Iron supplementation during pregnancy significantly lowered the risk of preterm birth <34 weeks’ gestation, but not <37 weeks’ gestation.¹³

Table 2: Results of systematic reviews of preventative interventions

Reference	Intervention	Outcome	RR (95% CI)
Smoking cessation			
Lumley et al. (2009) ⁹	Smoking cessation programmes (vs. no programme)	Preterm birth <37 or <36 weeks	0.86 (0.74 to 0.98); 14 studies
Antibiotics			
Van den Broek (2009) ¹⁴	Prophylactic antibiotics (vs. placebo)	Preterm birth <37 weeks	1.02 (0.86 to 1.22); 8 studies
Probiotics			
Othman et al. (2007) ¹⁵	Probiotics (vs. placebo, no treatment, antibiotics, or any other intervention to prevent preterm labour and birth)	Preterm birth <32 weeks	0.65 (0.03 to 15.88); 1 study
		Preterm birth <37 weeks	3.95 (0.36 to 42.91); 1 study

Reference	Intervention	Outcome	RR (95% CI)
Nutritional advice, energy and protein supplementation			
Ota et al. (2012) ¹⁰	Nutritional advice (vs. no advice)	Preterm birth <37 weeks	0.46 (0.21 to 0.98); 2 studies
	Balanced energy and protein supplementation (vs. placebo/no supplementation)	Preterm birth <37 weeks	0.96 (0.80 to 1.16); 5 studies
	High protein supplementation (vs. placebo/no supplementation)	Preterm birth <37 weeks	1.14 (0.83 to 1.56); 1 study
Long-chain n-3 fatty acids			
Salvig and Lamont (2011) ¹¹	Long-chain n-3 fatty acid supplementation (vs. placebo/no supplementation)	Preterm birth <34 weeks	0.32 (0.09 to 0.95); 3 studies
		Preterm birth <37 weeks	0.61 (0.40 to 0.93); 3 studies
Micronutrients			
Shah et al. (2009) ¹⁶	Prenatal multimicronutrients supplementation (vs. placebo)	Preterm birth <37 weeks	0.97 (0.82 to 1.13); 3 studies
	Prenatal multimicronutrients (vs. iron-folic acid supplementation)		0.99 (0.96 to 1.03); 9 studies
Lassi et al. (2013) ¹⁷	Folic acid supplementation during pregnancy (vs. no folic acid- placebo or same micronutrients but no folic acid)	Preterm birth <37 weeks	1.01 (0.73 to 1.38); 3 studies
Peña-Rosas et al. (2012) ¹³	Iron supplementation during pregnancy (vs. no iron- no treatment, placebo or same micronutrients but no iron)	Preterm birth <37 weeks	0.88 (0.77 to 1.01); 13 studies
		Preterm birth <34 weeks	0.51 (0.29 to 0.91); 5 studies
Peña-Rosas et al. (2012) ¹⁸	Intermittent oral iron supplementation during pregnancy (vs. daily regimen)	Preterm birth <34 weeks	0.98 (0.06 to 15.31); 2 studies
		Preterm birth <37 weeks	1.82 (0.75 to 4.40); 4 studies
Mori et al. (2012) ¹²	Zinc supplementation during pregnancy (vs. no zinc supplementation or placebo)	Preterm birth <37 weeks	0.86 (0.76 to 0.97); 16 studies
Buppasiri et al. (2011) ¹⁹	Calcium supplementation during pregnancy (vs. placebo or no treatment)	Preterm birth <34 weeks	1.11 (0.84 to 1.46); 3 studies
		Preterm birth <37 weeks	0.90 (0.73 to 1.11); 12 studies

Abbreviations: RR, relative risk; CI confidence interval

Two NICE guidelines have made recommendations regarding smoking cessation. The NICE Antenatal Care Guideline recommends that:²⁰

- Pregnant women should be informed about the specific risks of smoking during pregnancy, including the risk of preterm birth, and personalised information, advice and support on how to stop smoking should be offered.

NICE also has formal public health guidance on smoking cessation in pregnancy and following childbirth.²¹

The NICE Antenatal Care Guideline also notes that dental care is free during pregnancy and for a year after the birth of the baby.²⁰

Criterion 3 partially met: It is possible that cost-effective primary prevention interventions, which could be applied to all asymptomatic pregnant women, could be implemented and be more cost-effective than screening for preterm birth. The data identified shows a reduction in risk of preterm birth with zinc and iron supplementation, long chain fatty acids (fish oils), periodontal advice and smoking cessation. Two NICE guidelines have made recommendations regarding smoking cessation and dental care is free in the UK during pregnancy.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Not applicable

5. There should be a simple, safe, precise and validated screening test

The HTA by Honest et al. (2009) reviewed 22 tests.² The report concluded that *“in asymptomatic antenatal women, tests that appear to have potential were ultrasonographic cervical length measurement, cervicovaginal fetal fibronectin screening, detection of uterine contraction (by home uterine monitoring device) and amniotic fluid C-reactive protein measurement.”*²

Honest et al. (2009) used likelihood ratios (LR) to interpret test accuracy (see Table 3).² They considered tests with a positive likelihood ratio (LR+) above five and a negative likelihood ratio (LR-) of less than 0.2 to be useful. These cut-offs are context specific, and depend on how effective, safe and expensive the interventions that follow are relative to costs and outcome of false-negative cases.

Ultrasonographic cervical length and funnelling measurement, and cervicovaginal fetal fibronectin screening had a LR+ more than five in asymptomatic antenatal women.² The detection of uterine contractions (by home uterine monitoring device) and amniotic fluid CRP measurement were found to have a LR- of less than 0.2.

Table 3: Guide to the interpretation of test accuracy represented by likelihood ratios used in Honest et al. (2009)²

	Likelihood ratio for a positive test result (LR+)	Likelihood ratio for a negative test result (LR-)	Interpretation
Very useful	>10	<0.1	Likely to generate large and often conclusive changes from pre-test to post-test probabilities
Useful	5-10	0.1-0.2	Likely to generate moderate shifts in pre-test to post-test probabilities
May be useful	2-5	0.2-0.5	Likely to generate small but sometimes important changes in pre-test to post-test probabilities
Not useful	1-2	0.5-1	May alter pre-test to post-test

			probabilities to a small (and rarely important) degree
--	--	--	--

No studies evaluating cervicovaginal fetal fibronectin or amniotic fluid CRP measurement or the detection of uterine contractions (by home uterine monitoring device) as tests for preterm labour and birth in asymptomatic, low-risk women or women at both high and low risk were identified in the update search. Several studies of cervical length measurement were identified and these are summarised below.

Transvaginal cervical length measurement

The cervical length is the distance between the internal os and the external os.²² Although measurement of cervical length is commonly reported, two studies (Greco et al. [2011]²³ and Souka et al. [2011]²⁴) drew attention to the importance of identifying the internal os correctly. Souka et al. (2011) states that this can be difficult during the first trimester, as the lower part of the uterus is often still not filled by the gestational sac, and as a result, the anterior and posterior uterine walls coincide in the isthmus, giving a false impression of the location of the internal os.²⁴ Both studies report that cervical length measurements were shorter than in some other studies, and that this may be because other studies did not differentiate between the endocervix and the isthmus.^{24,23}

Cervical length can be measured by ultrasound both transvaginally and transabdominally. The American College of Obstetricians and Gynecologists (ACOG) state that unlike the transabdominal approach, transvaginal cervical ultrasonography is not affected by maternal obesity, position of the cervix, and shadowing from the fetal presenting part.²² Two studies of transabdominal ultrasound measurement of cervical length were identified in the update search. Hernandez-Andrade et al. (2012) found that transabdominal measurement of uterine cervical length during pregnancy failed to identify a substantial number of women with a short cervix.²⁵ Rashed et al. (2009) found no significant difference between transabdominal ultrasonographic measurements of term and preterm deliveries ($p > 0.05$) in 294 low-risk women with a singleton pregnancy who were scanned at between 22 and 24 weeks' gestation.²⁶ In contrast, there was a significant difference in transvaginal cervical length measurements ($p < 0.05$). The authors concluded that transvaginal ultrasonography seems to be superior to transabdominal sonography in assessing the cervical length.

One systematic review and ten primary studies of transvaginal cervical length measurement for predicting preterm birth in asymptomatic low risk women or women at both high and low risk (i.e. not studies of only pregnant women at high risk of preterm birth due to multiple gestation, uterine anomaly or surgery, or history of preterm birth) were included from the updated search. The studies reported preterm birth at a range of gestational ages, from <30 weeks to <37 weeks. Studies are subdivided according to outcome, in decreasing gestational age at birth. The results of the studies are summarised in Table 4 to Table 8.

Systematic review

The systematic review and meta-analysis of transvaginal ultrasonographic measurement of cervical length during the second trimester as a predictor of spontaneous preterm birth among asymptomatic women with a singleton pregnancy, Domin et al. (2010), (search until October 2007) included 23 primary studies (26,792 women).²⁷ The review did not exclude studies on the basis of the women's risk of preterm birth. Seven of the studies included women at high risk of preterm delivery (women were considered high risk if the primary study authors considered

them to be high risk, which included a history of prior spontaneous preterm delivery, history of uterine anomalies, or prior cervical cone biopsy), six of the studies included only low-risk women, and the remaining ten included both. The definition of spontaneous preterm birth ranged from preterm birth <26 weeks to <37 weeks of gestation. Preterm birth <35 weeks (12 studies) and <37 weeks (nine studies) were the most common outcomes reported. The median incidence of preterm birth <37 weeks was 7.2% (interquartile range 3.4% to 11.2%) and <35 weeks was 4.3% (interquartile range 1.9% to 11.4%). Sensitivity ranged from 1.6% to 100% and specificity from 60.2% to 100%. LR+ ranged from 2.1 to 95.3 and LR- ranged from 0.1 to 1.0. A list of studies included in the systematic review, and their characteristics, can be found in Appendix 1.

In the meta-analysis of all 23 studies (the most conservative study having a cervical length cut-off ≤ 33.15 mm and the outcome of preterm delivery <37 weeks) the sensitivity was 32.7%, the specificity was 90.0%, the LR+ was 4.90, the LR- was 0.60 and the area under the ROC curve (AURC) was 0.83.

The researchers then performed stratified analyses, where they meta-analysed studies which used cut-offs of different cervical lengths and gestational age at birth. They report that the test performed best (according to ROC curves) when the cut-off was ≤ 20 mm and preterm delivery was <35 weeks (nine studies had cut-offs of ≤ 20 mm and reported preterm delivery <35 weeks). They calculated the sensitivity to be 22.1%, the specificity to be 98.2%, the LR+ to be 12.4 and the LR- to be 0.74, and the AURC to be 0.89.

The researchers also performed stratified analyses on patient risk status. They report that the test performed better in low-risk women (AURC 0.88 in low risk women vs. 0.80 in high risk women).

Primary studies

None of the primary studies identified in the update search were included in the systematic review, Domin et al. (2010)²⁷.

Of the ten primary studies identified, five were in low risk women, and five were in women at both low and high risk. The studies reported preterm birth at a range of gestational ages, from <30 weeks to <37 weeks. Eight studies reported on preterm birth <37 weeks.

Rates of preterm birth <37 weeks ranged from 4.8% (Davies et al. [2008]²⁸, mixed risk women, Canada) to 16% (Arora et al. [2012]²⁹, low risk women, India); rates of preterm birth <35 weeks ranged from 1.7% (Davies et al. [2008]²⁸, mixed risk women, Canada) to 10.5% (Ozdemir et al. [2007]³⁰, mixed risk women, Turkey); rates of preterm birth <34 weeks ranged from 1.1% (Greco et al. [2011]²³, mixed risk women, UK) to 2.5% (Matijevic et al. [2010]³¹, low risk women, Croatia). Two studies reported on preterm birth <32 weeks. The rate of preterm birth <32 weeks was 1% in one study (Arora et al. [2012]²⁹, low risk women, India) and 1.3% in the other (Souka et al. [2011]²⁴, mixed risk women, Greece). The rate of preterm birth <30 weeks was not reported in the one study with this as an outcome (Barber et al. [2010]³²).

Cervical length was assessed at between 10 weeks and 28 weeks' gestation.

One study (Dilek et al. [2007]³³) also reported whether change in cervical length can predict delivery.

Sensitivity, specificity, LR+ and LR- were extracted as reported from studies. In those studies where these outcomes were not reported, values were calculated (where possible).

Sensitivity ranged from 2.2% (Davies et al. [2008]²⁸, cut off ≤ 20 mm at 24 weeks for predicting birth <37 weeks' gestation, mixed risk women, Canada) to 100% (Arora et al. [2012]²⁹, cut off ≤ 30 mm for predicting birth <32 weeks' gestation, low risk women, India).

Specificity ranged from 20.8% (Arora et al. [2012]²⁹, cut off ≤ 35 mm at 20-24 weeks for predicting birth <37 weeks' gestation, low risk women, India) to 100% (Arora et al. [2012]²⁹, cut off ≤ 25 mm at 20-24 weeks for predicting preterm birth <37 weeks and Rashed et al. [2009]²⁶, cut off 27.5mm at 20-24 weeks for predicting preterm birth <37 weeks).

LR+ ranged from 1.09 (Souka et al. [2011]²⁴, cut-off not reported, but for a 25% fixed screen positive rate, for predicting preterm birth <37 weeks) and infinity (Arora et al. [2012]²⁹, cut off ≤ 25 mm at 20-24 weeks for predicting preterm birth <37 weeks and Rashed et al. [2009]²⁶, cut off 27.5mm at 20-24 weeks for predicting preterm birth <37 weeks).

LR- ranged from 0 (Arora et al. [2012]²⁹, cut off ≤ 30 mm for predicting birth <32 weeks' gestation, low risk women, India) to 0.98 (Davies et al. [2008]²⁸, cut off ≤ 20 mm at 24 weeks for predicting birth <37 weeks' gestation, mixed risk women, Canada)

Positive and negative likelihood ratios from two studies met the HTA criteria for both LR+ and LR-:

- A cut-off of ≤ 27 mm at 20-24 weeks for predicting preterm birth <35 weeks had a LR+ of 116.00 and a LR- of 0.19 in mixed risk women (Ozdemir et al. [2007]³⁰)
- A cut-off of ≤ 26 mm at 18-24 weeks for predicting preterm birth <34 weeks had a LR+ of 33.7 and a LR- of 0.13 in low risk women (Matijevic et al. [2010]³¹)

Table 4: Accuracy for transvaginal cervical length measurements for the prediction of preterm birth or preterm labour <37 weeks' gestation
Numbers in italics have been calculated. Other numbers are as reported. If cells are blank numbers were not reported and not enough data was reported in the paper to calculate figures. Likelihood ratios in bold with shaded cells have a LR+>5 or a LR-<0.2.

Preterm birth <37 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Domin et al. (2010) ^{27*}		SYSTEMATIC REVIEW Mixed risk. Systematic review of 23 studies of asymptomatic women with singleton gestation and transvaginal cervical length measurements during the second trimester which reported spontaneous preterm delivery data. Seven studies included only women at high risk for preterm delivery (study author's definition), 6 studies only included low risk patients, 10 studies included both.	Median 7.2% (IQR 3.4% to 11.2%)	During the second trimester but before 24 weeks (between 14 and 24 6/7 weeks in the included studies)	≤33.15mm	32.7%	90.0%			4.90	0.60	AURC 0.83
		SYSTEMATIC REVIEW <i>Not reported how many studies this was based on, but 10 studies scanned women at 20 weeks' gestation or later.</i>		More than 20 weeks	<i>Not reported, but the greatest cervical length cut-off was ≤33.15mm</i>	58%	82.0%			3.22	0.51	
		SYSTEMATIC REVIEW <i>Not reported how many studies this was based on, but 3 studies scanned women at less than 20 weeks' gestation.</i>		Less than 20 weeks	<i>Not reported, but the greatest cervical length cut-off was ≤30mm</i>	28.2%	98.5%			18.8	0.72	
		SYSTEMATIC REVIEW			Not	40.0%	96.1%			10.26	0.62	AURC

Preterm birth <37 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		Low risk <i>Six studies only included low risk patients.</i>			<i>reported, but the greatest cervical length cut-off was $\leq 33.15\text{mm}$</i>							0.88
Arora et al. (2012) ²⁹	India	Low risk. 200 asymptomatic women with singleton pregnancies. Women were excluded if they had a medical disorder, were smokers, had fetal malformations at the 20 week scan or had factors predisposing to preterm labour including previous preterm delivery, or 2 nd trimester abortion, surgery on the cervix or preeclampsia.	16% (32 women)	20-24 weeks	$\leq 25\text{mm}$	31.3%	100%	100%	88.4%	Not calculable	0.69	
					$\leq 30\text{mm}$	53.13%	79.7%	33.3%	89.9%	2.63	0.59	
					$\leq 35\text{mm}$	90.6%	20.8%	17.9%	92.1%	1.14	0.45	
Barber et al. (2012) ³⁴	Gran Canaria, Spain	Low risk. 306 asymptomatic low-risk pregnant women with live singleton pregnancies. No history of preterm delivery or uterine surgery.	7.2% (18 women)	20-22 weeks	32.5mm	66.7%	79.3%	16.7%	97.4%	3.22	0.42	AURC 0.703 RR 7.65 (95% CI 2.19 to 26.69)
Souka et al. (2011) ²⁴	Greece	Mixed risk. 528 women with viable singleton pregnancies. †Pregnancies ending in miscarriage during the second trimester or termination were excluded. Cases with iatrogenic preterm delivery were not	9.1% (48 women)	11-14 weeks	Not reported	27% (for a fixed 25% screen positive rate)	75.2%	9.8%	91.2%	1.09	0.97	AURC 0.596 OR 0.90 (95% CI 0.522 to 0.671)

Preterm birth <37 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		considered in the prediction of preterm delivery analysis. 2.8% of cohort had previous cervical surgery; 1.3% had history of preterm delivery 34-37 weeks; 1.3% had history of preterm delivery <34 weeks; 0.8% had history of miscarriage 16-24 weeks; 15.9% had history of miscarriage <16 weeks (NB these values are for the full cohort of 800 women, pregnancy outcomes were only available for 528 women)										
Barber et al. (2010) ³²	Gran Canaria, Spain	Mixed risk. 2351 asymptomatic pregnant women with singleton pregnancies. Women who had induced or primary caesarean deliveries were excluded.†	7.2% (184 women)	18-22 weeks	3 rd percentile (28mm)	26%	98%	63.6%	93.57%	13.00	0.76	OR 25.47 (95% CI 15.5 to 41.73)
					5 th percentile (29mm)	34%	97%	51%	94%	11.33	0.68	OR 16.98 (95% CI 11.51 to 25.05)
					10 th percentile (30mm)	39%	92%	31%	94%	4.88	0.66	OR 7.55 (95% CI 5.44 to 10.5)
Matijevic et al. (2010) ³¹	Croatia	Low risk. 316 low risk women with an uncomplicated singleton pregnancy. Exclusion criteria: history of preterm labour; pregnancy following assisted reproduction treatment; suspected chorioamnionitis; PPROM	7.2% (23 women)‡	18-24 weeks	≤26mm (5th percentile)	47.8% (CI 27.4 to 68.9)	98.6% (CI 96.3 to 99.5)	73.3% (CI 44.8 to 91.1)	96.1% (CI 92.9 to 97.8)	35.1 (CI 12.1 to 101.4) LR+ weighted for prevalence 2.7 (CI 1.1 to 6.7)	0.53	

Preterm birth <37 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		or vaginal haemorrhage; cervical surgery; müllerian anomalies; cervical cerclage; sexual intercourse or use of vaginal preparations in the 24 hours pre-ceding the scheduled test; conditions known to be associated with pre-term labour; major fetal anomalies or intrauterine death										
Rashed et al. (2009) ²⁶	Jordan	Low risk. 294 women with singleton pregnancies. Women with additional risk factors were excluded (multiple gestation, pre-eclampsia, diabetes, premature rupture of membranes, fetal anomalies, cervical incompetence, uterine abnormalities, previous cervical surgery, history of previous preterm delivery)	10.8% (32 women)	20-24 weeks	35mm (mean - 1 SD)	43.3%	86.7%	36.2%	89%	3.26	0.65	
					27.5mm (mean - 2 SD)	5.9%	100%	100%	86.6%	Not calculable	0.94	
Davies et al. (2008) ²⁸	Canada	Mixed risk. 964 women with a singleton pregnancy who went onto deliver spontaneously. † 9.2% of women had had a previous spontaneous preterm birth. 0.2% received tocolysis and 0.1% underwent cervical cerclage. Exclusion criteria included presence of cervical cerclage, placenta previa, or major fetal	4.8% (46 women)	24 weeks	≤20mm	2.2%	99.6%	20.0%	95.3%	5.0	0.98	RR 4.3
					≤25mm	13.0%	97.3%	19.4%	95.7%	4.8	0.89	RR 4.5
					≤30mm	26.1%	85.8%	8.5%	95.9%	1.8	0.86	RR 2.0
				28 weeks	≤20mm	7.0%	98.9%	23.1%	95.7%	6.2	0.94	RR 5.3
					≤25mm	16.3%	95.6%	15.2%	96.0%	3.7	0.88	RR 3.8
≤30mm	30.2%	81.8%	7.4%	96.1%	1.7	0.85	RR 1.9					

Preterm birth <37 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		anomaly, being the recipient of oocyte donation, having multiple gestation, or a lack of previous fetal anatomic assessment.										
Dilek et al. (2007) ³³	Turkey	Low risk. 257 low-risk women with singleton pregnancies. Exclusion criteria were a history of preterm delivery, preterm premature rupture of membranes, cervical incompetence, multiple pregnancies, previously detected cervical funnelling and patients with known Müllerian anomalies	7.4% (19 women)	16 weeks	35.3mm	26.3%	93.7%	25%	94.1%	4.17	0.79	AURC 0.574 (0.419-0.730)
				24 weeks	34.3mm	84.2%	81.5%	26.7%	98.5%	4.55	0.19	AURC 0.914 (0.637-0.907) RR 4.56 (95% CI 3.51 to 5.62)
				Change in cervical length between 16 and 24 weeks	6.6mm	73.7%	81.9%	24.6%	97.5%	4.07	0.32	AURC 0.888 (0.843-0.924) RR 4.08 (95%CI 2.23 to 5.93)

Abbreviations: PPV: Positive predictive value; NPV negative predictive value; AURC area under the ROC curve; RR relative risk; OR odds ratio; CI confidence interval; IQR interquartile range; LR+, positive likelihood ratio; LR- negative likelihood ratio.

*for a full list of studies included in the systematic review and their characteristics, see Appendix 1

†population not selected on basis of risk factors for preterm birth: not necessarily all at low risk

‡preterm labour

Table 5: Accuracy for transvaginal cervical length measurements for the prediction of preterm birth or preterm labour <35 weeks' gestation
Numbers in italics have been calculated. Other numbers are as reported. If cells are blank numbers were not reported and not enough data was reported in the paper to calculate figures. Likelihood ratios in bold with shaded cells have a LR+>5 or a LR-<0.2.

Preterm birth <35 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Domin et al. (2010) ^{27*}		SYSTEMATIC REVIEW Mixed risk. Not reported how many studies this was based on, but 17 studies used cut-offs of 25mm or less and preterm delivery defined as less than 35 weeks. Seven studies included high risk women, 2 included low risk women, and 8 included both.			≤25mm	33.3%	95.9%			6.30	0.65	AURC 0.85
		SYSTEMATIC REVIEW Mixed risk. Not reported how many studies this was based on, but 9 studies used cut-offs of 20mm or less and preterm delivery defined as less than 35 weeks. Two of these studies included high risk women, 1 included low risk women, and 6 included both.			≤20mm	22.1%	98.2%			12.4	0.74	AURC 0.89
Davies et al. (2008) ²⁸	Canada	Mixed risk. 964 women with a	1.7% (16 women)	24 weeks	≤20mm	6.3%	99.6%	20.0%	98.4%	14.8	0.94	RR 12.8

Preterm birth <35 weeks' gestation													
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported	
					≤25mm	25.0%	97.1%	12.9%	98.7%	8.8	0.77	RR 10.0	
					≤30mm	50.0%	85.9%	5.6%	99.0%	3.5	0.58	RR 5.8	
					28 weeks	≤20mm	7.1%	98.7%	7.7%	98.6%	5.5	0.94	RR 5.5
					≤25mm	21.4%	95.3%	6.5%	98.8%	4.6	0.82	RR 5.3	
					≤30mm	57.1%	81.8%	4.5%	99.2%	3.1	0.52	RR 5.8	
Ozdemir et al. (2007) ³⁰	Turkey	Mixed risk. 152 women with singleton pregnancies. † Women were excluded from the study if they had previous cervical conisation, placenta previa, foetal anomaly, or the induction of labour for medical indications before term.	10.5% (16 women)	10-14 weeks	≤39mm	75%	67.9%	21.40%	95.8%	2.34	0.37	AURC 0.713	
				20-24 weeks	≤27mm	81.2%	99.3%	92.9%	97.9%	116.00	0.19	AURC 0.874	

Abbreviations: PPV: Positive predictive value; NPV negative predictive value; AURC area under the ROC curve; RR relative risk; OR odds ratio; CI confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio.

*for a full list of studies included in the systematic review and their characteristics, see Appendix 1

†population not selected on basis of risk factors for preterm birth: not necessarily all at low risk

Table 6: Accuracy for transvaginal cervical length measurements for the prediction of preterm birth or preterm labour <34 weeks' gestation. Numbers in italics have been calculated. Other numbers are as reported. If cells are blank numbers were not reported and not enough data was reported in the paper to calculate figures. Likelihood ratios in bold with shaded cells have a LR+>5 or a LR-<0.2.

Preterm birth <34 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Greco et al. (2011) ²³	UK	Mixed risk. 1,508 pregnant women.† 1% of women had a history of preterm birth <34 weeks' gestation. Included singleton pregnancies with delivery at or after 24 weeks' gestation. Excluded pregnancies ending in miscarriage, termination, fetal death, or iatrogenic delivery <34 weeks and women with preeclampsia, cerebral haemorrhage and placenta previa.	1.1% (16 women)	11-13 weeks	<25mm	37.5%	97.2%	12.5%	99.3%	13.32	0.64	
					<30mm	93.8%	72.6%	3.5%	99.9%	3.42	0.09	
Souka et al. (2011) ²⁴	Greece	Mixed risk. 528 women with viable singleton pregnancies.† Pregnancies ending in miscarriage during the second trimester or termination were excluded. Cases with iatrogenic preterm delivery were not considered in the prediction of preterm delivery analysis. 2.8% of cohort had previous cervical surgery; 1.3% had history of preterm delivery 34-37 weeks; 1.3% had history of preterm delivery <34 weeks; 0.8% had history of miscarriage 16-	2.3% (12 women)	11-14 weeks	Not reported	50% (for a fixed 25% screen positive rate)	75.6%	4.5%	98.5%	2.05	0.66	AURC 0.759 OR 0.746; 95% CI 0.649 to 0.869

Preterm birth <34 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		24 weeks; 15.9% had history of miscarriage <16 weeks (NB values for the full cohort of 800 women, pregnancy outcomes only available for 528 women)										
Barber et al. (2010) ³²	Gran Canaria, Spain	Mixed risk. 2351 asymptomatic pregnant women with singleton pregnancies. Women who had induced or primary caesarean deliveries were excluded.†	Not reported	18-22 weeks	3rd percentile (28mm)							OR 28.7 (95% CI 14.54 to 41.73)
					5 th percentile (29mm)						OR 20.5 (95% CI 11.51 to 25.05)	
					10 th percentile (30mm)						OR 10.3 (95% CI 5.44 to 10.5)	
Matijevic et al. (2010) ³¹	Croatia	Low risk. 316 low risk women with an uncomplicated singleton pregnancy. Exclusion criteria: history of preterm labour; pregnancy following assisted reproduction treatment; suspected chorioamnionitis; PPRM or vaginal haemorrhage; cervical surgery; müllerian anomalies; cervical cerclage; sexual intercourse or use of vaginal preparations in the 24 hours pre-ceding the scheduled test; conditions known to be associated with pre-term labour; major fetal anomalies or	2.5% (8 women)‡	18-24 weeks	≤26mm	87.5% (46.7-99.3)	97.4% (94.7-98.8)	46.6% (22.3-72.6)	99.7% (97.9-99.9)	33.7 (16.2-70.1) LR+ weighted for prevalence 0.8 (0.4-1.8)	0.13	

Preterm birth <34 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		intrauterine death										

Abbreviations: PPV: Positive predictive value; NPV negative predictive value; AURC area under the ROC curve; RR relative risk; OR odds ratio; CI confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio.

†population not selected on basis of risk factors for preterm birth: not necessarily all at low risk

‡early preterm labour

Table 7: Accuracy for transvaginal cervical length measurements for the prediction of preterm birth or preterm labour <32 weeks' gestation
Numbers in italics have been calculated. Other numbers are as reported. If cells are blank numbers were not reported and not enough data was reported in the paper to calculate figures. Likelihood ratios in bold with shaded cells have a LR+>5 or a LR-<0.2.

Preterm birth <32 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Arora et al. (2012) ²⁹	India	Low risk. 200 asymptomatic women with singleton pregnancies. Women were excluded if they had a medical disorder, were smokers, had fetal malformations at the 20 week scan or had factors predisposing to preterm labour including previous preterm delivery, or 2nd trimester abortion, surgery on the cervix or preeclampsia.	1% (2 women)	20-24 weeks	≤30mm	100%	75.3%	3.9%	100%	4.04	0	
Souka et al. (2011) ²⁴	Greece	Mixed risk. 528 women with viable singleton pregnancies.† Pregnancies ending in miscarriage during the second trimester or termination were excluded. Cases with iatrogenic preterm delivery were not considered in the prediction of preterm delivery analysis. 2.8% of cohort had previous cervical surgery; 1.3% had history of preterm delivery 34-37 weeks; 1.3% had history of preterm delivery <34 weeks; 0.8% had history of miscarriage 16-24 weeks; 15.9% had	1.3% (7 women)	11-14 weeks	Not reported	55% (for a fixed 25% screen positive rate)	75.4%	2.9%	99.2%	2.24	0.60	AURC 0.774 OR 0.734; 95% CI 0.637 to 0.912

Preterm birth <32 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		history of miscarriage <16 weeks (NB values for the full cohort of 800 women, pregnancy outcomes only available for 528 women)										

Abbreviations: PPV: Positive predictive value; NPV negative predictive value; AURC area under the ROC curve; RR relative risk; OR odds ratio; CI confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio.

†population not selected on basis of risk factors for preterm birth: not necessarily all at low risk

Table 8: Accuracy for transvaginal cervical length measurements for the prediction of preterm birth or preterm labour <30 weeks' gestation
Numbers in italics have been calculated. Other numbers are as reported. If cells are blank numbers were not reported and not enough data was reported in the paper to calculate figures. Likelihood ratios in bold with shaded cells have a LR+>5 or a LR-<0.2.

Preterm birth <30 weeks' gestation												
Study	Country	Population	Incidence of preterm delivery	Timing of screen	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Barber et al. (2010) ³²	Gran Canaria, Spain	Mixed risk. 2351 asymptomatic pregnant women with singleton pregnancies. Women who had induced or primary caesarean deliveries were excluded. †	Not reported	18-22 weeks	3 rd percentile (28mm)							OR 29.8 (95% CI 15.54 to 41.73)
					5 th percentile (29mm)						OR 23.1 (95% CI 11.51 to 25.05)	
					10 th percentile (30mm)						OR 19.1 (95% CI 7.44 to 31.5)	

Abbreviations: PPV: Positive predictive value; NPV negative predictive value; AURC area under the ROC curve; RR relative risk; OR odds ratio; CI confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio

†population not selected on basis of risk factors for preterm birth: not necessarily all at low risk

Other predictors of preterm birth

Several studies compared transvaginal cervical length measurement with measurement of a different factor.

Barber et al. (2012) compared measurement of cervical length with cervical volume.³⁴ It found a high correlation between cervical length and cervical volume, and no difference in the sensitivity, specificity, positive predictive value, negative predictive value and relative risk between the two methods.

Matijevic et al. (2010) compared cervical length measurement with measurement of vaginal pH (used as a marker for bacterial vaginosis).³¹ It concluded that elevated vaginal pH was a better predictor of early preterm labour than a shortened cervical length in the study cohort of pregnant women at low risk.

Davies et al. (2008) compared cervical length measurement with measurement of serum relaxin levels.²⁸ The study concluded that neither measurement of serum relaxin levels nor cervical length is a useful screening tool.

The accuracy of the mentioned techniques and other techniques identified in the update search are summarised in Appendix 3.

Is cervical length screening safe and reliable?

The ACOG state that “when performed by trained operators, cervical length screening by transvaginal ultrasonography is safe, highly reproducible, and more predictive than transabdominal screening. Using a method in which the transvaginal probe is placed in the anterior fornix of the vagina with an empty maternal bladder results in measurements with interobserver variation of 5-10%.”²²

The Society for Maternal-Fetal Medicine (SMFM) reports that cervical length as a screening test in singleton gestations fulfils many of the criteria for an effective screening test.³⁵ It is well described, safe and acceptable (transvaginal ultrasonography is safe even in women with PPROM; 99% of women would have transvaginal ultrasonography again; <2% have severe pain), and the results are reproducible (<10% intraobserver and interobserver variability), and the results are accurate or valid.

Recommendations regarding cervical length screening

The 2008 NICE Guideline on antenatal care assessed the diagnostic value of 12 screening tests for asymptomatic women.³ They recommended that routine screening for preterm labour should not be offered, as the evidence does not justify screening using clinical examination, asymptomatic bacteriuria, vaginal swabs or ultrasound to assess cervical change, and further research is required investigating the value of screening using maternal serum CRP and cervico-vaginal fetal fibronectin levels, and the accuracy and cost-effectiveness of transvaginal ultrasound.³

The ACOG recommended that cervical length screening may be considered (although universal screening in women without a prior preterm birth is not mandated).²²

The Society for Maternal-Fetal Medicine concluded that “*Summary of randomized studies indicates that in women with singleton gestations, no prior [preterm birth], and short [cervical length] ≤ 20 mm at ≤ 24 weeks, vaginal progesterone, either 90-mg gel or 200-mg suppository, is associated with reduction in [preterm birth] and perinatal morbidity and mortality, and can be*

offered in these cases. The issue of universal [cervical length] screening of singleton gestations without prior [preterm birth] for the prevention of [preterm birth] remains an object of debate. [Cervical length] screening in singleton gestations without prior [preterm birth] cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners, following strict guidelines.”³⁵

Criterion 5: Partly met

Cervical length screening by transvaginal ultrasound measures the distance between the internal os and the external os. When measuring cervical length the measurement should differentiate between the endocervix and the isthmus, especially if the measurement is being taken in the first trimester.

A systematic review (consisting of 23 studies) and a further ten primary studies of transvaginal ultrasound measurement for predicting preterm birth were identified in the update search and included.

The systematic review found that the test performed best (according to ROC curves) when the cut-off was ≤ 20 mm and preterm delivery was < 35 weeks. It calculated the sensitivity to be 22.1%, the specificity to be 98.2%, the LR+ to be 12.4 and the LR- to be 0.74, and the AURC to be 0.89.

Ten primary studies, not included in the systematic review, were identified. These measured cervical length between 10 weeks and 28 weeks’ gestation, and assessed the accuracy of predicting preterm birth < 30 weeks to < 37 weeks’ gestation. Although there was a large variation in reported accuracy, two studies reported cervical length screening accuracy outcomes that fulfilled the HTA criteria for a useful test. A cut-off of ≤ 27 mm at 20-24 weeks for predicting preterm birth < 35 weeks had a LR+ of 116.00 and a LR- of 0.19 in mixed risk women in one study and a cut-off of ≤ 26 mm at 18-24 weeks for predicting preterm birth < 34 weeks had a LR+ of 33.7 and a LR- of 0.13 in low risk women in the other study. The positive predictive values were generally reported to be low. The relatively high false detection rate would therefore suggest that many women who test positive could be exposed to preventative treatments without any benefit to them. Furthermore, the negative aspects caused by the expected number of false positives (for example anxiety) should be noted when considering the value of the test.

The optimal cervical length cut-off and the gestational age at which screening should be performed remains to be determined. These may vary depending on what a screening programme is aiming to prevent. The majority of studies identified did not satisfy the HTA criteria for a useful test for the prediction of preterm birth. Although two studies met the criteria and the systematic review reported a favourable AURC, there remains significant uncertainty in the value of using cervical length screening. As outlined above, the variation in outcomes and the target population prohibits a conclusion being drawn.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

Distribution of cervical length measurements by transvaginal ultrasound in the target population

The distribution of cervical length measurements seen by transvaginal ultrasound in the cohort studies included in Criterion 5 are shown in Table 10. Where reported, the distributions of

cervical length measurements seen in randomised controlled trials (RCTs) of treatment of women with a short cervix included in Criterion 10 are also shown. One study (Dilek et al. [2007]³³) also reported whether change in cervical length can predict delivery. The distribution of changes in cervical length in this study is reported in Table 11.

Cervical lengths measured at between 16 and 28 weeks' gestation varied between 0mm and 68mm, with reported mean values between 31mm and 42.96mm. Some of this variation may be due to gestational age when measurements were made, and population studied. As noted in Criterion 5 it is important to distinguish between endocervical length and the length of the cervico-isthmic complex. Some studies may have reported endocervical length whilst others reported the length of the cervico-isthmic complex. It will be important when specifying cut-offs to distinguish whether the endocervical length or the length of the cervico-isthmic complex is being measured.

One study on a UK population was identified. In Greco et al. (2011), the median endocervical length at 20 to 24 weeks' gestation was 32.2mm (5th centile 24.6mm, 95th centile 40.2mm).²³ Median length of the cervico-isthmic complex was 40.4mm (5th centile 26.1mm, 95th centile 60.6mm).

Cut-offs

The cohort studies in Criterion 5 used a wide range of cervical length cut-offs to predict preterm birth. For example, cut-offs between 20mm and 35.3mm at between 16 and 28 weeks' gestation were used to predict preterm birth prior to 37 weeks' gestation in women at low or unspecified risk (i.e. an unselected population of pregnant women) of preterm birth. The systematic review of transvaginal ultrasonographic measurement of cervical length during the second trimester as a predictor of spontaneous preterm birth among asymptomatic women with a singleton pregnancy found that the test performs best (according to ROC curves) when a cut-off of ≤ 20 mm at 14 to 24 weeks is used to predict preterm delivery <35 weeks' gestation.²⁷

The RCTs that have assessed progesterone treatment after cervical length used different cut-offs, and only identified a proportion of the women who went onto have a preterm birth. The cut-offs used for inclusion into the treatment trials of progesterone and cervical pessary (described in Criterion 10), and the frequency of the cut-offs are shown in Table 9.

Table 9: Cut-offs used in RCT of treatments to prevent preterm birth

Study	Gestational age	Cut-off	Frequency of cut-off
Hassan et al. (2011) ³⁶	19+0 to 23+6 weeks	10-20mm	2.3%
Fonseca et al. (2007) ³⁷	20 to 25 weeks	≤ 15 mm	1.7%
Grobman et al. (2012) ³⁸	16 to 22 3/7 weeks	<30mm	10.3%
Goya et al. (2012) ³⁹	18 to 22 weeks	≤ 25 mm	6%

Fonseca et al. (2007) noted that less than one third of the scanned women who had spontaneous preterm delivery <34 weeks' gestation had a cervical length of ≤ 15 mm (cut-off applied in this study).³⁷ They screened 24,620 women with singleton or twin pregnancies in the UK, Greece, Brazil and Chile. Pregnancy outcomes were obtained for 23,795 women. Spontaneous delivery <34 weeks occurred in 489 women (2.1%). Including women who participated in the trial, the cervical length was ≤ 15 mm in 408 women (1.7%), of whom 126 (30.9%) delivered preterm, accounting for 25.8% of the deliveries <34 weeks. The cervical length was 16 to 25mm in 1,975 (8.3%) women, of whom 100 delivered <34 weeks, accounting for 20.4% of the deliveries <34 weeks.

Goya et al. (2012) identified more than two thirds of the scanned women who had a spontaneous preterm delivery <34 weeks' gestation with their cut-off of $\leq 25\text{mm}$.³⁹ They screened 11,875 women who consented to transvaginal cervical length measurement during routine second trimester ultrasonography at 18 to 22 weeks' gestation in Spain.³⁹ Pregnancy outcomes were obtained from 11,518 women (including women who participated in the trial); 227 (2%) of women had a spontaneous preterm birth <34 weeks. Of the women who had a spontaneous preterm birth <34 weeks the cervical length was $\leq 25\text{mm}$ in 152 women (67.0%; 12 in the pessary group, 51 in the expectant management group, 89 declined to participate) and $>25\text{mm}$ in 75 women (33.0%).

The other RCTs of treatment identified did not report this information.

The SMFM and ACOG define a short cervix as $\leq 20\text{mm}$ at ≤ 24 weeks' gestation.^{22,35} However, the SMFM state that $<25\text{mm}$ was traditionally considered as short in the US.⁴

Criterion 6 not met: A screening programme would have to define the cervical length cut-off, the gestational age at which screening should take place, and what the screening programme is aiming to prevent. The uncertainties around the diagnostic value of cervical length screening make defining cut-offs for these factors problematic.

Studies have reported the distribution of cervical lengths measured by transvaginal ultrasonography in different populations, including the UK, and at different gestational ages. Two studies have emphasised the importance of distinguishing between endocervical length and the length of the cervico-isthmic complex, especially when measuring cervical length during the first trimester.

There is not yet agreement on an appropriate cervical length cut-off, or on the timing of transvaginal ultrasonographic measurement for screening. These may vary depending on what a screening programme is aiming to prevent.

The cut-off used for screening will need to balance sensitivity and specificity. A systematic review of transvaginal ultrasonographic measurement of cervical length during the second trimester as a predictor of spontaneous preterm birth among asymptomatic women with a singleton pregnancy found that the test performs best (according to ROC curves) when a cut-off of $\leq 20\text{mm}$ at 14 to 24 weeks is used and preterm delivery is defined as <35 weeks' gestation. Primary studies used cervical length cut-offs between 20mm and 35.3mm, between 16 and 28 weeks' gestation to predict preterm birth prior to 37 weeks' gestation. In the two studies that fulfilled the HTA criteria for a useful test one used a cut-off of $\leq 27\text{mm}$ at 20-24 weeks for predicting preterm birth <35 weeks and the other used a cut-off of $\leq 26\text{mm}$ at 18-24 weeks for predicting preterm birth <34 weeks. Both the SMFM and the ACOG consider women with a cervical length $\leq 20\text{mm}$ at ≤ 24 weeks to have a short cervix. However, the SMFM state that $<25\text{mm}$ was traditionally considered as short in the US. RCTs that have assessed treatments for a short cervix used different cut-offs as inclusion criteria.

Table 10: Transvaginal cervical length measurements

Study	Country	Population	Timing of screen	Average	Range	Other
Arora et al. (2012) ²⁹	India	200 asymptomatic women with singleton pregnancies. Women were excluded if they had a medical disorder, were smokers, had fetal malformations at the 20 week scan or had factors predisposing to preterm labour including previous preterm delivery, or 2 nd trimester abortion, surgery on the cervix or preeclampsia.	20-24 weeks	Median 30mm Mean ± SD 32.44 ± 3.84mm	21mm to 44mm	Approximately normal distribution
Barber et al. (2012) ³⁴	Gran Canaria, Spain	306 asymptomatic low-risk pregnant women with live singleton pregnancies. No history of preterm delivery or uterine surgery.	20-22 weeks	35.4mm*	21 to 48mm	
		<i>Full term</i>		Mean ± SD 35.5 ± 3.4 mm		
		<i>Preterm</i>		Mean ± SD 32.5 ± 3.4 mm		
Goya et al. (2012) ³⁹	Spain	11,875 women who consented to a transvaginal ultrasonographic measurement of the cervix during routine 2nd trimester ultrasonography at 18-22 weeks' gestation.†	18-22 weeks	Median 34mm	Range 3 to 68mm	
Greco et al. (2011) ²³	UK	1,508 women with singleton pregnancies who delivered at or after 24 weeks' gestation (1.06% had had a previous preterm delivery between 24 and 33 weeks).† Pregnancies ending in termination, miscarriage or fetal death <24 weeks and those with iatrogenic delivery <34 weeks excluded and women with preeclampsia, cerebral haemorrhage and placenta previa.	11-13 weeks	Endocervical length Median 32.4mm (5 th centile 25.6mm, 95 th centile 40.2mm) Cervico-isthmic complex Median 45.3mm (5th centile 30.9mm, 95th centile 65.3 mm)		Isthmus Median 13.8mm (range 0 to 49.4mm)
		<i>34 weeks or later</i>		Endocervical length Median (IQR) 32.5mm (29.5 to 35.6mm) Cervico-isthmic complex Median (IQR) 45.4mm (39.0 to 53.1mm)		
		<i><34 weeks</i>		Endocervical length Median (IQR) 27.5mm		

Study	Country	Population	Timing of screen	Average	Range	Other
				(24.0 to 28.6mm) Cervico-isthmic complex Median (IQR) 41.4mm (34.8 to 45.8mm)		
		1320 women with singleton pregnancies who delivered at or after 24 weeks' gestation.† Pregnancies ending in termination, miscarriage or fetal death <24 weeks and those with iatrogenic delivery <34 weeks excluded	20-24 weeks	Endocervical length Median 32.2mm (5 th centile 24.6mm, 95 th centile 40.2mm) Cervico-isthmic complex Median 40.4mm (5th centile 26.1mm, 95th centile 60.6mm)		Isthmus Median 7.8mm (range 0 to 51.0mm)
			<i>34 weeks or later</i>	Endocervical length Median (IQR) 32.2mm (29.3 to 35.3mm) Cervico-isthmic complex Median (IQR) 40.7mm (33.9 to 47.7mm)		
			<i><34 weeks</i>	Endocervical length Median (IQR) 20.6mm (17.0 to 27.7mm) Cervico-isthmic complex Median (IQR) 27.0mm (17.0 to 33.8mm)		

Study	Country	Population	Timing of screen	Average	Range	Other
		<i>Preterm (< 37 weeks)</i>		Mean ± SD 35.95 ± 8.75 mm		
Matijevic et al. (2010) ³¹	Croatia	316 low risk women with an uncomplicated singleton pregnancy. Exclusion criteria included: a history of preterm labour, pregnancy following assisted reproduction treatment; suspected chorioamnionitis; preterm prelabour rupture of the membranes or vaginal haemorrhage; a previous surgical procedure involving the cervix; a developmental malformation of the müllerian duct system detected before the pregnancy; sexual intercourse or use of vaginal preparations that could influence vaginal pH in the 24 hours pre-ceeding the scheduled test; pre-eclampsia, autoimmune diseases, diabetes, or other conditions known to be associated with pre-term labour; and major fetal anomalies or intrauterine death	18-24 weeks	Mean ± SD 41 ± 8mm		
Rashed et al. (2009) ²⁶	Jordan	294 women with singleton pregnancies. Women with additional risk factors were excluded (multiple gestation, pre-eclampsia, diabetes, premature rupture of membranes, fetal anomalies, cervical incompetence, previous cervical surgery, uterine abnormalities, history of previous preterm delivery)	20-24 weeks	Mean ± SD 42.5 ± 6.4mm		
		<i>Term (n=262)</i>		Mean ± SD 43.7 ± 6.9mm		
		<i>Preterm (n=32)</i>		Mean ± SD 39.3 ± 10.2mm		

Study	Country	Population	Timing of screen	Average	Range	Other	
			28 weeks	Mean ± SD 36.7 ± 7.3mm	Range 6 to 62mm		
Davies et al. (2008) ²⁸	Canada	964 women with a singleton pregnancy who went onto deliver spontaneously. † 9.2% of women had had a previous spontaneous preterm birth. 0.2% received tocolysis and 0.1% underwent cervical cerclage. Exclusion criteria included presence of cervical cerclage, placenta previa, or major fetal anomaly, being the recipient of oocyte donation, having multiple gestation, or a lack of previous fetal anatomic assessment.	24 weeks	Mean ± SD 37.8 ± 7.1mm	Range 16 to 59mm		
Dilek et al. (2007) ³³	Turkey	257 low-risk women with singleton pregnancies. Exclusion criteria were a history of preterm delivery, preterm premature rupture of membranes, cervical incompetence, multiple pregnancies, previously detected cervical funnelling and patients with known Müllerian anomalies. <i>Term deliveries</i>	16 weeks	Mean ± SD 42.96 ± 6.67mm			
			<i>Preterm deliveries</i>	16 weeks	Mean ± SD 40.80 ± 6.62mm		
			<i>Term deliveries</i>	24 weeks	Mean ± SD 38.49 ± 5.70mm		
			<i>Preterm deliveries</i>	24 weeks	Mean ± SD 29.09 ± 5.14mm		
Ozdemir et al. (2007) ³⁰	Turkey	152 women with singleton pregnancies. † Exclusion criteria included previous cervical conisation, placenta previa, foetal anomaly, and the induction of labour for medical indications before term	10-14 weeks	Mean ± SD 40.5 ± 4.7mm			

Study	Country	Population	Timing of screen	Average	Range	Other
			20-24 weeks	Mean ± SD 37.1 ± 5.6mm		
Fonseca et al. (2007) ³⁷	UK, Chile, Brazil, Greece.	24,620 women with singleton (n=24,189) or twin (n=431) pregnancies undergoing routine ultrasonography. Exclusion criteria were no fetal abnormalities, painful uterine contractions, a history of ruptured membranes or a cervical cerclage.	20-25 weeks	Median 34mm	0 to 67mm	1.7% of women had a cervical length of ≤15mm

Abbreviations: SD, standard deviation, IQR, interquartile range.

*unclear whether this value is a median or a mean †not all women at low risk

Table 11: Change in cervical length

Study	Country	Population	Timing of screen	Average	Range	Other
Dilek et al. (2007) ³³	Turkey	257 low-risk women with singleton pregnancies. Exclusion criteria were a history of preterm delivery, preterm premature rupture of membranes, cervical incompetence, multiple pregnancies, previously detected cervical funnelling and patients with known Müllerian anomalies.	Change between 16 and 24 weeks	Mean ± SD 4.45 ± 3.02mm		
		<i>Term deliveries</i>				
		<i>Preterm deliveries</i>	Change between 16 and 24 weeks	Mean ± SD 11.75 ± 5.13mm		

Abbreviations: SD standard deviation

7. The test should be acceptable to the population

The SMFM, when assessing cervical length as a screening test in singleton gestations commented that transvaginal ultrasonography is safe even in women with PPROM; 99% of women would have transvaginal ultrasonography again and that <2% of women have severe pain.³⁵

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

There are no diagnostic tests that can confirm preterm labour risk.

The HTA report concludes: *“Screening typically involves use of a confirmatory test after initial testing, before institution of therapy. In this field, this is not the case because testing is used to identify a risk group in which preventative interventions (both intensive monitoring and treatments) are employed directly after the test results are known. In this situation, for a test to serve as a good tool for screening, it should perform very well.”*²

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Not applicable

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The HTA report concluded that *“beyond the screening issue, consensus is also lacking in the management of individuals who are screened as positive. There are many interventions that purportedly prevent spontaneous preterm birth (primary prevention)”*. In the review 38 treatment options for either primary prevention or secondary prevention were analysed. They conclude that *“among asymptomatic women in early pregnancy antibiotic treatment for bacterial vaginosis in women with intermediate flora, smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising (primary prevention).”*²

Treatment and interventions for low-risk/mixed risk asymptomatic women with a short cervix

This criterion will concentrate on treatments and interventions for low-risk/mixed risk asymptomatic women with a short cervix. Only systematic reviews and RCTs were included. Other interventions and treatments given after other screening tests are summarised in Appendix 3. The primary outcome for this criterion is the prevention of preterm birth, secondary outcomes related to this outcome will also be summarised below. The full details of studies included for this criterion can be found in Appendix 2.

Three systematic reviews and three RCTs of progesterone, one RCT of cervical pessary and three systematic reviews of cervical cerclage vs. placebo, no treatment, or expectant management in women with a short cervix, including women at low risk, reporting preterm birth as an outcome, were identified in the update search. The results of these studies are summarised in Table 12. In

addition, one study that compared cervical cerclage with progesterone was identified (see Table 14).

Cervical length inclusion criteria varied as did the gestational age used for the preterm birth outcome (from <33 weeks to <37 weeks).

Progesterone was found to reduce the risk of preterm birth in all three systematic reviews and in two of the three RCTs.^{36,37,40-42} It should be noted that the three identified systematic reviews of progesterone were based largely upon the results of either one or both of the two RCTs of vaginal progesterone (Hassan et al. [2011]³⁶ and Fonseca et al. [2007]³⁷). One RCT, of intramuscular progesterone, found no significant difference in preterm birth (Grobman et al. [2012]).³⁸ The results of this trial may be different to the other RCTs due to the form of progesterone used and how it was delivered (weekly 250mg 17-OHP intramuscular injections vs. bioadhesive gel with 90mg or capsules containing 200mg progesterone daily), the inclusion criteria for the trial (it included women with cervical lengths <30mm, longer than the other studies, where the longest cervical length was 20mm); the primary outcome (birth <37 weeks, in contrast to the other studies where the primary outcome was birth <33 or <34 weeks; however there was no significant difference in preterm birth at earlier gestations in this study); or other differences in the population (this study was done in nulliparous women, subgroup analyses for nulliparous women were not reported in Hassan et al. [2011]³⁶ and Fonseca et al. [2007]³⁷).

The two included RCTs comparing vaginal progesterone with placebo reported few significant benefits for neonatal health or mortality with progesterone. Hassan et al. (2011) reported significantly reduced risk of neonatal birth weight <1,500g (RR 0.47 [95% CI 0.26 to 0.85]), respiratory distress syndrome (RR 0.39 [95% CI 0.17 to 0.92]), and a composite measure of neonatal morbidity and mortality (RR 0.57 [95% CI 0.33 to 0.99]) with progesterone.³⁶ Progesterone did not reduce the risk of any neonatal health or mortality secondary outcomes assessed in Fonseca et al. (2007).³⁷

One of the three systematic reviews included that reported on outcomes for vaginal progesterone in comparison with placebo, which included both Fonseca et al. (2007)³⁷ and Hassan et al. (2011)³⁶ found study that in singleton pregnancies progesterone significantly reduced the risk of respiratory distress syndrome, a composite measure of neonatal morbidity/mortality, Apgar scores <7 at 5 minutes, birthweight <1,500g, and admission to neonatal intensive care (Romero et al. [2012]).⁴² It should be noted that this analysis included two further studies that were not included in this update review, as the women studied did not meet the inclusion criteria. The other systematic review (Likis et al., [2012]) found that progesterone significantly reduced the risk of neonatal death; progesterone did not alter the risk of other outcomes assessed.⁴¹

Cervical pessary was found to reduce the risk of spontaneous preterm birth <34 weeks in one RCT.³⁹ Compared to expectant management, cervical pessary also significantly reduced the risk of birth weight <2,500g and <1,500g, respiratory distress syndrome, treatment for sepsis, composite adverse outcomes and premature preterm rupture of membranes, as well as reducing the need for tocolysis and corticosteroid treatment. Cervical pessary did not significantly alter neonatal mortality rates.

Three systematic reviews were included that assessed cervical cerclage. None reported a significant change in risk of preterm birth.⁴³⁻⁴⁵

Table 12: Systematic reviews and RCTs of treatments and interventions for the prevention of preterm birth in women with a short cervix otherwise at low-risk or mixed risk of preterm birth vs. placebo, no treatment, or expectant management. The primary outcome is reported. Where available, results for populations nearest our scope were extracted (women without multiple pregnancies, history of preterm birth, PPROM or fetal loss in the second trimester, uterine anomalies or cervical surgery).

Study	Population	Primary outcome	RR (95% CI) of primary outcome with intervention vs. placebo, no intervention or expectant management
Progesterone			
<i>Vaginal progesterone</i>			
Likis et al. (2012) ⁴¹	Systematic review Mixed risk Women with a short cervix (not further specified) on midtrimester ultrasonography	Preterm birth <33 and <34 weeks	0.52 (0.36 to 0.70)†; 2 studies (included studies: Hassan et al. [2011] ³⁶ Fonseca et al. [2007] ³⁷)
Romero et al. (2012) ⁴²	Systematic review Mixed risk Women with singleton gestations and a cervical length ≤25mm	Preterm birth <33 weeks	0.56 (0.40 to 0.80); 4 studies (included studies: Hassan et al. [2011] ³⁶ Fonseca et al. [2007] ³⁷ and two additional studies)
Dodd et al. (2008) ⁴⁰	Systematic review Mixed risk Women with a short cervix identified on ultrasound (not further specified)	Preterm birth <34 weeks	0.58 (0.38 to 0.87); 1 study (included study: Fonseca et al. [2007] ³⁷)
Hassan et al. (2011) ³⁶	RCT Mixed risk 458 asymptomatic women with a singleton pregnancy identified by transvaginal ultrasound to have a short cervix (10-20mm) in the midtrimester (19+0 to 23+6 weeks' gestation)	Preterm birth <33 weeks	0.55 (0.33 to 0.92)
Fonseca et al. (2007) ³⁷	RCT Mixed risk 250 asymptomatic women with singleton (n=226) or twin (n=24) pregnancies who were found to have a cervical length ≤15mm on transvaginal ultrasonography at between 20 and 25 weeks' gestation	Spontaneous delivery <34 weeks	0.56 (0.32 to 0.91)‡
<i>17-alpha-hydroxyprogesterone(17-OHP) intramuscular injections</i>			
Grobman et al. (2012) ³⁸	RCT Low risk 657 nulliparous women with singleton pregnancies with a cervical length <30mm between 16 and 22 3/7 weeks on transvaginal ultrasound	Preterm birth <37 weeks	1.03 (0.79 to 1.35)
Pessary			
Goya et al. (2012) ³⁹	RCT Mixed risk 385 asymptomatic women with a singleton pregnancy identified by transvaginal ultrasound to have a cervical length ≤25mm during the second trimester	Spontaneous delivery <34 weeks	OR 0.18 (0.08 to 0.37)
Cerclage			
Alfirevic et al. (2012) ⁴³	Systematic review Low/unspecified risk	Preterm birth was not a primary	

Study	Population	Primary outcome	RR (95% CI) of primary outcome with intervention vs. placebo, no intervention or expectant management
	Studies comparing cervical stitch based on a one-off ultrasound scan of the cervix in women at low/unspecified risk for preterm birth (as opposed to women with a history of preterm birth of cervical surgery)	outcome.	
		Birth <34 weeks	0.82 (0.55 to 1.22); 3 studies
		Birth <37 weeks	0.80 (0.55 to 1.16); 3 studies
Berghella et al. (2010) ⁴⁴	Systematic review Low risk Women with a singleton gestation who had a cervix <25mm long (identified by 2nd trimester transvaginal ultrasound) and who had not previously had a preterm birth	Birth <35 weeks	0.84 (0.60 to 1.18); 4 studies
Jorgensen et al. (2007) ⁴⁵	Systematic review Mixed risk Women with confirmed or suspected cervical insufficiency	Preterm birth was not a primary outcome. Preterm birth at cut-offs between 16 and 37 weeks' gestation.	No statistical difference in preterm birth at cut-offs between 16 and 37 weeks' gestation (pooled ORs not reported)

Abbreviations: RR, Relative risk; OR, odds ratio; CI, confidence interval.

†95% credible interval

‡ Adjusted RR. Non-adjusted RR 0.56 (95% CI 0.36 to 0.86)

The number needed to treat to prevent one preterm birth (as defined by the study) could be calculated based on the results of the three RCTs with a significant result (Hassan et al. [2011]³⁶ and Fonseca et al. [2007]³⁷ [vaginal progesterone] and Goya et al. [2012]³⁹ [cervical pessary]). Based on the frequency in the studies of cervical lengths that fulfilled the entry criteria and the effectiveness of the interventions for the prevention of preterm birth (as defined by the study), the number needed to be screened to prevent one preterm birth could also be calculated. These are shown in Table 13.

Table 13: Number needed to treat and number needed to screen from RCTs with a significant result. Numbers in italics have been calculated.

Study	Intervention	Cut-off	Frequency of cut-off	Outcome	Number needed to treat	Number needed to screen†
Hassan et al. (2011) ³⁶	Vaginal progesterone	10-20mm	2.3%	Preterm birth <33 weeks	14 (95% CI 8 to 87)	604‡
Fonseca et al. (2007) ³⁷	Vaginal progesterone	≤15mm	1.7%	Spontaneous preterm birth <34 weeks	7‡	387‡
Goya et al. (2012) ³⁹	Pessary	≤25mm	6%	Spontaneous preterm birth <34 weeks	5	78

†Assuming that all women who screen positive receive the intervention.

‡Calculated by the SMFM³⁵

Based on the results of Hassan et al. (2011)³⁶, the SMFM calculated that approximately 604 women would need to be screened to prevent one preterm birth <33 weeks, if all women with a cervical length between 10 and 20 mm receive vaginal progesterone.³⁵ Once a cervical length

between 10 and 20mm is identified, the number needed to treat to prevent one preterm birth <33 weeks is about 14.³⁵

Based on the results of Fonseca et al. (2007)³⁷, the SMFM calculated that the number of women that need to be screened by cervical length measurement to prevent one spontaneous preterm birth <34 weeks is approximately 387, if all women with a cervical length ≤15mm receive vaginal progesterone.³⁵ Once cervical length ≤15mm has been identified, the number needed to treat was calculated to be about seven.³⁵

Similarly, based on the results of Goya et al. (2012)³⁹, the number of women that need to be screened by cervical length measurement to prevent one spontaneous preterm birth <34 weeks is approximately 78, if all women with a cervical length ≤25mm have a cervical pessary. Once cervical length ≤25mm has been identified, the number needed to treat was calculated to be about five.

Comparisons between treatments

Intramuscular injections of progesterone (17-alpha-hydroxyprogesterone [17-OHP]) were not significantly different to cerclage for the prevention of preterm birth in women with risk factors for spontaneous preterm birth and/or a short cervix in one RCT (Keeler et al. [2009]⁴⁶). There was no difference in the rate of preterm birth <35 weeks (Table 14).⁴⁶

Table 14: RCTs of cervical cerclage vs. intramuscular progesterone for the prevention of preterm birth in women with a short cervix otherwise at mixed risk of preterm birth

Study	Population	Primary outcome	Cerclage (% , n)	17-OHP (% , n)	RR (95% CI)
Cerclage vs. Progesterone					
Keeler et al. (2009) ⁴⁶	RCT Mixed risk 79 women with a cervical length ≤25mm at between 16 and 24 weeks	Preterm birth <35 weeks	38.1 (16/42)	43.2 (16/37)	1.14 (0.67 to 1.93)

Recommendations

The ACOG state that vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length ≤20mm ≤24 weeks’ gestation²²

The SMFM concluded that trials have shown that in women with singleton gestations, no prior preterm birth, and a cervical length ≤20mm at ≤24 weeks, vaginal progesterone, administered either as a 90mg gel or 200mg suppository, is associated with reduction in preterm birth and perinatal morbidity and mortality, and can be offered to women fulfilling this criterion, despite concluding the universal cervical length screening of low risk asymptomatic women cannot yet be universally mandated.³⁵

In 2012, however, an US Food and Drug Administration (FDA) panel rejected progesterone vaginal gel for the prevention of preterm birth. The complete response letter stated that the effect of treatment with progesterone vaginal gel 8% in reducing the risk of preterm birth in women with a short cervical length did not meet the level of statistical significance generally expected to support the approval of the product from a single trial. The FDA also raised the issue of robustness in efficacy in the US study participants.

Criterion 10 partially met:

Vaginal progesterone and cervical pessary were found to significantly reduce the risk of preterm birth (as defined by each study) compared to placebo or expectant management. Intramuscular progesterone and cerclage were not found to significantly reduce the risk of preterm delivery.

The evidence for vaginal progesterone comes from two RCTs.

One RCT found that 14 women with a cervical length between 10 and 20mm would need to be treated to prevent one preterm birth <33 weeks. Based on the frequency of a cervical length between 10 and 20mm seen in this study, 604 women would have to be screened to prevent one preterm birth <33 weeks. This is equivalent to preventing approximately 17 preterm births <33 weeks for every 10,000 women screened.

One RCT found that seven women with a cervical length ≤ 15 mm would need to be treated to prevent one spontaneous preterm birth <34 weeks. Based on the frequency of a cervical length ≤ 15 mm seen in this study, 387 women would have to be screened to prevent one spontaneous preterm birth <34 weeks. This is equivalent to preventing approximately 26 spontaneous preterm births <34 weeks for every 10,000 women screened.

However there was no evidence that vaginal progesterone reduces the risk of preterm birth <37 weeks.

Vaginal progesterone also significantly decreased the risk of some other adverse outcomes in some studies. For example, some studies found that vaginal progesterone reduced the risk of respiratory distress syndrome, composite measures of neonatal morbidity and mortality, admission to neonatal intensive care and neonatal death.

The optimal cervical length cut-off, treatment protocol (when to start/finish treatment) and formulation and dose of vaginal progesterone to use remains uncertain. The two RCTs had different cervical length inclusion criteria (between 10 and 20mm at 19+0 to 23+6 weeks' gestation or ≤ 15 mm at 20 to 25 weeks' gestation), used different formulations and doses of vaginal progesterone (bioadhesive gel with 90mg or capsules containing 200mg, both daily) and started and finished treatment at different gestational ages (between 20 to 23+6 and 36 weeks' gestation or between 24 and 34 weeks' gestation). Both trials also included women outside the scope of this review: one included women with twin gestations or prior preterm birth, the other included women with prior preterm birth.

One RCT was included that used cervical pessary to prevent preterm birth. It found that five women with a cervical length ≤ 25 mm would need to be treated to prevent one spontaneous preterm birth <34 weeks. Based on the frequency of a cervical length ≤ 25 mm seen in this study, 78 women would have to be screened to prevent one spontaneous preterm birth <34 weeks. This is equivalent to preventing approximately 128 spontaneous preterm births <34 weeks for every 10,000 women screened. In this trial, cervical pessary also reduced the risk of preterm birth <37 weeks, and the risk of other adverse outcomes (birthweight <2,500g, respiratory distress syndrome, treatment for sepsis, and a composite measure of adverse outcomes).

No studies were found that compared vaginal progesterone with cervical pessaries, therefore neither treatment can be assumed to be superior for the prevention of preterm birth at any gestational age.

A RCT of intramuscular progesterone did not reduce the risk of preterm birth vs. placebo and three systematic reviews of cervical cerclage found no significant benefit for the prevention of preterm birth

The ACOG and SMFM recommend the use of vaginal progesterone in women with short cervical length.

As the optimal cervical length cut-off and the gestational age at which screening should be performed remains to be determined (see Criterion 5), it remains unclear whether the treatments described in this criterion would be effective in screen-identified women.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Not assessed

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

Not assessed

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (eg. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

No RCTs comparing screening asymptomatic pregnant women with singleton gestations with transvaginal ultrasound to measure cervical length were identified.

Criterion 13 not met. No RCTs of cervical length screening were identified.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

Not assessed

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

Not assessed

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should

be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

The HTA report concluded that “an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach to reducing spontaneous preterm births among asymptomatic antenatal women in early pregnancy for primary prevention.”²

Cost-effectiveness of cervical length screening and progesterone treatment

Two studies of the cost-effectiveness of cervical length screening and treatment with progesterone were identified. Although both studies were performed from a US perspective, they both used the results of an RCT performed in the UK, Chile, Brazil and Greece for data on the effectiveness progesterone treatment following cervical length screening (Fonseca et al. [2007]³⁷, see Criterion 10 for more details)

Werner et al. (2011) investigated the cost-effectiveness of screening asymptomatic, low-risk women singleton pregnant women (without a history of prior preterm birth) with a single transvaginal ultrasound to measure cervical length between 18 and 24 weeks’ gestation compared to no screening.⁴⁷ Data in the model was based on published RCTs and prospective cohorts, and cost data from published literature; long term care costs only included direct medical costs. Adherence to therapy and effectiveness of progesterone was from Fonseca et al. (2007)³⁷, and progesterone administration to women with a short cervix (<15mm) was assumed to reduce deliveries <34 weeks by 45%.

In the model, women with short cervical lengths were offered vaginal progesterone nightly until delivery or 36 weeks’ gestation, and received two follow-up cervical-length ultrasound scans.

In the base-case analysis, screening and treating was cost saving: the model predicted that not screening cost \$1,314,520,247 per 100,000 low-risk women whilst screening and treating would cost \$1,302,400,300 per 100,000 low-risk women (saving 12,119,947 2010 US dollars). An estimated 248 births <34 weeks’ gestation and 22 neonatal deaths or neonates with long-term neurological deficits per 100,000 deliveries would be prevented. It was calculated that this would save 423.9 QALYs. Therefore screening was dominant, being both cost saving and producing improved outcomes.⁴⁷

The model was sensitive to changes in the cost of cervical-length ultrasound scans, the effectiveness of progesterone in preventing preterm delivery, the predictive value of a shortened cervix and the prevalence of a shortened cervix. However, the authors report that there was no plausible situation in which the no-screening strategy was dominant.⁴⁷

As an addendum, Werner at al reanalysed their results incorporating data from Hassan et al. (2011)³⁶. They modified their model, adding that vaginal progesterone treatment reduced preterm birth rates in women with mid-pregnancy cervical lengths between 15mm and 25mm. With this adjustment, universal length screening continued to be the dominant strategy.⁴⁷

A previous cost-effectiveness analysis, also using effectiveness data from Fonseca et al. (2007)³⁷ had also found universal cervical length screening and treatment of women with a short (≤ 15 mm) cervix with vaginal progesterone to dominate three other potential screening approaches: cervical length screening of women at increased risk for preterm birth (i.e. due to a

prior spontaneous preterm birth) and treatment of women with a short cervix with vaginal progesterone; no cervical length screening and treatment with 17-OHP based on obstetric history; and no screening and no treatment.⁴⁸

Criterion 16 partially met: Cervical length screening and progesterone treatment has been found to be cost-effective in two publications. However, no studies from a UK perspective were identified.

Both of cost-effectiveness studies included were based on the results a RCT conducted by the Fetal Medicine Foundation in the UK, Brazil, Greece and Chile in 250 asymptomatic women with singleton (n=226) or twin (n=24) pregnancies with a cervical length ≤ 15 mm on transvaginal ultrasonography at between 20 and 25 weeks' gestation. In both cost-effectiveness studies cervical length screening and treatment with progesterone was found to be the dominant strategy. In one study, screening and treatment was both cost saving and produced improved outcomes compared to no screening. In another study, screening was found to dominate three other potential screening approaches: cervical length screening of women at increased risk for preterm birth (i.e. due to a prior spontaneous preterm birth) and treatment of women with a short cervix with vaginal progesterone; no cervical length screening and treatment with 17-OHP based on obstetric history; and no screening and no treatment.⁴⁸

It should be noted that the RCT which the cost-effectiveness studies were based on was published after the HTA which concluded that *“an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective”*.

No cost-effectiveness studies of other screening-treatment combinations were identified.

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

Interventions available to all women independent of screening to prevent preterm births both before and during pregnancy have been assessed. Some of these are reviewed in Criterion 3. Systematic reviews of a number of interventions which could be given without preceding testing were identified. Smoking cessation programmes, nutritional advice, n-3 fatty acids and zinc supplementation were all found to reduce the risk of preterm birth. Interventions to improve preterm survival (antepartum, intrapartum and postnatal) have also been investigated.

The HTA report concluded that *“an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach to reducing spontaneous preterm births among asymptomatic antenatal women in early pregnancy for primary prevention.”*²

No studies assessing the cost-effectiveness of other options not yet implemented in practice vs. screening were identified.

Criterion 17 unclear.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

Not assessed

To ensure quality, the Perinatal Quality Foundation has set up a programme on the proper training for clinical use of transvaginal cervical length measurement, CLEAR (Cervical Length Education and Review).⁴⁹

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Not assessed

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

Not assessed

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

Not assessed

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Not applicable

Executive summary

The condition

Preterm birth is an important health problem, with both short- and long-term consequences including death, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, developmental problems and long-term neurological impairment. In England in 2011-12, 6.3% (34,925) of live singleton births were born prematurely at between 24 and 36 weeks' gestation, although it is unclear how many of these premature births were to low-risk women (without history of preterm birth, preterm prelabour rupture of membranes [PPROM] or fetal loss in the second trimester, uterine anomalies or cervical surgery).

The risk of adverse outcomes increases with increasing prematurity. Although preterm birth is defined as birth <37 weeks' gestation, it remains to be determined whether a screening programme should aim to prevent preterm births <37 weeks or to prevent earlier preterm births. A Health Technology Assessment (HTA) reported that complications of prematurity are significantly reduced after 32–34 weeks' gestation, and assessed the accuracy of tests to predict preterm birth and interventions to prevent preterm birth <34 weeks in addition to <37 weeks.

The decision of what a screening programme would aim to prevent is important as it may affect whether a test is judged to be accurate and whether a treatment is judged to prevent preterm birth.

The test

This evidence review concentrated on cervical length measurement, using transvaginal ultrasound, as a screening test.

Screening typically involves the use of a confirmatory test diagnostic test after a screening test. However, there is no diagnostic test for preterm birth. As such the HTA review suggested that a sufficient degree of test reliability was required.

Using the HTA criteria to demonstrate the utility of test as a reference point, the studies included in this review suggest that the accuracy of cervical length screening in the first trimester is unsatisfactory. The evidence relating to test accuracy in the second trimester has limitations because the majority of studies reported accuracy outcomes that did not meet the HTA criteria.

A systematic review and ten primary studies of transvaginal ultrasound measurement for predicting preterm birth were identified in the update search. These studies assessed cervical length in different populations, at different gestational ages, using different cut-offs, and aimed to predict preterm birth at different gestational ages.

The systematic review found that cervical length screening performed best (according to ROC curves) when the cervical length cut-off was ≤ 20 mm for the prediction of preterm delivery at <35 weeks. They calculated the sensitivity to be 22.1%, the specificity to be 98.2%, the LR+ to be 12.4 and the LR- to be 0.74, and the AUC to be 0.89.

The ten primary studies, not included in the systematic review, measured cervical length between 10 weeks and 28 weeks' gestation, and assessed the accuracy of predicting preterm birth <30 weeks to <37 weeks' gestation. There was a large variation in reported accuracy and just two studies fulfilled the HTA criteria for a useful test (LR+ >5 and LR- <0.2). A cut-off of ≤ 27 mm at 20-

24 weeks for predicting preterm birth <35 weeks had a LR+ of 116.00 and a LR- of 0.19 in mixed risk women in one study and a cut-off of ≤ 26 mm at 18-24 weeks for predicting preterm birth <34 weeks had a LR+ of 33.7 and a LR- of 0.13 in low risk women in the other study. The positive predictive value was generally reported to be low raising the possibility that many women who test positive could be exposed to preventative treatments without any benefit to them.

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) consider women with a cervical length ≤ 20 mm at ≤ 24 weeks' gestation to have a short cervix. However, the SMFM state that <25mm was traditionally considered as short in the US. However, as illustrated in the review, the optimal cervical length cut-off and the gestational age at which screening should be performed remains to be determined. The uncertainty regarding cervical length cut-offs is complicated further by the discovery that it is important to differentiate between the endocervix and the isthmus, especially if the measurement is taken in the first trimester.

The treatment

Vaginal progesterone and cervical pessary were found to significantly reduce the risk of preterm birth (as defined by each study) compared to placebo or expectant management. Intramuscular progesterone and cerclage were not found to significantly reduce the risk of preterm delivery.

The evidence for the effectiveness of vaginal progesterone comes from two RCTs. One found that 14 women with a cervical length between 10 and 20mm would need to be treated to prevent one preterm birth <33 weeks. Based on the frequency of a cervical length between 10 and 20mm seen in this study, 604 women would have to be screened to prevent one preterm birth <33 weeks. This is equivalent to preventing approximately 17 preterm births <33 weeks for every 10,000 women screened. The other RCT found that seven women with a cervical length ≤ 15 mm would need to be treated to prevent one spontaneous preterm birth <34 weeks. Based on the frequency of a cervical length ≤ 15 mm seen in this study, 387 women would have to be screened to prevent one spontaneous preterm birth <34 weeks. This is equivalent to preventing approximately 26 spontaneous preterm births <34 weeks for every 10,000 women screened. Despite the positive outcomes for preterm births at <34 and <33 weeks, there was no evidence that vaginal progesterone reduces the risk of preterm birth <37 weeks.

In some studies, vaginal progesterone also significantly decreased the risk of some other adverse outcomes. For example, vaginal progesterone was found to reduce the risk of respiratory distress syndrome, composite measures of neonatal morbidity and mortality, admission to neonatal intensive care and neonatal death; however the evidence for this was not consistent.

The optimal cervical length cut-off, treatment protocol (when to start/frequency of application/finish treatment) and formulation of vaginal progesterone to use remains uncertain. The two RCTs had different cervical length inclusion criteria (between 10 and 20mm at 19+0 to 23+6 weeks' gestation or ≤ 15 mm at 20 to 25 weeks' gestation), used different formulations and doses of vaginal progesterone (bioadhesive gel with 90mg or capsules containing 200mg, both daily) and started and finished treatment at different gestational ages (between 20 to 23+6 and 36 weeks' gestation or between 24 and 34 weeks' gestation). It should also be noted that the US Food and Drug Administration (FDA) did not approve vaginal progesterone gel for the prevention of preterm labour.

These trials also included women outside the scope of this review, for example women with twin gestations, or prior preterm birth.

A RCT of intramuscular progesterone did not reduce the risk of preterm birth vs. placebo. The difference in the result of this RCT compared to the RCTs of vaginal progesterone may be due to difference in the characteristics of women included in the trials, the form and dose of progesterone used and how it was delivered.

One RCT reported evidence for cervical pessary. It found that five women with a cervical length ≤ 25 mm would need to be treated to prevent one spontaneous preterm birth < 34 weeks. Based on the frequency of a cervical length ≤ 25 mm seen in this study, 78 women would have to be screened to prevent one spontaneous preterm birth < 34 weeks. This is equivalent to preventing approximately 128 spontaneous preterm births < 34 weeks for every 10,000 women screened.

In this trial, cervical pessary also reduced the risk of preterm birth < 37 weeks, and the risk of other adverse outcomes (birthweight $< 1,500$ g or $< 2,500$ g, respiratory distress syndrome, treatment for sepsis, and a composite measure of adverse outcomes).

The screening programme

No RCTs assessing the effectiveness of screening asymptomatic low-risk women for short cervix were identified.

Despite this, two cost-effectiveness analyses have been performed. Both of cost-effectiveness studies were done from a US perspective and based on the results of one of the RCTs that assessed vaginal progesterone for preventing preterm birth in women with a cervical length ≤ 15 mm. In both cost-effectiveness studies cervical length screening and treatment with progesterone was found to be the dominant strategy. It is unclear how applicable the results of these analyses would be to the UK.

It is also unclear whether an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be more cost-effective.

Estimating the effectiveness of a universal screening programme from the results of an RCT of treatment is problematic. There could be differences in population, logistical differences in screening methods, stretching of eligibility and management criteria (scope creep), and unintended consequences.

The RCTs which found a benefit of vaginal progesterone or pessary were all performed in populations of pregnant women at mixed risk: for example some women had a prior preterm birth, and in one study twin gestations were included. The number needed to screen and number needed to treat could be higher in exclusively low risk populations.

As the optimal cervical length cut-off and the gestational age at which screening should be performed remains to be determined, it is difficult to know whether the cervical length cut-offs used in the treatment RCTs were appropriate. However, in one RCT, less than one third of the scanned women who had spontaneous preterm delivery had a cervical length of ≤ 15 mm (cut-off applied in this study). In another, more than two thirds of the scanned women who had a spontaneous preterm delivery < 34 weeks' gestation had a cervical length ≤ 25 mm (cut-off applied in this study). It should be noted that these analyses included women who participated in the trials. The other treatment RCTs did not report this information.

Other authorities, notably the ACOG and SMFM, in the US and NICE in the UK have not recommended universal screening. This is due to concerns over quality assurance, availability,

the potential for women to receive unnecessary or unproven interventions as well as the absence of a RCT comparing screening with no screening and the problems of trying to estimate the results of universal screening from RCTs of treatment.

Implications for research

Future research should address:

- What a screening program would aim to prevent
- The optimal cut-off and gestational age for cervical length screening, and whether it fulfils the HTA criteria for the useful test
- The optimal treatment strategy
- Whether a screen-and-treat strategy reduces preterm birth
- Logistic consequences and population acceptability issues arising from screening.
- Large studies evaluating the use of cervicovaginal fetal fibronectin, amniotic fluid CRP measurement and uterine contractions (by home uterine monitoring device) test for screening in asymptomatic women

Appendix 1: Studies included in Domin et al. (2010)²⁷

Table 15: Studies included in the Domin et al. (2010) systematic review.²⁷

Author, Year	Number of women analysed	Patient population	Gestational age at ultrasound (week)	Cervical length cut-off (mm)	Gestational age at birth (week)	Incidence of spontaneous preterm delivery (%)	Modified STARD score
Airoldi, 2005	64	High risk History of uterine anomalies	14-24	<25	<35	10.9	4
Andrews, 2000	57	High risk Prior spontaneous preterm delivery at 16 to 30 weeks	16-24	≤22 ≤25	<35	26.0	4
Berghella, 1999	168	High risk Prior spontaneous preterm delivery 14-34 weeks, at least 2 dilation and curettage during first trimester, Mullerian anomalies, cone biopsy, Diethylstilbestrol exposure	14-18, 18-22	<25	<35	18.5	5
Berghella, 2004	109	High risk History of excisional cervical biopsy	16-24	<25	<35	12.8	3
Bittar, 2007	105	High risk Prior spontaneous preterm delivery <37 weeks	22-24	<20 ≤25	≤34 <37	11.4 23.81	3
Carvalho, 2003	529	Combination. Women with ultrasound at 11-14 and 22-24 weeks	22-24	≤20	<33	1.9	4
Carvalho, 2005	1958	Combination Women with ultrasound at 21-24 weeks	21-24	≤10 ≤15 ≤20 ≤25 ≤30	≤34	3.4	3
Dilek, 2006	250	Low risk	22	≤33.15	<37	7.2	4
Fukami, 2003	3030	Low risk	16-19	≤30	<32 <37	0.3 3.2	2
Grgic, 2006	327	Low risk	16-24	≤24	<34 <37	2.1 5.2	6
Guzman, 2001	469	High risk Prior spontaneous	15-24	≤25	<28 ≤32 <30	3.8 6.4 4.7	2

Author, Year	Number of women analysed	Patient population	Gestational age at ultrasound (week)	Cervical length cut-off (mm)	Gestational age at birth (week)	Incidence of spontaneous preterm delivery (%)	Modified STARD score
		preterm delivery 24-37 weeks, prior midtrimester loss, at least 2 terminations of pregnancy, uterine anomalies, previous Cerclage, cone biopsy, diethylstilbestrol exposure			<34	9.8	
Hassam, 2000	6877	Combination Routine anatomy scan	14-24	≤10 ≤15 ≤20 ≤25 ≤30	≤32 ≤36	3.6 10.0	1
Heath, 1998	1252	Combination Routine anatomy scan	22-24	≤10 ≤15 ≤20	≤32	1.5	1
Hebbar, 2006	168	Combination Routine anatomy scan	20-24	≤25	<37	7.7	4
Hibbard, 2000	760	Combination Routine anatomy scan	16-22 6/7	≤22 ≤27 ≤30	≤32 <35 <37	3.6 6.7 11.2	5
Iams, 1996	2915	Combination Women with ultrasound at 15-24 weeks	22-24 6/7	≤20 ≤25 ≤30	<35	4.3	7
Leung, 2005	2880	Combination Routine anatomy scan	18-22 6/7	≤20 ≤25 ≤30	<34	0.7	6
Matijevic, 2006	138	Low risk	16-24	≤24	<37	5.1	5
Owen, 2001	183	High risk Prior spontaneous preterm delivery <32 weeks	16-19	<15 <20 <25 <30	<35	26.2	5
Ozdemir, 2006	152	Combination Routine anatomy scan	20-24	≤27	<35	10.5	3
Pires, 2006	338	Low risk	21-24	<20	<35 <37	3.3 6.2	3
Taipale, 1998	3694	Combination Routine anatomy scan	18-22	<25 <29	<35 <37	0.8 2.4	6
Yazici, 2004	357	Low risk	24	<32.5	<36	6.2	4

Appendix 2: Results of studies included in criteria 10 in more detail

Progesterone

The update search identified:

- Two RCTs of vaginal progesterone vs. placebo
- Three systematic reviews which included these trials
- One RCT of intramuscular progesterone vs. placebo

RCTs of vaginal progesterone vs. placebo

Hassan et al. (2011) was a multicentre (44 centres in 10 countries) RCT that aimed to determine the efficacy and safety of micronized vaginal progesterone gel to reduce the risk of preterm birth (<33 weeks) and associated neonatal complications in women found to have a short cervix in the midtrimester.³⁶

The trial randomised 458 asymptomatic women with a singleton pregnancy identified by transvaginal ultrasound to have a short cervix (10-20mm) in midtrimester (19+0 to 23+6 weeks' gestation), to daily vaginal progesterone gel containing 90mg progesterone (n=235) or placebo (n=223)(from 20 to 23+6 weeks until 36+ 6 weeks, rupture of membranes or delivery).³⁶

Exclusion criteria included planned cerclage, acute cervical dilation, allergic reaction to progesterone, current or recent progesterone treatment, chronic medical conditions that would interfere with study participation or evaluation of treatment, major fetal anomaly or known chromosomal abnormality, uterine anatomic malformation, vaginal bleeding, and known or suspected clinical chorioamnionitis. Of the 458 women, 16% had a history of a previous preterm birth between 20 and 35 weeks' gestation.

The primary outcome of the study was preterm birth <33 weeks' gestation. The results for all outcomes are shown in Table 16.

Progesterone reduced risk of preterm birth <33 weeks' gestation (primary outcome, 8.9% vs. 16.1%, RR 0.55, 95% CI 0.33 to 0.92). It was calculated that 14 women with a cervical length between 10 and 20 mm would need to be treated with progesterone to prevent one case of preterm birth <33 weeks' gestation (95% CI 8 to 87). In women without a history of preterm birth (84% of the population), vaginal progesterone gel administration was associated with a significant reduction in the rate of preterm birth <33 weeks (7.6% vs. 15.3%, RR 0.50, 95% CI 0.27 to 0.90).³⁶

Progesterone also reduced risk of preterm birth <28 weeks' gestation and <35 weeks, although the reduction in births <37 weeks was not significant.³⁶

Progesterone reduced risk of respiratory distress syndrome (3.0% vs. 7.6%, RR 0.39, 95% CI 0.17 to 0.92) - it was calculated that 22 women would need to be treated to prevent one case of respiratory distress syndrome. Progesterone also reduced the risk of any neonatal morbidity or

mortality event and birth weight <1,500g. There was no statistical difference in other outcomes.³⁶

There were no differences in the incidence of treatment-related adverse events (12.8% vs. 10.8%, RR 1.19, 95% CI 0.72 to 1.96). The most frequently reported adverse events related to study treatment occurred in up to 2% of women and included vaginal pruritis, vaginal discharge, vaginal candidiasis and nausea. No fetal or neonatal safety signal detected.³⁶

It should be noted that this study did not address the management of women with a cervical length <10mm.

Table 16: Outcomes reported in Hassan et al. (2011)³⁶

Outcome	Progesterone (% , n) N=235	Placebo (% , n) N=223	RR (95% CI)	P value
Primary outcome				
Preterm birth <33 weeks	8.9 (21)	16.1 (36)	0.55 (0.33 to 0.92)	0.020
Secondary outcomes				
Preterm birth <28 weeks	5.1 (12)	10.3 (23)	0.50 (0.25 to 0.97)	0.036
Preterm birth <35 weeks	14.5 (34)	23.3 (52)	0.62 (0.42 to 0.92)	0.016
Preterm birth <37 weeks	30.2 (71)	34.1 (76)	0.89 (0.68 to 1.16)	0.376
Respiratory distress syndrome	3.0 (7)	7.6 (17)	0.39 (0.17 to 0.92)	0.026
Bronchopulmonary dysplasia	1.7 (4)	2.2 (5)	0.76 (0.21 to 2.79)	0.678
Proven sepsis	3.0 (7)	2.7 (6)	1.11 (0.38 to 3.24)	0.853
Necrotizing enterocolitis	2.1 (5)	1.8 (4)	1.19 (0.32 to 4.36)	0.797
Grade III or IV intraventricular haemorrhage	0	0.5 (1)	0.32 (0.01 to 7.73)	0.305
Periventricular leukomalacia	0	0	Not estimable	NA
Perinatal death	3.4 (8)	4.9 (11)	0.69 (0.28 to 1.68)	0.413
Fetal death	2.1 (5)	2.7 (6)	0.79 (0.25 to 2.57)	0.700
Neonatal death	1.3 (3)	2.2 (5)	0.57 (0.14 to 2.35)	0.431
Any morbidity/mortality (composite score)	7.7 (18)	13.5 (30)	0.57 (0.33 to 0.99)	0.043
Birth weight <2,500g	25.6 (60)	30.9 (68)	0.83 (0.62 to 1.11)	0.213
Birth weight <1,500g	6.4 (15)	13.6 (30)	0.47 (0.26 to 0.85)	0.010

Abbreviations: RR, Relative risk; CI, confidence interval.

Fonseca et al. (2007) was a RCT conducted by the Fetal Medicine Foundation in the UK, Brazil, Greece and Chile that aimed to evaluate the effect of vaginal progesterone on the incidence of spontaneous early preterm delivery (<34 weeks' gestation) in asymptomatic women found at routine midtrimester screening to have a short cervix.³⁷

Two hundred and fifty asymptomatic women with singleton (n=226) or twin (n=24) pregnancies who were found to have a cervical length 15mm or less on transvaginal ultrasonography at between 20 and 25 weeks' gestation were randomised to placebo (n=125) or 200mg of vaginal micronized progesterone (n=125)(every night from 24 to 34 weeks' gestation).³⁷ Exclusion criteria were major fetal abnormalities, painful regular uterine contraction, history of ruptured

membranes, or cervical cerclage. Of the 250 women, 15.2% had a history of preterm birth <34 weeks.

The primary outcome of the trial was spontaneous delivery <34 completed weeks' gestation. The results for all outcomes are shown in Table 17.

Spontaneous early preterm birth (<34 weeks, primary outcome) occurred in 19.2% of the progesterone group and 34.4% of the placebo group (adjusted relative risk 0.56, 95% CI 0.32 to 0.91).

Progesterone significantly reduced the risk of preterm delivery <34 weeks when only women without a history of delivery <34 weeks were considered (20 of 112 [17.9%] with progesterone vs. 34 of 109 [31.2%] with placebo; relative risk 0.57, 95% CI 0.35 to 0.93); or when only women with singleton gestations were considered (20 of 114 [17.5%] with progesterone v. 36 of 112 [32.1%] with placebo; RR 0.54, 95% CI 0.34 to 0.88).

There was no significant difference in any secondary outcomes.

None of the women reported any increase in the frequency or severity of general or local side effects, such as sleepiness, fatigue, headaches, or genital irritation, or any new symptoms after the onset of treatment.³⁷

Table 17: Outcomes reported in Fonseca et al. (2007)³⁷

Outcome	Progesterone (% n) N=125	Placebo (% n) N=125	Adjusted RR (95% CI)*	P value
Primary outcome				
Spontaneous delivery at <34 weeks	19.2 (24)	34.4 (43)	0.56 (0.32 to 0.91)	0.02
Secondary outcomes				
Any delivery at <34 weeks	20.8 (26)	36.0 (45)	0.60 (0.35 to 0.94)	0.02
Fetal death	0.7 (1)	0.7 (1)		
Neonatal death	1.5 (2)	5.1 (7)	0.34 (0.06 to 1.81)	0.22
Birth weight <2,500g	41.2 (56)	42.8 (59)	0.97 (0.68 to 1.29)	0.85
Birth weight <1,500g	13.2 (18)	19.6 (27)	0.74 (0.36 to 1.37)	0.35
Major adverse outcomes (composite measure)	8.1 (11)	13.8 (19)	0.57 (0.23 to 1.31)	0.19
Intraventricular haemorrhage	0.7 (1)	1.4 (2)	0.33 (0.01 to 8.84)	0.52
Respiratory distress syndrome	8.1 (11)	13.8 (19)	0.57 (0.23 to 1.31)	0.19
Retinopathy of prematurity	1.5 (2)	0		
Necrotizing enterocolitis	0	0.7 (1)		
Need for neonatal special care (composite measure)	25.0 (34)	32.6 (45)	0.75 (0.44 to 1.16)	0.20
Neonatal intensive care	24.3 (33)	30.4 (42)	0.80 (0.47 to 1.24)	0.34
Ventilation	11.8 (16)	18.1 (25)	0.64 (0.30 to 1.25)	0.20
Phototherapy	11.8 (16)	10.1 (14)	1.09 (0.50 to 2.19)	0.82
Treatment for sepsis	2.2 (3)	8.0 (11)	0.29 (0.07 to 1.10)	0.07
Blood transfusion	2.9 (4)	3.6 (5)	0.79 (0.19 to 3.10)	0.74

Abbreviations: RR, Relative risk; CI, confidence interval.

*For perinatal outcomes, the relative risks, 95% CI and P values were estimated by logistic regression clustered on maternal identifiers to account for nonindependence between twin pairs. Relative risks were adjusted for maternal age, body-mass index, smoking status, race, history of preterm birth, and cervical length at the time of randomisation.

Systematic reviews of vaginal progesterone vs. placebo

Likis et al. (2012) performed a systematic review and Bayesian meta-analysis of these two RCTs.⁴¹ The Bayesian meta-estimate for preterm birth (using the 33- and 34-week of gestation cut points) combining these two trials was a RR of 0.52 (95% Bayesian credible interval 0.36 to 0.70). The Bayesian meta-estimate for neonatal death combining the two trials was a RR of 0.40 (95% Bayesian credible interval 0.09 to 0.91). There was no evidence for the effectiveness of progesterone on the rate of intrauterine fetal death, neonatal death, or low birth weight <2,500g.

Romero et al. (2012) performed a systematic review and individual patient data meta-analysis.⁴² The meta-analysis included the two trials described above, which between them contributed data on 708 mothers and their 732 infants, and a further three RCTs which had data on 67 women with a cervical length of ≤ 25 mm and 95 infants. In these three trials, women with a short cervix were not the primary population. One trial recruited women with a preterm birth (at between 20 and 35 weeks) immediately preceding the current pregnancy, one trial recruited women with at least one previous spontaneous preterm birth, uterine malformation or twin pregnancy, and one trial recruited women with a diamniotic twin pregnancy. The primary outcome of the meta-analysis was preterm birth at <33 weeks' gestation.

Outcomes reported in Romero et al. (2012) are displayed in Table 18. Treatment with vaginal progesterone in patients with a sonographic short cervix was associated with a significant reduction in the risk of preterm birth <33 weeks (12.4% vs. 22.0%, RR 0.58, 95% CI 0.42 to 0.80). The number needed to treat with progesterone to prevent one preterm birth <33 weeks was 11.

Treatment with vaginal progesterone also significantly reduced the risk of preterm birth <28 weeks, <30 weeks, <34 weeks, <35 weeks, and marginally significantly reduced the risk of preterm birth <36 weeks, and significantly reduced the risk of spontaneous preterm birth <33 and <34 weeks. However, there was no statistically significant reduction in birth <37 weeks.⁴²

Infants whose mothers received vaginal progesterone had a significantly lower risk of respiratory distress syndrome, composite neonatal morbidity/mortality (respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, proven neonatal sepsis or neonatal death), birthweight <1,500g, admission to neonatal intensive care and mechanical ventilation.

There was no evidence of an effect of vaginal progesterone on necrotizing enterocolitis, intraventricular haemorrhage, proven neonatal sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia, Apgar score <7 at 5 minutes, birthweight <2,500g, or threatened preterm labour.⁴²

The rates of maternal adverse effects, discontinuation of treatment because of adverse effects and congenital anomalies did not differ between groups.⁴²

Among singleton gestations, the administration of vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth at <33, <35, and <28 weeks' gestation, respiratory distress syndrome, composite neonatal morbidity and mortality, Apgar score <7 at 5 minutes, birthweight <1,500g and admission to neonatal intensive care unit.

Most relevant to this review, vaginal progesterone was associated with a significant reduction in the risk of preterm birth <33 weeks' gestation in women with a singleton gestation with no previous preterm birth (RR 0.60; 95% CI 0.39 to 0.92).⁴²

Table 18: Outcomes reported in Romero et al. (2012)⁴². Numbers in italics were calculated.

Outcome	Pooled RR (95% CI)	NNT (95% CI)	Pooled RR (95% CI) in singleton pregnancies only†	NNT (to nearest whole person)
Primary outcome				
Preterm birth <33 weeks	0.58 (0.42 to 0.80)	11	0.56 (0.40 to 0.80)	<i>11</i>
Secondary outcomes				
Preterm birth <37 weeks	0.89 (0.75 to 1.06)		0.91 (0.75 to 1.10)	
Preterm birth <36 weeks	0.82 (0.67 to 1.00)			
Preterm birth <35 weeks	0.69 (0.55 to 0.88)	11 (7 to 27)	0.67 (0.51 to 0.87)	<i>10</i>
Preterm birth <34 weeks	0.61 (0.47 to 0.81)	9 (7 to 19)		
Preterm birth <30 weeks	0.58 (0.38 to 0.89)	18 (12 to 69)		
Preterm birth <28 weeks	0.50 (0.30 to 0.81)	18 (13 to 47)	0.51 (0.31 to 0.85)	<i>18</i>
Spontaneous preterm birth <33 weeks	0.57 (0.40 to 0.81)	13 (9 to 29)		
Spontaneous preterm birth <34 weeks	0.62 (0.46 to 0.84)	12 (8 to 28)		
Respiratory distress syndrome	0.48 (0.30 to 0.79)	15 (11 to 33)	0.47 (0.27 to 0.81)	<i>18</i>
Necrotizing enterocolitis	0.88 (0.30 to 2.64)		0.88 (0.29 to 2.62)	
Intraventricular haemorrhage	0.74 (0.27 to 2.05)		0.68 (0.22 to 2.13)	
Proven neonatal sepsis	0.64 (0.32 to 1.29)		0.80 (0.37 to 1.74)	
Retinopathy of prematurity	1.56 (0.46 to 5.28)		1.51 (0.40 to 5.69)	
Bronchopulmonary dysplasia	0.76 (0.21 to 2.79)			
Periventricular leukomalacia	Not estimable			
Fetal death	0.82 (0.28 to 2.42)		0.82 (0.28 to 2.40)	
Neonatal death	0.55 (0.26 to 1.19)		0.53 (0.20 to 1.39)	
Perinatal death	0.63 (0.34 to 1.18)		0.64 (0.31 to 1.31)	
Composite neonatal morbidity/mortality*	0.57 (0.40 to 0.81)	13 (10 to 30)	0.59 (0.38 to 0.91)	<i>17</i>
Apgar score <7 at 5 min	0.57 (0.32 to 1.02)		0.48 (0.24 to 0.95)	<i>29</i>
Birthweight <1,500g	0.55 (0.38 to 0.80)	13 (10 to 30)	0.52 (0.34 to 0.81)	<i>14</i>
Birthweight <2,500g	0.91 (0.76 to 1.08)		0.86 (0.69 to 1.07)	
Admission to NICU	0.75 (0.59 to 0.94)	14 (8-57)	0.67 (0.50 to 0.91)	<i>12</i>
Mechanical ventilation	0.66 (0.44 to 0.98)	24 (15-408)	0.65 (0.41 to 1.01)	
Congenital anomaly	0.89 (0.55 to 1.44)			
Any maternal adverse event	1.04 (0.79 to 1.38)			
Vaginal discharge	1.00 (0.87 to 1.15)			
Vaginal pruritus	1.08 (0.74 to 1.57)			
Discontinuation of treatment because of adverse events	1.01 (0.61 to 1.69)			
Threatened preterm labour	0.83 (0.68 to 1.02)			
Low ASQ developmental and socioemotional score at 18	1.02 (0.54 to 1.93)			

months of age				
---------------	--	--	--	--

Abbreviations: RR, Relative risk; CI, confidence interval; NNT number needed to treat; NICU, neonatal intensive care unit

*Occurrence of any of the following events: respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, proven neonatal sepsis or neonatal death

†Based on the results of four studies

Dodd et al. (2008) was a Cochrane systematic review of prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth.⁴⁰ It only identified the Fonseca et al. (2007) study comparing progesterone vs. placebo for women with a short cervix identified on ultrasound.³⁷ As this study has already been fully reported here, the results from this systematic review have not been further extracted.

RCT of intramuscular progesterone vs. placebo

Grobman et al. (2012) was a US RCT that compared 250mg 17-alpha-hydroxyprogesterone (17-OHP) with placebo (castor oil) weekly intramuscular injections for the prevention of preterm birth in nulliparous women with a cervical length <30mm.³⁸ Six hundred and fifty seven nulliparous women with a viable singleton gestation and a cervical length <30mm between 16 weeks 0 days and 22 weeks 3 days of gestation were randomised to weekly intramuscular injections of 250mg 17-OHP or placebo (castor oil) until 36 weeks 6 days of gestation or delivery, whichever occurred first. Exclusion criteria included selective fetal reduction to a singleton gestation, sonographic evidence of an additional fetal pole/embryo at ≥ 12 weeks' gestation, progesterone treatment within 14 weeks 6 days, vaginal bleeding within 15 weeks 6 days, amniotic membranes prolapsing beyond the external os, premature rupture of membranes, known major fetal anomaly or aneuploidy, current or planned cervical cerclage, müllerian abnormality, contraindication to intramuscular injections, maternal medical conditions that increase the probability of preterm delivery, prior cervical surgery, or planned indicated preterm delivery. The primary outcome of the study was preterm birth <37 weeks.

Enrolment in the trial was halted early (prior to planned sample size of 1,000 women) due to extremely low probability of finding a benefit.³⁸

Results of the trial are shown in Table 19. Preterm birth <37 weeks did not differ significantly between groups (25.1% of women in the 17-OHP group and 24.2% of women in the placebo group, RR 1.03; 95% CI 0.79 to 1.35).

Rates of preterm birth <35, <32, <28 weeks was also similar, and there was no significant difference in other selected maternal outcomes. Most women in both groups reported side effects from the injections, the majority of which were related to irritation at the injection site. There was no significant difference in most perinatal outcomes, including the composite adverse perinatal outcome, although early onset sepsis was significantly reduced with 17-OHP (0.9% vs. 3.4%, RR 0.27, 95% CI 0.08 to 0.97). However, the lack of difference in other outcomes led the study authors to suggest that this is a chance finding.³⁸

Table 19: Outcomes reported in Grobman et al. (2012)³⁸

Outcome	Progesterone (%), n N=327	Placebo (%), n N=330	RR (95% CI)
Primary outcome			
Delivery <37 weeks	25.1 (82)	24.2 (80)	1.03 (0.79 to 1.35)
Spontaneous	16.5 (54)	16.7 (55)	0.99 (0.70 to 1.40)
Medically induced	8.3 (27)	7.6 (25)	1.09 (0.65 to 1.84)
Fetal loss/abortion <20 weeks	0.3 (1)	0	
Secondary outcomes			
<i>Maternal outcomes</i>			
Delivery <35 weeks	13.5 (44)	16.1 (53)	0.84 (0.58 to 1.21)
Delivery <32 weeks	8.6 (28)	9.7 (32)	0.88 (0.54 to 1.43)
Delivery <28 weeks	4.6 (15)	6.7 (22)	0.69 (0.36 to 1.30)
Gestational age at delivery, weeks (mean ± standard deviation)	37.6 ± 3.9	37.4 ± 4.3	P=0.93
Preterm premature rupture of membranes	7.6 (25)	7.3 (24)	1.05 (0.61 to 1.80)
Hospital visit for preterm labour	44.3 (145)	45.8 (151)	0.97 (0.82 to 1.15)
Tocolytic therapy	10.9 (35)	12.9 (42)	0.84 (0.55 to 1.29)
Corticosteroid therapy	17.1 (55)	15.7 (51)	1.09 (0.77 to 1.55)
Cerclage placement	1.9 (6)	1.2 (4)	1.52 (0.43 to 5.33)
Gestational hypertension or preeclampsia	14.1 (46)	12.2 (40)	1.16 (0.78 to 1.72)
Gestational diabetes mellitus	4.6 (15)	3.9 (13)	1.16 (0.56 to 2.41)
Cholestasis	0.3 (1)	0	
Placental abruption	3.4 (11)	4.6 (15)	0.74 (0.34 to 1.58)
Chorioamnionitis	8.9 (29)	6.1 (20)	1.45 (0.84 to 2.52)
Caesarean	20.5 (67)	19.1 (63)	1.07 (0.79 to 1.46)
Side effects	68.4 (223)	67.1 (220)	1.02 (0.92 to 1.13)
Injection site	66.6 (217)	63.7 (209)	1.04 (0.93 to 1.17)
Urticaria	3.1 (10)	0.6 (2)	5.03 (1.11 to 22.78)
Nausea	2.1 (7)	3.0 (10)	0.70 (0.27 to 1.83)
<i>Fetal outcomes</i>			
Composite adverse outcome	7.0 (23)	9.1 (30)	0.77 (0.46 to 1.30)
Fetal death	1.2 (4)	0.3 (1)	4.04 (0.45 to 35.92)
Neonatal death	1.8 (6)	2.4 (8)	0.76 (0.27 to 2.16)
Respiratory distress syndrome	4.1 (13)	5.0 (16)	0.82 (0.40 to 1.68)
Bronchopulmonary dysplasia	0.9 (3)	1.6 (5)	0.60 (0.15 to 2.51)
Necrotizing enterocolitis, grade II or III	0.6 (2)	1.6 (5)	0.40 (0.08 to 2.06)
Intraventricular haemorrhage, grade III or IV	0.6 (2)	0.3 (1)	2.01 (0.18 to 22.08)
Periventricular leukomalacia	1.3 (4)	0.3 (1)	4.03 (0.45 to 35.81)
Early onset sepsis	0.9 (3)	3.4 (11)	0.27 (0.08 to 0.97)
Retinopathy of prematurity grade III or IV	0.3 (1)	0.9 (3)	0.34 (0.04 to 3.21)
Birthweight, g (mean ± standard deviation)	2,855 ± 747	2,824 ± 807	P=0.82
Birthweight <2,500g	22.3 (72)	22.9 (75)	0.97 (0.73 to 1.30)
Birthweight <1,500g	7.1 (23)	8.8 (29)	0.81 (0.48 to 1.36)
Small for gestational age, <10 th percentile	16.7 (54)	14.3 (47)	1.17 (0.81 to 1.67)
Small for gestational age, <3 rd percentile	4.6 (15)	4.3 (14)	1.09 (0.53 to 2.22)
5 minute Apgar <7	4.6 (15)	5.8 (19)	0.80 (0.41 to 1.55)
Major congenital anomaly	1.8 (6)	0.6 (2)	3.02 (0.61 to 14.85)
Patent ductus arteriosus	0.6 (2)	2.5 (8)	0.25 (0.05 to 1.18)
Seizures	0.3 (1)	0.6 (2)	0.50 (0.05 to 5.52)
NICU admission	19.6 (63)	21.0 (69)	0.93 (0.69 to 1.27)
Length of NICU stay, days [median (interquartile range)]	17 (6.0-43.0)	15.5 (6.0-57.5)	P=0.61

Abbreviations: RR, Relative risk; CI, confidence interval; NICU, neonatal intensive care

Cervical pessary

The update search identified:

- One RCT of cervical pessary vs. expectant management

RCT of cervical pessary vs. expectant management

Goya et al. (2012) was a Spanish RCT of cervical pessaries for women with a short cervix.³⁹ Women identified during routine 2nd trimester ultrasonography at 18-22 weeks' gestation as having a cervical length of 25mm or less using transvaginal ultrasonography were recruited into the study. Exclusion criteria were major fetal abnormalities, painful regular uterine contractions, active vaginal bleeding, ruptured membranes, placenta praevia, and a history of cone biopsy or cervical cerclage in situ. Women were randomised to receive a cervical pessary (removed during the 37th week of gestation unless active vaginal bleeding, risk of preterm labour with persistent contractions despite tocolysis, or severe patient discomfort) or expectant management. One hundred and ninety women were included in the intention to treat analysis in each group. Eleven percent (n=21 in the cervical pessary group and n=20 in the expectant management group) had a history of at least one previous preterm birth.

The primary outcome was spontaneous delivery <34 weeks' gestation.

Results are shown in Table 20. Spontaneous birth <34 weeks' gestation was lower in cervical pessary group (6% vs. 27% in the expectant management group, OR 0.18, 95% CI 0.08 to 0.37), as was spontaneous birth <37 weeks' gestation (22% vs. 59%, OR 0.19, 95% CI 0.12 to 0.30).³⁹

In addition, need for tocolysis and corticosteroid treatment for fetal maturation were greater in the expectant management group (tocolysis: 34% vs. 53%, OR 0.23, 95% CI 0.16 to 0.35; corticosteroids: 42% vs. 64%, OR 0.41, 95% CI 0.26 to 0.64).³⁹

The cervical pessary group also had significant reductions in the rate of premature preterm rupture of membranes, and in birthweight <1,500g and birthweight <2,500g, respiratory distress syndrome, treatment for sepsis, and composite adverse outcomes. No differences were noted in neonatal mortality rates.³⁹

No major adverse events were reported in the cervical pessary group. However, all women in the cervical pessary group had vaginal discharge after placement of the cervical pessary and some of these women required cervical pessary repositioning without removal (n=27, 14%) and one patient needed removal and replacement of the cervical pessary.³⁹

Women were also asked to score pain during pessary insertion and removal on a scale of 0, no complaints to 10, severe complaints. Pain during insertion scored an average of 4 and during removal scored an average of 7. Overall 181 (95%) of 190 patients recommended this intervention to other people.³⁹

Table 20: Outcomes reported in Goya et al. (2012)³⁹

Outcome	Cervical pessary (%, n) N=190	Expectant management (%, n) N=190	OR (95% CI)	P value
Primary outcome				
Spontaneous delivery <34 weeks	6 (12)	27 (51)	0.18 (0.08 to 0.37)	<0.0001
Secondary outcomes				
<i>Pregnancy outcomes</i>				
Spontaneous delivery <28 weeks	2 (4)	8 (16)	0.23 (0.06 to 0.74)	0.0058
Any delivery <34 weeks	7 (14)	28 (53)	0.21 (0.10 to 0.40)	<0.0001
Spontaneous delivery <37 weeks	22 (41)	59 (113)	0.19 (0.12 to 0.30)	<0.0001
Gestational age at delivery, weeks (mean \pm standard deviation)	37.7 \pm 2.0	34.9 \pm 4.0		<0.0001
Tocolytic treatment	34 (64)	53 (101)	0.23 (0.16 to 0.35)	<0.0001
Corticosteroid treatment for fetal maturation	42 (80)	64 (121)	0.41 (0.26 to 0.64)	<0.0001
Chorioamnionitis	3 (5)	3 (6)	0.82 (0.20 to 3.32)	0.7596
Pregnancy bleeding	4 (7)	5 (9)	0.77 (0.24 to 2.38)	0.6094
Premature preterm rupture of membranes	2 (3)	9 (17)	0.16 (0.03 to 0.58)	0.0013
Caesarean delivery	22 (41)	21 (40)		0.418
<i>Side effects</i>				
Vaginal discharge	100 (190)	46 (87)		0.002
Pessary repositioning without removal	14 (27)			
Pessary withdrawal	<1 (1)			
<i>Perinatal outcome</i>				
Fetal death	0	0		
Neonatal death	0	<1 (1)		
Birthweight <1,500g	5 (9)	14 (26)	0.31 (0.13 to 0.72)	0.0040
Birthweight <2,500g	9 (17)	29 (56)	0.23 (0.12 to 0.43)	<0.0001
<i>Adverse outcomes</i>				
Necrotising enterocolitis	0	1 (2)		0.4987
Intraventricular haemorrhage	0	1 (2)		0.4987
Respiratory distress syndrome	3 (5)	12 (23)	0.20 (0.06 to 0.55)	0.0003
Retinopathy	0	1 (2)		0.4987
Treatment for sepsis	2 (3)	6 (12)	0.24 (0.04 to 0.90)	0.0317
Composite adverse outcomes	3 (5)	16 (30)	0.14 (0.04 to 0.39)	<0.0001

Abbreviations: OR, Odds ratio; CI, confidence interval

Cerclage

The update search identified:

- Three systematic reviews of cerclage

Systematic reviews of cerclage vs. no cerclage

Alfirevic et al. (2012) performed a Cochrane systematic review (search until 31 October 2011) of cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy.⁴³ It included all RCTs that compared cervical stitch with no treatment or any other treatment in women considered to be at high risk due to history (e.g. previous preterm birth), cervical surgery (loop excision, cone biopsy, surgical termination of pregnancy), finding of a short cervix on ultrasound screening, or physical exam-detected cervical changes.⁴³ The primary outcomes of the review were perinatal loss and/or serious neonatal morbidity. Preterm birth was a secondary outcome.

Overall, when cerclage was compared to no treatment there was no statistical difference in perinatal deaths and neonatal morbidity, although there was a significant reduction in preterm births <37 weeks' completed gestation (average RR 0.80; 95% CI 0.69 to 0.95, nine trials, 2898 women). Women who received a cerclage had a higher rate of caesarean section (RR 1.19, 95% CI 1.01 to 1.40, eight trials, 2817 women).⁴³

A subgroup analysis of cervical stitch based on one-off ultrasound scan of the cervix in women at low/unspecified risk for preterm birth (as opposed to women with a history of preterm birth or surgery to the cervix) vs. no cerclage was performed. All results for this subgroup are presented in Table 21, as they are the most applicable for this review. No significant differences for any outcome were found.⁴³

Table 21: Results of the meta-analysis of studies assessing cervical stitch based on one-off ultrasound scan of the cervix in low/unspecified risk for preterm birth vs. no cerclage. From Alfirevic et al. (2012)⁴³

One-off ultrasound-indicated cerclage in women with a low/unspecified risk of preterm labour vs. no Cerclage	RR (95% CI)
All perinatal losses	1.01 (0.46 to 2.22); 3 studies
Serious neonatal morbidity	1.40 (0.61 to 3.23); 3 studies
Perinatal deaths and serious neonatal morbidity	1.08 (0.61 to 1.89); 3 studies
Stillbirths	0.95 (0.20 to 4.59); 2 studies
Neonatal deaths before discharge	0.63 (0.18 to 2.18); 2 studies
Miscarriages	1.72 (0.16 to 18.22); 3 studies
Preterm birth <37 completed weeks	0.80 (0.55 to 1.16); 3 studies
Preterm birth <34 completed weeks	0.82 (0.55 to 1.22); 3 studies
Preterm birth <28 completed weeks	1.01 (0.55 to 1.83); 3 studies
Serious intracranial pathology	0.95 (0.06 to 14.98); 2 studies
Serious respiratory morbidity	1.63 (0.39 to 6.86); 2 studies
Necrotising enterocolitis	0.0 (0.0 to 0.0); 1 study
Retinopathy of prematurity	0.32 (0.01 to 7.69); 1 study
Caesarean section (elective and emergency)	1.31 (0.84 to 2.04); 3 studies
Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	5.95 (1.36 to 26.06); 1 study
Pyrexia	6.66 (0.35 to 127.20); 1 study
PPROM	1.32 (0.78 to 2.23); 3 studies
Chorioamnionitis	1.29 (0.39 to 4.23) 1 study

Abbreviations: PPRM, preterm prelabour rupture of membranes

Berghella et al. (2010) performed a meta-analysis of patient-level data (search until June 2008) to investigate whether the effectiveness of cerclage for a short cervix varies by degrees of cervical length shortening.⁴⁴ The primary outcome was preterm birth <35 weeks. For women with a singleton gestation who had a cervix <25mm long (identified by 2nd trimester transvaginal ultrasound) and who had not previously had a preterm birth, no cervical length was found at which cerclage significantly reduced the risk of birth <35 weeks, or that predicted preterm birth at other gestational ages (<24 weeks, <28 weeks, <32 weeks, <37 weeks). This may be due to the small number of women included in their analysis (n=344). The overall results for women with a singleton gestation who had a cervix <25mm long are shown in Table 22.

Table 22: Outcomes for women with a singleton gestation who had a cervix <25mm long reported in Berghella et al. (2010)⁴⁴

Outcome	Cerclage (% , n) N=171	No cerclage (% , n) N=173	RR (95% CI)
Preterm birth <35 weeks	25.7 (44)	30.6 (53)	0.84 (0.60 to 1.18)

Preterm birth <37 weeks	39.2 (67)	42.8 (74)	0.92 (0.71 to 1.18)
Preterm birth <32 weeks	20.5 (35)	17.3 (30)	1.18 (0.76 to 1.83)
Preterm birth <28 weeks	13.5 (23)	12.7 (22)	1.06 (0.62 to 1.82)
Preterm birth <24 weeks	2.3 (4)	1.7 (3)	1.35 (0.34 to 5.35)

Abbreviations: RR, relative risk; CI, confidence interval

Jorgensen et al. (2007) performed a previous systematic review and individual patient data meta-analysis (search up to December 2005) of trials comparing cervical cerclage during pregnancy with expectant management or no cerclage in women with confirmed or suspected cervical insufficiency.⁴⁵ The primary outcome was pregnancy loss or neonatal death before discharge (which includes miscarriages, stillbirths and neonatal deaths before discharge).

It found no significant difference in pregnancy loss or death before discharge from hospital, or in neonatal morbidity, or preterm birth in women with singleton pregnancies. The risk of pyrexia was increased in women who received cerclage (OR 2.35, 95%CI 1.37 to 4.05) but there was no difference in other maternal morbidities (spontaneous labour, chorioamnionitis, preterm prelabour rupture of membranes, induced labour/need for caesarean-section). Obstetric history and cervical length did not have a significant effect and there was no evidence that the effect of cerclage in trials where the main indication for cerclage was short cervical length on ultrasound was different from the effect in trials where indication was based on obstetric history alone.⁴⁵

Table 23: Outcomes reported in Jorgensen et al. (2007)⁴⁵

Outcome	OR (95% CI)
Pregnancy loss or death before discharge	0.81 (0.60 to 1.10); 7 studies
Absence of neonatal morbidity (baby healthy when discharged from hospital)	1.06 (0.70 to 1.61); 4 studies
Spontaneous labour	0.81 (0.65 to 1.02); 4 studies
Pyrexia	2.35 (1.37 to 4.05); 3 studies
Chorioamnionitis	0.73 (0.36 to 1.46); 2 studies
Preterm premature rupture of membranes	0.92 (0.62 to 1.35); 5 studies
Induced labour/need for caesarean section	1.15 (0.90 to 1.48); 2 studies

Abbreviations: OR, Odds ratio; CI, confidence interval

Comparison of treatments: Cerclage vs. intramuscular progesterone

Keeler et al. (2009) performed a RCT in the US comparing weekly intramuscular injections of 250mg 17-OHP with McDonald cerclage for the prevention of preterm birth in women with risk factors for spontaneous preterm birth and/or a short cervix.⁴⁶ Women with risk factors for spontaneous preterm birth (history of spontaneous preterm birth, second trimester pregnancy loss, cervical surgery, document uterine anomaly) and women who were identified as having a short cervix during routine anatomical survey with transabdominal ultrasound were screened with transvaginal ultrasound. Women with a cervical length ≤ 25 mm at between 16 and 24 weeks (n=79) were randomised to McDonald cerclage or 250mg intramuscular 17-OHP weekly until 36 weeks' gestation. Exclusion criteria included any known fetal chromosomal or structural anomaly, multiple gestation, known allergy to progesterone, ruptured membranes, vaginal bleeding, evidence of active intra-amniotic infection, prolapse of endocervical membranes beyond the external cervical os, persistent uterine activity accompanied by cervical change, or an obstetrically indicated delivery. The primary outcome was spontaneous preterm birth <35 weeks' gestation.

Results of the study are shown in Table 24. There was no difference in the rate of spontaneous preterm birth <35 weeks (38.1% vs. 43.2%, RR 1.14, 95% CI 0.67 to 1.93). There was also no difference in rate of preterm birth <24, <28, <32 or <37 weeks, or in neonatal outcomes. A post hoc analysis of women with a cervical length ≤ 15 mm showed a reduction in spontaneous preterm birth <35 weeks in the cerclage group (RR 0.48, 95% CI 0.24 to 0.97) and also <37 weeks (RR 0.52 95% CI 0.32 to 0.86). However, *“the trial was stopped early by the authors because after 3 years of recruitment, an interim analysis showed no difference in outcome between treatment groups. With new data being presented regarding the benefits of progesterone supplementation, we felt it was impractical, unethical, and unreasonable to withhold progesterone from one study group to achieve our enrolment goal.”*

Table 24: Results from Keeler et al. (2009)⁴⁶

Outcome	Cerclage (% , n) N=42	17-OHP (% , n) N=37	RR (95% CI)
Primary outcome			
Spontaneous birth <35 weeks	38.1 (16)	43.2 (16)	1.14 (0.67 to 1.93)
Secondary outcomes			
Gestational age at delivery, weeks (mean \pm standard deviation)	32.9 \pm 6.4	33.0 \pm 5.9	P=0.96
Birth <37 weeks	52.4 (22)	59.4 (22)	1.14 (0.77 to 1.68)
Birth <32 weeks	35.7 (15)	35.1 (13)	0.98 (0.54 to 1.79)
Birth <28 weeks	23.8 (10)	18.9 (7)	0.79 (0.34 to 1.88)
Birth <24 weeks	11.9 (5)	8.1 (3)	0.68 (0.17 to 2.66)
Chorioamnionitis	28.6 (12)	21.6 (8)	0.76 (0.35 to 1.65)
Abruptio placentae	7.5 (3)	17.1 (6)	2.27 (0.61 to 8.44)
Preterm premature rupture of membranes	32.5 (13)	37.1 (13)	1.14 (0.61 to 2.12)
Rescue procedure	9.5 (4)	13.5 (5)	1.42 (0.41 to 4.89)
Neonatal morbidity (%)			P=0.34
None	66.7 (28)	56.8 (21)	
Mild	2.3 (1)	13.5 (5)	
Severe	21.4 (9)	18.9 (7)	
Death	11.9 (5)	10.8 (4)	
Cervical length ≤ 15 mm*			
Birth <37 weeks	45.5 (10)	86.7 (13)	0.52 (0.32 to 0.86)
Birth <35 weeks	31.8 (7)	66.7 (10)	0.48 (0.24 to 0.97)
Birth <32 weeks	31.8 (7)	53.3 (8)	0.60 (0.27 to 1.29)
Birth <28 weeks	22.7 (5)	33.3 (5)	0.68 (0.24 to 1.95)
Birth <24 weeks	13.6 (3)	20.0 (3)	0.68 (0.17 to 2.75)

Abbreviations: RR, relative risk; CI, confidence interval

* Cerclage (n=22), 17-OHP (n=15)

Appendix 3: Other tests to predict preterm labour and treatments to prevent preterm labour

In this appendix information on other screening tests, treatment of women with identified risk factors and studies of screening for these risk factors will be summarised.

5. There should be a simple, safe, precise and validated screening test

Studies of other screening tests

Studies evaluating the following screening tests for preterm labour were identified:

- Cervical volume
- Abnormal flora and bacterial vaginosis
- Serum relaxin

Honest et al. (2009) assessed bacterial vaginosis (assessed using clinical evaluation [Amsel criteria] or Gram staining [Nugent criteria]) and serum relaxin as tests for preterm labour in asymptomatic women.² These tests were not identified as having potential.

The results of the studies identified in the update search are summarised in Table 26.

Cervical volume

Barber et al. (2012) evaluated cervical volume as a screening test in low risk women.³⁴ The LR+ and LR- calculated from the results of this study did not meet the HTA's criteria for a useful test.

Abnormal vaginal flora and bacterial vaginosis

The update search identified two studies in asymptomatic women at low risk/mixed risk of preterm birth investigating abnormal vaginal flora and bacterial vaginosis to predict preterm birth.

Donders et al. (2009) assessed the predictive value of vaginal flora assessed by wet mount microscopy and culture in women at mixed risk.⁵⁰ *Mycoplasma hominis* had a LR+>5 for predicting preterm birth <37 and <35 weeks.

Matijevic et al. (2010) assessed vaginal pH as a screening test in women at low risk.³¹ It found that pH≥5.0 (the 95th percentile) at 18 to 24 weeks' gestation fulfilled the HTA's criteria as a useful test for preterm birth <34 weeks (LR+>5, LR-<0.2).

Matijevic et al. (2010) also assessed cervical length using transvaginal ultrasonography.³¹ Although no results for a test of statistical difference are reported, the researchers concluded that elevated vaginal pH is a better predictor of preterm labour and early preterm labour than cervical length.³¹ The accuracy of cervical length and vaginal pH as screening tests are shown in Table 25 for comparison.

Table 25: Accuracy of cervical length and vaginal pH as screening tests for preterm birth from Matijevic et al. (2010).³¹

Variable	Sensitivity	Specificity	PPV	NPV	LR+	LR+ weighted for prevalence
Outcome: preterm birth <37 weeks						

Cervical length ≤ 26 mm (5 th percentile)	47.8 (27.4-68.9)	98.6 (96.3-99.5)	73.3 (44.8-91.1)	96.1 (92.9-97.8)	35.1 (12.1-101.4)	2.7 (1.1-6.7)
Vaginal pH ≥ 5.0 (95 th percentile)	47.9 (27.4-68.9)	98.9 (96.7-99.7)	78.5 (48.8-94.2)	96.0 (92.9-97.8)	46.7 (14.0-155.7)	3.7 (1.3-10.4)
Outcome: preterm birth <34 weeks						
Cervical length ≤ 26 mm (5 th percentile)	87.5 (46.7-99.3)	97.4 (94.7-98.8)	46.6 (22.3-72.6)	99.7 (97.9-99.9)	33.7 (16.2-70.1)	0.8 (0.4-1.8)
Vaginal pH ≥ 5.0 (95 th percentile)	87.7 (46.7-99.3)	97.7 (95.2-99.0)	50.0 (24.0-75.9)	99.7 (97.9-99.9)	38.5 (17.7-83.0)	1.7 (1.1-3.1)

Serum relaxin

Davies et al. (2008) assessed serum relaxin as a screening test for women at mixed risk.²⁸ The LR+ and LR- calculated from the results of this study did not meet the HTA's criteria for a useful test.

Guidance regarding other screening tests

The NICE Guideline on antenatal care assessed the diagnostic value of 12 screening tests for asymptomatic women.³ They recommend that routine screening for preterm labour should not be offered, as the evidence does not justify screening using clinical examination, asymptomatic bacteriuria, vaginal swabs or ultrasound to assess cervical change, and further research is required investigating the value of screening using maternal serum CRP and cervico-vaginal fetal fibronectin levels, and the accuracy and cost-effectiveness of transvaginal ultrasound.³

The ACOG do not recommend that tests such as fetal fibronectin screening, bacterial vaginosis testing, and home uterine activity monitoring are used as screening strategies, as use of these tests has not demonstrated improved perinatal outcomes.²²

Criterion 5: Studies evaluating cervical volume, abnormal flora and bacterial vaginosis and serum relaxin as screening tests were identified. Screening for bacterial vaginosis using vaginal pH as an indicator fulfilled the HTA's criteria for a useful test in one study (LR+>5, LR-<0.2), however this conclusion is uncertain when the relatively small sample is considered. The HTA review by Honest et al. (2009) concluded that screening for bacterial vaginosis did not have potential. However, included studies used Amsel or Nugent criteria to diagnosis bacterial vaginosis. Further research would be required to establish the potential of vaginal pH as a screening test.

Table 26: Accuracy of other screening tests for the prediction of preterm birth
Numbers in italics have been calculated. Other numbers are as reported. If cells are blank numbers were not reported and not enough data was reported in the paper to calculate figures. Likelihood ratios in bold with shaded cells meet HTA criteria.

Study	Country	Population	Timing of screen	Test/cut-off	Incidence of preterm labour	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Cervical volume – Outcome: preterm birth <37 weeks												
Barber et al. (2012) ³⁴	Gran Canaria, Spain	Low risk. 306 asymptomatic low-risk pregnant women with live singleton pregnancies. No history of preterm delivery or uterine surgery.	20-22 weeks	37.8cm ³	7.2% (18 women)	66.7%	78.2%	16.0%	97.4%	3.06	0.43	AURC: 0.723 RR: 7.19 (95% CI 2.06 to 25.05)
Bacterial vaginosis/abnormal flora – Outcome: preterm birth <37 weeks												
Matijevec et al. (2010) ³¹	Croatia	Low risk. 316 low risk women with an uncomplicated singleton pregnancy. Exclusion criteria: history of preterm labour; pregnancy following assisted reproduction treatment; suspected chorioamnionitis; PPRM or vaginal haemorrhage; cervical surgery; müllerian anomalies; cervical cerclage; sexual intercourse or use of vaginal preparations in the 24 hours pre-ceding the scheduled test; conditions known to	18-24 weeks	Vaginal pH ≥5.0 (95 th percentile)	7.2% (23 women)	47.9% (CI 27.4 to 68.9)	98.9% (CI 96.7 to 99.7)	78.5% (CI 48.8 to 94.2)	96.0% (CI 92.9 to 97.8)	46.7 (CI 14.0 to 155.7) LR+ weighted by prevalence 3.7 (CI 1.3 to 10.4)	0.53	

Study	Country	Population	Timing of screen	Test/cut-off	Incidence of preterm labour	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		be associated with pre-term labour; major fetal anomalies or intrauterine death										

Study	Country	Population	Timing of screen	Test/cut-off	Incidence of preterm labour	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Donders et al. (2009) ⁵⁰	Belgium	Mixed risk 744 women with singleton pregnancies between 9 and 16 weeks' gestation with information on vaginal flora from wet mount microscopy and <i>M. hominis</i> cultures. Women who went on to have a miscarriage excluded.	9-16 weeks	Abnormal vaginal flora	7.39% (55 women)	18.18%	91.73%	14.93%	93.35%	2.20	0.89	OR 2.4, 95% CI 1.2 to 4.8
				Bacterial vaginosis	7.39% (55 women)	10.91%	92.31%	10.17%	92.85%	1.42	0.97	OR 2.43, 95% CI 1.1 to 4.7
				Partial bacterial vaginosis	7.39% (55 women)	7.27%	96.08%	12.90%	92.85%	1.86	0.97	OR 2.4, 95% CI 1.2 to 7.1
				Full bacterial vaginosis	7.39% (55 women)	3.64%	96.23%	7.14%	92.60%	0.96	1.00	Ns
				Coccolid aerobic flora	7.39% (55 women)	7.27%	92.02%	6.78%	92.55%	0.91	1.01	Ns
				Leukocytes	7.39% (55 women)	1.82%	96.81%	4.35%	92.51%	0.57	1.01	Ns
				Mycoplasma hominis	7.39% (55 women)	9.09%	98.84%	38.46%	93.16%	7.83	0.92	OR 8.5, 95% CI 2.8 to 25.5
Bacterial vaginosis/abnormal flora – Outcome: preterm birth <35 weeks												
Donders et al. (2009) ⁵⁰	Belgium	Mixed risk. 744 women with singleton pregnancies between 9 and 16 weeks' gestation with information on vaginal flora from wet mount microscopy and <i>M. hominis</i> cultures. Women who went on to have a miscarriage excluded.	9-16 weeks	Abnormal vaginal flora	1.88% (14 women)	42.86%	91.64%	8.96%	98.82%	5.13	0.62	OR 6.2, 95% CI 2.7 to 14.4
				Bacterial vaginosis	1.88% (14 women)	21.43%	92.33%	5.08%	98.39%	2.79	0.85	OR 5.3, 95% CI 2.1 to 12.9
				Partial bacterial vaginosis	1.88% (14 women)	14.29%	96.03%	6.45%	98.32%	3.60	0.89	OR 7.2, 95% CI 2.4 to 21.0
				Full bacterial vaginosis	1.88% (14 women)	7.14%	96.30%	3.57%	98.18%	1.93	0.96	NS
				Coccolid aerobic flora	1.88% (14 women)	7.14%	92.05%	1.69%	98.10%	0.90	1.01	OR 3.2, 95% CI 1.4 to 9.1
				Leukocytes	1.88% (14 women)	0.00%	96.85%	0.00%	98.06%	0.00	1.03	NS
				Mycoplasma hominis	1.88% (14 women)	14.29%	98.49%	15.38%	98.36%	9.48	0.87	OR 13.3, 95% CI 3.2 to 55
Bacterial vaginosis/abnormal flora – Outcome: preterm birth <34 weeks												

Study	Country	Population	Timing of screen	Test/cut-off	Incidence of preterm labour	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
Matijevic et al. (2010) ³¹	Croatia	Low risk. 316 low risk women with an uncomplicated singleton pregnancy. Exclusion criteria: history of preterm labour; pregnancy following assisted reproduction treatment; suspected chorioamnionitis; PPRM or vaginal haemorrhage; cervical surgery; müllerian anomalies; cervical cerclage; sexual intercourse or use of vaginal preparations in the 24 hours pre-ceding the scheduled test; conditions known to be associated with pre-term labour; major fetal anomalies or intrauterine death	18-24 weeks	Vaginal pH \geq 5.0	2.5% (8 women)	87.7% (CI 46.7-99.3)	97.7% (CI 95.2-99.0)	50.0% (CI 24.0-75.9)	99.7 (CI 97.9-99.9)	38.5 (CI 17.7-83.0) LR+ weighted for prevalence 1.7 (1.1-3.1)	0.13	
Serum relaxin – Outcome: preterm birth <37 weeks												
Davies et al. (2008) ²⁸	Canada	Mixed risk. 964 women with a singleton pregnancy who went onto deliver spontaneously.† 9.2% of women had had a previous spontaneous	24 weeks	90 th percentile	4.8% (46 women)							RR: 0.87, 95% CI 0.32 to 2.4
			28 weeks	90 th percentile	4.8% (46 women)							RR: 1.4 95% CI 0.62 to 3.3

Study	Country	Population	Timing of screen	Test/cut-off	Incidence of preterm labour	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Other variables reported
		preterm birth. 0.2% received tocolysis and 0.1% underwent cervical cerclage. Exclusion criteria: presence of cervical cerclage, placenta previa, or major fetal anomaly; being the recipient of oocyte donation; or a lack of previous fetal anatomic assessment.										

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; PPRM, preterm prelabour rupture of membranes; CI, confidence interval; LR+ positive likelihood ratio; LR- negative likelihood ratio; AUROC, area under ROC curve; RR relative risk

†population not selected on basis of risk factors for preterm birth: not necessarily all at low risk

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

The distribution of values observed studies that assessed the different screening tests described in Criterion 5 are shown in Table 27. Screening for bacterial vaginosis using vaginal pH as an indicator was the only test to fulfil the HTA's criteria for a useful test ($LR+ > 5$, $LR- < 0.2$). However, vaginal pH was only used as a marker in one study of 316 low risk women. This is not sufficient to define a cut-off.

Table 27: Distribution of test values in studies of other screening tests for the prediction of preterm birth

Study	Country	Population	Timing of screen	Average	Range	Other
Cervical volume						
Barber et al. (2012) ³⁴	Gran Canaria, Spain	306 asymptomatic low-risk pregnant women with live singleton pregnancies. No history of preterm delivery or uterine surgery.	20 to 22 weeks	51.9cm ³ *	23 to 103mm	
		<i>Full term</i>		Mean ± SD 53.0 ± 16.9 cm ³		
		<i>Preterm</i>		Mean ± SD 42.2 ± 20.6 cm ³		
Vaginal pH						
Matijevec et al. (2010) ³¹	Croatia	316 low risk women with an uncomplicated singleton pregnancy. Exclusion criteria included: a history of preterm labour, pregnancy following assisted reproduction treatment; suspected chorioamnionitis; preterm prelabour rupture of the membranes or vaginal haemorrhage; a previous surgical procedure involving the cervix; a developmental malformation of the müllerian duct system detected before the pregnancy; sexual intercourse or use of vaginal preparations that could influence vaginal pH in the 24 hours pre-ceeding the scheduled test; pre-eclampsia, autoimmune diseases, diabetes, or other conditions known to be associated with pre-term labour; and major fetal anomalies or intrauterine death	18 to 24 weeks	Median (interquartile [IQR] range) 4.4 (range, 4.0 to 4.7)		
Serum relaxin						
Davies et al. 2008 ²⁸	Canada	964 women with a singleton pregnancy who went onto deliver spontaneously. 9.2% of women had had a previous spontaneous preterm birth. 0.2% received tocolysis and 0.1% underwent cervical cerclage. Exclusion criteria included presence of cervical cerclage, placenta previa, or major fetal anomaly, being the recipient of oocyte donation, having multiple gestation, or a lack of previous fetal anatomic assessment.	24 weeks	Median (interquartile range) 658 (range 398 to 952) pmol/L		Positively skewed

*unclear whether this value is a median or a mean

Abbreviations: SD, standard deviation

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The HTA report concluded that *“beyond the screening issue, consensus is also lacking in the management of individuals who are screened as positive. There are many interventions that purportedly prevent spontaneous preterm birth (primary prevention)”*. In the review 38 treatment options for either primary prevention or secondary prevention were analysed. They conclude that *“among asymptomatic women in early pregnancy antibiotic treatment for bacterial vaginosis in women with intermediate flora, smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising (primary prevention).”*²

Systematic reviews of treatments for women with risk factors for preterm birth (other than a short cervix) that could be identified by screening are summarised in this section. If a systematic review was not available, RCTs were included.

In line with the rest of the report, included studies were performed in low risk women or women at mixed risk. Studies exclusively in high risk women (multiple gestation, history of preterm birth, PPRM or fetal loss in the second trimester, uterine anomalies or cervical surgery) were excluded.

Smaill and Vazquez (2007) systematically reviewed antibiotics for asymptomatic bacteriuria. Antibiotics did not significantly alter the risk of preterm delivery <38 weeks.⁵¹

Brocklehurst et al. (2013)⁵² systematically reviewed antibiotics for bacterial vaginosis. Antibiotics did not significantly alter the risk of preterm delivery at <32 weeks, <34 weeks or <37 weeks. Another systematic review, Lamont et al. (2011) systematically reviewed one particular antibiotic, clindamycin, for abnormal flora.⁵³ Clindamycin was found to significantly reduce the risk of preterm birth <37 weeks. Simcox et al. (2007) systematically reviewed antibiotics for women with risk factors for preterm birth.⁵⁴ They performed a subanalysis of women treated with antibiotics for vaginal flora. Antibiotics did not significantly alter the risk of preterm delivery <37 weeks.

Antibiotics were also used to treat women with other risk factors for preterm birth. Simcox et al. (2007) performed another subanalysis of women with fetal fibronectin positivity.⁵⁴ Antibiotics did not significantly alter the risk of preterm birth <37 weeks. Morency et al. (2007) systematically reviewed a specific type of antibiotics, macrolides, during the second trimester on the rate of preterm birth.⁵⁵ It found they significantly lowered the odds of preterm birth <37 weeks. In the three included studies, women were at higher risk of preterm delivery because of prior preterm birth or pre-gestational weight <50kg (one study), urogenital *Mycoplasma* infection (one study) or positive vaginal fetal fibronectin test (one study). In this systematic review clindamycin was also found to significantly reduce the odds of preterm birth, in this case four studies were in women with abnormal vaginal flora or bacterial vaginosis and one in women with a previous spontaneous preterm delivery. Metronidazole was not found to reduce the risk of preterm delivery (two studies in women with vaginal fetal fibronectin positivity, one study in women with periodontitis, four studies in women with bacterial vaginosis or vaginal infection- in one of these studies women also had a history of preterm labour or miscarriage, one study in women with a history of preterm labour or who had a pre-pregnancy weight of less than 50 kg), and when only studies in which metronidazole was given alone were meta-analysed, metronidazole was found to increase the odds of preterm birth.

Krauss-Silva et al. (2011) was a RCT that compared probiotics vs. placebo in women with bacterial vaginosis.⁵⁶ Probiotics did not significantly alter the risk of preterm birth <34 weeks or <37 weeks.

Khanprakob et al. (2012) systematically reviewed COX inhibitors for preventing preterm labour in high-risk women.⁵⁷ Only one study was included. Women were at high risk because of at least two previous second trimester losses or early preterm deliveries <30 weeks, one previous second trimester loss or early preterm birth <30 weeks and cervical length ≤ 15 mm from 14 to 24 weeks, or cervical changes requiring Cerclage in current pregnancy determined either by ultrasound criteria or clinically. COX inhibitors increased the risk of preterm birth <37 weeks.

Whitworth et al. (2011) systematically reviewed specialised antenatal care for women at high risk of preterm birth.⁵⁸ Specialised antenatal care did not significantly alter the risk of preterm birth <28 weeks, <34 weeks or <37 weeks.

Criterion 10: Antibiotic treatment of asymptomatic bacteriuria, probiotics for bacterial vaginosis, and specialised antenatal treatments for women at high risk of preterm birth were not found to significantly alter the risk of preterm birth. COX inhibitors increased the risk of preterm birth based on the results of one RCT.

Systematic reviews of antibiotic treatment of bacterial vaginosis/abnormal flora or in women with other risk factors for preterm birth, for example a positive fetal fibronectin result, have found conflicting results, with some studies finding that antibiotic treatment had no effect, some finding that antibiotic treatment reduced the risk of preterm birth, and some studies finding that antibiotic treatment increased the risk of preterm birth. The results may differ due to the inclusion/exclusion criteria of the different studies, the antibiotic used, the indication or the gestational period in which treatment was given.

Table 28: The effect of interventions for women with risk factors for preterm birth (other than a short cervix) that could be identified by screening on the risk of preterm birth

Study	Indication	Population	Intervention	Outcome	RR (95% CI)*
Antibiotics for asymptomatic bacteriuria					
Small and Vazquez (2007) ⁵¹	Asymptomatic bacteriuria	Systematic review. Included studies of pregnant women found on antenatal screening to have asymptomatic bacteriuria, as defined by the study authors, at any stage of pregnancy	Antibiotics to treat asymptomatic bacteriuria (vs. placebo or no treatment)	Preterm delivery <38 weeks	0.37 (0.10 to 1.36); 3 studies
Antibiotics for bacterial vaginosis/abnormal flora					
Brocklehurst et al. (2013) ⁵²	Bacterial vaginosis	Systematic review. Included studies of women of any age at any stage of pregnancy with a diagnosis of bacterial vaginosis	Antibiotics to treat bacterial vaginosis vs. placebo or no treatment	Preterm birth <32 weeks	1.13 (0.77 to 1.68); 4 studies
				Preterm birth <34 weeks	1.16 (0.52 to 2.59); 3 studies
				Preterm birth <37 weeks	0.88 (0.71 to 1.09); 13 studies
			Metronidazole vs. clindamycin	Preterm birth <37 weeks	0.89 (0.63 to 1.26); 1 study
			Oral vs. vaginal antibiotics	Preterm birth <37 weeks	1.09 (0.78 to 1.52); 2 studies
			Antibiotic vs. another treatment (oral vitamin C)	Preterm birth <34 weeks	1.05 (0.25 to 4.42); 2 studies
			Preterm birth <37 weeks	0.85 (0.22 to 3.30); 2 studies	
Lamont et al. (2011) ⁵³	Abnormal flora	Systematic review. Women with abnormal vaginal flora at <22 weeks' gestation	Clindamycin vs. placebo	Preterm birth <37 weeks	RR 0.60 (0.42 to 0.86); 5 studies
Antibiotics in women with a known risk factor for preterm birth					
Simcox et al. (2007) ⁵⁴	Risk factor for preterm birth (past obstetric history, fetal fibronectin status, abnormal vaginal flora)	Systematic review. Women with abnormal vaginal flora including bacterial vaginosis; previous preterm delivery with or without bacterial vaginosis; fetal fibronectin positivity	Any antibiotic vs. placebo	Preterm birth <32 weeks	1.22 (0.88 to 1.68); 9 studies
			Any antibiotic vs. placebo	Preterm birth <37 weeks	1.03 (0.86 to 1.24); 17 studies
			Clindamycin vs. placebo	Preterm birth <37 weeks	1.02 (0.69 to 1.48); 7 studies
			Metronidazole alone or in combination vs. placebo	Preterm birth <37 weeks	1.06 (0.81 to 1.39); 8 studies
			Erythromycin alone or in combination vs. placebo	Preterm birth <37 weeks	0.87 (0.73 to 1.03); 4 studies
	Abnormal vaginal flora	Abnormal vaginal flora	Any antibiotic vs. placebo	Preterm birth <37 weeks	0.97 (0.78 to 1.21); 14 studies
Fetal fibronectin positivity	Fetal fibronectin positivity	Any antibiotic vs. placebo	Preterm birth <37 weeks	1.23 (0.77 to 1.96); 2 studies	
Morency et al. (2007) ⁵⁵		Systematic review. Women with fetal	Macrolide (vs. placebo) during	Preterm birth <37 weeks	OR 0.72 (0.56 to 0.93); 3 studies

Study	Indication	Population	Intervention	Outcome	RR (95% CI)*
		fibronectin positivity; urogenital Mycoplasma infection; prior preterm birth or pre-pregnancy weight <50kg	the second trimester		
		Systematic review. Women with bacterial vaginosis; abnormal flora; prior preterm birth	Clindamycin (vs. placebo) during the second trimester	Preterm birth <37 weeks	OR 0.68 (0.49 to 0.95); 5 studies
		Systematic review. Women with fetal fibronectin positivity; periodontitis; bacterial vaginosis; asymptomatic Trichomonas vaginalis; prior preterm birth or pre-pregnancy weight <50kg	Metronidazole (vs. placebo) during the second trimester	Preterm birth <37 weeks	OR 1.10 (0.95 to 1.29); 8 studies
		Systematic review. Women with fetal fibronectin positivity; periodontitis; bacterial vaginosis; asymptomatic Trichomonas vaginalis	Metronidazole alone (vs. placebo) during the second trimester	Preterm birth <37 weeks	OR 1.31 (1.08 to 1.58); 6 studies
Probiotics for bacterial vaginosis					
Krauss-Silva et al. (2011) ⁵⁶	Asymptomatic bacterial vaginosis or intermediate-degree infections	605 women with singleton pregnancies with vaginal pH≥4.5 and Nugent score >4 at between 8 and 20 weeks' gestation without a history of preterm birth.	Probiotics (<i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14) vs. placebo	Preterm delivery <34 weeks	0.330 (0.03 to 3.16)
				Preterm delivery <37 weeks	0.495 (0.17 to 1.43)
Oral betamimetics (isoxsuprine, hexoprenaline, orciprenaline, ritodrine, terbutaline, salbutamol) for women at high risk of preterm birth					
Khanprakob et al. (2012) ⁵⁷	Risk of preterm birth	Systematic review. Women at risk of preterm birth (one included study, risk factors were at least two previous second trimester losses or early preterm deliveries <30 weeks, one previous second	Rofecoxib vs. placebo	Preterm birth <37 weeks	1.65 (1.11 to 2.45); 1 study

Study	Indication	Population	Intervention	Outcome	RR (95% CI)*
		trimester loss or early preterm birth <30 weeks and cervical length ≤ 15 mm from 14 to 24 weeks, and cervical changes requiring Cerclage in current pregnancy determined either by ultrasound criteria or clinically)			
Specialised antenatal clinics for women at high risk of preterm birth					
Whitworth et al. (2011) ⁵⁸	Women at risk of preterm birth	Systematic review. Women at risk of preterm birth (due to score on Creasey scoring system, Papiernik-Creasey Scoring system, or because 'high risk' not further defined)	Specialised antenatal clinics	Preterm birth <28 weeks	0.77 (0.26 to 2.25); 1 study
				Preterm birth <34 weeks	1.05 (0.50 to 2.21); 1 study
				Preterm birth <37 weeks	0.87 (0.69 to 1.08); 3 studies

*RR except where noted

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (eg. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

Screening and treatment of antenatal lower genital tract infection/bacterial vaginosis/abnormal flora

Sangkomkhang et al. (2008) performed a systematic review of RCTs of antenatal lower genital tract infection screening and treatment programmes for preventing preterm delivery.⁵⁹ It identified one trial that recruited and screened 4,155 pregnant women by Gram stain for asymptomatic vaginal infection. Results were only revealed to the intervention group who then received standard treatment. The risk of preterm birth (<37 weeks’ gestation) was significantly reduced in women randomised to the screen-and-treat intervention (3% vs. 5%, RR 0.55, 95% CI 0.41 to 0.75). The screen-and-treat programme also reduced the risk of preterm low birthweight ($\leq 2,500$ g) and preterm very low birthweight ($\leq 1,500$ g). None of the women in this trial reported any adverse effects during the treatment period.

Following the results of this RCT, Kiss et al. (2010) reported results of the implementation of the screen-and-treat programme at one hospital in Austria, and compared the results for 1,273 women presenting with singleton pregnancies between 11+0 weeks and 24+6 weeks to

outcomes for 1,713 women who had delivered two years prior to the introduction of the programme (irrespective of obstetric history).⁶⁰

In the programme women were screened for asymptomatic vaginal infection using Gram stain. Women were screened and treated for bacterial vaginosis (Nugent grade 3, treated for 6 days with clindamycin 2% vaginal cream and, for persistent or recurrent disease 300mg oral clindamycin twice daily for 7 days, followed by treatment [all] with vaginal capsules containing live lactobacilli for 6 days), vaginal candidiasis (spores and hyphae, treated with local clotrimazole 0.1g for 6 days, persistent or recurrent infection re-treated), and infection with *Trichomonas vaginalis* (treated with 500mg local metronidazole for 7 days, partner also treated, persistent or recurrent infection re-treated). Almost 25% of women screened underwent infection treatment and follow-up. The rate of preterm birth (<37 weeks) was significantly lower with the screen and treat programme compared to the historical control group (8.2% vs. 12.1%), as was the rate of very preterm birth (<33 weeks, 1.9% vs. 5.4%) and the number of preterm infants with birthweights $\leq 2,500\text{g}$.⁶⁰

Koumans et al. (2011) performed a retrospective cohort study of early screening (<22 weeks' gestation), treatment and rescreening/retreatment for abnormal flora/bacterial vaginosis in the US.⁶¹ It also reported a reduction in preterm birth with screening. The Syracuse Healthy Start programme recommended that pregnant women residing in zip codes with the highest infant mortality rates be Gram stain screened at the first prenatal visit, and those with an abnormal Gram stain treated, rescreened 4-6 weeks later and retreated if required. Treatments included 500mg metronidazole twice daily for 7 days, 250mg metronidazole three times daily for 7 days, 2g of metronidazole once, intravaginal metronidazole for 5 days and intravaginal clindamycin. In this study, charts for 838 women screened at <22 weeks' gestation who delivered a live-born infant were reviewed. Outcomes for women with bacterial vaginosis/abnormal flora who were treated (n=290) were compared to outcomes for women with bacterial vaginosis/abnormal flora who were not treated (n=202), and women who had normal flora (n=346). It was not reported why some women with positive screen results were not treated. After adjustment for maternal race, age, pre-pregnancy weight, gravidity, prenatal care provider, trimester of onset of prenatal care, prior preterm birth and smoking status, compared with no treatment of bacterial vaginosis/abnormal flora, treatment of bacterial vaginosis/abnormal flora was significantly associated with a reduction in the risk of preterm delivery (<37 weeks, adjusted OR 0.5, 95% CI 0.3 to 0.8). The proportion of premature deliveries among women whose Gram stain showed normal flora did not differ statistically from women who had bacterial vaginosis/abnormal flora and were treated.

Sungkar et al. (2012), a RCT of screening and treatment in Indonesia found no difference in preterm birth in the screen and treat groups and the control groups, although this may be due to limitations in the screening protocol, which meant that not all women underwent microbiology testing.⁶² In the trial, 331 women with singleton pregnancies at 14 to 18 weeks' gestation (without fetal anomalies or uterine malformation) were randomised to usual prenatal care or to education about preterm birth and its risk factors, self-examination of vaginal acidity, and microbiologic testing (Gram staining) for bacterial vaginosis. Screening was performed at study entry, at week 16 to 18, at week 18 to 20, at week 20 to 22 and at week 22 to 24. Not all women could undergo microbiology testing, so women with a positive result on the self-examination vaginal acidity test and those with symptomatic complaints were prioritised. Women diagnosed with bacterial vaginosis on the basis of the Gram stain result were treated twice daily with 500mg oral metronidazole for 7 days. There was no statistical difference in

preterm births in the screen and treat group (3.8%) and the control group (5.4%) (OR 1.01, 95% CI 0.97 to 1.07).

Criterion 13 unclear: RCTs of screening and treatment of antenatal lower genital tract infection/bacterial vaginosis/abnormal flora have been performed. Despite the fact that the effectiveness of treating these conditions on reducing the incidence of preterm birth has been questioned, a RCT performed in a European country has found that a screen-and-treat programme significantly reduced the risk of preterm birth. A follow-up cohort study with a historical control group confirmed this finding. In addition, a US cohort study has also found that women with bacterial vaginosis identified by screening who were treated also had a reduced risk of preterm delivery compared to women with bacterial vaginosis were not treated. However, a RCT of screening and treatment in Indonesia did not find any evidence of benefit, but this may have been due to limitations in the screening programme. The evidence found in this criterion conflicts with the findings for the diagnostic accuracy and treatment of abnormal vaginal flora/bacterial vaginosis found earlier, where both conclusions highlight the uncertainty of the prediction and prevention of preterm birth in women with abnormal vaginal bacterial flora/bacterial vaginosis.

Executive summary – Other tests to predict preterm labour and treatments to prevent preterm labour (including testing and treatment for bacterial vaginosis)

The test

Screening for preterm birth using vaginal flora, cervical volume or serum relaxin did not meet the HTA's criteria for a useful test.

Screening for bacterial vaginosis using vaginal pH as an indicator fulfilled the HTA's criteria for a useful test in one study of 316 low risk women. The HTA review by Honest et al. (2009) concluded that screening for bacterial vaginosis did not have potential. However, included studies used Amsel or Nugent criteria to diagnose bacterial vaginosis. The potential of vaginal pH as a screening test should be examined further.

The treatment

Antibiotic treatment of asymptomatic bacteriuria, probiotics for bacterial vaginosis, and specialised antenatal treatments for women at high risk of preterm birth were not found to significantly alter the risk of preterm birth. COX inhibitors increased the risk of preterm birth based on the results of one RCT.

Systematic reviews of antibiotic treatment of bacterial vaginosis/abnormal flora or in women with other risk factors for preterm birth, for example a positive fetal fibronectin result, have found conflicting results, with some studies finding that antibiotic treatment had no effect, some finding that antibiotic treatment reduced the risk of preterm birth, and some studies finding that antibiotic treatment increased the risk of preterm birth. The results may differ due to the inclusion/exclusion criteria of the different studies, the antibiotic used, the indication or the gestational period in which treatment was given.

Future research should aim to determine the cause of the conflicting results, and whether treatment of bacterial vaginosis/abnormal flora or the administration of antibiotics to women with other risk factors for preterm birth reduces the risk of preterm birth.

The screening programme

The studies included in the review found conflicting outcomes of the efficacy for a prospective bacterial vaginosis/abnormal flora screening programme. A RCT performed in a European country has found that screening for asymptomatic vaginal infection significantly reduced the risk of preterm birth. A follow-up cohort study with a historical control group confirmed this finding. In addition, a US cohort study has also found that women with bacterial vaginosis identified by screening who were treated also had a reduced risk of preterm delivery compared to women with bacterial vaginosis were not treated. However, a RCT of screening and treatment in Indonesia did not find any evidence of benefit, but this may have been due to limitations in the screening programme. Larger studies would be needed to explore the effectiveness of screening and treatment further.

No cost-effectiveness analyses were identified.

Methodology

The update report was prepared by Bazian Ltd., and then adapted in line with comments from the National Screening Committee.

Search strategy

BACKGROUND: The current UK NSC policy not to offer screening for preterm labour is based on the following:

NICE. (2008) CG62 Antenatal care: routine care for the healthy pregnant woman.

Honest H, et al. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technology Assessment 2009; 13(43)

SOURCES SEARCHED: Medline, Embase, and the Cochrane Library.

DATES OF SEARCH: January 2007 – 1 May 2013

The last search for the NICE antenatal guidance was carried out in June 2007, therefore, January 2007 was chosen as the start date for these new searches so as not to miss any potentially relevant evidence that may not have been indexed during the previous search.

SEARCH STRATEGY:

1. exp Obstetric Labor, Premature/ (16708)
2. ((premature or preterm or pre term) adj3 birth\$.tw. (13930)
3. ((premature or preterm or pre term) adj3 deliver\$.tw. (11044)
4. ((premature or preterm or pre term) adj3 (labor or labour)).tw. (8493)
5. premature parturition.tw. (80)
6. 1 or 2 or 3 or 4 or 5 (33561)
7. Mass Screening/ (77286)
8. predict\$.tw. (790537)
9. (test or tests or testing).tw. (1400782)
10. (evaluat\$.tw. (1983052)
11. 7 or 8 or 9 or 10 (3632769)
12. fibronectin.tw. (30413)
13. fFN.tw. (157)
14. (cervical adj (length or shortening or funelling)).tw. (887)
15. Cervical Length Measurement/ (151)
16. Cervix Uteri/us [Ultrasonography] (823)
17. Vaginosis, Bacterial/ (2218)
18. bacterial vaginosis.tw. (2660)
19. 12 or 13 or 14 or 15 or 16 or 17 or 18 (34712)
20. 11 and 19 (6648)
21. 6 and 20 (935)
22. Epidemiology/ (11337)
23. incidence/ or prevalence/ (319929)
24. (incidence or prevalence).ti. (143395)
25. 22 or 23 or 24 (399484)
26. 6 and 25 (2123)

- 27. Pregnancy Outcome/ (35205)
- 28. 1 and 27 (2916)
- 29. 28 (2916)
- 30. 21 or 26 or 29 (5477)
- 31. limit 30 to yr="2007 -Current" (2303)

A similar search was carried out in Embase and a simple search carried out in the Cochrane Library.

Search results. All searches carried out on 1 May 2013

Medline: 2303

Embase: 871

Cochrane Library: 618

Total: 3792

Inclusions and exclusions

The above search strategies retrieved 3792 references in total. After duplicate references were removed a total of

3129 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for preterm labour, focussing on the following:

- Natural history of preterm labour and preterm birth
- Epidemiology of preterm labour or birth
- Cervical length as a predictor of preterm labour or birth in asymptomatic women
- Fetal fibronectin as a predictor of preterm labour or birth in asymptomatic women
- Bacterial vaginosis as a predictor of preterm labour or birth in asymptomatic women
- Treatment in asymptomatic women
- Screening programme
- Cost-effectiveness

666 references were deemed to be relevant. This set of references was then passed to the expert reviewer for further appraisal and possible inclusion in the review. (The expert reviewer will also consider the reference lists from relevant papers at this appraisal stage.)

References have been categorised as follows:

<p>Systematic reviews, meta-analyses, and guidelines</p> <ul style="list-style-type: none"> • Guidelines (6) • The condition (8) • The test (12) • The treatment (64) <p>Antenatal steroids (8)</p>	94
--	-----------

Progesterone (9) Cerclage (4) Tocolytics (14) Supplements (4) Antibiotics (6) Delivery method (3) Preterm labour clinic (1) Activity restriction (2) Comparison of interventions (2) Neonatal interventions (7) Miscellaneous (4) <ul style="list-style-type: none"> • The screening programme (4) 	
Structured abstracts	22
Non-systematic reviews	25
The condition <ul style="list-style-type: none"> • Epidemiology (49) • Pregnancy/neonatal outcomes (24) • Longer-term outcomes (54) 	127
The test <ul style="list-style-type: none"> • Cervical length (73) • Cervical length and fetal fibronectin (31) • Fetal fibronectin (20) • Bacterial vaginosis (11) 	135
The treatment <ul style="list-style-type: none"> • Reviews (12) • Antenatal steroids (40) • Progesterone (63) • Cerclage (44) • Tocolytics (30) • Supplements (15) • Antibiotics (10) • Delivery method (7) • Pessary (10) • Preterm labour clinic (3) • Activity restriction (1) • Comparison of interventions (6) • Neonatal interventions (13) 	254
The screening programme	9
Total	666

Quality

Non-systematic reviews, editorials, other opinion pieces and case series of were excluded. Where available, the results of systematic reviews were used.

References

1. NICE. Preterm labour and birth: Final scope. London: National Institute for Health and Clinical Excellence; 2013. Available from: <http://www.nice.org.uk/nicemedia/live/14004/64413/64413.pdf>.
2. Honest H, Forbes CA, Duree KH et al. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess*. 2009;13(43):1-627.
3. NICE. Antenatal care. CG 62. London: National Institute for Health and Clinical Excellence; 2008. Available from: <http://www.nice.org.uk/nicemedia/live/11947/40145/40145.pdf>.
4. Lawn JE, Gravett MG, Nunes TM et al. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. *BMC Pregnancy Childbirth*. 2010;10 Suppl 1:S1.
5. Gouyon JB, Iacobelli S, Ferdynus C et al. Neonatal problems of late and moderate preterm infants. *Semin Fetal Neonatal Med*. 2012;17(3):146-52.
6. Beck S, Wojdyla D, Say L et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010;88(1):31-8.
7. Health and Social Care Information Centre. NHS Maternity Statistics - England, April 2011 to March 2012: Summary report. Leeds: Health and Social Care Information Centre; 2012. Available from: <http://www.hscic.gov.uk/catalogue/PUB09202/nhs-mate-eng-2011-2012-rep.pdf>.
8. Health and Social Care Information Centre. NHS Maternity Statistics- England, April 2011 to March 2012: NHS Maternity Statistics tables. Leeds: Health and Social Care Information Centre; 2012. Available from: <http://www.hscic.gov.uk/catalogue/PUB09202/nhs-mate-eng-2011-2012-tab-v1.xls>.
9. Lumley J, Chamberlain C, Dowswell T et al. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2009;(3):CD001055.
10. Ota E, Tobe-Gai R, Mori R et al. Antenatal dietary advice and supplementation to increase energy and protein intake. *Cochrane Database Syst Rev*. 2012;9:CD000032.
11. Salvig JD, Lamont RF. Evidence regarding an effect of marine n-3 fatty acids on preterm birth: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2011;90(8):825-38.
12. Mori R, Ota E, Middleton P et al. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev*. 2012;7:CD000230.

13. Pena-Rosas JP, De-Regil LM, Dowswell T et al. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev.* 2012;12:CD004736.
14. Broek NR, White SA, Goodall M et al. The APPLe study: a randomized, community-based, placebo-controlled trial of azithromycin for the prevention of preterm birth, with meta-analysis. *PLoS Med.* 2009;6(12):e1000191.
15. Othman M, Neilson JP, Alfirevic Z. Probiotics for preventing preterm labour. *Cochrane Database Syst Rev.* 2007;(1):CD005941.
16. Shah PS, Ohlsson A, Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. *CMAJ.* 2009;180(12):E99-108.
17. Lassi ZS, Salam RA, Haider BA et al. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. *Cochrane Database Syst Rev.* 2013;3:CD006896.
18. Pena-Rosas JP, De-Regil LM, Dowswell T et al. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev.* 2012;7:CD009997.
19. Buppasiri P, Lumbiganon P, Thinkhamrop J et al. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database Syst Rev.* 2011;(10):CD007079.
20. NICE. Antenatal care. CG 62. London: National Institute for Health and Clinical Excellence; 2010. Available from: <http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf>.
21. NICE. Quitting smoking in pregnancy and following childbirth. PH 26. London: National Institute for Health and Clinical Excellence; 2010. Available from: <http://publications.nice.org.uk/quitting-smoking-in-pregnancy-and-following-childbirth-ph26/recommendations>.
22. Committee on Practice Bulletins-Obstetrics TACoOaG. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol.* 2012;120(4):964-73.
23. Greco E, Lange A, Ushakov F et al. Prediction of spontaneous preterm delivery from endocervical length at 11 to 13 weeks. *Prenat Diagn.* 2011;31(1):84-9.
24. Souka AP, Papastefanou I, Michalitsi V et al. Cervical length changes from the first to second trimester of pregnancy, and prediction of preterm birth by first-trimester sonographic cervical measurement. *J Ultrasound Med.* 2011;30(7):997-1002.
25. Hernandez-Andrade E, Romero R, Ahn H et al. Transabdominal evaluation of uterine cervical length during pregnancy fails to identify a substantial number of women with a short cervix. *J Matern Fetal Neonatal Med.* 2012;25(9):1682-9.

26. Rashed M, Rawashdeh M, Be-Kaen K. Prediction of preterm labor by ultrasonographic cervical length. *Rawal Medical Journal*. 2009;34 (2):191-4.
27. Domin CM, Smith EJ, Terplan M. Transvaginal ultrasonographic measurement of cervical length as a predictor of preterm birth: a systematic review with meta-analysis. *Ultrasound Q*. 2010;26(4):241-8.
28. Davies G, Ottenhof C, Woodman M et al. Cervix length and relaxin as predictors of preterm birth. *J Obstet Gynaecol Can*. 2008;30(12):1124-31.
29. Arora P, Maitra NK, Agarwal S. Cervical length measurement by transvaginal ultrasound at 20 to 24 weeks gestation and the timing and mode of delivery. *Journal of South Asian Federation of Obstetrics & Gynecology*. 2012;4(1):22-4.
30. Ozdemir I, Demirci F, Yucel O et al. Ultrasonographic cervical length measurement at 10-14 and 20-24 weeks gestation and the risk of preterm delivery. *Eur J Obstet Gynecol Reprod Biol*. 2007;130(2):176-9.
31. Matijevic R, Grgic O, Knezevic M. Vaginal pH versus cervical length in the mid-trimester as screening predictors of preterm labor in a low-risk population. *Int J Gynaecol Obstet*. 2010;111(1):41-4.
32. Barber MA, Eguiluz I, Plasencia W et al. Preterm delivery and ultrasound measurement of cervical length in Gran Canaria, Spain. *Int J Gynaecol Obstet*. 2010;108(1):58-60.
33. Dilek TU, Yazici G, Gurbuz A et al. Progressive cervical length changes versus single cervical length measurement by transvaginal ultrasound for prediction of preterm delivery. *Gynecol Obstet Invest*. 2007;64(4):175-9.
34. Barber MA, Medina M, Cabrera F et al. Cervical length vs VOCAL cervical volume for predicting pre-term delivery in asymptomatic women at 20-22 weeks' pregnancy. *J Obstet Gynaecol*. 2012;32(7):648-51.
35. Society for Maternal-Fetal Medicine Publications Committee waoVB. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol*. 2012;206(5):376-86.
36. Hassan SS, Romero R, Vidyadhari D et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol*. 2011;38(1):18-31.
37. Fonseca EB, Celik E, Parra M et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*. 2007;357(5):462-9.
38. Grobman WA, Thom EA, Spong CY et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. *Am J Obstet Gynecol*. 2012;207(5):390-8.

39. Goya M, Pratcorona L, Merced C et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet*. 2012;379(9828):1800-6.
40. Dodd JM, Flenady V, Cincotta R et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev*. 2006;(1):CD004947.
41. Likis FE, Edwards DR, Andrews JC et al. Progestogens for preterm birth prevention: a systematic review and meta-analysis. *Obstet Gynecol*. 2012;120(4):897-907.
42. Romero R, Nicolaides K, Conde-Agudelo A et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol*. 2012;(2):124.
43. Alfirevic Z, Stampalija T, Roberts D et al. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev*. 2012;(4):CD008991.
44. Berghella V, Keeler SM, To MS et al. Effectiveness of cerclage according to severity of cervical length shortening: a meta-analysis. *Ultrasound Obstet Gynecol*. 2010;35(4):468-73.
45. Jorgensen AL, Alfirevic Z, Tudur SC et al. Cervical stitch (cerclage) for preventing pregnancy loss: individual patient data meta-analysis. *BJOG*. 2007;114(12):1460-76.
46. Keeler SM, Kiefer D, Rochon M et al. A randomized trial of cerclage vs. 17 alpha-hydroxyprogesterone caproate for treatment of short cervix. *J Perinat Med*. 2009;37(5):473-9.
47. Werner EF, Han CS, Pettker CM et al. Universal cervical-length screening to prevent preterm birth: a cost-effectiveness analysis. *Ultrasound Obstet Gynecol*. 2011;38(1):32-7.
48. Cahill AG, Odibo AO, Caughey AB et al. Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: a decision and economic analysis. *Am J Obstet Gynecol*. 2010;(6):548.
49. The Perinatal Quality Foundation. CLEAR Cervical Length Education and Review [Internet]. Oklahoma City (OK): Perinatal Quality Foundation; 2013 [cited 2013 Aug 2]. Available from: <https://www.perinatalquality.org/CLEAR/default.aspx>.
50. Donders GG, Van Calsteren K, Bellen G et al. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. *BJOG*. 2009;116(10):1315-24.
51. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2007;(2):CD000490.

52. Brocklehurst P, Gordon A, Heatley E et al. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev.* 2013;(1):CD000262.
53. Lamont RF, Nhan-Chang CL, Sobel JD et al. Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2011;205(3):177-90.
54. Simcox R, Sin WT, Seed PT et al. Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. *Aust N Z J Obstet Gynaecol.* 2007;47(5):368-77.
55. Morency AM, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. *J Obstet Gynaecol Can.* 2007;29(1):35-44.
56. Krauss-Silva L, Moreira ME, Alves MB et al. A randomised controlled trial of probiotics for the prevention of spontaneous preterm delivery associated with bacterial vaginosis: preliminary results. *Trials.* 2011;12:239.
57. Khanprakob T, Laopaiboon M, Lumbiganon P et al. Cyclo-oxygenase (COX) inhibitors for preventing preterm labour. *Cochrane Database Syst Rev.* 2012;(10):CD007748.
58. Whitworth M, Quenby S, Cockerill RO et al. Specialised antenatal clinics for women with a pregnancy at high risk of preterm birth (excluding multiple pregnancy) to improve maternal and infant outcomes. *Cochrane Database Syst Rev.* 2011;(9):CD006760.
59. Sangkomkarn US, Lumbiganon P, Prasertcharoensook W et al. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *Cochrane Database Syst Rev.* 2008;(2):CD006178.
60. Kiss H, Petricevic L, Martina S et al. Reducing the rate of preterm birth through a simple antenatal screen-and-treat programme: A retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol.* 2010;153(1):38-42.
61. Koumans EH, Lane SD, Aubry R et al. Evaluation of Syracuse Healthy Start's program for abnormal flora management to reduce preterm birth among pregnant women. *Matern Child Health J.* 2011;15(7):1020-8.
62. Sungkar A, Purwosunu Y, Aziz MF et al. Influence of early self-diagnosis and treatment of bacterial vaginosis on preterm birth rate. *Int J Gynaecol Obstet.* 2012;117(3):264-7.