National Institute for Health and Care Excellence

Final

Twin and Triplet Pregnancy

[D] Evidence review for ultrasound screening for prediction of the risk of spontaneous preterm birth

NICE guideline NG137

Evidence review

September 2019

Final

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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ISBN: 978-1-4731-3513-0

Contents

Ultrasound screening for prediction of the risk of spontaneous preterm birth

Review question

What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Introduction

Spontaneous preterm birth and iatrogenic preterm birth that are secondary to other complications occur more frequently in twin and triplet pregnancies than in singleton pregnancies. Preterm birth (even near-term birth) is associated with increased morbidity and use of healthcare resources, with many preterm babies being admitted to neonatal units. Extremely preterm birth (at less than 28 weeks' gestation) is associated with even greater morbidity and mortality and greater use of healthcare resources. The aim of this review is to determine the optimal screening programme to predict the risk of spontaneous preterm birth in asymptomatic women with twin or triplet pregnancy. The effectiveness of interventions to prevent spontaneous preterm birth is reviewed in evidence report B2 which also includes the original economic model that combines screening for preterm birth and interventions aimed to prevent preterm birth.

Summary of the protocols

Please see Table 1 for a summary of the Population, Prognostic Factor, and Outcome (PPO) characteristics of the prognostic component of this review. This aims to identify measures and potential risk factors that predict later preterm birth.

Table 1: Summary of protocol (Population, Prognostic Factor, and Outcome [PPO]) table

Population	Monochorionic / dichorionic twin and all triplet pregnancies identified by the 11^{+0} – 13^{+6} week ultrasound scan (not symptomatic, not in labour). Setting: Secondary or tertiary care centres
Prognostic factor	**Screening methods** • Imaging: ○ cervical length measurement by transvaginal ultrasound (diagnostic predictor: shortened cervical length) • Biochemical testing: ○ fibronectin test (diagnostic predictor: positive test) • Clinical electronic monitoring: ○ ambulatory uterine activity monitoring (diagnostic predictor: increased contraction frequency) • Prior maternal risk factors as diagnostic predictors for spontaneous preterm birth: ○ previous obstetric history ○ previous preterm labour (<37 completed weeks) ○ cervical surgery ○ midtrimester loss (<24 weeks) The above tests will be considered in isolation or both if they were used in sequence, for example first cervical length measurement and then fetal fibronectin testing

Outcomes	• Predictive value of screening tests to predict spontaneous preterm birth: ○ adjusted odds ratios, relative risks, hazard ratios

Table 2 summarises the Population, Index test, Reference standard and Outcome (PIRO) characteristics of the diagnostic component of this review which looks at measures that accurately diagnose preterm birth.

Table 2: Summary of protocol (Population, Index test, Reference standard and Outcome [PIRO]) table

Population	Twin or triplet pregnancies identified by the 11 weeks 0 days to 13 weeks 6 days' (11^{+0} – 13^{+6} weeks') ultrasound scan (not symptomatic, not in labour). Monochorionic/dichorionic twin and all triplet pregnancies Setting: Secondary or tertiary care centres
Index Test	**Ultrasound scan:** • cervical length measurement • fibronectin test • ambulatory uterine activity monitoring • previous obstetric history: ○ previous preterm labour (<37 completed weeks) ○ cervical surgery ○ midtrimester loss (<24 weeks) The above tests will be considered in isolation or both if they were used in sequence, for example first cervical length measurement and then fetal fibronectin testing
Reference Standard	**Spontaneous preterm birth:** • ≤36^{+0} gestational weeks for monochorionic twins • ≤37^{+0} gestational weeks for dichorionic twins • ≤36^{+0} gestational weeks for triplets
Outcomes	**Diagnostic value of screening tests** **Critical:** • sensitivity • specificity

For full details see the review protocols in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A and for a full description of the methods see supplementary document C.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from March 2017 until March 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Two systematic reviews (Conde-Agudelo 2010; Conde-Agudelo 2010a), 5 prospective cohort studies (Guzman 2000; Leveque 2015; Schaaf 2012; Soriano 2002; Vayssiere 2002) and 12 retrospective cohort studies (Ehsanipoor 2012; Fichera 2018; Fox 2010; Fox 2012; Fox 2015; Klein 2008; Matthews 2017; Michaluk 2013; Pagani 2016; Roman 2012; Roman 2018; Skentou 2001) were included in the review.

One of the systematic reviews (Conde-Agudelo 2010) included 16 studies on asymptomatic women (11 studies were prospective and 4 were retrospective cohort studies; 1 study was a conference abstract which was not included in the current evidence report) and assessed the accuracy of sonographic cervical length in detecting spontaneous preterm birth in women with twin pregnancy. Estimates (as reported) in the relevant meta-analyses in the Conde-Agudelo's 2010 systematic review were used in the current evidence report.

The other systematic review (Conde-Agudelo 2010a) included 15 studies but only 7 reported on asymptomatic women with twin pregnancy (5 studies were prospective and 1 was a retrospective cohort study; 1 study was a conference abstract that assessed the accuracy of cervicovaginal fetal fibronectin in detecting spontaneous preterm birth in women with multiple pregnancy (it was not included in the current evidence report). Estimates (as reported) in the relevant meta-analyses in the Conde-Agudelo's 2010a systematic review were used in the current evidence report. Three studies (Leveque 2015; Roman 2018; Skentou 2001) assessed the diagnostic accuracy of cervical length measurement to detect spontaneous preterm birth in women with twin pregnancy, respectively. Three studies (Ehsanipoor 2012; Fox 2010; Klein 2008) and 4 studies (Fox 2012; Matthews 2017; Soriano 2002; Vayssiere 2002) assessed the usefulness of cervical length measurement or fetal fibronectin testing in predicting spontaneous preterm birth in women with twin pregnancy, respectively.

One study (Fox 2015) examined the usefulness of cervical length measurement and fetal fibronectin testing to predict spontaneous preterm birth in women with twin pregnancy. Another study (Pagani 2016) looked at the diagnostic accuracy and usefulness of cervical length measurement in detecting and predicting spontaneous preterm birth in women with twin pregnancy.

Two studies (Fichera 2018; Guzman 2000) assessed the diagnostic accuracy and one study (Fishera 2018) also examined the usefulness of cervical length measurement in detecting and predicting spontaneous preterm birth in women with triplet pregnancy. Another study (Roman 2012) measured the diagnostic accuracy of fetal fibronectin testing to detect spontaneous preterm birth in women with triplet pregnancy.

Two studies (Michaluk 2012; Schaaf 2012) assessed the usefulness of previous preterm birth to predict spontaneous preterm birth in women who had a twin birth following a previous singleton preterm birth.

There were no studies identified that reported on diagnostic accuracy or the usefulness of ambulatory uterine activity monitoring to predict spontaneous preterm birth.

The clinical studies included in this evidence review are summarised in Table 3.

See also the literature search strategy in appendix B, study selection flow chart in appendix C, clinical evidence tables in appendix D and GRADE tables in appendix F.

Excluded studies

Studies excluded from this systematic review, with reasons for their exclusion, are listed in appendix K.

Summary of clinical studies included in the evidence review

A summary of include studies is provided in Table 3.

Table 3: Summary of included studies

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
Conde-Agudelo 2010 Systematic review USA Includes 16 studies on asymptomatic women but only 11 were included in meta-analyses; other 6 were included separately *Prospective cohort study:* Aboulghar 2009 Arabin 2006 Gibson 2004 Goldenberg 1996 Guzman 2000 Sperling 2005 Soriano 2002 To 2006 Yang 2000 Vayssiere 2002 Wennerholm 1997	N=11 relevant studies (9 prospective, 2 retrospective) N=3,213 twin pregnancies	CL measurement	Reference standard: spontaneous PTB	Diagnostic accuracy of CL measurement (cut-offs (mm): 20, 25, 30, 35) to predict spontaneous PTB <28, <32, <34, <37 weeks' gestation (sensitivity and specificity)	Between 20 and 24 weeks, and after 24 weeks

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
Retrospective cohort study: Fait 2005 Fox 2009 Imseis 1997 Klein 2008 Grisaru-Granovsky 1998 is an abstract					
Conde-Agudelo 2010a Systematic review USA Includes 15 studies but only 7 on asymptomatic women *Prospective cohort study:* Gibson 2004 Goldenberg 1996 Oliveira 1998 Ruiz 2004 Wennerholm 1997 *Retrospective cohort study:* Fox 2009 Ramirez 1999 is a conference abstract	N=7 relevant studies (5 prospective, 1 retrospective, 1 unclear study design) N=634 twin pregnancies	fFN testing (all studies cut-off value 50 ng/ml)	Reference standard: spontaneous PTB	Diagnostic accuracy of fFN (cut-off 50 ng/ml) testing to predict spontaneous PTB <32, <34, <37 weeks' gestation (sensitivity and specificity)	Gestational age at sampling: between 22 and 34 weeks Sampling frequency: serial, every 2/3 weeks (5 studies), serial weekly (1 study), or single (1 study) Sampling site: vaginal fornix and cervix (5 studies), vaginal fornix (2 studies)

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
Ehsanipoor 2012 Retrospective cohort USA	N=561 twin pregnancies	Not applicable	Prognostic factor: CL measurement	CL measurement as a predictor for spontaneous PTB <35 weeks' gestation (adjusted ORs)	CL surveillance performed at least once between 13 and 34+6 weeks' gestation
Fichera 2018 Retrospective cohort Italy	N=96 triplet pregnancies (excluding those complicated by TTFS, treated with laser therapy, cerclage or pessary))	CL measurement	Reference standard: spontaneous PTB Prognostic factor: CL measurement	Diagnostic accuracy of CL measurement (cut-offs (mm): 15, 20, 25) to predict spontaneous PTB <28, <30, <32 weeks' gestation (sensitivity and specificity) CL measurement as a predictor for spontaneous PTB <32 weeks' gestation (adjusted ORs)	CL measurement performed between 18 and 24 weeks' gestation. Women were managed according to the local protocol, including an ultrasound examination performed every 2-4 weeks depending on the chorionicity (fortnightly in mono/dichorionic pregnancies and every 3-4 weeks in trichorionic pregnancies)
Fox 2010 Retrospective cohort USA	N=309 twin pregnancies	Not applicable	Prognostic factor: CL measurement	CL measurement as a predictor for spontaneous PTB <28, <32, <35 weeks' gestation (adjusted ORs)	CL measurement routinely done every 2-4 weeks. CL measurement perfumed at 16-17, 18-19, 20-21, 22-23 weeks' gestation
Fox 2012 Retrospective cohort USA	N=244 twin pregnancies	Not applicable	Prognostic factor: fFN testing	fFN testing as a predictor for spontaneous PTB <32 weeks' gestation (adjusted ORs)	All women had a CL >25 mm. Positive fFN concentration defined as 50 ng/mL. CL measurement and fFN testing performed at 2- to 4-week

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
					intervals from 22-32 weeks' gestation
Fox 2015 Retrospective cohort USA	N=611 twin pregnancies	Not applicable	Prognostic factor: CL measurement and fFN testing	CL measurement and fFN testing as predictors for spontaneous PTB <28, <32, <35 weeks' gestation (adjusted ORs)	CL measurement and fFN testing performed at 2- to 4-week intervals from 22-31^{+6} weeks' gestation. Positive fFN concentration defined as 50 ng/mL
Guzman 2000 Prospective cohort USA	N=50 triplet pregnancies	CL measurement	Reference standard: spontaneous PTB	Diagnostic accuracy of CL measurement (cut-offs (mm): ≤20, ≤25) to predict spontaneous PTB <28, <30, <32 weeks' gestation (sensitivity and specificity)	No information provided
Klein 2008 Retrospective cohort Austria	N=223 twin pregnancies	Not applicable	Prognostic factor: CL measurement and previous PTB (<34 weeks' gestation)	CL measurement and previous PTB as predictors for spontaneous PTB <34 weeks' gestation (adjusted ORs)	CL measurement performed between 20-25 weeks' gestation
Leveque 2015 Prospective cohort France	N=116 twin pregnancies	CL measurement	Reference standard: spontaneous PTB	Diagnostic accuracy of CL measurement (cut-offs (mm): <25, <35) to predict spontaneous PTB <34 weeks' gestation (sensitivity and specificity)	CL measurement performed between 21-23 and 26-28 weeks' gestation

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
Matthews 2017 Retrospective cohort USA	N=155 twin pregnancies	Not applicable	Prognostic factor: fFN testing	fFN testing as a predictor for spontaneous PTB <28, <30, <32, <34, <35, <37 weeks' gestation (adjusted ORs)	All women had a CL≤25 mm. CL measurement performed routinely every 2-4 weeks from 16-32 weeks and concurrent fFN testing performed from 22-32 weeks' gestation.
Michaluk 2013 Retrospective cohort Canada	N=576 women who had a twin birth following a previous index singleton PTB	Not applicable	Prognostic factor: previous PTB	Previous PTB as a predictor for spontaneous PTB ≤34, ≤37 weeks' gestation (adjusted ORs)	Visits were scheduled every 2 weeks starting at 20 weeks, a cervical examination at each visit starting at 24 weeks' gestation
Pagani 2016 Retrospective cohort Italy	N=940 twin pregnancies	CL measurement	Reference standard: spontaneous PTB Prognostic factor: CL measurement	Diagnostic accuracy of CL measurement (cut-off (mm): <36) to predict spontaneous PTB <32 weeks' gestation (sensitivity and specificity) CL measurement as a predictor for spontaneous PTB <32 weeks' gestation (adjusted ORs)	Monochorionic-diamniotic and dichorionic-diamniotic twin pregnancies were followed up every 2 and 4 weeks, respectively; if any complications occurred, the frequency of examinations was increased as necessary
Roman 2012 Retrospective cohort USA	N=56 triplet pregnancies	fFN testing	Reference standard: spontaneous PTB	Diagnostic accuracy of fFN testing to predict spontaneous PTB <28, <30, <32 weeks' gestation (sensitivity and specificity)	Serial fFN samples were collected every 2-3 weeks from 22 0/7 until 31 6/7 weeks' gestation, or until birth if the woman gave birth before 32 weeks. Positive fFN concentration

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
					defined as 50 ng/mL
Roman 2018 Retrospective cohort USA and Italy	N=580 twin pregnancies	CL measurement	Reference standard: spontaneous PTB	Diagnostic accuracy of CL measurement (cut-off (mm): ≤5, ≤10, ≤15, ≤25, ≤30) to predict spontaneous PTB <32 weeks' gestation (sensitivity and specificity)	CL was measured at the time of a routine second trimester fetal ultrasound exam at 18 0/7–23 6/7 weeks' gestation
Schaaf 2012 Prospective cohort the Netherlands	N=232 women who had a twin birth following a previous index singleton PTB	Not applicable	Prognostic factor: previous PTB	Previous PTB as a predictor for spontaneous PTB between 22^{+0} to 29^{+6}, 30^{+0} to 33^{+6}, 34^{+0} to 36^{+6}, <37 weeks' gestation (adjusted ORs)	No information provided
Skentou 2001 Retrospective cohort UK	N=434 twin pregnancies	CL measurement	Reference standard: spontaneous PTB	Diagnostic accuracy of CL measurement (cut-offs (mm): ≤15, ≤20, ≤25) to predict spontaneous PTB <33 weeks' gestation (sensitivity and specificity)	Women attended the author's unit for the 23-week fetal anatomy and growth scan; CL was measured on 1 occasion
Soriano 2002 Prospective cohort Israel	N=44 twin pregnancies	Not applicable	Prognostic factor: CL measurement	CL measurement as a predictor for spontaneous PTB ≤35 weeks' gestation (adjusted ORs)	CL measurement performed between 18 and 24 weeks' gestation (mean 22.7)

Study	Population	Index test	Reference standard / Prognostic factor	Outcomes	Gestational age at testing/sampling and frequency
Vayssiere 2002 Prospective cohort France	N=251 twin pregnancies at 22 weeks, N=215 twin pregnancies at 27 weeks' gestation	Not applicable	Prognostic factor: CL measurement	CL measurement as a predictor for spontaneous PTB <32, <35 weeks' gestation (adjusted ORs)	CL measurement performed between 21-23 and 26-28 weeks' gestation. These 2 periods were assessed independently and women could be included in 1 or both

CL: cervical length; fFN: fetal fibronectin; OR: odds ratio; PTB: preterm birth; TTFS: twin-twin transfusion syndrome

See appendix D for the full evidence tables.

Quality assessment of clinical studies included in the evidence review

The evidence for this review question is presented in Table 4, Table 5 and Table 6 for prognostic data (where evidence quality is indicated by the assessment of the risk of bias for the study using the QUIPS checklist), and in appendix F (where evidence quality is assessed using a modified GRADE approach for diagnostic test accuracy data). All studies were observational. Quality assessment was performed for each individual study included in Conde-Agudelo 2010 and Conde-Agudelo 2010a systematic reviews, and for all additional included studies.

See appendix F for the full GRADE tables.

Table 4: Summary clinical evidence profile for cervical length measurement as a predictor for spontaneous preterm birth in twin and triplet pregnancy

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
Twin pregnancy			
Spontaneous preterm birth <28 weeks' gestation			
CL measurement at 16-17 6/7 weeks' gestation (Fox 2010)	309 (1)	0.95 (0.81 to 1.1)[1]	Very serious[2]
CL measurement at 18-19 6/7 weeks' gestation (Fox 2010)	309 (1)	1 (0.8 to 1.2)[1]	Very serious[2]
CL measurement at 20-21 6/7 weeks' gestation (Fox 2010)	309 (1)	0.92 (0.81 to 1)[1]	Very serious[2]
CL measurement at 22-23 6/7 weeks' gestation (Fox 2010)	309 (1)	0.88 (0.8 to 0.97)[1]	Very serious[2]
CL measurement at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	0.78 (0.64 to 0.95)[3]	Very serious[4]
CL measurement and fFN testing at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	for CL 0.90 (0.85 to 0.95)[5] for fFN not reported (reported that it was not statistically significant)	Very serious[4]
Spontaneous preterm birth <32 weeks' gestation			

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
CL measurement at 16-17 weeks' gestation (Fox 2010)	309 (1)	1 (0.93 to 1.1)[1]	Very serious[2]
CL measurement at 18-19 weeks' gestation (Fox 2010)	309 (1)	1 (0.91 to 1.1)[1]	Very serious[2]
CL measurement at 18-23 weeks' gestation (Pagani 2016)	940 (1)	0.94 (0.90 to 0.99)[6]	Serious[7]
CL measurement at 22-21 weeks' gestation (Fox 2010)	309 (1)	0.96 (0.9 to 1)[1]	Very serious [2]
CL measurement at 22-23 weeks' gestation (Fox 2010)	309 (1)	0.93 (0.88 to 0.98)[1]	Very serious[2]
CL measurement at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	0.85 (0.76 to 0.95)[3]	Very serious[4]
CL measurement at 21-23 weeks' gestation, CL cut-off ≤30 mm (Vayssiere 2002)	251 (1)	7 (2.2 to 22.5)[8]	Very serious[9]
Spontaneous preterm birth <34 weeks' gestation			
CL measurement at 20-25 weeks' gestation (Klein 2008)	223 (1)	1.08 (1.02 to 1.16)[10]	Serious[11]
Spontaneous preterm birth <35 weeks' gestation			
CL measurement at 13-35 weeks' Gestation (Ehsanipoor 2012)	561 (1)	0.95 (0.93 to 0.97)[12]	Very serious[13]
CL measurement at 16-17 weeks' gestation (Fox 2010)	309 (1)	0.98 (0.92 to 1)[1]	Very serious[2]
CL measurement at 18-19 weeks' gestation (Fox 2010)	309 (1)	0.92 (0.87 to 0.98)[1]	Very serious[2]
CL measurement at 18-24 weeks' Gestation, CL cut-off ≤35 mm (Soriano 2002)	44 (1)	33.3 (4.55 to 100)[14]	Very serious[15]
CL measurement at 20-21 weeks' gestation (Fox 2010)	309 (1)	0.96 (0.92 to 1)[1]	Very serious[2]
CL measurement at 21-23 weeks' gestation, CL cut-off ≤30 mm (Vayssiere 2002)	251 (1)	3.2 (3.1 to 7.9)[6]	Very serious[7]
CL measurement at 22-23 weeks' gestation (Fox 2010)	309 (1)	0.94 (0.9 to 0.98)[1]	Very serious[2]
CL measurement and fFN testing at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	0.96 (0.94 to 0.98)[16]	Very serious[4]
CL measurement at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	for CL 0.88 (0.80 to 0.96)[17] for fFN 1.04 (0.45 to 1.64)[17]	Very serious[4]
CL measurement at 26-28 weeks' gestation, CL cut-off ≤25 mm (Vayssiere 2002)	215 (1)	7.8 (3.2 to 19.1)[6]	Very serious[7]
Triplet pregnancy			
Spontaneous preterm birth <32 weeks' gestation (excluding those complicated by twin-twin transfusion syndrome, treated with laser therapy, cerclage or pessary)			

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
CL measurement at 18-24 weeks' gestation, CL cut-off ≤20 mm (Fichera 2018)	96 (1)	4 (0.19 to 83.54)[18]	Serious[19]
CL measurement at 18-24 weeks' gestation, CL cut-off ≤25 mm (Fichera 2018)	96 (1)	7.9 (0.44 to 139.08)[18]	Serious[19]

CI: confidence interval; CL: cervical length; fFN: fetal fibronectin; mm: millimetre; OR: odds ratio; RoB: risk of bias
1 Adjusted for maternal age, in vitro-fertilization, multifetal reduction, prior preterm and term births, pre-pregnancy BMI, and cerclage
2 2.6% of the participants received a cerclage after 16 weeks; participants/providers were not blinded to test results; spontaneous preterm birth is not defined
3 Adjusted for gestational age, includes an interaction term for [gestational age x CL]
4 Participants/providers were not blinded to test results; adjusted for gestational age and CL/fFN only
5 Adjusted for gestational age, CL and fFN also included in the model
6 Adjusted for maternal age, parity, smoking, chorionicity, CL, and cervical procedures
7 Not reported if participants/providers were blinded to test results; 4.4% women with either cervical cerclage or Arabin's pessary were included
8 Adjusted for the presence of funnelling
9 Not reported if women were blinded to test results; not all participants were included in the analyses; 4 women received a cerclage after membrane prolapse into cervix that was observed at the 22-week ultrasound measurement; adjusted for the presence of funnelling only
10 Adjusted for previous preterm birth before 34 weeks' gestation, chorionicity, maternal age, BMI, smoking habit, and parity
11 Not reported if or how many women were treated with cerclage or cervical pessary; not reported if participants/providers were blinded to test results; spontaneous preterm birth is not defined
12 Adjusted for parity and conception with assisted reproductive technology
13 Providers were not blinded to test results; spontaneous preterm birth is not defined; adjusted for parity and conception with assisted reproductive technology only
14 Adjusted for maternal age, BMI, smoking habit, and work during pregnancy
15 Participants/providers were not blinded to test results; spontaneous preterm birth is not defined; no exclusion criteria were reported
16 Adjusted for gestational age
17 Adjusted for gestational age, includes an interaction term for [gestational age X CL], CL and fFN also included in the model
18 Adjusted for nulliparity
19 Not reported if participants/providers were blinded to test results; spontaneous preterm birth is not defined; adjusted for nulliparity only

Table 5: Summary clinical evidence profile for fetal fibronectin testing as a predictor for spontaneous preterm birth in twin pregnancy

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
Spontaneous preterm birth <28 weeks' gestation			
fFN testing at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	2.91 (1.32 to 4.5)[1]	Very serious[2]
fFN testing at 22-32 weeks' gestation (Matthews 2017)	155 (1)	9.5 (2.4 to 37.5)[3]	Very serious[4]
Spontaneous preterm birth <30 weeks' gestation			
fFN testing at 22-32 weeks' gestation (Matthews 2017)	155 (1)	6.4 (1.9 to 21.0)[3]	Very serious[4]
Spontaneous preterm birth <32weeks' gestation			
fFN testing at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	2.29 (1.56 to 3.02)[1]	Very serious[2]

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
fFN testing at 22-32 weeks' gestation (Fox 2012)	244 (1)	6.8 (1.42 to 32.2)[5]	Very serious[6]
fFN testing at 22-32 weeks' gestation (Matthews 2017)	155 (1)	3.54 (1.3 to 9.9)[3]	Very serious[4]
Spontaneous preterm birth <34weeks' gestation			
fFN testing at 22-32 weeks' gestation (Matthews 2017)	155 (1)	7.1 (2.6 to 19.1)[3]	Very serious[4]
Spontaneous preterm birth <35weeks' gestation			
fFN testing at 22-31^{+6} weeks' gestation (Fox 2015)	611 (1)	1.51 (0.94 to 2.08)[1]	Very serious[2]
fFN testing at 22-32 weeks' gestation (Matthews 2017)	155 (1)	8.6 (2.9 to 25.7)[3]	Very serious[4]
Spontaneous preterm birth <37weeks' gestation			
fFN testing at 22-32 weeks' gestation (Matthews 2017)	155 (1)	10.7 (1.4 to 84.3)[3]	Very serious[4]

CI: confidence interval; fFN: fetal fibronectin; OR: odds ratio; RoB: risk of bias
1 Adjusted for gestational age
2 Participants/providers were not blinded to test results; adjusted for gestational age and Cl/fFN only
3 Adjusted for baseline CL
4 Not reported if participants/providers were not blinded to test results; adjusted only for baseline CL; although at the time of fFN testing no women had vaginal progesterone or cervical pessary, all women with a CL ≤20 mm prior to 28 weeks received vaginal progesterone and some had a pessary placed
5 Adjusted for maternal age, chorionicity, prior preterm birth, in vitro-fertilization, multifetal reduction, and maternal BMI
6 Participants/providers were not blinded to test results; spontaneous preterm birth is not defined

Table 6: Summary clinical evidence profile for history of preterm birth as a predictor for spontaneous preterm birth in twin pregnancy

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
Spontaneous preterm birth 22+0 - 29+6 weeks' gestation			
History of (singleton) preterm birth (not defined) (Schaaf 2012)	232 (1)	9.5 (1.8 to 48.9)[1]	Very serious[2]
Spontaneous preterm birth 30+0 - 33+6 weeks' gestation			
History of (singleton) preterm birth (not defined) (Schaaf 2012)	232 (1)	14 (3.9 to 50.5)[1]	Very serious[2]
Spontaneous preterm birth <34 weeks' gestation			
History of preterm birth (<34 weeks) (Klein 2008)	223 (1)	4.95 (0.41 to 59.6)[3]	Serious[4]
History of (singleton) preterm birth (not defined) (Michaluk 2013)	576 (1)	3.07 (1.78 to 5.72)[5]	Serious[6]
Spontaneous preterm birth 34+0 - 36+6 weeks' gestation			
History of (singleton) preterm birth (not defined) (Schaaf 2012)	232 (1)	7.3 (5 to 10.6)[1]	Very serious[2]
Spontaneous preterm birth <37 weeks' gestation			
History of (singleton) preterm birth (not defined) (Schaaf 2012)	232 (1)	7.8 (5.5 to 11.2)[1]	Very serious[2]
History of (singleton) preterm birth (not	576 (1)	3.23 (1.75 to 5.98)[5]	Serious[6]

Outcome / Predictor	No of participants (studies)	Adjusted OR (95% CI)	RoB
defined) (Michaluk 2013)			

CI: confidence interval; OR: odds ratio; RoB: risk of bias
1 Adjusted for reproductive technology and socio-economic status
2 Not reported if or how many women were treated with cerclage or cervical pessary; not reported if participants/providers were blinded to test results; spontaneous preterm birth is not defined; adjusted for artificial reproductive technology and socio-economic status only; data were collected from a perinatal registry via a linkage of 3 different registries, however, only 53% second births in the perinatal registry were linked to the first matching birth
3 Adjusted for CL at 20-25 weeks' gestation, chorionicity, maternal age, BMI, smoking habit, and parity
4 Not reported if or how many women were treated with cerclage or cervical pessary; not reported if participants/providers were blinded to test results; spontaneous preterm birth is not defined
5 Adjusted for ethnicity, maternal age, smoking, chorionicity, and pregnancy following in vitro fertilization, time interval between the twin and singleton pregnancies
6 Not reported if participants/providers were blinded to test results; spontaneous preterm birth is not defined

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

See the appendix B for the economic search strategy and appendix G for the economic evidence selection flow chart for further information.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Summary of studies included in the economic evidence review

No economic studies were identified which were applicable to this review question.

Economic model

No new economic evidence was identified for this review and therefore an original model was developed for this guideline update to reflect the new clinical evidence identified. The model is summarised below with full details available in appendix J in evidence review [B2] (interventions for the prevention of spontaneous preterm birth).

The model took the form of a cost utility analysis and evaluated the following 6 screening strategies for twin pregnancies in an NHS setting:

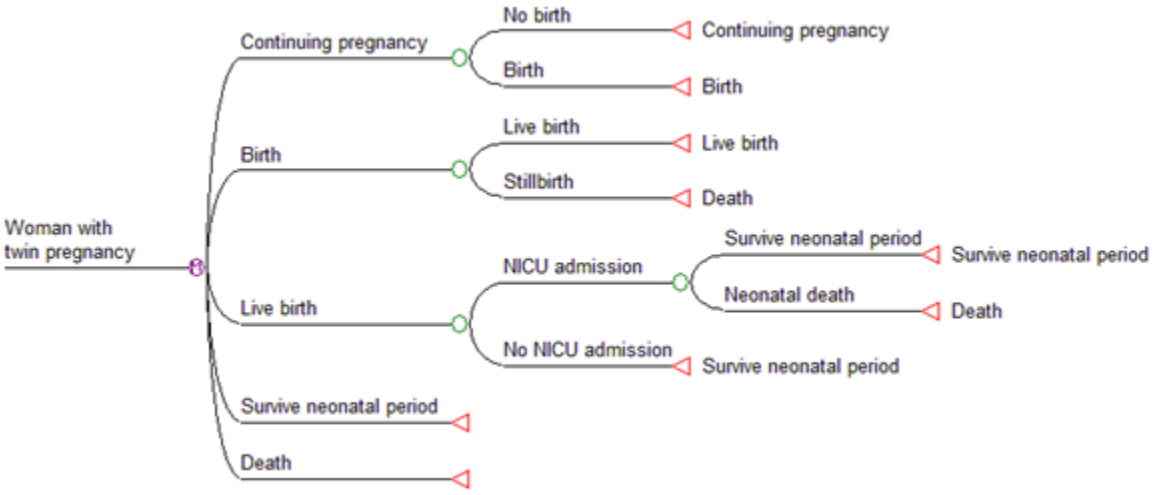
1. no screening
2. cervical length ≤ 5mm
3. cervical length ≤ 10mm
4. cervical length ≤ 15mm
5. cervical length ≤ 20mm
6. cervical length ≤ 25mm

If a pregnancy was identified as being at higher risk of spontaneous preterm birth by the screening strategy, the woman would be treated with daily vaginal progesterone until birth.

A Markov approach was used to model the pregnancy from a gestational age of 24 weeks to a maximum of 37 weeks. Pregnant women with twins enter the model in the state of

'continuing pregnancy' but for each week of gestational age they can transition to the state of 'birth'. From the 'birth' state, transitions are possible to 'live birth', and subsidiary states reflecting implications for longer term outcome and cost, or 'stillbirth'. This approach is illustrated in Figure 1 below. The transition probabilities to different states vary with gestational age.

Figure 1: Schematic to illustrate Markov approach across pregnancy and the neonatal period



In order to estimate the proportion of pregnancies that would be identified as being at higher risk of spontaneous preterm birth the model factored in a distribution of cervical length at the time of screening. In the base case analysis this was estimated from personal communication (Liem, 2018). Data from Kindinger (2016), included in this review for ultrasound screening for prediction of the risk of spontaneous preterm birth, was then used to estimate the baseline risk of spontaneous preterm birth by gestational age for twin pregnancies according to their cervical length at the time of screening. Data from an individual patient data meta-analysis (Romero 2017) was then used to modify these baseline risks for pregnancies identified by screening as being at higher risk of preterm birth and treated with vaginal progesterone, using the risk ratio reported for gestations of <28 weeks', <32 weeks' and <36 weeks'.

In order to estimate the impact of screening and intervention on health-related quality of life and "downstream" costs related to perinatal mortality and morbidity, the model included the following clinical outcomes for babies related to preterm birth:

- Stillbirth
- Neonatal death
- Post neonatal death
- Neonatal intensive care unit admission
- Cerebral palsy
- Intraventricular haemorrhage
- Respiratory distress syndrome

For each of these outcomes the analysis modelled a relationship between the risk and gestational age at birth. Depending on the outcome, costs and quality adjusted life years (QALYs) were assigned to these outcomes.

The results of the analysis suggested that it was cost effective to screen for the risk of spontaneous preterm birth using a cervical length threshold of 25 mm and to treat those pregnancies identified at being at higher risk of preterm birth. Probabilistic sensitivity analysis showed that using a screening strategy with a cervical length threshold of 25 mm as a basis for treatment had an incremental net monetary benefit (NMB) of £1,013 when compared to the no screening strategy with a 98.5% probability of being the most cost effective strategy. In the probabilistic analysis, screening using a cervical length threshold of 25 mm and treating those pregnancies identified as being at a higher risk of spontaneous preterm birth had a small incremental cost of £35 relative to no screening when savings from averted perinatal mortality and morbidity were taken into account. However, the deterministic analysis suggested that this strategy could be cost saving overall, with the reduction in costs from fewer adverse outcomes more than offsetting the costs of screening and intervention. Screening was an important driver of the costs of the intervention as recommendations would apply to all twin pregnancies and would represent a significant resource impact to the NHS in the absence of any offsetting savings from reduced perinatal mortality and morbidity.

Sensitivity analysis indicated that the cost effectiveness of screening for spontaneous preterm birth using a cervical length threshold of 25 mm and treatment of those pregnancies identified at being at higher risk of preterm birth was not particularly sensitive to changes in model input parameters. Therefore, the committee considered that a recommendation to offer daily vaginal progesterone to women whose pregnancy had been identified as being at higher risk of preterm birth would be cost effective to the NHS.

Evidence statements

Only sensitivity and specificity values are provided in the evidence statements below. When assessing the diagnostic accuracy of sensitivity and specificity the following thresholds were used: high accuracy: more than 90%; moderate accuracy: 75% to 90%; and, low accuracy: less than 75%. For prognostic measures (adjusted risk or odds ratios) numerical values are not provided and associations are described below in terms of statistical significance.

Adjusted risk or odds ratios are reported in Table 4, Table 5 and Table 6. For further details see the methods described in supplement document C.

Cervical length as a predictor for spontaneous preterm birth in twin and triplet pregnancy (diagnostic prediction, outcomes are adjusted odds ratios)

Twin pregnancy

Spontaneous preterm birth <28 weeks' gestation

Cervical length measurement at 16-17 6/7 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <28 weeks' gestation.

Cervical length measurement at 18-19 6/7 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <28 weeks' gestation.

Cervical length measurement at 20-21 6/7 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <28 weeks' gestation.

Cervical length measurement at 22-23 6/7 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <28 weeks' gestation.

Cervical length measurement at 22-31 6/7 weeks' gestation – prediction factor

One study (N=611) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <28 weeks' gestation. The same study (N=611) also showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <28 weeks' gestation when adjusted for fetal fibronectin testing. The estimate for fetal fibronectin testing was not reported, reported only that it was not statistically significant.

Spontaneous preterm birth <32 weeks' gestation

Cervical length measurement at 16-17 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 18-19 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 18-23 weeks' gestation – prediction factor

One study (N=940) with a serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 22-21 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 22-23 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 22-31+6 weeks' gestation – prediction factor

One study (N=611) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 21-23 weeks' gestation – prediction factor

One study (N=251) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <32 weeks' gestation.

Spontaneous preterm birth <34 weeks' gestation

Cervical length measurement at 20-25 weeks' gestation – prediction factor

One study (N=223) with a serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <34 weeks' gestation.

Spontaneous preterm birth <35 weeks' gestation

Cervical length measurement at 13-35 weeks' gestation – prediction factor

One study (N=561) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 16-17 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 18-19 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 18-24 weeks' gestation – prediction factor

One study (N=44) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 20-21 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was no statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 21-23 weeks' gestation – prediction factor

One study (N=251) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 22-23 weeks' gestation – prediction factor

One study (N=309) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Cervical length measurement at 22-31+6 weeks' gestation – prediction factor

One study (N=611) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation. The same study (N=611) showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation when adjusted for fetal fibronectin testing. There was no statistically

significant association between fetal fibronectin testing and spontaneous preterm birth <35 weeks' gestation when adjusted for cervical length.

Cervical length measurement at 26-28 weeks' gestation – prediction factor

One study (N=215) with a very serious risk of bias showed that there was a statistically significant association between cervical length measurement and spontaneous preterm birth <35 weeks' gestation.

Triplet pregnancy (excluding those complicated by twin-twin transfusion syndrome, treated with laser therapy, cerclage or pessary)

Spontaneous preterm birth <32 weeks' gestation

Cervical length measurement at 18-24 weeks' gestation – prediction factor

One study (N=96) with a serious risk of bias showed that there was no statistically significant association between cervical length measurement (neither for CL cut-of ≤20 mm nor for CL cut-off ≤25 mm) and spontaneous preterm birth <32 weeks' gestation.

Fetal fibronectin as a predictor for spontaneous preterm birth in twin pregnancy

Spontaneous preterm birth <28 weeks' gestation

Fetal fibronectin testing at 22-31+6 weeks' gestation – prediction factor

One study (N=611) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <28 weeks' gestation.

Fetal fibronectin testing at 22-32 weeks' gestation – prediction factor

One study (N=155) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <28 weeks' gestation.

Spontaneous preterm birth <30 weeks' gestation

Fetal fibronectin testing at 22-32 weeks' gestation – prediction factor

One study (N=155) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <30 weeks' gestation.

Spontaneous preterm birth <32 weeks' gestation

Fetal fibronectin testing at 22-31+6 weeks' gestation – prediction factor

One study (N=611) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <32 weeks' gestation.

Fetal fibronectin testing at 22-32 weeks' gestation – prediction factor

One study (N=244) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <32 weeks' gestation. Another study (N=155) with a very serious risk of bias showed that there

was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <32 weeks' gestation.

Spontaneous preterm birth <34 weeks' gestation

Fetal fibronectin testing at 22-32 weeks' gestation – prediction factor

One study (N=155) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <34 weeks' gestation.

Spontaneous preterm birth <35 weeks' gestation

Fetal fibronectin testing at 22-31+6 weeks' gestation – prediction factor

One study (N=611) with a very serious risk of bias showed that there was no statistically significant association between fetal fibronectin testing and spontaneous preterm birth <35 weeks' gestation.

Fetal fibronectin testing at 22-32 weeks' gestation – prediction factor

One study (N=155) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <35 weeks' gestation.

Spontaneous preterm birth <37 weeks' gestation

Fetal fibronectin testing at 22-32 weeks' gestation – prediction factor

One study (N=155) with a very serious risk of bias showed that there was a statistically significant association between fetal fibronectin testing and spontaneous preterm birth <37 weeks' gestation.

History or previous preterm birth as a predictor for spontaneous preterm birth in twin pregnancy

Spontaneous preterm birth at 22+0 - 29+6 weeks' gestation

One study (N=232) with a very serious risk of bias showed that there was a statistically significant association between the history of singleton preterm birth and spontaneous preterm birth at 22+0 and 29+6 weeks' gestation.

Spontaneous preterm birth at 30+0 - 33+6 weeks' gestation

One study (N=232) with a very serious risk of bias showed that there was a statistically significant association between the history of singleton preterm birth and spontaneous preterm birth at 30+0 and 33+6 weeks' gestation.

Spontaneous preterm birth at <34 weeks' gestation

One study (N=223) with a serious risk of bias showed that there was no statistically significant association between the history of preterm birth (<34 weeks' gestation) and spontaneous preterm birth <34 weeks' gestation. Another study (N=576) with a serious risk of bias showed that there was a statistically significant association between the history of singleton preterm birth and spontaneous preterm birth <34 weeks' gestation.

Spontaneous preterm birth at 34+0 - 36+6 weeks' gestation

One study (n=232) with a very serious risk of bias showed that there was a statistically significant association between the history of singleton preterm birth and spontaneous preterm birth at 34+0 and 36+6 weeks' gestation.

Spontaneous preterm birth at <37 weeks' gestation

One study (N=232) with a very serious risk of bias showed that there was a statistically significant association between the history of singleton preterm birth and spontaneous preterm birth <37 weeks' gestation. Another study (N=576) with a serious risk of bias also showed that there was a statistically significant association between the history of singleton preterm birth and spontaneous preterm birth <37 weeks' gestation.

Cervical length screening to detect spontaneous preterm birth in twin and triplet pregnancy (diagnostic accuracy, outcomes are sensitivity and specificity)

Twin pregnancy

Spontaneous preterm birth <28 weeks' gestation

Cervical length measurement at 20-24 weeks' gestation – index test

Low quality evidence from three studies (N=591) showed that the overall sensitivity and specificity for CL measurement (cut-off 20 mm) was 35% (14 to 62) and 93% (91 to 95) to detect spontaneous preterm birth <28 weeks' gestation. Very low quality evidence from three studies (N=637) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 64% (41 to 83) and 93% (91 to 95) to detect spontaneous preterm birth <28 weeks' gestation. Very low quality evidence from three studies (N=637) showed that the overall sensitivity and specificity for CL measurement (cut-off 35 mm) was 82% (60 to 95) and 66% (62 to 69) to detect spontaneous preterm birth <28 weeks' gestation.

Spontaneous preterm birth <32 weeks' gestation

Cervical length measurement at 18-23 weeks' gestation – index test

Very low quality evidence from one study (N=940) showed that the sensitivity and specificity for CL measurement (cut-off 36 mm) was 64% (52 to 75) and 63% (59 to 66) to detect spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 18 0/6 – 23 6/7 weeks' gestation – index test

Monochorionic diamniotic twin pregnancy

Moderate quality evidence from one study (N=175) showed that the sensitivity and specificity for CL measurement cut-off 5 mm was 13% (7 to 29) and 99% (98 to 100); cut-off 10 mm was 29% (19 to 39) and 98% (97 to 99); cut-off 15 mm was 42% (39 to 61) and 97% (95 to 97); and cut-off 25 mm was 59% (48 to 66) and 89% (87 to 91) in monochorionic diamniotic twin pregnancy. Low quality evidence from the same study showed that the sensitivity and specificity for CL measurement cut-off 30 mm was 70% (56 to 79) and 79% (71 to 80) in monochorionic diamniotic twin pregnancy.

Dichorionic diamniotic twin pregnancy

Moderate quality evidence from one study (N=405) showed that the sensitivity and specificity for CL measurement cut-off 5 mm was 12% (10 to 24) and 99% (98 to 100); cut-off 10 mm was 29% (23 to 33) and 98% (97 to 99); cut-off 15 mm was 40% (39 to 47) and 97% (95 to 97); and cut-off 25 mm was 57% (51 to 65) and 88% (87 to 90) in dichorionic diamniotic twin pregnancy. Low quality evidence from the same study showed that the sensitivity and

specificity for CL measurement cut-off 30 mm was 67% (62 to 76) and 77% (73 to 80) in dichorionic diamniotic twin pregnancy.

Cervical length measurement at 20-24 weeks' gestation – index test

Low quality evidence from 5 studies (N=1955) showed that the overall sensitivity and specificity for CL measurement (cut-off 20 mm) was 39% (31 to 48) and 96% (95 to 97) to detect spontaneous preterm birth <32 weeks' gestation. Low quality evidence from 6 studies (N=2039) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 54% (45 to 62) and 91% (90 to 92) to detect spontaneous preterm birth <32 weeks' gestation. Low quality evidence from 4 studies (N=1812) showed that the overall sensitivity and specificity for CL measurement (cut-off 30 mm) was 65% (56 to 74) and 78% (76 to 80) to detect spontaneous preterm birth <32 weeks' gestation. Very low quality evidence from 5 studies (N=1889) showed that the overall sensitivity and specificity for CL measurement (cut-off 35 mm) was 81% (73 to 87) and 58% (56 to 61) to detect spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement after 24 weeks' gestation – index test

Very low quality evidence from 3 studies (N=511) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 65% (45 to 81) and 76% (72 to 79) to detect spontaneous preterm birth <32 weeks' gestation.

Spontaneous preterm birth <33 weeks' gestation

Cervical length measurement at 20-24 weeks' gestation – index test

Very low quality evidence from 1 study (N=18) showed that the sensitivity and specificity for CL measurement (cut-off 35 mm) was 50% (9 to 91) and 94% (72 to 99) to detect spontaneous preterm birth <33 weeks' gestation.

Spontaneous preterm birth <34 weeks' gestation

Cervical length measurement at 20-24 weeks' gestation – index test

Low quality evidence from 5 studies (N=1760) showed that the overall sensitivity and specificity for CL measurement (cut-off 20 mm) was 29% (23 to 35) and 97% (96 to 98) to detect spontaneous preterm birth <34 weeks' gestation. Low quality evidence from 6 studies (N=1987) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 40% (38 to 46) and 93% (92 to 94) to detect spontaneous preterm birth <34 weeks' gestation. Low quality evidence from 5 studies (N=2014) showed that the overall sensitivity and specificity for CL measurement (cut-off 30 mm) was 56% (50 to 62) and 81% (79 to 83) to detect spontaneous preterm birth <34 weeks' gestation. Very low quality evidence from 6 studies (N=1884) showed that the overall sensitivity and specificity for CL measurement (cut-off 35 mm) was 79% (74 to 84) and 60% (57 to 62) to detect spontaneous preterm birth <34 weeks' gestation. Very low quality evidence from 1 study (N=193) showed that the sensitivity and specificity for CL measurement (cut-off 38 mm) was 68% (55 to 78) and 50% (42 to 58) to detect spontaneous preterm birth <34 weeks' gestation.

Cervical length measurement at 21-23 weeks' gestation – index test

Moderate quality evidence from 1 study (N=116) showed that the sensitivity and specificity for CL measurement (cut-off 35 mm) was 39% (12 to 65) and 71% (62 to 80) to detect spontaneous preterm birth <34 weeks' gestation.

Cervical length measurement at 22-24 weeks' gestation – index test

Low quality evidence from 1 study (N=434) showed that the sensitivity and specificity for CL measurement (cut-off 15 mm, cut-off 20 mm and cut-off 25 mm) was 18% (7 to 35) and 99% (97 to 100); 26% (13 to 44) and 97% (95 to 98); and 35% (20 to 54) and 92 (89 to 94) to detect spontaneous preterm birth <34 weeks' gestation, respectively.

Cervical length measurement after 24 weeks' gestation – index test

Low quality evidence from 4 studies (N=594) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 44% (34 to 53) and 81% (78 to 85) to detect spontaneous preterm birth <34 weeks' gestation. Very low quality evidence from 1 study (N=85) showed that the sensitivity and specificity for CL measurement (cut-off 35 mm) was 94% (73 to 99) and 49% (37 to 60) to detect spontaneous preterm birth <34 weeks' gestation.

Cervical length measurement at 26-28 weeks' gestation – index test

Low quality evidence from 1 study (N=116) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 54% (27 to 81) and 87% (81 to 94) to detect spontaneous preterm birth <34 weeks' gestation.

Spontaneous preterm birth <35 weeks' gestation

Cervical length measurement after 24 weeks' gestation – index test

Very low quality evidence from 1 study (N=101) showed that the sensitivity and specificity for CL measurement (cut-off 33 mm) was 68% (47 to 84) and 54% (44 to 65) to detect spontaneous preterm birth <35 weeks' gestation

Spontaneous preterm birth <37 weeks' gestation

Cervical length measurement at 20-24 weeks' gestation – index test

Low quality evidence from 4 studies (N=434) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 21% (15 to 27) and 95% (92 to 98) to detect spontaneous preterm birth <37 weeks' gestation. Low quality evidence from 2 studies (N=218) showed that the overall sensitivity and specificity for CL measurement (cut-off 30 mm) was 29% (18 to 43) and 91% (86 to 95) to detect spontaneous preterm birth <37 weeks' gestation. Low quality evidence from 2 studies (N=134) showed that the overall sensitivity and specificity for CL measurement (cut-off 35 mm) was 56% (43 to 68) and 63% (50 to 74) to detect spontaneous preterm birth <37 weeks' gestation.

Cervical length measurement after 24 weeks' gestation – index test

Low quality evidence from 2 studies (N=276) showed that the overall sensitivity and specificity for CL measurement (cut-off 25 mm) was 43% (35 to 51) and 77% (68 to 84) to detect spontaneous preterm birth <37 weeks' gestation. Very low quality evidence from 1 study (N=101) showed that the sensitivity and specificity for CL measurement (cut-off 33 mm) was 69% (53 to 82) and 60% (48 to 71) to detect spontaneous preterm birth <37 weeks' gestation.

Triplet pregnancy

Spontaneous preterm birth <28 weeks' gestation

Cervical length measurement at 18-24 weeks' gestation – index test

Low quality evidence from the 1 study (N=96) showed that the sensitivity and specificity for CL measurement (cut-off 15 mm, cut-off 20 mm, cut-off 25 mm) was 11% (0 to 48) and 95% (87 to 99), 22% (3 to 60) and 93% (86 to 97), and 33% (8 to 70) and 90% (81 to 95) to detect spontaneous preterm birth <28 weeks' gestation, respectively.

Cervical length measurement at 15-20 weeks' gestation – index test

Very low quality evidence from the 1 study (N=50) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 5% (16 to 84) and 100% (92 to 100) to detect spontaneous preterm birth <28 weeks' gestation.

Cervical length measurement at 21-24 weeks' gestation – index test

Very low quality evidence from the 1 study (N=50) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 86% (42 to 100) and 79% (64 to 90) to detect spontaneous preterm birth <28 weeks' gestation.

Cervical length measurement at 25-28 weeks' gestation – index test

Very low quality evidence from the 1 study (N=46) showed that the sensitivity and specificity for CL measurement (cut-off 20 mm) was 100% (40 to 100) and 57% (41 to 72) to detect spontaneous preterm birth <28 weeks' gestation.

Spontaneous preterm birth <30 weeks' gestation

Cervical length measurement at 18-24 weeks' gestation – index test

Low quality evidence from 1 study (N=96) showed that the sensitivity and specificity for CL measurement (cut-off 15 mm, cut-off 20 mm, cut-off 25 mm) was 17% (4 to 41) and 97% (91 to 100), 22% (6 to 48) and 95% (88 to 98), and 28% (10 to 53) and 91% (82 to 96) to detect spontaneous preterm birth <30 weeks' gestation to detect spontaneous preterm birth <30 weeks' gestation, respectively.

Cervical length measurement at 15-20 weeks' gestation – index test

Low quality evidence from the 1 study (N=49) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 36% (11 to 69) and 100% (91 to 100) to detect spontaneous preterm birth <30 weeks' gestation.

Cervical length measurement at 21-24 weeks' gestation – index test

Very low quality evidence from the 1 study (N=49) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 70% (35 to 93) and 82% (66 to 92) to detect spontaneous preterm birth <30 weeks' gestation.

Cervical length measurement at 25-28 weeks' gestation – index test

Very low quality evidence from the 1 study (N=46) showed that the sensitivity and specificity for CL measurement (cut-off 20 mm) was 100% (59 to 100) and 62% (45 to 77) to detect spontaneous preterm birth <30 weeks' gestation.

Spontaneous preterm birth <32 weeks' gestation

Cervical length measurement at 18-24 weeks' gestation – index test

Low quality evidence from 1 study (N=96) showed that the sensitivity and specificity for CL measurement (cut-off 15 mm, cut-off 20 mm, cut-off 25 mm) was 9% (2 to 24) and 97% (89

to 97), 21% (9 to 38) and 97% (89 to 100), and 27% (13 to 44) and 95% (87 to 99) to detect spontaneous preterm birth <32 weeks' gestation, respectively.

Cervical length measurement at 15-20 weeks' gestation – index test

Low quality evidence from the 1 study (N=47) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 25% (7 to 52) and 100% (89 to 100) to detect spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 21-24 weeks' gestation – index test

Very low quality evidence from the 1 study (N=47) showed that the sensitivity and specificity for CL measurement (cut-off 25 mm) was 60% (32 to 84) and 84% (67 to 95) to detect spontaneous preterm birth <32 weeks' gestation.

Cervical length measurement at 25-28 weeks' gestation – index test

Very low quality evidence from the 1 study (N=44) showed that the sensitivity and specificity for CL measurement (cut-off 20 mm) was 83% (52 to 98) and 66% (47 to 81) to detect spontaneous preterm birth <32 weeks' gestation.

Fetal fibronectin screening to detect spontaneous preterm birth in twin and triplet pregnancy

Twin pregnancy

Spontaneous preterm birth <32 weeks' gestation

Fetal fibronectin testing at 22-34 weeks' gestation – index test

Very low quality evidence from 2 studies (N=302) showed that the overall sensitivity and specificity for fetal fibronectin testing was 33% (14 to 60) and 94% (85 to 97) to detect spontaneous preterm birth <32 weeks' gestation.

Spontaneous preterm birth <34 weeks' gestation

Fetal fibronectin testing at 22-34 weeks' gestation – index test

Very low quality evidence from 6 studies (N=576) showed that the overall sensitivity and specificity for fetal fibronectin testing was 39% (29 to 51) and 80% (74 to 86) to detect spontaneous preterm birth <34 weeks' gestation.

Spontaneous preterm birth <37 weeks' gestation

Fetal fibronectin testing at 22-34 weeks' gestation – index test

Very low quality evidence from 5 studies (N=520) showed that the overall sensitivity and specificity for fetal fibronectin testing was 33% (25 to 45) and 87% (80 to 94) to detect spontaneous preterm birth <37 weeks' gestation.

Triplet pregnancy

Spontaneous preterm birth <28 weeks' gestation

Fetal fibronectin testing at 22-32 weeks' gestation – index test

Very low quality evidence from 1 study (N=56) showed that the sensitivity and specificity for fetal fibronectin testing was 75% (19 to 99) and 83% (70 to 92) to detect spontaneous preterm birth <28 weeks' gestation.

Spontaneous preterm birth <30 weeks' gestation

Fetal fibronectin testing at 22-32 weeks' gestation – index test

Very low quality evidence from 1 study (N=56) showed that the sensitivity and specificity for fetal fibronectin testing was 75% (35 to 97) and 85% (72 to 94) to detect spontaneous preterm birth <30 weeks' gestation.

Spontaneous preterm birth <32 weeks' gestation

Fetal fibronectin testing at 22-32 weeks' gestation – index test

Very low quality evidence from 1 study (N=56) showed that the sensitivity and specificity for fetal fibronectin testing was 60% (32 to 84) and 85% (71 to 94) to detect spontaneous preterm birth <32 weeks' gestation.

Economic evidence

Evidence from the guideline economic analysis suggested that screening for spontaneous preterm birth using a cervical length threshold of 25 mm and daily vaginal progesterone for women whose pregnancies were identified as being at higher risk of spontaneous birth was cost effective compared to screening thresholds using a shorter cervical length and to no screening, with an incremental NMB of £952 and a 98.5% probability of being the most cost effective strategy. The economic analysis is directly applicable to the NICE decision-making context, and is characterised by minor limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised the diagnostic accuracy measure of sensitivity as a critical outcome because it is important to identify women with twin or triplet pregnancy who are at risk of spontaneous preterm birth. The committee also discussed the usefulness of cervical length, fetal fibronectin, ambulatory uterine activity monitoring and prior maternal risk factors as predictors for spontaneous preterm birth. This was also considered helpful in decision making because a good predictive ability (for instance related to maternal risk factors) may also link to an associated management strategy.

The quality of the evidence

Studies that reported on predictors of spontaneous preterm birth were rated as having very serious and some as having serious risk of bias using the QUIPS checklist. This was mainly due to the uncertainty around the blinding of participants and/or health professionals to the test results.

The quality of the diagnostic accuracy of test results was assessed for the whole evidence base related to each index test using a modified GRADE approach (for a full description of the methods see supplementary document C).

For the diagnostic accuracy measures the evidence was rated as very low to moderate quality. This was mainly due to risk of bias in the individual studies which often related to lack of clarity about whether participants and/or health professionals were blinded to the test results. In addition, there was often imprecision in the evidence base with wide confidence intervals indicating uncertainty in the estimate of the accuracy measurement. The committee took the imprecision into consideration.

Also, some of the studies were relatively small which meant that there was a lot of uncertainty around the estimates which led to the evidence being downgraded.

Benefits and harms

Information for the woman

As preterm birth is a common complication in multiple pregnancies and the risk and severity of neonatal mortality and morbidity are directly related to the gestational age at birth, the committee discussed and agreed that the focus of screening should be on early preterm birth. The committee were in agreement that the risk of preterm birth needs to be explained to the woman so that she understands the importance of screening for preterm birth to enable informed shared decision making (see also for example evidence report D related to timing of birth). Based on experience and expertise they also agreed that the woman should be informed about an increased risk of spontaneous preterm birth if she has other risk factors and highlighted previous spontaneous preterm birth as an example because there was evidence that history of preterm birth increased the risk of spontaneous preterm birth. This would then balance out the potential reservations that a woman may have about acceptability of the transvaginal scan to the woman and discomfort with the procedure. The committee acknowledged that this would also link to the timing of birth (see evidence report D) and that a discussion should take into account these recommendations. The woman would therefore be aware of the risk of preterm birth but also the timing of birth as pregnancy continues.

Confidence in the evidence

After reviewing the evidence, the committee acknowledged the heterogeneity of the published studies, in particular the gestational age at the screening assessment, the cut-off of the screening parameter measured and the gestational age cut-off used to define preterm birth. Also, despite the fact that the committee agreed to prioritise sensitivity as a prediction accuracy measure, it was highlighted while assessing the evidence that the sensitivity is correlated with the chosen cut-off for specificity, which partially explains the heterogeneity in the published literature. Furthermore, some studies have reported the prediction accuracy for the findings of a short cervix (using various cut-offs), while others analysed the prediction accuracy using the cervical length as a continuous parameter. They therefore used only some of the evidence as well as their experience and expertise to make recommendations.

Fetal fibronectin and uterine activity monitoring

The committee were not confident in the findings related to fetal fibronectin as the evidence was of very low quality. They were aware that there had been some evidence (as reported in the previous guideline) suggesting that the ability of fetal fibronectin to identify women who were at a significantly higher risk of preterm birth was improved if used in conjunction with cervical length. However, the new evidence did not convince the committee since it was of very low quality. They therefore decided that fetal fibronectin should not be used as a single indicator to screen for preterm birth. There was no new evidence identified that reported on diagnostic accuracy or the usefulness of ambulatory uterine activity monitoring to predict spontaneous preterm birth in twin or triplet pregnancy. The committee was aware that there was evidence in the previous guideline and that ambulatory uterine activity monitoring was not an accurate measure to predict preterm birth, therefore they agreed not to recommend this. The committee therefore retained the existing 2011 recommendations that fetal

fibronectin testing and home uterine activity monitoring should not be used to predict the risk of spontaneous preterm birth because there was no new evidence identified suggesting they were accurate.

Why the committee did not recommend cervical length screening

The evidence in twin pregnancy suggests that the cervical length is a moderate predictor of early onset spontaneous preterm birth. The committee discussed the negative association between cervical length and the risk of preterm birth in twin and triplet pregnancies. Following the appraisal of the existing evidence, the committee supported the final conclusion of recommending cervical length as a predictor for preterm birth in twin pregnancies. Establishing that a woman is at risk of preterm birth allows an intervention to be offered, and there is some evidence that vaginal progesterone may reduce this risk in women with a twin pregnancy. However, the committee was also aware that new evidence would be emerging about the use of progesterone in subgroups of women with a short cervix that could change their conclusions about its effectiveness. This uncertainty meant the committee could not recommend vaginal progesterone to prevent preterm birth. Because of this, the committee also decided they could not recommend cervical length screening in the absence of an effective intervention to offer women with a higher risk of preterm birth. The committee noted that this was in line with the conclusions reached by Public Health England about the use of screening. In their published 'Criteria for appraising the viability, effectiveness and appropriateness of a screening programme' point 9 states that '*There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.*'

Cost effectiveness and resource use

An original model was developed for the guideline which jointly assessed the cost effectiveness of both screening to predict the risk of spontaneous preterm birth, undertaken by measurement of cervical length using transvaginal ultrasound, and intervention with micronised vaginal progesterone to delay or prevent preterm birth. The committee considered this analysis when making recommendations on screening to predict the risk of preterm and the use of vaginal interventions to prevent or delay spontaneous preterm birth.

The analysis demonstrated that it was cost effective to screen using a cervical length threshold of 25 mm when compared with other cervical length thresholds as it identified more pregnancies that would benefit from treatment without incurring any additional cost of identification when compared to lower cervical length thresholds. However, screening was only cost effective relative to no screening because the benefits of vaginal progesterone in preventing spontaneous preterm birth were large relative to the combined costs of screening and intervention, especially in the context of "downstream" savings from reduced perinatal mortality and morbidity. The results of the economic analysis suggested that screening to predict the risk of spontaneous preterm birth using a cervical length threshold of 25 mm, measured by transvaginal ultrasound, and a daily dose of micronised vaginal progesterone for women whose pregnancies were identified as being at higher risk of preterm birth would represent a cost effective use of NHS resources. However, the committee was aware of new evidence that would be emerging on the use of progesterone that could alter their conclusions about its effectiveness. Given this uncertainty with respect to treatment effectiveness, the committee decided they could not change current practice and recommend cervical length screening.

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Appendices

Appendix A – Review protocols

2.1: Review protocol – diagnostic prediction component for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Table 7: Review protocol for spontaneous preterm birth prediction

ID	Field (based on PRISMA-P	Content
I	Review question	What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?
II	Type of review question	Diagnostic prediction
III	Objective of the review	To determine if screening methods performed routinely predict the risk of spontaneous preterm birth in women who are asymptomatic of labour who have a twin or triplet pregnancy
IV	Eligibility criteria – population	Monochorionic/dichorionic twin or triplet pregnancies identified by the 11^{+0} – 13^{+6} week ultrasound scan (not symptomatic, not in labour). Setting: Secondary or tertiary care centres
V	Eligibility criteria – prognostic factor(s)	**Screening methods** • Imaging: ○ cervical length measurement by transvaginal ultrasound (diagnostic predictor: shortened cervical length). • Biochemical testing: ○ fibronectin test (diagnostic predictor: positive test) • Clinical electronic monitoring: ○ ambulatory uterine activity monitoring (diagnostic predictor: increased contraction frequency) • Prior maternal risk factors as diagnostic predictors for spontaneous preterm birth: ○ previous obstetric history - previous preterm labour (<37 completed weeks) - cervical surgery - midtrimester loss (<24 weeks) The above tests will be considered in isolation or both if they were used in sequence, for example first cervical length measurement and then fetal fibronectin testing.
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	Spontaneous preterm birth: • ≤36^{+0} gestational weeks for monochorionic twins

		• ≤37+^{0} gestational weeks for dichorionic twins • ≤36+^{0} gestational weeks for triplets
VII	Outcomes and prioritisation	Predictive value of screening tests to predict spontaneous preterm birth: • adjusted odds ratios, relative risks, hazard ratios. Only estimates derived from multivariate analysis will be included
VIII	Eligibility criteria – study design	Systematic reviews of studies reporting predictive value of screening methods. Individual cohort studies reporting predictive value of screening methods. Prospective cohort studies will be prioritised if: • insufficient data are available from prospective cohort studies, then retrospective cohort studies will be considered • no prospective or retrospective cohort study data is identified, case control studies may be considered for inclusion Conference abstracts will not be considered
IX	Other inclusion exclusion criteria	Exclude: • women with a quadruplet or higher-order pregnancy as per scope • studies that do not report results specifically for twin and/or triplet pregnancies • studies that do not report adjusted estimates • women with known serious fetal anomaly • women in labour or requiring imminent birth • studies where 95% CIs for point estimates are not presented or where 95% CI for point estimates cannot be calculated
X	Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • twin pregnancies • triplet pregnancies 1. Gestational age at screening • <20 weeks • 20–24 weeks 2. Gestational age at birth • 24^{+1} to 27^{+6} weeks • 28^{+0} to 33^{+6} weeks • 34^{+0} to 36^{+6} weeks Only estimates from multivariable regression analysis (adjusted for any confounders) will be included.

		Important confounders for the prediction of spontaneous preterm birth outcome: • maternal age • ethnicity • parity • previous gynaecological surgery • previous obstetric history Estimates derived from multivariate analysis that do not adjust for the factors above will be included and the limitation noted
XI	Selection process – duplicate screening/selection/analysis	This review question was selected as a high priority for health economic analysis and so will be subject formal dual sifting of 10% of search results. Discrepancies will be discussed between reviewers with resolution of any disputes by discussion with the senior reviewer. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
XII	Data management (software)	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists.
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Search limits: • limit to English language • limit to human-only studies • no limit on study design • limit year of publication to 2010 (date of previous guideline searches) Supplementary search techniques: no supplementary search techniques will be used.
XIV	Identify if an update	This is an update of a review performed in 2011. Question: What is the optimal screening programme to predict the risks of spontaneous preterm delivery? Chapter 8 of full guideline Recommendations **1.5 Preterm birth** **1.5.1 Predicting the risk of preterm birth**

		1.5.1.1 Be aware that women with twin pregnancies have a higher risk of spontaneous preterm birth if they have had a spontaneous preterm birth in a previous singleton pregnancy. 1.5.1.2 Do not use fetal fibronectin testing alone to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. 1.5.1.3 Do not use home uterine activity monitoring to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. 1.5.1.4 Do not use cervical length (with or without fetal fibronectin) routinely to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. **Research recommendation** RR 12 Which clinical factors or laboratory tests are accurate predictors of spontaneous preterm birth in twin and triplet pregnancies?
XV	Author contacts	Developer: National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
XVI	Highlight if amendment to previous protocol	For details please see the guideline methods section and section 4.5 of Developing NICE guidelines: the manual 2014 For details please see appendix B
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	Risk of bias of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews • QUIPS for cohort studies or case control studies reporting prognostic outcomes For details please see section 6.2 of Developing NICE guidelines: the manual 2014. 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working

		group http://www.gradeworkinggroup.org/ or any adaptation of this will not be used to evaluate risk of bias across all available evidence for each outcome
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
XXII	Methods for analysis – combining studies and exploring (in)consistency	A full description of this is provided in the methods in supplementary material C.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the methods chapter of the full guideline and section 6.2 of Developing NICE guidelines: the manual 2014
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Anthony Pearson in line with section 3 Developing NICE guidelines: the manual 2014. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. A full description of this is provided in the methods in supplementary material C.
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXIX	Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
XXX	PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register for Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; QUIPS: Quality In Prognosis Studies tool

2.1: Review protocol – prediction component for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Table 8: Review protocol for ultrasound screening for spontaneous preterm birth

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?
II	Type of review question	Diagnostic accuracy
III	Objective of the review	To determine the optimal screening programme (screening methods and their frequency) performed routinely to predict the risk of spontaneous preterm birth in twin and triplet pregnancy
IV	Eligibility criteria – population/disease/condition/issue/domain	Twin or triplet pregnancies identified by the 11^{+0} – 13^{+6} week ultrasound scan (not symptomatic, not in labour). Monochorionic/dichorionic twin and all triplet pregnancies Setting: Secondary or tertiary care centres

V	Eligibility criteria – intervention(s)/exposure(s)/ prognostic factor(s)	**Screening methods:**
		• cervical length measurement
		• fibronectin test
		• ambulatory uterine activity monitoring
		• previous obstetric history:
		  ○ previous preterm labour (<37 completed weeks)
		  ○ cervical surgery
		  ○ midtrimester loss (<24 weeks)
		
		The above tests will be considered in isolation or both if they were used in sequence, for example first cervical length measurement and then fetal fibronectin testing

VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Reference standard** **Spontaneous preterm birth:** • ≤36^{+0} gestational weeks for monochorionic twins • ≤37^{+0} gestational weeks for dichorionic twins • ≤36^{+0} gestational weeks for triplets
VII	Outcomes and prioritisation	**Diagnostic value of screening tests** **Critical:** • sensitivity • specificity
VIII	Eligibility criteria – study design	Systematic reviews of diagnostic accuracy studies of screening strategies Individual diagnostic accuracy studies including:

ID	Field (based on PRISMA-P)	Content
		• cross-sectional studies • cohort studies Prospective cohort studies will be prioritised over retrospective If insufficient data are available from prospective cohort studies, then retrospective cohort studies will be considered Conference abstracts will not be considered
IX	Other inclusion exclusion criteria	Exclude: • women with a quadruplet or higher-order pregnancy as per scope • studies that do not report results specifically for twin and/or triplet pregnancies • women with known serious fetal anomaly • women in labour or requiring imminent birth • studies where 95% CIs for diagnostic accuracy estimates are not presented or where 2 x 2 contingency data are not presented or cannot be calculated
X	Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • twin pregnancies • triplet pregnancies 1. Gestational age at screening • <20 weeks • 20–24 weeks 2. Gestational age at birth • 24^{+1} to 27^{+6} weeks • 28^{+0} to 33^{+6} weeks • 34^{+0} to 36^{+6} weeks
XI	Selection process – duplicate screening/selection/analysis	This review question was selected as a high priority for health economic analysis and so will be subject formal dual sifting of 10% of search results. Discrepancies will be discussed between reviewers with resolution of any disputes by discussion with the senior reviewer. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of

ID	Field (based on PRISMA-P)	Content
		disputes will be by discussion between the senior reviewer, Topic Advisor and Chair
XII	Data management (software)	Meta-analyses will be performed using Cochrane Review Manager (RevMan5) and WinBUGS if available data permit A modified 'GRADE' method will be used to assess the quality of evidence for each index test. This will be described in the separate methods chapter for the guideline NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Search limits: • limit to English language • limit to human-only studies • no limit on study design • limit year of publication to 2010 (date of previous guideline searches) Supplementary search techniques: no supplementary search techniques will be used
XIV	Identify if an update	This is an update of a review performed in 2011 Question: What is the optimal screening programme to predict the risks of spontaneous preterm delivery? Chapter 8 of full guideline Recommendations **1.5 Preterm birth** **1.5.1 Predicting the risk of preterm birth** 1.5.1.1 Be aware that women with twin pregnancies have a higher risk of spontaneous preterm birth if they have had a spontaneous preterm birth in a previous singleton pregnancy. 1.5.1.2 Do not use fetal fibronectin testing alone to predict the risk of spontaneous preterm birth in twin or triplet pregnancies.

ID	Field (based on PRISMA-P)	Content
		1.5.1.3 Do not use home uterine activity monitoring to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. 1.5.1.4 Do not use cervical length (with or without fetal fibronectin) routinely to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. **Research recommendation** RR 12 Which clinical factors or laboratory tests are accurate predictors of spontaneous preterm birth in twin and triplet pregnancies?
XV	Author contacts	Developer: National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
XVI	Highlight if amendment to previous protocol	For details please see the guideline methods section and section 4.5 of Developing NICE guidelines: the manual 2014
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables)
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables)
XX	Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews • QUADAS-II for cross-sectional or cohort studies reporting diagnostic accuracy outcomes For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014

ID	Field (based on PRISMA-P)	Content
XXII	Methods for analysis – combining studies and exploring (in)consistency	A full description of this is provided in the methods in supplementary material C
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
XXIV	Assessment of confidence in cumulative evidence	For details please see the methods chapter of the guideline and sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the guideline
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Anthony Pearson in line with section 3 of Developing NICE guidelines: the manual 2014 Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. A full description of this is provided in the methods in supplementary material C
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXIX	Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
XXX	PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register for Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; QUADAS: Quality Assessment of Diagnostic Accuracy Studies

Appendix B – Literature search strategies

Literature search for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Clinical Searches

Date of initial search: 27/02/2018

Database(s): Embase 1980 to 2018 Week 08, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 06/09/2018

Database(s): Embase 1980 to 2018 Week 36, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Pregnancy, Multiple/ use ppez
2	exp multiple pregnancy/ use emez
3	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or monochorionic* or dichorionic* or trichorionic*).tw.
5	or/1-4
6	Cervical Length Measurement/ use ppez
7	cervical length measurement/ use emez
8	6 or 7
9	Cervix Uteri/ use ppez
10	uterine cervix/ use emez
11	9 or 10
12	Ultrasonography, Prenatal/ use ppez
13	exp fetus echography/ use emez
14	Ultrasonography/ use ppez
15	Echography/ use emez
16	(ultraso* or sonogra* or echogra* or doppler*).tw.
17	or/12-16
18	11 and 17
19	Cervix Uteri/dg use ppez
20	uterine cervix/di use emez
21	(((cervical or cervix or uterocervi*) adj2 (length or measur*)) or clm).tw.
22	Fibronectins/ use ppez
23	Fibronectin/ use emez
24	((foetal or fetal or foetus* or fetus*) adj2 fibronectin*).tw.
25	(fibronectin* adj5 (test* or analy* or monitor* or screen* or assay* or evaluat*)).tw.
26	Uterine Monitoring/ use ppez
27	fetus monitoring/ use emez

#	Searches
28	uterine activity monitoring/ use emez
29	((uterine or uterus) adj5 (activity adj5 monitor*)).tw.
30	exp Obstetric Labor, Premature/ use ppez
31	premature labor/ use emez
32	((history or previous or prior) adj3 (obstetric* or prematur* or preterm or pre?term or miscarri* or stillbirth* or stillborn*)).tw.
33	((history or previous or prior) adj2 ((cervix or cervical) adj2 (surgery or surgical))).tw.
34	Prenatal Care/ use ppez
35	prenatal care/ use emez
36	((additional or extra or increas* or number or frequency or more or schedule* or routine) adj5 ((visit* or care or contact*) adj2 (antenatal or prenatal))).tw.
37	or/8,18-36
38	5 and 37
39	limit 38 to (english language and yr="2010 -Current")
40	Letter/ use ppez
41	letter.pt. or letter/ use emez
42	note.pt.
43	editorial.pt.
44	Editorial/ use ppez
45	News/ use ppez
46	exp Historical Article/ use ppez
47	Anecdotes as Topic/ use ppez
48	Comment/ use ppez
49	Case Report/ use ppez
50	case report/ or case study/ use emez
51	(letter or comment*).ti.
52	or/40-51
53	randomized controlled trial/ use ppez
54	randomized controlled trial/ use emez
55	random*.ti,ab.
56	or/53-55
57	52 not 56
58	animals/ not humans/ use ppez
59	animal/ not human/ use emez
60	nonhuman/ use emez
61	exp Animals, Laboratory/ use ppez
62	exp Animal Experimentation/ use ppez
63	exp Animal Experiment/ use emez
64	exp Experimental Animal/ use emez
65	exp Models, Animal/ use ppez
66	animal model/ use emez
67	exp Rodentia/ use ppez
68	exp Rodent/ use emez
69	(rat or rats or mouse or mice).ti.
70	or/57-69
71	39 not 70
72	remove duplicates from 71

Date of initial search: 27/02/2018

Database(s): the Cochrane Library, issue 2 of 12, February 2018

Date of updated search: 06/09/2018

Database(s): the Cochrane Library, issue 9 of 12, September, 2018

ID	Search
#1	MeSH descriptor: [Pregnancy, Multiple] explode all trees
#2	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) near/3 (birth* or pregnan* or gestation* or foetus* or foetal or fetus* or fetal))
#3	(chorionicity or monochorionic* or dichorionic* or trichorionic*)
#4	{or #1-#3}
#5	MeSH descriptor: [Cervical Length Measurement] this term only
#6	MeSH descriptor: [Cervix Uteri] this term only
#7	MeSH descriptor: [Ultrasonography, Prenatal] explode all trees
#8	MeSH descriptor: [Ultrasonography] this term only
#9	(ultraso* or sonogra* or echogra* or doppler*)
#10	{or #7-#9}
#11	#6 and #10
#12	MeSH descriptor: [Cervix Uteri] this term only and with qualifier(s): [Diagnostic imaging - DG]
#13	(((cervical or cervix or uterocervi*) near/2 (length or measur*)) or clm)
#14	MeSH descriptor: [Fibronectins] this term only
#15	((foetal or fetal or foetus* or fetus*) near/2 fibronectin*)
#16	(fibronectin* near/5 (test* or analy* or monitor* or screen* or assay* or evaluat*))
#17	MeSH descriptor: [Uterine Monitoring] this term only
#18	((uterine or uterus) near/5 (activity near/5 monitor*))
#19	MeSH descriptor: [Obstetric Labor, Premature] explode all trees
#20	((history or previous or prior) near/3 (obstetric* or prematur* or preterm or pre-term or miscarri* or stillbirth* or stillborn*))
#21	((history or previous or prior) near/2 ((cervix or cervical) near/2 (surgery or surgical)))
#22	MeSH descriptor: [Prenatal Care] this term only
#23	((additional or extra or increas* or number or frequency or more or schedule* or routine) near/5 ((visit* or care or contact*) near/2 (antenatal or prenatal)))
#24	{or #5, #11-#23}
#25	#4 and #24 Publication Year from 2010 to 2018

Health economics searches

For the Cochrane Library, see above

Date of initial search: 27/02/2018

Database(s): Embase 1980 to 2018 Week 08, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 06/09/2018

Database(s): Embase 1980 to 2018 Week 36, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Pregnancy, Multiple/ use ppez
2	exp multiple pregnancy/ use emez
3	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or monochorionic* or dichorionic* or trichorionic*).tw.
5	or/1-4
6	Cervical Length Measurement/ use ppez
7	cervical length measurement/ use emez
8	6 or 7
9	Cervix Uteri/ use ppez
10	uterine cervix/ use emez
11	9 or 10
12	Ultrasonography, Prenatal/ use ppez
13	exp fetus echography/ use emez
14	Ultrasonography/ use ppez
15	Echography/ use emez
16	(ultraso* or sonogra* or echogra* or doppler*).tw.
17	or/12-16
18	11 and 17
19	Cervix Uteri/dg use ppez
20	uterine cervix/di use emez
21	(((cervical or cervix or uterocervi*) adj2 (length or measur*)) or clm).tw.
22	Fibronectins/ use ppez
23	Fibronectin/ use emez
24	((foetal or fetal or foetus* or fetus*) adj2 fibronectin*).tw.
25	(fibronectin* adj5 (test* or analy* or monitor* or screen* or assay* or evaluat*)).tw.
26	Uterine Monitoring/ use ppez
27	fetus monitoring/ use emez
28	uterine activity monitoring/ use emez
29	((uterine or uterus) adj5 (activity adj5 monitor*)).tw.
30	exp Obstetric Labor, Premature/ use ppez
31	premature labor/ use emez

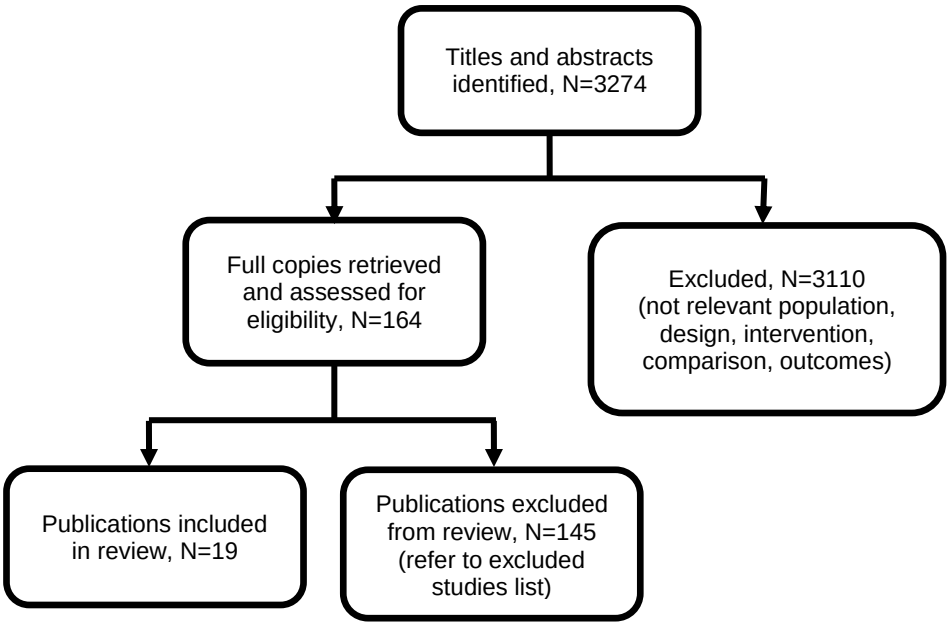
#	Searches
32	((history or previous or prior) adj3 (obstetric* or prematur* or preterm or pre?term or miscarri* or stillbirth* or stillborn*)).tw.
33	((history or previous or prior) adj2 ((cervix or cervical) adj2 (surgery or surgical))).tw.
34	Prenatal Care/ use ppez
35	prenatal care/ use emez
36	((additional or extra or increas* or number or frequency or more or schedule* or routine) adj5 ((visit* or care or contact*) adj2 (antenatal or prenatal))).tw.
37	or/8,18-36
38	5 and 37
39	limit 38 to (english language and yr="2010 -Current")
40	Letter/ use ppez
41	letter.pt. or letter/ use emez
42	note.pt.
43	editorial.pt.
44	Editorial/ use ppez
45	News/ use ppez
46	exp Historical Article/ use ppez
47	Anecdotes as Topic/ use ppez
48	Comment/ use ppez
49	Case Report/ use ppez
50	case report/ or case study/ use emez
51	(letter or comment*).ti.
52	or/40-51
53	randomized controlled trial/ use ppez
54	randomized controlled trial/ use emez
55	random*.ti,ab.
56	or/53-55
57	52 not 56
58	animals/ not humans/ use ppez
59	animal/ not human/ use emez
60	nonhuman/ use emez
61	exp Animals, Laboratory/ use ppez
62	exp Animal Experimentation/ use ppez
63	exp Animal Experiment/ use emez
64	exp Experimental Animal/ use emez
65	exp Models, Animal/ use ppez
66	animal model/ use emez
67	exp Rodentia/ use ppez
68	exp Rodent/ use emez
69	(rat or rats or mouse or mice).ti.
70	or/57-69
71	39 not 70
72	Economics/
73	Value of life/
74	exp "Costs and Cost Analysis"/
75	exp Economics, Hospital/
76	exp Economics, Medical/

#	Searches
77	Economics, Nursing/
78	Economics, Pharmaceutical/
79	exp "Fees and Charges"/
80	exp Budgets/
81	(or/72-80) use ppez
82	health economics/
83	exp economic evaluation/
84	exp health care cost/
85	exp fee/
86	budget/
87	funding/
88	(or/82-87) use emez
89	budget*.ti,ab.
90	cost*.ti.
91	(economic* or pharmaco?economic*).ti.
92	(price* or pricing*).ti,ab.
93	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
94	(financ* or fee or fees).ti,ab.
95	(value adj2 (money or monetary)).ti,ab.
96	or/89-94
97	81 or 88 or 96
98	71 and 97
99	remove duplicates from 98

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Figure 2: Flow diagram of clinical article selection for the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Conde-Agudelo, A, Romero, R, Hassan, S. S, Yeo, L., Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 203, 128.e1-12, 2010 **Ref Id** 794614 **Country/ies where the study was carried out** USA **Study type** Systematic review	**Sample size** N=3,213 asymptomatic women (16 studies, but only 11 studies were included in meta-analyses, the remaining ones could not be included because of the CL cut-off values used and outcome measures evaluated) Goldenberg (1996): N=147 Imseis (1997): N=85 Wennerholm (1997): N=101 Grisaru-Granovsky (1998): N=38 Yang (2000): N=65 Guzman (2000): N=131	**Tests** **Index test:** Transvaginal sonographic CL **Reference standard:** Spontaneous preterm birth at <37, <34, <32, and <28 weeks' gestation	**Methods** Gestational age at testing grouped as: <20, 20 to 24, and >24 weeks' gestation. Studies reporting spontaneous preterm birth before 35 weeks' gestation were included in the group of studies with spontaneous preterm birth before 34 weeks' gestation in the data synthesis because of the relatively similar neonatal outcomes. Studies reporting spontaneous preterm birth before 36 weeks' gestation were considered with those reporting spontaneous preterm birth before 37 weeks' gestation.	**Results** **Pooled estimates for CL in predicting spontaneous preterm birth - number of studies/sample size (N/n), sensitivity (%), specificity (%) and 95% CIs** Testing at 20 to 24 weeks' gestation Preterm birth <28 weeks CL 20mm: 3/591 Sensitivity: 35 (14 to 62) Specificity: 93 (91 to 95) CL 25mm: 3/637 Sensitivity: 64 (41 to 83) Specificity: 93 (91 to 95) CL 30mm: 3/637 Sensitivity: 82 (60 to 95) Specificity: 66 (62 to 69) Preterm birth <32 weeks CL 20mm: 5/1,955 Sensitivity: 39 (31 to 48) Specificity: 96 (95 to 97)	**Limitations** **AMSTAR** Did the research questions and inclusion criteria for the review include the components of PICO? Yes Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes Did the review authors explain their selection of the study designs for inclusion in the review? Yes Did the review authors use a comprehensive literature search strategy? Yes (5 databases,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To assess the accuracy of transvaginal sonographic CL in predicting spontaneous preterm birth in women with twin pregnancies. **Study dates** Databases were searched from 1966 to November 2009. Included studies were published between 1996 and 2009. **Source of funding** Supported by the Perinatology Research Branch: Division of Intramural Research of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes	Soriano (2002): N=44 Vayssiere (2002): N=251 Gibson (2004): N=91 Sperling (2005): N=383 Fait (2005): N=18 Arabin (2006): N=153 To (2006): N=1,135 Klein (2008): N=223 Aboulghar (2009): N=193 Fox (2009): N=155 **Characteristics** <u>GA at testing (weeks)</u> Goldenberg (1996): 24, 28 Imseis (1997): 24 to 26 Wennerholm (1997): 24 to 43		**Statistical analysis** Data were analysed separately for women with spontaneous preterm birth <28, <32, <34 and <37 weeks' gestation. 2x2 contingency tables were calculated. Where tables contained cells with a 0 values, 0.5 was added to allow calculation of variances. Sensitivity and specificity for each study were calculated and plotted in receiver operating characteristic (ROC) plots according to timing of transvaginal ultrasonography (20 to 24, and >24 weeks' gestation) and definition of spontaneous preterm birth (<28, <32, <34 and <37 weeks' gestation). Summary ROC curves were constructed for each	<u>CL 25mm:</u> 6/2,036 Sensitivity: 54 (45 to 62) Specificity: 91 (90 to 92) <u>CL 30mm:</u> 4/1,812 Sensitivity: 65 (56 to 74) Specificity: 78 (76 to 80) <u>CL 35mm:</u> 5/1,889 Sensitivity: 81 (73 to 87) Specificity: 58 (56 to 61) <u>Preterm birth <34 weeks</u> <u>CL 20mm:</u> 5/1,760 Sensitivity: 29 (23 to 35) Specificity: 97 (96 to 98) <u>CL 25mm:</u> 6/1,987 Sensitivity: 40 (38 to 46) Specificity: 93 (92 to 94) <u>CL 30mm:</u> 5/2,014 Sensitivity: 56 (50 to 62) Specificity: 81 (79 to 83) <u>CL 35mm:</u> 6/1,884 Sensitivity: 79 (74 to 84) Specificity: 60 (57 to 62)	proceedings and international meetings, reference lists, textbooks, previously published systematic reviews, authors contacted for unpublished data) Did the review authors perform study selection in duplicate? Yes Did the review authors perform data extraction in duplicate? Yes Did the review authors provide a list of excluded studies and justify the exclusions? No Did the review authors describe the included studies in adequate detail? Yes Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? Yes (QUADAS but only 4 of the 14 items)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
of Health, Department of Health and Human Services.	Grisaru-Granovsky (1998): 18 to 29 (mean 25) Yang (2000): 18 to 26 (91% at <24 weeks) Guzman (2000): 15 to 20, 21 to 24, 25 to 28 Soriano (2002): 18 to 24 (mean 22.7) Vayssiere (2002): 21 to 23, 26 to 28 Gibson (2004): 18, 24, 28, 32 Sperling (2005): 23 Fait (2005): 15.9 +- 0.3 Arabin (2006): 20 to 25 To (2006): 22 to 24 Klein (2008): 20 to 25 Aboulghar (2009): mean 20 Fox (2009): 22 to 24, 25 to 32		outcome using a bivariate random-effects approach and area under the summary ROC curves were calculated with their corresponding 95% confidence intervals (CIs). A bivariate, random-effects meta-regression model was used to calculate pooled estimates of sensitivity and specificity with 95% CIs. Likelihood ratios with 95% CIs were derived from the pooled sensitivities and specificities for each outcome reported. Estimates of pre-test probabilities of preterm birth <28, <32, <34, and <37 weeks' gestation were obtained from the global prevalence of these	Preterm birth <37 weeks CL 25mm: 4/434 Sensitivity: 21 (15 to 27) Specificity: 95 (92 to 98) CL 30mm: 2/218 Sensitivity: 29 (18 to 43) Specificity: 91 (86 to 95) CL 35mm: 2/134 Sensitivity: 56 (43 to 68) Specificity: 63 (50 to 74) Testing at >24 weeks' gestation Preterm birth <32 weeks CL 25mm: 3/511 Sensitivity: 65 (45 to 81) Specificity: 76 (72 to 79) Preterm birth <34 weeks CL 25mm: 4/594 Sensitivity: 44 (34 to 53) Specificity: 81 (78 to 85) Preterm birth <37 weeks CL 25mm: 2/276	Did the review authors report on the sources of funding for the studies included in the review? Yes If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Yes If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Yes Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? Yes Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	CL cut-off (mm) Goldenberg (1996): 25 Imseis (1997): 35 Wennerholm (1997): 33 Grisaru-Granovsky (1998): 30 Yang (2000): 25, 30, 35 Guzman (2000): 20 Soriano (2002): 35 Vayssiere (2002): 25, 30 Gibson (2004): 25, 22 Sperling (2005): 20, 25, 30, 35 Fait (2005): 35 Arabin (2006): 25, 30 To (2006): 5 to 55* Klein (2008): 25, 30, 35 Aboulghar (2009): 38		outcomes across the studies. Statistical heterogeneity was investigated through visual examination of forest plots and ROC plots, and using the I^2 statistic. Potential sources of heterogeneity were explored using meta-regression analysis of subgroups defined *a priori* (study setting, sample size, year of publication). Study quality was also assessed (those that met all 4 methodological criteria versus <4).	Sensitivity: 43 (35 to 51) Specificity: 77 (68 to 84) **Predictive accuracy of CL for spontaneous preterm birth in studies not included in meta-analysis** Testing at 20 to 24 weeks' gestation Preterm birth at <33 weeks (CL 35mm) Fait (2005) Sensitivity: 50 (9 to 91) Specificity: 94 (72 to 99) Preterm birth <34 weeks' gestation (CL 38mm) Aboulghar (2009) Sensitivity: 68 (55 to 78) Specificity: 50 (42 to 58) Testing >24 weeks' gestation Preterm birth <34 weeks Imseis (1997) (CL 35mm) Sensitivity: 94 (73 to 99) Specificity: 49 (37 to 60) Grisaru-Granovsky (1998) (CL 30mm) Sensitivity: 100 (65 to 100) Specificity: 58 (41 to 74)	observed in the results of the review? Yes If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Yes Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Yes **Risk of bias for each relevant study included in Conde-Agudelo 2010 systematic review was assessed using QUADAS-II (conducted by the NGA 2019 technical team)** **Goldenberg (1996):** **A. Risk of Bias** **Patient Sampling**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Fox (2009): 20, 25, 35 *<20, <25, <30 and <35 mm as cut-off values. **Inclusion Criteria** 1] Cohort or cross-sectional study. 2] Studies assessing the accuracy of transvaginal sonographic CL measurement to predict spontaneous preterm birth in asymptomatic or symptomatic women with twin pregnancy. 2] Outcomes included any category of spontaneous preterm birth <37 weeks' gestation. 3] Studies providing sufficient information to			<u>Preterm birth <35 weeks (CL 33mm)</u> <u>Wennerholm (1997)</u> Sensitivity: 68 (47 to 84) Specificity: 54 (44 to 65) <u>Preterm birth <37 weeks (CL 33mm)</u> <u>Wennerholm (1997)</u> Sensitivity: 69 (53 to 82) Specificity: 60 (48 to 71)	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined; 65% of the population had preterm labour symptoms) **Index Test** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	generate 2 x 2 tables. 4] Women had no therapeutic intervention resulting from the test result. <u>Individual studies inclusion criteria</u> Goldenberg (1996): twins Imseis (1997): twins Wennerholm (1997): twins Grisaru-Granovsky (1998): twins, triplets, quadruplets Yang (2000): twins Guzman (2000): twins Soriano (2002): twins Vayssiere (2002): twins Gibson (2004): twins				Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Sperling (2005): twins Fait (2005): triplets reduced to twins Arabin (2006): twins To (2006): twins Klein (2008): twins Aboulghar (2009): twin ICSI pregnancies Fox (2009): twins **Exclusion Criteria** 1] Studies reporting results together for singleton and twin pregnancies. 2] Case-control studies. 3] Studies not providing data on predictive estimates and sufficient information to calculate them not available.				interpreted without knowledge of the results of the index tests? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	4] Women with cervical cerclage, previous cervical surgery, or premature rupture of membranes. <u>Individual studies exclusion criteria</u> Goldenberg (1996): cervical cerclage, placenta previa, major fetal anomaly Imseis (1997): cervical cerclage Wennerholm (1997): not reported Grisaru-Granovsky (1998): not reported Yang (2000): cervical cerclage, placenta previa or bleeding Guzman (2000): cervical cerclage Soriano (2002): not reported				Could the patient flow have introduced bias? Low concern **Imseis (1997):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Vayssiere (2002): cervical cerclage, placenta previa, major fetal anomaly, twin-to-twin transfusion syndrome, premature rupture of membranes Gibson (2004): fetal anomaly, twin-to-twin transfusion syndrome Sperling (2005): cervical cerclage, prior conisation Fait (2005): cervical cerclage Arabin (2006): not reported To (2006): cervical cerclage, major fetal abnormalities, premature rupture of membranes, monochorionic twins with severe twin-to-twin transfusion syndrome				('spontaneous' preterm birth not defined) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Klein (2008): not reported Aboulghar (2009): cervical cerclage Fox (2009): monoamniotic twins, fetal aneuploidy, major fetal abnormalities				Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Wennerholm (1997):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Are there concerns that the included patients and setting do not match the review question? Unclear concern (not reported e.g. how many women were treated with cerclage or cervical pessary intervention; exclusion criteria not reported) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Flow and Timing **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Yang (2000):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. Concerns regarding applicability Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? No (for clinicians, unclear for women) Could the reference standard, its conduct, or its interpretation have introduced bias? High risk

					B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Guzman (2000):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Soriano (2002):** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Patient Sampling Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk (also, no exclusion criteria were reported) **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined)

					Index Test **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpreted without knowledge of the results of the index tests? No Could the reference standard, its conduct, or its interpretation have introduced bias? High risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? Low concern **Vayssiere (2002):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern (4 women received a cerclage

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					after membrane prolapse into cervix that was observed at the 22-week ultrasound measurement) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Reference Standard **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear if women were blinded to test results Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

					Flow and Timing **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? No Could the patient flow have introduced bias? High concern **Gibson (2004):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. Concerns regarding applicability: Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined; not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk

					B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Sperling (2005):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Partially (the results were blinded for the clinicians if the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					cervical length was ≥15 mm, n=12 cases) Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? Low concern **Fait (2005):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern (in two

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					women a cerclage was performed at 21 and 23 weeks' gestation because of cervical shortening and dilatation; 'spontaneous' preterm birth not defined; population includes women with triplet gestations reduced to twins) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Arabin (2006):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? High concern ('spontaneous' preterm birth not defined; no exclusion criteria were reported; not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Yes (unclear if

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					the results were blinded for women) Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? Low concern **To (2006):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern (women cervical length of 19

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					mm or less were referred to their obstetrician for expectant management, in some cases they had cervical cerclage or the administration of progesterone vaginal pessaries) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? No Could the reference standard, its conduct, or its interpretation have introduced bias? High risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

					Flow and Timing **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Klein (2008):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. Concerns regarding applicability: Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined; not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk

					B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Aboulghar (2009):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern

					Fox (2009): **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous ' preterm birth not defined; not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were the reference standard results interpreted without knowledge of the results of the index tests? No Could the reference standard, its conduct, or its interpretation have introduced bias? High risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** Five studies met all 4 methodological criteria, the remainder did not meet at least one criteria (most common was failure to blind investigators to test results).
Full citation Conde-Agudelo,A, Romero,R., Cervicovaginal fetal fibronectin for the prediction of spontaneous preterm birth in multiple pregnancies: a systematic review and meta-analysis, Journal of Maternal-Fetal and Neonatal Medicine, 23, 1365-1376, 2010a	**Sample size** N=1,221 women with multiple pregnancies (1,233 twins, 57 triplets, 2 quadruplets, 29 unspecified) 15 studies, 7 studies on asymptomatic women with twin pregnancy: Goldenberg (1996): N=147	**Tests** **Index test:** cervicovaginal fetal fibronectin testing (all studies cut-off value 50 ng/ml) **Reference standard**: spontaneous preterm birth	**Methods** In studies where serial fetal fibronectin samples were collected, any positive result was considered as a positive result overall. Studies reporting spontaneous preterm birth before 35 weeks' gestation were included in the group of studies with spontaneous preterm birth before 34	**Results** **Pooled estimates for cervicovaginal fetal fibronectin in predicting spontaneous preterm birth in asymptomatic women - N (number of studies)/n (number of women), sensitivity (%), specificity (%) and 95% CIs** Twin pregnancy: <u>Preterm birth <32 weeks:</u> 2/302 Sensitivity (95% CI): 33 (14 to 60) Specificity (95% CI): 94 (85 to 97) <u>Preterm birth <34 weeks:</u> 6/576 Sensitivity (95% CI): 39 (29 to 51)	**Limitations** **AMSTAR** Did the research questions and inclusion criteria for the review include the components of PICO? Yes Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 798856 **Country/ies where the study was carried out** USA **Study type** Systematic review **Aim of the study** To evaluate the accuracy of cervicovaginal fetal fibronectin for the prediction of spontaneous preterm birth in women with multiple pregnancies. **Study dates** Databases were searched from inception to 30 September 2010. Study dates ranged from 1996 to 2009. **Source of funding** Supported by the Perinatology	Wennerholm (1997): N=101 Oliveira (1998): N=52 Ramirez & Turrentine (1999): N=57 Gibson (2004): N=74 Ruiz (2004): N=48 Fox (2009): N=155 (total N from 7 studies is 634) **Characteristics** GA at sampling (weeks), 7 studies on asymptomatic women with twin pregnancy: Goldenberg (1996): 24 to 30 Wennerholm (1997): 24 to 34 Oliveira (1998): 24 to 34 Ramirez & Turrentine (1999): 24 to 34		weeks' gestation in the data synthesis because of the relatively similar neonatal outcomes. Studies reporting spontaneous preterm birth before 36 weeks' gestation were considered with those reporting spontaneous preterm birth before 37 weeks' gestation. **Statistical analysis** Data were analysed separately for women with spontaneous preterm birth before 32, 34 and 37 weeks' gestation. 2x2 contingency tables were calculated. Where tables contained cells with a 0 values, 0.5 was added to allow calculation of variances. Sensitivity and specificity for each study were calculated and plotted in receiver	Specificity (95% CI): 80 (74 to 86) Preterm birth <37 weeks: 5/520 Sensitivity (95% CI): 33 (25 to 45) Specificity (95% CI): 87 (80 to 94)	significant deviations from the protocol? Yes Did the review authors explain their selection of the study designs for inclusion in the review? Yes Did the review authors use a comprehensive literature search strategy? Yes (5 databases, proceedings and international meetings, reference lists, textbooks, previously published systematic reviews, and review articles, authors contacted for unpublished data) Did the review authors perform study selection in duplicate? Yes Did the review authors perform data extraction in duplicate? Yes Did the review authors provide a list of excluded studies and justify the exclusions? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Research Branch: Division of Intramural Research of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services	Gibson (2004): 24, 28 and 32 Ruiz (2004): 22 to 34 Fox (2009): 22 to 32 <u>Sampling frequency (sampling site), 7 studies on asymptomatic women with twin pregnancy:</u> Goldenberg (1996): serial, every two weeks (vaginal fornix and cervix) Wennerholm (1997): serial, every two weeks (vaginal fornix and cervix) Oliveira (1998): serial, every two weeks (vaginal fornix and cervix) Ramirez & Turrentine (1999): serial, every two weeks		operating characteristic (ROC) plots. A bivariate, random-effects meta-regression model was used to calculate pooled estimates of sensitivity and specificity with 95% CIs. Likelihood ratios with 95% CIs were derived from the pooled sensitivities and specificities for each outcome reported. Estimates of pre-test probabilities of preterm birth <32, <34, and <37 weeks' gestation, and within 7 and 14 days of testing were obtained from the global prevalence of these outcomes across the studies. Statistical heterogeneity was investigated through visual examination of forest plots and ROC plots, and using the I^2 statistic. Potential sources of		Did the review authors describe the included studies in adequate detail? Yes Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? Yes (QUADAS but only 4 of the 14 items) Did the review authors report on the sources of funding for the studies included in the review? Yes If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Yes If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	(vaginal fornix and cervix) Gibson (2004): single (vaginal fornix) Ruiz (2004): serial, weekly (vaginal fornix and cervix) Fox (2009): serial, every two to three weeks (vaginal fornix) **Inclusion Criteria** 1] Cohort or cross-sectional studies. 2] Evaluated the accuracy of cervicovaginal fetal fibronectin testing to predict spontaneous preterm birth in asymptomatic or symptomatic women with multiple pregnancies. 3] Reported necessary data to construct 2 x 2 tables.		heterogeneity were explored using meta-regression analysis of subgroups defined *a priori* (study setting, sample size, year of publication, pregnancy plurality, method for measuring fetal fibronectin, and sampling frequency).		Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? Yes Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Yes If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Yes Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Yes **Risk of bias for each relevant study included in Conde-Agudelo 2010**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	<u>Individual studies inclusion criteria (7 studies on asymptomatic women with twin pregnancy only):</u> Goldenberg (1996): twins Wennerholm (1997): twins; intact membranes Oliveira (1998): twins Ramirez & Turrentine (1999): twins Gibson (2004): twins Ruiz (2004): twins Fox (2009): twins **Exclusion Criteria** 1] Studies reporting results for singleton and multiple pregnancies combined. 2] Case-control studies, case				**systematic review was assessed using QUADAS-II (conducted by the NGA 2019 technical team)** **Goldenberg (1996):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	series or reports, editorials, comments or reviews without original data. 3] Accuracy test estimates not published and sufficient information to calculate them not available. <u>Individual studies exclusion criteria (7 studies on asymptomatic women with twin pregnancy only)</u> Goldenberg (1996): cervical cerclage, placenta previa, severe fetal anomaly Wennerholm (1997): Not reported Oliveira (1998): Not reported Ramirez & Turrentine				question? Unclear concern ('spontaneous' preterm birth not defined; 65% of the population had preterm labour symptoms) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	(1999): Not reported Gibson (2004): fetal anomaly, suspected twin-to-twin transfusion Ruiz (2004): cervical incompetence, fetal death, uterine malformations Fox (2009): monoamniotic twins				question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Wennerholm (1997):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. Concerns regarding applicability: Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern (not reported e.g. how many women were treated with cerclage or cervical pessary intervention; exclusion criteria not reported) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Oliveira (1998):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous ' preterm birth not defined) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Yes Could the reference standard, its conduct,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Ramirez & Turrentine (1999):**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Not possible to assess as it is a conference abstract **Gibson (2004):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous ' preterm birth not defined; not reported

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Ruiz (2004):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? High risk **B. Concerns regarding applicability:**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined; women were recruited from a high-risk clinic; not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. Concerns regarding applicability Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Fox (2009):** **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous ' preterm birth not defined; not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? No Could the reference standard, its conduct,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					or its interpretation have introduced bias? High risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Five studies fulfilled all four methodological criteria (not specified); the remaining studies had at least one methodological flaw (lack of blinding of investigators to test results and failure to report loss to follow-up or exclusions).
Full citation Ehsanipoor, R. M, Haydon, M. L, Lyons Gaffaney, C, Jolley, J. A, Petersen, R, Lagrew, D. C, Wing, D. A., Gestational age at cervical length measurement and preterm birth in twins, Ultrasound in Obstetrics & Gynecology, 40, 81-6, 2012 **Ref Id** 794721 **Country/ies where the study was carried out** USA	**Sample size** N=561 twin pregnancies **Characteristics** Prior preterm birth (<37 weeks): 16 (2.9%); Dichorionic pregnancy: 473 (84.3%) **Inclusion Criteria** Asymptomatic women **Exclusion Criteria** Pregnancies with major fetal	**Tests** Adjusted odds ratios to measure the association between CL measurement and spontaneous preterm birth <35 weeks of gestation.	**Methods** Included women had undergone transvaginal sonographic cervical length surveillance at least once between 13 and 34+6 weeks' gestation. Neither vaginal nor intramuscular progesterone was routinely administered, even with the finding of a shortened cervix. The practitioners were not blinded to the cervical length measurements and there was no standard management protocol in place for	**Results** <u>OR (95% CI) for CL to predict spontaneous preterm birth prior <35 weeks:</u> OR for CL = 0.95 (0.93–0.97) OR adjusted for parity and conception with assisted reproductive technology	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** low risk of bias **Prognostic factor measurement:** high risk of bias (providers were not blinded to test results; not reported if women were blinded to test result) **Outcome measurement:** moderate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** moderate risk of bias (adjusted only for

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Retrospective cohort study **Aim of the study** To estimate the risk of preterm birth prior to 35 weeks' gestation in twin pregnancies based on cervical length and gestational age at measurement. **Study dates** Between 1999 and 2005 **Source of funding** This research study was made possible through a grant from the Memorial Medical Centre Foundation, Long Beach, California, USA.	anomalies or intrauterine death, multifetal pregnanc y reduction, medically indicated birth before 35 weeks, twin–twin transfusion syndrome and cerclage placement were excluded.		cases of cervical shortening.		parity and conception with assisted reproductive technology, other potentially important confounding factors were not adjusted for) **Analysis and Reporting:** low risk of bias **Other information**
Full citation	**Sample size**	**Tests**	**Methods**	**Results**	**Limitations**
Fichera, A, Pagani, G, Stagnati, V,	N=120 triplet pregnancies but	**Index test**	CL measurements performed	Diagnostic accuracy of CL measurement to predict spontaneous preterm birth (excluding	Risk of bias was assessed using

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Cascella, S, Faiola, S, Gaini, C, Lanna, M, Pasquini, L, Raffaelli, R, Stampalija, T, Tommasini, A, Prefumo, F., Cervical length measurement at mid gestation to predict spontaneous preterm birth in asymptomatic triplet pregnancies, Ultrasound in Obstetrics & Gynecology, 13, 13, 2017 **Ref Id** 798859 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** To evaluate the predictive value of second-trimester CL measurement for	N=96 when excluding those complicated by TTTS and those treated with laser therapy, cerclage or pessary **Characteristics** Maternal age (years, median (IQR)): 34 (32-36); Previous PTB: 2 (2.1%); ART: 65 (67.7); Dichorionic: 28 (29.2); Trichorionic: 65 (67.7); Gestational age at birth (weeks, median (IQR)): 33+2 (30+0 to 34+4) **Inclusion Criteria** The presence of three viable fetuses in a patient asymptomatic for preterm labour and	CL measurement (testing performed transvaginally between 18 and 24 weeks' gestation) **Reference standard** Spontaneous preterm birth Prior: 1) <28 weeks 2) <30 weeks 3) <32 weeks Adjusted odds ratios to measure the association between Cl measurement and preterm birth <32 weeks of gestation.	transvaginally between 18 and 24 weeks using a standardized technique were included in the analysis. Women were followed up and managed according to the local protocol, which included an ultrasound examination performed every 2–4 weeks depending on the chorionicity (fortnightly in mono/dichorionic pregnancies and every 3–4 weeks in trichorionic ones).	<u>those complicated by twin–twin transfusion syndrome, treated with laser therapy, cerclage or pessary):</u> Prior: *1) <28 weeks:* CL <25 mm: sensitivity (95% CI) = 33.3 (7.5–70.1); specificity (95% CI) = 89.7 (81.3–95.2) CL <20 mm: sensitivity (95% CI) = 22.2 (2.8–60.0); specificity (95% CI) = 92.7 (85.5–97.0) CL <15 mm: sensitivity (95% CI) = 11.1 (0.3–48.3); specificity (95% CI) = 95.4 (88.6–98.7) *2) <30 weeks* CL <25 mm: sensitivity (95% CI) = 27.8 (9.7–53.5); specificity (95% CI) = 91.0 (82.4–96.3) CL <20 mm: sensitivity (95% CI) = 22.2 (6.4–47.6); specificity (95% CI) = 94.8 (88.3–98.3) CL <15 mm: sensitivity (95% CI) = 16.7 (3.6–41.4); specificity (95% CI) = 97.4 (91.0–99.7) *3) <32 weeks* CL <25 mm: sensitivity (95% CI) = 26.5 (12.9–44.4); specificity (95% CI) = 95.2 (86.5–99.0) CL <20 mm: sensitivity (95% CI) = 20.6 (8.7–37.9); specificity (95% CI) = 96.8 (88.8–99.6) CL <15 mm: sensitivity (95% CI) = 8.8 (1.8–23.7); specificity (95% CI) = 96.7 (88.8–99.6) <u>OR (95% CI) for CL to predict spontaneous preterm birth prior <32 weeks (excluding those</u>	QUADAS2 for diagnostic accuracy **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined; women with cerclage or cervical pessary intervention and pregnancies

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
preterm birth in a large cohort of asymptomatic triplet pregnancies. **Study dates** Between 2002 and 2015 at five Italian tertiary referral centres. **Source of funding** Not reported.	with at least one measurement of CL, performed transvaginally between 18 and 24 weeks' gestation. **Exclusion Criteria** Pregnancies with incomplete data, a diagnosis of one or more fetal demises, whether spontaneous or following multifetal pregnancy reduction, or with an indicated preterm birth.			<u>complicated by twin–twin transfusion syndrome, treated with laser therapy, cerclage or pessary):</u> OR for CL <20 mm = 4.00 (0.19–83.54) OR for CL <25 mm = 7.86 (0.44–139.08) OR adjusted for nulliparity	complicated with FFTS, and treated with laser ablation of placental anastomoses were included) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderat e risk of bias for the main analysis (women with cerclage or cervical pessary intervention and pregnancies complicated with FFTS, and treated with laser ablation of placental anastomoses were included) **Attrition:** low risk of bias **Prognostic factor measurement:** moder ate risk of bias (not reported if participants/providers

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					were blinded to test results) **Outcome measurement:** moder ate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** modera te risk of bias (adjusted only for nulliparity and smoking in the main analysis, and only for nulliparity in the sub-analysis; other potentially important confounding factors were not adjusted for). **Analysis and Reporting:** low risk of bias **Other information** None
Full citation Fox,N.S, Rebarber,A, Roman,A.S, Klauser,C.K, Saltzman,D.H., Association between second-trimester cervical	**Sample size** N=309 women with twin pregnancies **Characteristics** Prior preterm birth: 7.1%,	**Tests** Adjusted odds ratios to measure the association between CL measurement (mm) and spontaneous preterm birth	**Methods** Second-trimester CL measurements are routinely done for twin pregnancies in author's practice every 2 to 4 weeks. Women and obstetricians	**Results** OR (95% CI) for CL measurement (mm) to predict spontaneous preterm birth of twin pregnancy defined as birth before: *1) 28 weeks' gestation:* CL measured at 16 - 17 6/7 weeks: OR (95% CI) = 0.95 (0.81 to 1.1)	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderat e risk of bias (8 women (2.6%) received a cerclage after 16 weeks,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
length and spontaneous preterm birth in twin pregnancies, Journal of Ultrasound in Medicine, 29, 1733-1739, 2010 **Ref Id** 794792 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To define the normal values for the mean and median CL measurements in twin pregnancies at 16 to 17 6/7, 18 to 19 6/7, 20 to 21 6/7, and 22 to 23 6/7 weeks; to evaluate the association betwee n short CLs at each of these second	dichorionic pregnancies: 88.7%, monochorionic pregnancies: 11.3%, in vitro-fertilized pregnancies: 68.3%, multifetal reduction: 9.1%, cerclage after 16 weeks: 2.6%, mean gestational age at birth: 35.8 weeks (+-2.6), spontaneous preterm birth before 35 weeks: 19%, before 32 weeks: 7.2% and before 28 weeks: 2.9% **Inclusion Criteria** Women with twin pregnancies with a CL measurement betw	(defined as birth before 28, 32, 35 weeks)	were not blinded to the CL measurements. Most of included twin pregnancies have more than 1 CL measurement between 16 and 23 6/7 weeks. However, because each 2-week window was evaluated separately and CL measurements from different 2-week windows were not combined, there was no adjustment done for multiple measureme nts in the same woman. If any woman had 2 CL measurements within one 2-week window, the first CL measurement in that window was used for analysis.	CL measured at 18 - 19 6/7 weeks: OR (95% CI) = 1(0.8 to 1.2) CL measured at 20 - 21 6/7/ weeks: OR (95% CI) = 0.92 (0.81 to 1) CL measured at 22 - 23 6/7/ weeks: OR (95% CI) = 0.88 (0.8 to 0.97) 2) 32 *weeks' gestation:* CL measured at 16 - 17 6/7 weeks: OR (95% CI) = 1 (0.93 to 1.1) CL measured at 18 - 19 6/7 weeks: OR (95% CI) = 1 (0.91 to 1.1) CL measured at 20 - 21 6/7/ weeks: OR (95% CI) = 0.96 (0.9 to 1) CL measured at 22 - 23 6/7/ weeks: OR (95% CI) = 0.93 (0.88 to 0.98) *3) 35 weeks' gestation:* CL measured at 16 - 17 6/7 weeks: OR (95% CI) = 0.98 (0.92 to 1) CL measured at 18 - 19 6/7 weeks: OR (95% CI) = 0.92 (0.87 to 0.98) CL measured at 20 - 21 6/7/ weeks: OR (95% CI) = 0.96 (0.92 to 1) CL measured at 22 - 23 6/7/ weeks: OR (95% CI) = 0.94 (0.9 to 0.98) OR adjusted for maternal age, chorionicity, in vitro-fertilization, multifetal reduction, prior term	however in the multivariable analysis this was accounted for) **Attrition:** low risk of bias **Prognostic factor measurement:** high risk of bias (participants/providers were not blinded to test results) **Outcome measurement:** moder ate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** low risk of bias **Analysis and Reporting:** low risk of bias **Other information** None

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
trimester gestational age periods and SPTB in twin pregnancies. **Study dates** Between June 2005 and April 2010 **Source of funding** Not reported	een 16 and 23 6/7 weeks' gestation. **Exclusion Criteria** Excluded were monoamniotic twins, pregnancies with aneuploidy or major fetal anomalies discovered before or after birth, women with a cerclage placed before 16 weeks, also women with an indicated preterm birth; also all tests done in labour and birth.			births, prior preterm births, previous pregnancy BMI, and cerclage	
Full citation Fox,N.S, Rebarber,A, Roman,A.S, Klauser,C.K, Saltzman,D.H., The significance of a positive fetal fibronectin in the setting of a normal cervical length in twin pregnancies, American Journal of	**Sample size** N=244 women with twin pregnancy and a normal CL (defined as a CL >25 mm) from 22 to 32 weeks. n=14 (5.7%) positive fFN and n=230 (94.3%) negative fFN.	**Tests** Adjusted odds ratios to measure the association between a positive fFN test and spontaneous preterm birth (defined as birth before 32 weeks).	**Methods** Baseline characteristics and pregnancy outcomes were obtained from a computerized medical record. A normal CL was defined as a CL >25 mm. An fFN concentration of 50 ng/mL or greater was	**Results** <u>OR (95% CI) for a positive fFN test to predict spontaneous preterm birth of twin pregnancy defined as birth before 32 weeks' gestation:</u> OR (95% CI) = 6.8 (1.42 to 32.2) OR adjusted for maternal age, chorionicity, prior preterm birth, IVF, multifetal reduction and maternal body mass index	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** low risk of bias **Attrition:** low risk of bias **Prognostic factor measurement:** high risk of bias (participants/providers

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Perinatology, 29, 267-272, 2012 **Ref Id** 794794 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To evaluate the association of positive fFN testing and preterm birth in asymptomatic women with twin pregnancies and a normal CL. **Study dates** Between 2005 and 2010 **Source of funding** Not reported	**Characteristics** Mean gestational age at birth: normal CL and fFN positive: 34.1 weeks (+-3.37), normal CL and fFN negative: 36.19 weeks (+-2.17); Dichorionic: fFN positive: 11 (78.6%), fFN negative: 31 (86.5%); Prior preterm birth: fFN positive: 2 (14.3%), fFN negative: 15 (6.5%). **Inclusion Criteria** All women with twin pregnancies were eligible for inclusion. **Exclusion Criteria** Women with monochorionic-monoamniotic placentation, cercla ge placed during		considered to be positive. CL and fFN testing is performed routinely at 2- to 4-week intervals from 22 to 32 weeks. Patients and obstetricians were not blinded to the CL measurements or fFN results.		were not blinded to test results) **Outcome measurement:** moder ate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** low risk of bias **Analysis and Reporting:** low risk of bias **Other information** None

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	pregnancy, and those without both CL and fFN testing at 22 to 32 weeks. Also women with a CL ≤25 mm from 22 to 32 weeks. Tests done during labour or birth were excluded; also those that were done on symptomatic women as part of preterm evaluation.				
Full citation Fox, N. S, Saltzman, D. H, Fishman, A, Klauser, C. K, Gupta, S, Rebarber, A., Gestational age at cervical length and fetal fibronectin assessment and the incidence of spontaneous preterm birth in twins, Journal of Ultrasound in Medicine, 34, 977-84, 2015	**Sample size** N=611 women with twin pregnancy **Characteristics** Mean gestational age at birth: 35.8 weeks (+-2.6); monochorionic: 13.1%; dichorionic: 86.9%; Prior preterm birth: 7.1%.	**Tests** Adjusted odds ratios to measure the association between: 1) CL and spontaneous preterm birth (defined as birth before 35 weeks) 2) positive fFN test and spontaneous preterm birth (defined as birth before 35 weeks)	**Methods** The charts of all women with twin pregnancies greater than 22 weeks who gave birth in a single maternal-fetal medicine practice between June 2005 and June 2013 were reviewed. CL and fFN testing is performed routinely at 2- to 4-week intervals from until 32 weeks but only CL measurements after	**Results** OR (95% CI) for CL measurement (mm) to predict spontaneous preterm birth of twin pregnancy defined as birth before 35 weeks' gestation: SPTB <35 weeks: coefficient (95% CI) = -0.041 (-0.059 to -0.023); exponentiated coefficient OR = 0.96 (0.94 to 0.98)* OR adjusted for gestational age. OR (95% CI) for fFN to predict spontaneous preterm birth of twin pregnancy defined as birth before 35 weeks' gestation: SPTB <35 weeks: coefficient (95% CI) = 1.51 (0.94 to 2.08)	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderate risk of bias (not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Attrition:** low risk of bias **Prognostic factor measurement:** high risk of bias (participants/providers

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 794796 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To estimate the risk of spontaneous preterm birth in twin pregnancies based on transvaginal sonographic cervical length, fFN testing, and the gestational age at which these tests were performed. **Study dates** Between June 2005 and June 2013. **Source of funding** Not reported	**Inclusion Criteria** For the analysis, CL measurements afte r 22 weeks were included. **Exclusion Criteria** Women with monochorionic monoamniotic placentation, major fetal congenital anomalies discovered before or after birth, and twin-twin transfusion syndrome. Also women with an indicated preterm birth, such as for preeclampsia or fetal growth restriction. All tests done during labour and birth were excluded.		22 weeks were included in the analysis. Fetal FN testing was from 22 weeks to 31 weeks 6 days. An fFN concentration of 50 ng/mL or greater was considered to be positive. Physicians were not blinded to CL or fFN results. Tests done during labour and birth were excluded, as they were done on symptomatic women as part of a preterm labour evaluation. Spontaneous preter m birth was defined as preterm birth resulting from preterm labour or premature rupture of membranes.	OR adjusted for gestational age. <u>OR (95% CI) for CL measurement (mm) and fFN to predict spontaneous preterm birth of twin pregnancy defined as birth before 35 weeks' gestation:</u> SPTB <35 weeks: coefficient (95% CI) for CL = -0.13 (-0.22 to -0.037); exponentiated coefficient OR = 0.88 (0.80 to 0.96)* SPTB <35 weeks: OR (95% CI) for fFN = 1.04 (0.45 to 1.64) OR adjusted for gestational age, also includes an interaction term for [gestational age x CL], also includes CL and fFN. <u>OR (95% CI) for CL measurement (mm) to predict spontaneous preterm birth of twin pregnancy defined as birth before 32 weeks' gestation:</u> SPTB <32 weeks: coefficient (95% CI) = -0.168 (-0.280 to -0.055); exponentiated coefficient OR = 0.85 (0.76 to 0.95)* OR adjusted for gestational age, also includes an interaction term for [gestational age x CL]. <u>OR (95% CI) for fFN to predict spontaneous preterm birth of twin pregnancy defined as birth before 32 weeks' gestation:</u> SPTB <32 weeks: OR (95% CI) = 2.29 (1.56 to 3.02)	were not blinded to test results) **Outcome measurement:** low risk of bias **Confounding:** modera te risk of bias (adjusted only for gestational age and CL or fFN, other potentially important confounding factors were not adjusted for). **Analysis and Reporting:** low risk of bias **Other information** None

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				OR adjusted for gestational age. <u>OR (95% CI) for CL measurement (mm) to predict spontaneous preterm birth of twin pregnancy defined as birth before 28 weeks' gestation:</u> SPTB <28 weeks: coefficient (95% CI) = -0.249 (-0.449 to -0.049); exponentiated coefficient OR = 0.78 (0.64 to 0.95)* OR adjusted for gestational age, also includes an interaction term for [gestational age x CL]. <u>OR (95% CI) for fFN to predict spontaneous preterm birth of twin pregnancy defined as birth before 28 weeks' gestation:</u> SPTB <28 weeks: OR (95% CI) = 2.91 (1.32 to 4.50) OR adjusted for gestational age. <u>OR (95% CI) for CL measurement (mm) and fFN to predict spontaneous preterm birth of twin pregnancy defined as birth before 28 weeks' gestation:</u> SPTB <28 weeks: coefficient (95% CI) for CL = -0.106 (-0.159 to -0.054); exponentiated coefficient OR = 0.90 (0.85 to 0.95)* SPTB <28 weeks: OR (95% CI) for fFN = not reported OR adjusted for gestational age.	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				*calculated by the NGA 2019 technical team using this online calculator: https://keisan.casio.com/exec/system/1223447896	
Full citation Guzman,E.R., Walters,C., O'reilly-Green,C., Meirowitz,N.B., Gipson,K., Nigam,J., Vintzileos,A.M., Use of cervical ultrasonography in prediction of spontaneous preterm birth in triplet gestations, American Journal of Obstetrics and Gynecology, 183, 1108-1113, 2000 **Ref Id** 221299 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study	**Sample size** N=51 triplet pregnancies (4 women with who gave birth because of maternal or fetal indications and 3 women who got cerclages were excluded from the analysis) **Characteristics** Gestational age at birth: median: 33 weeks (range 20 -37); mean: 31 weeks (+-4.2) **Inclusion Criteria** Triplet pregnancies **Exclusion Criteria**	**Tests** **Index test** CL measurement (testing performed transvaginally between 15 and 28 weeks' gestation.) Reference standard Preterm birth prior: 1) <28 weeks 2) <30 weeks 3) <32 weeks	**Methods** The shortest cervical length were evaluated at 15 to 20, 21 to 24, 15 to 24, and 25 to 28 weeks' gestation.	**Results** Diagnostic accuracy of CL measurement (≤20 mm or ≤25 mm) to predict spontaneous preterm birth: *1) CL of 25 mm measured between 15 and 20 week's gestation:* <28 weeks: TP=4, FP=0, FN=4, TN=42 <30 weeks: TP=4, FP=0, FN=7, TN=38 <32 weeks: TP=4, FP=0, FN=12, TN=31 *2) CL of 25 mm measured between 21 and 24 week's gestation:* <28 weeks: TP=6, FP=9, FN=1, TN=34 <30 weeks: TP=7, FP=7, FN=3, TN=32 <32 weeks: TP=9, FP=5, FN=6, TN=27 3) *CL of 20 mm measured between 25 and 28 week's gestation:* <28 weeks: TP=4, FP=18, FN=0, TN=24 <30 weeks: TP=7, FP=15, FN=0, TN=24 <32 weeks: TP=10, FP=11, FN=2, TN=21	**Limitations** Risk of bias was assessed using QUADAS2 **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Unclear risk ('spontaneous' preterm birth not defined) **B. Concerns regarding applicability:** Patient characteristics and setting

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To compare various ultrasonographic cervical parameters with respect to the ability to predict varying degrees of spontaneous preterm birth in triplet gestations evaluated between 15 and 28 weeks' gestation. **Study dates** Between September 1993 and June 1999. **Source of funding** Not reported	Women who gave birth due to maternal or fetal indications. Also measurement taken after placement of a cervical cerclage were excluded from the analysis.				Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Reference Standard **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** None
Full citation Klein,K., Gregor,H., Hirtenlehner-Ferber,K., Stammler-Safar,M., Witt,A., Hanslik,A., Husslein,P., Krampl,E., Prediction of spontaneous preterm delivery in twin pregnancies by cervical length at mid-gestation, Twin Research and Human Genetics: the Official Journal of the International Society for Twin	**Sample size** N=223 women with twin pregnancies **Characteristics** Median gestational age at birth: 36.1 weeks (age 25.1 to 39.1); median of CL: 36 mm (range 7 to 74); CL <25 mm: 5% **Inclusion Criteria**	**Tests** 1) Adjusted odds ratios to measure the association between CL measurement (at 20-25 weeks) and spontaneous preterm birth (defined as birth before 34 weeks) 2) Adjusted odds ratios to measure the association between previous preterm birth (before 34 weeks) and spontaneous preterm birth	**Methods** Over a period of 3 years, 262 consecutive women with twin pregnancies older than 18 years had a scan of the cervical length.	**Results** <u>OR (95% CI) for CL measurement (at 20 to 25 weeks) to predict spontaneous preterm birth of twin pregnancy defined as birth before 34 weeks' gestation:</u> OR (95% CI) = 1.08 (1.02 to 1.16) OR adjusted for previous preterm birth before 34 weeks of gestation, chorionicity, maternal age, body-mass-index, smoking habit and parity <u>OR (95% CI) for previous preterm birth (before 34 weeks) to predict spontaneous preterm birth of twin pregnancy defined as birth before 34 weeks' gestation:</u> OR (95% CI) = 4.95 (0.41 to 59.6)	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderate risk of bias (not reported e.g. how many women were treated with cerclage or cervical pessary intervention) **Attrition:** low risk of bias **Prognostic factor measurement:** moderate risk of bias (not reported if participants/providers

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Studies, 11, 552-557, 2008 **Ref Id** 270857 **Country/ies where the study was carried out** Austria **Study type** Retrospective cohort study **Aim of the study** To evaluate the association of cervical length at 20–25 weeks of gestation on spontaneous birth b efore 34 weeks in twin pregnancies in a country with a high incidence of preterm birth compared to other European countries. **Study dates** Over a period of 3 years (not specified)	Women with twin pregnancies older than 18 years who had a scan of the cervical length. **Exclusion Criteria** Women who were symptomatic at 20 to 25 weeks (uterine contractions or vaginal bleeding) and who gave birth because of other reasons than spontaneous labour and preterm rupture of membranes or at term.	(defined as birth before 34 weeks)		OR adjusted for CL at 20-25 weeks, chorionicity, maternal age, body-mass-index, smoking habit and parity	were blinded to test results) **Outcome measurement:** moder ate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** low risk of bias **Analysis and Reporting:** low risk of bias **Other information** None

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported					
Full citation Leveque, C, Vayssiere, C, Favre, R, Audibert, F, Chauvet, M. P, Maillard, F, Elhinger, V, Arnaud, C, Research Group in, Obstetrics, Gynecology,, Cervical length in asymptomatic twin pregnancies: prospective multicenter comparison of predictive indicators, Journal of Maternal-Fetal & Neonatal Medicine, 28, 37-40, 2015 **Ref Id** 795124 **Country/ies where the study was carried out** France **Study type**	**Sample size** N=116 women with twin pregnancy **Characteristics** Mean CL at 22 weeks: 39.5 mm (+-10.3), mean CL at 27 weeks: 35 (+-11), spontaneous preterm birth before 34 weeks: 11.2% **Inclusion Criteria** Women with asymptomatic twin pregnancies whose CL was routinely measured by transvaginal ultrasound twice, first between 21 and 23 weeks (22 weeks) and then again between 26	**Tests** **Index test** 1) CL measurement (CL ≤35 mm, testing performed transvaginally between 21 and 23 weeks (22 weeks) 2) CL measurement (CL ≤25 mm, testing performed transvaginally between 26 and 28 weeks (27 weeks) **Reference standard** Spontaneous preterm birth prior 34 weeks	**Methods** The study was performed in 13 French hospital centres. The study population comprised consecutive series at each centres of women with asymptomatic twin pregnancies whose CL was routinely measured by transvaginal ultrasound twice, first between 21 and 23 weeks (22 weeks) and then again between 26 and 28 weeks (27 weeks). The results of these measurements were neither communicated to women nor used for their management. Preterm birth before 34 weeks was considered spontaneous when labour was	**Results** <u>Diagnostic accuracy of CL measurement (CL <35 mm, measured between 21-23 weeks) to predict spontaneous preterm birth prior 34 weeks:</u> CL <35 mm: sensitivity (95% CI) = 38.5 (12.0 - 64.9); specificity (95% CI) = 70.9 (62.1 - 79.7) <u>Diagnostic accuracy of CL measurement (CL <25 mm, measured between 26-28 weeks) to predict spontaneous preterm birth prior 34 weeks:</u> CL <25 mm: sensitivity (95% CI) = 53.9 (26.8 - 81.0); specificity (95% CI) = 87.4 (81.0 - 93.8)	**Limitations** Risk of bias was assessed using QUADAS-II for diagnostic accuracy **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** To determine the diagnostic value of cervical shortening between two examinations performed at two predefined gestational age periods (21–23 weeks and 26–28 weeks). **Study dates** Between January 1997 and March 1999 **Source of funding** Not reported	and 28 weeks (27 weeks). **Exclusion Criteria** Women with prophylactic cerclage, placenta previa, major fetal anomalies, twin–twin transfusion syndrome, premature rupture of the membranes (PROM) or an undetermined gestational age. Also those for whom labour was induced before 34 weeks, for either maternal and/or fetal reasons and without spontaneous PROM.		either spontaneous or induced after PROM.		question? Low concern **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** None
Full citation Matthews, K. C, Gupta, S, Lam-Rachlin, J, Saltzman, D. H, Rebarber, A, Fox, N. S., The association between fetal fibronectin and spontaneous preterm birth in twin pregnancies with a shortened cervical length, Journal of Maternal-Fetal & Neonatal Medicine, 01-May, 2017 **Ref Id** 798866	**Sample size** N=155 women with twin pregnancies who had a CL ≤25 mm from 22 to 28 weeks' gestation. n=26 (16.8%) positive fFN and n=129 (83.2%) negative fFN. **Characteristics** Dichorionic: fFN positive: 21 (80.8%), fFN negative: 103 (79.8%); Monochorionic: fFN positive: 5 (19.2%),	**Tests** Adjusted odds ratios to measure the association between a positive fFN test and spontaneous preterm birth (defined as birth before 32 weeks).	**Methods** Charts of all women with twin pregnancies who gave birth in a single Maternal-Fetal Medicine practice between 2005 and 2016. All women routinely underwent serial CL assessments every 2–4 weeks from 16 to 32 weeks and concurrent fFN testing from 22 to 32 weeks in an outpatient setting. All tests starting at 22 weeks were included. For each woman, the first CL that was ≤25 mm	**Results** OR (95% CI) for a positive fFN test to predict spontaneous preterm birth of twin pregnancy defined as birth before 28, 30, 32, 34, 35 or 37 weeks' gestation (women with CL of ≤25 mm measured at 22-32 weeks): SPTB <37 weeks: OR (95% CI) = 10.7 (1.4 to 84.3); SPTB <35 weeks: OR (95% CI) = 8.6 (2.9 to 25.7); SPTB <34 weeks: OR (95% CI) = 7.1 (2.6 to 19.1); SPTB <32 weeks: OR (95% CI) = 3.54 (1.3 to 9.9); SPTB <30 weeks: OR (95% CI) = 6.4 (1.9 to 21.0); SPTB <28 weeks: OR (95% CI) = 9.5 (2.4 to 37.5)	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderate risk of bias (although at the time of fFN testing no women had vaginal progesterone or cervical pessary, all women with a CL ≤20 mm prior to 28 weeks received vaginal progesterone and some had a pessary placed which limits the generalizability of the predictability of fFN to women not receiving vaginal

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** Retrospective cohort study **Aim of the study** To estimate the association between a positive fFN and spontaneous preterm birth in a large cohort of asymptomatic twin pregnancies with a shortened CL. **Study dates** Between 2005 and 2016. **Source of funding** Not reported.	fFN negative: 26 (20.2%); Prior preterm birth: fFN positive: 4 (15.4%), fFN negative: 10 (7.8%). **Inclusion Criteria** Women with a shortened CL, defined as ≤25 mm. **Exclusion Criteria** Women with monoamniotic twins, twin–twin transfusion syndrome, pregnancies affected by aneuploidy, and pregnancies with any major fetal congenital anomalies.		between 22 and 28 weeks' gestation was used, and only the fFN result obtained on the same date. Women with a CL of ≤20 mm prior to 28 weeks received vaginal progesterone and starting in 2013, women also received a cervical pessary. In all participants, fFN testing was done prior to initiating vaginal progesterone or placing a pessary. At the time of fFN testing no women had vaginal progesterone or cervical pessary; however, all women with a CL ≤20 mm prior to 28 weeks received vaginal progesterone and some had a pessary placed. Spontaneous preterm birth was defined as preterm birth resulting from preterm labour or	OR adjusted for baseline CL	progesterone or cervical pessary.) **Attrition:** low risk of bias **Prognostic factor measurement:** moderate risk of bias (not reported if participants/providers were blinded to test results) **Outcome measurement:** low risk of bias **Confounding:** moderate risk of bias (adjusted only for baseline CL, other potentially important confounding factors were not adjusted for). **Analysis and Reporting:** low risk of bias **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			premature rupture of membranes.		
Full citation Michaluk, A, Dionne, M. D, Gazdovich, S, Buch, D, Ducruet, T, Leduc, L., Predicting preterm birth in twin pregnancy: was the previous birth preterm? A Canadian experience, Journal of Obstetrics & Gynaecology Canada: JOGC, 35, 793-801, 2013 **Ref Id** 798867 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort study **Aim of the study** To determine the risk of preterm birth	**Sample size** N=576 women who had a twin birth following a previous index singleton birth **Characteristics** Preterm birth (<37 weeks): 53.6%, term birth (≥37 weeks): 46.4% ; preterm birth: spontaneous labour 290 out of 309; Of the twins born preterm: born at: <30 completed weeks: 17%, 30-33 weeks: 33%, 34-36 weeks: 50%; first twin was born vaginally: 41%, second twin born vaginally: 36%; dichorionic-diamniotic: 50%,	**Tests** Adjusted odds ratios to measure the association between history of preterm birth and subsequent risk of spontaneous preterm birth in twin pregnancies (defined as birth at ≤34 completed weeks or ≤37 completed weeks).	**Methods** Patient charts were examined for twin births in multiparous women and those who gave birth to a singleton baby immediately before their twin pregnancy. Preterm birth was defined as <37 completed weeks' gestation. There were scheduled visits every two weeks starting at 20 weeks, a cervical examination at each visit starting at 24 weeks and multivitamin supplementation throughout. Serial ultrasound examinations for fetal biometry and amniotic fluid evaluation were performed every 2 to 4 weeks starting at 18 to 20 weeks.	**Results** OR (95% CI) for history of singleton preterm birth to predict a subsequent risk of spontaneous preterm birth of twin pregnancy defined as preterm birth at ≤34 weeks or ≤37 weeks of gestation: *Birth ≤34 weeks:* OR = 3.07 (1.78 to 5.72) *Birth ≤37 weeks:* OR = 3.23 (1.75 to 5.98) ORs adjusted for ethnicity, maternal age, smoking, chorionicity, pregnancy following in vitro fertilization, time interval between the twin and singleton pregnancies	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** low risk of bias **Attrition:** low risk of bias **Prognostic factor measurement:** moder ate risk of bias (not reported if participants/providers were blinded to test results) **Outcome measurement:** moder ate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** low risk of bias **Analysis and Reporting:** low risk of bias **Other information** None

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
in t win pregnancy subsequent to a previous preterm singleton birth. **Study dates** Between 1994 and 2008 **Source of funding** Not reported	monochorionic-diamniotic: 63% **Inclusion Criteria** Women with twin pregnancy subsequent to a singleton birth **Exclusion Criteria** A twin or multiple birth in the immediately preceding birth, preterm twin birth for medical maternal or fetal reasons not encountered in the previous (singleton) pregnancy, presence of twin-to-twin transfusion syndrome and with suggestive findings of fetal echocardiography, presence of fetal chromosomal or structural anomalies, fetal death of one twin, and transfer from another hospital		There were no cases of cervical cerclage.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	with incomplete medical data. Preterm inductions and caesarean sections for non-recurrent maternal of fetal health reasons; twin-twin transfusion syndrome				
Full citation Pagani, G, Stagnati, V, Fichera, A, Prefumo, F., Cervical length at mid-gestation in screening for preterm birth in twin pregnancy, Ultrasound in Obstetrics & Gynecology, 48, 56-60, 2016 **Ref Id** 795362 **Country/ies where the study was carried out** Italy **Study type**	**Sample size** N=940 twin pregnancies **Characteristics** Maternal age (median (IQR)): birth <32 weeks = 34 (30-39), birth ≥32 weeks = 33 (29-37); previous preterm birth (n (%)): birth <32 weeks = 5 (6.4), birth ≥32 weeks = 26 (3); cerclage/pessary placement (n (%)): birth <32 weeks = 11 (14.1), birth ≥32 weeks = 30 (3.5);	**Tests** **Index test** CL measurement (testing performed transvaginally between 18 and 23 weeks' gestation) **Reference standard** Spontaneous preterm birth prior 32 weeks	**Methods** Twin pregnancies with 2 live fetuses (where the first scan was performed before 16+0 weeks' gestation) were identified from the ultrasound electronic database. Cervical cerclage or Arabin's pessary placement were offered after individualized counselling in case of a CL ≤20mm or cervical dilatation (at any stage) with membranes at or beyond the external cervical on clinical examination.	**Results** Diagnostic accuracy of CL measurement to predict spontaneous preterm birth <32 weeks: CL <36 mm: sensitivity (95% CI) = 64.1 (52.4 - 74.66); specificity (95% CI) = 62.76 (59.4 - 66.0)	**Limitations** Risk of bias was assessed using QUADAS-II for diagnostic accuracy **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Retrospective cohort study **Aim of the study** To assess the predictive value of CL for spontaneous PTB <32 weeks' gestation in twin pregnancies and to calculate the cut-off point that has the best sensitivity and specificity. **Study dates** Between June 2001 and December 2013 **Source of funding** Not reported	CL (mm) (median (IQR)): birth <32 weeks = 34.5 (28.5-40.0), birth ≥32 weeks = 38.0 (34.0-42.0) **Inclusion Criteria** Twin pregnancies **Exclusion Criteria** At least 1 fetus with structural or chromosomal abnormalities; higher order pregnancy; monoamniotic pregnancy; pregnancy referred after 16 weeks; cases complicated by twin-to-twin transfusion syndrome (TTTS) or those that required intrauterine therapy; pregnancies with indicated PTB; or follow-up data unavailable.		Spontaneous PTB was defined as spontaneous onset of labour and subsequent birth of at least one live fetus between 24 and 32 weeks' gestation, regardless of the mode of birth.		**B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern (in 4.4% women either cervical cerclage or Arabin's pessary was placed) **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. Concerns regarding applicability Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderate risk of bias for the main analysis (4.4% women with either cervical cerclage or Arabin's pessary were included)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Attrition: low risk of bias **Prognostic factor measurement:** moder ate risk of bias (not reported if participants/providers were blinded to test results) **Outcome measurement:** low of bias **Confounding:** low risk of bias **Analysis and Reporting:** low risk of bias **Other information** None
Full citation Roman,A.S, Pessel,C, Fox,N, Klauser,C.K, Saltzman,D, Rebarber,A., Vaginal fetal fibronectin as a predictor of spontaneous preterm delivery in triplet gestations, Journal of Maternal-Fetal and Neonatal	**Sample size** N=56 triplet pregnancies **Characteristics** Median age at birth: 34.4 weeks (range 23.1-37.1); Chorionicity: tri/tri: 44 (79%); di/tri: 12 (21%)	**Tests** **Index test** fFN (testing performed between 22 and 32 weeks' gestation) **Reference standard** Preterm birth before: 1) <28 weeks	**Methods** Serial fetal fibronectin samples were collected every 2–3 weeks from 22 0/7 until 31 6/7 weeks of gestation, or until birth if the woman gave birth prior to 32 weeks. A fetal fibronectin concentration of 50 ng/mL or greater was	**Results** <u>Diagnostic accuracy of fetal fibronectin to predict spontaneous preterm birth before:</u> 1) <28 weeks: TP=3, FP=9, FN=1, TN=43 2) <30 weeks: TP=6, FP=7, FN=2, TN=41 3) <32 weeks: TP=9, FP=6, FN=6, TN=35	**Limitations** Risk of bias was assessed using QUADAS-II **A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Medicine, 25, 1921-1923, 2012 **Ref Id** 798868 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To assess the diagnostic accuracy of vaginal fetal fibronectin sampling for predicting preterm birth in asymptomatic women with triplet gestations. **Study dates** Between 1998 and 2010 **Source of funding** Not reported.	**Inclusion Criteria** Women with triplet pregnancies who were asymptomatic for signs of preterm labour and for whom fFN testing was performed between 22 and 32 weeks' gestation. **Exclusion Criteria** Women with a medically indicated preterm birth e.g. due to preeclampsia or intrauterine growth restriction.	2) <30 weeks 3) <32 weeks	considered to be positive. Routine evaluation of cervical length and fFN in all triplet pregnancies approximately every 2 weeks from 22 to 32 weeks of gestation. Spontaneous preterm birth was defined as birth as a consequence of preterm labour or preterm, premature rupture of membranes. For the purpose of this study, a woman with a positive fFN test result at any time from 22–32 weeks' gestation was considered to have a positive fFN result. For the outcomes of spontaneous preterm birth <28, <30 and <32 weeks' gestation, only fFN testing was included that was done before those		Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			gestational ages, respectively.		introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? No Could the reference standard, its conduct, or its interpretation have introduced bias? High risk **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** None
Full citation Roman, A., Saccone, G., Dude, C. M., Ward, A., Anastasio, H., Dugoff, L., Zullo, F., Berghella, V.,	**Sample size** N=580 women with twin pregnancies (n=175 (30.2%) were monochorionic diamniotic	**Tests** **Index test** CL measurement (CL ≤5 mm, ≤10 mm, ≤15 mm, ≤25 mm, ≤30 mm,	**Methods** Data on all consecutive asymptomatic women with twin pregnancy who underwent	**Results** <u>Diagnostic accuracy of CL measurement (measured at 18 0/7–23 6/7 weeks) to predict spontaneous preterm birth prior 32 weeks in monochorionic diamniotic twin pregnancies:</u>	**Limitations** Risk of bias was assessed using QUADAS2 for diagnostic accuracy

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Midtrimester transvaginal ultrasound cervical length screening for spontaneous preterm birth in diamniotic twin pregnancies according to chorionicity, European Journal of Obstetrics Gynecology and Reproductive Biology, 229, 57-63, 2018 **Ref Id** 898003 **Country/ies where the study was carried out** USA and Italy **Study type** Retrospective cohort study **Aim of the study** To compare the transvaginal ultrasound cervical length at midtrimester in screening for	pregnancies, n=405 (69.8%) were dichorionic pregnancies). **Characteristics** Maternal age (mean (SD)): monochorionic = 31.2 (4.79); dichorionic = 32.0 (5.1) Prior spontaneous preterm birth: monochorionic = 15 (8.6%); dichorionic = 33 (8.1%) **Inclusion Criteria** All consecutive asymptomatic women twin pregnancy who underwent transvaginal ultrasound cervical length screening at University of Naples Federico II (Naples, Italy), at Division of Maternal Fetal Medicine Thomas Jefferson University Hospital	testing performed transvaginally between 18 0/7–23 6/7 weeks' gestation) **Reference standard** Spontaneous preterm birth prior 32 weeks	transvaginal ultrasound cervical length screening at University of Naples Federico II (Naples, Italy), at Division of Maternal Fetal Medicine Thomas Jefferson University Hospital (Philadelphia, PA), and at Division of Maternal Fetal Medicine University of Pennsylvania (Philadelphia, PA) at the time of routine second trimester fetal ultrasound exam at 18 0/7–23 6/7 weeks from January 2014 to January 2017 were included in a dedicated database. Spontaneous PTB defined as either spontaneous onset of preterm labour or PPROM.	CL ≤5 mm: sensitivity (95% CI) = 13% (7–29); specificity (95% CI) = 99% (98–100) CL ≤10 mm: sensitivity (95% CI) = 29% (19–39); specificity (95% CI) = 98% (97–99) CL ≤15 mm: sensitivity (95% CI) = 42% (39–61); specificity (95% CI) = 97% (95–97) CL ≤25 mm: sensitivity (95% CI) = 59% (48–66); specificity (95% CI) = 89% (87–91) CL ≤30 mm: sensitivity (95% CI) = 70% (56–79); specificity (95% CI) = 79% (71–80) <u>Diagnostic accuracy of CL measurement (measured at 18 0/7–23 6/7 weeks) to predict spontaneous preterm birth prior 32 weeks in dichorionic diamniotic twin pregnancies:</u> CL ≤5 mm: sensitivity (95% CI) = 12% (10–24); specificity (95% CI) = 99% (98–100) CL ≤10 mm: sensitivity (95% CI) = 29% (23–33); specificity (95% CI) = 98% (97–99) CL ≤15 mm: sensitivity (95% CI) = 40% (39–47); specificity (95% CI) = 97% (95–97) CL ≤25 mm: sensitivity (95% CI) = 57% (51–65); specificity (95% CI) = 88% (87–90) CL ≤30 mm: sensitivity (95% CI) = 67% (62–76); specificity (95% CI) = 77% (73–80)	**A. Risk of Bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Low risk **Index Test** **A. Risk of Bias** Were the index test results interpreted without knowledge of the results of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
spontaneous preterm birth in asymptomatic twins in monochorionic diamniotic compared to dichorionic diamniotic pregnancy. **Study dates** Between January 2014 to January 2017 **Source of funding** No financial support was received for this study.	(Philadelphia, PA), and at Division of Maternal Fetal Medicine University of Pennsylvania (Philadelphia, PA) at the time of routine second trimester fetal ultrasound exam at 18 0/7–23 6/7 weeks from January 2014 to January 2017. **Exclusion Criteria** Women with monoamniotic twins, twin pregnancies with twin-twin transfusion syndrome, use of vaginal progesterone, pessary or cerclage in place, major fetal malformations or genetic anomalies at the time of the transvaginal ultrasound cervical length scan. Fetal demise or selective reduction of any of the twins before				reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	birth were excluded from the analysis.				Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information None
Full citation Schaaf, J. M, Hof, M. H, Mol, B. W, Abu-Hanna, A, Ravelli, A. C., Recurrence risk of preterm birth in subsequent twin pregnancy after preterm singleton delivery, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 119, 1624-9, 2012 **Ref Id** 795508 **Country/ies where the study was carried out** the Netherlands **Study type** Prospective cohort study **Aim of the study** To investigate the recurrence risk of preterm birth in	**Sample size** N=4071 women who had a twin birth following a previous index singleton birth (n=232 preterm singleton, n=3839 term singleton). **Characteristics** Mean maternal age: preterm singleton: 29.8 years(+-3.8); term singleton: 29.4 years (+-4); median interval to subsequent twin pregnancy: preterm singleton: 28 months (IQR 21-39); term singleton: 20 months (IQR 22-37)	**Tests** Adjusted odds ratios to measure the association between history of preterm birth and subsequent risk of spontaneous preterm birth in twin pregnancies (defined as birth before 37 completed weeks).	**Methods** This study was performed in a nationwide prospective cohort using The Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing informatio n on pregnancies, births and (re)admissions until 28 days after birth. Preterm birth was defined as birth before 37 completed weeks of gestation.	**Results** <u>OR (95% CI) for history of singleton preterm birth to predict a subsequent risk of spontaneous preterm birth of twin pregnancy defined as birth before 37 weeks of gestation):</u> OR = 7.8 (5.5 to 11.2) <u>OR (95% CI) for history of singleton preterm birth to predict a subsequent risk of spontaneous preterm birth of twin pregnancy defined as birth between 34+0 and 36+6 weeks of gestation:</u> OR = 7.3 (5.0 to 10.6) <u>OR (95% CI) for history of singleton preterm birth to predict a subsequent risk of spontaneous preterm birth of twin pregnancy defined as birth between 30+0 to 33+6 weeks of gestation:</u> OR = 14.0 (3.9 to 50.5) <u>OR (95% CI) for history of singleton preterm birth to predict a subsequent risk of spontaneous preterm birth of twin pregnancy defined as birth between 22+0 to 29+6 weeks of gestation:</u>	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderat e risk of bias (data were collected from a perinatal registry via a linkage of 3 different registries; however, only 53% second births in the perinatal registry were linked to the first matching birth; not reported e.g. how many women were treated with cerclage or cervical pessary intervention, or pregnancies complicated with FFTS) **Attrition:** low risk of bias **Prognostic factor measurement:** moder ate risk of bias (not reported if participants/providers were blinded to test results)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
subsequent twin pregnancy following previous preterm singleton delivery. **Study dates** Between 1 January and 31 December 2007. **Source of funding** None	**Inclusion Criteria** From the linked cohort all multiparous women who gave birth to twins (second birth) after a previous singleton pregnancy (first birth). **Exclusion Criteria** All pregnancies with antepartum fetal mortality, those involving major congenital anomalies and iatrogenic preterm births in the subsequent twin pregnancies.			OR = 9.5 (1.8 to 48.9) reference: term birth OR adjusted for artificial reproductive technology and socio-economic status	**Outcome measurement:** moderate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** moderate risk of bias (adjusted only for ART and socio-economic status, other potentially important confounding factors were not adjusted for) **Analysis and Reporting:** low risk of bias **Other information** None
Full citation	**Sample size**	**Tests**	**Methods**	**Results**	**Limitations**
Skentou,C., Souka,A.P., To,M.S., Liao,A.W., Nicolaides,K.H., Prediction of preterm delivery in twins by cervical assessment at 23 weeks, Ultrasound	N=434 twin pregnancies (n=313 (67.5%) dichorionic, n=151 (32.5%) monochorionic)	**Index test** CL measurement (testing performed transvaginally between 22-24 weeks' gestation)	Data on pregnancy outcome were obtained from the computerized system in a labour ward, and in those women who gave birth in other hospitals, from either the women	<u>Diagnostic accuracy of CL measurement to predict spontaneous preterm birth prior 33 weeks:</u> CL <15 mm: sensitivity (95% CI) = 0.18 (0.07 - 0.35); specificity (95% CI) = 0.99 (0.97 - 1.00) CL <20 mm: sensitivity (95% CI) = 0.26 (0.13 - 0.44); specificity (95% CI) = 0.97 (0.95 - 0.98)	Risk of bias was assessed using QUADAS-II for diagnostic accuracy **A. Risk of Bias** **Patient Sampling**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
in Obstetrics and Gynecology, 17, 7-10, 2001 **Ref Id** 270845 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** To examine the possible value of cervical assessment at 23 weeks in the prediction of risk for spontaneous early preterm birth **Study dates** Not reported **Source of funding** The study was supported by a grant from The Fetal Medicine	**Characteristics** Maternal age: n=203 (44%) ≤35 years; n=100 (22%) had 1 or more miscarriages and/or terminations or pregnancy before 16 weeks of gestation; n=26 (5.6%) had had 1 or more previous spontaneous preterm birth; Spontaneous preterm birth before 33 weeks was 7.8% (8.1% for dichorionic and 7.2% for monochorionic twins). **Inclusion Criteria** Twin pregnancies **Exclusion Criteria**	**Reference standard** Spontaneous preterm birth before 33 weeks	**themselves or their** general medical practitioners. In 13 women with short cervical lengths (0-19 mm) a cervical suture was placed; other women were managed expectantly without bed rest or prophylactic antibiotics or tocolytics.	CL <25 mm: sensitivity (95% CI) = 0.35 (0.20 - 0.54); specificity (95% CI) = 0.92 (0.89 - 0.94)	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** Patient characteristics and setting Are there concerns that the included patients and setting do not match the review question? Unclear concern ('spontaneous' preterm birth not defined; in n=13 women with short cervical lengths (0-19 mm) a cervical suture was placed) **Index Test** **A. Risk of Bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Foundation (Charity no. 1037116)	Women with iatrogenic birth before 33 weeks				Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern **Reference Standard** **A. Risk of Bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern **Flow and Timing** **A. Risk of Bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? Low concern **Other information** None
Full citation Soriano,D., Weisz,B., Seidman,D.S., Chetrit,A., Schiff,E., Lipitz,S., Achiron,R., The role of sonographic assessment of cervical length in the prediction of preterm birth in primigravidae with twin gestation conceived after infertility treatment, Acta Obstetricia et Gynecologica Scandinavica, 81, 39-43, 2002 **Ref Id** 271132 **Country/ies where the study was carried out** Israel	**Sample size** N=44 women with twin pregnancies **Characteristics** 2 out of 44 twins were monochorionic; CL measurement was performed at a mean of 22.7 weeks (+-2.5); mean gestational age at birth: 36.1 weeks (+-2.6); birth before or at 34 weeks due to premature labour: 20.5%; premature rupture of membranes: 10.4%	**Tests** Adjusted odds ratios to measure the association between CL measurement (at 18-24 weeks) and spontaneous preterm birth in twin pregnancies (defined as birth before or at 35 weeks).	**Methods** The information on cervical measurements was kept blinded from women and caregivers, and was not used for clinical management. Therefore, no cervical cerclage was performed. Data regarding the obstetric outcome were collected via review of the prenatal office charts, and maternal inpatient records.	**Results** <u>OR (95% CI) for CL measurement (cut-off 35 mm) to predict spontaneous preterm birth of twin pregnancy defined as birth before or at 35 weeks of gestation:</u> OR = 33.3 (4.55 to 100)* reference: birth after 35 weeks OR adjusted for maternal age, body mass index, smoking, and work during pregnancy *calculated by the NGA 2019 technical team	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderate risk of bias (no exclusion criteria were reported) **Attrition:** low risk of bias **Prognostic factor measurement:** high risk of bias (participants/providers were not blinded to test results) **Outcome measurement:** moderate risk of bias ('spontaneous' preterm birth not defined) **Confounding:** low risk of bias

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** To investigate our ability to accurately predict the risk of preterm birth in women carrying twin pregnancies. **Study dates** Between January 1996 and December 1996 **Source of funding** Not reported	**Inclusion Criteria** Women pregnant for the first time, for whom accurate dating was available, as they all conceived as a result of infertility treatment; those who had a normal uterine cavity proven by hysterosalpingography (HSG) or hysteroscopy; those had a routine second trimester (18–24weeks) ultrasonographic anatomic survey. **Exclusion Criteria** Not reported				**Analysis and Reporting:** low risk of bias **Other information** None
Full citation Vayssiere,C., Favre,R., Audibert,F., Chauvet,M.P., Gaucherand,P., Tardif,D., Grange,G., Novoa,A., Descamps,P.,	**Sample size** N=251 women with twin pregnancies at 22 weeks' gestation, N=215 women twin pregnancies at 27 weeks' gestation, N=121 women	**Tests** 1) Adjusted odds ratios to measure the association between CL measurement (at 21-23 weeks) and spontaneous preterm birth in twin pregnancies	**Methods** This was a prospective multicenter study between January 1997 and March 1999 at 13 centers in France. The population consisted of the twin	**Results** 1) OR (95% CI) for CL measurement (at 21-23 weeks) to predict spontaneous preterm birth of twin pregnancies (defined as birth before 32 or 35 weeks of gestation): *Spontaneous preterm birth <32 weeks:* CL ≤30 mm OR = 7.0 (2.2 to 22.5) reference: CL >30 mm	**Limitations** Limitations assessed with the QUIPS for prognostic factors: **Participants:** moderate risk of bias (4 women received a cerclage after membrane prolapse into cervix that was

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Perdu,M., Andrini,E., Janse-Marec,J., Maillard,F., Nisand,I., Cervical length and funneling at 22 and 27 weeks to predict spontaneous birth before 32 weeks in twin pregnancies: a French prospective multicenter study, American Journal of Obstetrics and Gynecology, 187, 1596-1604, 2002 **Ref Id** 270304 **Country/ies where the study was carried out** France **Study type** Prospective cohort study **Aim of the study** To assess the accuracy of routine screening for very preterm twin births by ultrasound	were included at both periods The population consisted of the twin pregnancies with routine ultrasound examinations that were scheduled between 21 and 23 completed weeks of gestation (22 weeks) and between 26 and 28 weeks completed weeks of gestation (27 weeks). These two periods were assessed independently, and women could be included in one or both. **Characteristics** Previous preterm birth at 25-32 weeks: 21-23 weeks' gestation: 1.2%, 26-28 weeks' gestation: 1.9%; previous preterm birth at 32-37 weeks: 21-23	(defined as birth before at <32 or <35 weeks) 2) Adjusted odds ratios to measure the association between CL measurement (at 26-28 weeks) and spontaneous preterm birth in twin pregnancies (defined as birth before at <35 weeks)	pregnancies with routine ultrasound examinations that were scheduled between 21 and 23 completed weeks of gestation and between 26 and 28 weeks completed weeks of gestation. These two periods were assessed independently, and women could be included in one or both. The ultrasonography data were recorded and stored in research charts that were not available routinely to the clinical staff, except in the case of an obvious prolapse of the membranes into the cervix (5 cases), defined by a water sac visible in the cervix with a speculum. Spontaneous preterm birth defined as the onset of spontaneous labour	*Spontaneous preterm birth <35 weeks:* CL ≤30 mm OR = 3.2 (3.1 to 7.9) reference: CL >30 mm OR adjusted for the presence of funneling <u>2) OR (95% CI) for CL measurement (at 26-28 weeks) to predict spontaneous preterm birth of twin pregnancies (defined as birth before 35 weeks gestation):</u> CL ≤25 mm OR = 7.8 (3.2 to 19.1) reference: CL >25 mm OR adjusted for the presence of funneling	observed at the 22-week ultrasound measurement) **Attrition:** moderate risk of bias (not all women were included in the analyses) **Prognostic factor measurement:** moderate risk of bias (unclear if women were blinded to test results) **Outcome measurement:** low risk of bias **Confounding:** moderate risk of bias (adjusted only for the presence of funneling, other potentially important confounding factors were not adjusted for). **Analysis and Reporting:** low risk of bias **Other information** None

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
measurements of cervical length and funneling at 22 and 27 weeks of gestation in a large multicenter study. **Study dates** Between January 1997 and March 1999 **Source of funding** Not reported	weeks' gestation: 2.4%, 26-28 weeks' gestation: 2.3%; mean CL: 21-23 weeks' gestation: 40.6 mm (+-9.6), 26-28 weeks' gestation: 34.5 mm (+-10.7); mean gestational age at birth: 21-23 weeks' gestation: 35.8 weeks (+-2.8), 26-28 weeks' gestation: 36 weeks (+-2.3); spontaneous preterm birth <32 weeks: 21-23 weeks' gestation: 5.2%, 26-28 weeks' gestation: 3.3%; spontaneous preterm birth <35 weeks: 21-23 weeks' gestation: 13.2%, 26-28 weeks' gestation: 12.1%; presence of funneling: 21-23 weeks' gestation: 12.9%, 26-28		or preterm premature rupture of membranes (PPROM), regardless of whether the labour that followed the rupture was spontaneous or induced.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	weeks' gestation: 26.5%; **Inclusion Criteria** Twin pregnancies with routine ultrasound examinations that were scheduled between 21 and 23 completed weeks of gestation (22 weeks) and between 26 and 28 weeks completed weeks of gestation (27 weeks) **Exclusion Criteria** Women with prophylactic cerclage, placenta previa, major fetal anomaly, twin-twin transfusion syndrome, ruptured membranes, or undetermined gest ational age.				

Appendix E – Forest plots

Forest plots for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

No meta-analysis was undertaken for this review and so there are no forest plots.

Appendix F – GRADE tables

GRADE profile for review question: What is the optimal screening programme to predict the risk of the risk of spontaneous preterm birth in twin and triplet pregnancy?

Table 9: Clinical evidence profile for cervical length screening to predict the risk of spontaneous preterm birth in twin and triplet pregnancy

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Twin pregnancy										
Preterm birth <28 weeks' gestation										
Measurement at 20-24 weeks' gestation										
CL cut-off (mm): 20	3	591	Very serious[1]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.35 (0.14 to 0.62)	0.93 (0.91 to 0.95)	⨁⨁⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25	3	637	Very serious[2]	Not possible to assess as no data reported	No serious indirectness	Serious[3]	0.64 (0.41 to 0.83)	0.93 (0.91 to 0.95)	⨁⊖⊖⊖ VERY LOW	CRITICAL
CL cut-off (mm): 35	3	637	Very serious[2]	Not possible to assess as no data reported	No serious indirectness	Very serious[3]	0.82 (0.60 to 0.95)	0.66 (0.62 to 0.69)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <32 weeks' gestation										
Measurement at 18-23 weeks' gestation										

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
CL cut-off (mm): 36	1	940	Very serious[4]	No serious inconsistency	No serious indirectness	Serious[3]	0.64 (0.52 to 0.75)	0.63 (0.59 to 0.66)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Measurement at 18 0/6 and 23 6/7 weeks' gestation										
Monochorionic diamniotic										
CL cut-off (mm): 5	1	175	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.13 (0.07 to 0.29)	0.99 (0.98 to 1.00)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 10	1	175	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.29 (0.19 to 0.39)	0.98 (0.97 to 0.99)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 15	1	175	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.42 (0.39 to 0.61)	0.97 (0.95 to 0.97)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 25	1	175	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.59 (0.48 to 0.66)	0.89 (0.87 to 0.91)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 30	1	175	Serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	0.70 (0.56 to 0.79)	0.79 (0.71 to 0.80)	⊕⊕⊖⊖ LOW	CRITICAL
Dichorionic diamniotic										
CL cut-off (mm): 5	1	405	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.12 (0.10 to 0.24)	0.99 (0.98 to 1.00)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 10	1	405	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.29 (0.23 to 0.33)	0.98 (0.97 to 0.99)	⊕⊕⊕⊖ MODERATE	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
CL cut-off (mm): 15	1	405	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.40 (0.39 to 0.47)	0.97 (0.95 0.97)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 25	1	405	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	0.57 (0.51 to 0.65)	0.88 (0.87 to 0.90)	⊕⊕⊕⊖ MODERATE	CRITICAL
CL cut-off (mm): 30	1	405	Serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	0.67 (0.62 to 0.76)	0.77 (0.73 to 0.80)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement at 20-24 weeks' gestation										
CL cut-off (mm): 20	5	1955	Very serious[6]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.39 (0.31 to 0.48)	0.96 (0.95 to 0.97)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25	6	2039	Vey serious[7]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.54 (0.45 to 0.62)	0.91 (0.90 to 0.92)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 30	4	1812	Very serious[8]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.65 (0.56 to 0.74)	0.78 (0.76 to 0.80)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 35	5	1889	Very serious[9]	Not possible to assess as no data reported	No serious indirectness	Serious[3]	0.81 (0.73 to 0.87)	0.58 (0.56 to 0.61)	⊕⊖⊖⊖ VERY LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Measurement after 24 weeks' gestation										
CL cut-off (mm): 25	3	511	Very serious[10]	Not possible to assess as no data reported	No serious indirectness	Serious[3]	0.65 (0.45 to 0.81)	0.76 (0.72 to 0.79)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <33 weeks' gestation										
Measurement at 20-24 weeks' gestation										
CL cut-off (mm): 35	1	18	Very serious[11]	No serious inconsistency	No serious indirectness	Very serious[3]	0.50 (0.9 to 0.91)	0.94 (0.72 to 0.99)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <34 weeks' gestation										
Measurement at 20-24 weeks' gestation										
CL cut-off (mm): 20	5	1760	Very serious[12]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.29 (0.23 to 0.35)	0.97 (0.96 to 0.98)	⨁⨁⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25	6	1987	Very serious[13]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.40 (0.38 to 0.46)	0.93 (0.92 to 0.94)	⨁⨁⊖⊖ LOW	CRITICAL
CL cut-off (mm): 30	5	2014	Very serious[14]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.56 (0.50 to 0.62)	0.81 (0.79 to 0.83)	⨁⨁⊖⊖ LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
CL cut-off (mm): 35	6	1884	Very serious[15]	Not possible to assess as no data reported	No serious indirectness	Serious[3]	0.79 (0.74 to 0.84)	0.60 (0.57 to 0.62)	⊕⊖⊖⊖ VERY LOW	CRITICAL
CL cut-off (mm): 38	1	193	Very serious[16]	No serious inconsistency	No serious indirectness	Serious[3]	0.68 (0.55 to 0.78)	0.50 (0.42 to 0.58)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Measurement at 21-23 weeks' gestation										
CL cut-off (mm): 35	1	116	Serious[17]	No serious inconsistency	No serious indirectness	No serious imprecision	0.39 (0.12 to 0.65)	0.71 (0.62 to 0.80)	⊕⊕⊕⊖ MODERATE	CRITICAL
Measurement at 22-24 weeks' gestation										
CL cut-off (mm): 15	1	434	Very serious[18]	No serious inconsistency	No serious indirectness	No serious imprecision	0.18 (0.07 to 0.35)	0.99 (0.97 to 1.00)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 20	1	434	Very serious[18]	No serious inconsistency	No serious indirectness	No serious imprecision	0.26 (0.13 to 0.44)	0.97 (0.95 to 0.98)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25	1	434	Very serious[18]	No serious inconsistency	No serious indirectness	No serious imprecision	0.35 (0.20 to 0.54)	0.92 (0.89 to 0.94)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement after 24 weeks' gestation										
CL cut-off (mm): 25	4	594	Very serious[19]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.44 (0.34 to 0.53)	0.81 (0.78 to 0.85)	⊕⊕⊖⊖ LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
CL cut-off (mm): 35	1	85	Very serious[20]	No serious inconsistency	No serious indirectness	Serious[3]	0.94 (0.73 to 0.99)	0.49 (0.37 to 0.60)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Measurement at 26-28 weeks' gestation										
CL cut-off (mm): 25	1	116	Serious[17]	No serious inconsistency	No serious indirectness	Serious[3]	0.54 (0.27 to 0.81)	0.87 (0.81 to 0.94)	⊕⊕⊖⊖ LOW	CRITICAL
Preterm birth <35 weeks' gestation										
Measurement after 24 weeks' gestation										
CL cut-off (mm): 33	1	101	Very serious[21]	No serious inconsistency	No serious indirectness	Serious[3]	0.68 (0.47 to 0.84)	0.54 (0.44 to 0.65)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <37 weeks' gestation										
Measurement at 20-24 weeks' gestation										
CL cut-off (mm): 25	4	434	Very serious[22]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.21 (0.15 to 0.27)	0.95 (0.92 to 0.98)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 30	2	218	Very serious[23]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.29 (0.18 to 0.43)	0.91 (0.86 to 0.95)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 35	2	134	Very serious[24]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.56 (0.43 to 0.68)	0.63 (0.50 to 0.74)	⊕⊕⊖⊖ LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Measurement after 24 weeks' gestation										
CL cut-off (mm): 25	2	276	Very serious[24]	Not possible to assess as no data reported	No serious indirectness	No serious imprecision	0.43 (0.35 to 0.51)	0.77 (0.68 to 0.84)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 33	1	101	Very serious[21]	Not applicable	No serious indirectness	Serious[3]	0.69 (0.53 to 0.82)	0.60 (0.48 to 0.71)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Triplet pregnancy										
Preterm birth <28 weeks' gestation										
Measurement at 18-24 weeks' gestation										
CL cut-off (mm): 15 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.11 (0 to 0.48)	0.95 (0.87 to 0.99)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 20 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.22 (0.03 to 0.60)	0.93 (0.86 to 0.97)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25[25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.33 (0.08 to 0.70)	0.90 (0.81 to 0.95)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement at 15-20 weeks' gestation										
CL cut-off (mm): 25[27]	1	50	Very serious[28]	No serious inconsistency	No serious indirectness	Serious[3]	0.5 (0.16 to 0.84)	1.00 (0.92 to 1.00)	⊕⊖⊖⊖ VERY LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Measurement at 21-24 weeks' gestation										
CL cut-off (mm): 25[27]	1	50	Very serious[28]	No serious inconsistency	No serious indirectness	Very serious[3]	0.86 (0.42 to 1.00)	0.79 (0.64 to 0.90)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Measurement at 25-28 weeks' gestation										
CL cut-off (mm): 20[27]	1	46	Very serious[28]	No serious inconsistency	No serious indirectness	Very serious[3]	1.00 (0.40 to 1.00)	0.57 (0.41 to 0.72)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <30 weeks' gestation										
Measurement at 18-24 weeks' gestation										
CL cut-off (mm): 15 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.17 (0.04 to 0.41)	0.97 (0.91 to 1)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 20 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.22 (0.06 to 0.48)	0.95 (0.88 to 0.98)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.28 (0.10 to 0.53)	0.91 (0.82 to 0.96)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement at 15-20 weeks' gestation										
CL cut-off (mm): 25 [27]	1	49	Very serious[28]	No serious inconsistency	No serious indirectness	No serious imprecision	0.36 (0.11 to 0.69)	1.00 (0.91 to 1.00)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement at 21-24 weeks' gestation										
CL cut-off (mm): 25 [27]	1	49	Very serious[28]	No serious inconsistency	No serious indirectness	Very serious[3]	0.70 (0.35 to 0.93)	0.82 (0.66 to 0.92)	⊕⊖⊖⊖ VERY LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Measurement at 25-28 weeks' gestation										
CL cut-off (mm): 20 [27]	1	46	Very serious[28]	No serious inconsistency	No serious indirectness	Very serious[3]	1.00 (0.59 to 1.00)	0.62 (0.45 to 0.77)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <32 weeks' gestation										
Measurement at 18-24 weeks' gestation										
CL cut-off (mm): 15 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.09 (0.02 to 0.24)	0.97 (0.89 to 0.97)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 20 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.21 (0.09 to 0.38)	0.97 (0.89 to 1)	⊕⊕⊖⊖ LOW	CRITICAL
CL cut-off (mm): 25 [25]	1	96	Very serious[26]	No serious inconsistency	No serious indirectness	No serious imprecision	0.27 (0.13 to 0.44)	0.95 (0.87 to 0.99)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement at 15-20 weeks' gestation										
CL cut-off (mm): 25 [27]	1	47	Very serious[28]	No serious inconsistency	No serious indirectness	No serious imprecision	0.25 (0.07 to 0.52)	1.00 (0.89 to 1.00)	⊕⊕⊖⊖ LOW	CRITICAL
Measurement at 21-24 weeks' gestation										
CL cut-off (mm): 25 [27]	1	47	Very serious[28]	No serious inconsistency	No serious indirectness	Serious[3]	0.60 (0.32 to 0.84)	0.84 (0.67 to 0.95)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Measurement at 25-28 weeks' gestation										
CL cut-off (mm): 20 [27]	1	44	Very serious[28]	No serious inconsistency	No serious indirectness	Very serious[3]	0.83 (0.52 to 0.98)	0.66 (0.47 to 0.81)	⊕⊖⊖⊖ VERY LOW	CRITICAL

CI: confidence interval; CL: cervical length; mm: millimetre; RoB: risk of bias

1 (2 very high RoB) Unclear if selection of participants may have introduced bias in 2 studies; spontaneous preterm birth is not defined in all 3 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 3 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 2 studies; the reference standard results were interpreted with knowledge of the results of the index test in 1 study
2 (2 very high RoB) Unclear if selection of participants may have introduced bias in 2 studies; spontaneous preterm birth is not defined in 2 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 3 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 2 studies; the reference standard results were interpreted with knowledge of the results of the index test in 1 study; in 1 study some women had cervical cerclage or the administration of progesterone vaginal pessaries
3 The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results are judged to be very seriously imprecise
4 Unclear if selection of participants may have introduced bias; in 4.4% women either cervical cerclage or Arabin's pessary was placed; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test
5 Unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test
6 (most very high RoB) Unclear if selection of participants may have introduced bias in 4 studies; spontaneous preterm birth is not defined in 3 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 5 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 2 studies; the reference standard results were interpreted with knowledge of the results of the index test in 2 studies; in 2 studies some women had cervical cerclage or the administration of progesterone vaginal pessaries; in 1 study not all participants were included in the analysis
7 (most very high RoB) Unclear if selection of participants may have introduced bias in 5 studies; spontaneous preterm birth is not defined in 4 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 6 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 3 studies; in 2 studies some women had cervical cerclage or the administration of progesterone vaginal pessaries; in 1 study not all participants were included in the analysis; in 1 study 65% of the population had preterm labour symptoms
8 (most very high RoB) Unclear if selection of participants may have introduced bias in 3 studies; spontaneous preterm birth is not defined in 2 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 4 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 2 studies; in 2 studies some women had cervical cerclage or the administration of progesterone vaginal pessaries; in 1 study not all participants were included in the analysis
9 (most very high RoB) Unclear if selection of participants may have introduced bias in 4 studies; spontaneous preterm birth is not defined in 3 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 5 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 3 studies; in 2 studies some women had cervical cerclage or the administration of progesterone vaginal pessaries; in 1 study not all participants were included in the analysis
10 (most very high RoB) Unclear if selection of participants may have introduced bias in 3 studies; spontaneous preterm birth is not defined in 2 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 3 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 1 study; in 1 study 65% of the population had preterm labour symptoms; in 1 study not all participants were included in the analysis
11 Unclear if selection of participants may have introduced bias; spontaneous preterm birth is not defined; in two women a cerclage was performed at 21 and 23 weeks' gestation because of cervical shortening and dilatation; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

12 (most very high RoB) Unclear if selection of participants may have introduced bias in 3 studies; spontaneous preterm birth is not defined in 4 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 2 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 5 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 2 studies; in 1 study some women had cervical cerclage or the administration of progesterone vaginal pessaries

13 (most very high RoB) Unclear if selection of participants may have introduced bias in 4 studies; spontaneous preterm birth is not defined in 5 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 3 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 6 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 4 studies; in 1 study some women had cervical cerclage or the administration of progesterone vaginal pessaries; in 1 study 65% of the population had preterm labour symptoms

14 (most very high RoB) Unclear if selection of participants may have introduced bias in 4 studies; spontaneous preterm birth is not defined in 3 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 2 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 5 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 2 studies; the reference standard results were interpreted with knowledge of the results of the index test in 3 studies; in 1 study some women had cervical cerclage or the administration of progesterone vaginal pessaries; in 1 study not all participants were included in the analysis

15 (most very high RoB) Unclear if selection of participants may have introduced bias in all 4 studies; spontaneous preterm birth is not defined in all 4 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 2 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 4 studies; the reference standard results were interpreted with knowledge of the results of the index test in 2 studies; in 1 study some women had cervical cerclage or the administration of progesterone vaginal pessaries

16 Spontaneous preterm birth is not defined; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

17 Unclear if the index test results were interpreted without knowledge of the results of the reference standard

18 Unclear if selection of participants may have introduced bias; in n=13 women with short cervical lengths (0-19 mm) a cervical suture was placed; spontaneous preterm birth is not defined; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

19 (both very high RoB) Unclear if selection of participants may have introduced bias in both studies; spontaneous preterm birth is not defined in both studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all both studies; the reference standard results were interpreted with knowledge of the results of the index test in both studies; in 1 study 65% of the population had preterm labour symptoms

20 Unclear if selection of participants may have introduced bias; spontaneous preterm birth is not defined; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

21 Unclear if selection of participants may have introduced bias; not reported e.g. how many women were treated with cerclage or cervical pessary intervention; exclusion criteria not reported; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

22 (most very high RoB) Unclear if selection of participants may have introduced bias in 4 studies; spontaneous preterm birth is not defined in 5 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 3 studies; in 1 study no exclusion criteria were reported; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all 6 studies and if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; the reference standard results were interpreted with knowledge of the results of the index test in 5 studies; in 1 study 65% of the population had preterm labour symptoms

23 (both very high RoB) Unclear if selection of participants may have introduced bias in both studies; spontaneous preterm birth is not defined in both studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in both studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all both studies; the reference standard results were interpreted with knowledge of the results of the index test in 1 study

24 (both very high RoB) Unclear if selection of participants may have introduced bias in both studies; spontaneous preterm birth is not defined in 1 study; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in all both studies; the reference standard results were interpreted with knowledge of the results of the index test in 2 studies
25 analysis excludes cases complicated by twin-twin transfusion syndrome, treated with laser therapy, cerclage or pessary
26 Spontaneous preterm birth is not defined; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test
27 analysis excludes measurement taken after placement of a cervical cerclage
28 Unclear if selection of participants may have introduced bias; spontaneous preterm birth is not defined; unclear if the index test results were interpreted without knowledge of the results of the reference standard and if the reference standard results were interpreted without knowledge of the results of the index test

Table 10: Clinical evidence profile for fetal fibronectin screening to predict the risk of spontaneous preterm birth in twin and triplet pregnancy

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Twin pregnancy										
Testing at 22-34 weeks' gestation										
Preterm birth <32 week' gestation	2	302	Very serious[1]	Serious[2]	No serious indirectness	No serious imprecision	0.33 (0.14 to 0.60)	0.94 (0.85 to 0.97)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <34 weeks' gestation	6	576	Very serious[3]	Serious[2]	No serious indirectness	No serious imprecision	0.39 (0.29 to 0.51)	0.80 (0.74 to 0.86)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <37 weeks' gestation	5	520	Very serious[4]	Serious[2]	No serious indirectness	No serious imprecision	0.33 (0.25 to 0.45)	0.87 (0.80 to 0.94)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Triplet pregnancy										
Testing at 22-32 weeks' gestation										

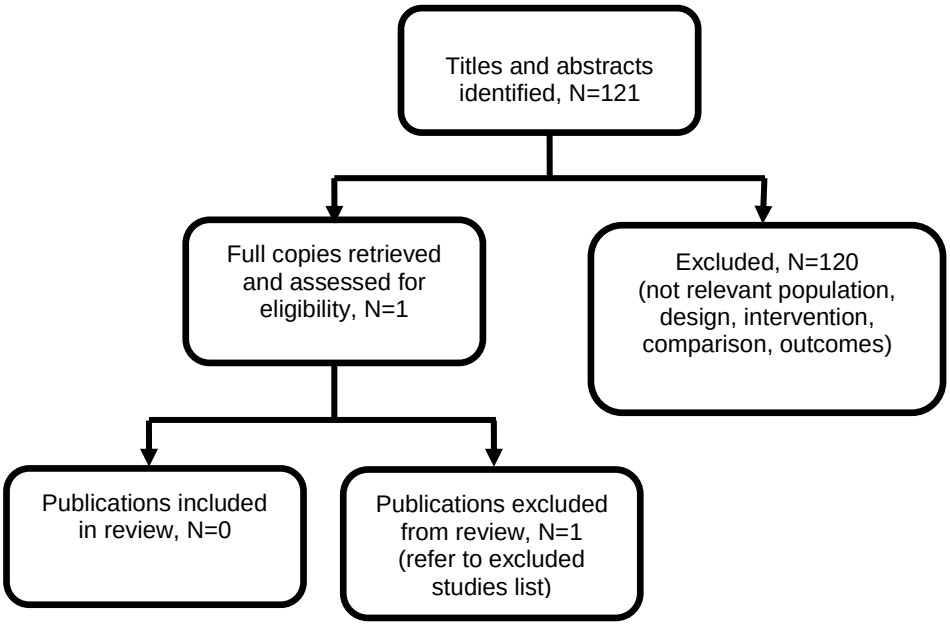
Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Quality of the evidence (GRADE)	Importance
Preterm birth <28 weeks' gestation	1	56	Very serious[5]	No serious inconsistency	No serious indirectness	Very serious[6]	0.75 (0.19 to 0.99)	0.83 (0.70 to 0.92)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <30 weeks' gestation	1	56	Very serious[5]	No serious inconsistency	No serious indirectness	Very serious[6]	0.75 (0.35 to 0.97)	0.85 (0.72 to 0.94)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Preterm birth <32 weeks' gestation	1	56	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	0.60 (0.32 to 0.84)	0.85 (0.71 to 0.94)	⊕⊖⊖⊖ VERY LOW	CRITICAL

CI: confidence interval; RoB: risk of bias
1 (both very high RoB) Unclear if selection of participants may have introduced bias in both studies; spontaneous preterm birth is not defined in both studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 1 study; unclear if the index test results were interpreted without knowledge of the results of the reference standard in both studies; the reference standard results were interpreted with knowledge of the results of the index test in 1 study; in 1 study 65% of the population had preterm labour symptoms
2 The quality of the evidence was downgraded by 1 level because of heterogeneity as the authors of Conde-Agudelo 2010a systematic review stated that "there was a graphical and statistical heterogeneity of predictive performance among studies as confirmed by I^2 values greater than 50% in almost all meta-analyses"
3 (most very high RoB) Unclear if selection of participants may have introduced bias in 6 studies; spontaneous preterm birth is not defined in 4 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 4 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in 5 studies; the reference standard results were interpreted with knowledge of the results of the index test in 1 study and unclear in 2 studies; no exclusion criteria were reported in 1 study; in 1 study 65% of the population had preterm labour symptoms
4 (most very high RoB) Unclear if selection of participants may have introduced bias in 4 studies; spontaneous preterm birth is not defined in 3 studies; not reported if or how many women treated, for example, with cerclage or cervical pessary intervention or similar in 3 studies; unclear if the index test results were interpreted without knowledge of the results of the reference standard in 4 studies; the reference standard results were interpreted with knowledge of the results of the index test in 1 study and unclear in 2 studies; no exclusion criteria were reported in 1 study; in 1 study 65% of the population had preterm labour symptoms. 1 study is an abstract so it was not possible to assess the risk of bias
5 Unclear if the index test results were interpreted without knowledge of the results of the reference standard; the reference standard results were interpreted with knowledge of the results of the index test
6 The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results are judged to be very seriously imprecise

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal screening programme to predict spontaneous preterm birth in twin and triplet pregnancy?

Figure 3: Flow diagram of economic article selection for the optimal screening programme to predict spontaneous preterm birth in twin and triplet pregnancy



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix J – Economic analysis

Economic analysis for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

A single economic analysis was undertaken to assess both the cost effectiveness of screening to predict the risk of spontaneous preterm birth and intervention to prevent preterm birth in twin pregnancy. This analysis is described in evidence review [B2] (interventions for the prevention of spontaneous preterm birth).

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal screening programme to predict the risk of spontaneous preterm birth in twin and triplet pregnancy?

Clinical studies

Study	Reason for Exclusion
Aboulghar,M.M., Aboulghar,M.A., Mourad,L., Serour,G.I., Mansour,R.T., Ultrasound cervical measurement and prediction of spontaneous preterm birth in ICSI pregnancies: a prospective controlled study, Reproductive Biomedicine Online, 18, 296-300, 2009	Included in Conde-Agudelo 2010 systematic review
Adeyemi,O., Osoba,L., The role of phosphorylated insulin-like growth factor binding protein-1 in predicting pre-term labour in twin pregnancies, Journal of Obstetrics and Gynaecology, 30, 571-573, 2010	Not a predictive test outlined in the review protocol
Alexander, Sophie, Boulvain, Michel, Ceysens, Gilles, Haelterman, Edwige, Zhang, Wei-Hong, Repeat digital cervical assessment in pregnancy for identifying women at risk of preterm labour, Cochrane Database of Systematic Reviews, 2010	Relevant papers from this review were assessed for a potential inclusion
Amodeo Hernandez, M., De La Hoz Freitas, E., Rodriguez Rodriguez, B., Mantrana Bermejo, E., Ostos Serna, M. R., Garrido Teruel, R., Preterm birth risk on multiple gestation: Value of the transvaginal ultrasound cervical length measurement and the fetal fibronectin test, Journal of Maternal-Fetal and Neonatal Medicine, 23, 307, 2010	Conference abstract
Ananth, C. V., Kirby, R. S., Vintzileos, A. M., Recurrence of preterm birth in twin pregnancies in the presence of a prior singleton preterm birth, J Matern Fetal Neonatal Med, 21, 289-95, 2008	A mixed population as it includes symptomatic and asymptomatic women
Arabin, B., Roos, C., Kollen, B., van Eyck, J., Comparison of transvaginal sonography in recumbent and standing maternal positions to predict spontaneous preterm birth in singleton and twin pregnancies, Ultrasound Obstet Gynecol, 27, 377-86, 2006	Included in Conde-Agudelo 2010 systematic review
Asnafi,N, Basirat,Z, Hajian-Tilaki,K, Dadvar,S., Assessment of cervical length by transvaginal ultrasonography to predict preterm delivery in twin pregnancy, Journal of Maternal-Fetal and Neonatal Medicine, 26, 1435-1438, 2013	The study does not report diagnostic accuracy measures
Azria, E, The use of progestatives for the prevention of spontaneous preterm birth, Journal de gynecologie obstetrique ET biologie de la reproduction, 45, 1280-1298, 2016	Not in English language
Beckmann,C.A., Beckmann,C.R., Stanziano,G.J., Bergauer,N.K., Martin,C.B., Accuracy of maternal perception of preterm uterine activity, American Journal of Obstetrics and Gynecology, 174, 672-675, 1996	The study does not look at the prediction of the risk of spontaneous preterm birth

Study	Reason for Exclusion
Bergelin, I., Valentin, L., Cervical changes in twin pregnancies observed by transvaginal ultrasound during the latter half of pregnancy: A longitudinal, observational study, Ultrasound in Obstetrics and Gynecology, 21, 556-563, 2003	The study evaluates whether cervical width and length changes are associated with preterm birth in twin pregnancies
Bergh, E, Rebarber, A, Oppal, S, Saltzman, D. H, Klauser, C. K, Gupta, S, Fox, N. S., The association between maternal biomarkers and pathways to preterm birth in twin pregnancies, Journal of Maternal-Fetal & Neonatal Medicine, 28, 504-8, 2015	The study does not present 95% CIs for point estimates
Berghella,V., Progesterone and preterm birth prevention: Translating clinical trials data into clinical practice, American Journal of Obstetrics and Gynecology, 206, 376-386, 2012	Narrative review
Berghella,V., Baxter,J.K., Hendrix,N.W., Cervical assessment by ultrasound for preventing preterm delivery, Cochrane Database of Systematic Reviews, 2009. Article Number, -, 2009	Review of studies that included women in labour who could not be distinguished in the study
Berghella,V., Talucci,M., Desai,A., Does transvaginal sonographic measurement of cervical length before 14 weeks predict preterm delivery in high-risk pregnancies?, Ultrasound in Obstetrics and Gynecology, 21, 140-144, 2003	Singleton pregnancies
Blanc, J., Bretelle, F., Predictive tools of preterm birth in asymptomatic high-risk pregnancy, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 45, 1261-1279, 2016	Not in English language
Blondel, Béatrice, Bréart, Gérard, Berthoux, Yves, Berland, Michel, Mellier, Georges, Rudigoz, René-Charles, Thoulon, Jean-Marie, Home uterine activity monitoring in France: A randomized, controlled trial, American Journal of Obstetrics and Gynecology, 167, 424-429, 1992	The population is mixed as it includes not only twin pregnancies but also other pregnant women at high risk of preterm labour
Blondel,B., Breart,G., Berthoux,Y., Berland,M., Mellier,G., Rudigoz,R.C., Thoulon,J.M., Home uterine activity monitoring in France: a randomized, controlled trial, American Journal of Obstetrics and Gynecology, 167, 424-429, 1992	Less than a half of the population with twin gestations
Bloom, S. L., Yost, N. P., McIntire, D. D., Leveno, K. J., Recurrence of preterm birth in singleton and twin pregnancies, Obstet GynecolObstetrics and gynecology, 98, 379-85, 2001	No adjusted estimates were reported
Brizot, M. L, Hernandez, W, Liao, A. W, Bittar, R. E, Francisco, R. P, Krebs, V. L, Zugaib, M., Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study, American Journal of Obstetrics & Gynecology, 213, 82.e1-9, 2015	The study evaluates the effect of vaginal progesterone for the prevention of preterm birth in twin pregnancies
Brizot, M. L., Hernandez, W., Liao, A. W., Bittar, R. E., Francisco, R. P., Krebs, V. L., Zugaib, M., Vaginal	The study evaluates the effect of prophylactic administration of vaginal

Study	Reason for Exclusion
progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study, American Journal of Obstetrics & Gynecology, 213, 82.e1-9, 2015	natural progesterone on mean gestational age at birth and rate of spontaneous preterm birth at <34 weeks in twin pregnancies
Cetingoz,E., Cam,C., Sakalli,M., Karateke,A., Celik,C., Sancak,A., Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial, Archives of Gynecology and Obstetrics, 283, 423-429, 2011	The study evaluates whether prophylactic administration of vaginal progesterone can reduce the preterm birth in high-risk pregnancy groups including singleton and twin pregnancies
Chauhan,S.P., Scardo,J.A., Hayes,E., Abuhamad,A.Z., Berghella,V., Twins: Prevalence, problems, and preterm births, American Journal of Obstetrics and Gynecology, #203, 305-315, 2010	Review article, no new data
Colton,T., Kayne,H.L., Zhang,Y., Heeren,T., A metaanalysis of home uterine activity monitoring, American Journal of Obstetrics and Gynecology, 173, 1499-1505, 1995	Relevant studies from this review were assessed for a potential inclusion
Combs, C. A, Garite, T, Maurel, K, Das, A, Porto, M, Obstetrix Collaborative Research, Network, 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial, American Journal of Obstetrics & Gynecology, 204, 221.e1-8, 2011	The study evaluates whether prophylactic treatment with 17-alpha-hydroxyprogesterone caproate in twin pregnancy reduces neonatal morbidity by prolonging pregnancy
Combs, C. A, Garite, T. J, Maurel, K, Das, A, Obstetrix Collaborative Research, Network, Fetal fibronectin versus cervical length as predictors of preterm birth in twin pregnancy with or without 17-hydroxyprogesterone caproate, American Journal of Perinatology, 31, 1023-30, 2014	The outcome is preterm and not spontaneous preterm birth
Combs,C.A., Vaginal progesterone for asymptomatic cervical shortening and the case for universal screening of cervical length, American Journal of Obstetrics and Gynecology, 206, 101-103, 2012	Editorial
Conde-Agudelo, A, The prevention of preterm birth in twin gestations, Journal of Perinatal Medicine, 43, 2015	Conference abstract
Conde-Agudelo, A, Romero, R., Predictive accuracy of changes in transvaginal sonographic cervical length over time for preterm birth: a systematic review and metaanalysis, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 213, 789-801, 2015	Systematic review that examines the accuracy of changes in transvaginal sonographic cervical length over time in predicting preterm birth. Relevant studies from this review were assessed for a potential inclusion
Conde-Agudelo,A, Romero,R., Prediction of preterm birth in twin gestations using biophysical and biochemical tests, American Journal of Obstetrics and Gynecology, 211, 583-595, 2014	Narrative review
Crane, J. M., Van den Hof, M., Armson, B. A., Liston, R., Transvaginal ultrasound in the prediction of preterm delivery: singleton and twin gestations, Obstet Gynecol, 90, 357-63, 1997	Ineligible patient population as symptomatic women

Study	Reason for Exclusion
Crane,J.M., Hutchens,D., Follow-up cervical length in asymptomatic high-risk women and the risk of spontaneous preterm birth, Journal of Perinatology, 31, 318-323, 2011	Singleton pregnancies
Davey, M. A., Watson, L., Rayner, J. A., Rowlands, S., Risk scoring systems for predicting preterm birth with the aim of reducing associated adverse outcomes, Cochrane Database of Systematic Reviews, CD004902, 2011	Protocol of a Cochrane review
Dilek,T.U., Yazici,G., Gurbuz,A., Tasdelen,B., Gulhan,S., Dilek,B., Dilek,S., Progressive cervical length changes versus single cervical length measurement by transvaginal ultrasound for prediction of preterm delivery, Gynecologic and Obstetric Investigation, 64, 175-179, 2007	Singleton pregnancies
Dimassi, K., Bouriel, I., Triki, A., Mrabet, A., Gara, M. F., Ultrasound monitoring of cervical length in twin pregnancies, Tunisie Medicale, 95, 192-195, 2017	Not in English language
Dodd, J. M, Crowther, C. A., Specialised antenatal clinics for women with a multiple pregnancy for improving maternal and infant outcomes, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD005300, 2012	Outcomes not relevant to protocol - Cochrane review (no studies identified reporting spontaneous pre-term birth)
Dodd, J. M, Dowswell, T, Crowther, C. A., Specialised antenatal clinics for women with a multiple pregnancy for improving maternal and infant outcomes, The Cochrane Database of Systematic Reviews, 11, CD005300, 2015	Outcomes not relevant to protocol - Cochrane review (no studies identified reporting spontaneous pre-term birth)
Dodd, Jodie M, Jones, Leanne, Flenady, Vicki, Cincotta, Robert, Crowther, Caroline A, Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth, Cochrane Database of Systematic Reviews, 2013	Not a diagnostic accuracy study. The study assesses prevention of pre-term birth in women at risk
Dong, X., Iwashita, M., Ai, F., Jiang, J., Liu, H., Wu, Y., Clinical application of the combined determination of neutrophil elastase, fetal fibronectin, and cervical length in predicting preterm birth of twin pregnancies, Biomedical Research (India), 28, 4688-4695, 2017	Not clear from the paper if the reference standard is spontaneous preterm birth
Driul, L., Londero, A. P., Adorati-Menegato, A., Vogrig, E., Bertozzi, S., Fachechi, G., Forzano, L., Cacciaguerra, G., Perin, E., Miceli, A., Marchesoni, D., Therapy side-effects and predictive factors for preterm delivery in patients undergoing tocolysis with atosiban or ritodrine for threatened preterm labour, Journal of Obstetrics & Gynaecology, 34, 684-9, 2014	A mixed population as it includes only 16% multiple pregnancies
Durnwald, C. P, Momirova, V, Rouse, D. J, Caritis, S. N, Peaceman, A. M, Sciscione, A, Varner, M. W, Malone, F. D, Mercer, B. M, Thorp, J. M, Jr, Sorokin, Y, Carpenter, M. W, Lo, J, Ramin, S. M, Harper, M, Spong, C. Y, Eunice Kennedy Shriver National Institute of Child, Health, Human Development Maternal-Fetal Medicine Units, Network, Second trimester cervical length and risk of preterm birth in women with twin gestations treated	The study evaluates the rates of preterm birth before 35 weeks gestation in women with a twin gestation who received 17-alpha hydroxyprogesterone caproate compared with placebo based on their cervical length measurement at 16-20 weeks

Study	Reason for Exclusion
with 17-alpha hydroxyprogesterone caproate, Journal of Maternal-Fetal & Neonatal Medicine, 23, 1360-4, 2010	
Dyson, D. C., Crites, Y. M., Ray, D. A., Armstrong, M. A., Prevention of preterm birth in high-risk patients: the role of education and provider contact versus home uterine monitoring, American Journal of Obstetrics & Gynecology, 164, 756-62, 1991	No adjusted estimates or diagnostic accuracy measures were reported
Dyson,D.C., Danbe,K.H., Bamber,J.A., Crites,Y.M., Field,D.R., Maier,J.A., Newman,L.A., Ray,D.A., Walton,D.L., Armstrong,M.A., Monitoring women at risk for preterm labor, New England Journal of Medicine, 338, 15-19, 1998	No adjusted estimates or diagnostic accuracy measures were reported
Ebell, M., What is the best way to monitor women at risk for preterm labor?, Evidence-Based Practice, 1, 5-6, 1998	A full-text copy of the article could not be obtained
Ekwo, E. E., Gosselink, C. A., Moawad, A., Previous pregnancy outcomes and subsequent risk of preterm rupture of amniotic sac membranes, Br J Obstet GynaecolBritish journal of obstetrics and gynaecology, 100, 536-41, 1993	Study population includes singleton pregnancies with no separate reporting for twin and/or triplet pregnancies
El-Gharib, M. N, Albehoty, S. B., Transvaginal cervical length measurement at 22- to 26-week pregnancy in prediction of preterm births in twin pregnancies, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 30, 729-732, 2017	The study does not present 95% CIs for point estimates
Facco, F. L., Nash, K., Grobman, W. A., Are women who have had a preterm singleton delivery at increased risk of preterm birth in a subsequent twin pregnancy?, Am J PerinatolAmerican journal of perinatology, 25, 657-9, 2008	No adjusted estimates or diagnostic accuracy measures were reported
Fait,G., Har-Toov,J., Gull,I., Lessing,J.B., Jaffa,A., Wolman,I., Cervical length, multifetal pregnancy reduction, and prediction of preterm birth, Journal of Clinical Ultrasound, 33, 329-332, 2005	Included in Conde-Agudelo 2010 systematic review
Faron, G., Balepa, L., Parra, J., Fils, J. F., Gucciardo, L., The fetal fibronectin test: 25 years after its development, what is the evidence regarding its clinical utility? A systematic review and meta-analysis, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 1-701, 2018	Relevant studies from this review were assessed for a potential inclusion
Fichera,A., Prefumo,F., Zanardini,C., Stagnati,V., Frusca,T., Rapid cervical phIGFBP-1 test in asymptomatic twin pregnancies: role in mid-pregnancy prediction of spontaneous preterm delivery, Prenatal Diagnosis, 34, 450-459, 2014	Non relevant test
Fox, N., Bergh, E., Oppal, S., Saltzman, D., Klauser, C., Gupta, S., Rebarber, A., The association between a short cervix, fetal fibronectin, and preterm birth in twin pregnancies, analyzed by cause of preterm birth: Preterm labor, premature rupture of membranes, and	Conference abstract

Study	Reason for Exclusion
indicated preterm birth, American Journal of Obstetrics and Gynecology, 1), S400, 2014	
Fox,N.S, Rebarber,A, Klauser,C.K, Peress,D, Gutierrez,C.V, Saltzman,D.H., Prediction of spontaneous preterm birth in asymptomatic twin pregnancies using the change in cervical length over time, American Journal of Obstetrics and Gynecology, 202, 155-4, 2010	Study focuses on change in cervical length which was not specified as a relevant index test in the review protocol
Fox,N.S, Rebarber,A, Roman,A.S, Klauser,C.K, Peress,D, Saltzman,D.H., Combined fetal fibronectin and cervical length and spontaneous preterm birth in asymptomatic triplet pregnancies, Journal of Maternal-Fetal and Neonatal Medicine, 25, 2308-2311, 2012	The study does not present 95% CIs for point estimates
Fox,N.S., Jean-Pierre,C., Predanic,M., Chasen,S.T., Short cervix: is a follow-up measurement useful?, Ultrasound in Obstetrics and Gynecology, 29, 44-46, 2007	Singleton pregnancies
Fox,N.S., Saltzman,D.H., Klauser,C.K., Peress,D., Gutierrez,C.V., Rebarber,A., Prediction of spontaneous preterm birth in asymptomatic twin pregnancies with the use of combined fetal fibronectin and cervical length, American Journal of Obstetrics and Gynecology, 201, 313-315, 2009	Included in Conde-Agudelo 2010 and 2010a systematic reviews
Fuchs, F, Senat, M. V., Multiple gestations and preterm birth, Seminars In Fetal & Neonatal Medicine, 21, 113-20, 2016	Narrative review
Fuchs, F., Lefevre, C., Senat, M. V., Fernandez, H., Accuracy of fetal fibronectin for the prediction of preterm birth in symptomatic twin pregnancies: a pilot study, Sci RepScientific reports, 8, 2160, 2018	Non relevant population as symptomatic women
Fuchs,I., Tsoi,E., Henrich,W., Dudenhausen,J.W., Nicolaides,K.H., Sonographic measurement of cervical length in twin pregnancies in threatened preterm labor, Ultrasound in Obstetrics and Gynecology, 23, 42-45, 2004	Women with symptoms of preterm labour.
Gibson,J.L., Macara,L.M., Owen,P., Young,D., Macauley,J., Mackenzie,F., Prediction of preterm delivery in twin pregnancy: a prospective, observational study of cervical length and fetal fibronectin testing, Ultrasound in Obstetrics and Gynecology, 23, 561-566, 2004	Included in Conde-Agudelo 2010 and 2010a systematic reviews
Goldenberg,R.L., Iams,J.D., Das,A., Mercer,B.M., Meis,P.J., Moawad,A.H., Miodovnik,M., VanDorsten,J.P., Caritis,S.N., Thurnau,G.R., Dombrowski,M.P., Roberts,J.M., McNellis,D., The Preterm Prediction Study: sequential cervical length and fetal fibronectin testing for the prediction of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, American Journal of Obstetrics and Gynecology, 182, 636-643, 2000	The study reports relative risks but it does not specify what confounding factors were added in the regression model

Study	Reason for Exclusion
Goldenberg,R.L., Iams,J.D., Miodovnik,M., Van Dorsten,J.P., Thurnau,G., Bottoms,S., Mercer,B.M., Meis,P.J., Moawad,A.H., Das,A., Caritis,S.N., McNellis,D., The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, American Journal of Obstetrics and Gynecology, 175, 1047-1053, 1996	Included in Conde-Agudelo 2010 and 2010a systematic reviews
Gordon, M. C, McKenna, D. S, Stewart, T. L, Howard, B. C, Foster, K. F, Higby, K, Cypher, R. L, Barth, W. H., Transvaginal cervical length scans to prevent prematurity in twins: a randomized controlled trial, American Journal of Obstetrics & Gynecology, 214, 277.e1-7, 2016	The study evaluates whether use of routine transvaginal cervical length ultrasound prolongs gestation in twin pregnancies. No relevant adjusted estimates reported
Goya, M, Calle, M, Pratcorona, L, Merced, C, Rodó, C, Muñoz, B, Juan, M, Serrano, A, Llurba, E, Higueras, T, Carreras, E, Cabero, L, Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins), American Journal of Obstetrics and Gynecology, 214, 145-152, 2016	The paper examines the use of cervical pessary for the prevention of preterm birth
Grewal, J., Grantz, K. L., Zhang, C., Sciscione, A., Wing, D. A., Grobman, W. A., Newman, R. B., Wapner, R., D'Alton, M. E., Skupski, D., Nageotte, M. P., Ranzini, A. C., Owen, J., Chien, E. K., Craigo, S., Albert, P. S., Kim, S., Hediger, M. L., Louis, G. M. B., Cohort profile: NICHD fetal growth studies- Singletons and twins, International Journal of EpidemiologyInt J Epidemiol, 47, 25-25l, 2018	No diagnostic accuracy data were reported
Grisaru-Granovsky, S; Farine, D; Barrett, J; Van Eyk, N; Ryan, G; Seaward, PGR; Windrim, R. , Is a single ultrasound measurement of cervical length a predictor of the risk of preterm delivery in multifetal pregnancy?, Am J Obstet Gynecol, 178, 191S, 1998	Conference abstract
Guzman,E.R., Walters,C., O'reilly-Green,C., Kinzler,W.L., Waldron,R., Nigam,J., Vintzileos,A.M., Use of cervical ultrasonography in prediction of spontaneous preterm birth in twin gestations, American Journal of Obstetrics and Gynecology, 183, 1103-1107, 2000	Included in Conde-Agudelo 2010 systematic review
Heazell, Alexander Ep, Whitworth, Melissa, Duley, Lelia, Thornton, Jim G, Use of biochemical tests of placental function for improving pregnancy outcome, Cochrane Database of Systematic Reviews, 2015	Non relevant test
Hermans, F. J, Schuit, E, Liem, S. M, Lim, A. C, Duvekot, J, Scheepers, L. C, Woiski, M. M, Franssen, M. M, Oudijk, M. A, Bloemenkamp, K. W, Bijvanck, B. N, Bekedam, D. J, Opmeer, B. C, Mol, B. W., Indicators for Cervical Length in Twin Pregnancies, American Journal of Perinatology, 32, 1151-7, 2015	Outcomes not relevant to protocol. The study assesses the association between cervical length and maternal characteristics
Hester, A. E, Ankumah, N. E, Chauhan, S. P, Blackwell, S. C, Sibai, B. M., Twin transvaginal cervical length at 16-20 weeks and prediction of preterm birth, Journal of Maternal-Fetal & Neonatal Medicine, 01-May, 2017	The study does not present 95% CIs for point estimates

Study	Reason for Exclusion
Hiersch, L, Rosen, H, Okby, R, Freeman, H, Barrett, J, Melamed, N., The greater risk of preterm birth in triplets is mirrored by a more rapid cervical shortening along gestation, American Journal of Obstetrics and Gynecology, 215, 357.e1-357.e6, 2016	The study assesses the association between cervical length and gestational age at birth. Only reports Spearman's correlation; not possible to calculate 2x2 contingency tables
Hiilesmaa, Vilho, Taipale, Pekka, Ultrasonography of the uterine cervix and preterm delivery, Fetal and Maternal Medicine Review, 11, 7-16, 1999	Narrative review article with no new data
Hill, W. C., Fleming, A. D., Martin, R. W., Hamer, C., Knuppel, R. A., Lake, M. F., Watson, D. L., Welch, R. A., Bentley, D. L., Gookin, K. S., et al.,, Home uterine activity monitoring is associated with a reduction in preterm birth, Obstet GynecolObstetrics and gynecology, 76, 13s-18s, 1990	The population is mixed as it includes not only twin pregnancies but also other pregnant women at high risk of preterm labour
Hofmeister, C, Brizot Mde, L, Liao, A, Francisco, R. P, Zugaib, M., Two-stage transvaginal cervical length screening for preterm birth in twin pregnancies, Journal of Perinatal Medicine, 38, 479-84, 2010	The study does not present 95% CIs for point estimates
Honest, H., Bachmann, L. M., Coomarasamy, A., Gupta, J. K., Kleijnen, J., Khan, K. S., Accuracy of cervical transvaginal sonography in predicting preterm birth: a systematic review, Ultrasound Obstet GynecolUltrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 22, 305-22, 2003	There is a more up to date systematic review available that contains many of the same studies. This systematic review does not report enough data to allow sensitivity and specificity to be calculated, and it does not report which studies were included in each meta-analysis or the number of women in each analysis
Iams, JD; Johnson, FE; O'Shaughnessy, RW., A prospective random trial of home uterine activity monitoring in pregnancies at increased risk of preterm labor. Part II. , American Journal of Obstetrics and Gynecology, 159, 595-603, 1988	Less than a half of the population with multiple gestations
Iams,J.D., Goldenberg,R.L., Meis,P.J., Mercer,B.M., Moawad,A., Das,A., Thom,E., McNellis,D., Copper,R.L., Johnson,F., Roberts,J.M., The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network, New England Journal of Medicine, 334, 567-572, 1996	Singleton pregnancies
Iams,J.D., Goldsmith,L.T., Weiss,G., The preterm prediction study: maternal serum relaxin, sonographic cervical length, and spontaneous preterm birth in twins, Journal of the Society for Gynecologic Investigation, 8, 39-42, 2001	Study mainly investigates maternal serum relaxin as a predictor of preterm labour
Imseis,H.M., Albert,T.A., Iams,J.D., Identifying twin gestations at low risk for preterm birth with a transvaginal ultrasonographic cervical measurement at 24 to 26 weeks' gestation, American Journal of Obstetrics and Gynecology, 177, 1149-1155, 1997	Included in Conde-Agudelo 2010 systematic review
Jaffe Lifshitz, S., Razavi, A., Bibbo, C., Rebarber, A., Roman, A. S., Saltzman, D. H., Fox, N. S., Routine	No diagnostic accuracy data were reported

Study	Reason for Exclusion
cervical length and fetal fibronectin screening in asymptomatic twin pregnancies: Is there clinical benefit?, Journal of Maternal-Fetal and Neonatal Medicine, 27, 566-570, 2014	
Kazemier, B. M, Buijs, P. E, Mignini, L, Limpens, J, de Groot, C. J, Mol, B. W, Ebm, Connect, Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 121, 1197-208; discussion 1209, 2014	Relevant papers from this review were assessed for a potential inclusion
Khalil,M.I, Alzahrani,M.H, Ullah,A., The use of cervical length and change in cervical length for prediction of spontaneous preterm birth in asymptomatic twin pregnancies, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 169, 193-196, 2013	The study evaluates the association between cervical length and the shortening of cervical length over two measurements and preterm birth in twin pregnancies. However, no confidence intervals were reported for the relevant outcomes
Kindinger, L. M, Poon, L. C, Cacciatore, S, MacIntyre, D. A, Fox, N. S, Schuit, E, Mol, B. W, Liem, S, Lim, A. C, Serra, V, Perales, A, Hermans, F, Darzi, A, Bennett, P, Nicolaides, K. H, Teoh, T. G., The effect of gestational age and cervical length measurements in the prediction of spontaneous preterm birth in twin pregnancies: an individual patient level meta-analysis, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 123, 877-84, 2016	Non relevant outcome, i.e. predicted probability of preterm birth. Potentially relevant papers from this review were assessed for inclusion. In consideration for health economic review
Knight, J. C., Tenbrink, E., Onslow, M., Patil, A. S., Uterocervical Angle Measurement Improves Prediction of Preterm Birth in Twin Gestation, American Journal of Perinatology, 2017	The study does not present 95% CIs for point estimates
Liem, S. M, van de Mheen, L, Bekedam, D. J, van Pampus, M. G, Opmeer, B. C, Lim, A. C, Mol, B. W., Cervical length measurement for the prediction of preterm birth in symptomatic women with a twin pregnancy: a systematic review and meta-analysis, Obstetrics & Gynecology InternationalObstet Gynecol Int, 2013, 125897, 2013	Ineligible patient population as symptomatic women
Liem, S., Schuit, E., Hegeman, M., Bais, J., de Boer, K., Bloemenkamp, K., Brons, J., Duvekot, H., Bijvank, B. N., Franssen, M., Gaugler, I., de Graaf, I., Oudijk, M., Papatsonis, D., Pernet, P., Porath, M., Scheepers, L., Sikkema, M., Sporken, J., Visser, H., van Wijngaarden, W., Woiski, M., van Pampus, M., Mol, B. W., Bekedam, D., Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial, Lancet, 382, 1341-9, 2013	The study evaluates the effectiveness of a pessary to prevent preterm birth in multiple pregnancy
Liem, S., Schuit, E., Hegeman, M., Bais, J., De Boer, K., Bloemenkamp, K., Brons, J., Duvekot, H., Bijvank, B. N., Franssen, M., Gaugler, I., De Graaf, I., Oudijk, M.,	Conference abstract

Study	Reason for Exclusion
Papatsonis, D., Pernet, P., Porath, M., Scheepers, L., Sikkema, M., Sporken, J., Visser, H., Van Wijngaarden, W., Woiski, M., Van Pampus, M., Willem Mol, B., Bekedam, D., Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): A multicentre, open-label randomised controlled trial, Obstetrical and Gynecological Survey, 69, 73-75, 2014	
Lifshitz,S.J, Razavi,A, Bibbo,C, Rebarber,A, Roman,A.S, Saltzman,D.H, Fox,N.S., Routine cervical length and fetal fibronectin screening in asymptomatic twin pregnancies: is there clinical benefit?, Journal of Maternal-Fetal and Neonatal Medicine, 27, 566-570, 2014	Not assessing the accuracy of diagnostic tests. This study compares outcomes between women managed with routine serial screening versus women undergoing screening as clinically indicated
Lim, A. C, Hegeman, M. A, Huis In, T. Veld M. A, Opmeer, B. C, Bruinse, H. W, Mol, B. W., Cervical length measurement for the prediction of preterm birth in multiple pregnancies: a systematic review and bivariate meta-analysis, Ultrasound in Obstetrics & GynecologyUltrasound Obstet Gynecol, 38, 10-Jul, 2011	The study does not present 95% CIs for point estimates
Lim, A. C., Schuit, E., Papatsonis, D., van Eyck, J., Porath, M. M., van Oirschot, C. M., Hummel, P., Hasaart, T. H., Kleiverda, G., de Graaf, I. M., van Ginkel, A. A., Mol, B. W., Bruinse, H. W., Effect of 17-alpha hydroxyprogesterone caproate on cervical length in twin pregnancies, Ultrasound in Obstetrics & Gynecology, 40, 426-30, 2012	The study investigates whether 17-alpha hydroxyprogesterone caproate treatment has an effect on cervical shortening in twin pregnancies
Lim, Ac, Schuit, E, Papatsonis, D, Eyck, J, Porath, Mm, Oirschot, Cm, Hummel, P, Hasaart, Th, Kleiverda, G, Graaf, Im, Ginkel, Aa, Mol, Bw, Bruinse, Hw, Effect of 17-alpha hydroxyprogesterone caproate on cervical length in twin pregnancies, Ultrasound in Obstetrics & Gynecology, 40, 426-430, 2012	The study examines whether 17-alpha hydroxyprogesterone caproate treatment has an effect on cervical shortening in twin pregnancy (a secondary analysis of a randomised clinical trial on the effectiveness of 17-OHPC in preventing preterm birth in multiple pregnancies (the AMPHIA-trial))
Marcellin, L., Prevention of preterm birth by uterine cervical cerclage, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 45, 1299-1323, 2016	Not in English language
Maslovitz,S., Hartoov,J., Wolman,I., Jaffa,A., Lessing,J.B., Fait,G., Cervical length in the early second trimester for detection of triplet pregnancies at risk for preterm birth, Journal of Ultrasound in Medicine, 23, 1187-1191, 2004	The study does not present 95% CIs for point estimates
Matsui, M, Takahashi, Y, Iwagaki, S, Chiaki, R, Asai, K, Kawabata, I., Preliminary preventive protocol from first trimester of pregnancy to reduce preterm birth rate for dichorionic-diamniotic twins, Taiwanese Journal of Obstetrics & Gynecology, 56, 23-26, 2017	This study assessed risk factors (threatened abortion, history of chorioamnionitis, cervicitis, and bacterial vaginosis) and management of women before versus after 14 weeks gestation

Study	Reason for Exclusion
Maymon,R., Herman,A., Jauniaux,E., Frenkel,J., Ariely,S., Sherman,D., Transvaginal sonographic assessment of cervical length changes during triplet gestation, Human Reproduction, 16, 956-960, 2001	The study does not present 95% CIs for point estimates
McIntosh, J., Feltovich, H., Berghella, V., Manuck, T., The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention, American Journal of Obstetrics and Gynecology, 215, B2-B7, 2016	Review on indications for cervical length screening to prevent preterm birth in various common clinical scenarios. Potentially relevant papers from this review were assessed for inclusion
McMahon,K.S., Neerhof,M.G., Haney,E.I., Thomas,H.A., Silver,R.K., Peaceman,A.M., Prematurity in multiple gestations: identification of patients who are at low risk, American Journal of Obstetrics and Gynecology, 186, 1137-1141, 2002	The study does not report data for twin or triplet pregnancies
Medley, N., Poljak, B., Mammarella, S., Alfirevic, Z., Clinical guidelines for prevention and management of preterm birth: a systematic review, BJOG: An International Journal of Obstetrics & Gynaecology, 20, 20, 2018	Review of clinical practice guidelines for prevention and management of preterm birth in singleton and multiple pregnancies
Melamed, N, Hiersch, L, Gabbay-Benziv, R, Bardin, R, Meizner, I, Wiznitzer, A, Yogev, Y., Predictive value of cervical length in women with twin pregnancy presenting with threatened preterm labor, Ultrasound in Obstetrics & Gynecology, 46, 73-81, 2015	Women not relevant to protocol as symptomatic women
Melamed, N, Pittini, A, Hiersch, L, Yogev, Y, Korzeniewski, S. J, Romero, R, Barrett, J., Do serial measurements of cervical length improve the prediction of preterm birth in asymptomatic women with twin gestations?, American Journal of Obstetrics & Gynecology, 215, 616.e1-616.e14, 2016	The outcome is preterm and not spontaneous preterm birth
Mheen, L, Schuit, E, Lim, Ac, Porath, Mm, Papatsonis, D, Erwich, Jj, Eyck, J, Oirschot, Cm, Hummel, P, Duvekot, Jj, Hasaart, Th, Groenwold, Rh, Moons, Kg, Groot, Cj, Bruinse, Hw, Pampus, Mg, Mol, Bw, Prediction of preterm birth in multiple pregnancies: development of a multivariable model including cervical length measurement at 16 to 21 weeks' gestation, Journal d'obstetrique et gynecologie du Canada : JOGC [Journal of obstetrics and gynaecology Canada : JOGC], 36, 309-319, 2014	No subgroup analysis by the number of fetuses
Missfelder-Lobos, H., Viehweg, B., Vogtmann, Ch, Faber, R., [Perinatal management of triplet pregnancies from 1997 to 2001], Z Geburtshilfe Neonatol, 207, 179-85, 2003	Not in English language
Mol, Bwj, Cervical pessary in the reduction of preterm birth, Journal of Perinatal Medicine, 41, 2013	Conference abstract
Morin, L., Lim, K., No. 260-Ultrasound in Twin Pregnancies, Journal of Obstetrics and Gynaecology Canada, 39, e398-e411, 2017	Clinical practice guideline on ultrasound in twin pregnancies

Study	Reason for Exclusion
Moroz, L. A, Brock, C. O, Govindappagari, S, Johnson, D. L, Leopold, B. H, Gyamfi-Bannerman, C., Association between change in cervical length and spontaneous preterm birth in twin pregnancies, American Journal of Obstetrics & Gynecology, 216, 159.e1-159.e7, 2017	The study evaluates whether the rate of change in transvaginal cervical length over time is associated with spontaneous preterm birth in women with diamniotic twin pregnancies, and also describes parameters associated with an increased risk for preterm birth
Morrison, J. C., Chauhan, S. P., Magann, E. F., Istwan, N. B., Rhea, D., Stanziano, G. J., Excessive uterine contractions: Effect on the incidence of preterm delivery in twin gestation, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 50, 923-927, 2005	Study includes symptomatic women (experiencing an episode of preterm labour), no separate results for asymptomatic non-labouring women
Morrison, J. C., Naef, R. W., 3rd, Botti, J. J., Katz, M., Belluomini, J. M., McLaughlin, B. N., Prediction of spontaneous preterm birth by fetal fibronectin and uterine activity, Obstet Gynecol, 87, 649-55, 1996	The study does not report data for twin or triplet pregnancies
Mou,S.M., Sunderji,S.G., Gall,S., How,H., Patel,V., Gray,M., Kayne,H.L., Corwin,M., Multicenter randomized clinical trial of home uterine activity monitoring for detection of preterm labor, American Journal of Obstetrics and Gynecology, 165, 858-866, 1991	Less than a half of the population with multiple gestations
Naba, TS., Endovaginal echography for screening preterm labor, Revue Medicale Libanaise, 12, 27-31, 2000	A full-text copy of the article could not be obtained
O'Connor, C., McAuliffe, F. M., Breathnach, F. M., Geary, M., Daly, S., Higgins, J. R., Dornan, J., Morrison, J. J., Burke, G., Higgins, S., Mooney, E., Dicker, P., Manning, F., McParland, P., Malone, F. D., Prediction of outcome in twin pregnancy with first and early second trimester ultrasound, Journal of Maternal-Fetal and Neonatal Medicine, 26, 1030-1035, 2013	The article examines the ultrasound biometric parameters in the first and early second trimester to predict adverse pregnancy outcome
O'Connor,M.C., Arias,E., Royston,J.P., Dalrymple,I.J., The merits of special antenatal care for twin pregnancies, British Journal of Obstetrics and Gynaecology, 88, 222-230, 1981	Study includes women in labour
Oh,K.J, Park,K.H, Jeong,E.H, Lee,S.Y, Ryu,A, Kim,S.N., The change in cervical length over time as a predictor of preterm delivery in asymptomatic women with twin pregnancies who have a normal mid-trimester cervical length, Twin Research and Human Genetics: the Official Journal of the International Society for Twin Studies, 15, 516-521, 2012	The study evaluates whether change in cervical length is associated with preterm birth in twin pregnancies
Oliveira, T., de Souza, E., Mariani-Neto, C., Camano, L., Fetal fibronectin as a predictor of preterm delivery in twin gestations, International Journal of Gynaecology & Obstetrics, 62, 135-9, 1998	Included in Conde-Agudelo 2010a systematic review
Oliveira TA, Carvalho CM, de Souza E, Mariani-Neto C, Camano L. Detection of fetal fibronectin in twin pregnancies in relation to gestational age. Sao Paulo Medical Journal, 117, 121-4, 1999	The same population as in Oliveira 1999 which is included in Conde-Agudelo 2010a systematic review

Study	Reason for Exclusion
Ong,S., Smith,A., Smith,N., Campbell,D., Wilson,A., Cervical length assessment in twin pregnancies using transvaginal ultrasound, Acta Obstetricia et Gynecologica Scandinavica, 79, 851-853, 2000	No adjusted estimates or diagnostic accuracy measures were reported
Owen, J., Yost, N., Berghella, V., MacPherson, C., Swain, M., Dildy, G. A., 3rd, Miodovnik, M., Langer, O., Sibai, B., Can shortened midtrimester cervical length predict very early spontaneous preterm birth?, 191, 298-303, 2004	Singleton pregnancies
Papiernik, E., Prediction of the preterm baby, Clinics in Obstetrics & Gynaecology, 11, 315-36, 1984	Narrative review of articles, not a systematic review
Paternoster, D.M., De Paoli, M., Plebani, M., Risk factors and predictors of preterm delivery, Prenatal and Neonatal Medicine, 4, 308-11, 1999	Study does not include twin/triplet pregnancies
Ramirez, M; Turrentine, M., Comparison of fetal fibronectin and home uterine monitoring as predictors of preterm delivery in twin gestations, Am J Obstet Gynecol, 180S, 104S, 1999	Conference abstract; data on fFN testing from this paper were included in Conde-Agudelo 2010a systematic review
Reichmann, J. P., Home uterine activity monitoring: an evidence review of its utility in multiple gestations, Journal of Reproductive Medicine, 54, 559-62, 2009	Narrative review
Rode, L, Klein, K, Nicolaides, K. H, Krampl-Bettelheim, E, Tabor, A, Predict Group, Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 38, 272-280, 2011	The study evaluates whether in twin gestations treatment with progesterone pessaries, compared with placebo treatment, reduces the rate of birth before 34 weeks' gestation
Rode,L., Klein,K., Nicolaides,K.H., Krampl-Bettelheim,E., Tabor,A., Prevention of preterm delivery in Twin gestations (PREDICT): A multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone, Obstetrical and Gynecological Survey, 67, 18-19, 2012	Commentary on Rode 2011 RCT
Roman,A.S., Koklanaris,N., Paidas,M.J., Mulholland,J., Levitz,M., Rebarber,A., "Blind" vaginal fetal fibronectin as a predictor of spontaneous preterm delivery, Obstetrics and Gynecology, 105, 285-289, 2005	The study does not report data for twin or triplet pregnancies
Roman,A.S., Rebarber,A., Sfakianaki,A.K., Mulholland,J., Saltzman,D., Paidas,M.J., Minior,V., Lockwood,C.J., Vaginal fetal fibronectin as a predictor of spontaneous preterm delivery in the patient with cervical cerclage, American Journal of Obstetrics and Gynecology, 189, 1368-1373, 2003	Study includes women who were already at risk of preterm labour (not asymptomatic)
Rosen, H, Hiersch, L, Freeman, H, Barrett, J, Melamed, N., The role of serial measurements of cervical length in asymptomatic women with triplet pregnancy, Journal of Maternal-Fetal & Neonatal Medicine, 01-Jul, 2017	The study does not present 95% CIs for point estimates

Study	Reason for Exclusion
Ruiz,R.J., Fullerton,J., Brown,C.E., The utility of fFN for the prediction of preterm birth in twin gestations, JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing, 33, 446-454, 2004	Included in Conde-Agudelo 2010a systematic review
Sauvanaud, C., Equy, V., Faure, C., Boussat, B., Hoffmann, P., Sergent, F., [Transvaginal sonographic cervical length and prediction of preterm delivery in twin pregnancies with preterm labor], J Gynecol Obstet Biol Reprod (Paris), 42, 488-92, 2013	Not in English language
Sayin, NC; Varol, FG; Yilmaz, O; Kurt, I. , Efï¬• ciency of cervical sonography for the determination of preterm birth in singleton and twin pregnancies after 25 weeksâ□™ gestation, Turkish German Gynecol Assoc, 6, 229-234, 2005	Not in English language
Schwartz,R, Prieto,J., Shortened cervical length as a predictor of preterm delivery in twin gestations, Journal of Reproductive Medicine, 55, 147-150, 2010	The study does not present 95% CIs for point estimates
Senat, M. V, Porcher, R, Winer, N, Vayssiere, C, Deruelle, P, Capelle, M, Bretelle, F, Perrotin, F, Laurent, Y, Connan, L, Langer, B, Mantel, A, Azimi, S, Rozenberg, P, Groupe de Recherche en Obstetrique et, Gynecologie, Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial, American Journal of Obstetrics & Gynecology, 208, 194.e1-8, 2013	The study evaluates the use of 17 alpha-hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a twin pregnancy and a cervical length of 25 mm or less
Sentilhes, L., Senat, M. V., Ancel, P. Y., Azria, E., Benoist, G., Blanc, J., Brabant, G., Bretelle, F., Brun, S., Doret, M., Ducroux-Schouwey, C., Evrard, A., Kayem, G., Maisonneuve, E., Marcellin, L., Marret, S., Mottet, N., Paysant, S., Riethmuller, D., Rozenberg, P., Schmitz, T., Torchin, H., Langer, B., Prevention of spontaneous preterm birth: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF), European Journal of Obstetrics, Gynecology, & Reproductive Biology, 210, 217-224, 2017	Guidelines on prevention of spontaneous preterm birth
Serra,V, Perales,A, Meseguer,J, Parrilla,J.J, Lara,C, Bellver,J, Grifol,R, Alcover,I, Sala,M, Martinez-Escoriza,J.C, Pellicer,A., Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 50-57, 2013	The study evaluates the efficacy and safety of two different daily doses of vaginal natural progesterone compared with placebo
Shiozaki, A, Yoneda, S, Nakabayashi, M, Takeda, Y, Takeda, S, Sugimura, M, Yoshida, K, Tajima, A, Manabe, M, Akagi, K, Nakagawa, S, Tada, K, Imafuku, N, Ogawa, M, Mizunoe, T, Kanayama, N, Itoh, H, Minoura, S, Ogino, M, Saito, S., Multiple pregnancy, short cervix, part-time worker, steroid use, low educational level and male fetus are risk factors for preterm birth in Japan: A multicenter, prospective study,	Study population includes multiple pregnancies with no separate reporting for twin and/or triplet pregnancies

Study	Reason for Exclusion
Journal of Obstetrics and Gynaecology Research, 40, 53-61, 2014	
Souka,A.P., Heath,V., Flint,S., Sevastopoulou,I., Nicolaides,K.H., Cervical length at 23 weeks in twins in predicting spontaneous preterm delivery, Obstetrics and Gynecology, 94, 450-454, 1999	An extended analysis (To 2006) of this study was included in Conde-Agudelo 2010 systematic review
Sperling,L., Kiil,C., Larsen,L.U., Qvist,I., Bach,D., Wojdemann,K., Bladh,A., Nikkila,A., Jorgensen,C., Skajaa,K., Bang,J., Tabor,A., How to identify twins at low risk of spontaneous preterm delivery, Ultrasound in Obstetrics and Gynecology, 26, 138-144, 2005	Included in Conde-Agudelo 2010 systematic review
Sullivan, S. A., Newman, R., Prediction and prevention of preterm delivery in multiple gestations, Clin Obstet GynecolClinical obstetrics and gynecology, 47, 203-15, 2004	Narrative review
Tanaka, K, Yamada, K, Matsushima, M, Izawa, T, Furukawa, S, Kobayashi, Y, Iwashita, M., Prediction of spontaneous preterm delivery in asymptomatic twin pregnancies using cervical length and granulocyte elastase, Taiwanese Journal of Obstetrics & Gynecology, 56, 188-191, 2017	No adjusted estimates or diagnostic accuracy measures were reported
To,M.S., Fonseca,E.B., Molina,F.S., Cacho,A.M., Nicolaides,K.H., Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins, American Journal of Obstetrics and Gynecology, 194, 1360-1365, 2006	Included in Conde-Agudelo 2010 systematic review
Tolino,A., Ronsini,S., Zullo,F., Pellicano,M., Regine,V., Nappi,C., Fetal fibronectin as a screening test for premature delivery in multiple pregnancies, International Journal of Gynaecology and Obstetrics, 52, 3-7, 1996	The study does not report data for twin or triplet pregnancies
Tsikouras,P., Galazios,G., Zalvanos,A., Bouzaki,A., Athanasiadis,A., Transvaginal sonographic assessment of the cervix and preterm labor, Clinical and Experimental Obstetrics and Gynecology, 34, 159-162, 2007	The study does not include multiple pregnancy
Turitz, A. L., Ackerman, C. M., Johnson, D. L., Bank, T. C., Duong, J. K., Lee, S. M., Gyamfi-Bannerman, C., A comparison of prevaginal and postvaginal manipulation fetal fibronectin, American Journal of Obstetrics and Gynecology, 214, 646e1-646e6, 2016	The study examines whether there are differences between fetal fibronectin results obtained before and after vaginal manipulation in the form of sterile vaginal examination or transvaginal ultrasound, and to compare test characteristics of prevaginal and postvaginal manipulation fetal fibronectin tests in predicting preterm birth
Urquhart, Christine, Currell, Rosemary, Harlow, Francoise, Callow, Liz, Home uterine monitoring for detecting preterm labour, Cochrane Database of Systematic Reviews, 2017	Relevant papers from this review were assessed for a potential inclusion

Study	Reason for Exclusion
Wagura, P., Wasunna, A., Laving, A., Wamalwa, D., Ng'ang'a, P., Prevalence and factors associated with preterm birth at kenyatta national hospital, BMC Pregnancy and Childbirth, 18 (1) (no pagination), 2018	A mixed study population that includes singleton and twin pregnancies
Wennerholm,U.B., Holm,B., Mattsby-Baltzer,I., Nielsen,T., Platz-Christensen,J., Sundell,G., Hosseini,N., Hagberg,H., Fetal fibronectin, endotoxin, bacterial vaginosis and cervical length as predictors of preterm birth and neonatal morbidity in twin pregnancies, British Journal of Obstetrics and Gynaecology, 104, 1398-1404, 1997	Included in Conde-Agudelo 2010 and 2010a systematic reviews
Yang,J.H., Kuhlman,K., Daly,S., Berghella,V., Prediction of preterm birth by second trimester cervical sonography in twin pregnancies, Ultrasound in Obstetrics and Gynecology, 15, 288-291, 2000	Included in Conde-Agudelo 2010 systematic review
Yoshizato,T, Inoue,Y, Fukami,T, Sanui,A, Miyamato,S, Kawarabayashi,T., Longitudinal changes in canal length at 16-35 weeks in normal twin pregnancies and twin pregnancies with preterm labor and delivery, Journal of Obstetrics and Gynaecology Research, 36, 733-738, 2010	Women not relevant to protocol as symptomatic women
Yoshizato,T., Inoue,Y., Fukami,T., Sanui,A., Miyamato,S., Kawarabayashi,T., Longitudinal changes in canal length at 16-35 weeks in normal twin pregnancies and twin pregnancies with preterm labor and delivery, Journal of Obstetrics and Gynaecology Research, 36, 733-738, 2010	Not a predictive test outlined in the review protocol

Economic studies

Study	Reason for Exclusion
Liem,S.M., van Baaren,G.J., Delemarre,F.M., Evers,I.M., Kleiverda,G., van Loon,A.J., Langenveld,J., Schuitemaker,N., Sikkema,J.M., Opmeer,B.C., van Pampus,M.G., Mol,B.W., Bekedam,D.J., Economic analysis of use of pessary to prevent preterm birth in women with multiple pregnancy (ProTWIN trial), Ultrasound in Obstetrics and Gynecology, 44, 338-345, 2014	Relates to prevention rather than prediction of preterm birth

Appendix L – Research recommendations

No research recommendations were made for this review.