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PREDICTIVE ACCURACY OF CHANGES IN TRANSVAGINAL SONOGRAPHIC CERVICAL LENGTH OVER TIME FOR PRETERM BIRTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

OBJECTIVE—To determine the accuracy of changes in transvaginal sonographic cervical length over time in predicting preterm birth in women with singleton and twin gestations.

DATA SOURCES—PubMed, Embase, Cinahl, Lilacs, and Medion (all from inception to May 31, 2015), bibliographies, Google scholar, and conference proceedings.

STUDY ELIGIBILITY CRITERIA—Cohort or cross-sectional studies reporting on the predictive accuracy for preterm birth of changes in cervical length over time.

STUDY APPRAISAL AND SYNTHESIS METHODS—Two reviewers independently selected studies, assessed risk of bias, and extracted data. Summary receiver operating characteristic curves, pooled sensitivities, specificities and likelihood ratios were generated.

RESULTS—Fourteen studies met the inclusion criteria, of which 7 provided data on singleton gestations (3374 women) and 8 on twin gestations (1024 women). Among women with singleton gestations, the shortening of cervical length over time had a low predictive accuracy for preterm birth at <37 and <35 weeks of gestation with pooled sensitivities, specificities, and positive and negative likelihood ratios ranging from 49–74%, 44–85%, 1.3–4.1, and 0.3–0.7, respectively. In women with twin gestations, the shortening of cervical length over time had a low to moderate predictive accuracy for preterm birth at <34, <32, <30, and <28 weeks of gestation with pooled sensitivities, specificities, and positive and negative likelihood ratios ranging from 47–73%, 84–

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89%, 3.8–5.3, and 0.3–0.6, respectively. There were no statistically significant differences between the predictive accuracies for preterm birth of cervical length shortening over time and the single initial and/or final cervical length measurement in 8 of 11 studies that provided data for making these comparisons. In the largest and highest quality study, a single measurement of cervical length obtained at 24 or 28 weeks of gestation was significantly more predictive of preterm birth than any decrease in cervical length between these gestational ages.

CONCLUSIONS—Change in transvaginal sonographic cervical length over time is not a clinically useful test to predict preterm birth in women with singleton or twin gestations. A single cervical length measurement obtained between 18–24 weeks of gestation appears to be a better test to predict preterm birth than changes in cervical length over time.

Keywords

shortening in cervical length; singleton gestation; twin gestation; predictive value of test; screening; prematurity; longitudinal studies

INTRODUCTION

Preterm birth is one of the “great obstetrical syndromes” which are characterized by multiple etiologies, a long preclinical stage, frequent fetal involvement, clinical manifestations that are often adaptive in nature, and complex interactions between the fetal and maternal genome and the environment that may predispose to the syndrome.^{1,2} Transvaginal sonographic measurement of cervical length (CL) provides useful information about one of the mechanisms of disease implicated in the etiology of the preterm parturition syndrome. In 1990, Andersen et al.³ published a seminal study in which a transvaginal sonographic CL below the 50th percentile at 30 weeks of gestation was associated with a 3.7-fold increased risk of preterm birth compared with a CL at or above the 50th percentile. Logistic regression analysis showed a progressive and statistically significant trend toward higher risk of preterm birth with a shorter CL. Moreover, it was reported that a CL <39 mm had a sensitivity of 76% and a specificity of 59% to predict preterm birth at <37 weeks of gestation. Since then, transvaginal sonographic CL has been extensively investigated as a predictor of preterm birth.^{4–11} Several meta-analyses have now provided compelling evidence that a transvaginal sonographic CL measurement at 18–24 weeks of gestation is one of the strongest and most consistent predictors of preterm birth in asymptomatic women with singleton gestations, regardless of whether they have a history of preterm birth,^{12–15} and twin gestations.^{16–18}

More recently, analysis of serial measurements of transvaginal sonographic CL has shown that assessment of risk for preterm birth can be further refined. Several studies have reported that shortening of transvaginal sonographic CL over time is associated with an increased risk of preterm birth,^{9,19–23} whereas other studies have not been able to demonstrate this association.^{24–26} Recently, there has been a renewed interest in the relationship between CL changes over time and the risk of preterm birth.²⁷ The shortening of transvaginal sonographic CL over time has been proposed as a better predictor of spontaneous preterm birth than a single CL measurement.⁹ However, to the best of our knowledge, there are no studies that have systematically evaluated the predictive performance of this test.

The primary aim of this study was to determine the accuracy of changes in transvaginal sonographic CL over time to predict preterm birth in women with singleton and twin gestations through the use of formal methods for systematic reviews and meta-analytic techniques.

MATERIALS AND METHODS

This study followed a prospectively prepared protocol and is reported in accordance with recommended methods for systematic reviews of diagnostic test accuracy.^{28,29} The two authors independently retrieved and reviewed studies for eligibility, assessed their risk of bias, and extracted data. All disagreements encountered in the review process were resolved through consensus.

Data sources and searches

To identify potentially eligible studies, we searched PubMed, Embase, Cinahl, Lilacs, and Medion (all from inception to May 31, 2015) using an existing literature search strategy for systematic reviews of predictive tests for preterm birth.³⁰ Google Scholar, proceedings of congresses on preterm birth, ultrasound in obstetrics and maternal-perinatal medicine, and reference lists of identified studies were also searched. No language restrictions were applied.

Eligibility criteria

The systematic review focused on cohort or cross-sectional studies that reported on the accuracy of changes in transvaginal sonographic CL over time to predict preterm birth in asymptomatic pregnant women with a singleton or twin gestation, and that allowed construction of 2×2 contingency tables. Studies were excluded if they: (1) were case-control studies, because there is consistent evidence that they are associated with higher diagnostic or predictive accuracy compared with cohort studies;³¹ (2) assessed CL changes over time in women with cervical cerclage or pessary, preterm labor, premature rupture of membranes, or those who were receiving progestogens; (3) were reviews, case series or reports, editorials, or letters without original data; or (4) did not publish accuracy test estimates and sufficient information to calculate them could not be retrieved. For studies that resulted in multiple publications, the data from the one with the largest sample size were used and supplemented if additional information appeared in the others.

Reference standard outcomes

In women with singleton gestations: spontaneous preterm birth at <37 and <35 weeks of gestation; in women with twin gestations: spontaneous preterm birth at <34, <32, <30, and <28 weeks of gestation.

Assessment of risk of bias

Study quality was assessed using a modified version of the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool.³² The assessments were judged as “low risk”, “high risk”, or “unclear risk” of bias. The items were evaluated and interpreted were as follows:

1. *Patient selection* - “low risk of bias”: women consecutively or randomly selected; “high risk of bias”: convenience sampling (arbitrary recruitment or non-consecutive recruitment).
2. *Description of the test* - “low risk of bias”: the study described sufficient details of the technique used for measuring CL such as the plane in which images were obtained, anatomic references for the determination of CL, and number of measurements; “high risk of bias”: if this information was not reported.
3. *Reference standard* - “low risk of bias”: spontaneous preterm birth, defined as a preterm delivery after the spontaneous onset of contractions or preterm premature rupture of membranes, regardless of whether the delivery was vaginal, by cesarean section, or, in the case of rupture of membranes, induced; “high risk of bias”: inclusion of both spontaneous and indicated preterm birth in the reference standard.
4. *Blinding* - “low risk of bias”: the study clearly stated that clinicians managing the patient did not have knowledge of the CL measurement results; “high risk of bias”: unmasking of clinicians to test results.
5. *Inclusion of women in the analysis* - “low risk of bias”: if at least 90% of women recruited into the study were included in the analysis; “high risk of bias”: if less than 90% of women recruited into the study were included in the analysis.
6. *Use of interventions aimed to prevent preterm birth based on the test results* - “low risk of bias”: clinicians did not use interventions based on the results of the CL measurements; “high risk of bias”: clinicians used interventions based on the results of the test (e.g. cerclage, pessary, vaginal progesterone).

If there was insufficient information available to make a judgment about these items, then they were scored as “unclear risk of bias”. We did not calculate a summary score estimating the overall quality of each study because of the well-known problems associated with such scores.³³

Data extraction

Data were extracted from each article using a specifically designed form for capturing information on study characteristics, patients characteristics (inclusion and exclusion criteria, risk classification for preterm birth, sample size, plurality of pregnancy, and demographics), risk of bias, how the test was carried out (technique used for measuring CL, gestational ages at testing, and cutoff values used for single CL measurements and CL changes over time), and reference standard outcomes. For each study, for all reported cutoff values for single CL measurements and CL changes over time, and for all categories of preterm birth, we then extracted the number of true-positive, false-positive, true-negative, and false-negative test results. When predictive accuracy data were not available, we recalculated them from the reported results including scatter-plot graphs.

Data were extracted separately for singleton (unselected population, and low and high risk for preterm birth) and twin gestations, and for each reference standard outcome assessed. Studies that reported preterm birth at <36 weeks of gestation were grouped with those that

reported preterm birth at <37 weeks of gestation, and those reporting preterm birth at <35 weeks of gestation were considered alongside studies reporting preterm birth at <34 weeks of gestation.

Data synthesis

Data from individual studies were synthesized separately for singleton and twin gestations and stratified according to the predefined reference standard outcomes, regardless of the gestational ages at which CL was measured and cutoff values used to define shortening of CL. For singleton gestations, we synthesized data for all women, those at high risk for preterm birth, those at high risk for preterm birth with an initial normal CL, those at low risk for preterm birth, and those from unselected populations.

Data extracted from each study were arranged in 2×2 contingency tables. When any single cell in these tables contained a zero, we added 0.5 to each cell to enable calculation of likelihood ratios (LRs) and confidence intervals (CIs).³⁴ Sensitivity and specificity with 95% CIs were calculated separately for all reported cutoff values and reference standard outcomes reported. We then constructed summary receiver operating characteristic (ROC) curves by means of a bivariate random-effects approach³⁵ and calculated area under the summary ROC curves with their corresponding 95% CIs.³⁶ A two-sided $P < .05$ was considered to be statistically significant. We used random-effects bivariate regression models to meta-analyze the logit-transformed sensitivity and specificity to obtain pooled estimates and 95% CIs of these variables.^{35,37} Thereafter, we calculated LRs with 95% CIs from the pooled sensitivities and specificities for each reference standard outcome considered.³⁸ LRs for a positive test result above 10 and LRs for a negative test result below 0.1 are considered to provide strong predictive evidence in most circumstances. Moderate prediction can be achieved with LRs values of 5–10 and 0.1–0.2 whereas those <5 and >0.2 give only minimal prediction.³⁹

We assessed the heterogeneity of the results among studies through visual examination of forest plots of sensitivities and specificities and by means of the quantity I^2 .⁴⁰ A substantial level of heterogeneity was defined as an $I^2 \geq 50\%$.⁵⁰ We explored potential sources of heterogeneity by performing meta-regression analysis of subgroups defined *a priori* (study's risk of bias, gestational ages at testing, cutoff values used, sample size, prevalence of the reference standard outcome, and setting).⁴¹ We planned to assess publication and location biases,⁴² but this was not performed because there were <10 studies in each meta-analysis. Finally, we compared the predictive accuracy for spontaneous preterm birth of the initial and/or final CL measurements and the changes in CL over time in individual studies that provided this information. When comparing the performance of two predictive tests, it is more convenient to summarize the predictive accuracy with one single overall measurement. We calculated the Youden index⁴³ for the initial and/or final CL measurements and the shortening of CL over time in each study. This index is formally defined as $Sensitivity + Specificity - 1$ and its value ranges from 0 for a useless test to 1 for an ideal test. A Z-score test was then used to estimate the statistical significance of the difference between the Youden index of shortening of CL over time and that of the initial or final CL measurement.⁴³ A two-sided $P < .05$ was considered to be statistically significant.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and Review Manager (RevMan) version 5.3.5 (The Nordic Cochrane Centre, København, Denmark).

RESULTS

Selection, characteristics, and quality of studies

A total of 1732 citations were identified, of which 105 were retrieved for full text review. Of these, 91 were excluded, mainly because they did not provide data on CL changes over time, were not a test accuracy study, were duplicate publications, or provided insufficient data to construct 2×2 tables (Figure 1). Fourteen studies,^{4,44–56} including a total of 4398 women, met the inclusion criteria of which six provided data on women with singleton gestations (n=3236),^{4,44,47,49,50,53} seven on women with twin gestations (n=871),^{45,46,51,52,54–56} and one on women with singleton (n=138) and twin (n=153) gestations.⁴⁸

The main characteristics of the included studies are listed in Table 1. Five studies were conducted in the United States, four in European countries, three in Asia, and one each in Canada and Brazil. The sample size ranged from 68⁴⁹ to 2531⁴ in women with singleton gestations and from 20⁴⁵ to 209⁵⁵ in women with twin gestations. Among the seven studies performed in women with singleton gestations, five included exclusively women at high risk for preterm birth, one included only women at low risk, and the remainder included an unselected population. Prophylactic cerclage and major fetal anomalies were reported as exclusion criteria in half of the included studies. The gestational ages at initial and final CL measurement ranged from 10–28 weeks and 20–30 weeks, respectively. The initial CL measurement was carried out at 10–13 weeks in one study, at 14–19 weeks in 7 studies, at 20–24 weeks in 5 studies, and at 25–30 weeks in one study. The final CL measurement was carried out at 20–24 weeks in six studies and at 25–30 weeks in eight studies. The test result was considered abnormal if there was a shortening of CL over time 20%,^{45,51,54,56} or 25%,⁵⁵ or 13%,⁵⁴ or >10%,⁵³ or >2 mm/wk,⁵² or 2.5 mm/wk,⁴⁶ or 6.6 mm,⁵⁰ or 6 mm,⁴ or >5, >10 and >15 mm.⁴⁸ Two studies that included women with an initial CL 25 mm⁴⁴ or >30 mm⁴⁷ used a shortening of CL to <25 mm⁴⁴ or 30 mm⁴⁷ at follow up transvaginal sonography to indicate an abnormal test result. Any decrease in CL defined abnormality in two studies.^{4,49} Seven studies used ROC curve analysis to determine the optimal cutoff value for defining an abnormal change in CL over time.^{46,50–52,54–56} The remaining studies used arbitrary cutoff values to define an abnormal test result. Twelve studies provided data on the predictive accuracy of shortening in CL over time for preterm birth at <34 or <35 weeks of gestation, 4 each on preterm birth at <37 and <32 weeks of gestation, and 3 each on preterm birth at <30 and <28 weeks of gestation. The risk of bias in each included study is shown in Figure 2. Five studies (36%) fulfilled all six criteria. Nine studies (64%) had two or more methodological flaws. The most common deficiencies were related to blinding of clinicians to the test results and the use of interventions aimed to prevent preterm birth based on the test results.

Predictive accuracy for preterm birth in singleton and twin gestations

Figure 3 shows the summary ROC curves of changes in CL over time to predict spontaneous preterm birth. The shortening of CL over time had a higher predictive accuracy for preterm birth among women with twin gestations with areas under the summary ROC curves (95% CI) of 0.81 (0.74–0.89) for preterm birth at <32 weeks of gestation and 0.76 (0.69–0.83) for preterm birth at <34 weeks of gestation. Among women with singleton gestations, the areas under the summary ROC curves to predict preterm birth at <35 and <37 weeks of gestation were 0.64 (0.56–0.72) and 0.71 (0.62–0.80), respectively. The sensitivity and specificity of any shortening of CL to predict preterm birth in the single studies are shown in Figure 4. Pooled estimates of accuracy of CL changes over time for the prediction of spontaneous preterm birth are presented in Table 2. Overall, regardless of the risk status of women, reference standard outcome assessed and definition of an abnormal test result, the predictive ability of shortening of CL over time for preterm birth was low among women with singleton gestations (pooled sensitivities, specificities, and positive and negative LR_s ranging from 49–74%, 44–85%, 1.3–4.1, and 0.3–0.7, respectively) and low to moderate among women with twin gestations (pooled sensitivities, specificities, and positive and negative LR_s ranging from 47–73%, 84–89%, 3.8–5.3, and 0.3–0.6, respectively). In women with singleton gestations, the pooled positive and negative LR_s of any shortening of CL to predict preterm birth at <37 and <35 weeks of gestation were 3.2 and 0.6, and 1.3 and 0.7, respectively. In women with twin gestations, the pooled positive and negative LR_s of any shortening of CL to predict preterm birth at <34 and <32 weeks of gestation were 4.0 and 0.6 and 5.3 and 0.5, respectively. There was a substantial level of heterogeneity among studies in the meta-analyses of preterm birth at <34 weeks of gestation among women with twin gestations, which was explained entirely by the study of Khalil et al.⁵⁵ In fact, when we removed this study from the meta-analyses, the I^2 was 0% and the pooled positive likelihood ratios decreased from 4.0 to 3.0 for any shortening of CL, and from 3.8 to 2.5 for shortening of CL 20–25%.

Eleven studies (three among women with singleton gestations^{4,48,50} and eight among women with twin gestations^{45,46,48,51,52,54–56}) provided data that allowed us to compare the predictive accuracy for preterm birth of CL shortening over time and the final CL measurement (Table 3). In addition, five of these studies^{4,46,50,52,56} also allowed comparison of the predictive accuracy for preterm birth of CL shortening over time and the initial CL measurement. In eight studies,^{45,46,48,50–52,54,56} there were no statistically significant differences between the predictive accuracies of shortening of CL over time and the single initial and/final CL measurement. Two studies^{46,56} showed no differences in the predictive accuracy of shortening in CL over time and the single initial CL measurement. In one study,⁵⁵ a shortening of CL 25% was significantly more predictive of preterm birth at <34 weeks of gestation than the single final measurement of CL taken at 23–28 weeks ($P=0.03$). In two studies, the shortening of CL over time was significantly more predictive of preterm birth than the single initial CL measurement taken at 16 weeks ($P=.02$ for preterm birth at <37 weeks of gestation),⁵⁰ and at 18–21 weeks ($P=.02$ for preterm birth at <32 weeks of gestation and $P=.04$ for preterm birth at <34 weeks of gestation).⁵² In the study by Iams et al.,⁴ the largest and highest quality study included in the review, a single measurement of CL taken at 24 or 28 weeks was significantly more predictive of spontaneous preterm birth at

<35 weeks of gestation than any decrease in CL between these gestational ages ($P=.049$ at 24 weeks and $P=.008$ at 28 weeks). In this study,⁴ there were no significant differences in the accuracy to predict preterm birth at <35 weeks between a single measurement of CL taken at 24 or 28 weeks of gestation and a shortening of CL ≥ 6 mm. Overall, the predictive performance of shortening in CL over time was not significantly superior to a single measurement (initial or final) of CL taken at 20–24 weeks of gestation in any study.

COMMENT

Main findings

The results of our systematic review shows that, overall, the change in CL over time has a low predictive accuracy for preterm birth at <35 and <37 weeks of gestation in women with singleton gestations, and a low to moderate predictive accuracy for preterm birth at <34, <32, <30 and <28 weeks of gestation in women with twin gestations. Subgroup analyses according to risk status of women and the cutoff value used to define an abnormal test result did not improve predictive accuracy. In addition, data from individual studies suggest that the predictive ability for preterm birth of CL shortening over time does not differ significantly from that of a single CL measurement obtained at 18–23 or 24–28 weeks of gestation.

Several systematic reviews have assessed the predictive accuracy for spontaneous preterm birth of single CL measurements in asymptomatic women with singleton^{12–15} and twin gestations.^{16–18} Overall, among women with singleton gestations, a single CL ≥ 25 mm had a pooled positive likelihood ratio of 6.3 when performed at <20 weeks of gestation, and 4.4–4.7 when performed at 20–24 weeks of gestation, for predicting spontaneous preterm birth at <34 or <35 weeks of gestation. The corresponding pooled negative likelihood ratios ranged from 0.6–0.8. Among women with twin gestations, a CL ≥ 20 mm at 20–24 weeks of gestation had pooled positive and negative likelihood ratios of 10.1 and 0.6, respectively, to predict preterm birth at <32 weeks of gestation, and 9.0 and 0.7, respectively, to predict spontaneous preterm birth at <34 weeks of gestation. In the current study, we found that a shortening in CL over time had pooled positive likelihood ratios of 1.3–3.2 and 4.0–5.3 to predict spontaneous preterm birth in women with singleton and twin gestations, respectively. The corresponding pooled negative likelihood ratios varied between 0.5 and 0.7. The reasons for the relatively poor performance of the change in CL over time to predict spontaneous preterm birth adequately are not clear. Factors that could have affected the predictive accuracy of changes in CL over time for preterm birth include the timing and interval of CL measurements, obstetrical history, concurrent risk factors for preterm birth, the baseline risk of preterm birth in the population studied, the inclusion of women who used interventions aimed to prevent preterm birth, and the cutoff values used to define a positive test result.

Strengths and limitations of the study

The strength of our review lies in the rigorous methodological criteria used for performing a systematic review of predictive test accuracy. These included, among others: (1) the use of a prospective protocol designed to address a highly specific research question; (2) the extensive literature searches without language restrictions; (3) the study quality assessment

that was based on strict predetermined criteria; (4) the quantitative synthesis of the evidence; (5) the use of contemporary statistical methods to obtain summary measures of predictive accuracy; (6) the exploration of potential sources of heterogeneity; and (7) the comparison of the predictive ability for preterm birth of the changes in CL over time and the single CL measurements taken at the initial and/or final transvaginal sonographic examination. Our review is subject to some potential limitations. First, only approximately one third of the studies included in the review could be considered at low risk of bias. In more than half of the included studies there was a lack of blinding of test results and omission of information on whether women received any interventions aimed to prevent preterm birth based on test results. This is particularly relevant because the use of preventive therapies could introduce bias in the assessment of the test's predictive accuracy. Second, there were considerable differences in cutoff values for defining abnormal changes in CL over time among studies, which limited our ability to make comparisons. Third, 13 studies were excluded because they did not report sufficient information to construct a 2×2 table resulting in a potential loss of relevant data. Ten of these studies reported that shortening in CL over time was associated with a significant increased risk of preterm birth or that mean or median rate of CL shortening over time was significantly higher in women who delivered preterm as compared to those who delivered at term. The remaining three studies found no association between CL shortening over time and the risk of preterm birth. Finally, the statistical power of some of our meta-analyses was limited by the small number of studies within each subgroup and the relatively small sample size of some included studies.

To be clinically useful, a predictive test should be associated with an intervention that reduces the risk of preterm birth and perinatal morbidity and mortality. Currently, there is strong evidence that the administration of vaginal progesterone to women with a sonographic CL ≥ 25 mm in the midtrimester, with or without previous spontaneous preterm birth, and singleton gestation is associated with a significant reduction in the risk of both spontaneous preterm birth and neonatal morbidity and mortality.⁵⁷ We previously demonstrated that either vaginal progesterone or cerclage are equally efficacious in reducing preterm birth at <32 weeks of gestation and perinatal morbidity and mortality among women with a sonographic CL <25 mm at midtrimester, previous spontaneous preterm birth, and singleton gestation.⁵⁸ Moreover, there is growing evidence that vaginal progesterone also reduces the risk of perinatal morbidity and mortality in women with a twin gestation and a sonographic CL ≥ 25 mm in the midtrimester.^{57,59} In addition, there is some evidence indicating that cervical pessary could be useful in reducing preterm birth among women with a singleton gestation and a CL ≥ 25 mm at 20–23 weeks of gestation.⁶⁰ At present, there is no effective intervention to prevent preterm birth in women with a singleton or twin gestation and shortening of CL over time. Vaginal progesterone might be a reasonable therapy for these patients. In fact, a secondary analysis from a large randomized controlled trial in women with a singleton gestation and a prior preterm birth showed that patients treated with vaginal progesterone had significantly less CL shortening over an approximate 8-week interval than those treated with placebo.⁶¹

Implications for practice and research

Currently, CL change as a function of time cannot be considered a clinically useful test to predict spontaneous preterm birth in women with singleton or twin gestations. A single CL measurement taken at 18–24 weeks of gestation appears to be a better test to predict preterm birth than changes in CL over time, and seems to be more cost-effective (due to fewer transvaginal sonographic examinations) than serial CL measurements.

Further well-designed prospective studies are required to more rigorously define “abnormal” CL change over time in different populations and to evaluate its predictive performance for preterm birth in women with singleton or twin gestations, mainly in those with a sonographic CL >25 mm at 18–24 weeks of gestation. If such studies demonstrate that a positive test result accurately identifies those who will deliver prematurely, the next step will be to demonstrate that use of changes in CL is associated with reductions in the risk of spontaneous preterm birth by means of randomized controlled trials in which women with an “abnormal” CL change over time are allocated to receive an intervention or placebo/no intervention. Moreover, the identification of distinct patterns of change in CL as a function of gestational age and the assessment of their predictive ability for preterm birth in women with singleton and twin gestations calls for further research.

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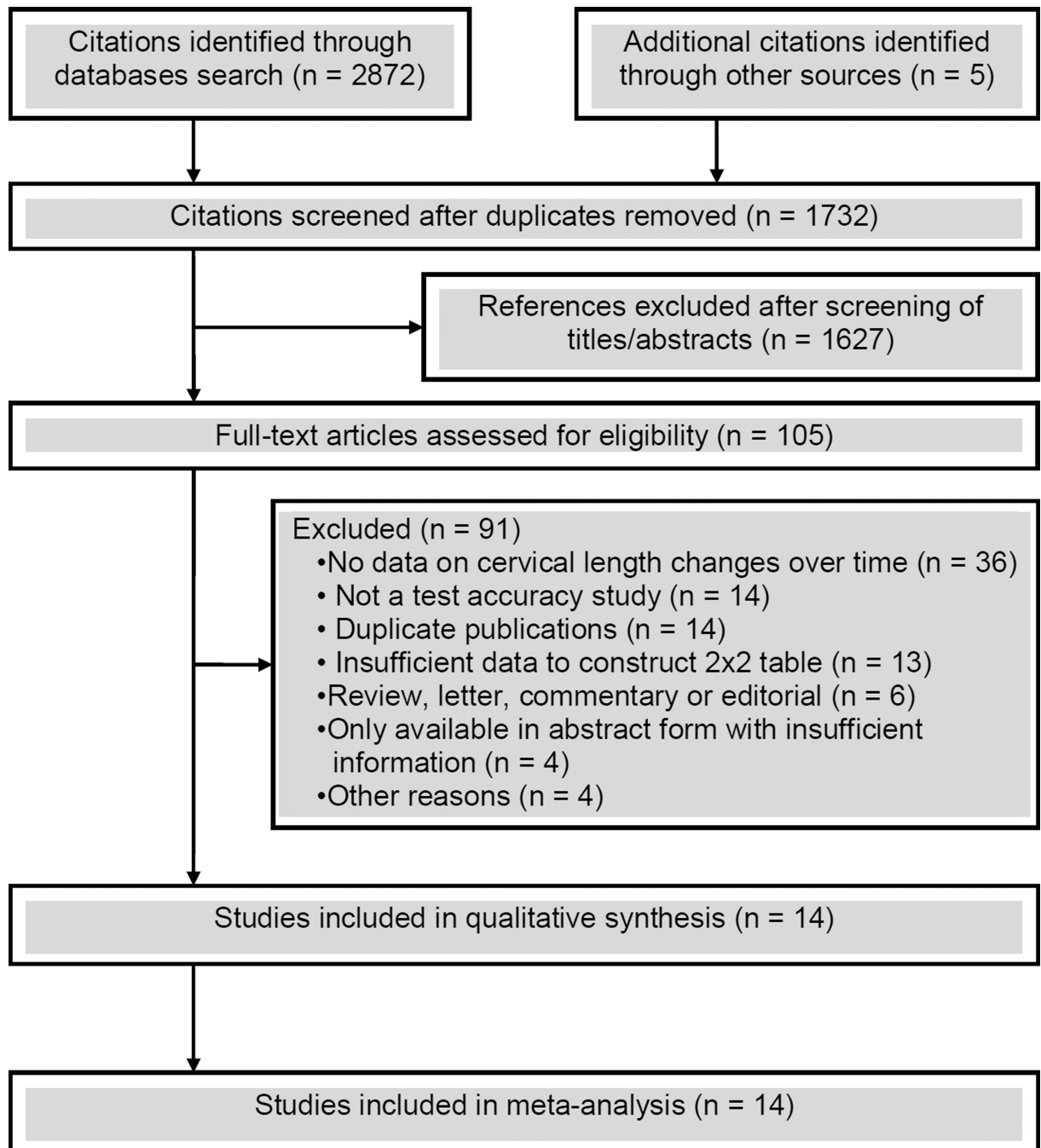


Figure 1.
Study selection process

	Women selection	Description of the test	Reference standard	Blinding	Inclusion of women in the analysis	Use of interventions to prevent preterm birth
Arabin 2006	+	+	+	?	?	?
Bergelin 2003	+	+	+	+	+	+
Berghella 2003	+	+	+	-	+	?
Crane 2011	+	+	+	-	?	?
Dilek 2007	+	+	+	?	+	?
Fox 2007	+	+	-	?	?	?
Fox 2010	+	+	+	-	?	-
Gibson 2004	+	+	+	+	+	+
Hofmeister 2010	+	+	+	-	?	-
Iams 1996	+	+	+	+	+	+
Khalil 2013	+	+	+	-	?	?
Levêque 2015	+	+	+	+	+	+
Oh 2012	+	+	+	-	+	?
Owen 2004	+	+	+	+	+	+

Figure 2. Methodological quality of studies included in the systematic review

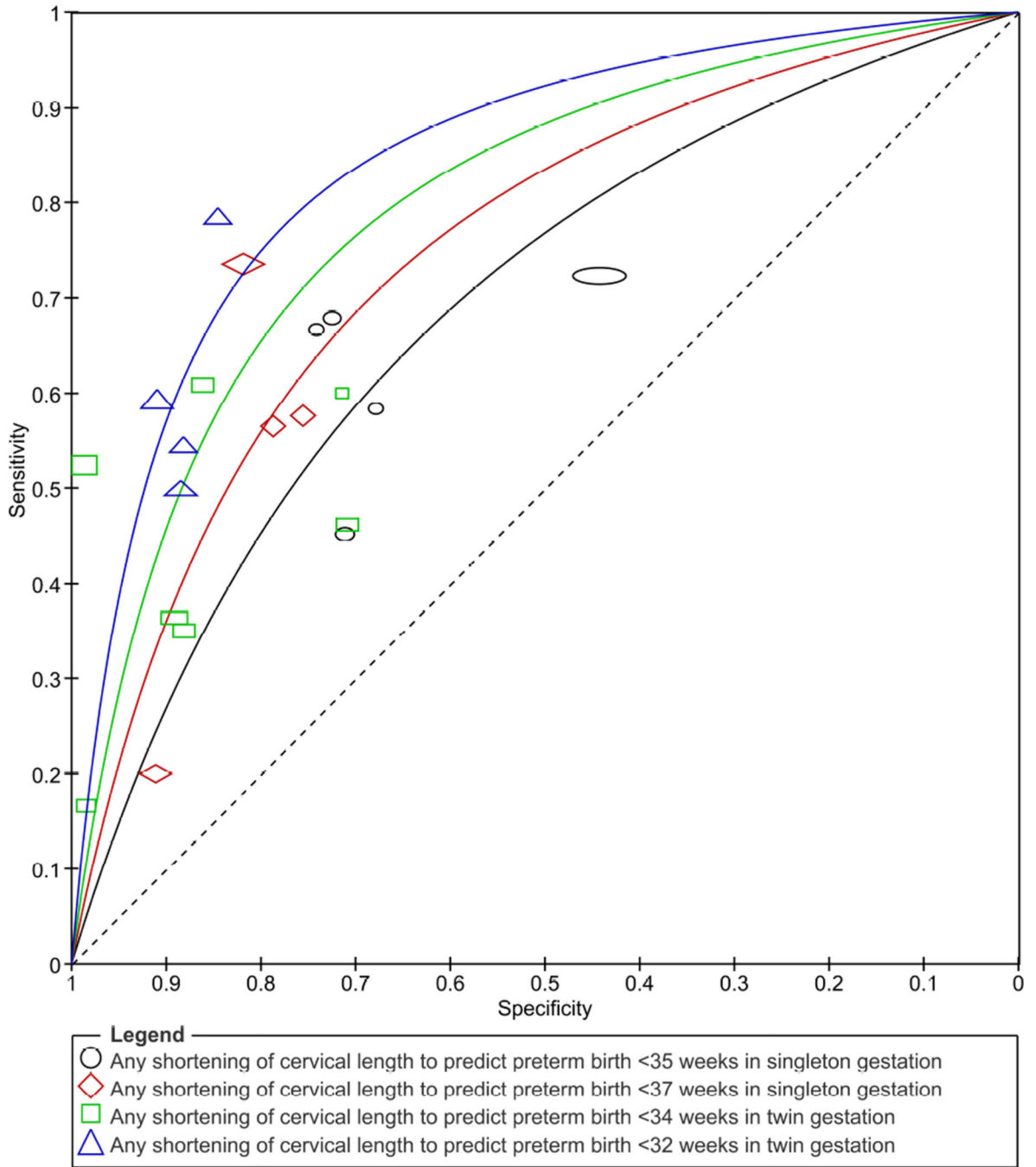
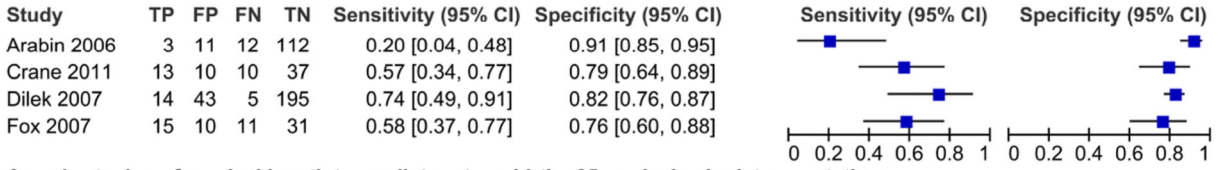
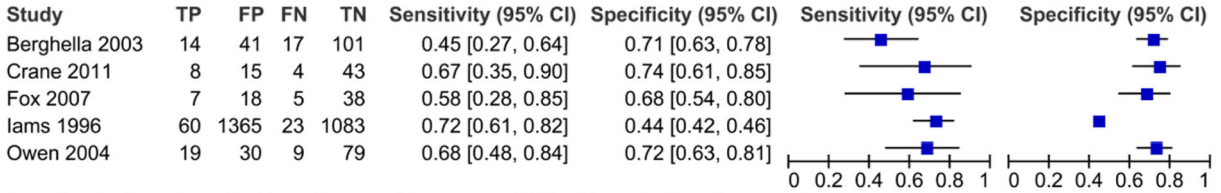


Figure 3. Summary receiver operating characteristic curves of changes in cervical length over time to predict spontaneous preterm birth

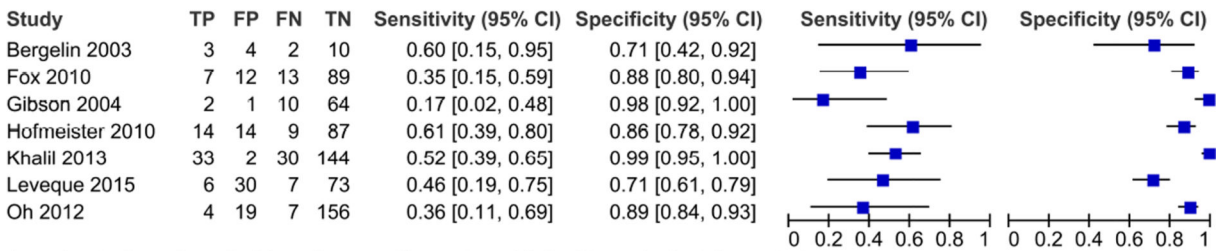
Any shortening of cervical length to predict preterm birth <37 weeks in singleton gestations



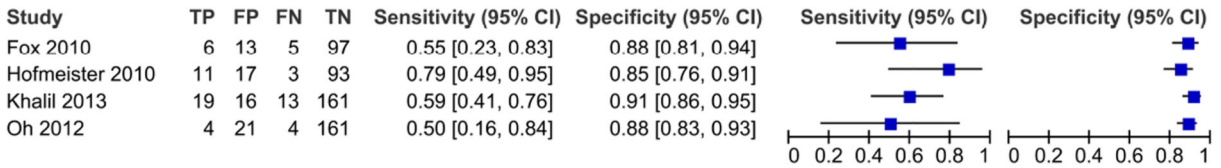
Any shortening of cervical length to predict preterm birth <35 weeks in singleton gestations



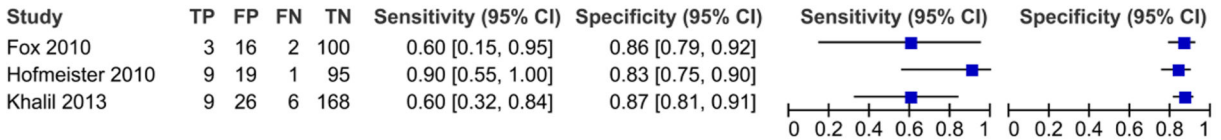
Any shortening of cervical length to predict preterm birth <34 weeks in twin gestations



Any shortening of cervical length to predict preterm birth <32 weeks in twin gestations



Any shortening of cervical length to predict preterm birth <30 weeks in twin gestations



Any shortening of cervical length to predict preterm birth <28 weeks in twin gestations

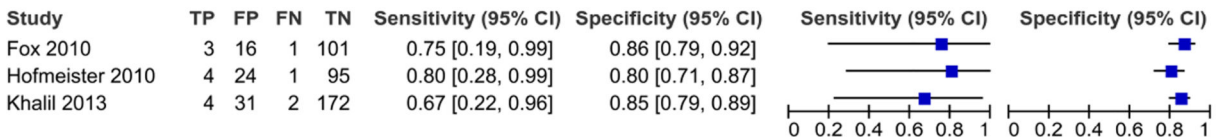


Figure 4. Forest plots of any shortening of cervical length to predict preterm birth in singleton and twin gestations

TABLE 1

Characteristics of studies included in the systematic review

Study, year (country)	No. of women	Inclusion criteria	Exclusion criteria	Gestational ages at testing (wks)	Abnormal test result	Reference standard outcome
Iams, ⁴ 1996 (United States)	2531	Singleton gestation (unselected population)	Multiple gestation, cerclage, placenta previa, major fetal anomaly	24 (range, 22–24) and 28 (range, 26–29)	Any decrease in CL; shortening of CL 6 mm	Spontaneous preterm birth <35 wk
Berghella, ⁴⁴ 2003 (United States)	173 ^a	Singleton gestation at high risk (1 previous spontaneous preterm birth between 14 and 34 wk or 2 dilatation and curettage procedures, Müllerian anomaly, cone biopsy, diethylstilbestrol exposure) with an initial CL 25 mm	Placenta previa, current drug abuse, severe fetal anomalies	10–13 and then every 2 to 4 wks up to 23 wks 6 days' gestation	Shortening of CL to <25 mm at 14–24 wks	Spontaneous preterm birth <35 wk
Bergelin, ⁴⁵ 2003 (Sweden)	20	Twin gestation	Pregnancy complications	24 and 28	Shortening of CL 20%	Spontaneous preterm birth <34 wk
Gibson, ⁴⁶ 2004 (United Kingdom)	91	Twin gestation	Twin-to-twin transfusion syndrome, fetal anomalies	18, 24, and 28	Shortening of CL 2.5 mm/wk between 18 and 28 wks' gestation	Spontaneous preterm birth <35 wk
Owen, ⁴⁷ 2004 (United States)	137 ^b	Singleton gestation at high risk (previous spontaneous preterm birth before 32 wk of gestation) with an initial CL >30 mm	Chronic medical or obstetric conditions, history of substance abuse, uterine anomalies, history-indicated cerclage	16–18 and then every two wk up to 23 wk 6 days' gestation	Shortening of CL to 30 mm at 19–24 wks	Spontaneous preterm birth <35 wk
Arabin, ⁴⁸ 2006 (The Netherlands)	291	Singleton gestation at high risk (previous spontaneous preterm birth or uterine anomaly) (N=138) and twin gestation (N=153)	Unreported	15–19 and 20–24	Shortening of CL >5, >10 and >15 mm ^c	Spontaneous preterm birth <36 wk
Fox, ⁴⁹ 2007 (United States)	68	Singleton gestation with a CL 25 mm at 16–28 wk of gestation and expectant management	Cerclage	16–28 (median, 22) and within 3 wk of the initial measurement (median, 23)	Any decrease in CL	Preterm birth <34 and <37 wk
Dilek, ⁵⁰ 2007 (Turkey)	257	Singleton gestation (low risk)	History of preterm birth, preterm PROM, cervical incompetence, multiple gestation, previously detected cervical funneling, Müllerian anomalies	16 and 24	Shortening of CL 6.6 mm	Spontaneous preterm birth <37 wk

Study, year (country)	No. of women	Inclusion criteria	Exclusion criteria	Gestational ages at testing (wks)	Abnormal test result	Reference standard outcome
Fox, ⁵¹ 2010 (United States)	121	Twin gestation	Monoamniotic twins, major fetal anomalies, preterm labor, aneuploidy, twin-to-twin transfusion syndrome	18–24 and within 2–6 wk of the initial measurement (98% at or before 25 wk)	Shortening of CL 20%	Spontaneous preterm birth <32, <28, <30, and <34 wk
Hofmeister, ⁵² 2010 (Brazil)	124	Twin gestation	Monoamniotic twins, twin-to-twin transfusion syndrome, polyhydramnios, intrauterine fetal death, fetal malformation, iatrogenic preterm birth	18–21 and 22–25	Shortening of CL >2 mm/wk	Spontaneous preterm birth <34, <28, <30, and <32 wk
Crane, ⁵³ 2011 (Canada)	70	Singleton gestation at high risk (previous spontaneous preterm birth or excisional cervical procedure, or uterine anomaly) with a CL <30 mm at 20–28 wk of gestation	Cerclage	20–28 (mean, ~26) and within 3 wk of the initial measurement (mean, ~28)	Shortening of CL >10%	Spontaneous preterm birth <35, <37, <34, and <32 wk
Oh, ⁵⁴ 2012 (Korea)	190	Twin gestation with a CL >25 mm at 20–24 wk of gestation	Prophylactic cerclage, PROM, preterm labor, major fetal anomalies, twin-to-twin transfusion syndrome, placenta previa, monoamniotic placenta	20–24 (mean, 21.9) and within 4–5 wk of the initial measurement (mean, 26.0)	Shortening of CL 13% and 20%	Spontaneous preterm birth <32 and <34 wk
Khalil, ⁵⁵ 2013 (Saudi Arabia)	209	Twin gestation with a CL >25 mm at first measurement	CL 25 mm on the first ultrasound, monoamniotic twins, preterm labor with or without PROM, abnormal vaginal discharge, severe twin-to-twin transfusion syndrome, aneuploidy, major fetal anomalies, elective cerclage	20–23 and within 3–5 wk of the initial measurement	Shortening of CL 25%	Spontaneous preterm birth <32, <34, <30, and <28 wk
Levéque, ⁵⁶ 2015 (France)	116	Twin gestation	Prophylactic cerclage, placenta previa, major fetal anomalies, twin-to-twin transfusion syndrome, PROM, undetermined gestational age	22 (range, 21–23) and 27 (range, 26–28)	Shortening of CL >20%	Spontaneous preterm birth <34 wk

CL, cervical length; PROM, premature rupture of the membranes

^aFrom the 183 women included in the study, we excluded 10 with an initial CL <25 mm without data on CL changes over time

^bFrom the 183 women included in the study, we excluded 46 with an initial CL 30 mm without data on CL changes over time

^cIn the meta-analyses performed, we used predictive values for “shortening in CL >10 mm” with women in recumbent position

TABLE 2

Pooled estimates for changes in cervical length over time to predict preterm birth

Population	Outcome	Abnormal test result	No. of studies/ total number of women	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	I ² (%)
Singleton gestation (all)	Preterm birth <37 wk	Any shortening of CL	4 ^{48,50,53} /532	54 (43–65)	84 (80–87)	3.2 (2.2–4.4)	0.6 (0.4–0.9)	0
	Preterm birth <35 wk	Any shortening of CL	5 ^{44,47,49,53} /2979	65 (57–72)	48 (46–50)	1.3 (1.1–1.4)	0.7 (0.6–0.9)	25
Singleton gestation at high risk	Preterm birth <37 wk	Any shortening of CL	3 ^{48,49,53} /275	49 (37–61)	85 (80–90)	3.3 (2.2–5.0)	0.6 (0.5–0.8)	0
	Preterm birth <35 wk	Any shortening of CL	4 ^{44,47,49,53} /448	58 (47–68)	72 (67–76)	2.0 (1.6–2.6)	0.6 (0.4–0.8)	12
Singleton gestation at high risk with an initial normal CL	Preterm birth <35 wk	Shortening of CL to <25 or <30 mm at 24 wks	2 ^{44,47} /310	56 (43–68)	72 (66–77)	2.0 (1.5–2.7)	0.6 (0.4–0.8)	63
	Preterm birth <35 wk (unselected)	Any decrease in CL	1 ⁴ /2531	72 (62–81)	44 (42–46)	1.3 (1.1–1.5)	0.6 (0.4–0.9)	NA
Singleton gestation at low risk	Preterm birth <37 wk	Shortening of CL 6.6 mm	1 ⁵⁰ /257	74 (51–88)	82 (77–86)	4.1 (2.8–6.0)	0.3 (0.1–0.7)	NA
Twin gestation	Preterm birth <34 wk	Any shortening of CL	7 ^{45,46,51,52,54–56} /852	47 (39–55)	88 (86–91)	4.0 (2.0–8.3)	0.6 (0.5–0.8)	66
	Preterm birth <32 wk	Shortening of CL 20– 25%	5 ^{45,51,54–56} /651	47 (38–57)	87 (84–90)	3.8 (2.8–5.1)	0.6 (0.5–0.7)	76
Preterm birth <32 wk	Any shortening of CL	Any shortening of CL	4 ^{51,52,54,55} /644	61 (49–73)	88 (85–91)	5.3 (3.4–7.2)	0.5 (0.3–0.6)	0
	Shortening of CL 20– 25%	Shortening of CL 20– 25%	3 ^{51,54,55} /520	56 (42–69)	89 (86–92)	5.2 (3.7–7.5)	0.5 (0.4–0.7)	0
Preterm birth <30 wk	Any shortening of CL	Any shortening of CL	3 ^{51,52,55} /454	70 (52–83)	86 (82–89)	4.8 (3.5–6.8)	0.4 (0.2–0.6)	0
	Preterm birth <28 wk	Any shortening of CL	3 ^{51,52,55} /454	73 (48–89)	84 (80–88)	4.5 (3.1–6.6)	0.3 (0.2–0.7)	0

CI, confidence interval; CL, cervical length; NA, not applicable

Comparison of the predictive accuracy for preterm birth of cervical length at first and/or last measurement and change in cervical length over time in individual studies using the Youden index

TABLE 3

Study	Outcome: preterm birth	Cervical length at initial measurement			Cervical length at final measurement			Change in cervical length over time		
		Cut-off value, (GA at testing, wks)	Youden index	P value ^a	Cut-off value, (GA at testing, wks)	Youden index	P value ^a	Abnormal test result	Youden index	
Singleton gestation										
Iams, ⁴ 1996	<35 wk	25 mm (24)	0.295	0.049	25 mm (28)	0.362	0.008	Any decrease in CL	0.165	
	<35 wk	25 mm (24)	0.295	0.44	25 mm (28)	0.362	0.12	Shortening of CL > 6 mm	0.241	
Arabin, ⁴⁸ 2006	<36 wk	Unreported (15–19)	NC	NA	25 mm (20–24)	0.080	0.66	Shortening of CL >10 mm	0.140	
Dilek, ⁵⁰ 2007	<37 wk	35.3 mm (16)	0.200	0.02	34.3 mm (24)	0.657	0.56	Shortening of CL > 6.6 mm	0.556	
Twin gestation										
Bergelin, ⁴⁵ 2003	<34 wk	Unreported (24)	NC	NA	25 mm (28)	0.129	0.56	Shortening of CL > 20%	0.314	
Gibson, ⁴⁶ 2004	<35 wk	25 mm (18)	0.128	0.87	25 mm (28)	0.042	0.43	Shortening of CL > 2.5 mm/week	0.151	
Arabin, ⁴⁸ 2006	<36 wk	Unreported (15–19)	NC	NA	20 mm (20–24)	0.080	0.06	Shortening of CL >10 mm	0.285	
Fox, ⁵¹ 2010	<32 wk	Unreported (18–24)	NC	NA	25 mm (20–25)	0.300	0.55	Shortening of CL > 20%	0.427	
	<34 wk	Unreported (18–24)	NC	NA	25 mm (20–25)	0.250	0.90	Shortening of CL > 20%	0.231	
Hofmeister, ⁵² 2010	<32 wk	5 th percentile (18–21)	0.264	0.02	5 th percentile (22–25)	0.478	0.35	Shortening of CL >2 mm/week	0.631	
	<34 wk	5 th percentile (18–21)	0.206	0.04	5 th percentile (22–25)	0.344	0.36	Shortening of CL >2 mm/week	0.470	
Oh, ⁵⁴ 2012	<32 wk	Unreported (20–24)	NC	NA	30 mm (24–29)	0.503	0.98	Shortening of CL > 13%	0.507	
	<34 wk	Unreported (20–24)	NC	NA	30 mm (24–29)	0.482	0.50	Shortening of CL > 13%	0.350	
Khalil, ⁵⁵ 2013	<32 wk	Unreported (20–23)	NC	NA	25 mm (23–28)	0.367	0.28	Shortening of CL > 25%	0.503	
	<34 wk	Unreported (20–23)	NC	NA	25 mm (23–28)	0.317	0.03	Shortening of CL > 25%	0.510	
Levéque, ⁵⁶ 2015	<34 wk	35 mm (22)	0.093	0.71	25 mm (27)	0.412	0.23	Shortening of CL > 20%	0.170	

CL, cervical length; GA, gestational age; NA, not applicable; NC, not calculable

^aFor the difference with Youden index of change in cervical length over time