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CERVICAL PHOSPHORYLATED INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1 TEST FOR THE PREDICTION OF PRETERM BIRTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

OBJECTIVE—To assess the accuracy of the cervical phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) test to predict preterm birth in women with and without symptoms of preterm labor through use of formal methods for systematic reviews and meta-analytic techniques.

DATA SOURCES—PubMed, Embase, Cinahl, Lilacs, and Medion (all from inception to June 20, 2015), reference lists, conference proceedings, and Google scholar.

STUDY ELIGIBILITY CRITERIA—Cohort or cross-sectional studies that reported on the predictive accuracy of cervical phIGFBP-1 test for preterm birth.

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

RESULTS—Forty-three studies met the inclusion criteria of which 15 provided data on asymptomatic women (n=6583) and 34 on women with an episode of preterm labor (N=3620). Among asymptomatic women, the predictive accuracy of cervical phIGFBP-1 test for preterm birth at <37, <34 and <32 weeks of gestation was minimal with pooled sensitivities and

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specificities, and summary positive and negative likelihood ratios ranging from 14-47%, 76-93%, 1.5-4.4, and 0.6-1.0, respectively. Among women with an episode of preterm labor, the test had a low predictive performance for delivery within 7 and 14 days of testing, and preterm birth at <34 and <37 weeks of gestation with pooled sensitivities and specificities, and summary positive and negative likelihood ratios that varied between 60 and 68%, 77 and 81%, 2.7 and 3.5, and 0.4 and 0.5, respectively. A negative test result in women with an episode of preterm labor had a low to moderate accuracy to identify women who are not at risk for delivering within the next 48 hours (summary negative likelihood ratio of 0.28 in all women and 0.23 in women with singleton gestations).

CONCLUSION—Cervical pHIGFBP-1 has potential utility to identify patients with an episode of preterm labor who will not deliver within 48 hours. However, its overall predictive ability for the identification of symptomatic and asymptomatic women at risk for preterm birth is limited.

Keywords

preterm labor; biomarker; predictive value; fetal fibronectin; prematurity; common pathway of parturition

INTRODUCTION

Preterm birth and its complications constitute a major health problem in high- and low/middle-income countries. In 2010, it was estimated that 11.1% of all live births were preterm, a worldwide total of 14.9 million babies.¹ The estimated preterm birth rate ranged from about 5% in several northern European countries to 18% in some African countries. Despite the fact that the preterm birth rate in the United States has declined for the seventh straight year to 11.39% in 2013,² this country continues to be one of ten with the highest numbers of preterm births (~450,000).¹ Preterm birth was the leading cause of both neonatal mortality (35% of 2.8 million deaths) and child mortality (17% of 6.3 million deaths) worldwide in 2013.^{3,4} In addition to its contribution to mortality, preterm birth is also associated with an increased risk of long-term neurodevelopmental impairment among surviving babies.^{5,6}

About two-thirds of preterm births are spontaneous, following spontaneous onset of labor or premature rupture of the membranes, whereas the remaining third is medically indicated because of maternal or fetal complications.⁷ Spontaneous preterm labor is a syndrome caused by multiple pathologic processes^{8,9} whose prediction has been a long-standing challenge.¹⁰⁻¹⁴ The accurate prediction of preterm birth in asymptomatic women in early pregnancy could allow the use of prophylactic interventions and more intensive antenatal surveillance. In addition, being able to identify women at low risk of preterm birth would avoid the use of unnecessary and sometimes costly interventions. On the other hand, the prediction of preterm birth in patients with symptoms and signs of preterm labor could allow interventions to prevent or delay birth and to avoid or reduce adverse neonatal outcomes associated to prematurity.

Several tests have been proposed to predict preterm birth in both asymptomatic and symptomatic women including cervical phosphorylated insulin-like growth factor binding

protein-1 (phIGFBP-1). The insulin-like growth factors and their binding proteins are important for placental and fetal growth and development.^{15,16} PhIGFBP-1 is a major protein synthesized in decidualized endometrium cells during pregnancy. Tissue disruption at the choriodecidual interface due to uterine contractions can result in leakage of phIGFBP-1 into cervical secretions.¹⁵ In 2001, Kekki et al.¹⁷ and Kurkinen-Räty et al.¹⁸ reported that high levels of phIGFBP-1 in cervical secretions could identify symptomatic women at risk of preterm birth. Since then, several authors have reported that cervical phIGFBP-1 can accurately predict preterm birth in women with an episode of preterm labor and intact membranes, and that, compared to cervicovaginal fetal fibronectin, it has several advantages. Specifically, results are not affected by recent sexual intercourse or contamination with urine, lower costs, and faster testing.¹⁹ Nevertheless, the predictive ability of this test for preterm birth has also been challenged in some reports.^{20,21} Currently, the cervical phIGFBP-1 test is used in many countries around the world such as United Kingdom, Canada, Germany, Italy, France, Japan, Australia, New Zealand, India, and Israel among others. Therefore, a critical appraisal of its predictive performance is timely and necessary. We carried out a systematic review and meta-analysis to assess the accuracy of cervical phIGFBP-1 to predict preterm birth in women with and without symptoms of preterm labor.

MATERIALS AND METHODS

This study was conducted according to a prospective protocol and in accordance with recommended methods for systematic reviews of diagnostic test accuracy.^{22,23}

Literature search

We undertook a search in PubMed, Embase, Cinahl, Lilacs, and Medion (all from inception to June 20, 2015), and Google Scholar using an existing search strategy for systematic reviews of accuracy studies evaluating tests for predicting preterm birth.²⁴ Proceedings of several meetings on preterm birth and maternal-fetal medicine, bibliographies of the retrieved articles, and review articles were also searched. In addition, we contacted investigators involved in the field to locate unpublished studies. There were no language restrictions.

Study selection

We included cohort or cross-sectional studies that reported on the accuracy of the cervical phIGFBP-1 test to predict preterm birth in asymptomatic and/or symptomatic women with a singleton or twin gestation, and that allowed construction of 2×2 contingency tables. Studies were excluded if they: were case-control studies because there is consistent evidence that they are associated with higher diagnostic or predictive accuracy compared with cohort studies;²⁵ were reviews, case series or reports, editorials, or letters without original data; assessed cervical phIGFBP-1 in women with suspected or established preterm premature rupture of membranes; assessed phIGFBP-1 only in vaginal secretions, amniotic fluid or blood; reported data for cervical phIGFBP-1 only as mean or median values; or they did not publish accuracy test estimates and sufficient information to calculate them could not be

retrieved. In cases of duplicate publication, we included only the most recent or complete version.

All of the potentially relevant studies were retrieved and reviewed independently by the two authors to determine inclusion. Disagreements were resolved through consensus.

Reference standard outcomes

In asymptomatic women: preterm birth (both spontaneous and indicated) and spontaneous preterm birth at <32, <34, and <37 weeks of gestation; in women with an episode of preterm labor: delivery within 48 hours, and 7 and 14 days of testing, and preterm birth at <34 and <37 weeks of gestation.

Methodological quality assessment

Study quality was assessed using a modified version of the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool.²⁶ The assessments were judged as “low risk”, “high risk”, or “unclear risk” of bias. The items evaluated and how they were interpreted were as follows:

1. *Patient selection* - “low risk of bias”: pregnant women consecutively or randomly selected; “high risk of bias”: convenience sampling (arbitrary recruitment or non-consecutive recruitment).
2. *Selection of test cutoff value* - “low risk of bias”: prespecified; “high risk of bias”: determined by a data-driven approach.
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 caesarean 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 phIGFBP-1 test 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 results of the test* - “low risk of bias”: clinicians did not use interventions based on the results of the cervical phIGFBP-1 test; “high risk of bias”: clinicians used interventions based on the results of the test (e.g. tocolytics, vaginal progesterone, 17-alpha hydroxyprogesterone caproate).

If there was insufficient information available to make a judgment about these items, then they were scored as “unclear risk of bias”. Summary quality score for each study was not calculated because of the well-known problems associated with such scores.²⁷ The risk of

bias in each included study was assessed independently by the two investigators. Any differences of opinion regarding assessment of risk of bias were resolved by discussion.

Data extraction

The two reviewers independently extracted data on characteristics of the study (authors, setting, year of publication, method of recruiting women, prospective or retrospective data collection, blinding of test results, flow diagram, percentage of women recruited into the study that were included in the analysis, and use of interventions to prevent preterm birth); patient characteristics (inclusion and exclusion criteria, risk classification for preterm birth, sample size, plurality of pregnancy, and demographic characteristics); how the test was carried out (gestational age at sampling, laboratory methods used, and cutoff value used); reference standard outcomes assessed and their prevalences; and numbers 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. The corresponding authors of primary studies were contacted to obtain additional information on methods used and/or unpublished relevant data. Only two authors supplied additional data. Inter-reviewer disagreements were resolved by discussion.

Data were extracted separately for asymptomatic and symptomatic women, singleton 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 asymptomatic and symptomatic women and stratified according to the predefined reference standard outcomes, plurality of pregnancy, and risk status of women for preterm birth. For asymptomatic women, we synthesized data for all women, those with singleton and twin gestations, those with a singleton gestation and previous spontaneous preterm birth, and those at high risk for preterm birth. For patients with an episode of preterm labor, we synthesized data for all women, those with a singleton gestation, and those with a singleton gestation and a sonographic cervical length ≥ 30 mm.

Data extracted from each study were arranged in 2×2 contingency tables. Where 2×2 tables contained zero cells, we added 0.5 to each cell to enable calculations.²⁸ Sensitivity and specificity with 95% confidence intervals (CIs) were calculated separately for each study and reference standard outcome reported. Then, we constructed summary receiver operating characteristic (ROC) curves for each predefined reference standard outcome and derived pooled estimates and 95% CIs of sensitivity and specificity using random-effects bivariate meta-regression models.^{29,30} Thereafter, we calculated summary likelihood ratios with 95% CIs from the pooled sensitivities and specificities.³¹ Likelihood ratios for a positive test result above 10 and likelihood ratios for a negative test result below 0.1 are considered to provide strong predictive evidence in most circumstances. Moderate prediction can be achieved with likelihood ratios of 5-10 and 0.1-0.2, whereas those <5 and >0.2 give only

minimal prediction.³² Finally, we planned to calculate the post-test probabilities of the most important reference standard outcomes by combining likelihood ratios obtained from meta-analyses for positive and negative test results, and a global prevalence (pre-test probability) of these reference standard outcomes across the studies.³²

Heterogeneity of the results among studies was assessed through visual examination of both forest plots of sensitivities and specificities and ROC plots, and by means of the quantity I^2 .³³ A substantial level of heterogeneity was defined as an $I^2 \geq 50\%$.³³ We explored potential sources of heterogeneity by performing meta-regression analysis of subgroups defined *a priori* (study setting, sample size, study's year of publication, prevalence of the reference standard outcome, and study quality).³⁴ If there were at least 10 studies included in a meta-analysis, we assessed publication and related biases by examining the symmetry of funnel plots with the Deeks' test.³⁵ A $P < .10$ for the slope coefficient indicated significant asymmetry of the funnel plot.

Bivariate random-effects models were fitted using the NLMIXED procedure of SAS version 9.2 (SAS Institute Inc, Cary, NC). Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to construct forest plots of sensitivity and specificity and summary ROC curves.

RESULTS

Selection, characteristics, and quality of studies

Figure 1 summarizes the process of identification and selection of studies. The searches produced 417 citations, of which 65 were considered relevant. Of these, 22 were excluded, mainly because they were not a test accuracy study, were duplicate publications, or did not report original data. A total of 43 studies, including 10,203 women, met the inclusion criteria, of which nine provided data on asymptomatic women ($n=6131$),³⁶⁻⁴⁴ 28 on symptomatic women ($n=3212$),^{18,45-71} and six on both asymptomatic ($n=452$) and symptomatic ($n=408$) women.^{17,72-76}

The main characteristics of included studies are displayed in Table 1. Twenty studies (47%) were performed in European countries, 16 (37%) in Asia, three (7%) in South America, and four (9%) in Canada. The sample size ranged from 18⁷² to 4984⁴⁰ (median, 88) in asymptomatic women and from 30⁵⁷ to 350⁶⁹ (median, 70) in symptomatic women. Among the 34 studies performed in symptomatic women, only seven (21%) defined preterm labor as the presence of uterine contractions with evidence of cervical changes.^{45,48,55,58,60,61,68} Twelve studies (35%) did not include cervical changes in the diagnosis of preterm labor;^{17,46,50,51,59,65,66,72-76} one study included women with or without cervical changes;¹⁸ and 14 studies did not report clearly on the definition of preterm labor.^{47,49,52-54,56,57,62-64,67,69-71} All studies were limited to women with intact membranes. Two studies included exclusively twin gestations, both in asymptomatic women.^{39,44}

Of the 15 studies in asymptomatic women, 10 performed the test from 20-36 weeks of gestation,^{17,36-38,43,72-76} three from 23-26 weeks,^{39,41,42} and one at 16-25 weeks.⁴⁴ The remaining study measured the concentration of cervical phIGFBP-1 at 12-13 and 18-20

weeks of gestation.⁴⁰ Most studies in symptomatic women assessed the test between 22-24 and 34-36 weeks of gestation. In all studies, the concentration of phIGFBP-1 in cervical secretions was measured by an immunoenzymometric assay involving monoclonal antibodies specific for the phosphorylated form of IGFBP-1. All studies except two^{18,42} used a concentration 10 µg/l to indicate an abnormal test result. Most studies in both asymptomatic and symptomatic women reported on the predictive accuracy of cervical phIGFBP-1 for preterm birth at <37 weeks of gestation. Twenty-five studies (58%) reported data for more than one reference standard outcome.

Figure 2 summarizes the quality assessment of included studies. Ten studies (23%), nine among symptomatic and one among asymptomatic women, fulfilled 5 criteria. Twenty-five studies (58%) had 3 methodological flaws. The most common shortcomings were the lack of information regarding blinding of clinicians to the test results and follow-up of women, and the reference standard outcome assessed. Only 14 studies reported clearly that the reference standard outcome assessed was spontaneous preterm birth.

Cervical phIGFBP-1 in asymptomatic women

Figure 3A shows the sensitivity and specificity of the cervical phIGFBP-1 test in the individual studies to predict preterm birth in asymptomatic women. The summary ROC curves showed that the cervical phIGFBP-1 test had a similar predictive ability for preterm birth at <37 and at <34 weeks of gestation (Figure 4A). Overall, regardless of the risk status of women, plurality of pregnancy and reference standard outcome assessed, the predictive accuracy of this test for preterm birth at <37, <34 and <32 weeks of gestation was minimal with pooled sensitivities and specificities, and summary positive and negative likelihood ratios ranging from 14-47%, 76-93%, 1.5-4.4, and 0.6-1.0, respectively (Table 2).

Cervical phIGFBP-1 in women with an episode of preterm labor

The sensitivity and specificity of the cervical phIGFBP-1 test in the individual studies to predict preterm birth in women with an episode of preterm labor are summarized in Figure 3B. Summary ROC curves of the cervical phIGFBP-1 test to predict preterm birth in symptomatic women are depicted in Figure 4B. The best predictive accuracy was for delivery within 48 hours of testing and the worst was for preterm birth at <37 weeks of gestation. Similar summary ROC curves were obtained for the prediction of delivery within 7 and 14 days of testing and preterm birth at <34 weeks of gestation. Pooled estimates of the predictive accuracy of cervical phIGFBP-1 for preterm birth are presented in Table 3. Among all women and those with a singleton gestation, the cervical phIGFBP-1 test had a low predictive performance for delivery within 7 and 14 days of testing, and preterm birth at <34 and <37 weeks of gestation with pooled sensitivities and specificities, and summary positive and negative likelihood ratios that varied between 60 and 68%, 77 and 81%, 2.7 and 3.5, and 0.4 and 0.5, respectively. A negative test result had a low to moderate accuracy to identify women who were not at risk for delivering within the next 48 hours (summary negative likelihood ratio of 0.28 in all women and 0.23 in women with singleton gestations), which would decrease its pre-test probability from 6.6% to 1.6-1.9%. Among women with a singleton gestation and a cervical length 30 mm, a positive cervical phIGFBP-1 test (summary likelihood ratio of 5.5) increased the pre-test probability of delivery within 7 days

of testing from 17.8% to 54.4%, whereas a negative test result (summary likelihood ratio of 0.3) decreased the risk to 6.1%.

There was a substantial level of heterogeneity among studies in 13 of 21 meta-analyses performed. Meta-regression analyses showed that study setting, sample size, the study's year of publication, prevalence of the reference standard outcome, and study quality did not provide an explanation for heterogeneity. Most women included in the meta-analyses of preterm birth at <32 and <37 weeks of gestation among asymptomatic women were enrolled in a single study.⁴⁰ Sensitivity analyses, in which we did not include this study, revealed similar pooled accuracy results. Among symptomatic women, pooled predictive accuracy estimates obtained from studies that met 5 methodological criteria did not differ significantly from those obtained from studies that met 4 criteria (data not shown). The funnel plots of the six meta-analyses that included at least ten studies showed no significant asymmetry ($P > .10$ for all, by Deeks' test).

COMMENT

Main findings

There is consensus that a clinically useful predictive test for preterm birth should identify asymptomatic women who are at increased risk for delivery before 34 and 37 weeks of gestation in order to target preventive interventions more appropriately.¹¹ Among women who present with an episode of preterm labor, a predictive test would be clinically meaningful if it identifies those who would deliver within 48 hours to 7 days of presentation with the purpose of guiding the rational use of antenatal corticosteroids and tocolytic agents as well as *in utero* transfer to a tertiary intensive neonatal care unit.¹¹ The results of our systematic review show that, overall, the cervical phIGFBP-1 test has a low predictive accuracy for preterm birth at <34 and <37 weeks of gestation in both asymptomatic and symptomatic women, and for delivery within 7 and 14 days of testing among symptomatic women. Subgroup and sensitivity analyses did not improve predictive accuracy. However, pooled data from six studies (791 women) suggest that a negative cervical phIGFBP-1 test among patients with an episode of preterm labor has a low to moderate predictive accuracy to identify those who are not at risk for delivering within the next 48 hours. In addition, pooled data from two studies (410 women) suggest that a positive test result has a moderate ability to predict delivery within 7 days of testing among patients with an episode of preterm labor, singleton gestation, and a cervical length ≥ 30 mm.

Strengths and limitations

The strength of this review lies in the rigorous methodology used: (1) it followed guidelines for the conduct and reporting of systematic reviews of predictive test accuracy; (2) the use of a prospective protocol designed to address a highly specific research question; (3) the comprehensive literature search without language restrictions which allowed us to locate and include studies that were published in English, Korean, Portuguese, Spanish, French, Italian, and German; (4) the inclusion of a large number of studies in the review; (5) the strict study quality assessment using a modified version of QUADAS-2; (6) the use of contemporary statistical methods to obtain summary measures of predictive accuracy; (7) the performance

of subgroup and sensitivity analyses; (8) the exploration of potential sources of heterogeneity; (9) the quantitative synthesis of the evidence; and (10) the symmetric funnel plots which suggested the absence of publication and related biases in meta-analyses including at least 10 studies.

Our study has some limitations. First, the meta-analyses on the accuracy of cervical pHIGFBP-1 test to predict preterm birth at <34 weeks of gestation among asymptomatic women and delivery within 48 hours of testing among symptomatic women may be underpowered due to the small number of studies within each analysis and the relatively small sample size of some of them. Second, only one quarter of included studies could be considered at low risk of bias. However, sensitivity analyses that were restricted to these studies showed no significant differences in the results obtained with overall meta-analyses. Third, we were unable to explain the reasons for the substantial statistical heterogeneity that was found in about 60% of the meta-analyses performed, which may be due to differences in the study population, the definition of preterm labor used, and cervical dilation/effacement at study entry, among others; therefore, pooled estimates of predictive accuracy should be interpreted cautiously. Nevertheless, we used a random-effects meta-regression model that provides the most useful and conservative estimate for informing practice in the presence of unexplained heterogeneity. Fourth, there was no uniform definition of preterm birth across the studies included. In only one-third of studies, it was clear that the reference standard outcome assessed was spontaneous preterm birth. Notwithstanding, the pooled predictive accuracy estimates obtained from studies that assessed exclusively spontaneous preterm birth at <34 and <37 weeks of gestation in asymptomatic women were very similar to those obtained from studies that included both spontaneous and indicated preterm birth in the reference standard outcomes. Finally, information on whether women received any interventions aimed to prevent preterm birth based on test results was omitted or could not to be determined in half of included studies. This omission is particularly relevant because use of preventive therapies could introduce bias in the assessment of the test's predictive accuracy.

We identified two systematic reviews that assessed the predictive accuracy of cervical pHIGFBP-1 test for preterm birth.^{11,12} One review, which included 10 studies on symptomatic women published up to September 2005, reported summary positive and negative likelihood ratios of 2.5 and 0.3, 3.3 and 0.2, 3.0 and 0.2, and 4.3 and 0.3 for predicting delivery within 48 hours and 7 days of testing, and preterm birth at <34 and <37 weeks of gestation, respectively.¹¹ The other review, which included nine studies on asymptomatic women published up to October 2010, reported summary positive and negative likelihood ratios of 1.6 and 0.8, respectively, to predict preterm birth at <37 weeks of gestation.¹² Although our overall conclusions are consistent with those of the previous reviews, our results are more robust due to the inclusion of more studies (34 among women with an episode of preterm labor and 15 among asymptomatic women), and the performance of several subgroup analyses according to important clinical variables such as plurality of pregnancy and risk status of women for preterm birth, and sensitivity analyses according to study quality.

Implications for practice and research

Given that cervicovaginal fetal fibronectin and cervical pHIGFBP-1 are the most commonly used biochemical tests for the prediction of preterm birth among patients with an episode of preterm labor, we decided to compare the predictive accuracy of these tests using the estimates obtained in our meta-analysis and those obtained in recent systematic reviews on cervicovaginal fetal fibronectin^{13,77} (Table 4). Overall, it appears that the cervical pHIGFBP-1 test is more accurate to predict delivery within 48 hours of testing whereas cervicovaginal fetal fibronectin is more accurate to predict delivery within 7 days of testing and preterm birth at <34 and <37 weeks of gestation. However, it should be noted that indirect comparisons are prone to bias and that direct comparisons between cervical pHIGFBP-1 and cervicovaginal fetal fibronectin with adequate sample sizes are currently lacking.

Impact studies, usually randomized controlled trials, quantify the effect of using a predictive test on patient outcomes, clinical decision-making, or cost-effectiveness of care compared with not using such test. An alternative approach is that individuals with a positive or a negative test result are randomly assigned to receive an intervention or placebo/no intervention. We did not identify any randomized or non-randomized controlled trials that have evaluated the use of interventions based on cervical pHIGFBP-1 test results in women with or without symptoms of preterm labor.

In conclusion, there is no sufficient evidence to recommend the routine clinical use of cervical pHIGFBP-1 test in women with or without symptoms of preterm labor. Further well-designed prospective studies are required to evaluate the predictive ability of cervical pHIGFBP-1 test for delivery within 48 hours and 7 days of testing in symptomatic women, mainly those with a sonographic cervical length ≥ 30 mm. If such studies demonstrate that a negative test result accurately identifies those who will not deliver within 2-7 days, the next step will be to demonstrate that clinical use of the cervical pHIGFBP-1 test is associated with reductions in unnecessary patient transfers, hospital admissions and therapeutic interventions, health care resource use and its associated costs, and family and social disruption.

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Condensation

Overall, the predictive accuracy for preterm birth of the cervical phosphorylated insulin-like growth factor binding protein-1 test is low in both asymptomatic and symptomatic women

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Figure 1.
Study selection process

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

phIGFBP-1 to predict preterm birth <37 weeks in asymptomatic women **phIGFBP-1 to predict preterm birth <34 weeks in asymptomatic women** **phIGFBP-1 to predict preterm birth <32 weeks in asymptomatic women**

B. Women with an episode of preterm labor

Figure 3.
Forest plots of the cervical phIGFBP-1 test to predict preterm birth

A. Asymptomatic women

B. Women with an episode of preterm labor **Figure 4.**

Summary receiver operating characteristic curves of the cervical *phIGFBP*-1 test to predict preterm birth

TABLE 1

Characteristics of studies included in the systematic review

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
Asymptomatic women							
Patemoster, ³⁶ 2000	Italy	88	Gestation at high risk for preterm birth: multiple gestation, previous preterm birth or second-trimester miscarriage, prophylactic cerclage, placenta previa, uterine malformations, chronic or gestational hypertension, IUGR, polyhydramnios, and/or uteroplacental insufficiency	Not reported	24-34	10	Spontaneous preterm birth <37 weeks
Bittar, ³⁷ 2007	Brazil	105	Singleton gestation and at least one previous spontaneous preterm birth <37 weeks' gestation	Multiple gestation, history of cervical incompetence, previous cervical surgery, or previous preterm labor in the current pregnancy	24-34 Serial	10	Spontaneous preterm birth <34 and <37 weeks
Bali, ³⁸ 2008	Bosnia and Herzegovina	80	Singleton gestation	Uncertain gestational age, previous preterm delivery, history of pregnancy loss, urinary infection, uterine anomalies, or previous cesarean section	24-34	10	Preterm birth <37 weeks
Adeyemi, ³⁹ 2010	United Kingdom	40	Twin gestation	Not reported	26	10	Preterm birth <34 and <37 weeks
Rakhonen, ⁴⁰ 2010	Finland	4984	Singleton (99.4%) or multiple (0.6%) gestation	Not reported	12-13 and 18-20	10	Spontaneous preterm birth <32 and <37 weeks
Khambay, ⁴¹ 2012	United Kingdom	45	Gestation at high risk for preterm birth: history of previous preterm birth, second trimester miscarriage, cervical surgery,	PROM or vaginal bleeding	23-24	10	Preterm birth <34 and <37 weeks

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
			and/or uterine malformations and/or uterine malformations				
Riboni, ⁴² 2012	Italy	491	Singleton gestation	Uterine contractions, vaginal bleeding, placenta previa, multiple gestation, fetal abnormalities, or uterine anomalies	24	33	Preterm birth <37 weeks
Rolnik, ⁴³ 2013	Brazil	101	Singleton gestation and previous spontaneous preterm birth	Fetal malformations, use of progesterone, use of tocolytic agents followed by term birth	24-34 Serial	10	Spontaneous preterm birth <37 weeks
Fichera, ⁴⁴ 2014	Italy	197	Twin gestation	Active vaginal bleeding, PROM, death of one fetus, or use of cerclage or pessary	16-25	10	Spontaneous preterm birth <34, <32, <30, and <28 weeks
Women with symptoms of preterm labor							
Kurkinen-Räty, ¹⁸ 2001	Finland	77	Singleton gestation, preterm labor (uterine contractions or cervical shortening, opening or softening), and intact membranes	PROM or ongoing preterm delivery	22-32 Serial	6.4	Spontaneous preterm birth <37 weeks
Shine, ⁴⁵ 2001	Korea	32	Preterm labor (uterine contractions with cervical dilatation <2 cm) and intact membranes	Unreported	24-36	10	Preterm birth <34 and <37 weeks
Choi, ⁴⁶ 2003	Korea	42	Singleton gestation and preterm labor (2-3 uterine contractions/min for 30 min)	Not reported	20-36	10	Preterm birth <37 weeks
Heraud, ⁴⁷ 2003	France	93	Singleton or twin gestation, preterm labor (not defined), and intact membranes	PROM or indicated preterm delivery	23-35	10	Spontaneous preterm birth <37 weeks
Park, ⁴⁸ 2003	Korea	50	Preterm labor, cervical dilatation <3 cm, intact membranes, and no prior tocolysis	Unreported	24-34	10	Delivery within 7 days of testing, and preterm birth <34 and <37 weeks

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
Winograd, ⁴⁹ 2003	Argentina	85	Singleton gestation, preterm labor (not defined), and intact membranes	Multiple gestation or PROM	24-35	10	Delivery within 7 days of testing
Kwek, ⁵⁰ 2004	Singapore	42	Preterm labor (1 uterine contractions in 10 min) and intact membranes	Antepartum hemorrhage, PROM, cervical dilatation >3 cm, contraindications to tocolysis, or cerclage	23-33	10	Delivery within 48 hours and 7 days of testing, and preterm birth <36 weeks
Elizur, ⁵¹ 2005	Israel	64	Singleton (67%) or twin (33%) gestation, preterm labor (2 uterine contractions in 10 min), and intact membranes	Heavy vaginal bleeding, PROM, placenta previa, previous preterm induction of labor, or non-reassuring fetal condition	24-35	10	Spontaneous preterm birth <35 and <37 weeks
Halle, ⁵² 2005	Germany	93	Singleton gestation, preterm labor (not defined), and intact membranes	Unreported	23-32	10	Preterm birth <37 weeks
Tumell, ⁵³ 2005	Canada	100	Singleton or multiple gestation, idiopathic preterm labor (not defined), cervical dilatation <3 cm, and intact membranes	PROM, history of digital exam or sexual intercourse within the previous 24 hours, vaginal bleeding, suspected IU GR, or non-reassuring maternal or fetal status	24-35	10	Delivery within 14 days of testing
Sanchez Martinez, ⁵⁴ 2006	Spain	149	Singleton gestation, preterm labor (not defined) requiring admission, and no parturition within 24-48 hours after admission	Clinical chorioamnionitis, non-reassuring fetal status, or PROM	24-35	10	Delivery within 7 days of testing and spontaneous preterm birth <36 weeks
Larouche, ⁵⁵ 2007	Canada	55	Singleton gestation, preterm labor (cervical dilatation 2 cm and effacement <80%), intact membranes, and reassuring fetal well-being	History of sexual intercourse or use a speculum or lubricant in the previous 24 h, moderate or heavy vaginal bleeding, or PROM	24-34	10	Delivery within 14 days of testing and preterm birth <37 weeks

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
Ting, ⁵⁶ 2007	Singapore	94	Singleton gestation, preterm labor (not defined), and intact membranes	Multiple gestation, PROM, cerclage, cervical dilatation >3 cm, preeclampsia, IUGR, placenta previa, suspected fetal asphyxia, chorioamnionitis, or major fetal anomaly	24-34	10	Delivery within 48 hours, and 7 and 14 days of testing
Latifagi, ⁵⁷ 2008	Bosnia and Herzegovina	30	Singleton gestation, preterm labor (not defined), and intact membranes	Chronic diseases, maternal genital tract anomalies, fetal genetic/anatomical defects, or previous preterm delivery	24-34	10	Preterm birth <37 weeks
Sunagawa, ⁵⁸ 2008	Japan	76	Singleton gestation, preterm labor (6 uterine contractions in 60 min documented by external tocography or any uterine activity associated with cervical changes), and intact membranes	Multiple gestation, rupture of membranes, herniation of membranes protruding beyond the external cervical os, indicated preterm delivery, fetal congenital anomalies, or contraindications to tocolysis	22-34	10	Delivery within 72 hours and 7 days of testing
Rahkonen, ⁵⁹ 2009	Finland	246	Singleton gestation, preterm labor (uterine contractions confirmed with external tocography), and intact membranes	Major fetal anomalies, vaginal bleeding, or placenta previa	22-34	10	Delivery within 14 days of testing and spontaneous preterm birth >34 weeks
Tanir, ⁶⁰ 2009	Turkey	68	Singleton gestation, preterm labor (4 uterine contractions lasting at least 30 seconds in 20 min and cervical changes), cervical dilatation <3 cm, and intact membranes	Cerclage, massive vaginal bleeding, use of tocolytics at admission, history of vaginal douche, intercourse or digital examination within the previous 24 h, preeclampsia, multiple gestation, diabetes mellitus, hyperthyroidism, or asthma	24-36	10	Delivery within 7 and 14 days of testing, and preterm birth <34 weeks

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
Audibert, ⁶¹ 2010	Canada	62	Singleton (89%) or multiple (11%) gestation, preterm labor (uterine contractions 4 in 30 min and lasting at least 30 seconds with significant cervical changes), and intact membranes	PROM, cervical dilatation >3 cm, cerclage, vaginal bleeding, placenta previa, placental abruption, severe IUGR, preeclampsia, or medically indicated preterm delivery <34 weeks	24-34	10	Delivery within 14 days of testing, and preterm birth <34 and <37 weeks
Azlin, ⁶² 2010	Malaysia	51	Singleton gestation, preterm labor (not defined), and intact membranes	Multiple gestation, PROM, cervical incompetence, cerclage, placenta previa, placental abruption, or cervical dilatation >3 cm	24-36	10	Delivery within 7 days of testing
Brik, ⁶³ 2010	Spain	276	Singleton gestation, preterm labor (not defined), and intact membranes	PROM, vaginal bleeding, placental abruption, fetal distress, cord prolapse, cervical dilatation >3 cm or cervical effacement of 100%, cerclage, or fetal anomalies	24-34	10	Delivery within 48 hours and 7 days of testing, and spontaneous preterm birth <32 and <34 weeks
Randhawa, ⁶⁴ 2010	Singapore	293	Preterm labor (not defined) and intact membranes	Not reported	22-36	10	Delivery within 48 hours of testing
Danti, ⁶⁵ 2011	Italy	60	Singleton gestation, preterm labor (4 uterine contractions in 20 min), cervical length 30 mm, and intact membranes	Multiple gestation, vaginal bleeding, PROM, cervical dilatation >3 cm, cerclage, uterine or fetal abnormalities, and other pregnancy complications	24-32	10	Delivery within 7 days of testing, and preterm birth <34 and <37 weeks
Riboni, ⁶⁶ 2011	Italy	210	Singleton gestation, preterm labor (10 uterine contractions/ hour), and intact membranes	Cervical dilatation >2 cm, cervical examination or sexual intercourse within the last 24 h, vaginal bleeding, placenta previa, multiple gestations, fetal abnormalities, or uterine anomalies	24-34	10	Delivery within 7 days of testing, and preterm birth <34 and <37 weeks

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
Cooper, ⁶⁷ 2012	Canada	349	Singleton (94%) or multiple (6%) gestation, preterm labor (not defined), and intact membranes	PROM, antepartum hemorrhage, active labor or suspected chorioamnionitis	24-34	10	Delivery within 7 and 14 days of testing, and preterm birth <37 weeks
Singh, ⁶⁸ 2013	India	50	Preterm labor (regular uterine contractions), cervical dilatation of 1 to <3 cm, and intact membranes	PROM, vaginal bleeding, heart disease, or diabetes	28-36	10	Delivery within 48 hours and 7 days of testing, and preterm birth <34 and <37 weeks
Bruijn, ⁶⁹ 2014	The Netherlands	350	Singleton gestation, preterm labor (not defined), cervical length <30 mm, and intact membranes	Multiple gestation or PROM	24-34	10	Delivery within 7 days of testing
Abo El-Ezz, ⁷⁰ 2014	Kuwait	57	Singleton gestation, preterm labor (1 uterine contractions in 10 min), and intact membranes	PROM, multiple gestation, or vaginal bleeding	24-34	10	Delivery within 7 days of testing
Hadži-Lega, ⁷¹ 2014	Macedonia	58	Singleton gestation, preterm labor (not defined), cervical dilatation 3 cm, and intact membranes	Multiple gestation, PROM, antepartum hemorrhage, active labor, cerclage, or suspected chorioamnionitis	22-33	10	Delivery within 14 days of testing
Kekki, ¹⁷ 2001	Finland	121	Singleton or twin gestation without (N=58) and with (N=63) symptoms of preterm labor (uterine contractions), and intact membranes	PROM	22-36	10	Spontaneous preterm birth <32, <34, and <37 weeks
Lembet, ⁷² 2002	Turkey	54	Singleton gestation without (N=18) and with (N=36) symptoms of preterm labor (>10 uterine contractions per hour regardless of the cervical dilatation), and intact membranes.	Multiple gestation, vaginal bleeding, IUGR, uterine anomaly, congenital fetal abnormality, or preeclampsia	20-36	10	Delivery within 48 hours and 7 days of testing, and preterm birth <37 weeks
Akercan, ⁷³ 2004	Turkey	65	Singleton gestation without (N=20) and with (N=45) symptoms of preterm	Multiple gestation, PROM, cervical dilatation >2 cm, IUGR, vaginal	24-36	10	Preterm birth <37 weeks

Study, year	Country	No. of women	Inclusion criteria	Exclusion criteria	Gestational age at testing (weeks)	Cutoff value (µg/L)	Reference standard outcome
Eroglu, ⁷⁴ 2007	Turkey	141	labor (>4 contractions in 20 min) and intact membranes labor (>4 contractions in 20 min) and intact membranes labor (>4 contractions in 20 min) and intact membranes	uterine anomaly	24-35	10	Delivery within 7 days of testing and preterm birth <35 weeks
Patemoster, ⁷⁵ 2007	Italy	301	Singleton gestation without (N=90) and with (N=51) symptoms of preterm labor (10 uterine contractions per hour), and intact membranes	Vaginal bleeding, cervical dilatation 3 cm, PROM, sexual intercourse within the past 24 hours, multiple pregnancy, uterine anomalies, congenital fetal abnormality, placenta previa, placental abruption, IUGR, or preeclampsia	22-34	10	Preterm birth <37 weeks
Altinkaya, ⁷⁶ 2009	Turkey	178	Singleton gestation without (N=73) and with (N=105) symptoms of preterm labor (uterine contractions confirmed by external tocography), and intact membranes	Multiple gestation, PROM, cervical dilatation 2 cm, preeclampsia, vaginal bleeding, IUGR, fetal or uterine anomalies, history of preterm birth, or smoking	24-34	10	Delivery within 7 days of testing and preterm birth <37 weeks

IUGR, intrauterine growth restriction; PROM, premature rupture of membranes

TABLE 2
Pooled estimates for cervical phIGFBP-1 test in predicting preterm birth in asymptomatic women

Outcome	No of studies	No of women	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	I^2 (%)
All women							
Preterm birth <37 weeks	13 ^{17,36-43,72,73,75,76}	6287	38 (33-43)	77 (76-78)	1.7 (1.4-2.0)	0.8 (0.7-0.9)	65
Spontaneous preterm birth <37 weeks	5 ^{17,36,37,40,43}	5327	38 (32-44)	77 (76-78)	1.6 (1.3-2.0)	0.8 (0.7-0.9)	0
Preterm birth <34 weeks	5 ^{37,39,41,44,73}	476	34 (20-51)	90 (86-93)	3.4 (1.2-10.6)	0.7 (0.5-0.9)	85
Spontaneous preterm birth <34 weeks	2 ^{37,44}	301	39 (23-58)	90 (86-94)	3.9 (1.6-9.7)	0.7 (0.4-0.9)	94
Spontaneous preterm birth <32 weeks	2 ^{40,44}	5181	40 (24-58)	76 (75-77)	1.7 (1.0-2.5)	0.8 (0.5-1.0)	14
Unselected women with a singleton gestation							
Preterm birth <37 weeks	7 ^{38,40,42,70,73,75,76}	5828	41 (34-47)	77 (75-78)	1.8 (1.3-2.2)	0.8 (0.7-0.9)	70
Women with a twin gestation							
Preterm birth <34 weeks	2 ^{39,44}	237	16 (5-36)	93 (89-96)	2.3 (0.5-9.2)	0.9 (0.7-1.1)	0
Women with a singleton gestation and previous spontaneous preterm birth							
Preterm birth <37 weeks	2 ^{37,43}	197	47 (32-62)	89 (83-94)	4.4 (1.9-10.4)	0.6 (0.4-0.8)	0
All women at high risk for preterm birth							
Preterm birth <37 weeks	5 ^{36,37,39,41,43}	370	31 (22-40)	90 (86-93)	3.1 (1.6-5.9)	0.8 (0.6-0.9)	69
Preterm birth <34 weeks	3 ^{39,41,44}	272	14 (4-32)	91 (86-94)	1.5 (0.4-4.3)	1.0 (0.8-1.1)	0

CI, confidence interval

TABLE 3

Pooled estimates for cervical phIGFBP-1 test in predicting preterm birth in women with an episode of preterm labor

Outcome	No of studies	No of women	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	I^2 (%)
All women							
Delivery within 48 hours of testing	6 ^{50,56,63,64,68,72}	791	77 (65-87)	80 (77-83)	4.0 (2.2-7.9)	0.3 (0.2-0.5)	84
Delivery within 7 days of testing	18 ^{48,50,54,56,58,60,62,63,65,70,72,74,76}	2159	67 (62-72)	77 (75-79)	3.0 (2.3-4.1)	0.4 (0.3-0.6)	75
Delivery within 14 days of testing	8 ^{53,55,56,59,61,67,71}	1028	66 (57-74)	79 (76-81)	3.2 (2.6-3.7)	0.4 (0.3-0.6)	41
Preterm birth <34 weeks	12 ^{17,45,48,51,59-61,63,65,66,68,74}	1232	64 (56-72)	78 (76-81)	3.0 (2.4-3.9)	0.5 (0.3-0.7)	47
Preterm birth <37 weeks	21 ^{17,18,45,48,50-52, 54,55,57,61,65,68,72,73,75,76}	1814	60 (56-65)	78 (76-80)	2.7 (2.2-3.6)	0.5 (0.4-0.6)	61
Women with a singleton gestation							
Delivery within 48 hours of testing	3 ^{56,63,72}	406	85 (70-94)	67 (62-72)	2.6 (1.8-3.5)	0.2 (0.1-0.5)	69
Delivery within 7 days of testing	14 ^{49,54,56,58,60,62,63,65,66,69,70,72,74,76}	1668	68 (62-74)	78 (76-80)	3.1 (2.5-3.8)	0.4 (0.3-0.6)	81
Delivery within 14 days of testing	5 ^{55,56,59,60,71}	521	68 (58-77)	81 (77-84)	3.5 (2.7-4.4)	0.4 (0.3-0.5)	56
Preterm birth <34 weeks	6 ^{59,60,63,65,66,74}	911	62 (52-72)	78 (75-81)	2.9 (2.0-3.9)	0.5 (0.4-0.7)	68
Preterm birth <37 weeks	12 ^{18,46,52,54,55,57,65,66,72,73,75,76}	1010	65 (59-71)	79 (76-82)	3.1 (2.5-4.0)	0.4 (0.3-0.5)	30
Women with a singleton gestation and a cervical length ≥ 30 mm							
Delivery within 7 days of testing	2 ^{65,69}	410	77 (66-86)	86 (82-90)	5.5 (3.7-8.9)	0.3 (0.1-0.4)	85

CI, confidence interval

Table 4

Comparison of the predictive accuracy for preterm birth of cervical *phIGFBP-1* and cervicovaginal fetal fibronectin in women with an episode of preterm labor (based on findings from recent meta-analyses)

Reference standard outcome	Measure of predictive accuracy	<i>phIGFBP-1</i> ^a	Fetal fibronectin ^b	Fetal fibronectin ^c
Delivery within 48 hours of testing	Sensitivity (%)	77	NR	62
	Specificity (%)	80	NR	81
	Positive likelihood ratio	4.0	NR	3.3
	Negative likelihood ratio	0.28	NR	0.47
Delivery within 7 days of testing	Sensitivity (%)	67	77	75
	Specificity (%)	77	83	79
	Positive likelihood ratio	3.0	4.4	3.6
	Negative likelihood ratio	0.43	0.28	0.31
Delivery within 14 days of testing	Sensitivity (%)	66	NR	NR
	Specificity (%)	79	NR	NR
	Positive likelihood ratio	3.2	NR	NR
	Negative likelihood ratio	0.43	NR	NR
Preterm birth at <34 weeks	Sensitivity (%)	64	69	NR
	Specificity (%)	78	84	NR
	Positive likelihood ratio	3.0	4.4	NR
	Negative likelihood ratio	0.46	0.37	NR
Preterm birth at <37 weeks	Sensitivity (%)	60	61	NR
	Specificity (%)	78	85	NR
	Positive likelihood ratio	2.7	4.1	NR
	Negative likelihood ratio	0.51	0.46	NR

phIGFBP-1, phosphorylated insulin-like growth factor binding protein-1; NR, not reported

^aMeta-analysis by Conde-Agudelo and Romero (current study)

^bMeta-analysis by Deshpande et al 2013⁷⁷

^cMeta-analysis by Boots et al. 2014¹³