Prediction of preterm delivery in symptomatic women using placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk

Short Title: PTL biomarker review

Author Information:

- Juan Carlos MELCHOR, MD, PhD, Cruces University Hospital (UPV/EHU). BioCruces Health Research Institute; Vizcaya, Spain
- Asma KHALIL, MD, MSc, St George's University Hospital; London, United Kingdom
- Deborah WING, MD, MBA; Formerly of the University of California, Irvine; Orange, CA, USA
- Ekkehard SCHLEUSSNER, MD, Department of Obstetrics, Jena University Hospital; Jena, Germany
- Daniel SURBEK, MD, Department of Obstetrics and Gynecology, University Hospital, Inselspital, University of Bern; Bern, Switzerland

Corresponding Author:
Juan Carlos Melchor
Obstetrics and Gynecology Department Cruces University Hospital (UPV/EHU)
Address: Plaza de Cruces s/n. 48903 Barakaldo, Vizcaya, Spain
E-mail: jmelchorm@sego.es

Keywords: PAMG-1, placental alpha microglobulin-1, fFN, fetal fibronectin, phIGFBP-1, phosphorylated insulin-like growth factor binding protein, preterm birth, preterm labor.

Abstract

Objective: To assess the diagnostic accuracy of placental alpha- microglobulin-1 (PAMG-1), fetal fibronectin (fFN), and phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) tests in the prediction of spontaneous preterm birth in women with symptoms of preterm labor within 7 days (sPTB≤7d) of testing using formal methods for systematic

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.19119

review. Further analysis looking into performance in low, intermediate and high-risk patient groups.

Methods: Two reviewers independently searched the Cochrane, MEDLINE, PubMed and ResearchGate bibliographic databases. The search was done from inception- October 2017. Cohort studies that reported on the predictive accuracy of PAMG- 1, fFN, and phIGFBP-1 for the prediction of sPTB in women with symptoms of preterm labor within 7 days of testing were included. Summary ROC curve, SN, SP, PPV, NPV and LRs were generated using indirect methods for the calculation of pooled effect sizes with a bivariate linear mixed model for the logit of sensitivity and specificity, with each diagnostic test as a covariate described by Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.

Results: Bivariate mixed model pooled sensitivities (SN) for PAMG-1, fFN and phIGFBP-1 for sPTB≤7d were 76% (95% CI, 0.57-0.89), 58% (95% CI, 0.47-0.68), and 93% (95% CI, 0.88-0.96). Bivariate mixed model pooled specificities (SP) were 97% (95% CI, 0.95-0.98), 84% (95% CI, 0.81-0.87), and 76% (95% CI, 0.70-0.80). Bivariate mixed model pooled positive predictive values (PPV) for PAMG-1, fFN, and phIGFBP-1 for sPTB≤7d were 76.3% (95% CI, 0.69-0.84) [$p<0.05$], 34.1% (95% CI, 0.29-0.39), and 35.2% (95% CI, 0.31-0.40). Bivariate mixed model pooled negative predictive values (NPV) were 96.6% (95% CI, 0.94-0.99), 93.3% (95% CI, 0.92-0.95), and 98.7% (95% CI, 0.98-0.99). Bivariate mixed model pooled positive likelihood ratio (LR+) for PAMG-1, fFN, and phIGFBP-1 for sPTB≤7d were 22.51 (15.09-33.60) [$p<0.05$], 3.63 (2.93-4.50), and 3.80 (3.11-4.66). Bivariate mixed model pooled negative likelihood ratio (LR–) for PAMG-1, fFN, and phIGFBP-1 for sPTB≤7d were 0.24 (0.12-0.48) [$p<0.05$], 0.50 (0.39-0.64), and 0.09 (0.05-0.16). Area under the curve (AUC) for PAMG-1, fFN, and phIGFBP-1 for sPTB≤7d were 0.961, 0.874, and 0.801.

Conclusions: It is well understood that prevalence affects a diagnostic test's predictive performance, and that in lower-prevalence syndromes such as sPTB, using highly specific assays may optimize management. Our study confirms that the PAMG-1 test was found to have the highest PPV and LR+ across all risk stratification groups with statistical significance while the NPV and LR– remained similarly high across all three biomarkers.

Introduction

Accurate diagnosis of preterm birth (PTB) is a vexing challenge. PTB, and its complications, are the leading causes for neonatal morbidity and mortality; and are associated with the most common and costly obstetrical indications for hospital admissions.[1-4] Preterm labor (PTL) hospitalizations account for nearly 33% of all in-patient prenatal unit admissions, up to 85% of which do not deliver within the next 7 days.[5,6] This results in unnecessary and potentially harmful treatments including corticosteroids and tocolytics.[7-9]

Approximately 65-75% of PTB are spontaneous, while the remaining are iatrogenic.[10] Spontaneous PTB may be caused by multiple pathological processes;[11,12] thus, prediction of PTB has been a long-standing challenge, as clinical symptoms alone are not of adequate predictive accuracy.[13,14] The most notable methods for PTB prediction are cervical length (CL) measurement and biomarker tests based on fetal fibronectin (fFN), phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1), or placental alpha-microglobulin-1 (PAMG-1).

All three biomarkers were evaluated in multiple clinical settings and their performance showed considerable variation between studies, based on demographic and other factors underlying each cohort, such as the prevalence, ranging from 0.9%[15] to 52%,[16] of spontaneous PTB within 7 days of testing (sPTB≤7d). Concomitantly, the predictive values associated with each biomarker also varied. Positive predictive values (PPV) for PAMG-1, fFN, and phIGFBP-1, were 23.1%-100%,[15,17] 4.3-92.3%,[15,18] 2.2-81.3%.[18,19] Negative predictive values (NPV) for PAMG-1, fFN, and phIGFBP-1 were 93.0-100%,[20,21] 73.2-100%,[18,22] and 61.8- 98.4%.[16,19] The range of predictive values presents a challenge to clinicians evaluating biomarker tests for their population, which may have a different pre-test probability of sPTB≤7d than that reported by any one study. While the impact of

disease prevalence on the performance of a diagnostic test is well-established,[23] it has not yet been considered.

This review has two objectives. First, to perform the most up-to-date systematic review and meta-analysis of the PAMG-1, fFN and phIGFBP-1 biomarkers for the prediction of sPTB≤7d in symptomatic women using methods described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Second, to stratify each biomarker's test performance by the pretest probabilities of sPTB≤7d, associated with various cervical length measurement ranges, in PTL symptomatic women and who have clinically intact membranes and minimal cervical dilation (≤ 3 cm).

Methods and Materials

This study followed a prospective review protocol and is reported in accordance with recommended methods for systematic reviews of diagnostic test accuracy using the PRISMA Guidelines.[24,25]

Literature Review

The literature search was performed for PAMG-1, fFN, and phIGFBP-1 for test performance for the prediction of preterm birth in women with symptoms of preterm labor. The search was conducted from inception up to October 2017. Two reviewers independently searched the Cochrane, MEDLINE, PubMed and ResearchGate bibliographic databases using a combination of keywords, including "PartoSure", "PAMG-1"; "fetal fibronectin", "ffn", "fibronectin", "Rapid fFN", or "QuikChek"; "ActimPartus" or "phIGFBP-1". Additional citations were identified by reviewing the proceedings and submitted abstracts of multiple international meetings and conferences focused on maternal-fetal medicine or preterm birth. All references in the retrieved articles were screened for further studies relevant to the

objective of this review. Editorials and reviews, although themselves not included in the analysis, were also scanned for relevant studies.

Only prospective or cohort studies that met the following criteria were included in this analysis: (a) clinical study objective was to determine accuracy of specified biomarkers for prediction of preterm birth (b) reported or included sufficient information to calculate test performance metrics for the prediction of spontaneous preterm birth within 7 days of testing (i.e. the reference standard); (c) the study population had signs or symptoms suggestive of preterm labor, clinically intact membranes and minimal cervical dilatation (≤ 3 cm); and (d) the study population included patients <37 weeks gestation. Studies were excluded if they had any of the following characteristics: (a) clinical study objective was not to determine accuracy of specified biomarkers for prediction of preterm birth (b) the performance metrics for the prediction of preterm birth within 7 days of testing were either not reported or could not be calculated through the information provided; (c) the test studied either is not currently available commercially or was evaluated using a test procedure not recommended by the respective manufacturer; (d) was a reply or review article with no original data provided; or (e) reported duplicate performance metrics already reported by an earlier study. When in doubt, study authors were contacted to ensure that there was no overlap between study data.

Data Extraction

Information was extracted independently for each primary study using a specifically designed data collection form to capture the study characteristics (i.e. authors, setting, year of publication, year of recruitment, method of recruitment, prospective or retrospective data collection, percentage of women recruited included in the analysis); patient population characteristics (i.e. sample size, prevalence of birth within 7 days, and demographic information); inclusion and exclusion criteria (i.e. gestational age at sampling, singleton or

multiple gestations, cervical dilation, status of fetal membranes, presence of vaginal bleeding, intercourse in the past 24 hours, contraction frequency, cervical length); preterm birth endpoint used for test performance calculations; and numbers of true-positive, false-positive, true-negative, and false-negative test results for the prediction of spontaneous preterm birth within 7 days of testing. The studies with insufficient information, were excluded from the meta-analysis.

Assessment the Risk of Bias

Study quality was assessed using a modified version of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[26] All the included studies were judged as 'low risk', 'high risk', or 'unclear risk' of bias and were evaluated and interpreted in consideration of the following characteristics:

a. *Patient selection*. Patients who were recruited consecutively or randomly were considered to have low risk of bias. Studies that used convenience sampling, arbitrary recruitment, or nonconsecutive recruitment were considered to have a high risk of bias.
b. *Reference standard*. Studies that had at least one of their endpoints defined as spontaneous preterm birth within 7 days of testing were considered to have a low risk of bias. Studies that included only endpoints defined as either preterm birth, inclusive of iatrogenic preterm deliveries, or medically-indicated preterm birth alone within 7 days of testing, were considered to have a high risk of bias.
c. *Blinding*. Studies clearly stating that clinicians managing patient care did not have knowledge of biomarker test results were considered to have a low risk of bias. Studies where the managing clinicians had knowledge of biomarker test results were considered to have a high risk of bias.
d. *Inclusion of patients in the analysis*. Studies that included ≥85% of recruited patients into the calculations of test performance were considered to have a low risk of bias. Studies that included <85% of recruited patients into the calculations of test performance were

considered to have a high risk of bias.

A summary score was not calculated to estimate the overall quality of each study, as interpretation of such summary scores may be potentially misleading.[27]

Data Synthesis

Data from individual studies was synthesized for singleton gestations when possible. All studies that met inclusion criteria were stratified according to three pre-defined, clinically-relevant risk classifications based on the pre-test probability of sPTB≤7d. The three pre-defined groups were Low [Risk], Intermediate [Risk], and High [Risk]. The probability of sPTB≤7d in patients with cervical length measurements between 15 and 30 mm was used as the reference for the Intermediate group. Three studies were selected as reference, as they were the largest studies to date incorporating the use of a biomarker test along with cervical length measurements. The sPTB≤7d in this group of patients with cervical length measurements between 15 and 30 mm was 7.5%-10.7% (95% CI 4.58%-16.25%). [28-30] The Low Risk group was classified by rates of sPTB≤7d below the lower bound of the 95% CI of that range (i.e. those studies with a pre-test probability of sPTB≤7d less than 4.58%).[28] The Intermediate Risk group was classified by rates of sPTB≤7d within the 95% CI of that range, (i.e. those studies with a pre-test probability of sPTB≤7d between 4.58% and 16.25%).[28-30] The High Risk group was classified by rates of sPTB≤7d above the upper bound of the 95% CI of that range (i.e. those studies with a pre-test probability of sPTB≤7d greater than 16.25%).[30]

Statistical Analysis Comparing PAMG-1, fetal fibronectin, and phIGFBP-1

Data extracted from each study were arranged in 2x2 contingency tables. Pooled estimates were obtained for each risk classification group using a bivariate linear mixed model for the logit of sensitivity and specificity, with each diagnostic test as a covariate described by

Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[31] As evaluation of the performance of the three diagnostic tests was a central aim of this meta-analysis, analysis was also performed with the bivariate linear mixed effects model with type of test as a covariate to assess difference in test accuracy measures.[31] Pooled estimates are reported from this same model for formal statistical comparison. The bivariate mixed model accounted for differences in study sample sizes as well as both within and between study variability, while also accounting for correlation between the sensitivity and the specificity. Models were fit in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) using PROC NLMIXED as described in the METADAS SAS macro.[32-37] Model convergence could not be attained in the Low and Intermediate risk groups; therefore the model was simplified to include random study effect only without random effects for sensitivity and specificity by study, thereby removing estimate of correlation between sensitivity and specificity from the model. Sensitivity and specificity with 95% CIs were calculated as estimated from the bivariate models with the differences between diagnostics tests evaluated on the logit scale. The likelihood ratios were estimated thereafter from the pooled sensitivities and specificities for each biomarker test with 95% CIs with differences evaluated on the log scale. Similarly, the NPVs and PPVs for each risk classification group were calculated using the pooled estimates of sensitivity and specificity. Standard errors and confidence intervals were estimated based on the delta method with normal approximation. Global tests based on the F-statistics were performed to assess the difference in the outcomes among the three biomarker tests by each risk classification group. Pairwise comparisons were evaluated from the model with a t-statistic and all the p-values were two-sided. All the p-values presented were nominal with no adjustment for the test multiplicity with statistical significance set as $p<0.05$.

The summary receiver-operating characteristic (ROC) curve was estimated according to the

method of Rutter and Gatsonis (2001) as also described by Arends (2008).[38,39] The area under the curve (AUC) was computed using the R package meta4diag (The R Foundation, Vienna, Austria) assuming the SROC curve is that of Rutter and Gatsonis.

Results

Study Selection

The process of identification and selection of studies is summarized in **Figure 1**. The database search identified 2239 citations. From the identified citations, 2020 studies were excluded based on irrelevant titles and duplicates. The full text articles of the remaining citations were reviewed and further 253 studies were excluded for the following reasons: clinical study objective was not to determine accuracy of specified biomarkers for prediction of preterm birth (253), different reference standard (84), not original data (reply/review) (38), duplicate results (24) and other (7). The characteristics of studies included in the systematic review are summarized in **Table 1**.

Study Characteristics and Risk of Bias

Figure 2 summarizes the quality assessment of the studies included. Seven studies (11%) fulfilled all four of the quality criteria; 23 studies (35%) fulfilled three quality criteria. The remaining 36 studies (55%) fulfilled two or less quality criteria, suggesting potential methodological flaws.

Overall, there were 14 PAMG-1 studies (n=2278),[15,17,20,21,30,40-48] 40 fFN studies (n=7431),[14,15,18,20,22,28,29,40-42,49-78] and 22 phIGFBP-1 studies (n=3192)[16,18,19,28,30,48,54,73,79-92] were included in our final analysis. Of these, 10 studies included performance metrics for more than one biomarker. The studies enrolled patients at centers from different regions of the world, with the highest proportion from Europe (39%), second highest from North America

(21%), followed by Asia (15%), Middle East (14%), Latin America (5%), Oceania (5%) and Africa (2%). The sample sizes ranged from 22[77] to 725[52] subjects (mean, 170).

Prediction of spontaneous preterm birth within 7 days of testing

Figure 3 shows the sensitivity and specificity of all three biomarker tests in the individual studies to predict preterm birth within 7 days in symptomatic women. For Low Risk Group, three studies (n=1074)[15,40,43] met the criteria for PAMG-1, eight studies (n=2667)[15,22,40,49,52-55] met the criterial for fFN, and two studies (n=559)[19,54] for phIGFBP-1. For the Intermediate Risk Group, nine studies (n=929)[17,21,30,41,44-48] met the criteria for PAMG-1, 25 (n=3714)[14,29,41,50,51,56-75] met the criterial for fFN, and eight studies (n=1108)[30,48,73,79-83] for phIGFBP-1. For the High Risk Group, two studies (n=275)[20,42] met the criteria for PAMG-1, seven (n=1050)[18,20,28,42,76-78] met the criterial for fFN, and twelve studies (n=1525)[16,18,28,84-92] for phIGFBP-1. **Table 2** shows the pooled summary sensitivity and specificity results, as well as per risk group for each biomarker test with their 95% CIs from the bivariate mixed model, with each diagnostic test as a covariate. **Table 3** shows the PPV, NPV, LR+ and LR- that were estimated with the bivariate mixed model from the sensitivities and specificities for each biomarker test with their 95% CIs for each risk classification group. PAMG-1 had a statistically superior PPV ($p<0.05$) across all three risk classification groups, demonstrating a 2-to-6 fold higher PPV than those of fFN and phIGFBP-1. Furthermore, the pairwise comparisons of the NPV between tests did not show a statistically-significant difference.

As the clinical usefulness of a diagnostic test may be largely determined by the accuracy with which it identifies its target disorder, this accuracy is best determined by assessing the likelihood ratios.[52] An LR+ above 10 and an LR- below 0.1 are considered to provide strong predictive evidence in most circumstances. Moderate prediction can be achieved with LR+

and LR- values of 5-10 and 0.1-0.2, respectively, whereas those less than 5 and greater than 0.2 give only minimal prediction.[93] As with the predictive values, the positive likelihood ratios show a similar trend with PAMG-1 having a statistically superior LR+ ($p<0.05$) across all risk classification groups, as compared to fFN and phIGFBP-1. The PAMG-1 test is the only biomarker to have a LR+ above 10 in all the three risk classification groups, indicating strong predictive accuracy for this marker. On the other hand, a comparison of the LR- for each test did not show a statistically-significant difference among the different markers. Furthermore, we compared the AUC between the three tests (**Figure 4**) and found that PAMG-1 has the highest predictive accuracy for spontaneous preterm birth within 7 days of testing, with the phIGFBP-1 showing the lowest predictive accuracy: PAMG-1 0.961, fFN 0.874, phIGFBP-1 0.801.

When the bivariate model was fitted to each test separately for all available studies, the estimates of pooled sensitivities (SN) for PAMG-1, fFN and phIGFBP-1 for sPTB≤7d were 73.5% (95% CI, 0.63-0.82), 75.3% (95% CI, 0.69-0.81), and 71.0% (95% CI, 0.61-0.80); pooled specificities (SP) were 96.6% (95% CI, 0.95-0.98), 83% (95% CI, 0.80-0.86), and 80.2% (95% CI, 0.76-0.84); pooled positive likelihood ratios (LR+) were 21.69 (95% CI, 14.38-32.72), 4.40 (95% CI, 3.76-5.14), and 3.58 (95% CI, 2.73-4.70); pooled negative likelihood ratios (LR–) were 0.27 (95% CI, 0.19-0.40), 0.30 (95% CI, 0.24-0.37), and 0.35 (95% CI, 0.26-0.51).

Discussion

The results of our systematic review suggest that PAMG-1 has a strong predictive accuracy for sPTB≤7d in women with signs and symptoms of PTL. The reported PPV for PAMG-1 is a major improvement compared to phIGFBP-1 and fFN biomarker tests, which are used to rule out preterm labor, due to their high NPVs. The positivity rate of each biomarker

remained relatively consistent throughout the studies (7.9%, 23.0%, and 29.7% for PAMG-1, fFN, and phIGFBP-1, respectively). Given the potential of a positive biomarker test to influence the decision to admit and/or treat, a test with a lower positivity rate and higher PPV may lead to reductions in unnecessary hospitalizations and in-utero transfers to tertiary care centers and allow for more judicious use of therapeutic interventions, such as antenatal corticosteroids and tocolytic agents.

The strength of this review stems from its rigorous methodology, which included stringent study selection criteria, recent literature searches, and a highly specific area of focus. Additionally, a modified version of the QUADAS-2 quality assessment was used to determine study quality. Contemporary statistical methods were used to obtain summary measures of the predictive accuracies.

Our study has some important limitations. First, the study may be underpowered, as we weren't able to attain convergence in the Low and Intermediate Risk groups. Therefore, the model had to be simplified to include random study effects only, without random effects for sensitivity and specificity by study. Additionally, the three risk groups showed a variation of sensitivity and specificity. These metrics shouldn't dependent on the prevalence of the disease, as compared to predictive values. This heterogeneity could be due to within-study error and/or other population characteristics. The reason for variation across populations should be further investigated. Second, the three biomarkers didn't have the same number of subjects. Furthermore, only 45% of studies were considered at low risk of bias. This included studies that didn't specify their definition of PTB, and thus may have included medically-indicated deliveries. This effect is expected to be minimal given that few studies fell into this group, and more than two-thirds of PTBs are spontaneous. Given the complexity and

heterogeneity of available studies, the performance endpoints were limited to sPTB≤7d, as not all studies included information for other endpoints, such as 48 hours or 14 days.

Alternative analysis methods may produce different pooled estimates than found here. A simple pooled estimate may be obtained directly by summing numerators and denominators from the raw data across studies but has severe limitations as it assumes lack of heterogeneity across studies. Thus, random effects models are required to describe variability in test accuracy across studies, which in addition assumes independence of sensitivity and specificity. The bivariate mixed effects model of Reitsma, et. al. is a widely accepted method for meta-analysis of diagnostic tests as it overcomes the limitations of simple pooling by jointly modeling sensitivity and specificity.[31,36] Apart from accounting for between study variability due to both random error and inherent differences in studies due to design, population, or study procedures, the bivariate mixed effects model method also allows for inclusion of covariates.[33-37]

Lastly, our review didn't look at the impact of test performance on patient management and resource economics. This is an area for future research. Additionally, the heterogeneity of each test's performance using individual patient data (IPD) and meta-regression techniques looking at covariates such as gestational age, contraction frequency, and CL at presentation should be attempted.

To the best of our knowledge, this is the first systematic review to compare performance of the PAMG-1, fFN and phIGFBP-1 biomarkers for prediction of sPTB across different risk classification groups. While Boots et al.[94] discussed the effect of disease prevalence on test results, only the performance for a single pre-test probability (20%) was reported. As the pre-

test probability of sPTB≤7d varied significantly among the publications (0.9%[15]-52%[16]), the predictive values for one population with a certain pre-test probability may not apply to another. The pre-test probabilities for sPTB≤7d can vary among populations due to country or center-specific algorithms for PTL diagnosis that call for biomarker test use only with equivocal diagnosis, such as CL between 15-30mm[95] or those who present with any symptom of PTL and minimal cervical dilation.[15] While our conclusions on the performance of fFN and phIGFBP-1 are consistent with those in previous systematic reviews,[96,97] our work includes several studies published since then. Furthermore, our study reconfirms the effect of prevalence (or pre-test probability) on the performance of biomarker tests for the prediction of sPTB≤7d.

Based on the probability of sPTB≤7d in patients with CL between 15-30mm reported in major publications, [28-30] the following clinical inferences may be drawn from our data:

- For the regions or centers where the CL by transvaginal ultrasound are not routinely used (e.g. the U.S., U.K.), biomarker test performance for the prediction of sPTB≤7d would be commensurate with the performance reported for the Low Risk group (PPV 34.4%, 9.1%, 6.1%, and NPV 98.9%, 99.0%, 98.5% for PAMG-1, fFN, and phIGFBP-1, respectively).
- For the regions or centers where biomarker tests are only used in patients with a CL between 15-30mm (e.g. Europe), biomarker test performance for the prediction of sPTB≤7d would be commensurate with the performance reported for the Intermediate Risk group (PPV 69.4%, 28.8%, 25.4%, and NPV 97.6%, 97.2%, 96.1% for PAMG-1, fFN, and phIGFBP-1, respectively).
- For the regions or centers where biomarker tests are only used in patients with a CL <15mm, biomarker test performance for the prediction of sPTB≤7d would be commensurate with the performance reported for the High-Risk group (PPV 82.9%, 50.3%, 53.7%, and NPV 92.4%, 77.6%, 96.3% for PAMG-1, fFN, and phIGFBP-1, respectively).

We conclude that while all three biomarker tests had similarly high NPVs and LR-, the PAMG-1 test had the highest PPV and LR+ across all risk stratification groups ($p<0.05$). As such, our review supports the conclusions of the European Association of Perinatal Medicine (EAPM) guidelines, that the PAMG-1 test is the most accurate test to be used in women with a CL between 15-30mm.[95]

References

1. Blencowe H, Cousens S, Ostergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rodhe S, Say L, Lawn JE. National, regional and worldwide estimates of preterm birth. *Lancet* 2012; **379(9832)** : 2162-72.

2. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, Chou D, Say L, Modi N, Katz J, Vos T, Marlow N, Lawn JE. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatr Res* 2013; **74**(Suppl 1) :17-34.

3. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet* 2012 Feb 4; **379** : 445-52.

4. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Eds CP Howson, MV Kinney, JE Lawn. World Health Organization. Geneva, 2012.

5. Russell RB, Green NS, Steiner CA, Meikle S, Howse JL, Poschman K, Dias T, Potetz L, Davidoff MJ, Damus K, Petrini JR. Cost of hospitalization for preterm and low birth weight infants in the United States. *Pediatrics* 2007; **120** : 1-9.

6. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D. Hospitalizations for severe complications of pregnancy, 1987-1992. *Obstet Gynecol* 1997; **90** : 225-9.

7. Alfirevic Z, Allen-Coward H, Molina F, Vinuesa CP, Nicolaides K. Targeted therapy for threatened preterm labor based on sonographic measurement of the cervical length: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2007; **29** : 47-50.

8. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. *Obstet Gynecol* 1999; **94** : 869-77.

9. Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, Davies J, Hanlon-Lundberg K, Simpson L, Stone J, Wing D, Ogasawara K, Muraskas J. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. *JAMA* 2001 Oct 3; **286(13)** :1581-7.

10. Murphy KE, Hannah K, Willian AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gafni A, Lee SK, Armson BA, MACS Collaborative Group.Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. *Lancet* 2008 Dec 20; **372(9656)** : 2143-51.

11. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008 Jan 5; **371** :75-84.

12. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, Chaiworapongsa T, Mazor M. The preterm parturition syndrome. *BJOG* 2006; **113(Suppl 3)** :17-42.

13. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science* 2014; **345** : 760-5.

14. Iams JD, Casal D, McGregor JA, Goodwin TM. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. *Am J Obstet Gynecol* 1995 Jul;**173(1)** : 141-5.

15. Wing DA, Haeri S, Silber AC, Roth CK, Weiner CP, Echebiri NC, Franco A, Pappas LM, Yeast JD, Brebnor AA, Quirk JG, Murphy AM, Laurent LC, Field NT, Norton ME. Placental alpha microglobulin-1 compared with fetal fibronectin to predict preterm delivery in symptomatic women. *Obstet Gynecol* 2017 Dec; **130(6)** :1183-91.

16. Singh S, Singh S, Chandra M, Rani R, Verma S. A study to evaluate the efficacy of Actim Partus (a rapid bedside test) in the prediction of preterm labor. *Indian J Clin Pract* 2013; **24** : 260-3.

17. Heverhagen A. Placental alpha macroglobulin-1 in combination with transvaginal ultrasound for prediction of preterm birth. *J Perinat Med* 2015; **43(S1)** : 240.

18. Tripathi R, Tyagi S, Mala YM, Singh N, Pandey NB, Yadav P. Comparison of rapid bedside tests for phosphorylated insulin-like growth factor-binding protein 1 and fetal fibronectin to predict preterm birth. *Int J Gynaecol Obstet* 2016 Oct; **135(1)** : 47-50.

19. Cooper S, Lange I, Wood S, Tang S, Miller L, Ross S. Diagnostic accuracy of rapid phIGFBP-I assay for predicting preterm labor in symptomatic patients. *J Perinatol* 2012; **32** : 460-5.

20. Çekmez Y, Kıran G, Haberal ET, Dizdar M. Use of cervicovaginal PAMG-1 protein as a predictor of delivery within seven days in pregnancies at risk of premature birth. *BMC Pregnancy Childbirth* 2017 Jul 26; **17(1)** : 246.

21. Bolotskikh V, Borisova V. Combined value of placental alpha microglobulin-1 detection and cervical length via transvaginal ultrasound in the diagnosis of preterm labor in symptomatic patients. *J Obstet Gynaecol Res* 2017 Aug; **43(8)** : 1263-9.

22. Gao L, Zhang JP, Chen H, Guo ZJ, Chen LB, Tan JP, Wang YH, Zhang R, Liu YL, Cai WB. Fetal fibronectin detection for preterm birth prediction. *Genet Mol Res* 2014 Feb 28 ; **13(1)** : 1323-8.

23. Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. *Biometrics* 2000 Jun; **56**(2) : 345-51.

24. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HCW. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003; **326** : 41-4.

25. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;

149 : 889-97.

26. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang NM, Sterne JA, Bossuyt PM, QUADAS-2 Group: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155** : 529-36.

27. Whiting P, Harbord R, Kleijnen J. No role for quality scores in systematic reviews of diagnostic accuracy studies. *BMC Med Res Methodol* 2005; **5** : 19.

28. Bruijn MM, Vis JY, Wilms FF, Oudijk MA, Kwee A, Porath MM, Oei G, Scheeper HC, Spaanderman ME, Bloemenkamp KW, Haak MC, Bolte AC, Vanderbussche FP, Woiski MD, Bax CJ, Cornette JM, Dukevot JJ, Nij Bijvank BW, van Eyck J, Franssen MT, Sollie KM, van der Post JA, Bossuyt PM, Opmeer BC, Kok M, Mol BW, van Baaren GJ. Comparison of the Actim Partus test and the fetal fibronectin test in the prediction of spontaneous preterm birth in symptomatic women undergoing cervical length measurement. *Eur J Obstet Gynecol Reprod Biol* 2016 Nov; **206** : 220-4.

29. van Baaren GJ, Vis JY, Wilms FF, Oudijk MA, Kwee A, Porath MM, Oei G, Scheeper HC, Spaanderman ME, Bloemenkamp KW, Haak MC, Bolte AC, Bax CJ, Cornette JM, Dukevot JJ, Nij Bijvank BW, van Eyck J, Franssen MT, Sollie KM, Vandenbussche FP, Woiski M, Grobman WA, van der Post JA, Bossuyt PM, Opmeer BC, Mol BW. Predictive value of cervical length measurement and fibronectin testing in threatened preterm labor. *Obstet Gynecol* 2014 Jun; **123(6)** : 1185-92.

30. Nikolova T, Uotila J, Nikolova N, Borisova VY, Bolotskikh VM. Do PAMG-1 or phIGFBP-1 biomarkers improve the prediction of imminent spontaneous preterm delivery in PTL symptomatic women with non-obvious cervical length (CL)? *Am J Obstet Gynecol* 2017 Jan; 216(1 suppl) : S11-S12.

31. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration, 2010. Available from: http://srdta.cochrane.org/.

32. Takwoingi Y, Deeks JJ. MetaDAS. A SAS macro for meta-analysis of diagnostic accuracy studies. User Guide Version 1.3. 2010 July. Available from: http://srdta.cochrane.org/.

33. Ma X, Nie L, Cole SR, Chu H. Statistical methods for multivariate meta-analysis of diagnostic tests: an overview and tutorial. *Stat Methods Med Res* 2016 Aug; **25(4)** : 1596-619.

34. Trikalinos TA, Balion CM, Coleman CI, Griffith L, Santaguida PL, Vandermeer B, Fu R. Chapter 8: meta-analysis of test performance when there is a "gold standard". *J Gen Intern Med* 2012 Jun; **27 Suppl 1**: S56-66.

35. Riley RD, Ahmed I, Debray TPA, Willis BH, Noordzij JP, Higgins JPT, Deeks JJ. Summarising and validating test accuracy results across multiple studies for use in clinical practice. *Stat Med* 2015; **34(13)** : 2081-103.

36. Reitsma JB. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of Clinical Epidemiology. 2005; 58: 982-90.

37. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC. A unification of models for meta-analysis of diagnostic accuracy studies. Biostatistics. 2007; 8: 239–51.

38. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001 Oct 15; **20(19)** : 2865-84.

39. Arends LR, Hamza TH, van Houwelingen JC, Heijenbrok-Kal MH, Hunink MGM,

Stijnen T. Bivariate random effects meta-analysis of ROC curves. *Med Decis Making* 2008; **28** : 621-38.

40. Melchor JC, Navas H, Marcos M, Iza A, de Diego M, Rando D, Melchor I, Burgos J. Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit. *Ultrasound Obstet Gynecol* 2018 May; **51(5)**: 644-9.

41. Van Holsbeke C, Dam K, Staelens A, Mesens T, Corremans A. Comparison of the fetal fibronectin (Rapid fFN) and placental alpha microglobulin-1 (PartoSure) tests for predicting imminent spontaneous preterm birth. *Ultrasound Obstet Gynecol* 2016; **48(S1)** : 84.

42. Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. *J Perinat Med* 2015 Jul; **43(4)** : 395-402.

43. Ravi M, Beljorie M, Masry EL. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour. *J Pediatr Neonat Individual Med* 2017; **6(1)** : e060125.

44. Lotfi G, Faraz S, Al Swalhee N, Nasir R, Somini S, Abdeldayem R, Koratkar R, Ammar A. Evaluation of PAMG-1 for the prediction of preterm birth in patients symptomatic of preterm labor. *J Perinat Med*. 2015 **(43)**. DOI 10.1515/jpm-2015-2003

45. Fatkullin I, Akhmetgaliev A, Matveeva E, Seeger S. Utilization of a novel biomarker test (PartoSure PAMG-1) to reduce the length of stay in patients with threatened preterm labor and a short cervix. *J Matern Fetal Neonatal Med* 2016; **29(S1)** : 283.

46. Lou YY, Ajay B. Is PartoSure effective in assessing preterm birth? *BJOG* 2016; **123(S2)**

: 89.

47. Konoplyannikov A, Lysyuk I, Sokolyan A, Pipia N, Apresyan S, Karasova A. PAMG-1 biomarker test (PartoSure) in combination with transvaginal ultrasound for improved assessment of spontaneous preterm birth in patients with threatened preterm labor. *J Matern Fetal Neonatal Med* 2016; **29(S1)** : 278.

48. Hadzi Lega M, Maier JT, Helmer H, Hellmeyer L, Markova AD, Poposka A. Comparison of PartoSure (PAMG-1) and Actim Partus (phIGFBP-1) for the prediction of preterm delivery in patients with preterm labour and a short cervix. *Open Journal of Obstetrics and Gynecology* 2017; **7** : 358-68.

49. Bartnicki J, Casal D, Kreaden US, Saling E, Vetter K. Fetal fibronectin in vaginal specimens predicts preterm delivery and very-low-birth-weight infants. *Am J Obstet Gynecol* 1996; **174** : 971-4.

50. MacDonald WA, Bender M, Saxton A. Use of fetal fibronectin in the management of preterm labour in Nunavut. *Alaska Med* 2007; **49(Suppl. 2)** : 215-7.

51. Sakai M, Sasaki Y, Yamagishi N, Tanebe K, Yoneda S, Saito S. The preterm labor index and fetal fibronectin for prediction of preterm delivery with intact membranes. *Obstet Gynecol* 2003; **101** : 123-8.

52. Peaceman AM, Andrews WW, Thorp JM, Cliver SP, Lukes A, Iams JD, Coultrip L, Eriksen N, Holbrook RH, Elliott J, Ingardia C, Pietrantoni M. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. *Am J Obstet Gynecol* 1997; **177** : 13-8.

53. Desjardins PR, Dansereau J, Hoag GN. Comparing the clinical effectiveness of fetal fibronectin and IGFBP-1 measurements in cervico-vaginal secretions, in predicting preterm deliveries. *Clin Chem* 2008; **54** : A39-40.

54. Riboni F, Vitulo A, Dell'avanzo M, Plebani M, Battagliarin G, Paternoster D. Biochemical markers predicting pre-term delivery in symptomatic patients: phosphorylated insulin-like growth factor binding protein-1 and fetal fibronectin. *Arch Gynecol Obstet* 2011 Dec; **284(6)** : 1325-9.

55. LaShay N, Gilson G, Joffe G, Qualls C, Curet L. Will cervicovaginal interleukin-6 combined with fetal fibronectin testing improve the prediction of preterm delivery? *J Matern Fetal Med* 2000; **9** : 336-41.

56. Foxman EF, Jarolim P. Use of the fetal fibronectin test in decisions to admit to hospital for preterm labor. *Clin Chem* 2004; **50** : 663-5.

57. Swamy GK, Simhan HN, Gammill HS, Heine RP. Clinical utility of fetal fibronectin for predicting preterm birth. *J Reprod Med* 2005; **50** : 851-6.

58. Luzzi V, Hankins K, Gronowski AM. Accuracy of the rapid fetal fibronectin TLi system in predicting preterm delivery. *Clin Chem* 2003; **49** : 501-2.

59. Groom KM, Liu E, Allenby K. The impact of fetal fibronectin testing for women with symptoms of preterm labour in routine clinical practice within a New Zealand population. *Aust N Z J Obstet Gynaecol* 2006; **46** : 440-5.

60. Henrich W. Cervicometry and fibronectin role. Paper presented at 22nd European Congress of Perinatal Medicine; 26-29 May 2010; Granada, Spain. *J Matern Fetal Neonatal Med* 2010; **23(Suppl. 1)** : 39.

61. Tekesin I, Marek S, Hellmeyer L, Reitz D, Schmidt S. Assessment of rapid fetal fibronectin in predicting preterm delivery. *Obstet Gynecol* 2005; **105** : 280-4.

62. Benattar C, Taieb J, Fernandez H, Lindendaum A, Frydman R, Ville Y. Rapid fetal fibronectin swab-test in preterm labor patients treated by betamimetics. *Eur J Obstet Gynecol Reprod Biol* 1997; **72** : 131-5.

63. Lowe MP, Zimmerman B, Hansen W. Prospective randomized controlled trial of fetal fibronectin on preterm labor management in a tertiary care center. *Am J Obstet Gynecol* 2004; **190** : 358-62.

64. Sümer C, Yalvac S, Kandemir O, Karcaaltincaba D, Haberal A. The predictive value of sonographic cervical length measurement and fetal fibronection testing to determine true preterm labour. *Turk Jinekoloji ve Obstetrik Dernegi Dergisi* 2010; **7** : 189-95.

65. Malak TM, Sizmur F, Bell SC, Taylor DJ. Fetal fibronectin in cervicovaginal secretions as a predictor of preterm birth. *Br J Obstet Gynaecol* 1996; **103** : 648-53.

66. Liong S, Di Quinzio MK, Fleming G, Permezel M, Rice GE, Georgiou HM. New biomarkers for the prediction of spontaneous preterm labour in symptomatic pregnant women: a comparison with fetal fibronectin. *BJOG* 2015 Feb; **122(3)** : 370-9.

67. Tsoi E, Akmal S, Geerts L, Jeffery B, Nicolaides KH. Sonographic measurement of cervical length and fetal fibronectin testing in threatened preterm labor. *Ultrasound Obstet Gynecol* 2006; **27** : 368-72.

68. Closset E, Dufour P, Coeugnet C, Subtil D, Valat AS, Puech F. Value of fetal fibronectin research for predicting premature delivery. *Gynecol Obstet Fertil* 2001; **29** : 808-13.

69. Skoll A, St Louis P, Amiri N, Delisle M-F, Lalji S. The evaluation of the fetal fibronectin test for prediction of preterm delivery in symptomatic patients**.** *J Obstet Gynaecol Can* 2006; **28** : 206-13.

70. Lopez RL, Francis JA, Garite TJ, Dubyak JM. Fetal fibronectin detection as a predictor of preterm birth in actual clinical practice. *Am J Obstet Gynecol* 2000; **182** : 1103-6.

71. Giles W, Bisits A, Knox M, Madsen G, Smith R. The effect of fetal fibronectin testing on admissions to a tertiary maternal-fetal medicine unit and cost savings. *Am J Obstet Gynecol* 2000; **182** : 439-42.

72. McKenna DS, Chung K, Iams JD. Effect of digital cervical examination on the expression of fetal fibronectin. *J Reprod Med* 1999; **44** : 796-800.

73. Eroglu D, Yanik F, Oktem M, Zeyneloglu HB, Kuscu E. Prediction of preterm delivery among women with threatened preterm labor. *Gynecol Obstet Invest* 2007; **64** : 109-16.

74. Gomez R, Romero R, Medina L, Nien JK, Chaiworapongsa T, Carstens M, Gonzalez R, Espinoza J, Iams JD, Edwin S, Rojas I. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. *Am J Obstet Gynecol* 2005; **192** : 350-9.

75. Diaz J, Chedraui P, Hidalgo L, Medina M. The clinical utility of fetal fibronectin in the prediction of pre-term birth in a low socio-economic setting hospital in Ecuador. *J Matern Fetal Neonatal Med* 2009; **22** : 89-93.

76. Senden IP, Owen P. Comparison of cervical assessment, fetal fibronectin and fetal breathing in the diagnosis of preterm labour. *Clin Exp Obstet Gynecol* 1996; **23** : 5-9.

77. Cheung KW, Ngu SF, Lee CP. Fetal fibronectin test on Chinese women with symptoms of preterm labour: a pilot study. *Hong Kong Med J* 2013 Oct; **19(5)** : 424-8.

78. Magro-Malosso E, Seravalli V, Cozzolino M, Spitaleri M, Susini T, Di Tommaso M. Prediction of preterm delivery by fetal fibronectin in symptomatic and asymptomatic women with cervical length ≤20 mm. *J Matern Fetal Neonatal Med* 2017 Feb; **30(3)** : 294-7.

79. Danti L, Prefumo F, Lojacono A, Corini S, Testori A, Frusca T. The combination of short cervical length and phIGFBP-1 in the prediction of preterm delivery in symptomatic women. *J Matern Fetal Neonatal Med* 2011; **24** : 1262-6.

80. Fuchs F, Houllier M, Leparco S, Guyot A, Senat MV, Fernandez H. Performance of

cervical phIGFBP-1 test alone or combined with short cervical length to predict spontaneous preterm birth in symptomatic women. *Sci Rep* 2017 Sep 7; **7(1)** : 10856.

81. Brik M, Hernández AI, Pedraz CC, Perales A. Phosphorylated insulin-like growth factor binding protein-1 and cervical measurement in women with threatening preterm birth. *Acta Obstet Gynecol Scand* 2010; **89** : 268-74.

82. Azlin MI, Bang HK, An LJ, Mohamad SN, Manson NA, Yee BS, Zulkifli NH, Tamil AM. Role of phIGFBP-1 and ultrasound cervical length in predicting pre-term labor. *J Obstet Gynaecol* 2010; **30** : 456-9.

83. Altinkaya O, Gungor T, Ozat M, Danisman N, Mollamahmutoglu L. Cervical phosphorylated insulin-like growth factor binding protein-1 in prediction of preterm delivery. *Arch Gynecol Obstet* 2009 Mar; **279(3)** : 279-83.

84. Ting HS, Chin PS, Yeo GS, Kwek K. Comparison of bedside test kits for prediction of preterm delivery: phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1) test and fetal fibronectin test. *Ann Acad Med Singapore* 2007; **36** : 399-402.

85. Sanchez Martinez M, Palacio M, Cobo T, Figueras F, Coll O, Cararach V, Gratacos E. Comparison of ecographic cervical length at two different cut-off points and two biochemical markers as predictors of spontaneous preterm delivery in women admitted because of preterm labor. *Ultrasound Obstet Gynecol* 2006; **28** : 583-4.

86. Tanir HM, Sener T, Yildiz Z. Cervical phosphorylated insulin-like growth factor binding protein-1 for the prediction of preterm delivery in symptomatic cases with intact membranes. *J Obstet Gynaecol Res* 2009; **35** : 66-72.

87. Park OR, Kim JK, Chang BS, Kim HJ, Kim TS, Park IS. Usefulness of phosphorylated insulin-like growth factor binding protein-1 for prediction of preterm delivery [in Korean]. *Korean J Obstet Gynecol* 2003; **46** : 1378-84.

88. Sunagawa S, Takagi K, Ono K, Miyachi K, Kikuchi A. Comparison of biochemical markers and cervical length for predicting preterm delivery. *J Obstet Gynaecol Res* 2008; **34** : 812-9.

89. Kwek K, Khi C, Ting HS, Yeo GS. Evaluation of a bedside test for phosphorylated insulin-like growth factor binding protein-1 in preterm labor. *Ann Acad Med Singapore* 2004; **33** : 780-3.

90. Winograd R, Votta R, Camin P. Phosphorylated IGFBP-1 as marker for preterm delivery in women with symptoms of preterm labor [in Spanish]. Presented at the XXI Jornadas de Obstetricia y Ginecología SOGIBA, 2003, Buenos Aires, Argentina.

91. Lembet A, Eroglu D, Ergin T, Kuscu E, Zeyneloglu H, Batiglu S, Haberal A. New rapid bed-side test to predict preterm delivery: phosphorylated insulin-like growth factor binding protein-1 in cervical secretions. *Acta Obstet Gynecol Scand* 2002; **81** : 706-12.

92. Abo El-Ezz AE, Askar AE. Predictive value of phosphorylated insulin-like growth factor binding protein-1 (PIGFBP-1) (bedside test) in preterm labor. *J Egypt Soc Parasitol* 2014; **44** : 525-30.

93. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994; **271** : 703-7.

94. Boots AB, Sanchez-Ramos L, Bowers DM, Kaunitz AM, Zamora J, Schlattmann P. The short-term prediction of preterm birth: a systematic review and diagnostic metaanalysis. *Am J Obstet Gynecol* 2014; **210** : 54.e1-10.

95. Di Renzo GC, Cabero Roura L, Facchinetti F, Helmer H, Hubinont C, Jacobsson B, Jorgensen JS, Lamont RF, Mikhailov A, Papantoniou N, Radinsky V, Shennan A, Ville

Y, Wielgos M, Visser GHA. Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine. *J Matern Fetal Neonatal Med* 2017 Sep; **30(17)** : 2011-30.

96. Conde-Agudelo A, Romero R. Cervical phosphorylated insulin-like growth factor binding protein-1 test for the prediction of preterm birth: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2016; **214(1)** : 57-73.

97. Deshpande SN, van Asselt ADI, Tomini F, Armstrong N, Allen A, Noake C, Khan K, Severens JL, Kleijnen J, Westwood ME. Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis. *Health Technol Assess* 2013; **17(40)** : 1-138.

Table 1. Characteristics of studies included in the systematic review

Study	Year	Country(ies)	N	Study Design	Inclusion Criteria	Testing Gestation Week	Biomarker Studied	Reference Standard
Low Risk Group								
Bartnicki et al.[49]	1996	USA	116	Prospective	Symptoms of threatened preterm labor Minimal cervical dilatation (≤2 cm) Intact amniotic membranes	22 - 35 weeks	fFN	PTB ≤7 Days
Cooper et al.[19]	2012	Canada	349	Prospective	Symptoms of threatened preterm labor Singleton or multiple gestation Clinically intact membranes	24 - 32 weeks	phIGFBP-1	PTB ≤7 Days, ≤14 Days, PTB <37 weeks
Desjardins et al.[53]	2008	Canada	361	Retrospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation <3 cm	22 - 34 weeks	fFN	PTB ≤7 Days, ≤14 Days, <35 weeks
Gao et al.[22]	2014	China	124	Prospective	Symptoms of threatened preterm labor Cervical dilatation ≤2 cm Intact membranes No other serious pregnancy complications and concurrent disorders such as hypertensive disorders, placenta previa, heart disease, chronic nephritis, viral hepatitis Singleton pregnancy	20 - 34 weeks	fFN	PTB ≤7 days, ≤14 days, < 34 weeks, and < 37 weeks
LaShay et al.[55]	2000	USA	118	Prospective cohort	Symptoms of threatened preterm labor Intact amniotic membranes Cervical dilation <3 cm No prior history of coitus within the previous 24 hr, or a prior vaginal examination with lubricant, were also excluded	22 - 34 weeks	fFN	PTB < 48 hrs, ≤7 Days, <37 weeks
Melchor et al.[40]	2017	Spain	378	Retrospective cohort	Symptoms of threatened preterm labor Clinically intact amniotic membranes as determined by speculum examination Minimal cervical dilatation (<3 cm) Singleton gestation Valid biochemical test Recorded digital examination result	24 - 35 weeks	PAMG-1, fFN	sPTB ≤7 Days, ≤14 Days
Peaceman et al.[52]	1997	USA	725	Prospective	Symptoms of threatened preterm labor Intact membranes No prior tocolysis Cervical dilation <3 cm Singleton gestation	24 - 35 weeks	fFN	PTB ≤ 7 days, ≤14 days, < 37 weeks
Ravi et al.[43]	2017	United Arab Emirates	72	Prospective observational	Symptoms of threatened preterm labor Clinically intact amniotic membranes as determined by speculum examination Singleton gestation Minimal cervical dilatation (≤3 cm)	23 - 35 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Riboni et al.[54]	2011	Italy	210	Prospective	Symptoms of threatened preterm labor Clinically intact membranes	24 - 34 weeks	fFN, phIGFBP-1	PTB < 37 weeks, PTB <34 and <37 weeks

					Singleton gestation			
Wing et al.[15]	2017	USA	635	Prospective observational	Symptoms of threatened preterm labor Clinically intact amniotic membranes as determined by speculum examination Minimal cervical dilatation (<3 cm)	24 - 35 weeks	PAMG-1, fFN	sPTB ≤7 Days, ≤14 Days
Intermediate Risk Group								
Altinkaya et al.[83]	2009	Turkey	105	Prospective	Patients with and without symptoms of preterm labor (only patients with symptoms of preterm labor were included) Clinically intact membranes Singleton gestation	22 - 34 weeks	phIGFBP-1	PTB ≤7 Days, preterm birth <37 weeks
Azlin et al.[82]	2010	Malaysia	51	Prospective	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation Cervical dilations <3 cm	24 - 36 weeks	phIGFBP-1	PTB ≤7 days
Benattar et al.[62]	1997	France	124	Prospective Cohort	Symptoms of threatened preterm labor >5 contractions per hour associated cervical changes since the last examination	24 - 36 weeks	fFN	PTB ≤7 Days, <14 Days
Bolotskikh et al.[21]	2017	Russia	99	Prospective Observational	Symptoms of threatened preterm labor Contractions via CTG No clinical rupture of membranes (intact amniotic membranes upon vaginal exam) Singleton gestation Cephalic presentation	22 - 37 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Brik et al.[81]	2010	Spain	276	Consecutive	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation	24 - 34 weeks	phIGFBP-1	sPTB ≤48 hours, ≤7 Days, sPTB <32 and <34 Weeks
Closset et al.[68]	2001	France	61	Prospective Cohort	Symptoms of threatened preterm labor Singleton gestation Patients with symptoms of threatened preterm labor	24 - 36 weeks	fFN	PTB ≤7 Days
Danti et al.[79]	2011	Italy	60	Consecutive	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestations	24 - 32 weeks	phIGFBP-1	PTB ≤7 Days, PTB <34 and <37 weeks
Diaz et al.[75]	2009	Ecuador	180	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes First time singleton gestation Cervical dilation <3 cm	24 - 36 weeks	fFN	PTB ≤7 Days, ≤14 Days, ≤21 Days, <35 and <37 Weeks
Eroglu et al.[73]	2007	Turkey	51	Prospective	Patients with and without symptoms of preterm labor (only patients with symptoms of preterm labor were included) ≥10 contractions per hr Clinically intact membranes Singleton gestation	24 - 35 weeks	phIGFBP-1 fFN	PTB ≤7 Days, PTB <35
Fatkullin et al.[45]	2016	Russia	45	Prospective	Symptoms of threatened preterm labor	24 - 35 weeks	PAMG-1	sPTB ≤7 Days, ≤14

				Observational	Clinically intact membranes Minimal cervical dilation Cervical length ≤25 mm			Days
Foxman et al.[58]	2004	USA	139	Prospective	Symptoms of threatened preterm labor Singleton	22 - 34 weeks	fFN	PTB ≤7 Days
Fuchs et al.[80]	2017	France	180	Prospective Cohort	Symptoms of threatened preterm labor Singleton pregnancies Clinically intact membranes Cervical length < 25 mm	24 - 34 weeks	phIGFBP-1	sPTB ≤7 Days, ≤14 Days, <34 and <37 weeks
Giles et al.[71]	2000	Australia	150	Random Cohort	Symptoms of threatened preterm labor Contractions ≥2 in 10 minutes Clinically intact membranes Excludes vaginal bleeding, a history of sexual intercourse or vaginal examination in the preceding 24 hours	24 - 34 weeks	fFN	PTB ≤7 Days
Gomez et al.[74]	2005	Chile	215	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilatation ≤3 cm Singleton gestation Uterine contractility of 3 in 30 minutes	22 - 35 weeks	fFN	sPTB ≤48 hours, ≤7, ≤14 Days, Delivery ≤32 and ≤35 Weeks
Groom et al.[59]	2006	New Zealand	179	Retrospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation ≤3 cm	22 - 34 weeks	fFN	sPTB ≤7 Days, <34 Weeks and <37 Weeks
Hadzi-Lega et al.[48]	2017	Macedonia	57	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation Cervical dilation ≤3 cm	20 - 35 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Henrich et al.[60]	2010	Germany	81	Prospective Cohort	Symptoms of threatened preterm labor Regular uterine contractions Singleton gestation	22 - 33 weeks	fFN	PTB ≤7 Days, ≤14 Days, <35 Weeks, <38 Weeks
Heverhagen et al.[17]	2015	Switzerland	64	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation	24 - 37 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Iams et al.[14]	1995	USA & Canada	192	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation < 3cm	24 - 34 weeks	fFN	sPTB ≤7 Days, <14 Days, <21 Days
Konoplyannikov et al.[47]	2016	Russia	71	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation Cervical dilation <3 cm	20 - 37 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Liong et al.[66]	2015	Australia	64	Retrospective Cohort	Symptoms of threatened preterm labor Intact membranes Singleton gestation	22 - 36 weeks	fFN	sPTB ≤7 Days
Lopez et al.[70]	2000	USA	85	Retrospective	Symptoms of threatened preterm labor	24 - 35 weeks	fFN	sPTB ≤7 Days

				Cohort	Clinically intact membranes Cervical dilation ≤3 cm Singleton gestation			
Lotfi et al.[44]	2015	United Arab Emirates	151	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilatation ≤3 cm Singleton gestation	20 - 37 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Lou et al.[46]	2016	United Kingdom	65	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation Cervical dilatation <4 cm	24 - 35 weeks	PAMG-1	sPTB ≤7 Days, ≤14 Days
Lowe et al.[63]	2004	USA	41	Prospective	Symptoms of threatened preterm labor Uterine contractions and/or cervical change Women who were transferred already receiving tocolytic medications Maternal age >16 years Cervical dilation ≤3 cm for primigravid women and ≤4 cm for multiparous women	23 - 34 weeks	fFN	PTB ≤7 Days
Luzzi et al.[58]	2003	USA	133	Prospective	Symptoms of threatened preterm labor Intact membranes Cervical dilation <3 cm	24 - 35 weeks	fFN	sPTB ≤7 Days
MacDonald et al.[50]	2007	Canada	38	Retrospective Cohort	Patients with symptoms of preterm labor, including abdominal pain, back pain, abdominal cramps, lower abdominal pelvic pressure	24 - 35 weeks	fFN	PTB ≤7 Days
Malak et al.[65]	1996	United Kingdom	112	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation < 2 cm Singleton gestation	24 - 37 weeks	fFN	PTB ≤7 Days
McKenna et al.[72]	1999	USA	54	Prospective Cohort	Symptoms of threatened preterm labor	22 - 34 weeks	fFN	PTB <7 Days, <15 Days
Nikolova et al.[33]	2016	Finland; Macedonia; Russia	328	Prospective observational	Symptoms of threatened preterm labor Intact members Cervical dilation ≤3 cm Singleton gestation ≥ 18 years old	20 - 37 weeks	PAMG-1, phIGFBP-1	sPTB ≤7 Days, ≤14 Days
Sakai et al.[51]	2003	Japan	116	Retrospective	Symptoms of threatened preterm labor Clinically intact membranes Regular uterine contractions of >6 per hour by CTG Effacement >50% Cervical dilation >2 cm Singleton gestation	<37 weeks	fFN	PTB ≤7 Days,
Skoll et al.[69]	2006	Canada	149	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes No moderate or severe bleeding No indication for preterm delivery	24 - 34 weeks	fFN	PTB ≤7 Days, <34 weeks

Sümer et al.[64]	2010	Turkey	67	Prospective Cohort	Symptoms of threatened preterm labor Intact membranes Singleton gestation	26 - 36 weeks	fFN	PTB ≤7 Days
Swamy et al.[59]	2005	USA	404	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Last digital examination and sexual intercourse >24 hours Cervix <2cm dilated and >1cm long	22 - 34 weeks	fFN	PTB ≤7 Days
Tekesin et al.[61]	2005	Germany	170	Prospective Cohort	Symptoms of threatened preterm labor Intact membranes ≥4 contractions in 20 mins on CTG or >8 contractions per hour Cervical effacement >50% Dilatation >2 cm Singleton gestation	24 - 34 weeks	fFN	sPTB ≤7 Days, <14 Days, <21 Days
Tsoi et al.[67]	2006	South Africa	195	Prospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation <3 cm Singleton gestation	24 - 36 weeks	fFN	PTB ≤7 Days
Van Baaren et al.[29]	2014	Netherlands	665	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation <3 cm	24 - 34 weeks	fFN	sPTB ≤7 Days
Van Holsbeke et al.[41]	2016	Belgium	49	Prospective observational	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation <3 cm Cervical length <30 mm	22 - 34 weeks	PAMG-1, fFN	sPTB ≤7 Days, ≤14 Days
High Risk Group								
Abo Ek-Ezz et al.[89]	2014	Kuwait	57	Prospective	Symptoms of preterm labor Clinically intact membranes Singleton gestation	24 - 34 weeks	phIGFBP-1	PTB ≤7 days
Bruijn et al.[28]	2016	Netherlands	350	Prospective	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation Cervical length <30 mm	24 – 34 weeks	fFN, phIGFBP-1	sPTB ≤7 Days
Çekmez et al.[20]	2017	Turkey	72	Prospective Observational	Symptoms of threatened preterm labor ≥4 contractions in 60 mins on CTG Cervical dilation of >1 cm to <3 cm Effacement of >50% Cervical length of <30 mm Singleton pregnancy	24 - 34 weeks	PAMG-1, fFN	PTB ≤7 Days
Cheung et al.[77]	2013	China	22	Prospective Cohort	Symptoms of preterm labor ≥ 18 years old	24 - 34 weeks	fFN	PTB ≤24 Hours, ≤48 Hours, ≤7 Days, ≤14

					> 6 contractions per hour on CTG Cervical dilatation of ≤3 cm			Days, <34 weeks and <37 weeks
Kwek et al.[89]	2004	Singapore	42	Prospective	Symptoms of preterm labor ≥1 uterine contractions in 10 min Clinically intact membranes	23 – 33 weeks	phIGFBP-1	PTB ≤48 hours, ≤7 Days, PTB <34 and <36 weeks
Lembet et al.[91]	2002	Turkey	36	Prospective	Symptoms of preterm labor Clinically intact membranes Singleton gestation	20 - 36 weeks	phIGFBP-1	PTB ≤48 hours, ≤7 Days, PTB <37 weeks
Magro-Malosso et al.[78]	2016	Italy	43	Retrospective Cohort	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation Cervical length ≤20 mm	22 – 34 weeks	fFN	sPTB ≤48 Hours, ≤7 Days, ≤14 Days, ≤21 Days
Nikolova et al.[42]	2015	Macedonia; Russia	203	Prospective observational	Symptoms of threatened preterm labor Clinically intact amniotic membranes Minimal cervical dilatation (≤3 cm) Singleton gestation	20 - 37 weeks	PAMG-1, fFN	sPTB ≤7 Days, ≤14 Days
Park et al.[87]	2003	Korea	50	Not Reported	Patients with symptoms of preterm labor requiring admission Singleton gestation No parturition 24 – 48 hours after admission	24 - 34 weeks	phIGFBP-1	PTB ≤7 Days, PTB <34 and <37 weeks
Sanchez Martinez et al.[85]	2006	Spain	149	Prospective	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation <3 cm	24 - 35 weeks	phIGFBP-1	sPTB ≤7 Days, sPTB <36 weeks
Senden et al.[76]	1996	United Kingdom	29	Prospective	Symptoms of threatened preterm labor Singleton gestation Cervical dilations <4 cm	25 - 35 weeks	fFN	PTB ≤7 Days
Singh et al.[16]	2013	India	50	Prospective	Symptoms of preterm labor Clinically intact membranes Cervical dilation of 1 to <3 cm	28 - 36 weeks	phIGFBP-1	PTB ≤48 hours, ≤7 Days, PTB <34 and <36 weeks
Sunagawa et al.[88]	2008	Japan	76	Retrospective	Symptoms of preterm labor Clinically intact membranes Singleton gestation	22 - 34 weeks	phIGFBP-1	PTB ≤72 hours, PTB ≤7 days
Tanir et al.[86]	2009	Turkey	68	Prospective	Symptoms of threatened preterm labor Clinically intact membranes Cervical dilation <3 cm Singleton gestation	24 – 36 weeks	phIGFBP-1	PTB ≤72 hours, PTB ≤7 days
Ting et al.[84]	2007	Singapore	94	Prospective	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation	24 - 34 weeks	phIGFBP-1	PTB ≤48 hours, ≤7 Days, ≤14 Days
Tripathi et al.[18]	2016	India	468	Prospective Observational	Symptoms of threatened preterm labor Clinically intact membranes Singleton gestation	28 - 36 weeks	fFN, phIGFBP-1	PTB ≤7 Days, <34 Weeks, <37 Weeks
Winograd et al.[90]	2003	Argentina	85	Not Reported	Symptoms of preterm labor Clinically intact membranes	24 - 35 weeks	phIGFBP-1	sPTB ≤7 days

					Singleton gestation			

sPTB, spontaneous preterm birth; CTG, cardiotocography

Table 2. The summary estimates for the Sensitivity and Specificity for preterm birth within 7 days of the three biomarker tests[†]

Biomarker test	N	Sensitivity (95% CI)	Specificity (95% CI)
		Low Risk Group	
PAMG-1	1074	0.53 (0.29-0.76)	0.98 (0.96-0.99)
fFN	2667	0.65 (0.50-0.77)	0.85 (0.80-0.88)
phIGFBP-1	559	0.48 (0.23-0.74)	0.83 (0.75-0.88)
		Intermediate Risk Group	
PAMG-1	929	0.77 (0.64-0.86)	0.97 (0.94-0.98)
fFN	3714	0.77 (0.71-0.82)	0.81 (0.77-0.84)
phIGFBP-1	1108	0.68 (0.55-0.78)	0.80 (0.73-0.86)
		High Risk Group	
PAMG-1	275	0.78 (0.17-0.98)	0.94 (0.81-0.98)
fFN	1050	0.25 (0.10-0.50)	0.91 (0.84-0.95)
phIGFBP-1	1525	0.92 (0.81-0.97)	0.72 (0.60-0.81)
		All	
PAMG-1	2278	0.76 (0.57-0.89)	0.97 (0.95-0.98)
fFN	7431	0.58 (0.47-0.68)	0.84 (0.81-0.87)
phIGFBP-1	3192	0.93 (0.88-0.96)	0.76 (0.70-0.80)

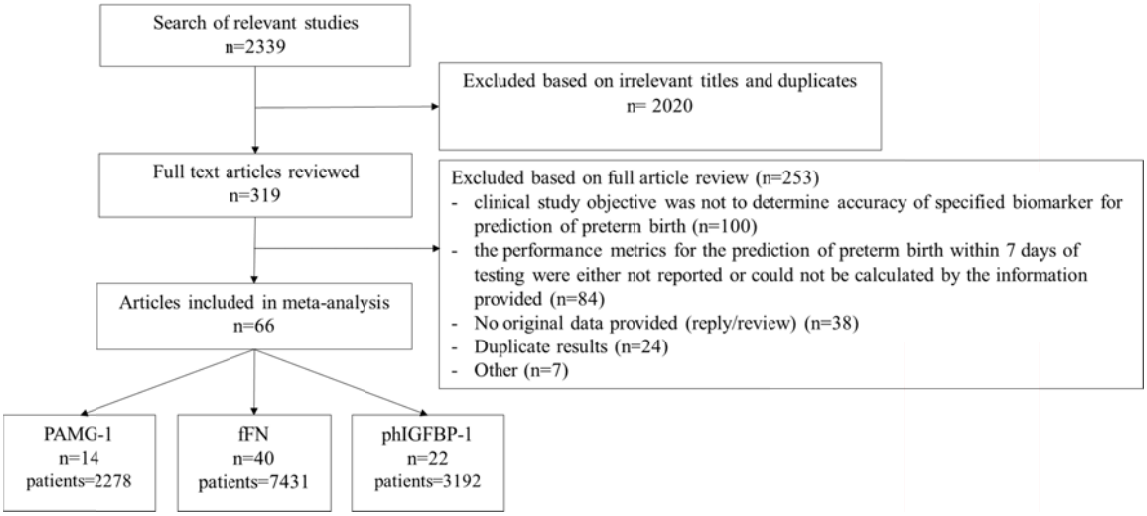
[†]*Pooled estimates were obtained for each risk classification group using a bivariate linear mixed model for the logit of sensitivity and specificity, with each diagnostic test as a covariate. CI, confidence interval; fFN, fetal fibronectin; phIGFBP-1, phosphorylated insulin-like growth factor-binding protein-1; PAMG-1, placental alpha-microglobulin-1*

Table 3. The summary estimates for the prediction of preterm birth within 7 days of the three biomarker tests†

Biomarker test	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)
Low Risk Group (weighted average pretest probability 0.023 or CL >30 mm)				
PAMG-1	0.34* (0.14-0.55)	0.99 (0.98-0.99)	22.27* (8.87-55.91)	0.48 (0.28-0.82)
fFN	0.09 (0.06-0.12)	0.99 (0.99-0.99)	4.23 (2.84-6.29)	0.42 (0.28-0.63)
phIGFBP-1	0.06 (0.01-0.11)	0.99 (0.98-0.99)	2.76 (1.23-6.18)	0.63 (0.35-1.12)
Intermediate Risk Group (weighted average pretest probability 0.091 or CL 15-30 mm)				
PAMG-1	0.69* (0.59-0.80)	0.98 (0.97-0.99)	22.63* (13.99-36.61)	0.24 (0.15-0.38)
fFN	0.29 (0.25-0.32)	0.97 (0.97-0.98)	4.04 (3.42-4.77)	0.28 (0.22-0.36)
phIGFBP-1	0.25 (0.20-0.31)	0.96 (0.95-0.97)	3.39 (2.54-4.54)	0.40 (0.29-0.56)
High Risk Group (weighted average pretest probability 0.261 or CL <15 mm)				
PAMG-1	0.83* (0.67-0.98)	0.92 (0.77-1.00)	13.72* (4.59-41.00)	0.23 (0.03-2.12)
fFN	0.50 (0.29-0.72)	0.78 (0.73-0.82)	2.87 (1.22-6.76)	0.82 (0.63-1.06)
phIGFBP-1	0.54 (0.45-0.62)	0.96 (0.93-1.00)	3.28 (2.33-4.64)	0.11 (0.04-0.27)
All				
PAMG-1	0.76* (0.69-0.84)	0.97 (0.94-0.99)	22.51* (15.09-33.60)	0.24 (0.12-0.48)
fFN	0.34 (0.29-0.39)	0.93 (0.92-0.95)	3.63 (2.93-4.50)	0.50 (0.39-0.64)
phIGFBP-1	0.35 (0.31-0.40)	0.99 (0.98-0.99)	3.80 (3.11-4.66)	0.09 (0.05-0.16)

†*Pooled estimates were obtained for each risk classification group using a bivariate linear mixed model for the logit of sensitivity and specificity, with each diagnostic test as a covariate. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CL, cervical length, PAMG-1, placental alpha-microglobulin-1; fFN, fetal fibronectin; phIGFBP-1, phosphorylated insulin-like growth factor-binding protein-1; *statistical superiority based on a two-sided pairwise comparison with p<0.05*

Figure 1. Flowchart of studies included in the meta-analysis



PAMG-1, placental alpha-microglobulin-1; fFN, fetal fibronectin; phIGFBP-1, phosphorylated insulin-like growth factor-binding protein-1

Figure 2. Methodological quality of studies included in the meta-analysis

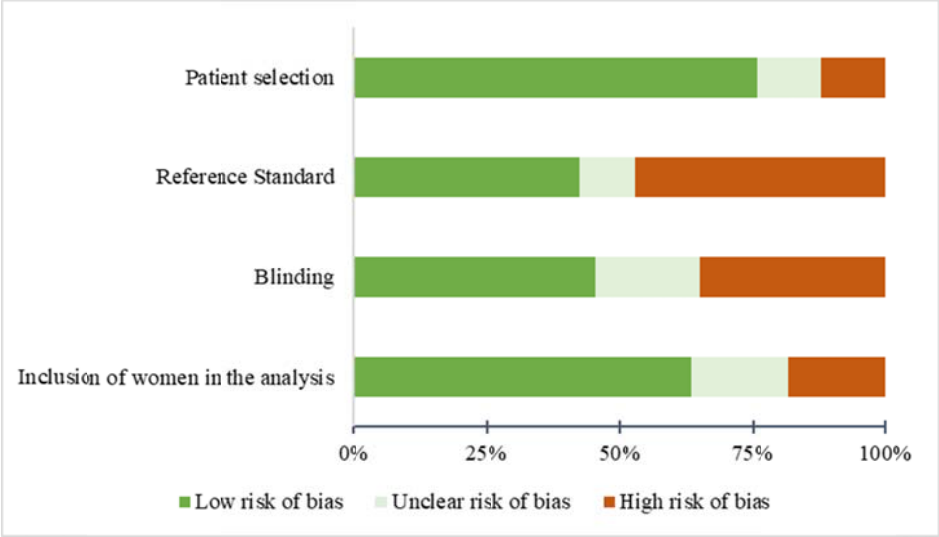
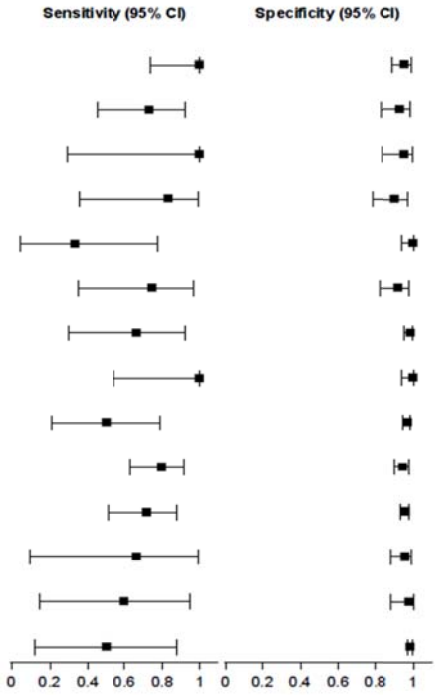


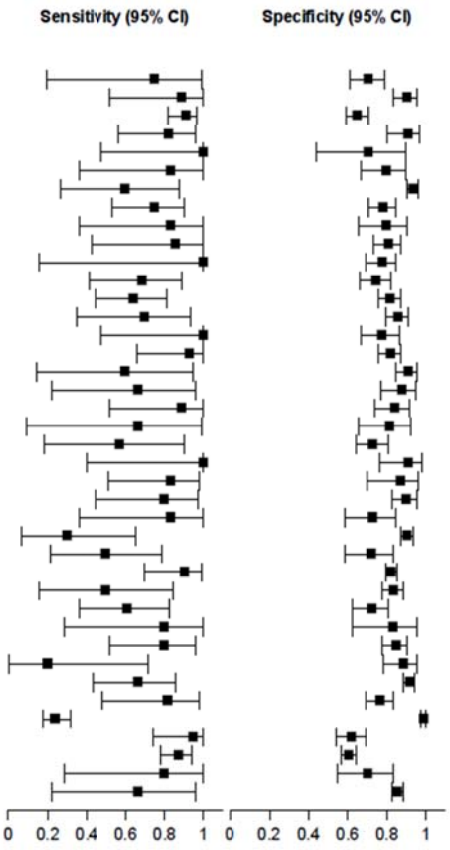
Figure 3. Forest plots of studies included in the meta-analysis

PAMG-1 for the prediction of preterm birth within 7 days in symptomatic women



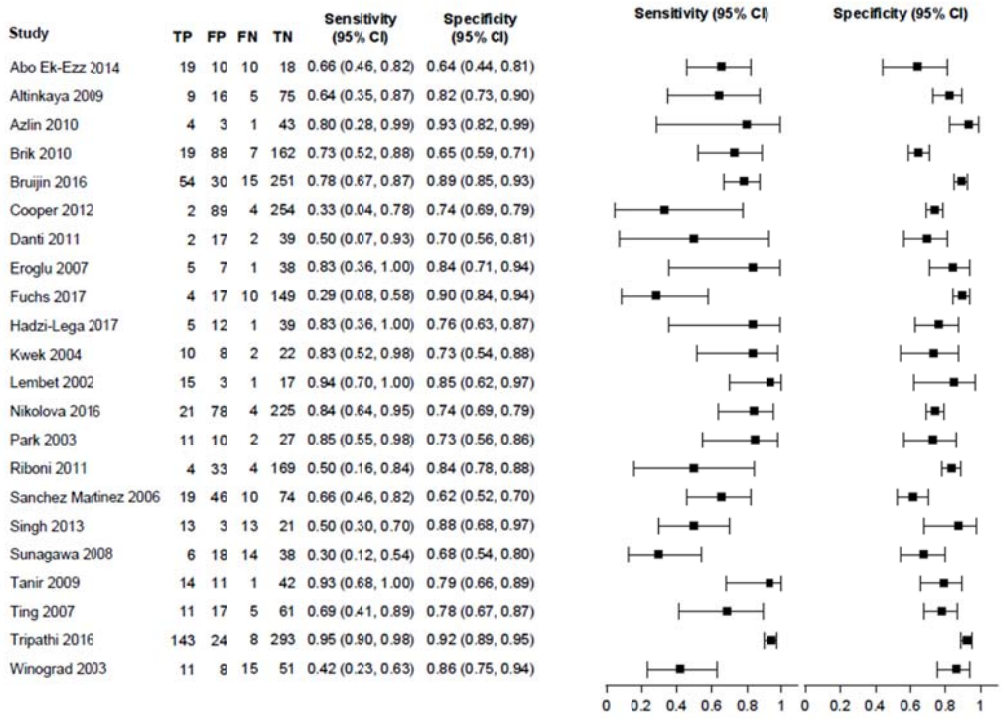
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bolotskikh 2017	12	4	0	83	1.00 (0.74, 1.00)	0.95 (0.89, 0.99)
Çekmez 2017	11	4	4	53	0.73 (0.45, 0.92)	0.93 (0.83, 0.98)
Fatkullin 2016	3	2	0	40	1.00 (0.29, 1.00)	0.95 (0.84, 0.99)
Hadzi-Lega 2017	5	5	1	46	0.83 (0.36, 1.00)	0.90 (0.79, 0.97)
Heverhagen 2015	2	0	4	58	0.33 (0.04, 0.78)	1.00 (0.94, 1.00)
Konoplyannikov 2016	6	5	2	58	0.75 (0.35, 0.97)	0.92 (0.82, 0.97)
Lotfi 2015	6	2	3	140	0.67 (0.30, 0.93)	0.99 (0.95, 1.00)
Lou 2016	6	0	0	59	1.00 (0.54, 1.00)	1.00 (0.94, 1.00)
Melchor 2017	6	11	6	344	0.50 (0.21, 0.79)	0.97 (0.95, 0.98)
Nikolova 2015	28	9	7	159	0.80 (0.63, 0.92)	0.95 (0.90, 0.98)
Nikolova 2016	18	12	7	291	0.72 (0.51, 0.88)	0.96 (0.93, 0.98)
Ravi 2017	2	3	1	66	0.67 (0.09, 0.99)	0.96 (0.88, 0.99)
Van Holsbeke 2016	3	1	2	43	0.60 (0.15, 0.95)	0.98 (0.88, 1.00)
Wing 2017	3	10	3	619	0.50 (0.12, 0.88)	0.98 (0.97, 0.99)

fFN for the prediction of preterm birth within 7 days in symptomatic women



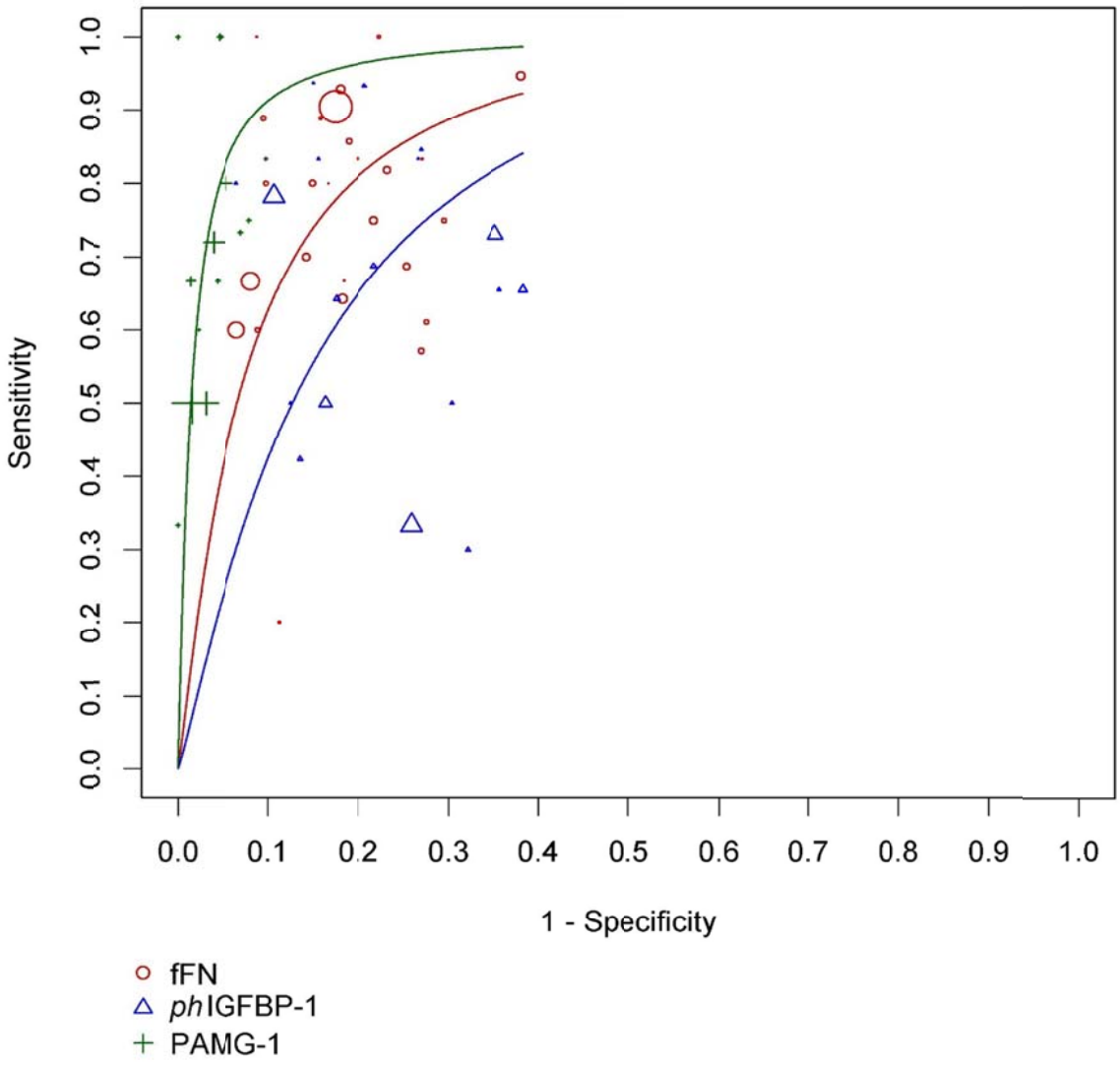
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bartnicki 1996	3	33	1	79	0.75 (0.19, 0.99)	0.71 (0.61, 0.79)
Benattar 1997	8	11	1	104	0.89 (0.52, 1.00)	0.90 (0.84, 0.95)
Bruijn 2016	63	99	6	182	0.91 (0.82, 0.97)	0.65 (0.59, 0.70)
Çekmez 2017	14	5	3	50	0.82 (0.57, 0.96)	0.91 (0.80, 0.97)
Cheung 2013	5	5	0	12	1.00 (0.48, 1.00)	0.71 (0.44, 0.90)
Closset 2001	5	11	1	44	0.83 (0.36, 1.00)	0.80 (0.67, 0.90)
Desjardins 2008	6	23	4	328	0.60 (0.26, 0.88)	0.93 (0.90, 0.96)
Diaz 2009	18	34	6	122	0.75 (0.53, 0.90)	0.78 (0.71, 0.84)
Eroglu 2007	5	9	1	36	0.83 (0.36, 1.00)	0.80 (0.65, 0.90)
Foxman 2004	6	25	1	107	0.86 (0.42, 1.00)	0.81 (0.73, 0.87)
Gao 2014	2	27	0	95	1.00 (0.16, 1.00)	0.78 (0.69, 0.85)
Giles 2000	11	34	5	100	0.69 (0.41, 0.89)	0.75 (0.66, 0.82)
Gomez 2005	18	34	10	153	0.64 (0.44, 0.81)	0.82 (0.76, 0.87)
Groom 2006	7	24	3	145	0.70 (0.35, 0.93)	0.86 (0.80, 0.91)
Henrich 2010	5	17	0	59	1.00 (0.48, 1.00)	0.78 (0.67, 0.86)
Iams 1995	13	32	1	146	0.93 (0.66, 1.00)	0.82 (0.76, 0.87)
LaShay 2000	3	10	2	103	0.60 (0.15, 0.95)	0.91 (0.84, 0.96)
Liong 2015	4	7	2	51	0.67 (0.22, 0.96)	0.88 (0.77, 0.95)
Lopez 2000	8	12	1	64	0.89 (0.52, 1.00)	0.84 (0.74, 0.92)
Lowe 2004	2	7	1	31	0.67 (0.09, 0.99)	0.82 (0.66, 0.92)
Luzzi 2003	4	34	3	92	0.57 (0.18, 0.90)	0.73 (0.64, 0.81)
MacDonald 2007	4	3	0	31	1.00 (0.40, 1.00)	0.91 (0.76, 0.98)
Magro-Malosso 2016	10	4	2	27	0.83 (0.52, 0.98)	0.87 (0.70, 0.96)
Malak 1996	8	10	2	92	0.80 (0.44, 0.97)	0.90 (0.83, 0.95)
McKenna 1999	5	13	1	35	0.83 (0.36, 1.00)	0.73 (0.58, 0.85)
Melchor 2017	3	35	7	333	0.30 (0.07, 0.65)	0.90 (0.87, 0.93)
Nikolova 2015	6	15	6	39	0.50 (0.21, 0.79)	0.72 (0.58, 0.84)
Peaceman 1997	19	123	2	581	0.90 (0.70, 0.99)	0.83 (0.80, 0.85)
Riboni 2011	4	33	4	169	0.50 (0.16, 0.84)	0.84 (0.78, 0.88)
Sakai 2003	11	27	7	71	0.61 (0.36, 0.83)	0.72 (0.63, 0.81)
Senden 1996	4	4	1	20	0.80 (0.28, 0.99)	0.83 (0.63, 0.95)
Skoll 2006	12	20	3	114	0.80 (0.52, 0.96)	0.85 (0.78, 0.91)
Sümer 2010	1	7	4	55	0.20 (0.01, 0.72)	0.89 (0.78, 0.95)
Swamy 2005	14	31	7	352	0.67 (0.43, 0.85)	0.92 (0.89, 0.94)
Tekesin 2006	9	37	2	122	0.82 (0.48, 0.98)	0.77 (0.69, 0.83)
Tripathi 2016	36	3	115	314	0.24 (0.17, 0.31)	0.99 (0.97, 1.00)
Tsoi 2006	18	67	1	109	0.95 (0.74, 1.00)	0.62 (0.54, 0.69)
Van Baaren 2014	70	231	10	354	0.88 (0.78, 0.94)	0.61 (0.56, 0.64)
Van Holsbeke 2016	4	13	1	31	0.80 (0.28, 0.99)	0.70 (0.55, 0.83)
Wing 2017	4	90	2	539	0.67 (0.22, 0.96)	0.86 (0.83, 0.88)

phIGFBP-1 for the prediction of preterm birth within 7 days in symptomatic women



PAMG-1, placental alpha-microglobulin-1; fFN, fetal fibronectin; phIGFBP-1, phosphorylated insulin-like growth factor-binding protein-1; TP, True Positive; FP, False Positive; FN, False Negative; TN, True Negative; CI, confidence interval

Figure 4. Summary ROC Curve for the prediction of preterm birth within 7 days using the three biomarker tests[†]



AUC for all studies. PAMG-1 AUC: 0.961; fFN AUC: 0.874; phIGFBP-1 AUC: 0.801

[†]*Pooled estimates were obtained for each risk classification group using a bivariate linear mixed model for the logit of sensitivity and specificity, with each diagnostic test as a covariate. ROC, receiver operator characteristic; AUC, area under the curve; PAMG-1, placental alpha-microglobulin-1; fFN, fetal fibronectin; phIGFBP-1, phosphorylated insulin-like growth factor-binding protein-1*