OBSTETRICS

Cervical phosphorylated insulin-like growth factor binding protein-1 test for the prediction of preterm birth: a systematic review and metaanalysis

Agustin Conde-Agudelo, MD, MPH, PhD; Roberto Romero, MD, DMedSci

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 the use of formal methods for systematic reviews and metaanalytic techniques.

DATA SOURCES: PubMed, Embase, Cinahl, Lilacs, and Medion (all from inception to June 30, 2015), reference lists, conference proceedings, and Google scholar.

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

STUDY APPRAISAL AND SYNTHESIS METHODS: Two reviewers independently selected studies, assessed the risk of bias, and extracted the 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 the cervical phIGFBP-1 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% to 47%, 76% to 93%, 1.5 to 4.4, and 0.6 to 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 the 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.

Key words: biomarker, common pathway of parturition, fetal fibronectin, predictive value, prematurity, preterm labor

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 1 of 10 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 pathological processes[8,9] whose prediction has been a long-standing challenge.[10-14] The

From the Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development/National Institutes of Health/Department of Health and Human Services, Bethesda, MD, and Detroit, MI (Drs Conde-Agudelo and Romero); Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI (Dr Romero); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI (Dr Romero); and Department of Molecular Obstetrics and Genetics, Wayne State University, Detroit, MI (Dr Romero).

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Corresponding author: Roberto Romero, MD, DmedSci. romeror@mail.nih.gov

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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 because of 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 with 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 the 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 metaanalysis 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 30, 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 the 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 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 2 authors to determine the inclusion. Disagreements were resolved through consensus.

Reference standard outcomes

In asymptomatic women, the reference standard outcomes were 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, the reference standard outcomes were 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 nonconsecutive 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 the preterm premature rupture of membranes, regardless of whether the delivery was vaginal, by cesarean delivery, 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