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Prediction of preterm birth in twin gestations using biophysical and biochemical tests

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The objective of this study was to determine the performance of biophysical and biochemical tests for the prediction of preterm birth in both asymptomatic and symptomatic women with twin gestations. We identified a total of 19 tests proposed to predict preterm birth, mainly in asymptomatic women. In these women, a single measurement of cervical length with transvaginal ultrasound before 25 weeks of gestation appears to be a good test to predict preterm birth. Its clinical potential is enhanced by the evidence that vaginal progesterone administration in asymptomatic women with twin gestations and a short cervix reduces neonatal morbidity and mortality associated with spontaneous preterm delivery. Other tests proposed for the early identification of asymptomatic women at increased risk of preterm birth showed minimal to moderate predictive accuracy. None of the tests evaluated in this review meet the criteria to be considered clinically useful to predict preterm birth among patients with an episode of preterm labor. However, a negative cervicovaginal fetal fibronectin test could be useful in identifying women who are not at risk for delivering within the next week, which could avoid unnecessary hospitalization and treatment. This review underscores the need to develop accurate tests for predicting preterm birth in twin gestations. Moreover, the use of interventions in these patients based on test results should be associated with the improvement of perinatal outcomes.

Key words: cervical length, fetal fibronectin, predictive value of tests, pregnancy, premature birth

The number of twin births has increased over the last decades in many developed countries.[1-3] From 1980 through 2012, the twin birth rate in the United States increased steadily from 18.9-33.1 per 1000 total births.[4,5] This has been attributed to older age at childbearing and the use of assisted reproductive technology (eg, in vitro fertilization) and nonassisted reproductive technology treatments such as ovulation stimulation.[1,2,6] Twin gestation is associated with an increased risk of maternal, perinatal, and infant morbidity and mortality, as well as long-term consequences of perinatal complications such as cerebral palsy and learning disabilities.[7-14] In addition, twin gestations impose financial and psychological burdens on the family and society.[15-17]

Prematurity is the principal issue that drives neonatal morbidity and mortality rates in twin gestations.[18] In the United States, the rates of preterm birth <37 and <32 weeks for twin gestations (57.3% and 11.3%, respectively) were 5.7 and 7.1 times the rates for singleton gestations (10.0% and 1.6%, respectively).[19] The identification of the patient at higher risk for preterm birth in twin gestations would allow the development of effective interventions to prevent adverse perinatal outcomes associated with preterm birth, and better understanding of the mechanisms of disease leading to spontaneous preterm parturition. Moreover, an advantage of risk assessment may be the avoidance of unnecessary and sometimes costly interventions in patients at decreased risk.

The aim of this study was to review the available evidence about the accuracy of biophysical and biochemical tests proposed for the prediction of preterm birth in both asymptomatic and symptomatic women with twin gestations. We used sensitivity, specificity, and likelihood ratios as measures of the accuracy of a test to identify women at risk for preterm birth (Figure). Likelihood ratios indicate the magnitude by which a given result raises or lowers the probability of having a condition (ie, preterm birth) and allow interpretation of the results within a clinical context.[20] A likelihood ratio >10 for a positive test and <0.1 for a negative test are considered to provide convincing (good) predictive evidence. Moderate prediction is generally considered when a test has a likelihood ratio of 5-10 and 0.1-0.2, whereas those <5 and >0.2 offer only minimal (low) prediction.[20] The area under the receiver operating characteristic (ROC) curve was used as a measure of overall predictive performance of a test if data to calculate likelihood ratios were not available. The area under the ROC curve

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FIGURE
Measures of accuracy of predictive test

		Disease +	Disease −
Test	+	a	b
	−	c	d

Sensitivity = a/(a + c)
Specificity = d/(b + d)
Likelihood ratio for positive test result = sensitivity/(1 − specificity) = [a/(a + c)]/[b/(b + d)]
Likelihood ratio for negative test result = (1 − sensitivity)/specificity = [c/(a + c)]/[d/(b + d)]

Guide to interpret likelihood ratios

	Positive likelihood ratio	Negative likelihood ratio
Convincing predictive accuracy	>10	<0.1
Moderate predictive accuracy	5–10	0.1–0.2
Minimal predictive accuracy	<5	>0.2

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ranges from 0.5 (poor discrimination/accuracy) to 1.0 (perfect discrimination/accuracy).[21] PubMed, Embase, Popline, Cinahl, and Lilacs databases (all from inception to May 31, 2014) were searched, along with Google scholar, using a combination of key words and text words related to *twin gestation*, *preterm birth*, and *prediction*, without language restrictions. Congress proceedings of international society meetings of maternal/fetal and reproductive medicine, as well as international meetings on preterm birth and twin or multiple gestations, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. Table 1 lists the tests proposed to predict preterm birth in women with a twin gestation.

Biophysical tests

Transvaginal sonographic cervical length

Single measurement. Transvaginal sonographic assessment of cervical length (CL) is an effective tool for predicting preterm birth, particularly in asymptomatic women with a singleton gestation or those at a higher risk of spontaneous preterm birth.[22-28] In 2010, a systematic review and metaanalysis assessed the value of a single transvaginal sonographic CL measurement for the prediction of spontaneous preterm birth in women with twin gestations.[29] Twenty-one studies involving a total of 3523 women were included,[30-50] of which 16 studies (3213 women) provided data on asymptomatic women[30-45] and 5 (310 women) on patients with threatened preterm labor.[46-50]

Among asymptomatic women, a CL ≤20 mm at 20-24 weeks of gestation had the following performance in predicting preterm birth at <32 and <34 weeks of gestation: pooled sensitivities, specificities, and positive and negative likelihood ratios of 39% and 29%, 96% and 97%, 10.1 and 9.0, and 0.64 and 0.74, respectively, increasing their pretest probabilities from 6.8-42.4%, and from 15.3-61.9%, respectively, whereas a CL >20 mm decreased the risk to 4.5% and 11.8%, respectively. A CL ≤25 mm at 20-24 weeks of gestation had a pooled positive likelihood ratio of 9.6 to predict preterm birth at <28 weeks of gestation. CL had a limited accuracy in predicting preterm birth at <37 weeks of gestation. Among women with an episode of preterm labor, the measurement of CL had a minimal predictive accuracy for preterm birth at <34 and <37 weeks of gestation (pooled sensitivities, specificities, and positive and negative likelihood ratios ranging between 49−79%, 32−74%, 1.2−1.9, and 0.7, respectively). Only one study (n = 87 women) reported on the predictive performance of CL for delivery within 7 days of testing, showing a sensitivity of 100% and a specificity of 31% (positive and negative likelihood ratios of 1.4 and 0.0, respectively) for a CL cutoff of 25 mm.[49]

Three further systematic reviews published after this metaanalysis confirmed its findings in both asymptomatic[51,52] and symptomatic[53] women. In summary, a single measurement of transvaginal sonographic CL at 20-24 weeks of gestation is a good predictor of spontaneous preterm birth at <28, <32, and <34 weeks of gestation in asymptomatic women with twin gestations. In patients with symptoms of preterm labor, the measurement of CL has a low accuracy to predict preterm birth.

Change in CL over time. Seven studies (n = 1004) that assessed the predictive value for preterm birth of the change in CL over time in asymptomatic women with twin gestations were reviewed.[38,41,54-58] Irrespective of the cutoff value used for defining CL shortening over time (≥2.5 mm at 18-28 weeks or ≥2.3 mm at 28-32 weeks[38]; >5, >10, or >15 mm between 15-20 and 25-30 weeks[41]; ≥20% between 18-24 weeks and 2-6 weeks later[54] or between 22-27 weeks[58]; ≥2 mm/wk between 18-21 and 22-25 weeks[55]; >13% between 20-24 weeks and 4-5 weeks later[56]; and ≥25% between 20-23 weeks and 3-5 weeks later[57]), the predictive accuracy of this test for preterm birth at <28 to at <36 weeks of gestation was minimal to moderate, with most studies reporting sensitivities between 15-75%, specificities between 70-90%, and positive and negative likelihood ratios between 1.6-5.5 and 0.3-0.8, respectively. In addition, 5 of the 7 studies reported that the predictive accuracy of the change in CL over time was not significantly superior to that of a single measurement of CL at 18-24 weeks of gestation.[38,55-58] The reasons why the