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

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Abstract

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.

Keywords

cervical length; fetal fibronectin; predictive value of test; 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 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 20mm 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 $\geq$ 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 symptomatic⁵³ 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 ($\geq$ 2.5 mm at 18–28 weeks or $\geq$ 2.3 mm at 28–32 weeks³⁸; $\geq$ 5, $\geq$ 10, or $\geq$ 15 mm between 15–20 and 25–30 weeks⁴¹; 20% between 18–24 weeks and 2–6 weeks later⁵⁴ or between 22–27 weeks⁵⁸; 2mm/wk between 18–21 and 22–25 weeks⁵⁵; $\geq$ 13% between 20–24 weeks and 4–5 weeks later⁵⁶; and 25% between 20–23 weeks and 3–5 weeks later⁵⁷), 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 predictive ability for preterm birth of change in CL over time did not differ significantly to that of a single measurement of CL at 20–24 weeks of gestation are not clear. One possible explanation could be the differences among studies in the timing and interval of CL measurements and the cutoff values used to define a positive test result (percent change in the CL over time vs absolute change). On the other hand, because no study compared CL between 15–19 and 20–24 weeks, it is likely that a short cervix at 20–24 weeks of gestation means that the patient had a longer cervix that became shorter before the first measurement of CL (early shortening).

Transvaginal sonographic cervical funneling

Seven studies (5 in asymptomatic women [n = 680]^{34,35,37,41,59} and 2 in patients with threatened preterm labor [n = 52]^{46,48}) assessed the predictive performance of cervical

funneling for preterm birth in twin gestations. We were able to pool results from 4 studies (n = 549 women) that evaluated cervical funneling at 18–26 weeks of gestation in asymptomatic women regardless of the parameter used for defining funneling.^{34,37,41,59} This analysis revealed that pooled sensitivities, specificities, and positive and negative likelihood ratios ranged between 24–53%, 87–94%, 2.2–6.1, and 0.5–0.8, respectively, to predict preterm birth at <32, <35, and <37 weeks of gestation. Another study (n = 131 women) reported a low predictive accuracy of 3 funneling-related parameters for preterm birth at <32 weeks of gestation in asymptomatic women with areas under the ROC curves that ranged between 0.50–0.70.³⁵ Only 2 small studies (n = 26 women each) evaluated the predictive ability for preterm birth of cervical funneling in patients with threatened preterm labor.^{46,48} The predictive values for preterm birth at <34 and <37 weeks of gestation were low (sensitivities between 25–60%, specificities between 79–86%, and positive and negative likelihood ratios between 1.2–4.2 and 0.5–1.0, respectively). Overall, the available evidence suggests that the presence of cervical funneling during transvaginal sonography is not a clinically useful test to predict preterm birth in both asymptomatic and symptomatic women with twin gestations.

Uterine artery Doppler ultrasonography

We reviewed 3 studies (n = 707) assessing the accuracy of uterine artery Doppler ultrasonography during the second trimester of pregnancy to predict preterm birth in twin gestations.^{60–62} One study reported that a resistance index >95th percentile and the presence of notching at 18–24 weeks of gestation had low predictive values for preterm birth at <32 and <37 weeks of gestation sensitivities, specificities, and positive and negative likelihood ratios between 13–26%, 92–95%, 2.5–3.4, and 0.8–0.9, respectively).⁶⁰ Another study reported that a pulsatility index >95th percentile and the presence of bilateral notching at 22–24 weeks of gestation had sensitivities, specificities, and positive and negative likelihood ratios that ranged from 12–19%, 97–98%, 5.1–5.7, and 0.8–0.9, respectively, for predicting preterm birth at <32 weeks of gestation.⁶¹ A third study reported that an increased pulsatility index at 24–32 weeks of gestation had a low predictive value for adverse pregnancy outcomes including preterm birth.⁶² In summary, this evidence suggests that uterine artery Doppler ultrasonography has minimal to moderate ability to predict preterm birth in twin gestations.

Discordance in sonographic growth

Significant discordance in crown-rump length detected at the 11- to 14-week scan has been associated with a higher risk of adverse perinatal outcomes in twin gestations. We identified one systematic review and metaanalysis that assessed the predictive value of this test for several adverse perinatal outcomes including preterm birth at <34 weeks of gestation.⁶³ Despite that crown-rump length discordance (>10%) detected at 11–14 weeks was significantly associated with preterm birth at <34 weeks (relative risk, 1.49; 95% confidence interval [CI], 1.23–1.80), the predictive accuracy of this test was poor (pooled sensitivity, specificity, and positive and negative likelihood ratios of 14%, 91%, 1.5, and 1.0, respectively; 3 studies; n = 4360).

Two large cohort studies have reported on the predictive accuracy for preterm birth of intertwin discordant sonographic growth in the late first and second trimesters.^{64,65} One study (n = 960) assessed discordance in abdominal circumference (>10%), biparietal diameter (>10%), femur length (>10%), and estimated fetal weight (>10%) at 11–22 weeks of gestation as predictor for preterm birth at <34 weeks of gestation.⁶⁴ In general, the predictive accuracy of these biometric data was low with sensitivities, specificities, and positive and negative likelihood ratios that ranged from 7–51%, 71–96%, 1.5–3.1, and 0.7–1.0, respectively. A recent retrospective cohort study (n = 2399) reported a poor predictive performance of discordance in abdominal circumference and estimated fetal weight at 20–22 weeks of gestation for preterm birth at <34 weeks of gestation (area under the ROC curve, 0.53; 95% CI, 0.49–0.56).⁶⁵ In conclusion, discordant sonographic growth detected in the first or second trimester has a poor predictive accuracy for preterm birth, thus limiting its use in clinical practice.

Nuchal translucency

First-trimester fetal nuchal translucency combined with biochemical markers appears to be an acceptable screening test for aneuploidies in twin gestations.⁶⁶ Only two studies have assessed nuchal translucency in predicting preterm birth in twin gestations.^{67,68} One small study including 20 monochorionic multiple gestations (18 twins and 2 triplets) uncomplicated by twin-to-twin transfusion syndrome or aneuploidies reported that 3 of the 4 gestations with increased nuchal translucency thickness in at least one fetus and 1 of the 16 with normal nuchal translucency thickness were delivered at <32 weeks of gestation (sensitivity of 75%, specificity of 94%, and positive and negative likelihood ratios of 12.0 and 0.3, respectively).⁶⁷ A recent retrospective cohort study involving 177 monochorionic diamniotic twin gestations found that intertwin discordance in nuchal translucency (20%) was a poor predictor for preterm birth at <28 weeks of gestation (area under the ROC curve, 0.52; 95% CI, 0.42–0.61).⁶⁸ These data have inherent limitations to allow firm conclusions other than suggesting that more studies are needed to determine the performance of first-trimester nuchal translucency as a predictive test for preterm birth in twin gestations.

Home uterine activity monitoring

To date, only the study by Newman et al⁶⁹ (n = 59 women) has clearly reported on the predictive accuracy of home uterine activity monitoring (HUAM) for preterm birth in asymptomatic women with twin gestations. Contraction frequency was recorded with HUAM 2 times per day on 2 days per week from 22–24 weeks until delivery or 36 weeks. Data on HUAM were masked. Overall, HUAM had very low predictive accuracy for spontaneous preterm birth at <35 weeks of gestation with sensitivities that ranged between 12–50%, specificities between 73–95%, and positive and negative likelihood ratios between 0.6–2.5 and between 0.6–1.1, respectively. In addition, the Cochrane review that assessed the effectiveness of HUAM in both singleton and twin gestations concluded that this intervention does not have an impact on the frequency of preterm birth and perinatal mortality.⁷⁰ In conclusion, HUAM is a poor predictor of spontaneous preterm birth among asymptomatic women with twin gestations, and its routine use in such patients does not reduce the rate of preterm birth and neonatal morbidity and mortality.

Biochemical tests

Cervicovaginal fetal fibronectin

In 2010, we published a systematic review and metaanalysis on the accuracy of cervicovaginal fetal fibronectin in predicting preterm birth in women with twin gestations.⁷¹ Fifteen studies (11 in asymptomatic women^{30,32,38,45,72–78} and 4 in patients with symptoms of preterm labor^{50,79–81}) involving 1133 women with twin gestations were included in the review. Among asymptomatic women, cervicovaginal fetal fibronectin had limited accuracy in predicting preterm birth at <32, <34, and <37 weeks of gestation (pooled sensitivities, specificities, and positive and negative likelihood ratios ranging from 33–39%, 80–94%, 2.0–5.1, and 0.7–0.8, respectively). In 2014, a retrospective cohort study including 560 twin gestations reported similar predictive values for preterm birth at <32 weeks of gestation from either preterm labor or premature rupture of membranes.⁸² Among patients with threatened preterm labor, our study found that the test was most accurate in predicting spontaneous preterm birth within 7 days of testing (pooled sensitivity, specificity, and positive and negative likelihood ratios of 85%, 78%, 3.9, and 0.2, respectively). Only 1.6% of patients with an episode of preterm labor who tested negative for cervicovaginal fetal fibronectin delivered in the next week. Unfortunately, only 3 studies (n = 168)^{79–81} provided data for the metaanalysis. Based on these findings, cervicovaginal fetal fibronectin has low to moderate accuracy in predicting spontaneous preterm birth in both asymptomatic and symptomatic women with twin gestations.

Fetoplacental proteins/hormone-related biomarkers

Alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and pregnancy-associated plasma protein (PAPP)-A have been used for the screening of fetal aneuploidy, neural tube defects, and other fetal abnormalities in the first or second trimesters of pregnancy. Abnormal values of these maternal serum analytes have also been associated with adverse pregnancy outcomes in women with normal fetuses.⁸³ Although several studies have reported an inverse relationship between elevated maternal serum AFP levels in the second trimester of pregnancy and gestational age at birth in women with twin gestations uncomplicated by neural tube defects,⁸³ only one study (n = 267) has reported on the accuracy of AFP to predict preterm birth in this population.⁸⁴ The predictive ability of elevated maternal AFP levels (≥ 3.5 multiples of the median [MoM]) at 15–20 weeks for preterm birth at <34 weeks of gestation was poor (sensitivity of 30%, specificity of 88%, and positive and negative likelihood ratios of 2.4 and 0.8, respectively).

We identified 4 studies that evaluated the second-trimester serum levels of hCG (2 studies; n = 1868)^{85,86} or the first-trimester serum levels of free b-hCG (2 studies; n = 174)^{87,88} for predicting preterm birth among women with twin gestations and normal fetuses. Overall, the predictive performance of high maternal serum levels of hCG (≥ 5.0 MoM⁸⁵ or >3 MoM⁸⁶) or free β-hCG (>75th percentile⁸⁷ or >90th percentile⁸⁸) for preterm birth at <32, <34, and <37 weeks of gestation was low (sensitivities between 7–24%, specificities between 75–97%, and positive and negative likelihood ratios between 0.9–3.0 and between 0.9–1.0, respectively).

Three studies (n = 515) have assessed the accuracy of the measurement of first-trimester maternal serum levels of PAPP-A levels to predict preterm birth in women with twin gestations and normal fetuses.^{87–89} The overall predictive ability of low serum levels of PAPP-A (defined as 25th percentile,⁸⁷ <10th percentile,⁸⁸ or <5th percentile⁸⁹) for preterm birth at <32, <34, <35, and <37 weeks of gestation was minimal (sensitivities ranging from 5–56%, specificities from 78–95%, and positive and negative likelihood ratios from 1.0–2.9 and 0.6–1.0, respectively).

Relaxin is a peptide hormone produced by the corpus luteum during pregnancy in response to stimulation by hCG. Elevated circulating maternal relaxin concentrations have been associated with an increased risk of preterm birth.⁹⁰ We identified 2 studies that evaluated the association between maternal serum levels of relaxin and the risk of preterm birth in twin gestations.^{91,92} A study involving 28 asymptomatic women found that serum relaxin levels >2 SD above the mean (1.4 ng/mL) at 32 weeks had a sensitivity, specificity, and positive and negative likelihood ratios of 30%, 100%, ∞, and 0.7, respectively, for predicting preterm birth at 35 weeks of gestation.⁹¹ A larger study (n = 188) reported that relaxin levels >90th percentile at 24 weeks had sensitivities, specificities, and positive and negative likelihood ratios that ranged from 10–14%, 91–95%, 1.1–2.3, and 0.9–1.0, respectively, to predict spontaneous preterm birth at <32, <35, and <37 weeks of gestation.⁹²

To date, only 2 studies (n = 237) have reported on the value of phosphorylated insulin-like growth factor binding protein (*phIGFBP*)-1 measured in cervical secretions for the prediction of preterm birth in asymptomatic women with twin gestations.^{93,94} Overall, the measurement of *phIGFBP*-1 had minimal predictive accuracy for preterm birth at <34 weeks of gestation (pooled sensitivity, specificity, and positive and negative likelihood ratios of 16%, 93%, 2.3, and 0.9, respectively). No study has evaluated *phIGFBP*-1 in women with twin gestations and threatened preterm labor. Additional longitudinal studies are needed.

In summary, the determination of maternal serum levels of first- and second-trimester markers used for screening of fetal aneuploidies and neural tube defects and relaxin does not appear to be useful in predicting preterm birth in twin gestations. There is insufficient evidence to assess the predictive ability of the measurement of cervical *phIGFBP*-1 for preterm birth.

Cytokines/chemokines

A considerable body of evidence supports a role for cytokines^{95–116} and chemokines^{117–127} in the mechanisms responsible for preterm labor and delivery and their potential use of biomarkers.^{128–130} In asymptomatic women with singleton gestations, measurement of serum,^{131,132} cervicovaginal^{133,134} and amniotic^{135,136} fluid concentrations of cytokines have been used for the prediction of spontaneous preterm delivery.¹³⁷ We analyzed 2 studies that evaluated the predictive accuracy of cytokines for spontaneous preterm birth in twin gestations.^{138,139} A cohort study assessed the ability of interleukin (IL)-1α, IL-6, and IL-8 concentrations in cervicovaginal secretions at 24–34 weeks to predict spontaneous preterm birth in 101 women with twin gestations.¹³⁸ IL-8, but not IL-1α or IL-6, was associated with a significant increase in the risk of spontaneous preterm birth at <37 weeks of gestation. However, the accuracy of IL-8 for predicting preterm birth at <37 weeks of gestation was

low (sensitivity of 79%, specificity of 46%, and positive and negative likelihood ratios of 1.5 and 0.5, respectively). Recently, a secondary analysis of a randomized placebo-controlled trial investigating the preventive effect of vaginal progesterone on the risk of preterm delivery in diamniotic twin gestations reported on the association between cytokine levels in dried blood spots and the risk of spontaneous preterm birth in twin gestations.¹³⁹ Concentrations of 24 inflammatory markers were measured upon enrollment into the study (18–25 weeks of gestation) and after 4–8 weeks of treatment. Among women in the placebo group ($n = 265$), only levels of IL-8 in the second blood sample were significantly increased in spontaneous deliveries <34 weeks of gestation compared with term deliveries ($P < .001$). None of the other investigated inflammatory markers showed any statistically significant association with preterm birth. Although that study did not report on the predictive accuracy of IL-8 for preterm birth at <34 weeks of gestation, its authors concluded that circulating IL-8 levels cannot be used as a predictive marker for spontaneous preterm birth in twin gestations.

25-Hydroxyvitamin D

A recent study evaluated the relationship between maternal 25-hydroxyvitamin D concentrations at 24–28 weeks of gestation and preterm birth in a cohort of 211 twin gestations.¹⁴⁰ Despite that a late second-trimester maternal 25-hydroxyvitamin D concentration <75nmol/L was associated with a significant increase in the risk of preterm birth at <35 weeks of gestation, it cannot be used as a predictive test for preterm birth in twin gestations because of its low predictive values: sensitivity of 56%, specificity of 68%, and positive and negative likelihood ratios of 1.8 and 0.6, respectively.

Bacterial vaginosis

Three studies have assessed whether the presence of bacterial vaginosis is predictive of preterm birth in asymptomatic women with twin gestations.^{30,32,77} A study by Goldenberg et al³⁰ ($n = 147$ women) reported that the presence of bacterial vaginosis at 24 and 28 weeks of gestation had very low predictive values for spontaneous preterm birth at <32, <35, and <37 weeks of gestation with sensitivities, specificities, and positive and negative likelihood ratios ranging between 0–23%, 78–82%, 0.6–1.0, and 1.0–1.2, respectively. Similar results were obtained in one study³² involving 101 asymptomatic women with twin gestations in which the presence of bacterial vaginosis at 24–34 weeks had a sensitivity, specificity, and positive and negative likelihood ratios of 14%, 92%, 1.8, and 0.9, respectively, for predicting spontaneous preterm birth at <37 weeks of gestation. Another study ($n = 48$ women) found no association between the presence of bacterial vaginosis at 22–34 weeks and preterm birth at <35 weeks of gestation.⁷⁷ In conclusion, the presence of bacterial vaginosis has a very modest predictive ability for preterm birth in women with twin gestations.

Cervicovaginal endotoxin

Endotoxin is a component of the cell wall of gram-negative bacteria, which has been detected in the amniotic fluid of women with preterm labor and preterm premature rupture of membranes.^{141,142} The interaction between endotoxin and host cells leads to an increased synthesis of cytokines, chemokines, and lipid mediators that appear to be associated with preterm birth.^{142–144} Only one study has assessed the accuracy of the measurement of

endotoxin in cervical fluid of women with twin gestations (n = 121 women) for predicting spontaneous preterm birth at <35 and <37 weeks of gestation.³² The presence of endotoxin in cervical fluid was not significantly associated with preterm birth neonatal morbidity. That study did not report predictive values.

Combination of biophysical and biochemical test

Combination of transvaginal sonographic CL and cervicovaginal fetal fibronectin

Two studies have reported on the ability of the combination of CL and cervicovaginal fetal fibronectin for predicting preterm birth among asymptomatic women with twin gestations.^{30,45} One study (n = 147) found that having either a CL ≥ 25 mm or a positive fetal fibronectin result, or both tests positive at 24 or 28 weeks of gestation, had a limited predictive accuracy for spontaneous preterm birth at <32, <35, and <37 weeks of gestation (sensitivities 26–83%, specificities 68–88%, and positive and negative likelihood ratios ranging from 1.7–3.3 and from 0.3–0.8, respectively).³⁰ Another study (n = 155) reported that having either a CL <20mm, a positive fetal fibronectin result, or both tests positive at 22–32 weeks of gestation had sensitivities, specificities, and positive and negative likelihood ratios that varied from 37–67%, 79–94%, 2.6–6.7, and 0.4–0.7, respectively, for predicting spontaneous preterm birth at all gestational ages considered.⁴⁵ Two studies assessed the combination of CL and fetal fibronectin to predict preterm birth in women with threatened preterm labor.^{50,145} One study (n = 44) reported that having either a CL <20 mm or a positive fetal fibronectin result, or both tests positive, had a sensitivity, specificity, and positive and negative likelihood ratios of 67%, 62%, 1.8, and 0.5, respectively, to predict preterm birth at <34 weeks of gestation.⁵⁰ A recent study assessed the predictive accuracy for spontaneous preterm birth of a sequential test (considered positive if CL ≥ 15 mm or CL between 16–30 mm with positive fetal fibronectin result) in 50 patients hospitalized for preterm labor between 24–34 weeks.¹⁴⁵ Overall, the sequential test had a low predictive accuracy for delivery within 7 and 14 days of testing (positive and negative likelihood ratios around 2.0 and 0.3, respectively) and preterm birth at <34 and <37 weeks of gestation (positive and negative likelihood ratios about 1.5 and 0.6, respectively). The predictive values of the sequential test were not significantly different from those of the individual tests. In summary, there is no evidence that the combination of fetal fibronectin and CL is a better predictor of preterm birth than either CL or fetal fibronectin alone among both asymptomatic and symptomatic women with twin gestations.

Conclusions

The predictive accuracy of biophysical and biochemical tests proposed for the prediction of preterm birth in women with twin gestations is summarized in Table 2. The ideal predictive test for preterm birth in both asymptomatic and symptomatic women with a twin gestation should be simple, innocuous, rapid, inexpensive, reproducible, and noninvasive, and have a high likelihood ratio to increase the probability of preterm birth in women with a positive test result, and a low likelihood ratio to confidently exclude preterm birth with a negative test result. In addition, in asymptomatic women, the test should be easy to perform early in gestation to allow for potential interventions to prevent not only preterm birth, but its

associated perinatal morbidity and mortality. At the present time, it is evident that a single measurement of transvaginal sonographic CL <25 weeks of gestation appears to meet several characteristics to be considered a good predictive test for preterm birth among asymptomatic women. In the present review, we have shown that a CL 20mm at 20–24 weeks of gestation had a pooled positive likelihood ratio of 10.1 for predicting preterm birth at <32 weeks of gestation, which would increase its pretest probability in the United States from 11.3%¹⁹ to 56.3%.

A key aspect of a predictive test is whether it is effective in reducing morbidity and mortality from spontaneous preterm birth. Even if a test will accurately and inexpensively identify women with twin gestations at an increased risk of preterm birth, it will have little public health value if early prediction and treatment do not have an impact on the ultimate outcome of those cases. In 2012, an individual patient data metaanalysis of randomized controlled trials assessed the effects of the administration of vaginal progesterone between 20–36 weeks of gestation in 52 asymptomatic women with a twin gestation and a sonographic short cervix (≤ 25 mm) detected at midtrimester.¹⁴⁶ The study demonstrated a 48% significant reduction in composite neonatal morbidity and mortality (23.9% in the vaginal progesterone group vs 39.7% in the placebo group; relative risk, 0.52; 95% CI, 0.29–0.93) and a 30% nonsignificant reduction in preterm birth at <33 weeks of gestation (30.4% in the vaginal progesterone group vs 44.8% in the placebo group; relative risk, 0.70; 95% CI, 0.34–1.44) associated with the use of vaginal progesterone. Further well-designed randomized controlled trials are required to evaluate the benefit of vaginal progesterone in women with twin gestations and a short cervix in preventing preterm birth, as well as neonatal morbidity and mortality.

A recent retrospective study compared the rates of preterm birth, spontaneous preterm birth, and antenatal corticosteroids exposure between a cohort of women with asymptomatic twin gestations who underwent routine serial measurement of sonographic CL (from 16–32 weeks) and fetal fibronectin (from 22–32 weeks) (n = 532) and other similar cohort in which these tests were only performed as deemed clinically indicated (n = 456).¹⁴⁷ Although the rates of preterm birth were similar between the two groups, the routine use of these tests was associated with significantly improved rates and timing of antenatal corticosteroid administration among patients who delivered prematurely. These findings suggest that routine measurement of sonographic CL and fetal fibronectin could potentially improve the perinatal outcomes in twin gestations delivered preterm by increasing antenatal corticosteroid exposure.

None of the tests proposed for the prediction of preterm birth in women with twin gestations and an episode of preterm labor fulfill the criteria to be considered clinically useful. However, our metaanalysis⁷¹ suggested that a negative cervicovaginal fetal fibronectin test could be useful in identifying patients who are not at risk for delivering within the next week, which could reduce health care resource use and costs associated with the management of patients with an episode of preterm labor (eg, maternal hospitalization, use of tocolytic agents). Further well-designed prospective studies are required to evaluate the predictive ability of fetal fibronectin alone or combined with CL before recommending its routine use in women with twin gestations and symptoms of preterm labor.

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		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

Figure.

Measures of accuracy of predictive test

Table 1

Tests proposed to predict preterm birth in women with twin gestations

Asymptomatic women	
Transvaginal sonographic cervical length	
Single measurement	
Change in cervical length over time	
Transvaginal sonographic cervical funneling	
Cervicovaginal fetal fibronectin	
Combination of transvaginal sonographic cervical length and cervicovaginal fetal fibronectin	
Uterine artery Doppler	
Discordance in sonographic growth	
Discordance in crown-rump length	
Discordance in abdominal circumference, biparietal diameter, femur length, and estimated fetal weight	
Nuchal translucency	
Home uterine activity monitoring	
Alpha-fetoprotein	
Human chorionic gonadotropin	
Pregnancy associated placental protein-A	
Relaxin	
Cervical phosphorylated insulin-like growth factor binding protein-1	
Cytokines	
25-hydroxyvitamin D	
Bacterial vaginosis	
Cervicovaginal endotoxin	
Women with threatened preterm labor	
Transvaginal sonographic cervical length	
Transvaginal sonographic cervical funneling	
Cervicovaginal fetal fibronectin	
Combination of transvaginal sonographic cervical length and cervicovaginal fetal fibronectin	

Table 2
Predictive accuracy of biophysical and biochemical tests for preterm birth in women with twin gestations

Test	No. of studies	No. of women	Cut-off	Outcome	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Asymptomatic women								
Transvaginal sonographic cervical length								
Single measurement ^a	3 ²⁹	637	25 mm	Preterm birth <28 wk	64	93	9.6	0.4
	5 ²⁹	1955	20 mm	Preterm birth <32 wk	39	96	10.1	0.6
	5 ²⁹	1760	20 mm	Preterm birth <34 wk	29	97	9.0	0.7
	4 ²⁹	434	25 mm	Preterm birth <37 wk	21	95	4.4	0.8
Change in cervical length over time	7 ^{38,41,54-58}	1004	Several	Preterm birth <28 to <36 wk	15-75	70-90	1.6-5.5	0.3-0.8
Transvaginal sonographic cervical funneling ^a	4 ^{34,37,41,59}	549	Several	Preterm birth <32, <35, and <37 wk	24-53	87-94	2.2-6.1	0.5-0.8
Cervicovaginal fetal fibronectin ^a	2 ⁷¹	302	50 ng/ml	Preterm birth <32 wk	33	94	5.1	0.7
	6 ⁷¹	576	50 ng/ml	Preterm birth <34 wk	39	80	2.0	0.8
	5 ⁷¹	520	50 ng/ml	Preterm birth <37 wk	33	87	2.6	0.8
Combination of cervical length and cervicovaginal fetal fibronectin	2 ^{30,45}	302	Either one test positive or both tests positive	Preterm birth <32, <35, and <37 wk	26-83	68-94	1.7-6.7	0.3-0.8
Uterine artery Doppler	3 ⁶⁰⁻⁶²	707	Several	Preterm birth <32 and <37 wk	12-26	92-98	2.5-5.7	0.8-0.9
Discordance in crown-rump length ^a	3 ⁶³	4360	10%	Preterm birth <34 wk	14	91	1.5	1.0
Discordance in abdominal circumference, estimated fetal weight, biparietal diameter, or femur length	2 ^{64,65}	3359	10%	Preterm birth <34 wk	7-51	71-96	1.5-3.1	0.7-1.0
Nuchal translucency	2 ^{67,68}	195	95th percentile for thickness ⁶² and 20% for discordance in nuchal translucency ⁶³	Preterm birth <28 and <32 wk	50-75	50-94	1.0-12.0	0.3-1.0
Home uterine activity monitoring	1 ⁶⁹	59	Several	Preterm birth <35 wk	12-50	73-95	0.6-2.5	0.6-1.1
Alpha fetoprotein	1 ⁸⁴	267	3.5 MoM	Preterm birth <34 wk	30	88	2.4	0.8
Human chorionic gonadotropin	2 ^{85,86}	1868	[3.0-5.0] MoM	Preterm birth <32 and <37 wk	7-10	95-97	1.1-3.0	0.9-1.0
Free β -human chorionic gonadotropin	2 ^{82,83}	174	[75-90]th percentile	Preterm birth <32, <34 and <37 wk	11-24	75-91	0.9-1.2	1.0
PAPP-A	3 ⁸⁷⁻⁸⁹	515	[5-25]th percentile	Preterm birth <32 to <37 wk	5-56	78-95	1.0-2.9	0.6-1.0
Relaxin	2 ^{91,92}	216	2 SD or 90th percentile	Preterm birth <32, <35 and <37 wk	10-30	91-100	1.1- ∞	0.7-1.0

Test	No. of studies	No. of women	Cut-off	Outcome	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
<i>pHGFBP-1</i> ^a	2 ^{93,94}	237	30 µg/l	Preterm birth <34 wk	16	93	2.3	0.9
Interleukin-8	1 ³⁸	101	1.75 ng/g mucus	Preterm birth <37 wk	79	46	1.5	0.5
25-hydroxyvitamin D	1 ⁴⁰	211	75 nmol/l	Preterm birth <35 wk	56	68	1.8	0.6
Bacterial vaginosis	2 ^{30,32}	248	Presence	Preterm birth <32, <35 and <37 wk	0–23	78–92	0.6–1.8	0.9–1.2
Women with threatened preterm labor								
Transvaginal sonographic cervical length ^a	1 ⁴⁹	87	25 mm	Delivery within 7 days of testing	100	31	1.4	0.0
	2 ²⁹	92	30 mm	Preterm birth <34 wk	79	32	1.2	0.7
	2 ²⁹	131	25 mm	Preterm birth <37wk	49	74	1.9	0.7
Transvaginal sonographic cervical funneling	2 ^{46,48}	52	Several	Preterm birth <34 and <37 wk	25–60	79–86	1.2–4.2	0.5–1.0
Cervicovaginal fetal fibronectin ^a	3 ⁷¹	168	50 ng/ml	Delivery within 7 days of testing	85	78	3.9	0.2
	2 ⁷¹	125	50 ng/ml	Delivery within 14 days of testing	64	76	2.7	0.5
	2 ⁷¹	131	50 ng/ml	Preterm birth <34 wk	53	71	1.8	0.7
	2 ⁷¹	82	50 ng/ml	Preterm birth <37wk	41	81	2.2	0.7
Combination of cervical length and cervicovaginal fetal fibronectin	1 ⁴⁵	50	CL 15 mm or CL between 16–30 mm with positive fetal fibronectin result	Delivery within 7 or 14 days of testing	83–89	55–56	1.8–2.0	0.2–0.3
	2 ^{50,145}	94	Either one test positive or both tests positive	Preterm birth <34 wk	67–70	56–62	1.6–1.8	0.5
	1 ⁴⁵	50	CL 15 mm or CL between 16–30 mm with positive fetal fibronectin result	Preterm birth <37wk	61	58	1.7	0.7

^a Pooled estimates calculated from meta-analytic techniques.

MoM, multiple of the median; *PAPP-A*, pregnancy-associated plasma protein A; *SD*, standard deviation; *pHGFBP-1*, cervical phosphorylated insulin-like growth factor binding protein-1