Prediction of spontaneous preterm birth in asymptomatic twin pregnancies with the use of combined fetal fibronectin and cervical length

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OBJECTIVE: The purpose of this study was to evaluate combined fetal fibronectin (fFN) test result and cervical length (CL) as predictors of spontaneous preterm birth in asymptomatic twin pregnancies.

STUDY DESIGN: We examined a retrospective cohort of 155 twin pregnancies with combined fFN and CL testing between 22 and 32 weeks gestation.

RESULTS: A positive fFN test result at 22-32 weeks or a CL <20 mm increased the risk of spontaneous preterm birth at <37, <34, <32, <30, and <28 weeks' gestation. The combination of a positive fFN test result and CL<20 mm had a significantly higher positive predictive value for delivery at all gestational ages than either positive test alone. On adjusted analysis, a positive fFN test result was a stronger predictor of spontaneous preterm birth than a short CL.

CONCLUSION: In asymptomatic twin pregnancies, fFN and CL testing between 22 and 32 weeks gestation can identify pregnancies that are at significantly increased risk for preterm birth, including deliveries at <28 weeks' gestation.

Key words: cervical length, fetal fibronectin, prediction, preterm birth, twins

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The number and rate of twin births continues to rise, from 2.2% of all United States live births in 1990 to 3.2% of all live births in 2005.[1] Preterm birth is the most common morbidity to be associated with twin pregnancies. A shortened cervix that can be identified by endovaginal ultrasound is strongly predictive of preterm birth in twin pregnancies.[2-5] In the Preterm Prediction Study, among 147 twin pregnancies, for women with a cervical length (CL) ≤25mm at 24 weeks' gestation, the odds ratio of preterm birth at <32 weeks' gestation was 6.9 (95% confidence interval [CI], 2.0–24.2), compared with women with twin pregnancies and a CL >25mm.[2]

The presence of cervicovaginal fetal fibronectin (fFN) is a predictor of preterm birth in asymptomatic and symptomatic singleton pregnancies[6,7] and in symptomatic twin pregnancies that are evaluated for preterm labor.[8,9] However, there are fewer data that demonstrate an association between a positive fFN test result and spontaneous preterm birth in asymptomatic twin pregnancies, especially for very preterm birth <32 weeks' gestation. One study of 121 asymptomatic twin pregnancies showed that a positive fFN test result at 24-34 weeks was associated with preterm birth <35 weeks' gestation (relative risk, 18.0; 95% CI, 2.2–145.9).[10] In the Preterm Prediction Study, in twins, a positive fFN test result at 24 weeks gestation was not associated significantly with spontaneous preterm birth, and a positive fFN test result at 28 or 30 weeks gestation was associated significantly only with preterm birth at <32 weeks' gestation.[2] However, the number of patients with a positive fFN test result was small (4.8% at 24 weeks' gestation); therefore, they may have been underpowered to assess fFN testing at this gestational age. The combination of CL and fFN testing at 24 and 28 weeks gestation was also studied as a predictor of preterm birth in twin pregnancies by the Preterm Prediction Study. Having either a positive fFN test result or a short CL was associated with a higher rate of preterm birth than having 2 negative tests; having both a positive fFN test result and a short CL was associated with the highest rates of preterm birth at <32, <35, and <37 weeks' gestation.

However, nearly all of their positive results of both 24 and 28 weeks' gestation were a short CL and not a positive fFN test result. Therefore, it is unclear whether the addition of fFN testing was valuable in the prediction of preterm birth among asymptomatic twin pregnancies that are already undergoing CL testing. In another prospective study of 91 asymptomatic twin pregnancies, fFN test results at 24, 28, and 32 weeks' gestation was not a significant predictor of

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TABLE 1
Prevalence of test positivity by gestational age

	Weeks of gestation (%)				
Variable	**22-24**	**24-26[a]**	**26-28[a]**	**28-30[a]**	**30-32[a]**
Fetal fibronectin positive	3.2	6.5	7.1	9.0	12.9
Cervical length <20 mm	1.3	5.2	6.5	10.3	16.8
Both fetal fibronectin positive and cervical length <20 mm	1.3	2.6	2.6	3.9	7.1

[a] Each frequency includes positive tests from previous gestational ages; fetal fibronectin and cervical length testing was performed from 22-32 weeks only.

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preterm birth.[11] Therefore, the current published literature does not support routine fFN testing in asymptomatic twin pregnancies.

The purpose of this study was to evaluate fFN, CL, and the combination of both as predictors of preterm birth in asymptomatic twin pregnancies.

Methods

A retrospective cohort of patients was obtained from twin pregnancies that were cared for in our Maternal Fetal Medicine practice between 2005 and 2008. Mount Sinai School of Medicine Institutional Review Board approval was obtained before the study was conducted. Women with twin pregnancies with a CL measurement and fFN testing between 22 and 32 weeks gestation were included. These tests are done routinely for twin pregnancies in our practice, primarily for patient reassurance. Additionally, they assist us in making management decisions, such as timing of steroids, activity modification, and tocolytic use.

All CL assessments and fFN testing were done in an outpatient setting on asymptomatic patients. All tests that were done at labor and delivery were excluded, because they were done on symptomatic patients as part of a preterm labor evaluation. Gestational age was based on the last known menstrual period and confirmed by first-trimester ultrasound in all patients. The following pregnancies were excluded: monoamniotic twins, pregnancies with aneuploidy, or pregnancies with major fetal anomalies that were discovered before or after birth. Patients and obstetricians were not blinded to the CL measurements or fFN results.

All CL measurements were measured by 4- to 8-MHz transvaginal probes (LOGIQ a200 and Voluson 530 and 730 Expert; GE Healthcare, Milwaukee, WI) with an empty bladder. The optimal image was defined according to the criteria reported by Iams et al.[12] The shortest functional CL was used because this has been found to be the most reproducible measurement.[13] A *short CL* was defined as a CL of <20 mm. We chose 20 mm as the cutoff (as opposed to 25 mm, which is used in some studies) to decrease the rate of false-positive test results. The cutoff of 20 mm has been validated in other studies.[5]

FFN testing was performed with a Dacron swab without the use of a speculum, which is according to an established protocol that has been validated previously by both our group[14] and others.[15] FFN testing was performed >24 hours from the last reported intercourse or endovaginal ultrasound. Vaginal swabs were sent for quantitative determination of fFN concentration with the use of an enzyme-linked immunosorbent assay (Fetal Fibronectin Immunoassay; Hologic Inc., Bedford, MA). An fFN concentration of ≥50 ng/mL was considered to be positive.

In our practice, we routinely evaluate CL and fFN in all twin pregnancies approximately every 2-3 weeks from 22-32 weeks' gestation. Therefore, most of our patients have multiple test results. For the purpose of this study, a patient with a CL<20 mm at any time between 22-32 weeks' gestation was considered as having a short CL; a patient with a positive fFN test result at any time from 22-32 weeks' gestation was considered to have a positive fFN result. However, for the outcomes of spontaneous preterm birth <28 and <30 weeks' gestation, we included only CL measurements and fFN testing that was done before those gestational ages, respectively.

Patients with a medically indicated preterm birth were excluded from analysis of spontaneous preterm birth at all later gestational ages. For example, if there was a medically indicated preterm birth at 31 weeks gestation, the patient was not included in the analysis for spontaneous preterm birth at <32 weeks' gestation but was considered as not having a spontaneous preterm birth <30 and <28 weeks' gestation. Fisher exact test, χ^2 test, Student t test, and 1-way analysis of variance were used when appropriate (SPSS for Windows 16.0; SPSS Inc, Chicago, IL). A probability value of < .05 was considered significant. To adjust for multiple tests that were performed at different points in pregnancy, a Cox proportional hazards model with time dependant covariates was used to explore the relationship between fFN/CL results and time to delivery. An adjusted model was also used, in which we controlled for gestational age at testing, maternal age, in vitro fertilization, previous preterm births, and previous term births.

Results

One hundred fifty-five patients had CL measurement and fFN testing from 22-32 weeks' gestation. The mean age of the women was 34.5 ± 6.9 years; 137 women (88.4%) had dichorionic placentation, and 18 pregnancies (11.6%) were monochorionic. Ninety-nine pregnancies (63.9%) were the result of in vitro fertilization. Mean gestational age at delivery was 35.7 ± 2.7 weeks. The proportion of patients with spontaneous preterm birth was 53.4% at <37 weeks' gestation, 24.2% at <35 weeks' gestation, 15.9% at <34 weeks' gestation, 8.5% at <32 weeks' gestation, 4.5% at <30 weeks' gestation, and 3.9% at <28 weeks' gestation. Table 1 describes the