

# Gestational Age at Cervical Length and Fetal Fibronectin Assessment and the Incidence of Spontaneous Preterm Birth in Twins

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**Objectives**—To estimate the risk of spontaneous preterm birth in twin pregnancies based on transvaginal sonographic cervical length, fetal fibronectin (fFN) testing, and the gestational age at which these tests were performed.

**Methods**—Women with twin pregnancies, cervical length assessment, and fFN testing between 22 weeks and 31 weeks 6 days in a single maternal-fetal medicine practice from 2005 to 2013 were included. All testing was done on asymptomatic women on an outpatient basis. Women with monochorionic monoamniotic twins and twin-twin transfusion were excluded. Logistic regression analysis was used to estimate the risk of spontaneous preterm birth before 35, 32, and 28 weeks.

**Results**—Six hundred eleven patients were included and underwent a total of 2406 cervical length measurements and 2279 fFN tests over the course of the study period. The likelihood values for spontaneous preterm birth before 35, 32, and 28 weeks were 19.1%, 6.3%, and 2.3%, respectively. The risk of spontaneous preterm birth before 35 weeks increased with a decreasing cervical length (coefficient for the log of the odds ratio [OR coefficient],  $-0.13$ ;  $P < .01$ ; 95% confidence interval [CI],  $-0.22$  to  $-0.037$ ), a positive fFN result (OR coefficient,  $1.04$ ;  $P < .01$ ; 95% CI,  $0.45$  to  $1.64$ ), as well as earlier gestational ages at testing (OR coefficient,  $-0.214$ ;  $P < .01$ ; 95% CI,  $-0.33$  to  $-0.10$ ). Similar results were seen for spontaneous preterm birth before 32 and 28 weeks.

**Conclusions**—In asymptomatic patients with twin pregnancies, the cervical length, fFN, and gestational age are all significantly associated with spontaneous preterm birth.

**Key Words**—cervical length; fetal fibronectin; gestational age; obstetric ultrasound; prematurity; twins

Received August 1, 2014, from Maternal Fetal Medicine Associates, PLLC, New York, New York USA (N.S.F., D.H.S., C.K.K., S.G., A.R.); Department of Obstetrics, Gynecology, and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, New York USA (N.S.F., D.H.S., C.K.K., S.G., A.R.); and Syms School of Business, Yeshiva University, New York, New York USA (A.F.). Revision requested September 8, 2014. Revised manuscript accepted for publication September 15, 2014.

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## Abbreviations

CI, confidence interval; fFN, fetal fibronectin; OR, odds ratio

doi:10.7863/ultra.34.6.977

The rate of twin births has risen from 1.9% of all US live births in 1980 to 3.3% of all US live births in 2011.<sup>1</sup> Although twins account for 3.3% of all live births in the United States, they account for a greater proportion of neonatal morbidity and mortality, principally due to the increased risk of prematurity. In the United States in 2011, 57.3% of twins delivered before 37 weeks, and 11.3% delivered before 32 weeks.<sup>2</sup>

The prediction of spontaneous preterm birth using cervical length measurement and fetal fibronectin (fFN) testing has been extensively studied in low- and high-risk singleton pregnancies, and it has been demonstrated that a short cervical length and a positive

fFN result are each associated with a significantly increased risk of preterm birth.<sup>3,4</sup> A short cervical length and positive fFN are significantly associated with preterm birth in twin pregnancies as well.<sup>5–8</sup>

For any cervical length measurement, the gestational age at which the cervical length is measured influences the risk of preterm birth, with an increasing risk of preterm birth with a short cervical length at earlier gestational ages. This effect of gestational age on the risk of preterm birth was demonstrated by Berghella et al<sup>9</sup> in singleton pregnancies and by Ehsanipoor et al<sup>10</sup> in twin pregnancies. In each of these studies, the authors presented reference tables to estimate the risk of preterm birth<sup>10</sup> or spontaneous preterm birth<sup>9</sup> before 35 and 32 weeks (and before 28 weeks in singletons<sup>9</sup>) based on the cervical length measurement and gestational age. However, similar data for fFN testing and combined cervical length/fFN testing are lacking. Since both cervical length and fFN are predictors of preterm birth in twin pregnancies, one would expect that each would add relevant information to the prediction tables.

The objective of this study was to estimate the risk of spontaneous preterm birth in twin pregnancies based on transvaginal sonographic cervical length, fFN testing, and the gestational age at which these tests were performed.

## Materials and Methods

After Biomedical Research Alliance of New York Institutional Review Board approval was obtained, the charts of all patients with twin pregnancies greater than 22 weeks delivered by a single maternal-fetal medicine practice between June 2005 (when our electronic medical record was established) and June 2013 were reviewed. We excluded patients with monochorionic monoamniotic placentation, major fetal congenital anomalies discovered before or after birth, and twin-twin transfusion syndrome. Baseline characteristics and pregnancy outcomes were obtained from our computerized medical record. Gestational age was determined by the last menstrual period and confirmed by sonography in all patients. The pregnancy was redated if there was a discrepancy of greater than 5 days up to 14 weeks or greater than 7 days after 14 weeks. If the pregnancy was the result of in vitro fertilization, gestational age was determined from in vitro fertilization dating.

In our practice, patients with twin pregnancies are followed with serial cervical length and fFN testing every 2 to 4 weeks until 32 weeks.<sup>6</sup> Cervical length screening is conducted from 16 weeks to 31 weeks 6 days; however, for this analysis, we only included cervical length measurements

after 22 weeks, as earlier measurements in twins have a much weaker association with preterm birth,<sup>7</sup> and fFN testing does not begin until 22 weeks. Fetal FN testing was from 22 weeks to 31 weeks 6 days. All cervical length assessments and fFN testing were done in an outpatient setting on asymptomatic patients. All tests done during labor and delivery were excluded, as they were done on symptomatic patients as part of a preterm labor evaluation. Measurements of cervical length were performed using a 4–8-MHz transvaginal probe with an empty bladder according to criteria established by Iams et al.<sup>3</sup> The shortest functional cervical length was used, as it has been found to be the most reproducible measurement.<sup>11</sup> Fetal FN testing was performed without the use of a speculum according to a published protocol<sup>12</sup> at least 24 hours from the last reported intercourse or endovaginal sonographic examination. Testing was not performed in the setting of vaginal bleeding. Swabs were sent for evaluation using an fFN assay, and a concentration of 50 ng/mL or greater was considered positive. Physicians were not blinded to cervical length or fFN results. Patients with a short cervical length and positive fFN results are typically evaluated for contractions and administered corticosteroids. Patients are not hospitalized for positive screening test results but, rather, only for clinical preterm labor (regular uterine contractions or cervical changes).

The primary outcome was spontaneous preterm birth before 35 weeks; we also decided a priori to examine spontaneous preterm birth before 32 and 28 weeks. Spontaneous preterm birth was defined as preterm birth resulting from preterm labor or premature rupture of membranes. Patients with an indicated preterm birth, such as for preeclampsia or fetal growth restriction, were excluded from analysis of spontaneous preterm birth at all later gestational ages. For example, if there was an indicated preterm birth at 31 weeks, the patient was not included in the analysis for spontaneous preterm birth before 32 and 35 weeks but was considered as not having a spontaneous preterm birth before 28 weeks. For the outcome of spontaneous preterm birth before 28 weeks, only cervical length and fFN tests done before 28 weeks were included.

To determine the predictive effects of fFN and cervical length on gestational age at delivery, 2 parallel sets of regression models were created. In the first set, gestational age at delivery was treated as a continuous variable, and ordinary least squares regression was computed. In the second set, gestational age at delivery was treated as a binary variable at 28, 32, and 35 weeks, and a propensity score was calculated by using a logit regression model at each of those 3 values. In all models, since observations were not inde-

pendent (ie, the same patient had multiple observations within the data set), we used regression models in which standard errors were heteroskedasticity-robust clustered, using the [regress, cluster] command in Stata release 11 software (StataCorp, College Station, TX).

For both sets of regression approaches, 3 separate models were constructed. In the first model, the independent variables were gestational age and cervical length with an added interaction term [gestational age  $\times$  cervical length] to accommodate the moderating effect of cervical length on gestational age at delivery depending on gestational age. In the second model, the independent variables were gestational age and fFN status, with an added interaction term [gestational age  $\times$  fFN] to accommodate the moderating effect of fFN status on gestational age at delivery depending on gestational age. The third model included gestational age, cervical length, fFN status, and an added interaction term between the appropriate variables.

## Results

During the study period, there were a total of 628 patients with twin pregnancies greater than 22 weeks delivered in our practice. Seventeen patients were excluded (10 monochorionic monoamniotic, 6 with twin-twin transfusion, and 1 with a uterine didelphys and double cervix with a twin in each uterus), leaving 611 patients for analysis. The mean gestational age  $\pm$  SD at delivery was  $35.8 \pm 2.6$  weeks. The likelihood values for spontaneous preterm birth before 35, 32, and 28 weeks were 19.1%, 6.3%, and 2.3%, respectively. There were a total of 2406 cervical length measurements (3.9 per patient) and 2279 fFN assessments (3.7 per patient). Baseline characteristics of the overall population are shown in Table 1.

Using logit regression, we calculated the effect of cervical length, fFN, and gestational age on the risk of spontaneous preterm birth. Since a logit regression calculates the natural logarithm of the odds ratio (OR) as its dependent variable, the effect of each independent variable on the dependent variable can only be estimated when given particular levels of the other independent variables (eg, gestational age).

The risk of spontaneous preterm birth before 35 weeks was significantly associated with a shorter cervical length measurement, positive fFN, as well as the gestational age at measurement. In the first model, we calculated the risk of spontaneous preterm birth before 35 weeks using gestational age and cervical length as predictive variables. In this model, the interaction effect for [gestational age  $\times$  cervical length] was not statistically significant ( $P > .20$ ), so we recalculated the model without an interaction term.

The coefficient for the log of the OR (OR coefficient) for gestational age was  $-0.063$  ( $P < .01$ , 95% confidence interval [CI],  $-0.082$  to  $-0.043$ ), and the OR coefficient for cervical length in millimeters was  $-0.041$  ( $P < .01$ ; 95% CI,  $-0.059$  to  $-0.023$ ). In the second model, we calculated the risk of spontaneous preterm birth before 35 weeks using the fFN test as well as gestational age. Again, the interaction effect for [gestational age  $\times$  fFN] was not statistically significant ( $P > .50$ ), so we recalculated the model without an interaction term. The OR coefficient for gestational age was  $-0.069$  ( $P < .01$ ; 95% CI,  $-0.091$  to  $-0.046$ ), and the OR coefficient for fFN was 1.51 ( $P < .01$ ; 95% CI, 0.94 to 2.08). In the third model, we calculated the risk of spontaneous preterm birth before 35 weeks using both cervical length and fFN as independent variables, as well as gestational age. In this model, the OR coefficient for fFN was 1.04 ( $P < .01$ ; 95% CI, 0.45 to 1.64); the OR coefficient for gestational age was  $-0.214$  ( $P < .01$ ; 95% CI,  $-0.33$  to  $-0.10$ ); the OR coefficient for cervical length was  $-0.13$  ( $P < .01$ ; 95% CI,  $-0.22$  to  $-0.037$ ); and the OR coefficient for the [gestational age  $\times$  cervical length] interaction effect was 0.003 ( $P = .06$ ; 95% CI, 0 to 0.01). No other second- or third-order interaction term was significant, so the model included only these terms.

Similarly, the risk of spontaneous preterm birth before 32 weeks was significantly associated with a shorter cervical length measurement, positive fFN, as well as the gestational age at measurement. In the first model, we calculated the risk of spontaneous preterm birth before 32 weeks using gestational age and cervical length as predictive variables.

**Table 1.** Characteristics of the Study Population

| Characteristic                      | Value          |
|-------------------------------------|----------------|
| Pregnancies, n                      | 611            |
| Cervical length measurements, n     | 2406           |
| fFN tests, n                        | 2279           |
| Maternal age, y                     | $34.2 \pm 6.6$ |
| Conception, %                       |                |
| Spontaneous                         | 23.3           |
| Ovulation induction                 | 11.9           |
| In vitro fertilization              | 64.8           |
| Multifetal pregnancy reduction, %   | 7.1            |
| White race, %                       | 87.2           |
| Prepregnancy BMI, kg/m <sup>2</sup> | $23.5 \pm 4.4$ |
| Prior term birth, %                 | 34.5           |
| Prior preterm birth, %              | 7.1            |
| Prior LEEP or cone biopsy, %        | 3.4            |
| Chorionicity, %                     |                |
| Monochorionic                       | 13.1           |
| Dichorionic                         | 86.9           |

Data are presented as mean  $\pm$  SD where applicable. BMI indicates body mass index; and LEEP, loop electrosurgical excision procedure.

In this model, the OR coefficient for gestational age was  $-0.291$  ( $P < .01$ ; 95% CI,  $-0.448$  to  $-0.133$ ); the OR coefficient for cervical length in millimeters was  $-0.168$  ( $P < .01$ ; 95% CI,  $-0.280$  to  $-0.055$ ); and the OR for the [gestational age  $\times$  cervical length] interaction term was  $0.004$  ( $P = .07$ ; 95% CI,  $-0.001$  to  $0.008$ ). In the second model, we calculated the risk of spontaneous preterm birth before 32 weeks using the fFN test as well as gestational age. The interaction effect for [gestational age  $\times$  fFN] was not statistically significant ( $P > .50$ ), so we recalculated the model without an interaction term. The OR coefficient for gestational age was  $-0.198$  ( $P < .01$ ; 95% CI,  $-0.261$  to  $-0.135$ ), and the OR coefficient for fFN was  $2.29$  ( $P < .01$ ; 95% CI,  $1.56$  to  $3.02$ ). In the third model, we calculated the risk of spontaneous preterm birth before 32 weeks using both cervical length and fFN as independent variables, as well as gestational age. In this model, the 3-way interaction effect [fFN  $\times$  cervical length  $\times$  gestational age] was significant ( $P < .02$ ), so all lower-order interaction terms were retained in the model, for a total of 7 OR coefficients.

Finally, the risk of spontaneous preterm birth before 28 weeks was also significantly associated with a shorter cervical length measurement, positive fFN, as well as the gestational age at measurement. In the first model, we calculated the risk of spontaneous preterm birth before 32 weeks using gestational age and cervical length as predictive variables. In this model, the OR coefficient for gesta-

tional age was  $-0.476$  ( $P < .01$ ; 95% CI,  $-0.757$  to  $-0.194$ ); the OR coefficient for cervical length in millimeters was  $-0.249$  ( $P < .02$ ; 95% CI,  $-0.449$  to  $-0.049$ ); and the OR for the [gestational age  $\times$  cervical length] interaction term was  $0.006$  ( $P = .11$ ; 95% CI,  $-0.001$  to  $0.013$ ). In the second model, we calculated the risk of spontaneous preterm birth before 28 weeks using the fFN test as well as gestational age. The interaction effect for [gestational age  $\times$  fFN] was not statistically significant ( $P > .50$ ), so we recalculated the model without an interaction term. The OR coefficient for gestational age was  $-0.519$  ( $P < .01$ ; 95% CI,  $-0.700$  to  $-0.338$ ), and the OR coefficient for fFN was  $2.91$  ( $P < .01$ ; 95% CI,  $1.32$  to  $4.501$ ). In the third model, we calculated the risk of spontaneous preterm birth before 28 weeks using both cervical length and fFN as independent variables, as well as gestational age. In this model, no third- or second-order interaction effects were significant, so we report only first-order coefficients. The OR coefficient for gestational age was  $-0.611$  ( $P < .01$ ; 95% CI,  $-0.819$  to  $-0.403$ ); the OR coefficient for cervical length was  $-0.106$  ( $P < .01$ ; 95% CI,  $-0.159$  to  $-0.054$ ); and the OR coefficient for fFN was not significant ( $P > .20$ ). The likelihood of spontaneous preterm birth before 35, 32, and 28 weeks based on cervical length, fFN, combined cervical length/fFN, and gestational age at measurement are shown in Tables 2–4.

Using the results from this analysis, we created an online calculator that can be used to estimate the risk of

**Table 2.** Likelihood of Spontaneous Preterm Birth Before 35 Weeks in Twin Pregnancies, Based on Cervical Length Alone, fFN Alone, and Combined Cervical Length and fFN

| Parameter                  | Likelihood by Gestational Age, % |           |           |           |           |
|----------------------------|----------------------------------|-----------|-----------|-----------|-----------|
|                            | 22–23 6/7                        | 24–25 6/7 | 26–27 6/7 | 28–29 6/7 | 30–31 6/7 |
| Cervical length alone      |                                  |           |           |           |           |
| 0–10 mm                    | 55.0                             | 54.3      | 52.9      | 50.3      | 47.4      |
| 11–20 mm                   | 53.5                             | 52.2      | 49.9      | 46.2      | 43.2      |
| 21–30 mm                   | 50.3                             | 47.6      | 43.2      | 37.4      | 34.5      |
| 31–40 mm                   | 41.4                             | 36.2      | 29.7      | 24.6      | 23.4      |
| $\geq 41$ mm               | 29.5                             | 27.4      | 26.2      | 26.1      | 26.6      |
| fFN alone                  |                                  |           |           |           |           |
| fFN negative               | 38.8                             | 39.5      | 40.4      | 41.3      | 42.1      |
| fFN positive               | 54.7                             | 54.8      | 54.8      | 53.6      | 50.5      |
| Cervical length and fFN    |                                  |           |           |           |           |
| 0–10 mm, fFN negative      | 54.8                             | 53.7      | 51.6      | 47.8      | 44.4      |
| 0–10 mm, fFN positive      | 59.2                             | 59.3      | 58.6      | 55.3      | 50.5      |
| 11–20 mm, fFN negative     | 53.4                             | 51.7      | 48.6      | 43.5      | 39.8      |
| 11–20 mm, fFN positive     | 58.3                             | 58.4      | 58.1      | 55.4      | 50.3      |
| 21–30 mm, fFN negative     | 50.6                             | 47.4      | 42.0      | 34.3      | 30.4      |
| 21–30 mm, fFN positive     | 55.4                             | 55.4      | 54.4      | 51.9      | 49.8      |
| 31–40 mm, fFN negative     | 42.4                             | 36.7      | 29.1      | 22.3      | 20.3      |
| 31–40 mm, fFN positive     | 49.9                             | 49.7      | 49.6      | 49.6      | 49.6      |
| $\geq 41$ mm, fFN negative | 33.9                             | 29.7      | 26.7      | 26.1      | 27.4      |
| $\geq 41$ mm, fFN positive | 45.9                             | 45.7      | 47.1      | 48.6      | 49.6      |

spontaneous preterm birth in asymptomatic patients with twin pregnancies. For a patient with twin pregnancy, the cervical length measurement, fFN result, and gestational age can be inputted, and the calculator will display the esti-

mated gestational age at delivery, as well as the likelihood of spontaneous preterm birth before 37, 35, 34, 32, 30, and 28 weeks. The online calculator can be found at [www.mfmnyc.com/twin](http://www.mfmnyc.com/twin).

**Table 3.** Likelihood of Spontaneous Preterm Birth Before 32 Weeks in Twin Pregnancies, Based on Cervical Length Alone, fFN Alone, and Combined Cervical Length and fFN

| Parameter               | Likelihood by Gestational Age, % |           |           |           |           |
|-------------------------|----------------------------------|-----------|-----------|-----------|-----------|
|                         | 22–23 6/7                        | 24–25 6/7 | 26–27 6/7 | 28–29 6/7 | 30–31 6/7 |
| Cervical length alone   |                                  |           |           |           |           |
| 0–10 mm                 | 44.1                             | 40.4      | 35.2      | 30.2      | 29.0      |
| 11–20 mm                | 38.8                             | 33.5      | 26.4      | 19.9      | 19.3      |
| 21–30 mm                | 28.8                             | 21.3      | 12.5      | 6.5       | 6.7       |
| 31–40 mm                | 10.5                             | 5.1       | 1.9       | 0.9       | 1.2       |
| ≥41 mm                  | 3.7                              | 3.0       | 3.0       | 3.6       | 4.7       |
| fFN alone               |                                  |           |           |           |           |
| fFN negative            | 9.6                              | 12.1      | 15.2      | 18.4      | 21.4      |
| fFN positive            | 49.1                             | 47.3      | 43.9      | 38.8      | 37.7      |
| Cervical length and fFN |                                  |           |           |           |           |
| 0–10 mm, fFN negative   | 44.8                             | 40.8      | 34.5      | 27.9      | 26.8      |
| 0–10 mm, fFN positive   | 54.8                             | 53.4      | 50.5      | 45.9      | 42.7      |
| 11–20 mm, fFN negative  | 39.9                             | 34.3      | 25.9      | 17.8      | 17.1      |
| 11–20 mm, fFN positive  | 52.3                             | 50.3      | 46.5      | 40.5      | 37.6      |
| 21–30 mm, fFN negative  | 30.4                             | 22.4      | 12.5      | 5.1       | 4.8       |
| 21–30 mm, fFN positive  | 47.5                             | 44.7      | 41.0      | 39.6      | 40.6      |
| 31–40 mm, fFN negative  | 12.5                             | 6.1       | 1.9       | 0.7       | 0.8       |
| 31–40 mm, fFN positive  | 42.2                             | 39.5      | 39.5      | 42.0      | 44.1      |
| ≥41 mm, fFN negative    | 8.2                              | 4.8       | 3.4       | 3.7       | 5.5       |
| ≥41 mm, fFN positive    | 40.1                             | 38.1      | 40.0      | 43.5      | 45.8      |

**Table 4.** Likelihood of Spontaneous Preterm Birth Before 28 Weeks in Twin Pregnancies, Based on Cervical Length Alone, fFN Alone, and Combined Cervical Length and fFN

| Parameter               | Likelihood by Gestational Age, % |           |           |
|-------------------------|----------------------------------|-----------|-----------|
|                         | 22–23 6/7                        | 24–25 6/7 | 26–27 6/7 |
| Cervical length alone   |                                  |           |           |
| 0–10 mm                 | 30.3                             | 23.8      | 16.3      |
| 11–20 mm                | 21.7                             | 14.3      | 7.1       |
| 21–30 mm                | 9.4                              | 3.8       | 0.7       |
| 31–40 mm                | 0.4                              | 0.0       | 0.0       |
| ≥41 mm                  | 0.0                              | 0.0       | 0.0       |
| fFN alone               |                                  |           |           |
| fFN negative            | 0.4                              | 0.9       | 1.9       |
| fFN positive            | 41.7                             | 37.4      | 30.2      |
| Cervical length and fFN |                                  |           |           |
| 0–10 mm, fFN negative   | 32.2                             | 25.2      | 16.3      |
| 0–10 mm, fFN positive   | 48.8                             | 45.4      | 39.8      |
| 11–20 mm, fFN negative  | 23.9                             | 15.8      | 7.3       |
| 11–20 mm, fFN positive  | 44.1                             | 39.4      | 31.6      |
| 21–30 mm, fFN negative  | 11.2                             | 4.6       | 0.8       |
| 21–30 mm, fFN positive  | 37.1                             | 31.1      | 24.9      |
| 31–40 mm, fFN negative  | 0.8                              | 0.1       | 0.0       |
| 31–40 mm, fFN positive  | 32.3                             | 26.9      | 27.1      |
| ≥41 mm, fFN negative    | 0.4                              | 0.1       | 0.0       |
| ≥41 mm, fFN positive    | 32.7                             | 28.7      | 31.1      |

## Discussion

In this study, we report the likelihood of spontaneous preterm birth before 35, 32, and 28 weeks in twin pregnancies, based on the cervical length alone, fFN alone, the combined cervical length/fFN results, and the gestational age at testing. This information can potentially be important to obstetricians who care for twin pregnancies. Most prior studies in twin pregnancies defined a short cervical length and then assigned risk based on the presence or absence of a short cervical length at a given gestational age period.<sup>5–8</sup> However, since the length of the cervix is a continuous variable, the risk would be higher with shorter cervical length measurements and lower with longer cervical length measurements. Additionally, similar to singleton pregnancies,<sup>9</sup> the gestational age at cervical length measurement in twin pregnancies also influences the risk.<sup>10</sup> For example, in our cohort, a cervical length of 11 to 20 mm at 26 weeks was associated with a 49.9%, 26.4%, and 14.3% risk of spontaneous preterm birth before 35, 32, and 28 weeks, respectively. The same cervical length measurement at 22 weeks had a 53.5%, 38.8%, and 21.7% risk of spontaneous preterm birth before 35, 32, and 28 weeks.

Additionally, fFN is another biomarker associated with preterm birth in twins and may in fact be a stronger predictor of preterm birth in twin pregnancies than cervical length.<sup>6,13</sup> Therefore, prediction tables used to estimate the likelihood of preterm birth that include fFN results should give more information than tables with cervical length data alone. Our results demonstrate this principle. For example, in the same hypothetical cervical length of 11 to 20 mm at 26 weeks, the risk of spontaneous preterm birth before 35 weeks is 42% if fFN is negative and 54.4% if fFN is positive. For spontaneous preterm birth before 32 weeks, these risks are 25.9% if fFN is negative and 46.5% if fFN is positive. For spontaneous preterm birth before 28 weeks, these risks are 7.3% if fFN is negative and 31.3% if fFN is positive. Therefore, when trying to predict the risk of preterm birth for patients with twin pregnancies, our data include several variables and can be used clinically.

We were also able to create an online calculator to estimate the risk of spontaneous preterm birth and the gestational age at delivery for twins, based on the cervical length measurement, fFN result, and gestational age. This calculator can be used for any asymptomatic patient with twins in whom this assessment is desired.

It is well known that the knowledge of an increased risk of preterm birth does not lead to a reduction in the incidence of preterm birth. Preterm birth is a process that can rarely be halted, and tocolytics are typically effective

only to prolong pregnancy long enough for corticosteroid administration. Therefore, we would not expect that routine screening for preterm birth would substantially change its frequency. In fact, when comparing two large populations of twin pregnancies, one of which underwent routine cervical length and fFN screening and the other of which only underwent these tests as clinically indicated, no difference was found in the gestational age at delivery or in the likelihood of preterm birth before 34 weeks.<sup>14</sup>

However, despite the fact that screening for preterm birth does not lead to a reduction in preterm birth, there are several reasons why one may potentially choose to screen patients with twin pregnancies. First, screening may be helpful in more outlying areas regarding decisions of whether to transfer care to a facility with increased neonatal supportive care and maternal-fetal medicine specialists before the onset of preterm labor, rather than waiting for patients who actually present with preterm labor. Second, patients may desire this information to prepare themselves mentally and practically if they are indeed at high risk for preterm birth. Some patients may choose not to have this information to avoid potentially unnecessary anxiety, but others with busy careers, other children, or travel plans may find this information valuable, and our data allow them the opportunity to assess their risk in an evidence-based manner. Finally, and perhaps most importantly, the knowledge that a patient is at increased risk for preterm birth could potentially improve antenatal corticosteroid administration rates to those who deliver before 34 weeks, which is specifically listed by the American College of Obstetricians and Gynecologists as a proposed performance measure in the management of preterm labor.<sup>15</sup> Although one might assume that this process could be accomplished simply by administering corticosteroids to women with preterm labor diagnosed clinically, the published studies suggest that this strategy does not lead to very high rates of corticosteroid exposure.<sup>16–20</sup> In fact, one recent study suggests that routine cervical length and fFN screening in twin pregnancies is associated with improved administration and timing of steroids, compared to twin pregnancies that do not undergo routine cervical length and fFN screening.<sup>14</sup> In this study, the rate of corticosteroid exposure to twins born before 34 weeks was significantly higher in the routine-screening group (91.3% versus 74.7%;  $P = .005$ ), without increased corticosteroid exposure to twins born before 37 weeks. The study also found that the timing of corticosteroid exposure was improved in the routine-screening group, which was defined both as within 1 to 14 days of delivery (54.7% versus 34.3%;  $P = .012$ ) as well as within 1 to 7 days of delivery (39.6% versus 24.3%;

$P = .035$ ). Therefore, obstetricians may be able to use the information in our tables to improve administration rates and timing of corticosteroids to patients with twins who deliver before 34 weeks. Finally, those pregnancies deemed at low risk for spontaneous preterm birth may be able to avoid unnecessary interventions and hospital evaluations for nonspecific symptoms such as pelvic pressure, contractions, and back pain, which are all common to twin pregnancies.

However, we cannot conclude from these data that cervical length and fFN screening is beneficial in patients with twin pregnancies. Ultimately, the final answer to whether routine screening with fFN and cervical length is clinically useful and cost-effective would need to come from a randomized trial. Until that point, the decision of whether to use these tests should be individualized on the basis of each specific patient or patient population. Should an obstetrician decide that screening is appropriate, our data provide a user-friendly and evidence-based estimate of the likelihood of preterm birth that can serve as an adjunct in counseling patients, particularly those who desire a more tangible estimation of risk.

Strengths to our study included the large sample size. By having 2406 cervical length measurements and 2279 fFN assessments, we were able to model the risk of preterm birth with high statistical significance. Also, since all of these tests were done in a single maternal-fetal medicine practice, there should be minimal variation between the samples with regard to acquisition standards. This study was not without limitations. Our patient population was relatively homogeneous, making extrapolation to other populations potentially inaccurate. Also, patients and providers were not blinded to cervical length and fFN results. However, as stated above, there is no evidence to suggest that this knowledge affects the gestational age at delivery or the likelihood of preterm birth. Also, for logistic reasons, not every patient had the exact same screening frequency. We typically screen every 2 weeks, but some patients are unable to come at exactly that frequency. This variability could potentially introduce bias as well. Finally, since this study was retrospective, ideally, the models we present will be tested prospectively in several populations to ensure their validity and assess outcomes in patients when using this tool.

In conclusion, we found that in twin pregnancies, the cervical length measurement, fFN result, and gestational age at testing are all associated with the risk of preterm birth. Our tables and online calculator can potentially be used as tools for patients with twin pregnancies and their providers to assess the risk of preterm birth.

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