The Independent Association of a Short Cervix, Positive Fetal Fibronectin, Amniotic Fluid Sludge, and Cervical Funneling with Spontaneous Preterm Birth in Twin Pregnancies

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Abstract

Objective To estimate the independent association of a short cervical length (CL), positive fetal fibronectin (fFN), amniotic fluid (AF) sludge, and cervical funneling with spontaneous preterm birth in twin pregnancies.

Methods Retrospective cohort study of twin pregnancies managed by a single maternal–fetal medicine practice from June 2005 to February 2014. All patients underwent transvaginal sonographic CL and fFN testing. We reviewed all images from the first CL at $22^{0/7}$ to $25^{6/7}$ weeks for the presence of (1) a short CL, which is defined as $\leq$25 mm, (2) AF sludge, and (3) cervical funneling, and also recorded (4) the fFN result from that time. Image reviewers were blinded to pregnancy outcomes. Patients with cerclage were excluded. Using logistic regression, we calculated the independent association between these four biomarkers and spontaneous preterm birth.

Results A total of 635 patients with twin pregnancies were included. The markers independently associated with spontaneous preterm birth <35 weeks were short CL (adjusted odds ratio [aOR]: 10.73; 95% confidence interval [CI]: 3.21–35.81), positive fFN (aOR: 3.25; 95% CI: 1.13–9.33), and AF sludge (aOR: 2.11; 95% CI: 1.04–4.27). Similarly, these three markers were independently associated with earlier gestational ages at delivery. Cervical funneling was not independently associated with spontaneous preterm birth <35 weeks nor gestational age at delivery. The risk of spontaneous preterm birth increased significantly with the number of positive biomarkers (short CL, positive fFN, and AF sludge).

Conclusion In twin pregnancies, a short CL, positive fFN, and AF sludge are independently associated with spontaneous preterm birth. Cervical funneling is not independently associated with spontaneous preterm birth in twins.

Keywords
- twins
- cervical length
- fetal fibronectin
- cervical funneling
- amniotic fluid sludge
- preterm birth

Cervical length (CL) and fetal fibronectin (fFN) are both significantly associated with spontaneous preterm birth in low- and high-risk pregnancies.[1–4] The use of these screening tests, specifically CL, has led to the implementation of interventions, such as cervical cerclage, pessary, or vaginal progesterone, that may reduce the risk of preterm birth in certain patients.[5–7] When

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evaluating CL by transvaginal ultrasound, other sonographic findings have been correlated with the risk of preterm birth, namely amniotic fluid (AF) sludge[8] and cervical funneling.[9] Although funneling is associated with an increased risk of preterm birth, its independent association with preterm birth after controlling for the CL itself has not been consistently demonstrated.[10,11] AF sludge refers to particulate matter in AF; when densely concentrated around the internal cervical os, it has been found to be a risk factor for preterm birth, preterm premature rupture of membranes, microbial invasion of the amniotic cavity, and histologic chorioamnionitis in singleton pregnancies.[12] The combination of a short cervix $<$ 25 mm and AF sludge in singletons is associated with a higher risk of preterm birth than a short cervix alone.[13]

Based on several large studies, CL and fFN are both significantly associated with the risk of spontaneous preterm birth in twin pregnancies.[14–16] However, there are fewer studies investigating the significance of AF sludge and cervical funneling in twin pregnancies. In 2014, Boyer et al found that in twin pregnancies with a CL of 25 mm or less between 16 and 26 weeks, the presence of AF sludge was significantly associated with a higher risk of preterm birth.[17] As in singletons, it remains uncertain if cervical funneling in twins remains an independent risk of preterm birth after controlling for the CL.[18] There are also few data in twin pregnancies looking at the independent association of CL, fFN, AF sludge, and cervical funneling, when all four biomarkers are tested on the same patient. In our study, we sought to determine the independent association of CL, fFN, AF sludge, and cervical funneling with the risk of spontaneous preterm birth in twin pregnancies.

Methods

After Biomedical Research Alliance of New York Institutional Review Board approval was obtained, we reviewed the charts of all patients with twin pregnancies delivered by a single maternal–fetal medicine practice between June 2005 (when our electronic medical record was established) and February 2014. We excluded patients with a cerclage, 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 last menstrual period and confirmed by ultrasound in all patients. The pregnancy was redacted if there was a $>$5 day discrepancy up to 14 weeks or a $>$7 day discrepancy after 14 weeks. If the pregnancy was the result of in vitro fertilization (IVF), gestational age was determined from IVF dating.

In our practice, patients with twin pregnancies are followed with serial CL and fFN testing every 2 to 4 weeks until 32 weeks.[19] For this study, to control for gestational age at measurement, for each patient we only included the first CL and fFN obtained between $22^{0/7}$ and $25^{6/7}$ weeks. All CL assessments and fFN testing were done in an outpatient setting on asymptomatic patients. Measurements of CL were performed using a 4- to 8-MHz transvaginal probe with an empty bladder according to criteria established by Iams et al.[1] The shortest functional CL was used as this has been found to be the most reproducible measurement.[20] Fetal fibronectin testing was performed without the use of a speculum using a published protocol[21] at least 24 hours from the last reported intercourse or endovaginal ultrasound. 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.

Two authors (J. S. and W. B.) who were blinded to clinical outcomes reviewed the ultrasound images from the CL measurement at $22^{0/7}$ to $25^{6/7}$ weeks to determine the CL, the presence and size of a cervical funnel, and the presence or not of AF sludge. A short cervix was defined as $\leq$25 mm. Cervical funneling was defined according the criteria defined by Berghella et al,[10] which is membrane prolapse greater than or equal to 5 mm (►**Fig. 1**). The presence of AF sludge was based on the criteria defined by Kusanovic et al[13] as the

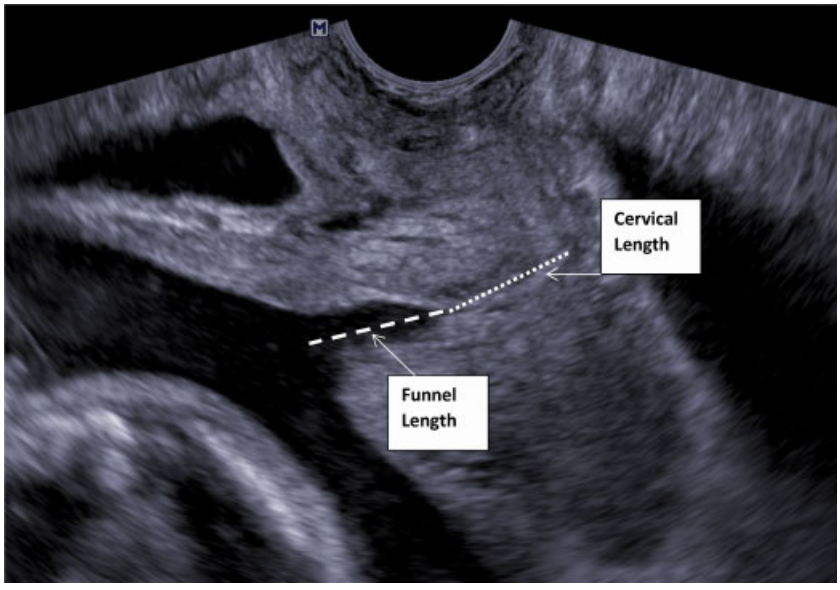

Fig. 1 Cervical funneling.

presence of dense aggregates of particulate matter in proximity to the internal cervical os (►**Fig. 2**). Fetal fibronectin results from the same gestational age as the CL were obtained from laboratory reports. Any discrepancies between the two reviewers were resolved by a third author (N. F.).

The primary outcome was spontaneous preterm birth <35 weeks, defined as preterm birth resulting from premature labor or premature rupture of membranes. Patients with an indicated preterm birth <35 weeks (due to preeclampsia or fetal growth restriction for example) were censored from this analysis. We also looked at gestational age at delivery. For each outcome, we compared patients with and without each individual positive biomarker (short CL, positive fFN, AF sludge, cervical funneling) using the chi-square test or Student's *t*-test, as appropriate. We then performed a logistic regression analysis with the outcome as the dependent variable and the four biomarkers as the independent variables. Adjusted odds ratios, 95% confidence intervals, and adjusted *p*-values were calculated (IBM SPSS for Windows 22.0, Armonk, NY). Then, after determining which biomarkers were independently associated with spontaneous preterm birth (short CL, positive fFN, AF sludge), we calculated the risk of spontaneous preterm birth at several gestational age cutoffs based on the presence of none, one, two, or three positive biomarkers at $22^{0/7}$ to $25^{6/7}$ weeks. For this analysis, we examined spontaneous preterm birth <35 weeks, <34 weeks, <32 weeks, <30 weeks, <28 weeks, and gestational age at delivery. For this analysis, patients with an indicated preterm birth 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 <32 weeks, but was considered as not having a spontaneous preterm birth <30 and <28 weeks. One-way analysis of variance and chi-square tests were used for trend. We performed the analysis for all spontaneous preterm births, and then a secondary analysis for all preterm births including all indicated preterm births as well.

Table 1 Characteristics of the twin population at $22^{0/7}$ to $25^{6/7}$ weeks

Characteristic	N (%) or mean (± SD)
No. of patients	635
Maternal age	34.3 ± 6.5 y
Prepregnancy body mass index	23.7 ± 4.6 kg/m^2
In vitro fertilization	411 (64.7%)
Chorionicity	
Dichorionic–diamniotic	547 (86.1%)
Monochorionic–diamniotic	88 (13.9%)
Multifetal pregnancy reduction	42 (6.6%)
White ethnicity	546 (86.0%)
Prior term birth	200 (31.5%)
Prior preterm birth	47 (7.4%)
History of LEEP or cone biopsy	20 (3.1%)
Mullerian anomaly	16 (2.5%)
Short cervical length ≤25 mm	45 (7.1%)
Fetal fibronectin (positive)	20 (3.1%)
Amniotic fluid sludge	61 (9.6%)
Cervical funneling	41 (6.5%)

Abbreviations: LEEP, loop electrosurgical excision procedure; SD, standard deviation.

Results

A total of 635 patients with twin pregnancies were included. The characteristics of the population are described in ►**Table 1**. The population was mostly white and 64.7% underwent IVF. At $22^{0/7}$ to $25^{6/7}$ weeks, the incidences of the biomarkers were–short CL: 45/635 (7.1%); positive fFN: 20/

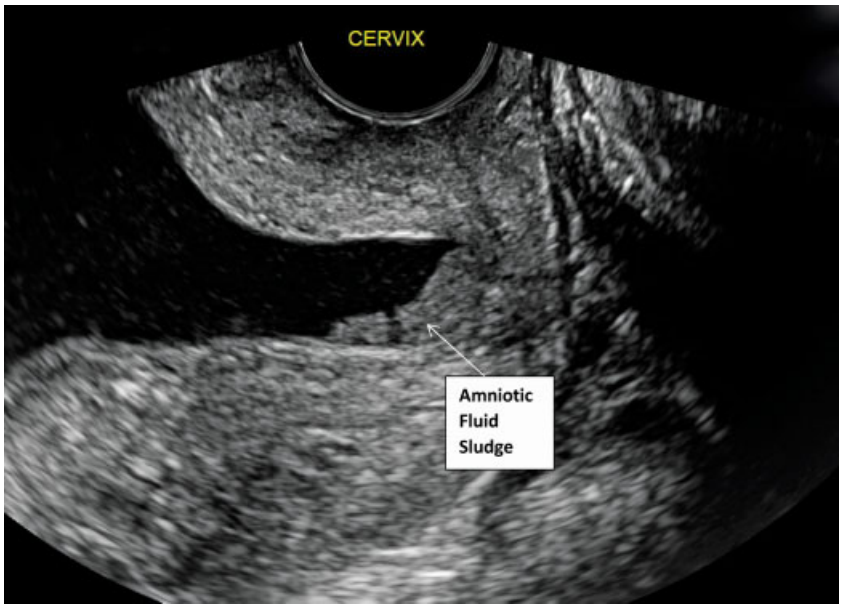

Fig. 2 Amniotic fluid sludge.

Table 2 Association between short cervical length, positive fetal fibronectin, amniotic fluid sludge, and cervical funneling in twin pregnancies at $22^{0/7}$ to $25^{6/7}$ weeks with spontaneous preterm birth <35 weeks

Biomarker	Risk of spontaneous preterm birth <35 wk if biomarker is positive (%)	Risk of spontaneous preterm birth <35 wk if biomarker is negative (%)	Unadjusted *p*-value	aOR (95% CI)[a]
Short CL (≤25 mm)	56.8	15.3	<0.001	10.73 (3.21–35.81)
Positive fFN	57.9	17.1	<0.001	3.25 (1.13–9.33)
Amniotic fluid sludge	36.8	16.5	<0.001	2.11 (1.04–4.27)
Cervical funnel	46.2	16.5	<0.001	0.35 (0.89–1.35)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CL, cervical length; fFN, fetal fibronectin.
[a]Adjusted for all biomarkers in the table.

635 (3.1%); AF sludge: 61/635 (9.6%); and cervical funneling: 41/635 (6.5%). On unadjusted analysis, all four biomarkers were significantly associated with spontaneous preterm birth <35 weeks (►**Table 2**) and gestational age at delivery (►**Table 3**). On regression analyses, the biomarkers independently associated with spontaneous preterm birth <35 weeks and gestational age at delivery were short CL, positive fFN, and AF sludge (►**Tables 2** and **3**). Cervical funneling was not independently associated with spontaneous preterm birth <35 weeks nor with gestational age at delivery.

Using the three biomarkers independently associated with spontaneous preterm birth (short CL, positive fFN, AF sludge), we calculated the risk of spontaneous preterm birth based on the presence of no, one, two, or three positive biomarkers at $22^{0/7}$ to $25^{6/7}$ weeks and the results are shown in ►**Table 4**. For all outcomes measured, the risk of spontaneous preterm birth increased significantly and the gestational age at delivery decreased significantly with the number of positive biomarkers. Results did not differ for any of the analyses when we included all indicated preterm births as well (data not shown).

Discussion

In this study of twin pregnancies at $22^{0/7}$ to $25^{6/7}$ weeks, short CL, AF sludge, and positive fFN were all independently associated with spontaneous preterm birth. The risk of

Table 3 Association between short cervical length, positive fetal fibronectin, amniotic fluid sludge, and cervical funneling in twin pregnancies at $22^{0/7}$ to $25^{6/7}$ weeks with gestational age at delivery

Biomarker	Gestational age at delivery if biomarker positive	Gestational age at delivery if biomarker negative	*p*-Value	Adjusted *P*-value[a]
Short CL (≤25 mm)	33.0 ± 4.2	36.0 ± 2.2	<0.001	<0.001
Positive fFN	32.7 ± 4.2	35.9 ± 2.4	<0.001	<0.001
Amniotic fluid sludge	34.3 ± 3.9	36.0 ± 2.3	0.002	<0.001
Cervical funnel	33.3 ± 4.5	36.0 ± 2.2	0.001	0.95

Abbreviations: CL, cervical length; fFN, fetal fibronectin.
[a]Adjusted for all biomarkers in the table.

Table 4 Risk of spontaneous preterm birth in twin pregnancies based on the number of positive biomarkers at $22^{0/7}$ to $25^{6/7}$ weeks

Outcome	No positive biomarkers[a] ($N = 536$)	One positive biomarker[a] ($N = 76$)	Two positive biomarkers[a] ($N = 19$)	Three positive biomarkers[a] ($N = 4$)	*P*-value
Gestational age at delivery	36.1 ± 2.1	35.0 ± 3.0	32.4 ± 4.5	28.1 ± 3.5	<0.001
SPTB < 28 wk	1.1%	6.6%	15.8%	75.0%	<0.001
SPTB < 30 wk	1.7%	6.6%	26.3%	75.0%	<0.001
SPTB < 32 wk	3.2%	11.8%	36.8%	75.0%	<0.001
SPTB < 34 wk	9.0%	20.3%	52.6%	100.0%	<0.001
SPTB < 35 wk	14.2%	32.9%	57.9%	100.0%	<0.001

Abbreviation: SPTB, spontaneous preterm birth.
[a]Positive biomarkers: cervical length ≤ 25 mm, fetal fibronectin is positive, and amniotic fluid sludge is present.

spontaneous preterm birth increased significantly and the gestational age at delivery decreased significantly with each additional positive biomarker. For example, for patients with a normal CL, negative fFN, and no evidence of AF sludge on ultrasound, the mean gestational age at delivery was 36.1 weeks, with a 1.1% risk of delivering prior to 28 weeks. In contrast, patients with three positive biomarkers had a mean gestational age at delivery of 28.1 weeks, with a 75% chance of delivering prior to 28 weeks. As in previous studies, after controlling for the CL, cervical funneling was not independently associated with spontaneous preterm birth.

Short cervix and positive fFN have consistently been shown to be risk factors for spontaneous preterm birth in singleton and twin pregnancies, and our study supports these finding. Additionally, similar to prior studies, although cervical funneling is associated with spontaneous preterm birth on univariate analysis, this only appears to be due to its association with a short CL. After controlling for CL, the cervical funneling itself is not independently associated with spontaneous preterm birth. AF sludge is a newer sonographic marker, named after its similar appearance to biliary sludge. Biliary sludge is characterized by low-level echoes that layer in the dependent portion of the gallbladder and is associated with microbial infection. In 2005, Espinoza et al sought to determine the prevalence and clinical significance of AF sludge and concluded that it is associated with intra-amniotic infection and preterm delivery.[12] In several studies on AF sludge in singleton pregnancies, preterm delivery rates were significantly increased in patients in which sludge was present.[13,22,23] In 2014, Boyer et al examined the significance of AF sludge in twin pregnancies.[17] Their study demonstrated that in twin pregnancies with a short cervix (defined as CL $\leq$ 25 mm at 16–26 weeks), the presence of AF sludge increased the risk for preterm delivery, chorioamnionitis, neonatal morbidity, and neonatal mortality. Our study supports their finding of the significant association of AF sludge with preterm birth in twin pregnancies. However, our study differs from Boyer et al in that we included all twin pregnancies at $22^{0/7}$ to $25^{6/7}$ weeks, and not just those with a short cervix. We actually had more patients with AF sludge ($n = 61$, 9.6%) than CL $\leq$ 25 mm ($n = 45$, 7.1%). Therefore, our study adds to the findings of Boyer et al by demonstrating that AF sludge is a risk factor for spontaneous preterm birth in twins independent of a short CL. Additionally, since we included CL, AF sludge, and fFN results, the percent risk of spontaneous preterm birth at different gestational age cutoffs can be calculated based on the presence or absence of these three biomarkers at 22 to 26 weeks.

Although it is possible to predict the risk of spontaneous preterm birth in twin pregnancies, at this time it is unknown if the routine use of these biomarkers is associated with improved neonatal outcomes, as interventions designed to reduce the risk of preterm birth have mostly shown limited or no benefit. However, there is recent data to support the use of vaginal progesterone[24] and cervical pessaries[25,26] in twin pregnancies with a short cervix. Another potential benefit to preterm birth risk stratification in twin pregnancies is the ability to select patients for transfer to a higher care facility with increased neonatal supportive care and maternal fetal medicine specialists. Some patients may also prefer simply to have this information to prepare themselves mentally and practically if they are at high risk for an early preterm birth. Finally, we have shown previously from retrospective data that these screening tests could potentially improve antenatal corticosteroid administration rates to twins delivered prior to 34 weeks.[27] Ultimately, however, until a prospective study that randomizes twin pregnancies to routine screening or no screening demonstrates significant benefit with routine screening, the decision whether or not to use these tests routinely needs to be individualized.

Strengths of our study include a large sample size, with all patients evaluated at a uniform gestational age and managed similarly in one maternal–fetal medicine practice. Also, all images were reviewed for accuracy, as opposed to relying on ultrasound reports. Although there is a measure of subjectivity in the determination of AF sludge and cervical funneling, reviewers of ultrasound images were blinded to pregnancy outcomes. Our study is limited by its retrospective nature, as neither patients nor physicians were blinded to the ultrasound findings or fFN results, and a homogenous study population, including mostly white patients who conceived via IVF. Further studies could examine the effect of gestational age on prediction of spontaneous preterm birth, as well as other potential markers for spontaneous preterm birth at this gestational age. As stated earlier, prospective studies randomizing patients to CL and fFN screening could ultimately help determine what benefit, if any, is associated with their routine use.

In conclusion, in twin pregnancies at $22^{0/7}$ to $25^{6/7}$ weeks, CL $\leq$ 25 mm, a positive fFN, and AF sludge are independently associated with spontaneous preterm birth, whereas cervical funneling is not independently associated with spontaneous preterm birth in twins. Each additional positive marker further increases the risk of spontaneous preterm birth.

Note
The study was presented at the Annual Scientific Meeting of the Society for Maternal-Fetal Medicine, Atlanta, GA, February 4–6, 2016 (poster presentation).

Conflict of Interest
None.

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