

ORIGINAL ARTICLE

Routine cervical length and fetal fibronectin screening in asymptomatic twin pregnancies: is there clinical benefit?*

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Abstract

Objective: To determine whether routine cervical length (CL) and fetal fibronectin (fFN) screening is associated with improved clinical outcomes in asymptomatic patients with twin pregnancies.

Study design: We compared outcomes between two large cohorts of twin pregnancies who delivered in New York City from 2003 to 2012. One cohort ($n = 532$) was managed by a single group practice, delivered at one large academic medical center, and underwent routine serial CL and fFN screening. The second cohort ($n = 456$) delivered at a second large academic center and only underwent CL and fFN testing as clinically indicated. Outcomes measured include cerclage placement, preterm birth (PTB), spontaneous PTB (sPTB), and antenatal corticosteroid (ACS) exposure.

Results: Rates of cerclage placement, PTB, and sPTB were similar between the two groups. However, routine CL and fFN screening was associated with improved rates of ACS exposure in patients who delivered <34 weeks (91.3% versus 74.7%, $p = 0.005$) and 34–36 6/7 weeks (41.3% versus 13.9%, $p < 0.001$) without increased ACS exposure in women who delivered at term. In patients who delivered <34 weeks, routine CL and fFN screening was significantly associated with improved rates of ACS exposure within 1–14 days of delivery and within 1–7 days of delivery.

Conclusion: In twin pregnancies, routine CL and fFN screening does not reduce the risk of PTB or sPTB. However, the routine use of these tests is associated with significantly improved ACS exposure and timing for women who deliver preterm without increasing ACS exposure to women who deliver at term.

Background and objective

Twin pregnancies now comprise 3.3% of all live births in the United States [1] and are continuously on the rise due to the increased use of assisted reproductive technologies. Preterm birth (PTB) less than 37 weeks occurs in 58.8% of twin pregnancies and at less than 32 weeks' gestation in 11.4% of twin pregnancies [1], accounting for the majority of morbidity and mortality associated with twin gestations.

Prediction of spontaneous preterm birth using cervical length (CL) measurement and fetal fibronectin (fFN) has

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been extensively studied in low- and high-risk singleton pregnancies [2–4]. A short CL or positive fFN is associated with preterm birth in both symptomatic and asymptomatic patients with singleton pregnancies. Shortened CL and positive fFN have also been shown to be significantly associated with preterm birth in twin pregnancies as well [5–8].

Although CL and fFN are both associated with preterm birth in twin pregnancies, it remains uncertain whether routine screening using these screening tests is associated with improved outcomes, such as preterm birth prevention. If not, their routine use may not be justified. It is also possible that the routine use of these tests is associated with improved outcomes aside from preterm birth prevention, such as increased antenatal corticosteroid (ACS) exposure in women who deliver preterm, which has been shown to improve outcomes in premature neonates. In fact, the ability to administer antenatal corticosteroids prior to preterm birth <34 weeks is specifically listed by the American Congress of Obstetricians and Gynecologists (ACOG) as the Proposed Performance Measure in the management of

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preterm labor [9]. Randomized data are lacking in regard to this important clinical question. If routine CL and fFN screening are associated with certain improved outcomes, they could be considered appropriate in all patients with twin pregnancies. However, if they are not associated with improved outcomes, their routine use would not be justified in most patients. In this study, we sought to determine whether routine CL and fFN screening is associated with improved clinical outcomes in asymptomatic patients with twin pregnancies.

Materials and methods

Two cohorts of patients with twin pregnancies managed in two tertiary care centers in New York City between 2003 and 2012 were compared in this retrospective study. One cohort was managed by a single group practice including maternal fetal medicine specialists and general obstetricians and gynecologists and delivered at one large academic medical center. This cohort underwent routine CL screening every 2–3 weeks from 16 to 32 weeks and fFN screening every 2–3 weeks from 22 to 32 weeks. The second cohort included all twin pregnancies delivered at a second large academic center. The patients were under the care of several groups of doctors, including maternal fetal medicine specialists and general obstetricians and gynecologists. The second cohort did not undergo routine CL or fFN screening; rather, this cohort of patients only had these tests done as deemed clinically indicated. For both cohorts, all ultrasounds, antepartum testing, antepartum admissions and antepartum complications were managed either directly by, or in consultation with, maternal fetal medicine specialists.

Inclusion criteria were age ≥ 18 years, delivery >24 weeks' gestation, and complete data being available. Pregnancies with aneuploidy, twin–twin transfusion syndrome, or major fetal anomalies discovered before or after birth were excluded from our analysis. Gestational age was based on a last menstrual period (LMP) and confirmed by ultrasound or based on a first-trimester ultrasound in all patients using the same criteria in both institutions. Pregnancies were re-dated if there was a >5 day discrepancy between LMP and ultrasound dating up to 14 weeks or a >7 day discrepancy after 14 weeks. Gestational age of pregnancies resulting from *in vitro* fertilization (IVF) was based on IVF dating. Patients in both cohorts underwent growth ultrasounds every 4 weeks or every 2–3 weeks for monochorionic twins. If intrauterine growth restriction was suspected, ultrasound assessment of fetal weight was performed every 2 weeks. Additionally, from 32 weeks until delivery, biophysical profiles or non-stress testing were performed weekly, or more frequently if indicated. In both cohorts, betamethasone was the ACS of choice, administered intramuscularly as two 12 mg doses given 24 h apart.

In the routine screening cohort, CL was measured every 2–3 weeks from 16 to 32 weeks. 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. [2].

In the routine screening cohort, fetal fibronectin testing was performed every 2–3 weeks from 22 to 32 weeks without the use of a speculum using a published protocol [10] at least

24 h from the last reported intercourse or endovaginal ultrasound. Testing was not performed in the setting of vaginal bleeding. Swabs were sent for evaluation using a fetal fibronectin assay, and a concentration of 50 ng/mL or greater was considered positive.

In the routine screening cohort, patients were not routinely hospitalized when they had a short CL or positive fFN unless they were actually in preterm labor (regular contractions and cervical change on physical exam). Patients with either a short CL (≤ 25 mm) or positive fFN are evaluated for preterm contractions and typically undergo ACS administration as outpatients if they have two out of three positive tests (short CL, positive fFN, regular contractions). Patients in preterm labor were hospitalized and given tocolytics in addition to ACS administration, but they were not advised to be on complete bed rest. Patients in the indicated testing cohort were managed at their providers' discretion based on symptoms, testing results and clinical findings.

Outcomes measured include cerclage placement, PTB <34 weeks, spontaneous PTB (sPTB) <34 weeks, ACS exposure overall, as well as "optimal" ACS exposure, defined both as ACS exposure within 1–14 days of delivery, as well as ACS exposure within 1–7 days of delivery. Patients who delivered prior to the completion of ACS exposure (prior to completion of the second injection, which was 24 h after the first injection) were considered as zero days from exposure and therefore, not optimal. Institutional review board approval was obtained at both centers prior to conducting the study. Chi-square test and Student's *t* test were used where appropriate (SPSS for Windows 16.0, Chicago, IL, 2007). A *p*-value of ≤ 0.05 was considered significant.

Results

A total of 988 patients were included in the study, 532 in the routine-screening cohort and 456 in the clinically indicated testing cohort. Demographic characteristics were similar between the two groups with the exception of a younger maternal age and greater number of Caucasian women in the routine-screening cohort (Table 1). The routine-screening cohort also had a higher proportion of patients with a prior preterm birth, although the absolute proportions in both cohorts were low (7.6% versus 3.8%, *p* = 0.018).

Pregnancy outcomes are listed in Table 2. Routine use of CL and fFN was not associated with a decreased incidence of PTB <34 weeks or sPTB <34 weeks, nor was it associated with an increased likelihood of cerclage placement. However, routine CL and fFN screening was significantly associated with improved rates of ACS exposure, both in patients who delivered at <34 weeks (91.5% versus 73.2%, *p* = 0.002) and in patients who delivered between 34 and 36 6/7 weeks (41.3% versus 13.9%, *p* < 0.001). ACS exposure in women who delivered at term (≥ 37 weeks) was low and was not greater in the routine screening group.

In regards to timing of ACS exposure, routine use of CL and fFN was significantly associated with improved ACS exposure within 1–14 days of delivery (54.7% versus 34.3%, *p* = 0.012), as well as ACS exposure within 1–7 days of delivery (39.6% versus 24.3%, *p* = 0.035) (Table 2). No patients in either cohort received more than two courses of ACS.

Table 1. Baseline characteristics, based on the utilization of routine CL and fFN screening in twin pregnancies.

	Institution A – No routine CL/fFN screening N = 456	Institution B – Routine CL/fFN screening N = 532	p
Chorionicity			
Dichorionic-Diamniotic	90.0%	85.2%	0.053
Monochorionic-Diamniotic	9.3%	13.2%	
Monochorionic-Monoamniotic	0.7%	1.7%	
Maternal age	36.6 ± 5.7	34.0 ± 6.7	<0.001
Prepregnancy weight (pounds)	141.2 ± 29.8	140.2 ± 29.4	0.594
Prepregnancy body mass index	23.3 ± 5.2	23.5 ± 4.5	0.629
In vitro fertilization	68.1%	64.3%	0.218
Multifetal pregnancy reduction	6.1%	7.4%	0.448
Prior term birth	32.8%	35.5%	0.391
Prior preterm birth	3.8%	7.6%	0.018
White race	78.8%	87.6%	<0.001

Table 2. Pregnancy outcomes, based on the utilization of routine CL and fFN screening in twin pregnancies.

	Institution A – No routine CL/fFN screening N = 456	Institution B – Routine CL/fFN screening N = 532	p
Cerclage	2.3%	4.0%	0.155
Gestational age at delivery	35.8 ± 2.5	35.6 ± 2.7	0.314
Preterm birth <34 weeks	18.4%	20.1%	0.502
Spontaneous preterm birth <34 weeks	13.1%	15.2%	0.372
Antenatal corticosteroids exposure, in women who delivered <34 weeks	73.2%	91.5%	0.002
Antenatal corticosteroids exposure within 1–14 days of delivery, in women who delivered <34 weeks	34.3%	54.7%	0.012
Antenatal corticosteroids exposure within 1–7 days of delivery, in women who delivered <34 weeks	24.3%	39.6%	0.035
Antenatal corticosteroids exposure, in women who delivered 34–36 6/7 weeks	13.9%	41.3%	<0.001
Antenatal corticosteroids exposure, in women who delivered ≥37 weeks	3.6%	8.4%	0.073

In the routine screening cohort, among patients who delivered <34 weeks and received ACS, the indications for ACS were an asymptomatic short CL or positive fFN (34.0%), symptomatic preterm labor or PPROM (21.6%), IUGR (14.4%), hypertension (11.3%), bleeding (3.1%) or other (15.5%). In the routine screening cohort, among patients who delivered within 7 days from ACS exposure, only 31% (13/42) received ACS due to preterm labor or PPROM, whereas 14.3% received ACS due to an asymptomatic short CL or positive fFN. Among patients who delivered within 14 days from ACS exposure only 29.3% (17/58) received ACS due to preterm labor or PPROM, whereas 24.1% (14/58) received ACS due to an asymptomatic short CL or positive fFN.

Comment

We found that routine use of CL and fFN screening in twin pregnancies was not associated with a reduced rate of PTB or SPTB. However, routine CL and fFN screening was associated with a significant improvement in ACS exposure for patients who delivered prematurely. The improvement in ACS exposure was noted both in patients delivering at <34 weeks and in patients delivering between 34 and 36 6/7 weeks (late preterm birth) and was without a significant increase in unnecessary ACS exposure in patients who delivered at term or an increase in the rate of cerclage placement. Routine CL and fFN screening was also associated with improved timing of ACS exposure to women who delivered <34 weeks.

The rate of ACS administration achieved in neonates born <34 weeks in the routine-screening cohort was higher than the rates published in multiple other studies using standard approaches to ACS administration from the United States, United Kingdom, Canada and Israel [11–14]. This indicates that the routine use of CL and fFN screening, although unlikely to reduce the risk of preterm birth, could potentially improve outcomes in twin pregnancies who deliver preterm by improving the overall ACS exposure, as well as the timing of ACS exposure.

It is not surprising that routine CL and fFN screening was not associated with reduced rates of preterm birth or spontaneous preterm birth. Since preterm birth is a process that can rarely be halted, and tocolytics are typically effective only to prolong pregnancy long enough for corticosteroid administration, we would not expect that routine screening for preterm birth would significantly change its frequency. However, since antenatal corticosteroids are currently the most effective method of improving neonatal outcomes in the setting of preterm birth, the ability to administer them in a timely manner is extremely important. In fact, the ability to administer antenatal corticosteroids prior to preterm birth <34 weeks is specifically listed by ACOG as the Proposed Performance Measure in the management of preterm labor [9]. Therefore, our finding of the significant association between routine CL and fFN testing and this outcome is important to clinical practice and potentially may alter routine prenatal care for twin pregnancies and further studies are

warranted to test this hypothesis. It is also noteworthy that among women who delivered <34 weeks, 34% of the women in the routine screening cohort received ACS due to an asymptomatic screen and only 21.6% received ACS due to symptomatic preterm labor or PPROM. This is important considering that even among women who received ACS within 14 days of delivery <34 weeks, 24.1% received them due to an asymptomatic screen.

In 1994, the NIH published its Consensus Statement regarding the effects of antenatal corticosteroids (ACS) use for fetal maturation, concluding that their use between 24 and 34 weeks of gestation results in decreased mortality, respiratory distress syndrome and intraventricular hemorrhage in preterm infants [15]. Subsequently, ACOG [16], the Royal College of Obstetricians and Gynaecologists (RCOG) [17] and the Society of Obstetricians and Gynaecologists of Canada [18] have also recommended ACS administration to women at risk of preterm birth between 24 and 34 weeks of gestation. While these recommendations were made on the basis of studies with small numbers of multiple gestations, there are observational data to suggest benefit in these pregnancies as well [11,12,19], and current guidelines do state that it is reasonable to administer ACS to women with multiple gestations at risk of preterm delivery [15–18].

Several groups have evaluated the success of appropriate ACS administration in twin pregnancies, which are at increased risk of preterm delivery at baseline, and have consistently shown low proportions of premature twins being exposed to ACS [11,12,14,20]. Data from the NICHD database revealed that only nearly half of patients delivering a twin with birth weight of 400–1500 grams received ACS [11]. Data from the Israel National database [12] showed that only 51.5% of twins born 24–32 weeks were exposed to ACS. A study by Murphy et al. [13] found that over 70% of neonates who would likely have benefitted from such therapy did not receive it with a standard approach to determining need for ACS administration. That same study showed no benefit to biweekly prophylactic ACS in an asymptomatic twin pregnancy cohort. One contemporary study reported the antenatal corticosteroid exposure rate to all premature neonates born in the state of California 2005–2007 [21]. In their cohort, they reported that among multiple gestation babies born <34 weeks, 3770/4555 (82.8%) were exposed to antenatal corticosteroids. They did not report the number of twins versus higher-order multiples, nor did they report the corticosteroid exposure rate to multiples born at term. Our 91.5% rate of ACS exposure for women delivering <34 weeks in our screened population was significantly higher than this reported rate as well ($p = 0.007$). The rate of ACS exposure in our clinically-indicated testing cohort (74.7%) is similar to published rates. Therefore, we do not believe that this rate seen in our study reflects substandard care of twin pregnancies. Rather, the finding of a significantly higher rate in our routinely screened cohort is the novel finding.

One potential question would be whether our routine use of CL and fFN screening simply led to overuse of ACS in general. Our data suggest the opposite. Only 8.4% of patients who delivered at term had any ACS exposure. Additionally, we found that the routine use of CL and fFN screening actually significantly improved the rates of “optimal” steroid

exposure, defined either as ACS exposure within 1–14 days of delivery or within 1–7 days of delivery. One study from the United States reported a 21.4% rate of ACS exposure within 1–7 days of delivery <34 weeks in twin pregnancies [14]. This rate is very similar to the 24.3% rate we found in the unscreened cohort in our study, and is significantly lower than the 39.6% rate seen in our cohort with routine CL and fFN screening ($p = 0.002$). Therefore, not only was routine CL and fFN screening associated with improved rates of ACS exposure, it also improved the timing of exposure, and did not increase the exposure overall.

Limitations to this study include all the limitations inherent to retrospective studies, including potential selection and reporting bias. In regards to studying two different populations, both cohorts were managed in major academic medical centers located within one mile of each other in Manhattan, both with management or supervision by maternal fetal medicine specialists. However, it is possible that other unmeasured or unknown differences in management of twin pregnancies contributed to our findings. It is also possible that differences in baseline characteristics, such as maternal age or race contributed to our findings. Certainly, a randomized trial would be ideal to study the effect of routine use of CL and fFN screening on pregnancy outcomes, and we believe our data support the undertaking of this kind of study. Additionally, our study does not address whether the increased exposure to ACS in twins born prematurely actually resulted in improved neonatal outcome in the routine-screening cohort. A prospective study could potentially address this important clinical outcome as well. Finally, it would be useful to study the relative cost to each management strategy, particularly if the routine use of CL and fFN in twin pregnancies is to be considered in large health systems.

To summarize, routine screening with CL and fFN in asymptomatic women carrying twin gestations was associated with improved rates and timing of ACS administration in women who deliver preterm, but not a reduction in risk of PTB or sPTB. Prospective studies should be designed to further test these hypotheses, as well as assess the effect of short- and long-term neonatal outcomes.

Declaration of interest

Dr Ashley Roman is a consultant for Hologic Inc., the company that makes and markets the fetal fibronectin test.

References

- Martin JA, Hamilton BE, Osterman MJK. Three decades of twin births in the United States, 1980–2009. NCHS data brief, no 80. Hyattsville, MD: National Center for Health Statistics; 2012.
- Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. *New Engl J Med* 2012;334:567–72.
- Goldenberg RL, Mercer BM, Meis PJ, et al. The preterm prediction study: fetal fibronectin testing and spontaneous preterm birth. NICHD Maternal Fetal Medicine Units Network. *Obstet Gynecol* 1996;87:643–8.
- Peaceman AM, Andrews WW, Thorp JM, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. *Am J Obstet Gynecol* 1997;177:13–18.
- Goldenberg RL, Iams JD, Miodovnik M, et al. The preterm prediction study: risk factors in twin gestations. *Am J Obstet Gynecol* 1996;175:1047–53.

6. Yang JH, Kuhlman K, Daly S, Berghella V. Prediction of preterm birth by second trimester cervical sonography in twin pregnancies. *Ultrasound Obstet Gynecol* 2000;15:288–91.
7. Fox NS, Saltzman DH, Klauser CK, et al. Prediction of spontaneous preterm birth in asymptomatic twin pregnancies with the use of combined fetal fibronectin and cervical length. *Am J Obstet Gynecol* 2009;201:313.e1–5.
8. Fox NS, Rebarber A, Roman AS, et al. The association between second trimester cervical length and spontaneous preterm birth in twin pregnancies. *J Ultrasound Med* 2010;29:1733–9.
9. ACOG Practice Bulletin Number 127. Management of preterm labor. *Obstet Gynecol* 2012;120:197–206.
10. Roman AS, Koklanaris N, Paidas MJ, et al. “Blind” vaginal fetal fibronectin as a predictor of spontaneous preterm delivery. *Obstet Gynecol* 2005;105:285–9.
11. Hashimoto LN, Hornung RW, Lindsell CJ, et al. Effects of antenatal glucocorticoids on outcomes of very low birth weight multifetal gestations. *Am J Obstet Gynecol* 2002;187:804–10.
12. Blickstein I, Reichman B, Lusky A, Shinwell ES. Israel Neonatal Network. Plurality-dependent risk of severe intraventricular hemorrhage among very low birth weight infants and antepartum corticosteroid treatment. *Am J Obstet Gynecol* 2006;194:1329–33.
13. Murphy DJ, Caukwell S, Joels LA, Wardle P. Cohort study of the neonatal outcome of twin pregnancies that were treated with prophylactic or rescue antenatal corticosteroids. *Am J Obstet Gynecol* 2002;187:483–8.
14. Turrentine MA, Wilson PD, Wilkins IA. A retrospective analysis of the effect of antenatal steroid administration on the incidence of respiratory distress syndrome in preterm twin pregnancies. *Am J Perinatol* 1996;13:351–4.
15. Report on the Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. U.S. Department of Health and Human Services, Public Health Service, NIH Pub No. 95-3784, November; 1994.
16. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 475: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2011;117:422–4.
17. RCOG Guidelines. Number 7. ACS to prevent respiratory distress syndrome. London: RCOG; 1996.
18. Crane J, Armon A, Brunner M, et al. Antenatal corticosteroid therapy for fetal maturation. *J Obstet Gynaecol Can* 2003;25: 45–52.
19. Donovan EF, Ehrenkranz RA, Shankaran S, et al. Outcomes of very low birth weight twins cared for in the National Institute of Child Health and Human Development Neonatal Research Network’s intensive care units. *Am J Obstet Gynecol* 1998;173:742–9.
20. Joseph KS, Allen AC, Dodds L, et al. Causes and consequences of recent increases in preterm birth among twins. *Obstet Gynecol* 2001;98:57–64.
21. Lee HC, Lyndon A, Blumenfeld YJ, et al. Antenatal steroid administration for premature neonates in California. *Obstet Gynecol* 2011;117:603–9.