OBSTETRICS

The prediction of recurrent preterm birth in patients on 17-alpha-hydroxyprogesterone caproate using serial fetal fibronectin and cervical length

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OBJECTIVE: The objective of the study was to estimate the predictive value of cervical length (CL) and fetal fibronectin (fFN) in patients being treated with 17-alpha-hydroxyprogesterone caproate (17P).

METHODS: This was a retrospective cohort of 176 patients with a prior spontaneous preterm birth being treated with weekly injections of 17P who underwent serial CL and fFN screening.

RESULTS: A short CL (≤25 mm) was significantly associated with an earlier gestational age at delivery and with recurrent preterm birth at less than 37, less than 35, less than 34, and less than 32 weeks. A positive fFN was not significantly associated with recurrent preterm birth. As a screening test for recurrent preterm birth, the positive and negative likelihood ratios for CL were 2.04 and 0.35, respectively, whereas for fFN they were 1.22 and 0.98, respectively, indicating that fFN did not offer any additional predictive value.

CONCLUSION: In patients being treated with 17P, cervical length at 22-32 weeks is predictive of recurrent preterm birth, but fetal fibronectin is not.

Key words: cervical length, fetal fibronectin, preterm birth, progesterone, recurrence

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Patients with a history of preterm birth have an increased risk of preterm birth in subsequent pregnancies.[1-3] In the Preterm Prediction Study, Iams et el[4] reported that in patients with a prior spontaneous preterm birth, the recurrence risk of preterm birth varies widely according to both fetal fibronectin (fFN) and cervical length (CL) at 22-24 weeks. Although the American College of Obstetricians and Gynecologists (ACOG) does not endorse routine CL or fFN screening in low-risk singleton pregnancies because of the low positive predictive value in these patients at low risk for preterm birth, based on the data from the Preterm Prediction Study, ACOG considers screening high-risk women, such as those with a history of preterm birth, with CL or fFN to be a reasonable strategy to predict recurrent preterm birth.[5]

Subsequent to the Preterm Prediction Study, one large randomized trial reported that the administration of weekly injections of 17-alpha-hydroxyprogesterone caproate (17P) beginning at 16-20 weeks significantly reduced the risk of recurrent preterm birth in patients with a prior spontaneous preterm birth of a singleton pregnancy.[6] Based on these data, ACOG supports the use of progesterone supplementation for the prevention of recurrent preterm birth in women with a singleton pregnancy and a prior spontaneous preterm birth.[7] Because the indications for 17P administration and CL/fFN testing are identical (prior spontaneous preterm birth of a singleton pregnancy), most patients who currently undergo screening for recurrent preterm birth with CL and fFN will also be taking 17P injections.

Considering that the original data supporting the association between CL and fFN and recurrent preterm birth preceded the widespread use of 17P, it is unknown whether progesterone use modifies the predictive value of CL and fFN in patients with a prior preterm birth. It is possible that for patients receiving 17P, the predictive value of either CL or fFN, or both, in predicting recurrent preterm birth could be significantly enhanced or reduced.

The objective of this study was to estimate the predictive value of CL and fFN in patients with a prior spontaneous preterm birth of a singleton pregnancy who are being treated with 17P.

Materials and Methods

After Biomedical Research Alliance of New York Institutional Review Board approval was obtained, we searched the patient database of one maternal-fetal medicine practice, which includes all patients delivered from July 2005 (when the database was created) to July 2011. We searched the database for all patients we delivered who had a history of a preterm birth in a prior pregnancy. All patients in the database have a listed parity (full-term births, preterm birth >20 weeks, pregnancy losses at <20 weeks, live births), and the search was done by

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TABLE 1
Descriptive characteristics of patients on 17P

Characteristics	Values
Number of patients	176
Number of prior spontaneous singleton preterm births <37 wks, n (%)	
1	112 (63.6)
2	37 (21.0)
3	18 (10.2)
>3	9 (5.1)
Gestational age of earliest prior preterm birth, wks	29.5 ± 5.2
Gestational age of most recent birth, wks	32.8 ± 5.8
Most recent birth was preterm	132 (75%)
Any prior term births	91 (51.7%)
Prior LEEP or cervical conization	5 (2.8%)
Age, y	31.8 ± 5.8
IVF	11 (6.2%)
Prepregnancy body mass index, kg/m^2	23.5 ± 8.8
White race	169 (96%)
Positive fFN	16 (9.1%)
Gestational age at positive fFN	28.2 ± 2.0
Shortened CL, ≤25 mm	67 (38.1%)
Gestational age at diagnosis of shortened CL, wks	27.0 ± 3.2
Mean CL at diagnosis of shortened CL, mm	21.0 ± 4.8
Both positive fFN and shortened CL, ≤25 mm	10 (5.7%)
Gestational age at delivery, wks	37.5 ± 2.4
Preterm birth <37 wks	56 (31.8%)
Preterm birth <35 wks	13 (7.4%)
Preterm birth <34 wks	9 (5.1%)
Preterm birth <32 wks	7 (4.0%)

Mean ± SD or n (%).
CL, cervical length; *fFN,* fetal fibronectin; *IVF,* in vitro fertilization; *LEEP,* loop electrosurgical excision procedure; *17P,* 17-alpha-hydroxyprogesterone caproate.

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identifying all patients with a number greater than zero for prior preterm birth.

The complete obstetrical histories for all of these patients were reviewed to select patients with a history of at least 1 prior spontaneous preterm birth (20 0/7 to 36 6/7 weeks) of a singleton pregnancy at any time in their past who were then managed by us in a subsequent singleton pregnancy. We then reviewed the complete charts for these patients.

In our practice, for patients with a prior spontaneous preterm birth of a singleton pregnancy, we recommend weekly 17P in a protocol similar to the study by Meis et al.[6] We also perform serial (every 2-3 weeks) sonographic CL measurements from 16 to 32 weeks. Beginning at 22 weeks, we perform serial fFN testing just prior to the CL measurement. Certain patients with a prior spontaneous preterm birth of a singleton pregnancy do not receive 17P or CL/fFN screening, including patients who decline, some patients with mixed obstetrical histories including some term and some preterm births, and certain patients who have a history of a late preterm birth (34 to 36 6/7 weeks) who, after counseling, decide against 17P and CL/fFN screening.

For this study, we excluded all the patients who did not have a combined CL and fFN screening from 22 to 32 weeks and all the patients who were not receiving weekly 17P. We also excluded patients who underwent cerclage placement at any time in pregnancy.

All CL measurements and fFN testing were done in an outpatient setting on asymptomatic patients. All tests done on labor and delivery were excluded because they were done on symptomatic patients as part of a preterm labor evaluation. Patients and obstetricians were not blinded to the CL measurements or fFN results. Gestational age was determined by the last menstrual period and confirmed by ultrasound in all patients. The pregnancy was redated if there was a more than 5 day discrepancy up to 14 weeks or a greater than 7 day discrepancy after 14 weeks. If the pregnancy was the result of in vitro fertilization (IVF), gestational age was determined from IVF dating.

All CL measurements were measured by 4-8 MHz transvaginal probes (LOGIQ a200 and Voluson 530 and 730 Expert; GE Healthcare, Milwaukee, WI) with an empty bladder with the optimal image defined according to the criteria reported by Iams et al.[8] The shortest functional CL was used as this has been found to be the most reproducible measurement.[9] A short CL was defined as a CL of 25 mm or less.

Fetal fibronectin testing was performed using a Dacron swab without the use of a speculum according to an established protocol that has been validated previously by both our group[10] and others.[11] Fetal fibronectin testing was performed more than 24 hours from the last reported intercourse or endovaginal ultrasound and was not performed in the setting of vaginal bleeding. Vaginal swabs were sent for quantitative determination of fetal fibronectin concentration using the rapid TLi system qualitative method (fetal fibronectin immunoassay; Hologic Inc, Bedford, MA). A fetal fibronectin concentration of 50 ng/mL or greater was considered to be positive.

In our practice, we do not hospitalize patients with a short CL or positive fFN aside from those actually in preterm labor. We typically administer corticoste-