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Gestational age at prior preterm birth does not affect cerclage efficacy

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Abstract

OBJECTIVE—To evaluate effect of earliest prior spontaneous preterm birth (SPTB) gestational age (GA) on cervical length (CL), pregnancy duration, and ultrasound-indicated cerclage efficacy in a subsequent gestation.

STUDY DESIGN—Planned secondary analysis of the NICHD- trial of cerclage for CL < 25 mm. Women with at least one prior SPTB between 17-33 6/7 weeks underwent serial vaginal ultrasound screening between 16 and 23 6/7 weeks; CL at qualifying randomization evaluation was utilized.

RESULTS—We observed a significant correlation (p=0.0008) between prior SPTB GA and qualifying CL. In a linear regression model when controlling for CL and cerclage, neither prior SPTB GA nor the interaction between cerclage and prior birth GA was significant predictor of subsequent birth GA.

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CONCLUSION—While there is an association between prior SPTB GA and CL in women with mid-trimester CL < 25 mm, there does not appear to be a disproportionate benefit of cerclage in women with earlier prior SPTB.

Keywords

Cerclage; cervical length; earliest gestational age; spontaneous preterm birth

INTRODUCTION

The rate of preterm birth is increasing and in 2007 reached 12.3%.1 Prior spontaneous preterm birth (SPTB) is considered one of the strongest historic risk factors for recurrent SPTB.2,3,4 Previous reports have linked the gestational age at prior SPTB to the gestational age at subsequent SPTB, and determined that the risk of SPTB before 37 weeks in the current gestation increased with decreasing gestational age of the earliest prior spontaneous preterm delivery. In one large observation study, gestational age strata were defined as <28, <30, <32, <35 and <37 weeks. An early prior SPTB between 23 and 27 weeks was associated with recurrence in the current gestation with relative risks of 3.1, 2.7 and 2.4 for earliest prior delivery at 23–27, 28–34 and 35–36 weeks, respectively. The strongest association between history and current outcome was found for early prior SPTB and early SPTB in the current gestation with 22.1-fold increase (95% confidence interval, 4.6–106.9) in the relative risk for early delivery (5.1% versus 0.23%, P=.001.)5 Other studies have confirmed the inverse relationship between increasing risk of recurrent SPTB and decreasing age of prior SPTB.4,6

We conducted a multi-center randomized trial to evaluate the utility of cerclage for shortened cervical length in women with a history of SPTB.[7] Cervical length shortening has been shown to increase the risk of SPTB in high-risk women with a prior spontaneous sPTB.[8,9,10] Cervical length in a subsequent pregnancy also correlates well with gestational age at prior preterm delivery.11 We have shown that cerclage prevents recurrent PTB in women with both a prior spontaneous PTB 17–33 6/7 weeks and also a short CL < 25 mm, identified between 16–22 6/7 weeks.[7] The findings of this clinical trial support the conclusion of a recent meta analysis (16) of 4 prior randomized trials (12–15): cerclage placed for cervical shortening significantly reduced preterm birth less than 35 weeks by 39% in women with a prior PTB.

In a secondary analysis from the same randomized, controlled trial, we examined the natural history of cervical length shortening in women who had at least one SPTB between 17–33 6/7 weeks' gestation. We compared the rate of cervical length shortening and the time to shortening for women whose earliest prior preterm birth was in the mid-trimester, defined as <24 weeks, vs. those at weeks 24–33. Similar comparisons were performed based on each patient's most recent birth history. In both cases we found that women with a prior spontaneous preterm birth at <24 weeks are at a higher risk of cervical shortening, and do so at a higher rate and at an earlier gestational age, than do women with a later preterm birth history.[17]

We seek in this investigation to estimate whether information regarding earliest gestational age at prior preterm birth would be informative for clinical management, since surveillance of cervical length in women with prior preterm birth is advantageous for risk assessment for recurrent preterm birth. Our null hypothesis is that there are no significant interaction effects between gestational age at prior SPTB and cerclage efficacy on subsequent GA at delivery. This analysis addresses whether cerclage intervention based on degree of cervical shortening and considering prior birth gestational age would offer relevant information once cervical shortening had been identified.

MATERIALS AND METHODS

This is a planned secondary analysis of the NICHD-sponsored randomized trial evaluating cerclage for women with singleton gestations, prior SPTB (17–33 6/7 wks), and CL < 25 mm measured with serial transvaginal ultrasound (TVU) evaluations between 16 and 22 6/7 weeks. This trial was performed at 15 U.S. Clinical Centers between January, 2003 and November, 2007[7]. Each center obtained Institutional Review Board approval. The methods and materials are described in detail in the report of the parent trial.7 Importantly, healthy, multiparous women with at least one prior spontaneous preterm birth between $17^{0/7}$ and $33^{6/7}$ weeks of gestation were recruited. Our process included confirmation of the obstetrical history by a review of the subject's medical records. When efforts to retrieve the records of the prior birth were unsuccessful, we accepted women as eligible if the events surrounding the prior birth included spontaneous causes such as preterm labor or preterm membrane rupture, and the reported birth weight was less than 2 kg. Exclusion criteria were fetal anomaly, planned history-indicated cerclage, and clinically significant maternal-fetal complications.[7] Gestational age was always confirmed by standard sonographic biometric measurements at less than 20 weeks' gestation. Sonologists underwent a uniform certification process by a single investigator (J.O.) to ensure uniformity in sonographic measurements of TVU CL screening.[7,8]

Women with prior SPTB were screened with TVU CL starting at 16 0/7 – 21 6/7 weeks, then every 2 weeks until 22 6/7 weeks unless the CL was observed to be 25–29 mm, after which the scan frequency was increased to weekly. Women who developed a CL <25mm at 16–22 6/7 weeks were randomized after informed consent to cerclage or no cerclage.

We examined the relationship between prior PTB GA and the shortest CL observed prior to randomization. The associations between prior PTB GA and GA of this delivery were examined with linear regression. The effects of cervical length, cerclage group, and the interaction between prior birth GA and cerclage group were also considered in multivariable linear regression models. Chi-square and Student t-tests were used to evaluate demographic characteristics. We selected an alpha level of < 0.05 to represent statistical significance.

RESULTS

Of 1014 women with prior SPTB who were screened with TVU CL at 16–22 6/7 weeks, 318 had a CL <25mm, of which 302 agreed to randomization. Of these, 301 with birth outcomes were available for this analysis, 148 were randomized to cerclage and 153 were randomized to no-cerclage. The demographic and sonographic characteristics for these subjects can be found in Table 1.

A weak (Pearson r=0.19) but significant correlation (p=0.0008) between prior SPTB and qualifying CL was observed. The relationship between earliest GA at prior SPTB and CL is depicted in Figure 1. When stratifying for CL measurements as <15 mm and 15–24 mm, we found a significant association between the <15mm measurement and randomization (p=0.006). In a multivariable linear regression model, when controlling for CL and cerclage group, prior SPTB GA was not a significant (p=0.06) predictor of subsequent birth GA. , We also found no significant interaction between cerclage and earliest GA of prior SPTB (p=0.20) for the prediction of subsequent birth GA.

Because not all enrolled women had experienced their earliest prior SPTB in their most recent pregnancy, we also analyzed the effect of the GA of the most recent birth, treatment with cerclage and subsequent birth GA. The correlation between most recent GA and qualifying CL was also significant (p<0.0001, Pearson r=0.23). The most recent birth GA was a predictor for subsequent GA at delivery when controlling for CL and cerclage in a linear model (p=0.02).

The interaction between cerclage and prior birth GA to this model demonstrated no significance for the prediction of subsequent birth GA, however (p=0.07).

COMMENT

The results from our secondary analysis reveal that there is little association between earliest gestational age at prior PTB, cerclage placement and subsequent birth GA.Similarly, there is no association between gestational age at most recent birth, treatment with cerclage and gestational age at recurrent PTB. We sought to determine if we could better identify those women at greatest risk for recurrent PTB with cerclage using cervical shortening in light of our recent findings which indicated that the earlier the gestational age for those women who had a prior PTB, the more likely they were to demonstrate cervical shortening, and the earlier they were to do so.[17] Nevertheless, the results of our secondary analysis provide no such clues by which to improve outcomes with the therapeutic intervention of cerclage despite being armed with the knowledge that cervical shortening will occur earlier and more frequently in those women with earlier prior SPTBs. Our results would also indicate that women with earlier deliveries do not disproportionately benefit from cerclage placement compared to those with later SPTBs.

The relationship between gestational age at prior PTB and recurrent PTB has been studied previously as a secondary analysis of the Preterm Prediction Study conducted by the NICHD, and replicated since by many others.[5,18] The ability to correlate this information with cervical shortening which required cerclage placement is unique, and therefore this is a strength of our study. An expected weakness is that this is a secondary analysis, but we planned for it near the inception of the primary study. Because the sample size was predetermined by the results of the clinical trial, this study had insufficient power to detect a clinically significant effect of gestational age at prior PTB, cervical length <15mm, and gestational age at subsequent PTB.

The role of imflammation[19], infection, genetic markers, enzymes (e.g. sialidases, collagenases), fetal fibronectin, and other factors will likely play a larger role in selection of these therapies for the woman with a short CL in the near future. More research is also needed to look at interactions of several possible therapies for short CL, such as progesterone, indomethacin, antibiotics, and others. Several trials and studies are currently ongoing and will soon provide more evidence to be able to answer these questions and guide clinical care.

The lack of a positive association between earliest GA at prior SPTB, cervical shortening, cerclage and gestational age at recurrent SPTB should not be disregarded. An investigation into the association of gestational age of prior PTBs and the significance of endovaginal sonographical cervical length less than 25 mm for the prediction of recurrent PTB <35 weeks' gestation found that the gestational age at prior PTB did not modify the predictive value of a shortened cervix at 16–19 weeks for recurrent PTB[11], and so it is perhaps not unsurprising that the addition of indicated cerclage also did not influence gestational age at recurrent PTB. We also evaluated the GA at most recent delivery here and there was no association found (data not shown). Regardless, the overwhelming body of evidence supports the utility of cervical length measurements as one of the best predictors of spontaneous preterm birth[20], so these results should not affect screening or treatment for cervical shortening.

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Figure 1.
Relationship of earliest gestational age at previous spontaneous preterm birth (wk) and shortest cervical length at randomization (cm)

Table 1

Baseline characteristics and treatment group differences for 301 subjects randomly assigned to cerclage or to no-cerclage groups.

	Cerclage (n = 148)	No-cerclage (n = 153)	P value
Maternal age (y)	26.4 ± 5.5	26.6 ± 5.1	0.75
Number of prior births (n)	2 (1,4)†	2 (1,4)†	0.66
Race/ethnicity Black (non-Hispanic) White (non-Hispanic) Hispanic Asian Other	80 (54) 25 (6.9) 27 (8.2) 1 (0.7) 15 (0.1)	93 (61) 28 (18) 17 (11) 0 (0) 15 (9.8)	0.36
Gestational age of earliest prior preterm birth (wks)	24.2 ± 4.8	24.5 ± 4.7	0.58
Gestational age of most recent birth (wks)	26.4 ± 6.7	27.1 ± 6.5	0.37
Gestational age at randomization (wks)	19.4 ± 1.9	19.5 ± 2.0	0.56
Cervical length at randomization (mm)	18.6 ± 6.3	19.5 ± 5.3	0.21

Data presented as n (%), mean (range), or mean ± 1 SD.

* Race and ethnic group are self-reported

† Median and interdecile range