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CERVICAL FUNNELING: EFFECT ON GESTATIONAL LENGTH AND ULTRASOUND-INDICATED CERCLAGE IN HIGH RISK WOMEN

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Abstract

OBJECTIVE—To assess funnel type and pregnancy duration in women with prior spontaneous preterm birth and cervical length <25 mm.

STUDY DESIGN—Secondary analysis of a multicenter randomized trial of cerclage. At the randomization scan documenting short cervix, presence and type of funnel (U or V) were recorded.

RESULTS—147 of 301 (49%) had funneling: 99 V; 48 U. U-funnel was significantly associated with preterm birth <24, <28, <35 and <37 weeks. In multivariable models controlling for randomization cervical length and cerclage, women with U- funnel delivered earlier than women with either V-funnel or no funnel. Interaction between cerclage and U-funnel was observed, and

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analyses stratified by cerclage showed that women with a U-funnel and cerclage delivered at a mean of 33.8 weeks (6.6) gestation compared to women who did not receive cerclage (28.9 weeks) (6.9).

CONCLUSION—U-funnels in high-risk women with short cervix are associated with earlier birth.

INTRODUCTION

Preterm birth (PTB) is the leading cause of perinatal morbidity and mortality (1,2). Most occur spontaneously and are not due to maternal-fetal indications (2,3). The incidence of PTB continues to rise largely due our poor understanding of the pathophysiology and the paucity of effective interventions, which, combined, has limited our ability to properly select patients for specific therapy. The relationship between shortened cervical length and PTB has been well-characterized in both unselected (4) and high-risk women (5). Cervical length assessment has been well standardized and is reproducible (6,7). Other lower uterine segment and cervical characteristics in addition to cervical length can be assessed by mid-trimester ultrasound (8). One of these characteristics is the presence of cervical funnel. It has been shown that the presence of a funnel is a significant risk factor for adverse perinatal outcome and that it is best measured as a categorical variable (present or absent) (9). Other investigators have suggested that the finding of a funnel at the internal os is a poor independent predictor of PTB once the effect of short cervix is considered (5). The shape of the funnel (U or V), percent funneling, and the depth and width of the funnel have all been described as methods of assessing cervical funneling. In high-risk women, the progression to a U-shaped funnel has been associated with an increased risk of preterm delivery (10). Thus the relationship between cervical funneling and PTB remains unclear.

In women with a prior early spontaneous PTB and shortened cervical length < 25 mm, cerclage has been shown to reduce PTB < 37 weeks, previable birth < 24 weeks, and perinatal mortality (11). However, the relationship between funneling and ultrasound-indicated cerclage has also not been well-characterized.

We postulated that funnel shape would be associated with different effects on gestational length and might respond differently to cerclage intervention. The aim of this study was to assess the relationship between the type of cervical funneling and pregnancy duration in women with prior spontaneous preterm birth and cervical length < 25 mm enrolled in a randomized intervention trial of ultrasound-indicated cerclage.

METHODS

This is a planned, secondary analysis of the NICHD-sponsored randomized trial of cerclage for PTB prevention, performed by a consortium of 15 U.S. Clinical Centers between January 2003 and November 2007 (11). Healthy, multiparous women who enrolled for prenatal care before 22 weeks were screened to identify those with at least one prior spontaneous preterm birth between $17^{0/7}$ and $33^{6/7}$ weeks' gestation. Exclusion criteria were fetal anomaly, planned history-indicated cerclage for a clinical diagnosis of cervical insufficiency, acute cervical insufficiency (defined as 2 cm dilation and visible membranes at the external os), and clinically significant maternal-fetal complications. Eligible women were invited to consent for the ultrasound screening phase of the trial. Other details of the study protocol are described elsewhere (11).

Consenting women underwent serial transvaginal sonographic evaluations, the first of which was scheduled in the temporal window $16^{0/7}$ to $21^{6/7}$ weeks' gestation. Subsequent scans were scheduled every 2 weeks unless the cervical length was observed to be 25–29 mm, after which scans were scheduled on a weekly basis. Women with a cervical length that remained at least 25 mm by the final sonographic evaluation, scheduled to be no later than $22^{6/7}$ weeks,

were ineligible for randomization and resumed their obstetric care. If on any evaluation the cervical length was < 25 mm, the woman became eligible for the randomization to either receive a McDonald cerclage or to enter a no cerclage group. Women who were assigned to no cerclage could receive a physical examination-indicated cerclage after randomization for the clinical diagnosis of acute cervical insufficiency.

Cervical length was measured using the standard technique as described by Iams (4). Trial sonologists underwent a uniform certification process by a single investigator (J.O.) to ensure uniformity in sonographic equipment, measurement technique, completion of study forms, and adherence to protocol. The cervical length at each visit was measured along a closed endocervical canal. Minimal degrees of apparent dilation less than 5 mm were considered closed. After a baseline cervical length was measured, fundal pressure was applied for 30 seconds as a provocative maneuver, and each scan included an evaluation period of at least 5 minutes to detect spontaneous cervical shortening. The shortest cervical length at each examination was recorded as the cervical length, regardless of whether the measurement was obtained with pressure or was the result of spontaneous dynamic shortening.

During the ultrasound examination, the presence and type of funnel (U-shaped or V-shaped) were recorded. Cervical funneling was defined as protrusion of the amniotic membranes of ≥ 5 mm into the internal os, as measured along the lateral border of the funnel. Care was taken to differentiate between a true funnel and a pseudo-funnel. A pseudo-funnel may occur when the lower uterine segment forms what appears to be a funnel above an otherwise normal-length cervix (12).

ANALYSIS

Study outcomes included gestational age at birth, rates of preterm birth at several gestational age cutoffs, and time to birth assessed by survival analysis. Gestational age at delivery was modeled as a function of funnel type in a simple linear regression model. The cervical length and funnel type at the qualifying evaluation for randomization were recorded. Women were classified as having U-funnel, V-funnel, or no cervical funneling. For this study, we considered actual cerclage placement, not assigned randomization group.

Multiple and pairwise comparisons for the rates of preterm birth in these funnel classification groups were evaluated with chi-square tests and logistic regression. Time to delivery was estimated with the Kaplan-Meier method and group differences evaluated with the log-rank statistic. Descriptive statistics for these three groups of patients were compared using ANOVA for continuous measures and chi-square tests for categorical measures. Multivariable linear regression, logistic regression, and Cox proportional hazards models were then considered for gestational age, rates of preterm birth, and time to delivery, respectively. An alpha level of 0.05 was selected to represent statistical significance for main effects and 0.10 for interactions. All analyses were performed using SAS 9.2 (Cary, NC).

The protocol and data forms were reviewed and approved by the human-use committees at all participating centers.

RESULTS

Of the 1044 women who were determined to have a qualifying prior preterm birth, 1014 (99%) were consented and underwent their initial sonographic assessment of cervical length. From this cohort, we observed 318 who experienced cervical length shortening < 25 mm. Sixteen patients were excluded (13 did not consent to randomization, 2 were ruled ineligible at the randomization visit and 1 withdrew from the trial), leaving 302 (95%) who were randomly assigned to no-cerclage (N=153) or cerclage groups (N=149) Primary outcome information

was available for all 153 in the no-cerclage group and for 148 of 149 in the cerclage group, leaving a total of 301 women in the analysis(11). As depicted in Fig. 1, of the 153 women assigned to no cerclage, 14 underwent cerclage placement; 4 were placed at the discretion of their managing physicans (off-protocol treatment crossover) while 10 were placed for a diagnosis of acute cervical insufficiency (protocol-sanctioned treatment crossover). Similarly, of the 149 assigned to receive cerclage, 11 did not undergo surgery; 8 declined to undergo surgery, whereas 3 procedures were contraindicated because of obstetric complications (intramniotic infection, fetal death and cervicitis). Thus the study cohorts included 152 who did and 149 who did not receive cerclage.

Of the 301 women who comprised the study population, 147 (49%) had a funnel present at their qualifying sonogram: 99 were V-shaped, and 48 were U-shaped. Selected characteristics for each of the 3 groups are presented in Table 1. Of note, shortest observed cervical length ($p < 0.0001$) and actual cerclage placement (0.015) differed among the funnel groups. In order to control for differences in cerclage placement and shortest cervical length, statistical models incorporating these 2 covariates as well as possible interactions were considered.

In simple linear regression analysis, gestational age at delivery was found to differ significantly among the funnel groups ($p < 0.0001$). In particular, the presence of a U-shaped funnel differed from both V-shaped ($p = 0.0003$) and no-funnel ($p < 0.0001$). There was no difference between V-shaped and no-funnel. Rates of preterm birth <24 weeks ($p = 0.004$), < 28 weeks ($p = 0.0004$), <35 weeks ($p = 0.001$), and <37 weeks ($p = 0.006$) differed among the funnel groups. Specifically, the presence of a U-shaped funnel (versus either V or none) was associated with preterm birth < 24 weeks ($p = 0.0019$), < 28 weeks ($p = 0.0002$), < 35 weeks ($p = 0.0004$), and < 37 weeks gestation ($p = 0.0023$). There was no statistically significant difference between no funnel and a V-shaped funnel for any preterm birth gestational age outcome.

Time to delivery differed significantly between funnel groups ($p = 0.0004$), where women with U-funnel demonstrated a significantly shorter time to delivery than women with either V-funnel or no funnel ($p < 0.0001$). There was no significant difference between V-funnel and no funnel.

There continued to be a significant difference between funnel groups ($p = 0.022$) in the covariate-adjusted models, where women with a U-shaped funnel demonstrated earlier GA at delivery than women with either V-shaped ($p = 0.012$) or no funnel ($p = 0.008$). Women with U-shaped funnel also demonstrated higher rates of preterm birth <24, 28, 35, and 37 weeks (Table 2). Furthermore, the hazard of earlier delivery remained significantly higher for women with U-shaped funnel (HR = 1.77; 95% CI: 1.25, 2.51; $p = 0.0013$).

A statistically significant interaction between cerclage and U-funnel was observed in the multivariable linear regression model for GA at delivery ($p = 0.072$). Women with a U-funnel and cerclage delivered 4.9 weeks later than women who did not receive cerclage (33.8 vs. 28.9). A similar interaction was seen in the Cox proportional hazards models of time to delivery ($p = 0.007$). The time-to-event interaction is illustrated in Figure 2, where women with U-funnel and no cerclage delivered earlier that women in any other group ($p = 0.001$). There was no significant difference in the Kaplan Meier plots for the remaining 3 groups ($p = 0.07$).

COMMENT

Lingering controversies exist over the importance of a cervical funnel: is there any clinical utility in the identification of a funnel, and are the clinical implications of a U-shaped funnel and a V- shaped funnel the same? The progression of a long and closed cervix (T-shaped), to a Y-shaped, then V-shaped, later evolving into a U-shaped funnel has been described in term laboring patients (13). These progressive changes may not be applicable to asymptomatic, high-risk women in the mid-trimester. Moreover, the clinical difference between these different

funnel types in high-risk women has not been widely studied. Although funneling appears to be common in the presence of a short cervix in high-risk women (49%), we have demonstrated that the finding of a V-shaped funnel does not have clinical significance beyond this association with short cervix. Conversely, in this high-risk population of women with prior spontaneous preterm birth and short cervix, the finding of a U-shaped funnel does have clinical implications for earlier birth.

We asked the question whether or not the presence of a U-shaped funnel was merely a surrogate for a shortened cervical length, which is known to be a strong predictor of preterm birth. To answer this question, we controlled for the shortest observed cervical length in all of our analyses. The relationship between a U-shaped funnel and earlier birth remained even after controlling for shortest cervical length. In the multivariable linear regression model, women with a U-shaped funnel and cerclage delivered a mean 4.9 weeks later in gestation than those women with a U-funnel who did not receive cerclage.

We acknowledge that funnel identification and characterization of shape is somewhat subjective, and that the recognition and characterization of a funnel may not be highly reproducible. In addition to the fact that prior reports on cervical funneling did not systematically distinguish between funnel types, this might explain the inconsistent effects of funneling in the literature. However, for this trial, sonologists were specifically trained in the recognition and characterization of funnels. Cervical funneling was clearly defined in the study protocol as protrusion of the amniotic membranes of > 5 mm into the internal os, as measured along the lateral border of the funnel. All sonologists were trained and certified by a single investigator and this training included those aspects of funnel recognition necessary to differentiate a V- from a U-shape. In particular U-shaped funnel assessment required both the funnel depth and width to be measured, whereas V-shaped funnels required only measurement of depth. Such training should help to reduce the subjectivity in clinical practice; however, sonologist interpretation of funneling was not reviewed by the primary investigator.

Other possible limitations to our study include the fact that we were only performing a 5 minute observation every 1–2 weeks and our data was censored at 22 6/7 weeks gestation. We do not have information regarding those women who may have developed a funnel later in gestation or those which may have been present, but resolved between scans. Additionally, although this was a planned secondary analysis the sample size was not selected nor was the study powered for the specific comparison of the three study groups. This might have limited our ability to detect differences between cohorts with V-shaped funnels and no funneling; however, given that the findings were significant between the U-funnel and no-funnel cohorts, beta error should not be a concern and should not affect our our results and conclusions.

U-shaped funnels may have a different pathophysiologic mechanism than V-shaped funnels as they appear to be associated with significantly earlier birth when compared to no funnel or V-shaped funnels. Women with a U-funnel and short cervix also appear to have enhanced benefit from ultrasound-indicated cerclage when compared to V-shaped funnel or no funnel. The development of a U-funnel may be in the evolution pathway of acute cervical insufficiency which might explain the disproportionate benefit from cerclage intervention when compared to women with no funnel or a V-funnel (14). Ten women who were not randomized to cerclage intervention later received a physical exam-indicated cerclage after presenting to their physicians and were found to have clinical evidence of acute cervical insufficiency. Seven of those women (70%) had a U-shaped funnel on their randomization scan. This further supports our postulate that a U-shaped funnel may be in the pathway of acute cervical insufficiency.

These findings have important clinical implications. High-risk women with a prior spontaneous preterm birth and short cervix benefit from cerclage, and this benefit increases as the cervical

length decreases (11). In the presence of a U-shaped funnel, this benefit is even more pronounced which provides important prognostic information when counseling women regarding the risks and benefits of ultrasound-indicated cerclage. Given that U-shaped funnels appear to be more amenable to cerclage therapy, this may provide important clues into the pathophysiologic mechanisms responsible for acute cervical insufficiency and which may direct further research.

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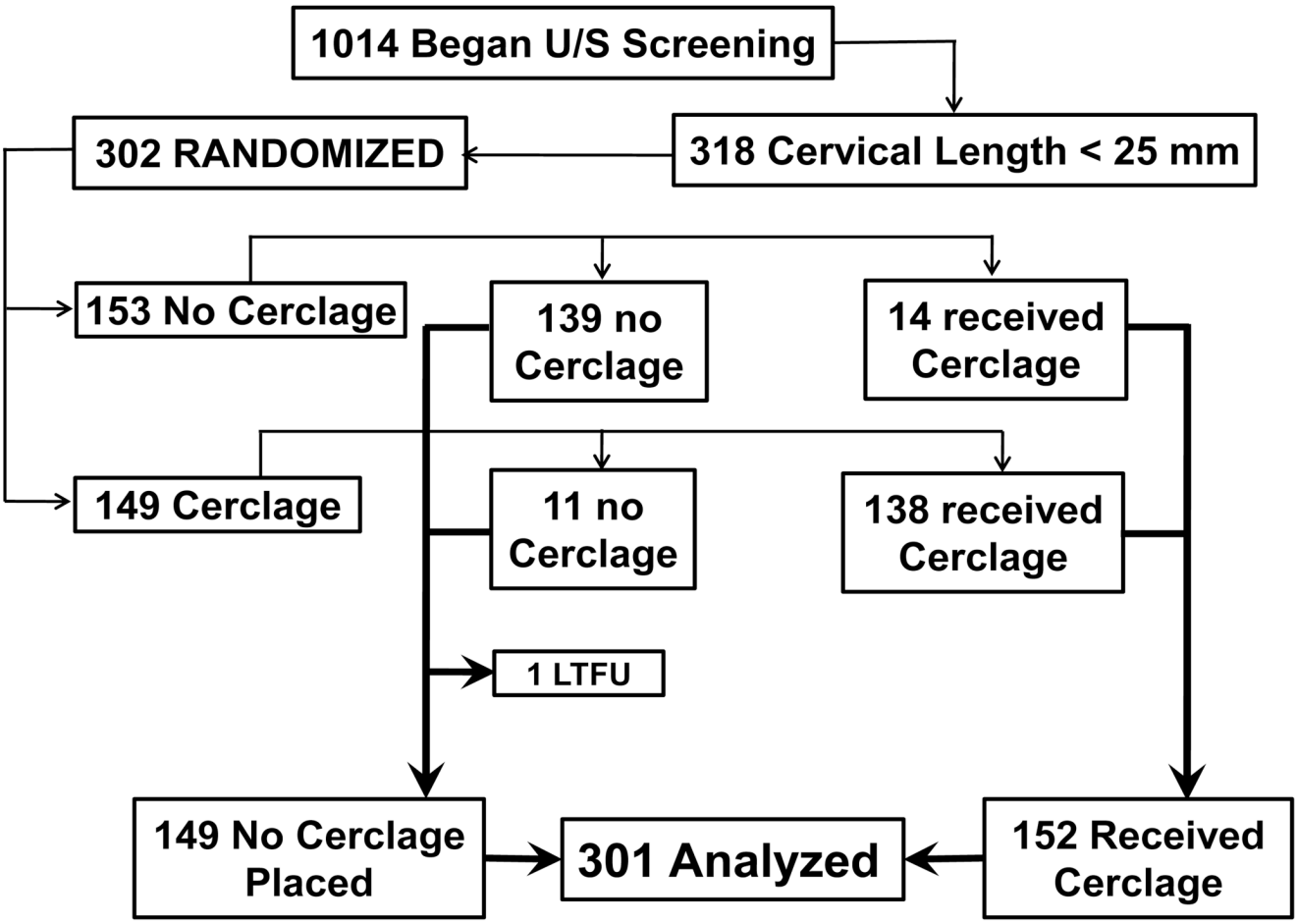

Figure 1.
Trial Flow Diagram

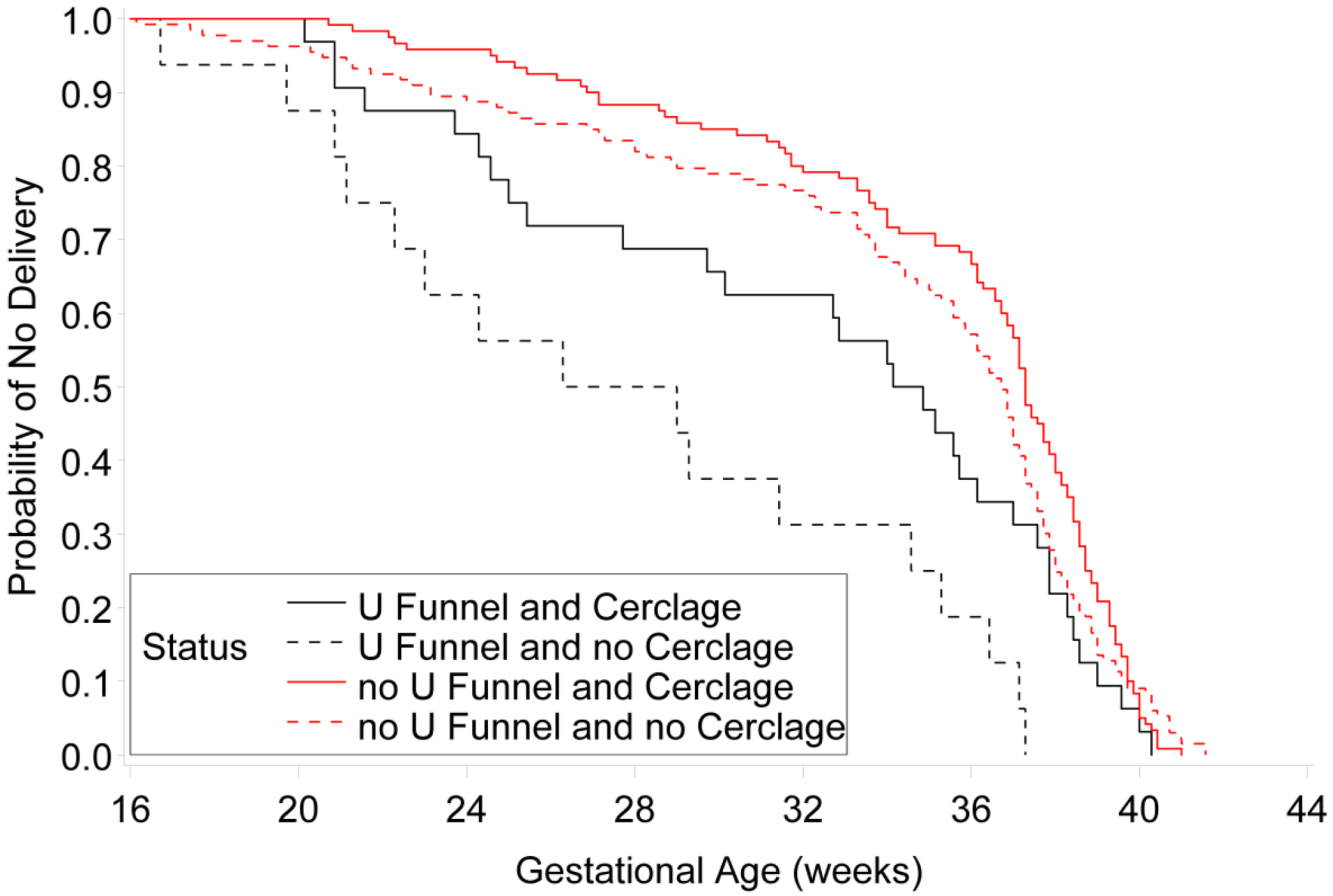

Figure 2.
Kaplan-Meier plot of rates of delivery by U-funnel status and cerclage placement.

Table 1

Demographic Characteristics

	Funnel Type			
	None (n=154)	**V (n=99)**	**U (n=48)**	**p-value**
Actual Cerclage Placement	67 (44)	53 (54)	32 (67)	0.015
Race/ethnicity* - no. (%) Black (non-Hispanic) White (non-Hispanic) Hispanic Other	89 (58) 31 (20) 23 (15) 11 (7)	62 (62) 15 (15) 11 (11) 11 (11)	22 (46) 7 (15) 10 (21) 9 (10)	0.14
Maternal age (y)	25.9 ± 5.4	26.5 ± 5.1	28.2 ± 4.8	0.03
Number of prior births (n)	2 (1, 4)†	2 (1, 4)†	1 (1, 3)†	0.15
Gestational age of earliest prior preterm birth (wks)	25.5 ± 4.6	23.9 ± 4.7	21.5 ± 3.9	< 0.0001
Weeks of gestation at first vaginal sonogram (wks)	17.5 ± 1.3	17.2 ± 1.2	17.4 ± 1.5	0.22
Weeks of gestation at randomization (wks)	19.4 ± 2.0	19.5 ± 2.0	19.3 ± 1.9	0.91
Baseline cervical length at randomization visit (mm)	23.6 ± 5.3	20.3 ± 5.6	14.2 ± 7.2	< 0.0001
Shortest cervical length at randomization visit (mm)	21.1 ± 4.3	18.8 ± 5.2	13.0 ± 6.7	< 0.0001

Plus-minus values are means and one standard deviation.

*Race and ethnic group are self-reported

†Median and interdecile range

Table 2

Covariate-adjusted odds ratios for preterm birth for women with U-shaped funnel vs. either V-shaped or no funnel. Covariates include actual cerclage placement and shortest observed cervical length at randomization visit.

Outcome	OR	Lower 95%	Upper 95%	p-value
PTB < 37	2.142	0.999	4.591	0.0502
PTB < 35	2.067	1.005	4.249	0.0484
PTB < 28	2.399	1.082	5.319	0.0313
PTB < 24	2.285	0.847	6.163	0.1026