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Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length

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OBJECTIVE: The objective of the study was to assess cerclage to prevent recurrent preterm birth in women with short cervix.

STUDY DESIGN: Women with prior spontaneous preterm birth less than 34 weeks were screened for short cervix and randomly assigned to cerclage if cervical length was less than 25 mm.

RESULTS: Of 1014 women screened, 302 were randomized; 42% of women not assigned and 32% of those assigned to cerclage delivered less than 35 weeks ($P = .09$). In planned analyses, birth less than 24 weeks ($P = .03$) and perinatal mortality ($P = .046$) were less frequent in the cerclage group. There was a significant interaction between cervical length and cerclage. Birth less than 35 weeks ($P = .006$) was reduced in the less than 15 mm stratum with a null effect in the 15-24 mm stratum.

CONCLUSION: In women with a prior spontaneous preterm birth less than 34 weeks and cervical length less than 25 mm, cerclage reduced previable birth and perinatal mortality but did not prevent birth less than 35 weeks, unless cervical length was less than 15 mm.

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Background and Objective

The role of cervical cerclage to prevent preterm birth is controversial. Ultrasound studies showing that the cervix appeared to shorten without contractions in women destined for preterm birth led many to consider cerclage, but several randomized trials have not supported this practice. More recently a patient-level metaanalysis of 4 randomized cerclage trials uncovered a relationship between pregnancy history and cerclage: intervention was effective only in singletons (there was significant harm observed in multiple gestations), and it was especially beneficial in women who had a prior preterm birth.

Thus, significant controversy remains regarding appropriate candidate selection for cerclage. We hypothesized that cerclage would reduce preterm birth before 35 weeks' gestation in women with a prior early spontaneous preterm birth before 34 weeks' gestation and a cervical length less than 25 mm.

Materials and Methods

This randomized trial was performed at 15 US centers from January 2003 through November 2007. Healthy women carrying singletons were screened to identify those with at least 1 prior spontaneous preterm birth at $17^{0/7}$ to $33^{6/7}$ weeks' gestation, confirmed by medical record review. When records were unavailable, women remained eligible if the prior birth was from spontaneous causes and the reported birthweight was less than 2 kg. Exclusions included fetal anomaly, planned history–indicated cerclage, and significant maternal-fetal complications.

The cervical length at each visit was measured along a closed endocervical canal. Fundal pressure was also applied 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 for each examination was recorded.

The first scan was scheduled at $16^{0/7}$ to $21^{6/7}$ weeks' gestation. Serial scans were scheduled every 2 weeks unless the cervical length was 25-29 mm, after which scans were scheduled weekly. 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.

★ EDITORS' CHOICE ★

If on any evaluation the cervical length was less than 25 mm, the woman became eligible for randomization to cerclage or no cerclage. At the qualifying evaluation, a sterile speculum examination was performed to rule out acute cervical insufficiency. If it was identified, managing physicians were notified and the woman became ineligible for randomization.

Consenting women assigned to cerclage were to be scheduled for surgery within 96 hours of the qualifying scan, with a McDonald procedure the technique of choice. Postrandomization management was similar in both groups and included the recommendation for pelvic rest and physical activity restrictions. Research nurses maintained weekly contact with participants. Women in the no-cerclage group could receive a physical examination–indicated cerclage for acute cervical insufficiency, whereas women who had undergone cerclage could undergo revision. Cerclage removal was planned for 37 weeks' gestation.

The primary study outcome was birth at less than 35 weeks' gestation, but planned secondary outcomes included the rates of previable birth (less than 24 weeks) and perinatal death. We also hypothesized an interaction between cerclage efficacy and cervical length at randomization.

Early in the trial, the results of a randomized trial of 17-alpha-hydroxyprogesterone caproate became available. In response to this report, progesterone for preterm birth prevention became an option for study participants, and an additional randomization stratum, reflecting the woman's intent to use progesterone, was added.

Intergroup comparisons were performed using the principle of intent to treat.

Results

Of the 1014 consenting, eligible participants who underwent sonographic cervical length assessment, 318 (31%) experienced cervical length shortening less than 25 mm and 302 were assigned to no-cerclage or cerclage groups; 1 woman in the cerclage group was lost to follow-up. Only 1 woman was excluded from randomization because of acute cervical insufficiency at the randomization visit. The 2 groups were well balanced with regard to important characteristics.

A total of 14 women assigned to the no-cerclage group (9.1%) underwent the procedure, 4 solely at the discretion of their managing physicians. Ten were placed for a diagnosis of acute cervical insufficiency, confirmed by medical record review. Eleven women in the cerclage group (7.4%) did not receive the intervention: 8 declined surgery, whereas 3 procedures were contraindicated because of obstetric complications.

The primary outcome of preterm birth less than 35 weeks' gestation was observed in 32% of women in the cerclage group vs 42% in the no-cerclage group (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.42–1.07; $P = .09$). Kaplan-Meier survival analysis, considering length of gestation, suggested a benefit from cerclage ($P = .053$).

The interaction between cervical length strata less than 15 mm (n = 64) vs 16-24 mm (n = 237) and treatment was significant ($P = .03$). Stratified logistic regression analyses indicated that in the less than 15 mm stratum, there was a significant benefit from cerclage for reducing birth less than 35 weeks (OR, 0.23; 95% CI, 0.08–0.66; $P = .006$) vs a null finding in the 15-24 mm stratum (OR, 0.84; 95% CI, 0.49–1.4; $P = .52$). As depicted in the Figure, the Kaplan-Meier graph and associated log-rank test ($P = .024$) demonstrated a significant beneficial effect of cerclage in the less than 15 mm stratum.

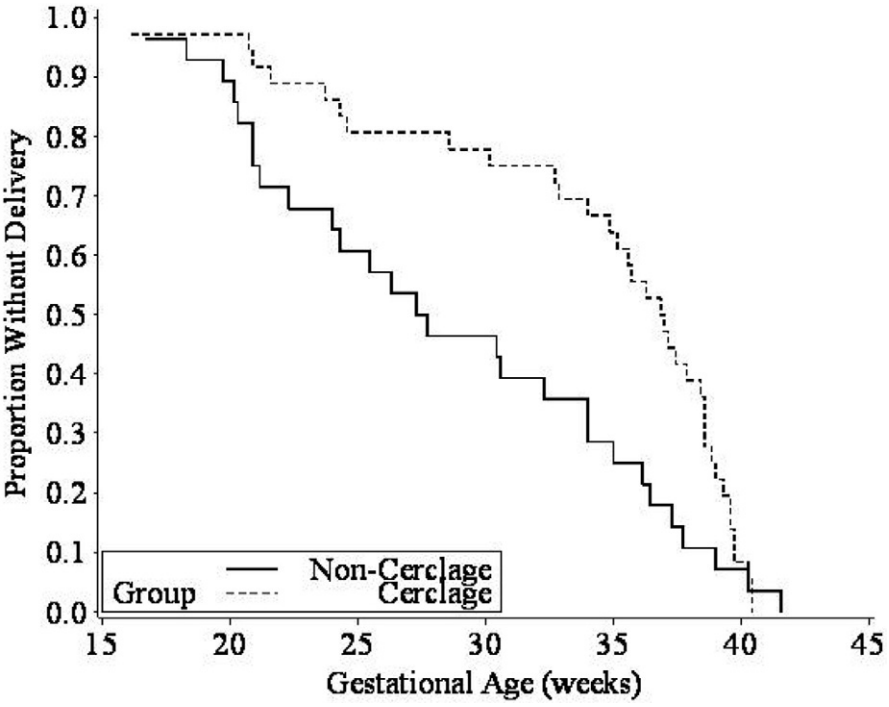
When the progesterone-use stratum was introduced, only 10 of the eventual 302 (3.3%) women had been randomized. Of the subsequent 292, 117 were randomized within the progesterone stratum. One woman who was lost to fol-

low-up was randomized both to the cerclage group and with the intent to use progesterone. In a logistic regression model, the effect of the patient's plan to use progesterone on preterm birth <35 weeks was null (OR, 0.97; 95% CI, 0.6–1.6).

Delivery <7 days from randomization was uncommon, affecting only 7 (2.3%) women, and the intergroup distribution was not significantly different ($P = .72$). However, previable birth at less than 24 weeks occurred in 14% of the no-cerclage group vs 6.1% of the cerclage group ($P = .03$). Intergroup rates of perinatal death were also significantly different: 8.8% in the cerclage group vs 16% in the no-cerclage group ($P = .046$).

Adverse events associated with cerclage placement were uncommon. Of the women who underwent protocol-directed cerclage (cerclage group, n = 138), emergent cerclage (no-cerclage group, n =14), or a cerclage revision (cerclage group, n =1), only 2 experienced a reported complication: 1 experienced chorioamnion rupture during the procedure and 1 experienced a postoperative hemorrhage.

FIGURE
Survival curves of women whose cervical length at randomization was <15 mm



Kaplan-Meier survival curves indicating the proportions of women in the cerclage and no-cerclage groups, limiting the analysis to the 64 women whose cervical length at randomization was less than 15 mm.

Owen. Cerclage for preterm birth prevention in shortened midtrimester cervical length. Am J Obstet Gynecol 2009.

Comment

We did not observe a statistically significant benefit from cerclage in preventing birth before a gestational age of 35 weeks. This endpoint was chosen to avoid cases of near-term birth, which are associated with much lower rates of neonatal morbidity. Nevertheless, our findings suggest that cerclage, used for short cervix in women with prior early spontaneous preterm birth, can improve pregnancy outcomes with essentially no demonstrable harm.

We have demonstrated a biologically predictable, differential benefit of cerclage when the cervical length is very short, less than 15 mm. We chose 15 mm as an alternate cutoff to define shortened cervical length because this has been utilized to assess both the predictive value of sonographic cervical length and cerclage effectiveness for short cervix. Unknown are the factors that incite pathologic shortening. Similarly, the mechanism of cerclage benefit is unknown, but it may support the immunologic barrier between the extraovular space and vaginal flora.

A possible limitation was the cap at $22^{6/7}$ weeks on the upper gestational age for screening and randomization, potentially limiting the generalizability of results beyond this gestational age. We were concerned about cerclage-associated complications at the threshold of viability and the possibility of an interaction with other postviability treatments for threatened preterm birth. Other investigators have extended this temporal window to include more of the midtrimester. The possibility of missing women who underwent rapid shortening and delivery during the sonographic screening was a concern, but only 1 woman was excluded from the randomized trial because of acute cervical insufficiency. To the extent that some of our patients may have continued to experience cervical shortening after completion of ultrasound screening and who might also have benefited from cerclage placement, our findings may underestimate cerclage benefit.

We emphasize that this study selected women with a prior spontaneous preterm birth of a singleton at less than 34 weeks' gestation. We recommend that women with this history be considered for serial cervical length assessment every 2 weeks beginning as early as 16 weeks, with weekly assessment if the cervical length is 25-29 mm. Nevertheless, our findings may not define the optimal cervical length cutoff for ultrasound-indicated cerclage. Although we demonstrated lower rates of previable birth and perinatal mortality using the trial's entry cervical length cutoff of 25 mm, we also recognize that the beneficial effect of cerclage is significantly pronounced with very shortened cervical length less than 15 mm.

CLINICAL IMPLICATIONS

- Cerclage can improve pregnancy outcome in women with a prior spontaneous preterm birth less than 34 weeks and cervical length less than 25 mm.
- The beneficial effect of cerclage for pregnancy prolongation is pronounced when the cervical length is less than 15 mm.
- Pathways to pathologic premature cervical shortening and the mechanism of cerclage benefit remain speculative and in need of further research.
- Sonographic cervical assessment of selected women with a well-documented preterm birth history can now be recommended. ■

The association between stillbirth in the first pregnancy and subsequent adverse perinatal outcomes

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OBJECTIVE: We sought to examine the association between first-pregnancy stillbirth and subsequent adverse perinatal outcomes.
STUDY DESIGN: This cohort study examined the first 2 singleton deliveries at 20-44 weeks' gestation from 1991-2008 (n = 71,315) using birth certificate, hospitalization, and outpatient encounter files. Multivariable logistic regression models were used to assess the association.
RESULTS: Stillbirth was observed in 5.3 of 1000 first deliveries. There was an increased risk of ischemic placental disease (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.2–2.1), fetal distress (OR, 2.8; 95% CI, 1.7–4.5), chorioamnionitis (OR, 2.3; 95% CI 1.5–4.3), extreme preterm birth (OR, 4.2; 95% CI, 1.8–9.9), and early neonatal mortality (OR, 8.3; 95% CI, 3.7–18.6) in pregnancies after stillbirth vs pregnancies after live birth. Interpregnancy intervals <2 and ≥4 years after stillbirth increased the risk of ischemic placental disease and spontaneous preterm birth. Risks varied by stillbirth subtype.
CONCLUSION: A first-pregnancy stillbirth may increase adverse perinatal outcomes in subsequent pregnancy.

Cite this article as: Getahun D, Lawrence JM, Fassett MJ, et al. The association between stillbirth in the first pregnancy and subsequent adverse perinatal outcomes. Am J Obstet Gynecol 2009;201:378.e1-6.

Background and Objective

Stillbirth, the birth of a dead fetus at ≥20 weeks of gestation, is a global public health problem that affects millions of women worldwide. It remains one of the major causes of perinatal mortality in developed countries and even more so in developing countries. In the United States, the incidence of stillbirth declined from 18.4 per 1000 births in 1950 to 6.2 per 1000 births in 2003.

★ EDITORS' CHOICE ★

The etiology of stillbirth remains largely unknown. Previous studies have identified numerous risk factors for stillbirth, including advanced maternal age, low socioeconomic status, obesity, genetic factors, multiparity, a history of stillbirth, smoking and alcohol use during pregnancy, inadequate prenatal care, and medical and obstetric complications. However, few data exist on the relationship between stillbirth and ischemic placental diseases (IPDs) and other adverse perinatal outcomes such as fetal distress, chorioamnionitis, spontaneous preterm birth (SPTB), and neonatal mortality in subsequent pregnancies. It is also unclear whether the magnitude of the association between a prior stillbirth and above-listed adverse perinatal outcomes is modified by the interval between pregnancies.

The purposes of this study were to examine the association between stillbirth in the first pregnancy and subsequent adverse perinatal outcomes and to determine whether risks are modified by interpregnancy interval.

Materials and Methods

A cohort study of successive singleton birth outcomes in Kaiser Permanente Southern California hospitals (1991–2008) was performed using data from

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