Original Research

Indomethacin and Antibiotics in Examination-Indicated Cerclage

A Randomized Controlled Trial

Emily S. Miller, MD, MPH, William A. Grobman, MD, MBA, Linda Fonseca, MD, and Barrett K. Robinson, MD, MPH

OBJECTIVE: To evaluate whether perioperative indomethacin and antibiotic administration at the time of examination-indicated cerclage placement prolongs gestation.

METHODS: This is a randomized controlled trial performed at a single tertiary care hospital between March 2010 and November 2012. Women older than 18 years of age with a singleton pregnancy between 16 0/7 and 23 6/7 weeks of gestation undergoing an examination-indicated cerclage were eligible. Women were randomly assigned to receive either perioperative indomethacin and antibiotics or no perioperative prophylactic medications. The primary outcome was gestational latency after cerclage placement. Fifty women were required to be randomized to show, with 80% power, a 28-day improvement in latency assuming a latency without intervention of 50±35 days.

RESULTS: Fifty-three patients were enrolled with three lost to follow-up. A greater proportion of pregnancies were prolonged by at least 28 days among women who received indomethacin and perioperative antibiotics (24 [92.3%] compared with 15 [62.5%], P=.01). However, gestational age at delivery and neonatal outcomes were statistically similar between groups.

CONCLUSIONS: Among women receiving an examination-indicated cerclage in the second trimester, gestation was significantly more likely to be prolonged by 28 days among women who received perioperative indomethacin and antibiotics.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01114516.

(Obstet Gynecol 2014;123:1311–6)

DOI: 10.1097/AOG.0000000000000228

LEVEL OF EVIDENCE: I

Cervical insufficiency, or painless second-trimester cervical dilation, which can lead to preterm delivery, occurs in approximately 1% of the obstetric population and has been implicated in as many as 10–25% of second-trimester pregnancy losses.[1] In some cases, cervical insufficiency is diagnosed before delivery when a woman presents with significant cervical dilation on physical examination, often with amniotic membranes present at or beyond the level of the internal cervical os. There is some evidence from observational studies and one randomized trial that in this setting, placement of an examination-indicated cerclage prolongs gestation and improves the chance of reaching a gestational age compatible with neonatal survival.[2–5]

Many investigators have used various tocolytic and antibiotic regimens alongside cerclage to prolong pregnancy in the setting of examination-indicated cerclage placement.[2–11] Novy and colleagues[12] have suggested that, in the setting of cervical insufficiency, the cerclage serves to protect the fetal membranes, whereas concomitant medications "remove inciting stimuli" and "restore homeostasis." Nevertheless, neither antibiotics nor indomethacin have been shown to improve outcome, and correspondingly, the American Congress of Obstetricians and Gynecologists suggests caution regarding their use in the setting of examination-indicated cerclage placement.[13]

This randomized trial was designed to evaluate whether the addition of perioperative indomethacin

From the Departments of Obstetrics and Gynecology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, University of Texas Southwestern–Austin, Austin, Texas, Indiana University School of Medicine, Indianapolis, Indiana.

Presented at the Society for Maternal-Fetal Medicine Annual Meeting, February 3–8, 2014, New Orleans, Louisiana.

Corresponding author: Emily S. Miller, MD, MPH, Northwestern University, Feinberg School of Medicine, Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, 250 E Superior Street, Suite 05-2185, Chicago IL 60611; e-mail: emily-miller-1@fsm.northwestern.edu.

Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/14

and antibiotics prolongs gestational latency after examination-indicated cerclage placement.

PATIENTS AND METHODS

Before initiation, this randomized trial was approved by the Northwestern University institutional review board. Enrollment began in March 2010 and was completed in November 2012. Follow-up was completed in March 2013. All pregnant women presenting to Northwestern Memorial's Prentice Women's Hospital with cervical dilation without regular uterine contractions or other evident etiology and who had opted for examination-indicated cerclage placement as part of their clinical care were screened for study participation. No women in this study had a cerclage placed only on the basis of a short cervical length on ultrasonography. Inclusion criteria were a viable singleton gestation between 16 0/7 and 23 6/7 weeks of gestation with intact membranes. Exclusion criteria were age younger than 18 years, human immunodeficiency virus-positive status, major fetal congenital anomalies, temperature of 100.4°F or higher, prior cerclage during the current pregnancy, a contraindication to indomethacin, or an allergy to both penicillin and clindamycin. Women also were excluded if they had received indomethacin or any antibiotics within 7 days before their presentation.

After patients were deemed eligible, they were provided informed consent. Those who consented to participate were randomized according to a random numbers table. Block sizes of 10 were used to prevent gross imbalances between study arms. Allocation concealment used sealed, sequentially numbered opaque envelopes; once consent was obtained, the next sequentially numbered envelope was opened to reveal the card inside that indicated whether a woman was placed in the control (cerclage placement only) or intervention (administration of indomethacin and antibiotics in addition to cerclage placement) group. Women who chose not to be in the study did not receive adjunctive therapies.

All cerclages were performed using the McDonald technique by a maternal-fetal medicine physician with the assistance of a resident, fellow, or both. An amniocentesis for assessment of subclinical intraamniotic infection was not routinely performed. Patients were placed in dorsal lithotomy with use of Trendelenburg positioning as needed. The perineum was cleaned with Betadine with intravaginal saline lavage performed at the surgeon's discretion. Ring forceps were placed on the cervix, traction applied, and a 5-mm Mersilene suture passed circumferentially through the cervical stroma as cephalad as possible. Ultrasonography was not used routinely to guide placement. Retrograde filling of the bladder and use of an intracervical Foley or a moistened sponge stick for reduction of prolapsed membranes were used when deemed necessary.

Participants in the intervention group received one oral dose of 50 mg indomethacin immediately postoperatively followed by a 50-mg oral dose 8 and 16 hours postoperatively. In addition, women in this group received three weight-based doses of intravenous cefazolin. Participants weighing less than 100 kg received 1 g cefazolin, and those weighing 100 kg or more received 2 g cefazolin. The first dose was given preoperatively, and the next two doses were given 8 and 16 hours postoperatively. For those with a penicillin allergy, 600 mg intravenous clindamycin was substituted. Because no prior studies have demonstrated best practice with regard to the perioperative antibiotic regimen, our choice was empiric. Participants in the control group did not receive any perioperative tocolytics or antibiotics.

All patients were hospitalized for approximately 24 hours after the cerclage and typically seen 1 week after hospital discharge and then thereafter at the health care provider's discretion. Participants did not receive any maintenance tocolytic or longer-term antibiotic treatment. Antenatal steroids were not routinely administered at any specific gestational age but, rather, were reserved for a clinical change suggesting imminent preterm birth between 24 and 34 weeks of gestation. The cerclage was removed either when preterm labor was suspected or at 36–37 weeks of gestation.

Demographic and historical information, including maternal age, race or ethnicity, parity, medical history, history of premature birth, and any prior receipt of progesterone during the pregnancy, were collected. Clinical information concerning cerclage placement including the presence of symptoms (ie, pelvic pressure or discharge) at the time of cerclage placement, the preoperative white blood cell count, the gestational age, and the cervical examination at diagnosis were abstracted from the medical records. The presence of membrane prolapse was made based on physical examination. Outcomes were obtained by collecting data from the maternal and neonatal medical records.

The primary outcome was gestational latency after cerclage placement. Based on reviewed outcomes of 116 women at our own institution, we assumed that gestational latency in the absence of intervention would be 50 days (±35 days). We aimed to detect a minimum difference in latency with adjunctive treatment of 28 days. As such, with 80% power and an α (two-sided) of 0.05, 25 patients were needed in each arm. Taking into account a potential loss to follow-up rate of 6%,

three additional patients were added to our total targeted enrollment.

Planned prespecified secondary outcomes included the following perinatal variables: gestational age at delivery, preterm delivery (less than 24 weeks, less than 28 weeks, and less than 36 weeks of gestation), preterm premature rupture of membranes, gestational age at preterm premature rupture of membranes, chorioamnionitis at the time of delivery, birth weight, neonatal intensive care admission, neonatal intensive care days, and neonatal survival until discharge. Select neonatal morbidities also were abstracted from the medical records, including respiratory distress syndrome, necrotizing enterocolitis, grade 3 or 4 intraventricular hemorrhage, retinopathy of prematurity, patent ductus arteriosis, and sepsis. A composite adverse neonatal outcome, defined as either fetal or neonatal demise or one of the aforementioned morbidities, was also compared between the groups.

Analyses were performed in an intent-to-treat manner using χ^2, Fisher's exact tests, Student's *t* tests, and Mann-Whitney *U* tests, as appropriate. Additionally, a survival analysis of gestational latency was performed. All tests were two-tailed and $P<.05$ was used to define statistical significance. All analyses were performed with Stata 13.

RESULTS

Fifty-eight patients were approached for participation in this study. One had a contraindication to indomethacin, one had recently received antibiotics for treatment of bacterial vaginosis, and three declined to participate. Therefore, 53 patients were consented and randomized with 27 assigned to the intervention group. Three patients were lost to follow-up. Figure 1 shows the patient flow diagram.

Baseline demographic and clinical information were similar between groups (Table 1). Of the women randomized to the intervention arm, 25 (96%) women received cephazolin and one (4%) received clindamycin. Median gestational latency did not significantly differ between the intervention and control groups (97 days [interquartile range 57–125] compared with 80 days [interquartile range 15–122], $P=.18$). Similarly, a Kaplan–Meier survival analysis did not demonstrate any statistically significant difference in gestational latency between the two groups ($P=.18$; Fig. 2). However, when latency was analyzed categorically, there was a significant increase in the frequency of latency greater than 28 days in those randomized to the intervention arm (92.3% compared with 62.5%, $P=.01$). This increase in gestational latency beyond 28 days, however, did not translate into a statistically

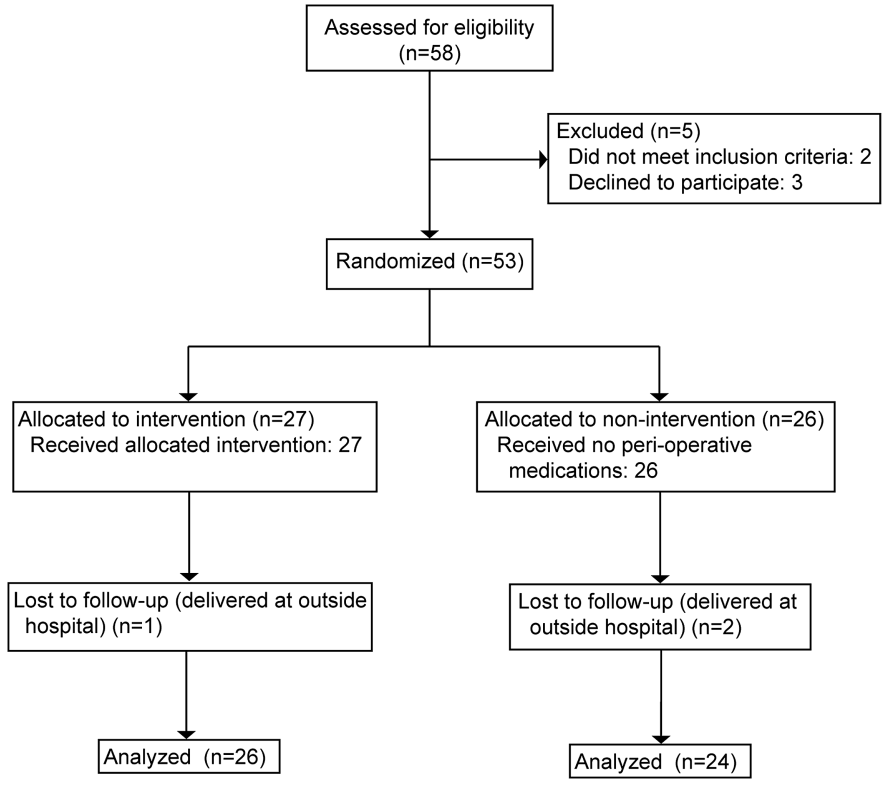

Fig. 1. Patient flow diagram.
Miller. Interventions in Examination-Indicated Cerclage. Obstet Gynecol 2014.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Intervention (n=26)	Nonintervention (n=24)
Age (y)	31.9±6.5	28.7±4.9
Race or ethnicity		
White	6 (23.1)	3 (12.5)
Black	13 (50.0)	14 (58.3)
Latina	6 (23.1)	5 (20.8)
Other	1 (3.8)	2 (8.3)
Nulliparous	11 (42.3)	13 (54.2)
Prior birth at less than 34 wk of gestation	9 (34.6)	9 (37.5)
Known Mullerian anomaly	1 (3.8)	1 (4.2)
Prior LEEP or cold knife cone	2 (7.7)	2 (8.3)
Gestational age at cerclage placement (wk)	20.1 (19.4–21.1)	20.7 (20.1–21.4)
Symptomatic at presentation	3 (11.5)	5 (20.8)
White blood cell count before cerclage (n=30)	10.2±2.4	10.2±2.9
Cervical dilation at cerclage placement	1.3 (1–2)	1 (1–1.5)
Dilation 2 cm or greater	8 (30.8)	4 (16.7)
Ultrasound-determined cervical length before cerclage (cm) (n=32)		
Less than 1	11 (45.8)	6 (23.1)
1–2	7 (29.2)	7 (26.9)
More than 2	6 (25.0)	13 (50.0)
Membranes within cervical canal	14 (53.8)	13 (56.5)
Membranes beyond external os	5 (19.2)	1 (4.2)

LEEP, loop electrosurgical excisional procedure.
Data are mean±SD, median (interquartile range), or n (%).

significant difference in gestational age at delivery (Table 2). Similarly, there were no differences in the frequency of preterm premature rupture of membranes or chorioamnionitis between the two groups (Table 2).

Table 3 demonstrates perinatal outcomes. There were no differences between the groups in birth weight, neonatal intensive care unit admission, or select severe neonatal morbidities. Additionally, neither survival nor the composite outcome (ie, respiratory distress syndrome, necrotizing enterocolitis, grade 3 or 4 intraventricular hemorrhage, retinopathy of prematurity, patent ductus arteriosis, sepsis, or death) differed between the groups.

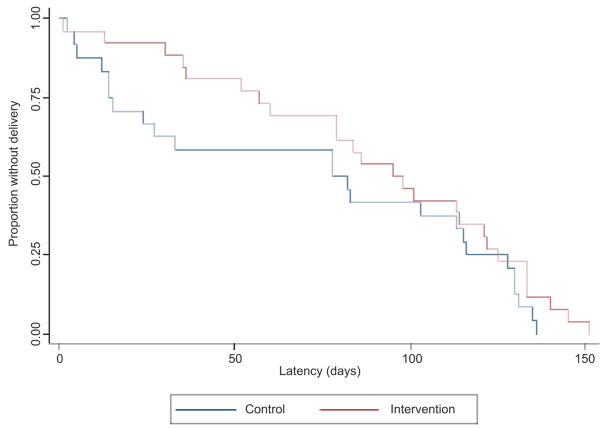

Fig. 2. Survival curve of gestational latency after cerclage placement. *P*=.18.

Miller. Interventions in Examination-Indicated Cerclage. Obstet Gynecol 2014.

DISCUSSION

This randomized controlled trial conducted among women with singleton gestations and second-trimester cervical dilation that resulted in cerclage placement demonstrated no difference in median gestational latency or frequency of preterm birth in women who received perioperative indomethacin and antibiotics. However, a greater proportion of pregnancies were prolonged by at least 28 days among women who received the intervention. This study was underpowered to translate this evidence of pregnancy prolongation into improvements in neonatal outcomes.

There is biologic plausibility behind this observed prolongation of gestational latency that extends only through the period proximate to surgical intervention. It has been demonstrated that patients with cervical dilation and prolapsed membranes have high circulating prostaglandin metabolite levels that increase further after cerclage placement.[14,15] The use of indomethacin, a nonsteroidal antiinflammatory drugs may quell uterine activity subsequent to intraoperative cervical manipulation and thereby avoid more rapid progression to preterm birth. Furthermore, because

Table 2. Obstetric Outcomes

Outcome	Intervention (n=26)	Nonintervention (n=24)	RR (95% CI)
Gestational latency (d)			
More than 28	24 (92.3)	15 (62.5)	1.48 (1.06–2.05)
More than 56	20 (76.9)	14 (58.3)	1.32 (0.89–1.96)
Gestational age at delivery (wk)			
Delivery less than 24	4 (15.4)	7 (29.2)	0.53 (0.18–1.58)
Delivery less than 28	7 (26.9)	11 (45.8)	0.59 (0.27–1.27)
Delivery less than 36	14 (53.9)	15 (62.5)	0.86 (0.54–1.38)
Preterm PROM	14 (53.9)	8 (33.3)	1.62 (0.83–3.15)
Chorioamnionitis	6 (23.0)	4 (17.4)	1.33 (0.43–4.12)

RR, relative risk; CI, confidence interval; PROM, premature rupture of membranes.
Data are n (%) unless otherwise specified.

cervical dilation may increase the risk of bacteria ascending from the colonized vagina, perioperative antibiotics may decrease the perioperative risk of bacterial seeding of the uterine cavity.

Unfortunately, given the early gestational age at which cervical insufficiency is diagnosed, increasing the frequency of gestational latency after examination-indicated cerclage placement past 28 days may not translate into improved perinatal outcomes. Although it is true that the point estimates of the frequency of preterm birth and perinatal morbidities were generally lower in the intervention group, these differences were not statistically significant. Because this study was not adequately powered to detect differences in perinatal outcomes, whether this adjunctive therapy affects these outcomes remains uncertain.

We chose to study a regimen that combined both tocolysis and antibiotics because the exact mechanism that underlies preterm delivery is uncertain and likely multifactorial itself. Additionally, many health care providers who place examination-indicated cerclages are proponents of the multifactorial approach. However, it could be that either transient uterine quiescence or the treatment of subclinical infection alone may improve perioperative latency. The design of this study precludes analysis of the independent effect of each of these interventions. An additional limitation is the nonblinded nature of the study. Nevertheless, because randomization occurred after the decision was made to place the cerclage and the primary outcome was not prone to ascertainment bias, it is unlikely that this affected the results of the study.

In summary, among women receiving an examination-indicated cerclage in the second trimester, although median latency was not affected, gestation was significantly more likely to be prolonged by at least 28 days among women who received perioperative indomethacin and antibiotics compared with women in a control group. This did not translate into a discernable reduction in either preterm birth or perinatal morbidity. Larger studies will be necessary to determine whether the observed pregnancy prolongation can translate into improvements in perinatal outcomes.

Table 3. Perinatal Outcomes

Outcome	Intervention (n=26)	Nonintervention (n=24)	*P* or RR (95% CI)
Birth weight (g)	2,850 (1,440–3,380)	2,488 (955–3,175)	.36
NICU admission	11 (42.3)	11 (45.8)	0.92 (0.49–1.72)
NICU days	43 (19–107)	95 (11–112)	.88
Neonatal morbidities			
Respiratory distress syndrome	3 (11.5)	6 (25.0)	0.46 (0.13–1.64)
Necrotizing enterocolitis	1 (3.9)	2 (8.3)	0.46 (0.04–4.77)
Intraventricular hemorrhage	0 (0.0)	0 (0.0)	1.00
Retinopathy of prematurity	2 (7.7)	2 (8.3)	0.92 (0.14–6.05)
Patent ductus arteriosus	1 (3.9)	2 (8.3)	0.46 (0.04–4.77)
Sepsis	1 (3.9)	1 (4.2)	0.92 (0.06–13.95)
Survival until discharge	21 (87.5)	17 (77.3)	1.13 (0.85–1.50)
Composite adverse outcome	8 (30.8)	12 (50.0)	0.62 (0.31–1.24)

RR, relative risk; CI, confidence interval; NICU, neonatal intensive care unit.
Data are median (interquartile range) or n (%) unless otherwise specified.

REFERENCES

1. McDonald IA. Cervical cerclage. Clin Obstet Gynaecol 1980;7: 461–79.
2. Althusius SM, Dekker GA, Hummel P, van Geijn HP; Cervical incompetence prevention randomized cerclage trial. Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone. Am J Obstet Gynecol 2003;189:907–10.
3. Novy MJ, Gupta A, Wothe DD, Gupta S, Kennedy KA, Gravett MG. Cervical cerclage in the second trimester of pregnancy: a historical cohort study. Am J Obstet Gynecol 2001; 184:1447–54.
4. Stupin JH, David M, Siedentopf JP, Dudenhausen JW. Emergency cerclage versus bed rest for amniotic sac prolapse before 27 gestational weeks: a retrospective, comparative study of 161 women. Eur J Obstet Gynecol Reprod Biol 2008;139:32–7.
5. Olatunbosun OA, Al-Nuaim L, Turnell RW. Emergency cerclage compared with bed rest for advanced cervical dilation in pregnancy. Int Surg 1995;80:170–4.
6. Terkildsen MF, Parilla BV, Kumar P, Grobman WA. Factors associated with success of emergent second-trimester cerclage. Obstet Gynecol 2003;101:565–9.
7. Mitra AG, Katz VL, Bowes WA Jr, Carmichale S. Emergency cerclages: a review of 40 consecutive procedures. Am J Perinatol 1992;9:142–5.
8. Latta RA, McKenna B. Emergent cervical cerclage: predictors of success or failure. J Matern Fetal Med 1996;5:22–7.
9. Lipitz S, Libshitz A, Oelsner G, Kokia E, Goldenberg M, Mashiach S, et al. Outcome of second-trimester, emergency cerclage in patients with no history of cervical incompetence. Am J Perinatol 1996;13:419–22.
10. Aarts JM, Brons JTJ, Bruinse HW. Emergency cerclage: a review. Obstet Gynecol Surv 1995;50:459–69.
11. Wong GP, Farquharson DF, Dansereau J. Emergency cervical cerclage: a retrospective review of 51 cases. Am J Perinatol 1993;10:341–7.
12. Novy MJ, McGregor JA, Iams JD. New perspectives on the prevention of extreme prematurity. Clin Obstet Gynecol 1995;38:790–808.
13. American College of Obstetricians and Gynecologists. Cervical insufficiency. ACOG Practice Bulletin No. 48. Obstet Gynecol 2003;102:1091–99.
14. Novy MJ, Ducsay CA, Stanczyk FZ. Plasma concentrations of prostaglandin $F2_{alpha}$ and prostaglandin E_2 metabolites after transabdominal and transvaginal cervical cerclage. Am J Obstet Gynecol 1987;156:1543–52.
15. Vitoratos N, Hassiakos D, Louridas C, Limuris G, Zourlas PA. Prostaglandin F1a and prostaglandin E2 plasma levels after transvaginal cervical cerclage. Clin Exp Obstet Gynecol 1996; 23:21–5.