OBSTETRICS

Cerclage in twin pregnancy with dilated cervix between 16 to 24 weeks of gestation: retrospective cohort study

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BACKGROUND: Cervical dilation in the second trimester is associated with a greater than 90% rate of spontaneous preterm birth and a poor perinatal prognosis.

OBJECTIVE: To compare the perinatal outcomes of twin pregnancies with dilated cervix in women who underwent either cerclage or expectant management.

STUDY DESIGN: Retrospective cohort study of asymptomatic twin pregnancies identified with cervical dilation of ≥1 cm at 16–24 weeks (1997–2014) at 7 institutions. Exclusion criteria were genetic or major fetal anomaly, multifetal reduction at >14 weeks, prior cerclage placement, monochorionic–monoamniotic placentation, active vaginal bleeding, labor, chorioamnionitis, elective termination of pregnancy, or medically indicated preterm birth. The primary outcome was incidence of spontaneous preterm birth at <34 weeks. Secondary outcomes were incidence of spontaneous preterm birth at <32 weeks, <28 weeks, and <24 weeks; perinatal mortality; and composite adverse neonatal outcome (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis).

RESULTS: A total of 76 women with twin pregnancy with dilated cervix of 1.0–4.5 cm were managed with either cerclage (n = 38) or expectant management (n = 38). Demographic characteristics were not significantly different. Analysis was adjusted for amniocentesis and vaginal progesterone use. In the cerclage group, 29 women (76%) received prophylactic indomethacin and 36 (94%) received prophylactic antibiotics, whereas the expectant management group did not. Interval from time at diagnosis of open cervix to delivery in the cerclage group was 10.46 ± 5.6 weeks vs 3.7 ± 3.2 weeks in the expectant management group, with a mean difference of 6.76 weeks (95% confidence interval [CI], 4.71–8.81). There were significant decreases in spontaneous preterm birth at <34 weeks (52.6% vs 94.7%; adjusted odds ratio [aOR], 0.06; 95% CI, 0.03–0.34), at <32 weeks (44.7% vs 89.4%; aOR, 0.08; 95% CI, 0.03–0.34); at <28 weeks (31.6% vs 89.4%; aOR, 0.05; 95% CI, 0.01–0.2); and at <24 weeks (13.1% vs 47.3%; aOR, 0.17; 95% CI, 0.05–0.54). There were also significant reductions in perinatal mortality (27.6% vs 59.2%; aOR, 0.24; 95% CI, 0.11–0.5), neonatal intensive care unit admission (75.9% vs 97.6%; aOR, 0.07; 95% CI, 0.01–0.66), and composite adverse neonatal outcome (33.9% vs 90.5%; aOR, 0.05; 95% CI, 0.01–0.21).

CONCLUSION: Cerclage, indomethacin, and antibiotics in twin pregnancies with dilated cervix ≥1 cm before 24 weeks were associated with significant longer latency period from diagnosis to delivery (6.7 weeks), decreased incidence of spontaneous preterm birth at any given gestational age, and improved perinatal outcome when compared with expectant management.

Key words: cerclage, dilated cervix, preterm birth, twin delivery

In the United States, the twin birth rate increased by 76% from 1980 through 2009 (from 18.9 to 33.2 per 1,000 total births), mostly due to the increased use of assisted reproductive technology and older maternal age.[1,2] Preterm birth (PTB) in twin pregnancies is 5 times greater than in singletons. In 2013, 56.5% of twin pregnancies delivered before 37 weeks and 11.3% before 32 weeks, whereas in singleton pregnancies 11.3% delivered before 37 weeks and 1.5% before 32 weeks.[1] Twins are also at increased risk for being low-birthweight infants (LBW), and for early neonatal and infant death and complications related to prematurity and LBW.[1,3]

In previous publications, a singleton pregnancy with second-trimester (16–28 weeks) cervical dilation of >1 cm was associated with a poor prognosis, with a greater than 90% rate of spontaneous PTB (SPTB), regardless of prior cervical length, obstetric history, or other risk factors for PTB.[4-8] Cerclage performed secondary to dilated cervix has also been called rescue, emergency, or urgent cerclage. It is defined as a cerclage placed in the presence of cervical changes of the internal os (eg, ≥1 cm dilated, or prolapsed membranes) detected on physical examination (with a speculum or digital examination); effacement is not required for this diagnosis.[9,10] After clinical examination to rule out uterine activity, intraamniotic infection, or both, placement of cerclage (if technically feasible) in patients with singleton gestations who have cervical change of the internal os may be beneficial.[4-8,10-12]

In twins, data on the efficacy of cerclage based on dilated cervix are limited. In contrast to singleton pregnancies, the use of cerclage for dilated cervix in twin pregnancies has not been studied in a dedicated randomized controlled trial (RCT). The only published RCT evaluating cerclage for cervical dilation compared 13 women who received cerclage and indomethacin and 10 women who received bed rest only; all women received antibiotics (the cohort

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included 7 twin pregnancies, 3 in the cerclage and 4 in the bed rest group). This RCT showed a significant decrease in PTB at <34 weeks of gestation and a longer latency interval from diagnosis to delivery (by 30 days); however, twin outcomes were not reported separately.[4] There are a few case series of twin pregnancies with second-trimester cervical dilation in which cerclage was associated with favorable outcomes.[13-16] Three studies compared cerclage in twin vs singleton pregnancies with cervical dilation, showing a high likelihood of delivery at >32 weeks with improved neonatal survival.[17-19] However, there are no studies in twin pregancies comparing the efficacy of cerclage based on physical examination with the appropriate control, namely, twin pregnancies with dilated cervix and expectant management. The risk of adverse perinatal outcome of twin pregnancies with dilated cervix ≥1 cm diagnosed before 24 weeks is unknown.

The risk of intraoperative rupture of membranes during the placement of cerclage in the presence of dilated cervix has been reported to be between 4% and 19%.[8,11,20-23] Common techniques to avoid this complication include the following: amnioreduction,[24,25] Trendelenburg position, gentle traction of the cervix with ring forceps, bladder filling with an infusion of 500 mL of saline solution, and/or reduction of membranes using a sponge stick or Foley balloon.[20-22]

The aim of our study was to evaluate whether the use of cerclage placement in twin pregnancies with asymptomatic cervical dilation of ≥1 cm before 24 weeks decreased the incidence of SPTB at <34 weeks' gestation and adverse neonatal outcomes when compared with expectant management.

Materials and Methods

This was a retrospective cohort study of twin pregnancies with asymptomatic cervical dilation of the internal os ≥1 cm or prolapsed membranes up to the external os, without signs of labor or chorioamnionitis at 16−24 weeks between 1997 and 2014 at Thomas Jefferson University Hospital (PA), North Shore University Hospital (NY), Long Island Jewish Medical Center (NY), University of Naples Federico II (Italy), Columbia University Medical Center (NY), Beth Israel Deaconess Medical Center (MA), and Robert Wood Johnson Medical School Rutgers University (NJ). Exclusion criteria were as follows: genetic or major fetal anomalies, history of multifetal pregnancy reduction to twins >14 weeks, elective termination of pregnancy, monochorionic−monoamniotic placentation, medically indicated PTB (twin−twin transfusion syndrome, severe preeclampsia, placental abruption, or placenta previa), cerclage placed for another indication (history or ultrasound indicated cerclage) or if, at diagnosis, prolapsed amniotic membranes beyond the external os, active vaginal bleeding, labor, preterm premature rupture of membranes (PPROM), or chorioamnionitis (clinical or subclinical).

Some patients were identified in the ultrasound unit when cervical length was suspected to be short based on either transabdominal or transvaginal ultrasound, and this prompted a physical examination because of concern for cervical insufficiency (the inclusion criteria were dilated cervix and no short cervix). Other patients were identified in the provider's office or the emergency room if the patients reported contractions or vaginal discharge. Patients were then evaluated in the labor and delivery suite for active labor or chorioamnionitis (either clinically or by amniocentesis of the presenting twin). Patients were deemed asymptomatic if, after an observation period, the symptoms subsided and the patients were clinically stable to be discharged from hospital care. Cerclage or expectant management was offered to those women who were considered asymptomatic by the physician. The management group was determined by the preference of the treating physician only.

The following variables were collected by retrospective chart review: age, parity, race/ethnicity, chorionicity, use of artificial reproductive technology, gestational age (GA) at the time of cervical dilation, cervical dilation (in centimeters), GA at the time of cerclage, type of cerclage (Shirodkar or McDonald), type of suture, amniocentesis, amnioreduction, manipulation of membranes during the cerclage, maternal comorbidities, PPROM, admission to the antenatal unit, hospital length of stay (LOS), administration of antenatal corticosteroids and tocolysis, GA at delivery, interval from diagnosis of cervical dilation to delivery, delivery indications, and mode of delivery. Neonatal outcomes were also collected, including the following: birthweight (BW), Apgar score at 5 minutes, admission to the neonatal intensive care unit (NICU), NICU LOS, and neonatal morbidities (respiratory distress syndrome [RDS], intraventricular hemorrhage [IVH] grade 3 or 4, necrotizing enterocolitis [NEC] grade 3 or 4 requiring surgery, sepsis, retinopathy of prematurity [ROP] requiring laser treatment, and neonatal survival at discharge).

GA was determined by last menstrual period and early ultrasound. Chorionicity was determined by early ultrasound. Cervical dilation was determined by pelvic and/or speculum examination between 16 and 24 weeks (by digital examination with dilated internal os ≥1 cm and palpable amniotic membranes, and/or by speculum examination with visible dilated cervix and visible membranes into the endocervical canal or at the external os but not beyond the external os). PPROM was defined by gross rupture of amniotic fluid, visualizing amniotic fluid on sterile speculum examination, and a positive nitrazine test result with a ferning pattern on microscopy. Active labor was defined as the presence of regular uterine contractions of 3 or more in 10 minutes with cervical change. Subclinical chorioamnionitis was defined by the following: (1) the combination of the presence of any bacteria in amniotic fluid Gram stain, amniotic fluid leukocyte count (≥6 leukocytes per high-power field or >30 cells/mm^3) and/or amniotic fluid glucose concentration of ≤15 mg/dL[26]; or (2) positive amniotic fluid culture results. Clinical chorioamnionitis was defined as follows: maternal

fever ≥38°C (≥100.4° F) plus 1 of the following: maternal tachycardia (>100 beats/min), fetal tachycardia, (>160 beats/min), marked leukocytosis (>15,000 cells/mm^3), uterine tenderness, or foul odor of the amniotic fluid.[27] Subjects were not randomly assigned to a particular management strategy; patients underwent cerclage or expectant management or any other particular therapy according to physician preference. Decisions to perform amniocentesis, amnioreduction, cerclage, and the surgical technique used were at the discretion of the attending physician after informed consent was obtained from the patient. Cerclage was performed if the patient had a dilated cervix of ≥1 cm, if the patient was clinically asymptomatic, and if preliminary results of amniotic fluid showed no evidence of inflammation (absence of bacteria or leukocytes in the Gram stain, negative leukocyte esterase, and normal levels of glucose in the amniotic fluid), without waiting for culture results.

The primary outcome was SPTB at <34 weeks. The main secondary outcomes were as follows: SPTB at <32 weeks, <28 weeks, or <24 weeks; perinatal mortality and composite neonatal adverse outcome, which required at least 1 of the following: RDS (ventilator support, intubation, continuous positive airway pressure [CPAP], or use of surfactant), IVH grade 3 and 4 as determined by cranial ultrasound or computed tomography (CT) according to the Papile classification,[28] NEC grade 3 and 4 requiring surgery,[29] proven sepsis (clinically ill infant with suspected infection plus positive blood, cerebrospinal fluid [CSF], or catheterized/suprapubic urine culture or cardiovascular collapse or unequivocal x-ray finding), or ROP requiring laser treatment.[30] The primary and secondary outcomes were evaluated in the subgroup of women with cervical dilation of <2 cm and ≥2 cm, to evaluate the efficacy of cerclage in less severe or more severe cases.

The institutional review boards at the participating institutions approved this study. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Inc, Armonk, NY). Data are shown as mean ± standard deviation (SD) or number (percentage). Differences between women who received cerclage and controls were analyzed using the χ^2 test or Fisher exact test for categorical variables. Results of primary and secondary outcomes were presented as odds ratio (OR) or as mean difference with 95% confidence interval (CI). An adjusted OR (aOR) was calculated after adjusting for confounders that were statistically different. Within-group comparison was performed using the Wilcoxon and Mann−Whitney tests. Kaplan−Meier curves were generated for gestational age at delivery by cervical dilation and compared using the log-rank test. A P value of <.05 was considered statistically significant. This study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines.[31]

Results

We identified 76 women with a twin pregnancy and asymptomatic cervical dilation from 1.0 cm to 4.5 cm by physical examination. Of the women, 38 underwent cerclage and 38 were followed up without a cerclage, with expectant management (controls). Demographic characteristics were not significantly different except for rate of amniocentesis. Use of vaginal progesterone was not significantly different between the 2 groups. However, because of the high frequency in the cerclage group (15.8% vs 5.2%, $P = .15$), we included this variable in the logistic regression (Table 1). Analysis was adjusted for amniocentesis and vaginal progesterone administration.

The primary outcome of SPTB at <34 weeks was significantly decreased in the cerclage group: 20 (52.6%) vs 36 (94.7%); adjusted odds ratio (OR): 0.06; 95% confidence interval (CI), 0.03−0.34. Secondary outcomes (rates of SPTB at different gestational ages, admission to antepartum unit, perinatal mortality, and neonatal outcomes) were all significantly decreased in the cerclage group when compared with the control (Table 2). Cerclage was associated with a longer latency period from diagnosis to delivery of 10.5 ± 5.6 vs 3.7 ± 3.2 weeks, with a mean difference of 6.76 weeks (95% CI, 4.71−8.81). The cerclage group also had less admissions to the antenatal unit, and less need of steroids for fetal maturation. Delivery occurred at a later GA in the cerclage group compared with the control group (31.2 ± 5.6 vs 24.3 ± 4.2 weeks; mean difference, 6.90 weeks; 95% CI, 4.67−9.13) (Table 2). PPROM presented also at a later GA (28.2 ± 6.1 vs 22.15 ± 2.5 weeks; mean difference, 6.05; 95% CI, 3.95−8.15). However, the incidence of PPROM or latency from PPROM to delivery were not significantly different. The perinatal mortality was significantly lower in the cerclage group when compared with the control group (21/76 [27.6%] vs 45/76 [59.2%], aOR, 0.24; 95% CI, 0.11−0.5; $P < .0001$). Among the 96 neonates born alive (54 [73.6%] in the cerclage group vs 42 [55.2%] in the control group), NICU admission, NICU LOS, perinatal mortality, and composite adverse neonatal outcome were significantly decreased in the cerclage group compared to the control group (Table 3).

Cerclage and control subjects were distributed evenly in the 17-year period of the study (2−5 cases per year). There were 20 cerclages before 2007 (2−5 cases in those years) vs 18 after 2007. There were no significantly differences in primary or secondary outcomes among cases or controls evaluated during the first half vs the second half of the 17-year period of evaluation.

In all, 29 of 76 women (38%) had CL evaluations before being included in the study (18 [47%] cerclage, 11 [28%] control; $P = .15$). The range and mean of CL were as follows: cerclage 1−16 mm with mean of 6 ± 4.8 mm; control, 1−22 mm with a mean of 9 ± 6.3 mm; $P = .68$. The difference in days between the CL evaluations and the physical examination that diagnosed cervical dilation was 0−1 day in 50% of cases; these women had a cervical length of <10 mm. In the other 50% of women, the time between CL measurements to cervical dilation was 7−28 days. The inclusion criterion

TABLE 1
Maternal demographics of twin pregnancies with dilated cervix

Variable	Cerclage n = 38	Control n = 38	*P* value
Maternal age, y	31.5 ± 5.8	30.0 ± 6.6	.51
Race/ethnicity			
White	24 (63.1)	22 (57.9)	.64
African American	9 (23.6)	9 (23.6)	1.00
Hispanic	4 (10.5)	4 (10.5)	1.00
Asian/Indian	1 (2.6)	3 (7.9)	.32
Nuliparity	22 (57.9)	22 (57.9)	1.00
Diamniotic–dichorionic	30 (78.9)	31 (81.5)	1.00
Assisted reproductive technology	17 (44.7)	19 (50)	.85
Prior PTB	3 (7.9)	4 (10.5)	.73
Prior cervical surgery, LEEP/CKC	1 (2.6)	2 (5.2)	1.0
Smoking	4 (10.5)	8 (21)	.22
BMI	31.37 ± 5.36	30.7 ± 5.8	.68
BMI ≥30	23 (60)	19 (50)	.36
GA at diagnosis, wk	20.7 ± 1.6	20.6 ± 1.9	.67
Cervical dilation at diagnosis, cm	2.0 ± 1.1	2.1 ± 0.9	0.52
Cervical dilation ≥2 cm at diagnosis	24 (63.1)	24 (63.1)	1.00
Membrane prolapse			
None	2	3	1.0
Into cervical canal	36	35	1.0
Amniocentesis	30 (79)	5 (13.1)	<.0001
Vaginal progesterone	6 (15.8)	2 (5.2)	.15
Prophylaxis at time of cervical dilation diagnosis			
Indomethacin	29 (76%)	0 (0)	<.0001
Antibiotics	36 (94%)	0 (0)	<.0001

Data are mean ± standard deviation or number (percentage).

BMI, body mass index; *CKC*, cold knife cone; *GA*, gestational age; *LEEP*, loop electrosurgical excision procedure; *PTB*, preterm birth.

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for this study was the presence of a dilated cervix with visible membranes at physical examination, independent of cervical length measurement by ultrasound, either recent or remote.

Vaginal progesterone was used in 6 women in the cerclage group and in 2 women in the expectant management group. The indication for the use of vaginal progesterone was a cervical length of <15 mm. If patients subsequently developed dilation of the cervix, use of vaginal progesterone was continued after the finding of the dilated cervix. There were no differences when these 2 groups were compared or when cerclage/progesterone vs cerclage/no progesterone were evaluated, likely because of the small sample size.

In all, 35 women underwent amniocentesis in the amniotic sac of twin A to assess for subclinical chorioamnionitis (cerclage, 30/38 [79%]; controls, 5/38 [13.1%]). All amniotic fluid samples had normal glucose levels, had negative Gram stains, were negative for white blood cell count, and had negative cultures at 5 days. Of the 35 women, 14 (40%) also had an amnioreduction (fluid removal of 50–500 cc) before cerclage placement. Women who underwent amnioreduction had no significant differences in SPTB at any GA compared to those who did not have this procedure. All women had a single-stitch McDonald cerclage. A total of 72 women (94%) had visible membranes on speculum examination. In the cerclage group, 17 of 38 (44.7%) required membrane manipulation with either a Foley balloon or a sponge. One of the women in the cerclage group had an intraoperative rupture of membranes, followed by vaginal delivery. Sutures used for cerclage included Mersilene tape in 28 cases (73.6%), Ethibon in 8 cases (21%), and Prolene in 2 cases (5.3%). In the cerclage group, 29 women (76%) received prophylactic indomethacin, and 36 (94%) received prophylactic antibiotics (mostly a combination of ampicillin and metronidazole), whereas none of the women in the expectant management group received indomethacin or antibiotics at the time of diagnosis with dilated cervix. During the antepartum period, women in the cerclage group had significantly fewer admissions to the hospital, and less need for antenatal corticosteroids. Women in the cerclage group had a higher rate of cesarean section (Table 1). However, once we removed women with previable GA (8/38 [21%] in cerclage group and 17/38 [44%] in the control group; $P = .049$), the rate of cesarean section was similar in both groups (23/32 [71.8%] in the cerclage group and 13/21 [62%] in the control group, $P = .55$).

We stratified women into those with cervical dilation <2 cm or ≥2 cm (less severe and more severe cervical dilation), and evaluated the perinatal outcomes. There were significant differences in primary and secondary outcomes in both of these groups. In women with a cervical dilation of <2 cm: (cerclage, 14; control, 14), the SPTB at <34 weeks was 5 (35.7%) vs 14 (100%) (aOR, 0.02; 95% CI, 0.01–0.33); composite neonatal outcome was 4/13 (30.7%) vs 6/7 (85.7%) (aOR, 0.07; 95% CI, 0.01–0.83); and longer latency period

from diagnosis to delivery (7.9 weeks; 11.9 ± 4.7 vs 4.0 ± 2.9, mean difference 7.90 weeks, 95% CI, 6.14−9.66) in the cerclage group. In women with a cervical dilation of ≥2 cm (cerclage, 24; and control, 24), the range of cervical dilation was 2.0−4.5 cm in each group, with similar means and SD ($P = .25$): SPTB at <34 weeks was 15 (62.5%) vs 22 (91.6%) (aOR, 0.15; 95% CI, 0.02−0.80); composite neonatal outcome was 9/19 (47.3%) vs 14/14 (100%) (aOR, 0.03; 95% CI, 0.01−0.62), and longer latency period from diagnosis to delivery: 6.1 weeks (9.6 ± 5.9 vs 3.5 ± 3.5, mean difference 6.10 weeks, 95% CI 3.92−8.28) in the cerclage group.

Kaplan−Meier curves were generated for GA at delivery by degree of cervical dilation comparing physical examination−indicated cerclage vs control. The log-rank test showed a significantly different hazard ratio (HR) of 0.33 (95% CI, 0.12−0.34; $P < .0001$) (Figure 1). For the subgroup of women with cervical dilation of <2 cm, the Kaplan−Meier curve showed an HR of 0.25 (95% CI 0.04−0.27), $P < .0001$) (Figure 2), and for women with cervical dilation of ≥2 cm an HR of 0.39 (95% CI, 0.15−0.55, $P = .0004$) (Figure 3).

TABLE 2
Antepartum and delivery outcomes of twin pregnancies with dilated cervix

Variable	Cerclage n = 38	Control n = 38	aOR (95% CI)	*P* value
SPTB at <34 weeks	20 (52.6)	36 (94.7)	0.06 (0.03−0.34)	<.0001
SPTB at <32 weeks	17 (44.7)	34 (89.4)	0.08 (0.03−0.34)	<.0001
SPTB at <28 weeks	12 (31.6)	34 (89.4)	0.05 (0.01−0.21)	<.0001
SPTB at <24 weeks	5 (13.1)	18 (47.3)	0.17 (0.05−0.54)	.02
Antepartum admission	14 (36.8)	24 (63.1)	0.35 (0.15−0.87)	.02
Antepartum LOS (days)	12.5 ± 16	4.3 ± 5.5	8.20 (2.79−13.61)[b]	.62
PPROM <34 weeks	8 (21)	12 (31.5)	0.5 (0.3−1.6)	.58
GA at PPROM	28.2 ± 6.1	22.15 ± 2.5	6.05 (3.95−8.15)[b]	.02
Antenatal steroids	11 (28.9)	21 (55.2)	0.33 (0.12−0.85)	.02
Tocolysis	5 (13.1)	8 (21)	0.55 (0.16−1.9)	.36
GA at delivery (weeks)	31.23 ± 5.6	24.3 ± 4.2	6.90 (4.67−9.13)[b]	<.0001
Diagnosis to delivery interval (weeks)	10.46 ± 5.6	3.7 ± 3.2	6.76 (4.71−8.81)[b]	<.0001
Mode of delivery				
Vaginal delivery both	15 (39.4)	25 (65.7)	0.61 (0.37−0.95)	.03
CS both	21 (55.3)	11 (28.9)	1.92 (1.07−3.39)	.03
Vaginal delivery twin A and CS twin B	2 (5.2)	2 (5.2)	1.00 (0.16−6.6)	1.0
Birthweight (g)[a]	1776 ± 948	825 ± 479	951 (613.3−1288.7)[b]	<.0001
Birthweight <1500g[a]	33/76 (43.4)	70/76 (92.1)	0.06 (0.02−0.17)	<.0001
Apgar score <7 at 5 min[a]	18/76 (23.6)	46/76 (60.5)	0.22 (0.12−0.44)	<.0001
Perinatal mortality[a]	21/76 (27.6)	45/76 (59.2)	0.24 (0.11−0.5)	<.0001
Both twins discharged home alive	25/38 (65.7)	14/38 (36.8)	3.2 (1.27−8.4)	.01
At least 1 twin discharged home alive	29/38 (76.3)	17/38 (44.7)	3.8 (1.4−10.6)	<.01

Data are mean ± standard deviation or number (percentage).

aOR, adjusted odds ratio; *CI*, confidence interval; *CS*, cesarean section; *GA*, gestational age; *LOS*, length of stay in the hospital; *MD*, mean difference; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

[a] Data from both twins; [b] Data correspond to mean difference.

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Comment

To our knowledge, this is the first retrospective cohort study comparing the efficacy of cerclage vs expectant management in twin pregnancies with dilated cervix of ≥1 cm. Most of the women in the cerclage group also received prophylactic indomethacin (76%) and antibiotics (94%), whereas the expectant management group did not. Therefore our findings most likely correspond to the combination of the 3 therapies. Overall, women with cerclage, indomethacin, and antibiotics, had significant longer latency periods from diagnosis of dilated cervix to delivery by 6.7 weeks, later GA at PPROM, a significantly decreased incidence of SPTB at <34 weeks, <32 weeks, <28 weeks, and <24 weeks by 90%−95%, less admission to the antenatal unit, and less admission to NICU. Composite neonatal complications were decreased by 90%, and perinatal mortality decreased by 75% in the cerclage group. Benefits were observed in subgroups of women with cervical dilation of ≥2 cm and those with dilation of <2 cm.

Most information on the efficacy of cerclage based on cervical dilation pertains to singletons; with only limited published data on twin gestations. We could only identify 1 RCT on emergency cerclage, which enrolled 23 women (16 singletons and 7 twins).[4] The authors showed a significant difference between diagnosis of dilated cervix to delivery in the cerclage group by 4 weeks (29.9 vs 25.9 weeks) and decreased SPTB at <34 weeks (53% vs 100%; $P = .02$); the outcomes of the 7 twins included in this cerclage-RCT study were not reported separately.[4]

In several retrospective case series of twin pregnancies with second-trimester cervical dilation (16−28 weeks), where cerclage was performed, cerclage was associated with favorable outcomes[13-15,17-19] delivering at significantly later GA (by approximately

TABLE 3
Neonatal outcomes

Variable (born alive only)	Cerclage n = 54	Control n = 42	aOR (95% CI)	*P* value
Composite neonatal outcome	18 (33.9)	38 (90.5)	0.05 (0.01–0.21)	<.0001
Admission to NICU	41 (75.9)	41 (97.6)	0.07 (0.01–0.66)	.02
NICU LOS (days)	32.1 ± 41	87.14 ± 51.9	−55.04 (−76.07 to −34.01)[a]	<.0001
RDS	25 (46.3)	39 (92.8)	0.06 (0.01–0.25)	<.0001
IVH stage 3, 4	2 (3.7)	17 (40.5)	0.05 (0.01–0.26)	<.0001
NEC stage 3, 4	5 (9.2)	12 (28.5)	0.27 (0.08–0.9)	.02
Sepsis	7 (12.9)	10 (23.8)	0.44 (0.1–1.3)	.18
ROP/laser	1 (1.8)	9 (21.4)	0.07 (0.01–0.57)	.01

Data are mean ± standard deviation or number (percentage).

aOR, adjusted odds ratio; *CI*, confidence interval; *IVH*, intraventricular hemorrhage; *LOS*, hospital length of stay; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit; *PDA*, persistent ductus arteriosus; *RDS*, respiratory distress syndrome; *ROP*, retinopathy of prematurity.

[a] Data correspond to mean difference.

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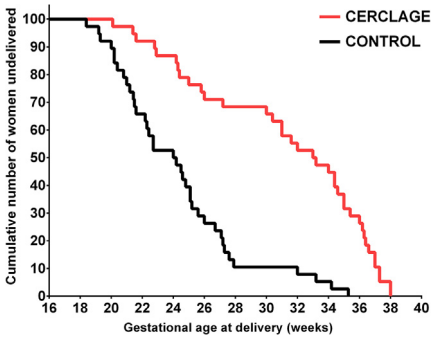
10 weeks). The incidence of SPTB at <32 weeks informed in those studies ranges from 25% to 52%. These studies, mostly with no appropriate control group, are summarized in Table 4.

The strengths of our study include the following: evaluation of neonatal morbidity data; and demonstration of a significant decrease in NICU admission, NICU LOS, and composite neonatal outcome by 90% in the cerclage group compared with expectant management. When neonatal outcomes were looked at individually, there were significantly decreased rates of RDS, NEC, IVH, and ROP in the cerclage group. Perinatal mortality was associated with delivery at <24 weeks in 70% of the cases. The exclusion of women in active labor, with PPROM before diagnosis of dilated cervix, elective termination of pregnancy, or chorioamnionitis was intended to minimize the number of women with preterm delivery unrelated to our study question.

Importantly, we offer for the first time some information regarding the risk of adverse perinatal outcomes in 38 women with twin pregnancies complicated by cervical dilation ≥1 cm at <24 weeks when no treatment was offered. These outcomes seem to be as devastating as the well-known outcomes in singleton pregnancies.

In our cohort, only 7 women (9.2%) had a history of PTB, and only 3 (3.9%) had a history of cervical surgery (LEEP or cone biopsy). There were no differences in outcomes when history of PTB was evaluated in cerclage vs control, confirming the prior report by Goldenberg et al[32] that prior PTB does not represent a strong risk factor for PTB in twin pregnancies, whereas short cervical length in the second trimester is the best predictor of PTB. This finding was confirmed by a recent meta-analysis.[33] Cerclage in twin pregnancies was reported as potentially harmful in a meta-analysis published in 2005 that suggested an increased risk of PTB in 215%.[34] In a new individual patient metaanalysis, using the same 49 women included in 3 RCT of twin pregnancies and short cervical length of <25 mm before 24 weeks,[35] no statistically significant differences in PTB at <34 weeks (aOR, 1.17; 95% CI, 0.23-3.79) were found after adjusting for previous PTB and GA at randomization. After adjusting for previous PTB and GA at randomization, no statistically significant differences in PTB at <34 weeks (aOR, 1.17; 95% CI, 0.23–3.79) were found. Rates of very low birth weight and of RDS were significantly higher in the cerclage group than in the control group. Of note, there were only 7 women (14.2%) with CL of ≤15 mm, 6 of them in the cerclage group. A recent large retrospective

FIGURE 1
Survival curves of twin pregnancies with dilated cervix that remained undelivered across gestation



Kaplan–Meier curves were generated for GA at delivery. Comparison of the cerclage and control groups using the log-rank test showed significant difference (hazard ratio, 0.33; 95% confidence interval, 0.12–0.34; $P < .0001$).

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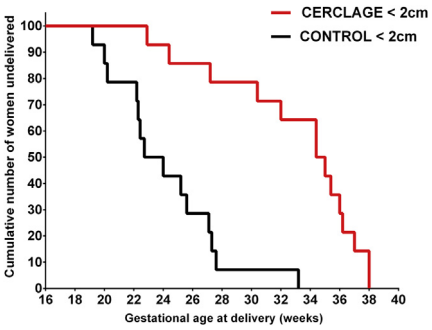
FIGURE 2
Survival curves of twin pregnancies with cervical dilation < 2cm that remained undelivered across gestation



Kaplan–Meier curves were generated for gestational age at delivery and cervical dilation <2 cm. Comparison of the cerclage and control groups using the log-rank test showed a significant difference (cervical dilation <2 cm: hazard ratio, 0.25; 95% confidence interval, 0.04–0.27; $P < .0001$).

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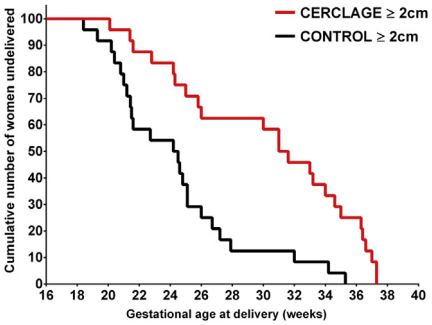
FIGURE 3
Survival curves of twin pregnancies with cervical dilation ≥ 2cm that remained undelivered across gestation



Kaplan–Meier curves were generated for gestational age at delivery and cervical dilation ≥2 cm. Comparison of the cerclage and control groups using the log-rank test showed a significant difference (cervical dilation ≥2 cm: hazard ratio, 0.39; 95% confidence interval, 0.15– 0.55; $P = .0004$).

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cohort showed that ultrasound indicated that cerclage in twin pregnancies was not harmful, and cerclage seems to be more effective as the cervical length becomes shorter than 15 mm (with a 49% decreased risk of SPTB at <34 weeks).[36] According to case series summarized in Table 4 and our retrospective cohort, cerclage seems to be beneficial as well when the cervix is found to be dilated by physical examination, even in more advanced dilation cases. These outcomes are similar to those found in singleton gestations in which ultrasound indicated that cerclage decreased PTB at < 37 weeks by 77% in women with prior PTB and CL of <15 mm,[37] and by 90% in women after physical examination–indicated cerclage.[8]

In our study, amniocentesis of the presenting twin to assess for subclinical chorioamnionitis was performed more often in the cerclage group (30 women; 79%) than in the control group (5 women; 13.1%), representing a possible selection bias. Our data were adjusted for this confounder. In singleton pregnancies, amniocentesis has been used to select better candidates for cerclage.[23,38] In 1 study, women with asymptomatic cervical dilation of ≥2 cm on digital examination in the second trimester, subclinical intramniotic infection was identified in approximately 51.5%. The most common microbial isolates were *Ureaplasma urealyticum, Gardnerella vaginalis, Candida albicans,* and Fusobacterium sp.[39] Other studies have suggested that, more than bacterial colonization in the amniotic cavity, the elevation of inflammatory cytokines (eg, interleukin-6) are more indicative of infection.[40,41] There is insufficient evidence to absolutely recommend an amniocentesis to assess for intraamniotic infection in women with cervical dilation during the second trimester before cerclage. However, it may be considered (recommendation class C, moderate).[42] No information has been published as to whether amniocentesis in twin pregnancies will improve outcomes by enabling the selection of better candidates for cerclage. In the largest reported series of cerclage based on cervical dilation in twin (104 cases) and singleton (338 cases) pregnancies, amniocentesis was not routinely used[18] (Table 4). Another potential reason that may have influenced providers in our study not to perform an amniocentesis in the expectant management group was that if cerclage or other therapy was not going to be performed, an amniocentesis should not be performed either, as that might increase the risk of pregnancy loss or preterm delivery.

In our cohort, of 29 of the 76 women (38%) who had CL evaluations before being included in the study, half of them were evaluated with pelvic examination 0–1 days after the CL measurement, and the concern of cervical insufficiency was confirmed. Other women shortened/opened their cervix in the next weeks after the CL measurement, and they were found to have a dilated cervix. Of the 76 women, 72 (94%) had visible membranes. This finding is also seen in singleton pregnancies in women who present with cervical insufficiency despite their normal CL measurement.

Other limitations of our study include its retrospective nature and the long time frame of the study (1997–2014). The data were collected retrospectively by chart review at different institutions and by different research personnel using the same questionnaire, in an attempt to unify the concept of cervical insufficiency according to ACOG guidelines.[10] A priori power analysis could not be assessed because of the retrospective nature of the study. We did not have complete documentation regarding cervical length before diagnosis of cervical dilation; some measurements were made transabdominally and others transvaginally, with unknown standardization of the cervical length measurement by the sonographer, time between cervical length and identification of the cervical dilation, or correlation between ultrasound and physical examination (speculum examination and/or digital examination of the cervix), presence of vaginal infection, clinical chorioamnionitis at the time of delivery, or histological chorioamnionitis. We did not include the location where the first pelvic examination took place when cervical dilation was identified as one of the variables (ultrasound, office, or labor and delivery suite), or the presence of symptoms of contraction or vaginal discharge before the observation period before patients were considered asymptomatic and ready for discharge, so we are unable to ascertain whether this variable had any impact in our results. The small number of cases precludes any recommendation in regard to cerclage technique. In addition, obstetric practice has changed during the last 17 years, with implementation of antenatal steroids, latency antibiotics, microbiology evaluation, advances in neonatology/NICU care, definitions of the different neonatal complications, gestational age of viability, use of surfactant, respiratory support, neonatal antibiotics, nutrition, head and body cooling, and so forth. Those changes may have affected the different maternal and neonatal outcomes.

In our cohort, women who had cerclage also received prophylactic indomethacin (76%) and prophylactic antibiotics (94%), whereas the expectant management group did not. This is similar to cerclage case series in twin pregnancies with dilated cervix, in which

TABLE 4
Studies on cerclage in twins with dilated cervix

Author	Type of study	Cerclage	Controls[a]	GA (weeks)	Prior PTB	Amniocentesis	Antibiotics	Tocolysis	Time interval until delivery (days)	Incidence of PTB at <28 weeks	Incidence of PTB at <32 weeks	Incidence of PTB at <34 weeks	Incidence of PPROM	Neonatal survival
Althuisius 2003[4b]	RCT	3	4	<27	Not specified	No	No	No	No data	No data	No data	No data	No data	No data
Parilla 2003[16b]	RC	11	Non specified	21.4 ± 2.2	Not specified	No	NA	NA	No data	No data	No data	No data	No data	No data
Gupta 2010[13b]	RC	11	0	<27	Not specified	No	Yes, not specified	Yes, not specified	No data	No data	No data	No data	No data	No data
Levin 2012[14]	RC	14	0	20.1 ± 2.5	3 (21.4)	No	All	No	71.1 ± 44.6	2 (14.3%)	NA	NA	2 (14.3)	16/20 (80%)
Rebarber 2013[17]	RC	12	0	14–23 6/7	1 (8.3)	12 (100)	12 (100)	12 (100)	92 (26–145)	2 (16.6%)	3 (25%)	7 (58.3%)	2 (16.6%)	20/24 (83%)
Zanardini 2013[15]	RC	14	0	16–26	0 (0)	No	14 (100)	14 (100)	9.9 (0.3–17.9) (weeks)	3 (21%)	7 (50%)	7 (50%)	4 (29 %)	24/28 (86 %)
Miller 2014[18]	RC	104	0	16–23 6/7	24 (23.1)	Not routinely used	56 (54.3)	59 (57.3)	69 (21–99)	35 (33.7%)	54 (51.9%)	NA	35 (33.7%)	No data
Barnabeu 2015[19]	RC	7	0	19.6 ± 4.0	No data	7 (100)	7 (100)	7 (100)	12.1 (4–16)	2 (28%)	No data	3 (42.8%)	1 (14.2)	14/14 (100%)

GA, gestational age; *NA*, not applicable; *RC*, retrospective cohort; *RCT*, randomized controlled trial; *PPROM*, preterm premature rupture of membranes; *PTB*, preterm birth.

[a] Controls refers to twin pregnancies with dilated cervix and no cerclage; [b] No data: This study included singletons and twin gestations and did not inform regarding outcomes separately.

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most women received both tocolysis and antibiotics (Table 4).[14,15,17-19] It is unknown whether any of these therapies, either separately or in combination, may have affected perinatal outcomes in our cohort. The RCT by Althuisius et al in 2003[4] used indomethacin, antibiotics, and bed rest in the physical examination–indicated cerclage group (13 women) but only antibiotics and bed rest in the control group (10 women), with significant differences in the latency period and reduction in PTB at <34 weeks. In a study by Pereira et al,[8] the largest retrospective cohort of physical examination–indicated cerclage in singletons, only 30% of all subjects received indomethacin and 57% received antibiotics; use of these medications was not different between the cerclage and expectantly managed groups, with no difference in gestational age at delivery. Gupta et al[13] evaluated predictors of success in 45 women with emergency cerclage, including 11 twin pregnancies. Neither perioperative indomethacin nor antibiotics affected GA at delivery in this study, or neonatal outcomes in the 2 previous cohorts.[8,13] Miller et al[43] randomized 50 women with singleton pregnancies with physical examination–indicated cerclage placement. Of the women, 26 were assigned to indomethacin and antibiotics and 24 women were given no additional treatment. The median latency from cerclage placement to delivery, gestational age at delivery, and neonatal outcomes were no different between groups, but post hoc analysis revealed a lower number of deliveries within 28 days of cerclage placement in patients receiving indomethacin and antibiotics (24 [92.3%] vs 15 [62.5%], $P < .01$). The available evidence on singletons is insufficient to assess the effects on health outcomes when using perioperative antibiotics (recommendation class D, low) but tocolysis may be considered (recommendation class C, low).[42] In our cohort, the combination of cerclage, indomethacin, and antibiotics significantly decreased the SPTB at different GA, increased median latency from cerclage placement to delivery, and improved perinatal outcomes. More studies are needed to evaluate each therapy separately and in combination.

No information has been published regarding the use of progesterone in twin pregnancies with a dilated cervix. In our cohort, 8 women received vaginal progesterone due to cervical length of <15 mm and continued after they were diagnosed with dilated cervix. A meta-analysis including 13 trials (3768 women and 7536 infants) showed that neither weekly 17-hydroxy progesterone caproate nor vaginal progesterone reduced the incidence of preterm birth nor adverse perinatal outcome in unselected uncomplicated twin pregnancies. In a subgroup of women with a cervical length of ≤25 mm, vaginal progesterone reduced adverse perinatal outcomes by 44% when cervical length was measured before 24 weeks of gestation,[44] and another meta-analysis reported a significant decrease in composite neonatal morbidity and mortality in 51 twin pregnancies with a TVU CL of ≤25 mm in the second trimester.[45] A recent meta-analysis evaluating 5 RCT (441 singleton gestations) showed that women who received vaginal progesterone maintenance tocolysis for arrested PTL had a 31% decreased rate of PTB <37 weeks.[46] More studies are needed to evaluate the use of progesterone in singletons and twins with advanced cervical dilation.

We did not have documentation regarding maternal physical activity. Bed rest significantly increased the risk of PTB at <34 weeks of gestation in asymptomatic twin gestations by 184%,[47] but it is unknown whether bed rest affects outcomes in this subgroup of women. To address all of these questions, we propose a prospective registry of women with twin pregnancies with short (≤15-mm) and dilated cervix before 24 weeks.

Although our data are promising, not enough information is available to make firm recommendations on the use of cerclage, indomethacin, antibiotics, or progesterone in twin pregnancies with dilated cervix before 24 weeks. There is a need for more studies that address strategies to reduce the incidence of SPTB in twin pregnancies. Based on the result of this study, a combination of cerclage, indomethacin, and antibiotics in asymptomatic twin pregnancies appears to be effective at improving neonatal outcome by increasing the median latency from cerclage placement to delivery and should be studied prospectively. We have initiated a prospective RCT to evaluate the effect of cerclage in twin pregnancies (protocol available at ClinicalTrials.gov ID#: NCT02490384) to help provide more definitive information about the efficacy of cerclage in twin gestations with dilated cervix before 24 weeks. ■

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