OBSTETRICS

Efficacy of ultrasound-indicated cerclage in twin pregnancies

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OBJECTIVE: We sought to compare the perinatal outcomes in twin pregnancies with short cervical length (CL) with ultrasound-indicated cerclage (UIC) vs no cerclage (control).

STUDY DESIGN: This was a retrospective cohort study of asymptomatic twin pregnancies with transvaginal ultrasound (TVU) CL ≤25 mm at 16-24 weeks from 1995 through 2012 at 4 separate institutions. Exclusion criteria were: genetic or major fetal anomaly, multifetal reduction >14 weeks, monochorionic-monoamniotic placentation, or medically indicated preterm birth (PTB). Primary outcome was spontaneous PTB (SPTB) <34 weeks. Secondary outcome was SPTB <28, <32, and <37 weeks. We also planned to evaluate primary and secondary outcome for the subgroup of twin pregnancies with CL ≤15 mm.

RESULTS: In all, 140 women with twin pregnancy and TVU-CL ≤25 mm were managed with either UIC (n = 57) or no cerclage (n = 83). Demographic characteristics were not significantly different except women who underwent UIC presented at an earlier gestational age (GA) at diagnosis of short CL. After adjusting for GA at presentation, there were no differences in GA at delivery or SPTB <28 weeks: 12 (21.2%) vs 20 (24.1%) (adjusted odds ratio [aOR], 0.3; 95% confidence interval [CI], 0.68−1.37), <32 weeks: 22 (38.6%) vs 36 (43.4%) aOR, 0.34; 95% CI, 0.1−1.13), or <34 weeks: 29 (50.9%) vs 53 (63.9%) (aOR, 0.37; 95% CI, 0.16−1.1). In the subgroup of women with CL ≤15 mm (32 with UIC and 39 controls) the interval between diagnosis to delivery was significantly prolonged by 12.5 ± 4.5 vs 8.8 ± 4.6 weeks ($P < .001$); SPTB <34 weeks was significantly decreased: 16 (50%) vs 31 (79.5%) (aOR, 0.51; 95% CI, 0.31−0.83) as was admission to neonatal intensive care unit: 38/58 (65.5%) vs 63/76 (82.9%) (aOR, 0.42; 95% CI, 0.24−0.81) when the UIC group was compared with the control group, respectively.

CONCLUSION: UIC in asymptomatic twin pregnancies with TVU-CL ≤25 mm was not associated with significant effects on perinatal outcomes compared to controls. However, in the planned subgroup analysis of asymptomatic twin pregnancies with TVU-CL ≤15 mm before 24 weeks, UIC was associated with a significant prolongation of pregnancy by almost 4 more weeks, significantly decreased SPTB <34 weeks by 49%, and admission to neonatal intensive care unit by 58% compared with controls.

Key words: cervical length, preterm birth, twin pregnancy, ultrasound-indicated cerclage

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In 2010, the twin birth rate was 33.1 twins per 1000 total births in the United States.[1] The twin birth rate increased steadily by 76% from 1980 through 2009 mostly due to the increased use of assisted reproductive technology. The overall incidence of preterm birth (PTB) <37 weeks in the United States is 11.5%, with 3.41% born <34 weeks in 2013.[1] The incidence of PTB in twin pregnancies before 37 and 34 weeks were 58% and 23%, respectively. Twins were 10 times more at risk of being low-birthweight (LBW) infants and had a 5 times greater risk of early neonatal death.[2] Disorders related to short gestation and LBW remain the second cause of infant death (17.2%).[3]

In twin pregnancies, only cervical length (CL) ≤25 mm at 24 weeks was significantly associated with spontaneous PTB (SPTB). The odds ratio (OR) and 95% confidence interval (CI) for SPTB at <32, <35, and <37 weeks were 6.9 (2.0−24.2), 3.2 (1.3−7.9), and 2.8 (1.1−7.7).[4] The risk of PTB in women with multiple pregnancies is inversely

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proportional to the CL.[5-7] In 215 asymptomatic women with twin pregnancies, the rate of SPTB at ≤32 weeks increased exponentially with decreasing CL at 23 weeks, from 4.7% at CL >25 mm to 31% at 16-25 mm and 66% at ≤15 mm.[5]

A recent Cochrane review evaluated the efficacy of cerclage in twin pregnancies.[8] Subgroup analysis of the ultrasound-indicated cerclage (UIC) in twins using patient-level metaanalysis of 3 randomized clinical trials including 49 twin gestations with a CL <25 mm before 24 weeks showed that the incidence of PTB at different gestational ages (GAs) was not significantly different in women who were randomized to cerclage compared with those with expectant management, specifically PTB <34 weeks 15/25 (63%) vs 6/25 (24%) (RR, 2.19; 95% CI, 0.72−6.63). However, UIC was associated with an increased risk of LBW (relative risk [RR], 1.39; 95% CI, 1.06−1.83), respiratory distress syndrome (RR, 5.07; 95% CI, 1.75−14.70), and a statistically significant increase in the risk of composite serious neonatal morbidity and perinatal mortality (RR, 2.52; 95% CI, 1.20−5.30).

Only 2 nonrandomized controlled studies have been published regarding the efficacy of cerclage vs no cerclage in twin gestations with second-trimester short transvaginal ultrasound (TVU) CL[9,10]; both reported no effect on PTB outcomes. Other interventions used in singleton pregnancies such as 17 hydroxyprogesterone caproate, vaginal progesterone, or history-indicated cerclage have not been effective in reducing the rate of PTB in women with twin gestations.[8,11-20] Two individual participant data metaanalyses have evaluated the effect of progesterone in twin pregnancy with a TVU CL ≤25 mm before 24 weeks of gestation: in Schuit et al[21] neither 17 alpha-hydroxyprogesterone caproate (n = 175) nor vaginal progesterone (n = 54) reduced PTB <34 weeks, but vaginal progesterone (n = 54) was associated with a significant 43% decrease in adverse perinatal outcome (14/52 vs 21/56; RR, 0.56; 95% CI, 0.42−0.75). The second metaanalysis by Romero et al[22] also reported no prevention of PTB, but did report a decrease in composite neonatal morbidity and mortality in 51 twin pregnancies with a TVU CL ≤25 mm in the second trimester (11/46 vs 23/58; RR, 0.52; 95% CI, 0.29−0.93).

The aim of our study was to evaluate if the use of UIC in twin pregnancies with an asymptomatic CL ≤25 mm before 24 weeks has an effect on the incidence of SPTB <34 weeks' gestation when compared to those with a short CL and no cerclage. We also planned a subgroup analysis of women with CL ≤15 mm and 16-25 mm by PTB.

Materials and Methods

This is a retrospective cohort study of twin pregnancies with short CL ≤25 mm by TVU at 16-24 weeks from 1995 through 2012 at North Shore University Hospital (Manhasset, NY), Long Island Jewish Medical Center (New Hyde Park, NY), Thomas Jefferson University Hospital (Philadelphia, PA), Maternal Fetal Medicine Associates PLLC (New York, NY), and Christiana Care Hospital (Wilmington, DE). Exclusion criteria included: genetic or major fetal anomalies, a history of multifetal pregnancy reduction >14 weeks to twins, monochorionic-monoamniotic placentation and medically indicated PTB (twin-twin transfusion syndrome, severe preeclampsia, abruption placenta, placenta previa), or cerclages placed for another indication (history-indicated cerclage or physical exam−indicated cerclage).

The following variables were collected by retrospective chart review: parity, race, chorionicity, GA at the time of shortest CL, CL in millimeters, GA at the time of cerclage, type of cerclage (Shirodkar or McDonald), maternal comorbidities, preterm premature rupture of membranes (PPROM), GA at delivery, interval from diagnosis of short CL and delivery, indications for delivery, and neonatal outcomes: birthweight, Apgar at 5 minutes, admission to the neonatal intensive care unit (NICU), and neonatal survival at discharge.

GA was determined by an evaluation of last menstrual period and crown-rump length measurement on early ultrasound and chorionicity was determined by ultrasound evaluation at the first trimester. CL was determined by TVU using standardized technique by trained sonographers, selecting the shortest CL obtained between 16-24 weeks. The decision to perform cerclage and the surgical technique used was at discretion of the attending physician. The primary outcome was SPTB <34 weeks. Secondary outcomes were: SPTB <28, <32, or <37 weeks; admission to NICU; and survival at discharge. We planned a subgroup analysis of women with CL ≤15 mm and 16-25 mm by PTB.

The institutional review board approved this retrospective study at each institution. Statistical analysis was conducted using software (SPSS 18.0; IBM Corp, Armonk, NY). Data are shown as means ± SD or number (percentage). Differences between women who received cerclage and controls were analyzed using χ^2 test and Fisher exact test for categorical variables and Student *t* test for continuous variables. A logistic regression was performed to correct data for those variables that were significantly different between groups. Kaplan-Meier curves were generated for GA at delivery by different CL and compared using the log-rank test. A P value < .05 was considered statistically significant.

Results

We identified 140 women with a twin pregnancy and a CL ≤25 mm who met inclusion criteria. In all, 57 women underwent UIC (cases) and 83 were followed up without a cerclage (controls). Demographic characteristics were not significantly different except that the UIC group presented at an earlier mean GA at diagnosis: 19.5 ± 1.8 vs 21.4 ± 1.6 weeks (P < .0001) (Table 1). After adjusting for GA at presentation, there were no statistically significant differences in GA at delivery; PPROM; interval between diagnosis to delivery or SPTB <24, <28, <32, <34, or <37 weeks; admission to NICU; Apgar <7; or perinatal mortality when UIC was compared with expectant management (Tables 2 and 3). McDonald cerclage was performed in 42/53 (80%) patients and a Shirodkar cerclage in 11/53 (20%). There were no significant differences in

GA at delivery when the 2 surgical techniques were compared: 31.9 ± 5.3 vs 32.6 ± 3.9 weeks ($P = .7$). Discharged home alive for both sets of twins was 50/57 (87%) for UIC vs 68/83 (82%) for expectant management ($P = .4$); demise of both twins prior to discharge occurred in 6 sets of twins in the UIC group and in 4 sets of twins in the expectant management group. Median GA at delivery for all demises prior to discharge was 23 (22.8-26.4) weeks. Kaplan-Meier curves were generated for GA at delivery by TVU CL ≤25 mm and compared using the log-rank test showing no significant difference: hazard ratio (HR), 0.88; 95% CI, 0.63−1.25; $P = .5$ (Figure 1).

Thirty women (21.4%) had a prior PTB. There were no significant differences in CL at the time of diagnosis of a short CL when compared with women without prior PTB: 15.56 ± 6.1 vs 15.86 ± 6.2 mm ($P = .8$). When we stratified both groups (cerclage vs control) by prior PTB there were no significant differences in GA at delivery at CL ≤25 mm (aOR, 0.67; 95% CI, 0.28−1.56; $P = .4$) or at CL ≤15 mm (aOR, 0.58; 95% CI, 0.19−1.81; $P = .4$).

We analyzed separately the subgroups with a CL between 16-25 mm and those with a CL ≤15 mm. In the subgroup of twin pregnancies with CL between 16-25 mm (25 had UIC vs 44 controls) there were no significant differences in any of the maternal demographics or the perinatal outcomes evaluated after adjusting for GA at diagnosis. (Table 3). Kaplan-Meier curves were generated for GA at delivery by TVU CL 16-25 mm and log-rank test showed no significant difference: HR 1.13 (95% CI, 0.68−1.88) $P = .63$ (Figure 2).

In all, 71 women with twin pregnancies had a CL ≤15 mm (32 UIC and 39 controls). Demographic maternal characteristics were not significantly different except that women in the UIC group presented at earlier GA at diagnosis: 19.8 ± 1.8 vs 21.46 ± 1.8 weeks ($P = .0003$). After adjusting for GA at presentation of short CL, there were significant differences found in the interval between diagnosis and delivery: 12.52 ± 4.5 vs 8.76 ± 4.65 weeks ($P < .001$), admission to NICU: 38/58 (65.6) vs 63/76 (82.9) (aOR, 0.41; 95% CI, 0.24−0.81), and SPTB <34 weeks: 16 (50) vs 31 (79.5) (aOR, 0.51; 95% CI, 0.31−0.83) (Table 3). There were no significant differences in PPROM: 3/32 (9.4%) vs 5/39 (12.8%) ($P = .72$) or perinatal mortality: 7/64 (11.3%) vs 13/78 (16.6%) ($P = .46$) when UIC was compared with no cerclage. Kaplan-Meier curves were generated for GA at delivery by TVU CL ≤15 mm and compared using the log-rank test: HR 0.64 (95% CI, 0.39−1.025) $P = .056$ (Figure 3).

TABLE 1
Maternal demographics of twin pregnancies with cervical length ≤25 mm

Variable	UIC, n = 57	Control, n = 83	*P* value
Maternal age, y	31.8 ± 5.8	31.4 ± 6.0	.76
Race			
Caucasian	40 (70.2)	51 (61.4)	.36
African American	11 (19.3)	21 (25.3)	.54
Hispanic	3 (5.6)	7 (8.4)	.52
Asian/Indian	3 (5.2)	5 (6.0)	1.0
Nulliparity	33 (57.8)	51 (61.4)	.72
Diamniotic-dichorionic	45 (78.9)	61 (73.5)	.51
Prior PTB	10 (17.5)	20 (24.1)	.53
Smoking	4 (7.0)	5 (6.0)	1.0
GA at diagnosis, wk	19.5 ± 1.8	21.4 ± 1.6	< .0001
CL, mm	15.3 ± 5.7	16.16 ± 6.5	.41

Variables described as mean ± SD or frequencies (percentage).

CL, cervical length; *GA*, gestational age; *PTB*, preterm birth; *UIC*, ultrasound-indicated cerclage.

Roman. Ultrasound-indicated cerclage in twins reduces preterm birth. Am J Obstet Gynecol 2015.

Comment

To our knowledge this is the largest retrospective cohort evaluating the effect of UIC in twin pregnancy. In 140 women with twin pregnancies and a CL ≤25

TABLE 2
Perinatal outcomes of twin pregnancies with cervical length ≤25 mm

Variable	UIC n = 57	Control n = 83	*P* value
GA at delivery, wk	32.05 ± 5.1	32.58 ± 4.63	.82
Birthweight, g[a]	1739 ± 767	1714 ± 737	.7
Birthweight <1500 g[a]	37/114 (32.4)	64/166 (38.5)	.26
Apgar <7 at 5 min[a]	14/114 (8.7)	21/166 (12.6)	1.0
PPROM	9 (15.7)	12 (14.5)	.81
Admission to NICU (born alive only)	68/102 (66.6)	111/156 (71.1)	.5
Perinatal mortality	20/114 (17.5)	19/166 (11.4)	1.0

Variables described as mean ± SD or frequencies (percentage).

GA, gestational age; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes; *UIC*, ultrasound-indicated cerclage.

[a] Data from both twins.

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TABLE 3
Perinatal outcomes by cervical length subgroups

Outcome	UIC	Control	aOR (95% CI)[a]	*P* value
GA at delivery, wk				
CL ≤25 mm	32.05 ± 5.1	32.58 ± 4.63	—	.82
CL 16–25 mm	31.7 ± 5.5	33.4 ± 4.4	—	.15
CL ≤15 mm	32.33 ± 4.8	30.22 ± 4.5	—	.06
Diagnosis to delivery interval, wk				
CL ≤25 mm	12.58 ± 4.83	10.53 ± 4.97	—	.02
CL 16–25 mm	12.66 ± 5.3	11.3 ± 5.1	—	.32
CL ≤15 mm	12.52 ± 4.5	8.76 ± 4.65	—	< .001
Admission to NICU (born alive only)				
CL ≤25 mm	68/102 (66.6)	111/156 (71)	0.7 (0.4–1.2)	—
CL 16–25 mm	28/44 (63.6)	50/82 (61)	0.86 (0.47–1.5)	—
CL ≤15 mm	38/58 (65.6)	63/76 (82.9)	0.41 (0.24–0.81)	—
PTB <37 wk				
CL ≤25 mm	49 (86)	75 (90.4)	0.31 (0.05–1.7)	—
CL 16–25 mm	23 (92)	36 (81.8)	1.29 (0.38–4.3)	—
CL ≤15 mm	26 (81.3)	36 (92.3)	0.63 (0.3–1.08)	—
PTB <34 wk				
CL ≤25 mm	29 (50.9)	53 (63.9)	0.37 (0.16–1.1)	—
CL 16–25 mm	13 (52)	22 (50)	1.05 (0.56–1.9)	—
CL ≤15 mm	16 (50)	31 (79.5)	0.51 (0.31–0.83)	—
PTB <32 wk				
CL ≤25 mm	22 (38.6)	36 (43.4)	0.34 (0.1–1.13)	—
CL 16–25 mm	9 (36)	13 (29.5)	1.1 (0.5–2.7)	—
CL ≤15 mm	13 (40.6)	22 (56.4)	0.7 (0.2–1.3)	—
PTB <28 wk				
CL ≤25 mm	12 (21.2)	20 (24.1)	0.3 (0.68–1.37)	—
CL 16–25 mm	6 (24)	6 (13.6)	1.3 (0.6–5.6)	—
CL ≤15 mm	6 (18.8)	13 (33.3)	0.63 (0.3–1.29)	—
PTB <24 wk				
CL ≤25 mm	7 (12.3)	5 (6.0)	1.7 (0.23–12.5)	—
CL 16–25 mm	3 (12)	2 (4.5)	1.5 (0.6–3.3)	—
CL ≤15 mm	4 (12.5)	2 (5.1)	1.5 (0.8–2.9)	—

Variables described as mean ± SD or frequencies (percentage).

CI, confidence interval; *CL*, cervical length; *GA*, gestational age; *NICU*, neonatal intensive care unit; *PTB*, preterm birth; *UIC*, ultrasound-indicated cerclage.

[a] Adjusted by GA at time of diagnosis of short CL.

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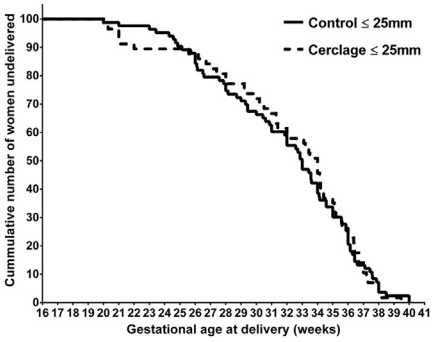
mm, we did not observe a statistically significant benefit from cerclage in preventing PTB <34 weeks or other secondary outcomes. Our findings also suggest that cerclage in this group of women was not associated with demonstrable harm, as has been suggested by a prior metaanalysis based on 49 randomized women.[23] As the risk of PTB is inversely proportional to CL measured by TVU <24 weeks we also planned to examine CL ≤15 mm as an

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



Kaplan-Meier curves were generated for gestational age at delivery by transvaginal ultrasound cervical length ≤25 mm. Comparison of cerclage and control groups using log-rank test showed no significant difference (hazard ratio, 0.88; 95% confidence interval, 0.63−1.25; $P = .49$).

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alternate cutoff. In this subgroup, we identified significant differences in the cerclage group when compared with control, with prolongation of pregnancy by almost 4 more weeks, decreased SPTB <34 weeks by 49%, and decreased admission to NICU by 58%. These findings are similar to those identified in the multicenter randomized trial of cerclage in high-risk women with singleton pregnancies and CL <25 mm prior to 22 weeks, where the benefit of cerclage was significantly higher in the subgroup of women with CL <15 mm, reducing the risk of PTB <34 weeks by 77% (OR, 0.23; 95% CI, 0.08−0.66; $P < .006$)[24] suggesting that cerclage as an intervention to prevent SPTB may be more effective at shorter CL.

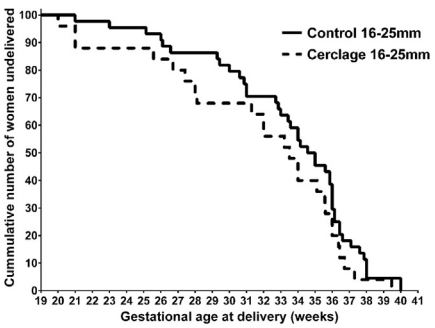
Goldenberg et al,[4] reported that prior PTB does not seem to represent a risk factor for PTB in twin pregnancies. In our cohort, 30 (21%) twin gestations had prior PTB, and this subgroup analysis showed no significant differences on CL or any of the other outcomes. However, we did not have available data on risk factors for women with CL >25 mm for further analysis.

The incidence of PTB at different cutoffs of CL was similar to previous retrospective studies, which validate our findings.[5-7] The GA at delivery <34 weeks was chosen to avoid cases of near-term birth, which are associated with lower rates of neonatal morbidity and only rare mortality, as this is a common outcome in other twin pregnancy studies.

Perinatal mortality was low in both groups; most of those cases were associated with previable or periviable delivery at a median of 23 weeks.

The limitations of our study are mostly due to its retrospective nature. We were unable to ascertain other variables that may have impacted in the perinatal outcome, such as use of progesterone during pregnancy, maternal physical activity, corticoids use, or admission to antepartum unit. We also were unable to compile neonatal outcome data such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia, or use of mechanical ventilation.

FIGURE 2
Survival curves of twin pregnancies with CL between 16-25 mm



Kaplan-Meier survival curves indicating proportions of women with twin pregnancy in ultrasound-indicated cerclage and control groups, limiting analysis to 69 women with transvaginal ultrasound cervical length (CL) between 16-25 mm. Log-rank test showed no significant difference (hazard ratio, 1.13; 95% confidence interval, 0.68−1.88; $P = .63$).

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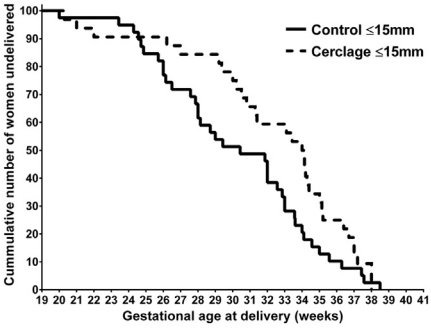
FIGURE 3
Survival curves of twin pregnancies with CL ≤15 mm



Kaplan-Meier survival curves indicating proportions of women with twin pregnancy in ultrasound-indicated cerclage and control groups, limiting analysis to 71 women whose transvaginal ultrasound cervical length (CL) was ≤15 mm. Log-rank test showed hazard ratio, 0.63; 95% confidence interval, 0.39−1.025; $P = .056$.

Roman. Ultrasound-indicated cerclage in twins reduces preterm birth. Am J Obstet Gynecol 2015.

Individual participant data meta-analysis of vaginal or intramuscular progesterone in asymptomatic twin pregnancy with or without CL ≤25 mm have not reported so far significant prolongation of pregnancy[21,22]; but a decrease in composite neonatal morbidity and mortality was seen in twin pregnancies with CL ≤25 mm[22]; the findings in both of these metaanalyses require further research because of the small numbers included in the studies. Hospitalization and bed rest has not been shown to decrease the rate of PTB or perinatal mortality; in fact, bed rest significantly increased the risk of PTB at <34 weeks of gestation in asymptomatic twin gestations (OR, 1.84; 95% CI, 1.01−3.34).[25]

The time frame of the study (1995 through 2012) included different CL screening and management approaches. The number of TVU CL measurements may have affected the sensitivity of screening and the effectiveness of the UIC as shortening of CL over 2 measurements <24 weeks has been shown to increase the risk of PTB.[26]

A prospective study to evaluate the effect of UIC in twin pregnancies

would be valuable. If we elect to evaluate the group at the highest risk of PTB with CL ≤15 mm prior to 24 weeks, a sample size of 78 women (39 per group) are needed to detect 40% reduction of PTB <34 weeks from 80-50% with a power of 0.80. Considering that CL ≤15 mm was identified in 4.2% of the twin pregnancies,[5] >2000 twin pregnancies would be required for screening. ■

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