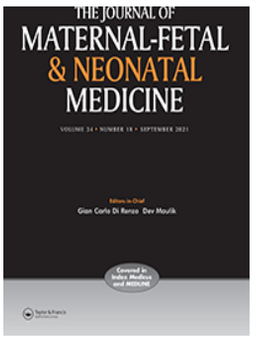

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ORIGINAL ARTICLE

Do patients with a short cervix, with or without an ultrasound-indicated cerclage, have an increased risk for a small for gestational age newborn?

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ABSTRACT

Introduction: Mothers with a short cervix have been shown to have increased risk of spontaneous preterm delivery (PTD) and newborn morbidity. Those who require an ultrasound-indicated cerclage experience the highest rates of morbidity. Inflammation has been linked to a short cervix, and it has been linked to pregnancies affected by small for gestational age (SGA) newborns. To date, there are no studies that have investigated an association between a short cervix, with or without an ultrasound-indicated cerclage, and a SGA newborn.

Methods: This was a case-control study examining all pregnancies with a transvaginal cervical length <25 mm found at their second trimester anatomy scan. Cases were subdivided into those who received an ultrasound-indicated cerclage (Group 1, $n = 52$) and those who did not (Group 2, $n = 139$). Controls were defined as pregnancies with a transvaginal cervical length >25 mm with no cerclage (Group 3, $n = 186$) whose due date was within 2 months of the case pregnancy. Each short cervix case was matched with a control from group 3 in a 1:1 ratio. The primary outcome was birthweight <10% (SGA). Unadjusted data was analyzed with simple odds ratios. A logistic regression was used to control for confounding variables and provide an adjusted odds ratios (aOR).

Results: The incidence of SGA among cases overall (group 1 + group 2) was 13.6% (26/191). In group 3, the SGA incidence was 4.3% (8/186). The adjusted odds ratio (aOR) for a SGA infant was significant, 2.8 (95% CI 1.2, 6.6). Subgroup analysis showed that Group 1 had an increased risk for an SGA infant [aOR 4.9 (95% CI 1.8, 13.7)], but Group 2 did not show a significant finding [aOR 2.3 (95% CI 0.9, 5.7)].

Conclusion: Pregnancies complicated by a short cervical length <25mm, with or without a cerclage, were associated with an increased risk for a SGA newborn. Most of this significance was due to the pregnancies which received an ultrasound-indicated cerclage for a mid-trimester short cervix.

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Short cervix; ultrasound-indicated cerclage; fetal growth restriction; intrauterine growth restriction; small for gestational age newborn

Introduction

Preterm birth (PTB) remains one of the most common causes of perinatal mortality and morbidity [1,2]. In the United States, the preterm delivery rate is 13% [1]. Prediction and prevention of preterm birth remains a challenge despite the recognition of numerous maternal and fetal risk factors. Of the recognized risk factors, a short cervical length and cervical insufficiency have been shown to be consistent predictors of spontaneous preterm birth [1–6].

Common etiologies for cervical ripening include prior cervical trauma from birth or surgical procedures, but altered inflammatory processes have also been shown to be important [7–9]. For example, amniotic fluid studies of patients with dilated cervices without regular uterine contractions have shown positive bacterial cultures [10,11]. In addition, human cervical biopsies during preterm cervical ripening have shown altered cytokine levels, suggesting dysregulation of inflammatory processes [9].

Inflammation has not only been linked to dysfunctional cervical ripening, but it has been linked to poor newborn outcomes overall. For example, Combs et al. found that intraamniotic inflammation was associated with higher rates of perinatal morbidity and mortality whether or not microbes were detected in the amniotic fluid [12]. The major obstetric issues of preterm labor and preeclampsia contribute significantly to newborn morbidity, and both have shown abnormal

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inflammation as part of their pathophysiology [13,14]. In several reviews, inflammation has also been linked with an increased risk for fetal growth restriction [15–17]. Specific examples include rat studies which demonstrate defective spiral artery remodeling and subsequent fetal growth restriction due to abnormal inflammation [18], or placental inflammatory conditions such as villitis of unknown etiology being found more frequently in placentas of growth restricted infants [19,20].

To our knowledge there are no studies that have investigated the risk of small for gestational age (SGA) infants in women with a short cervix, with or without cerclage. The purpose of our study is to determine if there is an association between these possibly related complications. We hypothesized that the pregnancies complicated by a short cervix would be associated with higher rates of SGA newborns.

Methods

We performed a case-control study at The University of Kansas Health System (TUKHS) after approval by the IRB (Protocol #4188, approved 7/1/2016). Data sample collection occurred between December 2014 and July 2020. An electronic query of the ultrasound database through the Center for Advanced Maternal and Fetal Care departments was employed to select cases and controls. Universal cervical length screening began at our institution in 2008. Cases included all singleton pregnancies that delivered at our institution with a transvaginal cervical length (TVCL) <25 mm between 16 weeks and 0 days and 24 weeks and 0 days gestation at their second trimester anatomy sonogram. A cervical length cutoff of <25 mm was chosen as this value represents <5 percentile for cervical length at a gestational age <24 weeks and has been associated with significant risks for preterm birth in previous investigations [21–23]. Since cervical inflammation, and therefore SGA, may differ between those with CL <25 mm who received an ultrasound-indicated cerclage and those who did not, we decided to subdivide the cases based on whether they also received an ultrasound-indicated cerclage or not. Controls were pregnancies with a transvaginal cervical length >25 mm reported on their second trimester anatomy sonogram whose due date was within 2 months of the identified case pregnancy. Thus, our defined groups were as follows: Group 1 had a CL <25 mm and an ultrasound-indicated cerclage placed; group 2 included those with a CL <25 mm but no cerclage, and group 3 included any singleton pregnancy with a transvaginal cervical length >25 mm who had a due date within 2 months of the case pregnancy. We planned to perform a sub-analysis of both group 1 and group 2. Exclusion criteria included advanced cervical dilation at initial TVCL, multiple gestations, fetal anomalies, and incomplete birth outcome data.

The primary outcome was the rate of SGA. SGA was defined as birthweight less than the tenth percentile according to newborn birth curves established by Lubchenco and Battaglia [24]. The secondary outcomes were birthweight and rate of preterm birth. As inflammation-related morbidity in pregnancy is present in both spontaneous preterm labor and iatrogenic situations such as preeclampsia and fetal growth restriction, we did not measure separately spontaneous or indicated preterm birth. Maternal demographic data including age, parity, progesterone use, ethnicity, history of cervical surgery, dilation and curettage, cervicitis (defined as positive urine or cervical specimen for gonorrhea or chlamydia), urinary tract infection, tobacco use, hypertensive disorders, and diabetes were compared between groups. Electronic and paper medical charts were reviewed to abstract the desired clinical data.

Our division's clinical practice is described below. All images of cervical length were obtained by sonographers who were CLEAR certified (https://clear.perinatalquality.org), and all CL measurements were reviewed by a maternal–fetal medicine physician. When CL measured below 25 mm, measurements were repeated weekly. When CL measured below 20 mm, nightly vaginal progesterone was recommended. Due to either cost of medication or patient choice, some patients did not self-administer vaginal progesterone nightly. In our institution, an ultrasound-indicated cerclage is typically placed when the cervical length becomes shorter than 15 mm. Occasionally, some ultrasound-indicated cerclages were placed with cervical lengths greater than 15 mm at the attending's discretion. Cerclages were placed by a Maternal-Fetal Medicine attending using a modified McDonald technique. All cerclage procedures included perioperative antibiotics (levofloxacin or cefazolin, chosen at the surgeon's discretion) and indomethacin.

The sample size was determined by our intention to detect a 3-fold increase in the rate of SGA in cases compared to controls. Our initial queries showed a SGA rate of 4% in our control population. We aimed for *p*-value of .05 and an 80% power level. Controls were selected in a 1:1 ratio with cases. The desired sample size was 360.

Statistical analysis was performed with the use of open source statistical software (OpenEpi.com) and IBM SPSS statistical software (IBM Corporation). Demographic variables were analyzed with simple t-tests, Chi-square tests, or Fisher Exact tests as appropriate. Odds ratios were calculated for pregnancy outcomes. Odds ratios were then adjusted for characteristics that were found to be significantly different among the groups. Logistic regression and ordinary least squares regression were used. A p-value of $<.05$ or a confidence interval excluding 1 were considered statistically significant.

Results

There was a total of 52 singleton pregnancies in group 1, 139 singleton pregnancies in group 2, and 186 singleton pregnancies in group 3. In general (Table 1), patients with a short cervix (G1 + G2) had a higher incidence of Black ethnicity, history of cervical surgery, history of dilation and curettage, cervicitis, and tobacco use compared to group 3. They had a lower incidence of Hispanic ethnicity. Finally, they had shorter cervical lengths at the screening ultrasound, and increased rates of funneling compared to group 3. Some specific differences in the subgroups were noticed. The G1 subgroup showed a higher rate of gestational diabetes and history of dilation and curettage compared to G3. The G2 subgroup showed a higher rate of tobacco use compared to G3.

Regarding obstetric and neonatal outcomes (Table 2), group 1 showed an SGA incidence of 19% (10/52), group 2 was 12% (16/139), and group 3 was 4% (8/186). The short cervix group (G1 + G2) had a combined SGA rate of 14% (26/191), and the unadjusted odds ratio compared to controls (G3) was 3.5 (95% CI 1.5, 8.0). The subgroup analysis reported unadjusted odds ratios of having an SGA newborn for group 1 as 5.3 (95% CI 2.0, 14.2) and for group 2 as 2.9 (95% CI 1.2, 7.0). As expected, there was an incremental increase in the birthweight and gestational age at delivery as one moved from group 1 to group 3. In similar fashion, the rate of preterm deliveries decreased as one moved from group 1 to group 3.

When we compared group 1 and group 2, we did not find any surprising differences (Table 3). Groups 1 and 2 differed in their cervical length (9.6 mm vs 18.9 mm, $p < .01$) and the amount of funneling (35.3% vs 7.9%, $p < .01$). These groups were mostly similar regarding their demographic and clinical variables, but group 1 did show a higher rate of gestational diabetes (25% vs 11.5%, $p = .04$). Group 1 had shorter latency times from diagnosis to delivery, earlier gestational age at delivery, higher rates of preterm delivery at 32, 34, and 37 weeks, and lower average birth weights.

A bivariate analysis of all demographic variables collected was performed, which showed that black ethnicity, Hispanic ethnicity, and gestational hypertension were associated with an SGA outcome. These 3 variables along with the group variable were included in the analysis by multivariable regression (Table 4). After controlling for the aforementioned variables, the adjusted OR for SGA infants in short cervix cases

Table 1. Patient characteristics of cohort.

Demographics	Group 1[a] ($n = 52$)	G1 vs. G3 p-Value	Group 2[a] ($n = 139$)	G2 vs. G3 p-Value	G1 + G2 ($n = 191$)	G1 + G2 vs. G3 p-Value	Group 3[a] ($n = 186$)
Age in years, mean (SD)	29.9 (6.0)	.62	29.6 (6.2)	.76	29.7 (6.1)	.65	29.4 (6.1)
Nullipara, n (%)	22 (42.3)	.204	44 (31.7)	.826	66 (34.6)	.719	61 (32.8)
GA at CL measurement, weeks (SD)	20.2 (2.2)	.691	20.5 (2.6)	.381	20.5 (2.5)	.566	20.3 (1.6)
TVCL in mm, mean (SD)	9.6 (6.0)	**<.01**	18.9 (5.4)	**<.01**	16.4 (7.0)	**<.01**	33.5 (4.7)
Cervical funneling, n (%)	18 (35.3)	**<.01**	11 (7.9)	**<.01**	29 (15.2)	**<.01**	0
Vaginal progesterone, n (%)	19 (36.5)	**<.01**	57 (41)	**<.01**	76 (39.8)	**<.01**	2 (1.1)
Intramuscular progesterone, n (%)	1 (1.9)	.057	1 (0.7)	.246	2 (1)	.162	0
African American ethnicity, n (%)	18 (34.6)	.063	50 (36)	**<.01**	68 (35.6)	**<.01**	41 (22)
Caucasian ethnicity, n (%)	21 (40.4)	.826	59 (42.4)	.497	80 (41.9)	.529	72 (38.7)
Hispanic ethnicity, n (%)	6 (11.5)	**.030**	21 (15.1)	**.020**	27 (14.1)	**<.01**	48 (25.8)
Asian ethnicity, n (%)	3 (5.8)	.757	6 (4.3)	.308	9 (4.7)	.347	13 (7)
Other ethnicity, n (%)	4 (7.7)	.749	3 (2.2)	.067	7 (3.7)	.215	12 (6.5)
History of cervical surgery, n (%)	5 (9.6)	.267	20 (14.4)	**<.01**	25 (13.1)	**<.01**	10 (5.4)
History of D & C, n (%)	11 (21.2)	**<.01**	16 (11.5)	.219	27 (14.1)	**.040**	14 (7.5)
Cervicitis during pregnancy, n (%)	4 (7.7)	.159	10 (7.2)	**.039**	14 (7.4)	**.017**	4 (2.2)
UTI during pregnancy, n (%)	4 (7.7)	.97	16 (11.6)	.219	20 (10.5)	.317	14 (7.5)
Tobacco use, n (%)	5 (9.6)	.624	28 (20.1)	**<.01**	33 (17.3)	**<.01**	14 (7.5)
Pre-existing hypertension, n (%)	8 (15.4)	.497	10 (7.2)	.164	18 (9.4)	.447	22 (11.8)
Gestational hypertension, n (%)	6 (11.5)	.873	21 (15.1)	.478	27 (14.1)	.610	23 (12.4)
Pre-existing Diabetes, n (%)	4 (7.7)	.529	7 (5)	.889	11 (5.8)	.873	10 (5.4)
Gestational diabetes, n (%)	13 (25)	**<.01**	16 (11.5)	.711	29 (15.2)	.147	19 (10.2)

GA: gestational age; CL: cervical length; SD: standard deviation; D&C: dilation and curettage; UTI: urinary tract infection.
[a]Group 1 (G1) consists of patients with cervical length <25 mm and an ultrasound-indicated cerclage. Group 2 (G2) consists of patients with cervical length <25 mm without cerclage. Group 3 (G3) consists of patients with cervical length > 25 mm.
The bold values highlight statistical significance as $p<.05$

Table 2. Obstetric outcomes between short cervix cases and controls.

Outcome	Group 1[a] ($n = 52$)	G1 vs. G3 *p*-Value	Group 2[a] ($n = 139$)	G2 vs. G3 *p*-Value	G1 + G2 ($n = 191$)	G1 + G2 vs. G3 *p*-Value	Group 3[a] ($n = 186$)
SGA, *n* (%)	10 (19.2)	**.01**	16 (11.5)	**.021**	26 (13.6)	**<.01**	8 (4.3)
GA at delivery, weeks Mean (SD)	34.3 (5.4)	**<.01**	37.6 (2.9)	**<.01**	36.7 (4.0)	**<.01**	38.7 (1.9)
PTD < 37 wk, *n* (%)	26 (50.0)	**<.01**	33 (23.7)	**<.01**	59 (30.9)	**<.01**	22 (11.8)
PTD < 34 wk, *n* (%)	18 (34.6)	**<.01**	11 (7.9)	**.01**	29 (15.2)	**<.01**	3 (1.6)
PTD < 32 wk, *n* (%)	15 (28.8)	**<.01**	7 (5.0)	**.02**	22 (11.5)	**<.01**	1 (0.5)
Latency from short cervix diagnosis[b] to delivery, days Mean (SD)	98.4 (36.3)	**<.01**	119.1 (27.0)	**<.01**	113.5 (31.1)	**<.01**	128.4 (16.3)
Birthweight in grams, mean (SD)	2321.6 (1052.6)	**<.01**	2956.0 (700.8)	**<.01**	2783.3 (856.9)	**<.01**	3207.5 (479.2)

GA: gestational age; SGA: small for gestational age; PTD: preterm delivery; SD: standard deviation.
[a]Group 1 (G1) consists of patients with cervical length <25 mm and an ultrasound-indicated cerclage. Group 2 (G2) consists of patients with cervical length <25 mm without cerclage. Group 3 (G3) consists of patients with cervical length >5 mm.
[b]For Group 3, we used the gestational age of CL measurement to calculate the latency time.
The Bold values indicate statistical significance as $p<.05$

Table 3. Comparison between short cervix + cerclage vs short cervix alone.

Demographics	Group 1[a] ($n = 52$) *n* (%)	Group 2[a] ($n = 139$) *n* (%)	G1 vs. G2 *p*-Value
Age in years, mean (SD)	29.9 (6.0)	29.6 (6.2)	.79
Nullipara, *n* (%)	22 (42.3)	44 (31.7)	.19
GA at CL measurement, weeks (SD)	20.2 (2.2)	20.6 (2.6)	.39
TVCL in mm, mean (SD)	9.6 (6.0)	18.9 (5.4)	**<.01**
Cervical funneling, *n* (%)	18 (35.3)	11 (7.9)	**<.01**
Vaginal progesterone, *n* (%)	19 (36.5)	57 (41.0)	.58
Intramuscular progesterone, *n* (%)	1 (1.9)	1 (0.7)	.47
African American ethnicity, *n* (%)	18 (34.6)	50 (36.0)	.86
Caucasian ethnicity, *n* (%)	21 (40.4)	59 (42.4)	.80
Hispanic ethnicity, *n* (%)	6 (11.5)	21 (15.1)	.53
Asian ethnicity, *n* (%)	3 (5.8)	6 (4.3)	.68
Other ethnicity, *n* (%)	4 (7.7)	3 (2.2)	.16
History of cervical surgery, *n* (%)	5 (9.6)	20 (14.4)	.39
History of D & C, *n* (%)	11 (21.2)	16 (11.5)	.13
Cervicitis during pregnancy, *n* (%)	4 (7.7)	10 (7.2)	.92
UTI during pregnancy, *n* (%)	4 (7.7)	16 (11.5)	.44
Tobacco use, *n* (%)	5 (9.6)	28 (20.1)	.05
Pre-existing hypertension, *n* (%)	8 (15.4)	10 (7.2)	.14
Gestational hypertension, *n* (%)	6 (11.5)	21 (15.1)	.53
Pre-existing diabetes, *n* (%)	4 (7.7)	7 (5.0)	.49
Gestational diabetes, n (%)	13 (25.0)	16 (11.5)	**.04**
SGA, *n* (%)	10 (19.2)	16 (11.5)	.21
GA at delivery, weeks Mean (SD)	34.3 (5.4)	37.6 (2.9)	**<.01**
PTD < 37 wk, *n* (%)	26 (50.0)	33 (23.7)	**<.01**
PTD < 34 wk, *n* (%)	18 (34.6)	11 (7.9)	**<.01**
PTD < 32 wk, *n* (%)	15 (28.8)	7 (5.0)	**<.01**
Latency from short cervix diagnosis[b] to delivery, days, mean (SD)	98.4 (36.3)	119.1 (27.0)	**<.01**
Birthweight in grams, mean (SD)	2321.6 (1052.6)	2956.0 (700.8)	**<.01**

GA: gestational age; CL: cervical length; SD: standard deviation; D&C: dilation and curettage; UTI: urinary tract infection.
[a]Group 1 (G1) consists of patients with cervical length <25 mm and an ultrasound-indicated cerclage. Group 2 (G2) consists of patients with cervical length <25 mm without cerclage.
[b]For Group 3, we used the gestational age of CL measurement to calculate the latency time.
The Bold values indicate statistical significance as $p<.05$

Table 4. Adjusted outcomes: odds ratios of SGA and newborn birthweight.

		Unadjusted OR	Adjusted OR	
SGA	G1 vs. G3	**5.3 (2.0, 14.2)**	**4.9 (1.8, 13.7)**	
	G2 vs. G3	**2.9 (1.2, 7.0)**	2.3 (0.9, 5.7)	
	G1 + G2 vs. G3	**3.5 (1.5, 8.0)**	**2.8 (1.2, 6.6)**	
		Unadjusted mean difference	Adjusted mean difference	*P*-value
Birthweight	G1 vs. G3	**-886.0 (150.1)**	**-846.9 (101.4)**	<.01
	G2 vs. G3	**-251.5 (69.0)**	**-224.6 (65.8)**	<.01
	G1 + G2 vs. G3	**-424.2 (71.3)**	**-385.1 (72.0)**	<.01

The bold values indicate statistical significance as the 95% CI does not cross 1.

(G1 + G2) was 2.8 (95% CI 1.2, 6.6). The subgroups analysis showed significance in group 1 (aOR 4.9 [1.8, 13.7]), but loss of significance in group 2 (aOR 2.3 [0.9, 5.7]). Additionalregressions did show that a short cervix was associated with a lower birthweight (–385.1 ± 72.0 gm, *p*-value <.01). The subgroup analyses showed that both Group 1 (-846 ± 101.4 gm, *p*-value <.01) and Group 2 (-224.6 ± 65.8 gm, *p*-value <.01) had significantly lower birthweight compared to controls.

Conclusion

This was a case-control study that investigated if women with a short cervix, with or without cerclage, were at increased risk of giving birth to a SGA infant. Our results suggested that women with a CL <25 mm before 24 weeks of gestation did appear to have an increased risk of having a SGA infant. This increased risk was most strongly seen in patients who received an ultrasound-indicated cerclage for a short cervix. Other demographic variables found to increase the risk for SGA included black ethnicity and gestational hypertension. Of interest, Hispanic ethnicity reduced the risk for SGA.

Our findings explicitly establish an association for short cervix pregnancies and small for gestational age infants, but indirect support for this association comes from prior studies that have suggested an increased incidence of SGA among PTD. For example, fetal biometry charts classify a greater proportion of PTD as SGA compared to population charts [25,26]. Another example is that there are increased rates of iatrogenic preterm delivery in pregnancies identified with fetal growth restriction [27]. Lastly, spontaneous preterm births show higher rates of failure to reach growth potential and may be examples of placental insufficiency triggering preterm labor [28]. Our results simply add short cervix, which is a risk factor for preterm delivery, to the already recognized relationship between preterm delivery and fetal growth restriction.

While growth restriction and short cervix may be easy to associate, it is harder to explain why the association exists. Inflammation appears to be active in the three processes of cervical ripening [10,29], placental insufficiency [17,20,30], and preterm labor [31]. Prior studies have established that inflammation is not always a marker for infection, but can be related instead to disruptions in metabolic homeostasis [32]. A minority hypothesis for the length of gestation in human pregnancy argues that there is a metabolic ceiling reached in gestation after which the body signals that it is time for labor to commence [33]. Under these assumptions, one could hypothesize that pregnancies which adapt poorly to the metabolic demands of pregnancy might create abnormal inflammation levels which then create increased rates of cervical ripening, fetal growth restriction, and ultimately preterm delivery.

The strengths of our study include its sample size, the personal abstraction of data in the electronic medical records, and the clear verification of controls and cases with their cerclage status. Limitations of this study include the lack of information about other potential confounders such as pre-pregnant body-mass index, gestational weight gain, socioeconomic status, depression, or nutritional status that were not collected due to lack of reporting in the medical record. In addition, our inner-city academic hospital population may not be generalizable to the general public. The US Census reported that the population percentage of Black ethnicity is 13.4% in the United States (www.census.gov/quickfacts/fact/table/US/PST045218). The same source reports that the population percentage is 24.2% in Kansas City, Kansas, and 28.7% in Kansas City, Missouri. As a reminder, our study cases (group 1 + 2) reported a 38% incidence of Black ethnicity.

In conclusion, this is the first study to our knowledge to evaluate explicitly the risk of SGA among women with a short cervix. We found that there is an increased risk for SGA in pregnancies complicated by a short cervix detected before 24 weeks, and this risk is strongest among patients who require an ultrasound-indicated cerclage due to their short cervix. We do not pretend to know exactly why this association may exist, but we hypothesize that metabolic insufficiency or uterine insufficiency may be causes of inflammation which then produce both preterm cervical ripening and growth restriction. We welcome more research to confirm our results.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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