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The association between maternal obesity, cervical length, and preterm birth

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Abstract

Objective—To determine if mid-trimester cervical length is associated with the inverse relationship between maternal body mass index (BMI) at delivery and spontaneous preterm birth (SPTB)

Methods—This was a retrospective cohort of women with a singleton pregnancy without prior SPTB who underwent routine transvaginal cervical length assessment between 18 and 24 weeks. Women were categorized into four BMI groups: (1) 18.5 – 24.9kg/m^2, (2) 25 – 29.9kg/m^2; (3) 30 – 34.9kg/m^2 and (4) ≥35kg/m^2. Univariable and multivariable analyses were conducted to determine whether BMI group was associated with SPTB at <37, 34, or 32 weeks independent of the cervical length.

Results—Of the 18,100 women in this analysis, 43.5% had a BMI ≥30. In univariable analysis, increasing BMI group was associated with longer cervical length, but not with cervical length< 10th percentile. SPTB at <37, 35 and 32 weeks was less common among women with higher BMI. In multivariable regression, a higher BMI group was associated with a lower frequency of SPTB at 37 weeks (aORs of 0.64, 0.68 and 0.51), at 34 weeks (aORs of 0.53, 0.54 and 0.31) and at 32 weeks (aORs of 0.47, 0.60 and 0.27) for BMI group 2, 3 and 4, respectively. This association persisted even when cervical length was entered into the model as a covariate.

Conclusion—Women with a higher BMI group had longer mid-trimester cervical length and, correspondingly reduced SPTB. However, the decreased risk of SPTB was not associated with cervical length. The reason for the potential protective effect from prematurity is unknown and its mechanisms require further investigation.

Précis

Higher body mass index was associated with longer mid-trimester cervical length; however this did not explain lower spontaneous preterm births among these women.

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Introduction

Preterm birth (PTB) accounts for approximately 12% of live births in the United States and is the leading cause of perinatal morbidity and mortality in developed countries.[1, 2] Although there has been a slight improvement in the PTB rate, it remains a significant individual and societal burden, as the health care costs for a premature infant are 10 times greater than for a term infant.[3, 4] Thus far, efforts to predict, prevent, and delay PTB have had some, but limited, success.[5]

One of the risk factors associated with spontaneous preterm birth (SPTB) is low body mass index (BMI).[6] However, the data regarding the risk for SPTB in obese women is conflicting with some studies showing a higher incidence of SPTB in these women, whereas others showing⁻ that they are less likely to have SPTB.[7–13] The reason for the possible potential protective effect from prematurity is unknown.

The finding of a short cervix on transvaginal ultrasound is a known risk factor for PTB.[14] A recent study reported an association between maternal characteristics and cervical length, with obese women having shorter mid-trimester cervical length.[15] In contrast, two older studies found a positive correlation between obesity and longer cervical length.[16, 17] The objective of this study was to determine if mid-trimester cervical length is associated with the relationship between BMI and SPTB.

Materials and Methods

This was a retrospective cohort study of women undergoing routine transvaginal mid-trimester CL assessment between December 2010 and January 2014, at a single tertiary care institution. Women were included in this cohort if they were at least 18 years of age, had a singleton gestation, had a mid-trimester ultrasound for cervical length measurement and delivered at the study institution.. Women with prior SPTB or stillbirth in the current pregnancy were excluded. Cervical length was obtained between 18 and 24 weeks at the time of the fetal anatomic survey as part of routine clinical care in all women. The cervical length was measured in accordance with methods previously described by Iams et al.[18]

Gestational age was based on the best obstetric estimate (last menstrual period compared with ultrasonography), determined by health care providers and used for clinical decision-making. Women's characteristics and pregnancy outcomes were compared based on four BMI groups[19], using the BMI value at the time of delivery: 18.5 – 24.9kg/m^2, 25 – 29.9kg/m^2; 30 – 34.9kg/m^2 and ≥35kg/m^2. BMI was measured routinely upon admission to the labor and delivery suit. One-hundred and fifteen women who did not have a BMI value documented in their chart were excluded from the analysis. Also, nineteen women who were underweight (BMI <18.5kg/m^2) were excluded from the analysis. Demographic and baseline clinical data, such as maternal age, race/ethnicity, and presence of diabetes or hypertension, as well as prior obstetric history were abstracted from the clinical records. Factors suggested by prior studies to be associated with SPTB such as history of cervical dysplasia, prior cervical excisional procedure, conception via in-vitro fertilization and tobacco use were abstracted as well. Cervical length measurements were compared between the four groups as

a continuous variable as well as a categorical measurement of < 3.0 cm (i.e. the 10th percentile at the gestational age of 18 to 24 weeks[18]). The primary outcome of this analysis was gestational age at the time of delivery. It was examined as a continuous variable and a categorical variable of SPTB <37, 34 or 32 weeks. In addition, we examined whether there was an interaction between cervical length and BMI towards the risk of PTB and SPTB.

All analyses were performed with Stata version 12.0 (StataCorp College Station, TX). All tests were two-tailed and P < .05 was used to define significance. Univariable comparisons of maternal characteristics (including mid-trimester cervical length) and the rate of PTB and SPTB across the BMI groups were conducted with Chi-square or one-way ANOVA tests, as well as non-parametric test for trends across four BMI groups. To determine whether there was any interaction between BMI group and cervical length towards the risk of PTB and SPTB, an interaction term of BMI group and cervical length was created. Multivariable logistic regression was used to estimate whether BMI category was associated with PTB or SPTB independent of the cervical length. Covariates entered into the regressions were those that had an association with BMI in the univariable analysis at a level of P < .05. Approval for this study was obtained from the Northwestern University Institutional Review Board prior to its initiation.

Results

Of the 18,100 women who met inclusion criteria, 2,403 (13.3%), 7,822 (43.2%), 2,962 (16.4%) and 4,913 (27.1%) women had BMI of 18.5– 25.9 kg/m^2 (Group 1), 25–29.9 kg/m^2 (Group 2), 30–34.9 kg/m^2 (Group 3) and ≥ 35 kg/m^2 (Group 4), respectively. Maternal characteristics and cervical length measurements, stratified by the BMI groups are shown in Table 1. Women in all four BMI groups differed in the majority of baseline characteristics except for the presence of fetal anomalies. However, higher BMI was not associated with the risk of having cervical length less than three centimeters. Of note, there were total of 83 women with cervical length < 2cm: 15 women in Group 1, 26 women in Group 2, 24 women in Group 3 and 19 women in Group 4. Of these, 27 also had cervical dilation on digital exam and received an exam-indicated cerclage, 40 received vaginal progesterone, 6 women received both cerclage and vaginal progesterone and the rest were monitored with serial digital exams.

Obstetric outcomes are depicted in Table 2. Mean gestational age at delivery as well as birth weight were significantly higher in groups 2, 3 and 4 compared to group 1. The frequencies of all PTB as well as all SPTB differed among the BMI groups, however a significant trend was not observed between the four BMI groups in frequencies of PTB less than 37, 34 and 32 weeks. The frequency of all SPTB was significantly lower at higher BMI groups, and a significant trend was observed in the difference of frequencies of SPTB less than 37 and less than 34 weeks across all 4 BMI groups. Out of 828 women with SPTB less than 37 weeks, 26 (3.1%) had a cervical length less than 2.0 cm.

After adjusting for potential confounding variables in multivariable regressions, a higher BMI group was associated with lower risk for PTB as well as SPTB at <37, <34 and <32 weeks (Table 3). These associations persisted when cervical length was entered into the

model as a covariate. There was no interaction between BMI group and cervical length with regard to the risk of PTB or SPTB in any of the gestational age categories (data not shown).

Discussion

In our study, a higher BMI group was associated with a lower risk for SPTB. The risk for all PTB was also lower with higher BMI; however this is explained by the fact that a large proportion of PTB in our cohort consisted of spontaneous deliveries (74.5%). Similar to Hendler et al[16] we also demonstrated a direct association between BMI and cervical length. Women with a delivery BMI >25 had a longer cervical length than normal-weight women. Nevertheless, the association between BMI and cervical length did not account for the association between BMI and PTB. In addition, we did not find an interaction between BMI and cervical length with respect to all PTB, including SPTB. These findings may be explained by examining the actual difference in cervical length between the groups. The difference in cervical length, although statistically significant, was at most 1.8mm (between normal weight women and women with BMI ≥ 35 kg/m^2), and thus it is unlikely that such small difference could explain the difference in risk of PTB among the BMI groups.

Although we observed a significant statistical difference among the groups in frequency of all PTBs, the trend tests for lower frequency of PTB as BMI increased were not significant across the groups. This is likely due to the fact that higher BMI groups had higher frequency of indicated PTB secondary to obesity related co-morbidities. In contrast, trend tests were significant for lower frequencies of SPTB<37 and SPTB<34 weeks as BMI increased across all four groups.

Obesity is an epidemic in the United States and the most recent reports from the Center for Disease Control state that 68% of the adult United States population is either overweight or obese.[20] A pregnancy complicated by obesity is at higher risk for adverse maternal and neonatal outcomes, including miscarriage, gestational diabetes, preeclampsia, cesarean delivery, infectious morbidity, congenital anomalies and stillbirth.[21–22] Although obese women have a higher incidence of indicated PTB, the relationship between obesity and SPTB is more complex.[7–13, 16, 23] A recent analysis of a large prospective Norwegian database showed that the risk of SPTB was higher in both overweight and obese women, defined by pre-pregnancy BMI, compared to those with a normal weight, yet the population studied was very different than ours in that only 9.4% were obese, and although the differences in SPTB were statistically significant among the weight groups, the overall rates of PTB were low (3%). [12] That study was followed by a population-based cohort analysis which demonstrated a direct dose-response association between maternal overweight and obesity and risks of PTB, including SPTB.[13] The effect of obesity on SPTB was especially prominent among extremely preterm deliveries. The authors hypothesized that the mechanism behind their findings was an elevated inflammatory state that is associated with maternal obesity, but no biomarkers were evaluated to explore this theory. However, older studies did not observe this correlation and either found no association between BMI and SPTB or actually reported a lower risk for SPTB with higher BMI.[7–10,16,23] Two of these studies attempted to investigate the mechanism behind this association. Hendler et al.[16] found that obese women had longer cervical lengths, and Ehrenberg et al.[23] reported less

uterine activity in overweight and obese women compared to normal or underweight women.

Although the mechanism behind the protective effect of obesity and PTB is unclear, it parallels the observations of postterm pregnancy being associated with obesity.[24–26] Moreover, the association between very low maternal weight and the risk of SPTB further supports the theory that there may be an inverse association between BMI and SPTB.[6, 27] The human parturition process is intricate and factors that control length of gestation are not well understood. Denison et al. hypothesized that the link to explain the effect of obesity on timing of delivery involves cortisol.[25] Placental production of corticotropin-releasing hormone is proposed as an early event regulating the cascade of events leading to parturition.[28] Circulating maternal plasma levels of corticotropin-releasing hormone increase progressively throughout the latter half of pregnancy with dramatic increases in the last few weeks before delivery.[29–30] In another study of non-pregnant women, there was an inverse association between plasma cortisol level and relative weight.[31] This may be due to increased cortisol clearance as well as decreased mineralocorticoid receptor response to circulating corticosteroids in an obese population.[32] Accordingly, obese women may have lower cortisol that contributes to their longer gestational length, however this is only a small component of the multifactorial physiological events leading to labor.

This study is not without its limitations. First, we examined the association between BMI at the time of delivery and the risk for PTB, as the data for pre-pregnancy BMI was not accessible. This limits our evaluation of the effect of gestational weight gain on the risk of PTB. However, studies exploring gestational weight gain and PTB also report conflicting results, some suggesting that excessive weight gain reduces the risk for PTB[33, 34] versus other suggesting the contrary.[35, 36] Assuming that BMI increases with gestational age, then our findings may have overestimated the odds of PTB with respect to BMI group but the trends in BMI and SPTB we identified would not have been less influenced by the timing of the BMI measurement. The second limitation is the lack of information about preterm rupture of membranes among our study population. There may be a separate association between BMI and preterm rupture of membranes, as was reported by Nohr et al.[8] In that study, obese women had a higher risk for preterm rupture of membranes and early induced PTB. The explanation for the association was hypothesized to be related to increased susceptibility for bacterial growth among obese women, leading to activation of cytokines and enhanced protease activity that degrades the fetal membranes. In our analysis, women with preterm rupture of membranes were not analyzed separately and thus we are unable to report on the association between BMI and preterm rupture of membranes. Finally, the overall rate of prematurity in our study was relatively low, at 6.1%. Consequently, we had very few women whose pregnancy was complicated by PTB <32 weeks, and we were unable to report meaningful analysis of the association between BMI and extremely preterm deliveries, between 24–28 weeks.

In conclusion, in this retrospective cohort study we found that women with higher BMI had longer mid-trimester cervical length and also reduced risk for SPTB. However, the decreased risk of SPTB was not associated with a longer cervical length. The reason for the potential

protective effect from prematurity is unknown and its mechanisms require further investigation.

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Table 1

Maternal clinical characteristics of the study population stratified by body mass index group

Characteristic	Group 1 18.5–24.9 kg/m^2 (n=2403)	Group 2 25–29.9 kg/m^2 (n=7822)	Group 3 30–34.9 kg/m^2 (n=2962)	Group 4 ≥35 kg/m^2 (n=4913)	P value	Post hoc analysis	Test for trend P value
Maternal Age (y)	31.6 ± 5.0	31.9 ± 5.1	31.3 ± 5.5	30.4 ± 5.8	<0.001	Group 1 and 2 p=0.086 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p= 0.232	<0.001
Race/Ethnicity White Black Hispanic Asian Native American Other	1388 (68.0) 135 (6.6) 250 (12.2) 223 (10.9) 9 (0.4) 35 (1.7)	4381 (65.4) 493 (7.4) 1130 (16.9) 533 (7.9) 46 (0.7) 117 (1.7)	2241 (52.1) 552 (12.8) 1152 (26.8) 229 (5.3) 23 (0.5) 105 (2.4)	912 (34.4) 642 (24.2) 943 (35.5) 68 (2.6) 17 (0.6) 71 (2.7)	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p<0.001	<0.001
Nulliparous	1328 (55.2)	4207 (53.7)	2503 (50.9)	1407 (47.4)	<0.001	Group 1 and 2 p =0.178 Group 2 and 3 p =0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p =0.005 Group1 and 3 p<0.001	<0.001
Prior loop electrosurgical excision procedure or cold-knife cone	198 (8.2)	614 (7.8)	361 (7.3)	142 (4.8)	<0.001	Group 1 and 2 p=0.580 Group 2 and 3 p=0.300 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p=0.200	<0.001
Diabetes mellitus *	85 (4.0)	318 (4.6)	301 (6.9)	333 (12.6)	<0.001	Group 1 and 2 p=0.209 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p<0.001	<0.001
Chronic hypertension	24 (1.0)	135 (1.7)	172 (3.5)	235 (8.0)	<0.001	Group 1 and 2 p=0.012 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p<0.001	<0.001
Gestational hypertension or preeclampsia	45 (1.9)	228 (2.9)	282 (5.7)	325 (11.0)	<0.001	Group 1 and 2 p=0.006 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p<0.001	<0.001
Smoking in current pregnancy	17 (0.8)	42 (0.6)	46 (1.0)	40 (1.5)	<0.001	Group 1 and 2 p=0.333 Group 2 and 3 p=0.008 Group 2 and 4 p<0.001 Group 1 and 4 p=0.025 Group 3 and 4 p=0.099 Group 1 and 3 p=0.314	<0.001
In vitro fertilization	115 (5.2)	327 (4.5)	175 (3.8)	89 (3.1)	0.001	Group 1 and 2 p=0.183 Group 2 and 3 p=0.055 Group 2 and 4 p=0.001 Group 1 and 4 p<0.001 Group 3 and 4 p=0.119 Group 1 and 3 p=0.007	<0.001
Cervical length (cm)	4.39 ± 0.83	4.48 ± 0.82	4.55 ± 0.85	4.57 ± 0.89	<0.001	Group 1 and 2 p=0.687 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001	<0.001

Characteristic	Group 1 18.5–24.9 kg/m^2 (n=2403)	Group 2 25–29.9 kg/m^2 (n=7822)	Group 3 30–34.9 kg/m^2 (n=2962)	Group 4 ≥35 kg/m^2 (n=4913)	P value	Post hoc analysis	Test for trend P value
						Group 3 and 4 p<0.001 Group 1 and 3 p<0.001	
Cervical length <3 cm	40 (1.7)	116 (1.5)	79 (1.6)	51 (1.7)	0.803		
Fetal anomalies	15 (1.9)	37 (1.4)	25 (1.4)	10 (1.0)	0.448		-

All data presented as mean ± standard deviation or N (%)

*includes pregestational and gestational diabetes

Table 2.

Pregnancy outcomes stratified by body mass index group

Outcome	Group 118.5–24.9 kg/m^2(n=2403)	Group 225–29.9 kg/m^2(n=7822)	Group 330–34.9 kg/m^2(n=2962)	Group 4≥35 kg/m^2(n=4913)	P value*	Post hoc analysis	Test for trend P value
Gestational age at delivery (wk)	39.0 ± 2.1	39.4 ± 1.6	39.3 ± 1.8	39.2 ± 2.0	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p=0.819 Group 2 and 4 p<0.001 Group 1 and 4 p=0.028 Group 3 and 4 p=0.001 Group 1 and 3 p<0.001	0.027
Birth weight (g)	3172 ± 512	3354 ± 490	3409 ± 538	3442 ± 583	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p=0.060 Group 1 and 3 p<0.001	<0.001
Mode of delivery Vaginal Cesarean	 2008 (83.6) 395 (16.4)	 6117 (78.2) 1705 (21.8)	 3484 (70.9) 1429 (29.1)	 1887 (63.7) 1075 (36.3)		Group 1 and 2 p<0.001 Group 2 and 3 p<0.001 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p=0.006 Group 1 and 3 p<0.001	<0.001
Preterm birth <37 (wk)	187 (7.8)	409 (5.2)	296 (6.0)	220 (7.4)	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p=0.056 Group 2 and 4 p<0.001 Group 1 and 4 p=0.629 Group 3 and 4 p=0.015 Group 1 and 3 p=0.005	0.298
Spontaneous preterm birth <37 (wk)	148 (6.1)	329 (4.2)	230 (4.7)	121 (4.1)	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p=0.202 Group 2 and 4 p=0.777 Group 1 and 4 p=0.001 Group 3 and 4 p=0.214 Group 1 and 3 p=0.007	<0.001
Preterm birth <34 (wk)	90 (3.7)	152 (1.9)	109 (2.2)	85 (2.9)	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p=0.332 Group 2 and 4 p=0.249 Group 1 and 4 p<0.001 Group 3 and 4 p=0.071 Group 1 and 3 p=0.002	0.454
Spontaneous preterm birth <34 (wk)	71 (3.0)	124 (1.6)	89 (1.8)	38 (1.3)	<0.001	Group 1 and 2 p=0.474 Group 2 and 3 p=0.929 Group 2 and 4 p<0.001 Group 1 and 4 p<0.001 Group 3 and 4 p<0.001 Group 1 and 3 p=0.456	<0.001
Preterm birth <32 (wk)	39 (1.6)	52 (0.7)	42 (0.8)	30 (1.0)	<0.001	Group 1 and 2 p<0.001 Group 2 and 3 p=0.223 Group 2 and 4 p=0.064 Group 1 and 4 p=0.049 Group 3 and 4 p=0.476 Group 1 and 3 p=0.003	0.267
Spontaneous preterm birth <32 (wk)	29 (1.2)	42 (0.5)	37 (0.8)	15 (0.5)	0.003	Group 1 and 2 p=0.001 Group 2 and 3 p=0.130 Group 2 and 4 p=0.844 Group 1 and 4 p=0.005 Group 3 and 4 p=0.190 Group 1 and 3 p=0.054	0.057

All data presented as mean ± standard deviation or N (%)

*p-value for the overall ANOVA

Table 3.

Multivariable regressions for the association between body mass index and preterm birth

	Adjusted odds ratio without CL*	**95% Confidence Interval**	**Adjusted odds ratio with CL****	**95% Confidence Interval**
Preterm delivery <37 weeks				
BMI (kg/m^2)	1.00	Referent	1.00	Referent
18.5 – 24.9	0.56	0.45 – 0.70 0.46 −0.74 0.43	0.58	0.46 – 0.73
25.0 – 29.9	0.59	– 0.73	0.66	0.52 – 0.83
30.0 – 34.9	0.56		0.66	0.51– 0.86
≥35				
Spontaneous preterm delivery <37 weeks				
BMI (kg/m^2)	1.00	Referent	1.00	Referent
18.5 – 24.9	0.62	0.48 – 0.78 0.49 – 0.83	0.64	0.50 – 0.81
25.0 – 29.9	0.64	0.34 – 0.64	0.68	0.52 – 0.88
30.0 – 34.9	0.47		0.51	0.37 – 0.69
≥35				
Preterm delivery <34 weeks				
BMI (kg/m^2)	1.00	Referent	1.00	Referent
18.5 – 24.9	0.45	0.32– 0.62	0.47	0.34 – 0.65
25.0 – 29.9	0.44	0.31– 0.63	0.48	0.34 – 0.68
30.0 – 34.9	0.42	0.28– 0.62	0.45	0.31 – 0.67
≥35				
Spontaneous preterm delivery <34 weeks				
BMI (kg/m^2)	1.00	Referent	1.00	Referent
18.5 – 24.9	0.49	0.35 – 0.69	0.53	0.37 – 0.75
25.0 – 29.9	0.49	0.33 – 0.72	0.54	0.37 – 0.80
30.0 – 34.9	0.28	0.17 – 0.45	0.31	0.19 – 0.52
≥35				
Preterm delivery <32 weeks				
BMI (kg/m^2)	1.00	Referent	1.00	Referent
18.5 – 24.9	0.37	0.22 – 0.60	0.39	0.23 −0.64
25.0 – 29.9	0.39	0.23 – 0.66	0.44	0.26 – 0.75
30.0 – 34.9	0.29	0.16 – 0.53	0.32	0.17 – 0.59
≥35				
Spontaneous preterm delivery <32 weeks				
BMI (kg/m^2)	1.00	Referent	1.00	Referent
18.5 – 24.9	0.43	0.24 – 0.74	0.47	0.27 – 0.83
25.0 – 29.9	0.52	0.29 – 0.92	0.60	0.33 – 1.08
30.0 – 34.9	0.22	0.10 – 0.50	0.27	0.12 – 0.61
≥35				

* Adjusted for maternal age, race/ethnicity, nulliparity, prior cervical excisional procedure, maternal diabetes, chronic hypertension, gestational hypertension/preeclampsia, smoking and IVF conception

** Adjusted for maternal age, race/ethnicity, nulliparity, prior cervical excisional procedure, maternal diabetes, chronic hypertension, gestational hypertension/preeclampsia, smoking, IVF conception and cervical length