

Original Article

Association between mid-trimester cervical length and risk of spontaneous preterm birth is modified by a prior cervical excisional procedure

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Abstract: To determine whether and how prior cervical excision modifies the association between a short residual mid-trimester cervical length and the risk of spontaneous preterm birth (SPB). This is a retrospective cohort study on spontaneous preterm birth (SPB) in a total of 1875 patients with and without prior cervical excisional procedure (CEP, loop electrosurgical excision procedure or cold knife cone). Adjusting for potential confounders, we conducted a logistic regression analysis, along with a test of interaction between prior history of CEP and cervical length on SPB. Among 1875 women, there were 274 patients who experienced preterm birth (33.9%). Risk of SPB is significantly associated with age, BMI, cervical length (CL), gestational week at measurement of CL by ultrasonography, multipara, history of preterm birth, *in vitro* fertilization (IVF) and CEP. Moreover, a test of interaction indicated a close association between risk of SPB and CL, which was modified by history of prior CEP. We identified a CL cutoff value of 2.8 cm at which the risk of SPB in patients with prior CEP was identical to the risk in patients without prior CEP. Given the same CLs which were less than 2.8 cm, prior CEP patients presented a higher risk of preterm birth than non-CEP ones. In contrast, given the same CLs which were more than 2.8 cm, prior CEP patients presented lower risk of preterm birth than non-CEP ones. Association between mid-trimester cervical length and risk of SPB was modified by a prior cervical excisional procedure. In patients with prior CEP compared to those without, there was an increased risk of SPB at CL < 2.8 cm and a decreased risk of SPB at CL > 2.8 cm.

Keywords: Cervical length, cervical excisional procedure, spontaneous preterm birth

Introduction

As a global health issue, preterm birth is and the most common cause of death among infants worldwide, which is the birth of a baby at fewer than 37 weeks gestational age. Preterm infants usually show varying degrees of physical signs of prematurity and are at risk of pathologic conditions affecting different organ systems. The cause of preterm birth is not completely defined, but some of the risk factors include diabetes, hypertension, multiple gestation, either obesity or underweight, vaginal infections, psychological stress, etc. [1, 2]. Notably, cervical length is inversely related to the risk of preterm labor [3, 4]. The specific reasons

for this phenomenon have yet been defined, but undoubtedly the uterine quiescence and the inherent tensile strength of the cervix play a role in preventing premature labor. Genital tract infection such as bacterial vaginosis is also a significant risk factor of preterm delivery. Hence, the cervix may play the role of mechanical and biologic barrier between amniotic cavity and the vagina [5]. Owen et al. [3] reported a prospective, blinded observational study to determine whether endovaginal sonography of the cervix at 16 weeks to 23 weeks 6 days' gestation would predict spontaneous preterm birth with sufficient accuracy to justify mid-trimester intervention trials in high-risk women. As a single measurement, cervical length of less than

25 mm at 16 to 18 weeks' gestation was a significant predictor of spontaneous preterm birth before 35 weeks. The results demonstrated that the natural history of cervical anatomy during mid-pregnancy can contribute significant information as to the risk of subsequent spontaneous preterm birth (SPB).

Prior cervical excisional procedures (CEP) [6, 7], either a loop electrosurgical excision procedure (LEEP) or cold knife cone, were also closely associated with increased risk of preterm birth [8, 9]. Jin et al. [10] reported a meta-analysis with data from 36,954 cases and 1,794,174 controls in 4 prospective cohorts and 22 retrospective studies, the author concluded that previous LEEP was associated with high risk of severe preterm delivery (RR = 1.98), extreme preterm delivery (RR = 2.33), preterm premature rupture of the membranes (RR = 1.88) and low birth weight RR = 2.48) in subsequent pregnancy. Compared with a control group, a cervical length of less than 3 cm in LEEP group was significantly increased (RR = 4.88).

Our initial purpose of this study is to determine whether a short residual mid-trimester cervical length is related to higher risk of preterm birth. Interestingly, we happened to discover that the significant interaction between prior history of CEP and mid-trimester cervical length on the risk of preterm birth.

Methods

Patients

This is a retrospective cohort study approved by Institutional Review Board (IRB No. 20180013) of Women's Hospital, Zhejiang University School of Medicine, a tertiary specialty care institution. Data were collected from August 2016 to July 2017 from the Hospital's Center for Medical Informatics. Patients were recruited in this study cohort if they were 18 years or older, had a singleton non-anomalous gestation, had regular antenatal examination and delivered at our institution. As a part of perinatal care in all patients, transabdominal cervical length was routinely assessed between 18 and 24 weeks in our hospital. If ultrasounds for cervical length were done many times on an individual patient, the measurement taken closest to 20 weeks of gestation was adopted

for analysis. Spontaneous preterm birth (SPB) was defined as spontaneous delivery at gestational age < 37 weeks.

Clinical data collection

A clinical data warehouse was created as a collaborative program between Zhejiang Women Hospital (Hangzhou, China) and Lejiu Health Technology Inc. (Shanghai, China). Data were extracted every 24 hours by Lex Clinical Data Application 1.0 (Lejiu Health, Shanghai, China) from the Hospital Health Information System (HIS) to a designated clinical data warehouse including admission/transfer/discharge, medication orders, laboratory orders/results, administration events, flow sheet entries, procedures, medical reports, admission notes, progress notes, and discharge summary. All original unstructured data (i.e. pathology report, radiology report, progress notes, admit/discharge summary etc.) were exclusively converted to a uniform structured format. Core elements of the data warehouse were completely de-identified in order to guarantee that all queries and analytics could be carried out without exposing the confidential health data, while users who were offered sufficient privilege could re-identify data to support operations and quality improvement applications.

Lex Clinical Data Application 1.0 is a self-service data access tool developed to query clinical data warehouse and return graphic data for analysis and visualization. Lex allows investigators and data analysts with minimal computer training to find study cohorts of interest based on their research hypothesis and study protocols. Investigators can use simple click actions to extract clinical data from the clinical data warehouse by specifying queries. More complex queries can be achieved by database manager using Structured Query Language (SQL). Lex outputs data in comma-separated, tab-separated, and attribute-related file formats which are appropriate for conversion to visualization tools and statistical analysis package.

Potential confounders of preterm birth extracted through Lex were age, BMI, gestational week at CL measurement by ultrasound, *in vitro* fertilization (IVF) conception, multipara, prior preterm birth, and prior CEP (either loop electrosurgical excision procedure or cold knife cone).

Table 1. Characteristics of patients with and without preterm birth

	Non-Preterm Birth (n = 1601)	Preterm Birth (n = 274)	P value
Age, mean \pm std	30.5 \pm 40.1	30.8 \pm 4.6	0.027
BMI, mean \pm std	25.9 \pm 3.6	25.0 \pm 4.2	< 0.001
Gestational Week (week), mean \pm std	21.5 \pm 2.1	21.9 \pm 1.9	< 0.001
*Cervical Length (cm), mean \pm std	3.6 \pm 0.7	3.1 \pm 1.2	< 0.001
Multipara, n (%)	239 (19.3)	141 (22.2)	0.142
History of preterm birth, n (%)	39 (3.11)	35 (5.50)	0.015
IVF conception, n (%)	47 (3.79)	70 (11.0)	< 0.001
CEP, n (%)	165 (10.31)	86 (31.39)	< 0.001

*Cervical Length (CL): median = 3.5 cm, min = 0.5 cm, max = 6.6 cm.

Statistical analysis

Numerical data are summarized as mean \pm standard deviation, while categorical data were presented as frequencies and percentages. To assess the risk factors associated with preterm birth, we performed multiple logistic regression to assess odds ratio (OR) of preterm. The potential confounders under the control were age, BMI, gestational week, IVF conception, multipara, prior history of preterm birth, mid-trimester cervical length, and prior CEP. Interaction test were added to examine whether there was any interaction between CL and preterm birth. If interactions were present, more analysis would be performed stratified by effector modifiers. The multiple logistic regression model was expressed as an odds ratio (OR) along with a 95% confidence interval (95% CI). $P < 0.05$ was set as statistical significance. SAS 9.0 was used for all statistical analyses (SAS Institute, Cary, NC).

Results

Among 1875 women, there were 274 patients experiencing SPB (33.9%). All these patients underwent a mid-trimester CL measurement during their perinatal care in our hospital. 251 (13.38%) patients had a prior history of CEP (either loop electrosurgical excision procedure, or cold knife cone) (**Table 1**). Risk of preterm birth was closely associated with age, BMI, cervical length (CL), gestational week at measurement of CL by ultrasonography, multipara, history of preterm birth, *in vitro* fertilization (IVF) and CEP.

Both univariate and multivariate analysis showed that increased risk was associated with patients with positive history of prior SPB (OR =

2.32), and IVF conception (OR = 3.73), while longer cervical length (CL > 3 cm) was associated with lower likelihood of SPB (OR = 0.22). Moreover, a test of interaction indicated that the close association between risk of preterm birth and CL was modified by prior CEP (**Table 2**, model 3). There were 251 cases of prior CEP among the

total of 1875 patients (**Table 3**). After plotting CL against probability of SPB, we identified that the curve representing prior CEP patients and the curve representing non-prior CEP was crossed at the point where CL was about 2.8 cm, implying that, at CL = 2.8 cm, the risk of SPB would be equal between patients with and without prior CEP. Furthermore, given CL < 2.8 cm, the risk of SPB was much higher in prior-CEP patients than in non-CEP patients (OR: 11.17 vs. 6.7). In contrast, if given CL was longer than 2.8 cm, risk of SPB was significantly lower in prior-CEP patients than in non-CEP patients (OR = 0.03 vs. 0.61). A significant trend of OR changing pattern in patients with and without CEP was similar in each stratum when CL was stratified by < 2 cm, 2-3 cm, 3-4 cm and > 4 cm (**Table 4**; **Figures 1** and **2**).

Discussion

It had been long reported by several authors that cervical length is inversely related to the risk of SPB [3, 4, 8, 11, 12]. However, interestingly, our data showed that short cervical length was not always linearly associated with the increased risk of SPB. This relation between cervical length and SPB was modified by the history of prior CEP to some extent. We identified 2.8 cm of CL as the cut off value where the risk of SPB in patients with prior CEP was identical to the risk in patients without prior CEP. Given the same CLs which were less than 2.8 cm, prior CEP patients presented higher risk of SPB than non-CEP ones. In contrast, given the same CLs which were more than 2.8 cm, prior CEP patients presented lower risk of SPB than non-CEP ones. We assumed such a mechanism as below: a certain cervical length is needed to support the maintenance of normal term preg-

Table 2. Univariate and multivariate analysis to assess risk of preterm birth

Variable	Model 1				Model 2				Model 3			
	OR	Lower 95% CL	Upper 95% CL	P value	OR	Lower 95% CL	Upper 95% CL	P value	OR	Lower 95% CL	Upper 95% CL	P value
Age	1.03	1.00	1.05	0.022	1.02	0.99	1.05	0.143	1.02	0.99	1.05	0.13
BMI	0.94	0.92	0.97	< 0.001	0.94	0.91	0.97	< 0.001	0.93	0.91	0.96	< 0.001
Gestational week	1.10	1.04	1.15	< 0.001	1.05	1.00	1.11	0.070	1.05	1.00	1.11	0.059
IVF conception	3.14	2.14	4.60	< 0.001	3.73	2.46	5.64	< 0.001	3.70	2.41	5.68	< 0.001
Multipara	1.19	0.94	1.51	0.142	1.39	1.06	1.82	0.018	1.37	1.04	1.80	0.024
History of preterm birth	1.79	1.12	2.86	0.014	2.32	1.40	3.83	0.001	2.19	1.31	3.65	0.003
CL \geq 3 cm	0.22	0.18	0.28	< 0.001	0.22	0.18	0.28	< 0.001	0.29	0.23	0.37	< 0.001
CEP	1.02	0.77	1.35	0.902	0.57	0.40	0.80	0.001	1.73	1.00	2.97	0.049
Interaction*									0.12	0.05	0.25	< 0.001

*Interaction = CL * CEP. Model 1: no adjustment (univariate analysis). Model 2: adjustment for age, BMI, gestational week, IVF conception, multipara, history of preterm birth and CEP. Model 3: adjustment for all variables of model 2 with interaction term. OR: Odds Ratio. BMI: Body Mass Index. 95% CL: 95% confidence interval. CL: cervical length. CEP: cervical excisional procedure.

Table 3. Summary of patients with and without prior CEP

Variable	Patients without CEP (N = 1624)	Patients with CEP (N = 251)	P value
Age (yr), mean \pm std	30.19 \pm 4.08	32.63 \pm 4.46	< 0.001
BMI	26.01 \pm 3.59	22.72 \pm 3.82	< 0.001
Gestational week (wk), mean \pm std	22 \pm 4	21 \pm 4	< 0.001
Cervical Length (cm), mean \pm std	3.45 \pm 0.96	3.11 \pm 0.81	< 0.001
IVF Conception, n (%)	89 (5.48)	28 (11.16)	< 0.001
Multipara, n (%)	297 (18.29)	83 (33.07)	< 0.001
History of Preterm Birth, n (%)	62 (3.82)	12 (4.78)	0.579
Preterm Birth, n (%)	188 (11.59)	86 (34.26)	< 0.001

nancy. When a small portion of cervix is removed to some extent, the residual cervix (along with uterine) might initiate a protective mechanism against preterm birth. Through such an overly compensated protection, the chance of preterm labor would be even lower than its counterpart: a non-resected intact cervix with the same length as the residual length of the resected one. However, if more cervical tissues were resected (we assumed a residual cervical length of 2.8 cm at mid-trimester could be a threshold of decompensation), risk of SPB would remarkably rise due to decompensated machine and/or biological supports.

The human uterine cervix undergoes extensive changes during pregnancy. Collagen is reorganized and consolidated early in gestation with proliferation and hyperplasia of the cellular component [13, 14]. As term pregnancy approaches, the joint action of multiple factors cause collagen to disperse and cervix to ripen (clinically become softer) in complex interactions. As the collagen bundles of cervix disperse and lose strength, the synergistic effect

of cytokines, hyaluronic acid, collagenases, and elastase allow effacement [13]. However, the underlying mechanism, which may be responsible for cervical incompetence, preterm delivery, post-term delivery, and proper “ripening” of the cervix, remains unknown. To interpret our data, we hypothesized that a “trigger effect”

may exist in the initiation of “premature cervical ripening” due to prior cervical surgery. Under a normal pregnancy, both cervix and fundus are touched bilaterally, so that the cervical canal is closed. However, if removing external cervix upwardly exceeds a certain point so that the remaining cervix is 2.8 cm or less, it may start the trigger effect resulting in preterm birth, although the exact mechanism is unclear.

Another potential underlying mechanism for this association is the loss of antimicrobial barrier of the endocervical mucus, normally present in the cervical transition zone. The cervical mucus is deemed to provide both a mechanical and chemical antimicrobial barrier, thus the change of the microenvironment in the cervical transition zone such as the loss of matrix metalloproteinases and other innate immune modulators could alter the risk of ascending infection [15, 16].

It was reported that the incidence of preterm birth was 11.1 per 100 live births out of all births worldwide [17]. Approximately, 11 million

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Table 4. Risk of preterm birth in patients with and without prior CEP stratified by cervical length

Cervical Length (cm)	CL: ≤ 2 cm			CL: 2-3 cm		CL: 3-4 cm			CL: >4 cm			P for trend
	N	OR (95% CI)	P value	N	OR (95% CI)	N	OR (95% CI)	P value	N	OR (95% CI)	P value	
All patients	133	6.59 (3.97-10.93)	< 0.001	479	Ref	873	0.36 (0.28-0.46)	< 0.001	390	0.49 (0.37-0.66)	< 0.001	< 0.001
Patients with CEP	26	11.17 (1.41-88.74)	< 0.001	80	Ref	119	0.04 (0.02-0.1)	< 0.001	26	0.03 (0-0.21)	0.002	< 0.001
Patients without CEP	107	6.7 (3.92-11.44)	< 0.001	399	Ref	754	0.48 (0.37-0.63)	< 0.001	364	0.61 (0.45-0.83)	< 0.001	< 0.001

All models adjusted for age, BMI, IVF conception, multipara and history of preterm birth. Linear trend test was used to test the ORs trend.

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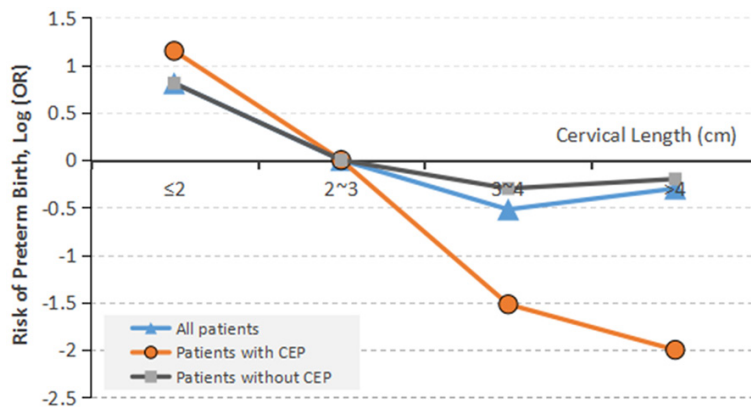


Figure 1. Risk of preterm birth stratified by CL.

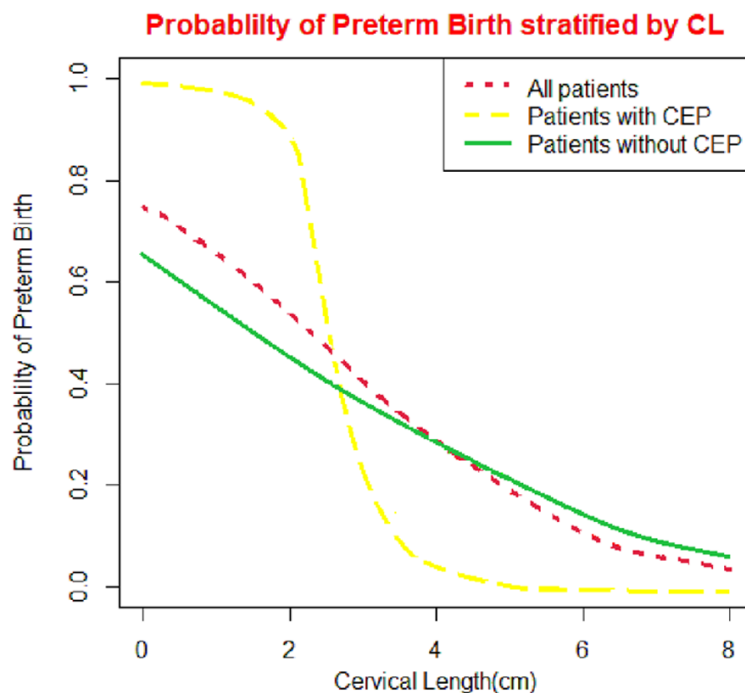


Figure 2. Probability of preterm birth stratified by CL.

(85%) of these preterm births were concentrated in Africa and Asia, while about 0.5 million occurred in Europe and North America (excluding Mexico) and 0.9 million in Latin America and the Caribbean. The highest rates of preterm birth were in Africa and North America (11.9% and 10.6% of all births, respectively), and the lowest were in Europe (6.2%) [18]. In China, incidence of preterm birth was around 2.6% to 6.8% [19-22]. Our hospital is a AAA (the highest grade in China) major academic medical center, as graded by the China Minister of Health in Zhejiang Province. We are the largest consult-

ing medical center to help low-grade hospitals manage high risk and complex patients province wide. Every year, a significant proportion of patients admitted to our hospital are referred and transferred from outside hospitals. Therefore, incidences of SPB in our institution are as high as 34%, which may represent the high-risk population.

Limitation of this study: (1) Although loop electrosurgical excision procedure or cold knife cone may have differential effects on cervical length and preterm birth, we were unable to explore this possibility given the distinction was not contained in the medical record. (2) Single center: our hospital is the major academic medical center in Zhejiang Province to serve as a consulting center for the entire province to manage high risk and complex patients. Our preterm labor rate in our institution was as high as 11.59%, which may imply our subject population was not representative.

Conclusions

In conclusion, association between mid-trimester cervical length and risk of preterm birth was modified by prior cervical excisional procedure.

In patients with prior CEP compared to those without, there was an increased risk of SPB at CL < 2.8 cm and a decreased risk of SPB at CL > 2.8 cm.

Acknowledgements

This is a retrospective cohort study approved by Institutional Review Board (IRB No. 20180013) of Women's Hospital, Zhejiang University School of Medicine. Participants have provided their written informed consent to participate in this study.

Disclosure of conflict of interest

None.

Abbreviations

SPB, spontaneous preterm birth; CEP, cervical excisional procedure; CL, cervical length; IVF, *in vitro* fertilization; LEEP, loop electrosurgical excision procedure; OR, odds ratio.

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