The Proportion of Excised Cone Volume for Cervical Lesions is the Best Predictor of Pregnancy Outcomes after Cervical Conization

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Research

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Abstract

Background: As much more women in the reproductive period are treated with a cervical conization, the risk of subsequent adverse pregnancy outcomes is also increasing. We carried the present study to evaluate whether absolute cone length/volume and the proportions of the cone length/volume correlate to spontaneous abortion (SAB) and spontaneous preterm birth (SPTB) and their predictive values.

Methods: The present retrospective observational study included 312 women undergoing cervical conization for cervical lesions at the Affiliated Hospital of Qingdao University during 2012–2019. The information about the pretreatment cervical dimensions and cone size and pregnancy outcomes were collected to assess the correlation between cone parameters and pregnancy outcomes.

Results: In the multivariate logistic regression models, the cervical length excised, the cervical volume excised, the proportion of the length excised, and the proportion of the cervical volume excised significantly correlated with SAB and SPTB, respectively (P<0.05). A most significant inverse correlation of the proportion of the cervical volume excised with pregnancy duration emerged (P<0.001, r=-0.220). The area under the curve (AUC) of the proportion of the cervical volume excised was greatest (0.700,95% CI 0.634-0.765). And the risk of SAB and SPTB increased with the proportion of the cervical volume excised increasing (OR 19.704, 95% CI 4.646-83.568). The cutoff *point* of the proportion of the cervical volume excised was 19.5% (sensitivity 0.635; specificity 0.655).

Conclusion: The cone length/volume and the proportions of cervical length/volume excised were associated with increased risks of SAB and SPTB. The proportion of the cervical volume excised is the best predictor for SAB and SPTB after cervical conization. When the proportion of the cervical volume excised is more than 19.5%, women should be informed about their future risk of SAB and SPTB after cervical conization for cervical lesions.

Background

Cervical cancer is the most common gynecological malignant tumor. The early identification and treatment of cervical intraepithelial neoplasia (CIN) produce a profound decrease for progression from precursor lesions to invasive cancer[1]. With the widespread of the cervical screening, diagnosis rate of women with CIN is much higher for the past decades[2]. Currently, excised treatments of CIN mainly include cold knife conization (CKC) and loop electrical excision procedure (LEEP). As more reproductive women undergoing excision do not finish their family plan, it increases the challenge that cervical lesion is removed effectively with preserving the competence of cervix. Over the recent years, there has been growing concern about the relationship between treatment for cervical diseases and subsequent risk of adverse pregnancy outcomes[3–5].

Intraoperative and postoperative short-and long-term complications of cervical conization have generally been thought to be uncommon and relatively mild. However, large amounts of previous studies and meta-analyses have demonstrated that cervical conization is associated to increased risks of adverse pregnancy outcomes, especially spontaneous abortion (SAB) and spontaneous preterm birth (SPTB)[1–3, 6, 7].

A meta-analysis made by Kyrgiou et al. indicated that the frequency and severity of adverse pregnancy outcomes increased with increasing cone depth[4]. Evidence from previous studies found a “dose–effect” relationship between cone length/volume and prematurity[8–10]. The cone length/volume appears to be a predictor for subsequent prematurity. As cervical length and volume vary between individuals, similar-sized cones would represent various proportions of excision in different women. Adverse outcomes are most probably related to the proportions of the cervical length and volume excised rather than the absolute depth and volume of the excision. Prospective studies have revealed that cervical regeneration and the proportional deficit at 6 months post-treatment are determined mainly by the proportion of the excised volume[11], and the proportions of the length/volume excised correlate with the pregnancy duration[12].

Although the impact of treatment for cervical lesions on adverse obstetric outcomes has been extensively described, the predictive value of the relative dimensions in the cervical conization for subsequent pregnancy outcomes has been relatively under-reported. We assessed the effects of length/volume of cervical cone and the proportions of the cervical length/volume removed after cervical conization for intraepithelial or early invasive cervical lesions on SAB and SPTB and their predictive values.

Materials And Methods

Data collection

The present study was a retrospective observational study conducted at the Affiliated Hospital of Qingdao University. The study enrolled all women of reproductive ages (20–45 years) who received excisional treatment (CKC and LEEP) for cervical lesions including CINI-III, adenocarcinoma in situ (AIS), stage IA1 of cervical cancer and wished to have future pregnancies, then conceived for the first time with singleton birth after treatment from January1st,2012 to December31st,2019. Women in case group had a SAB or SPTB (pregnancy duration < 37 weeks). Women in control group had a term birth (pregnancy duration ≥ 37 weeks). Women were recruited irrespective of their gravidity and parity. Women with history of previous cervical treatment and cervical conization during pregnancy were excluded. Those who had completed their family plan were excluded, as were women carrying multiple pregnancies. For enrolled women with deliveries more than once, only the most recent delivery was included. Women who smoked, had a history of infertility, cervical incompetence, had the history of recurrent spontaneous abortion and premature delivery were excluded. Women who had complications during pregnancy were also excluded.

We collected the information about cervical conization and pregnancy by medical records or contacting patients after discharge, including patient demographics, time interval between treatment and pregnancy, grade of the lesion, pretreatment cervical dimensions (cervical length, anteroposterior diameter of cervix and transverse diameter of cervix), cone size (depth of cone, anteroposterior diameter of cone and transverse diameter of cone), pregnancy duration, cervical incompetence (CIC) after excision, premature rupture of membranes (PROM) and pregestational maternal human papillomavirus (HPV) infection. In addition, margins at final histology of participants were negative. All included participants signed and provided their consent. Ethics approval was granted by the Ethics Committee of the affiliated hospital of Qingdao University.

Cone dimensions

The cervical volume before treatment was computed based on the volume formula for cylinders: volume = π [(anteroposterior diameter + transverse diameter)/4]^2× length[11, 12]. Cervical tissue excised were conducted fixation in 4% paraformaldehyde before measurement. The overall mean shrinkage caused by formalin fixation is 2.7% of the fresh specimens[13]. Actual cone size was that cone dimensions by measurement divided 0.973. The volume of the excised cone was calculated assuming a hemi-ellipsoid shape: volume=½ x 4/3 x π x transverse diameter/2 x anteroposterior diameter/2 x depth of the cone[14, 15]. The proportion of excised length = cone length/cervical length. The proportion of excised volume = cone volume/cervical volume.

Statistical analyses

About quantitative variables in normal distribution, the values were expressed as the mean ± the standard error of the mean. While in skew distribution, the values were expressed as the median or inter-quartile range. Groups were compared using two independent sample t test and Wilcoxon rank sum test (Non-parametric Test, Npar: Mann–Whitney U test). Differences in distributions for categorical variables were tested with ratio and constituent ratio. The chi-square test, chi-square test with correction, and Fisher's exact test were used for comparisons between groups of participants. We used SAB and SPTB after excision as a dependent variable and conducted univariate logistic regression analysis to study relative risk factors between women with and without term delivery. We applied Pearson correlation to analyze the association of the proportions of excised length/volume and cone length/volume with pregnancy duration at the end of pregnancy. Then, Parameters with significant statistical correlation ($p < 0.05$) were incorporated in multivariate logistic regression analysis, with SAB and SPTB as a dependent variable, to adjust potential confounders. Multivariate logistic regression models were established respectively. To estimate models' goodness of fit, Nagelkerke's R-Squared and Hosmer–Lemeshow tests and Percentage Correct were used. Receiver operating characteristic (ROC) curves were generated for the proportion of excised length/volume and cone length/volume. Area under the curve (AUC) and 95% confidence interval (CI) were determined. The best-performance cutoff points were calculated using the Youden index for which sensitivity and specificity were determined. Statistical analyses were performed using SPSS version 25.0 software (SPSS Inc., Chicago, IL). We adopted X-tile to test the cutoff points. And we used Medcalc to test whether AUC emerged a difference significantly. $P < 0.05$ was considered statistically significant.

Results

Comparison of risk factors between case group and control group

In this study, From January 2015 to February 2017, the total 312 participants were enrolled. Nine factors, including age at excision and pregnancy, conization to pregnancy interval, menstrual cycle, body mass index (BMI) at excision, gravidity, parity, grade of lesion, maternal HPV positive status before pregnancy, between two groups didn't show statistical differences significantly ($P > 0.05$). The mean age at excision was 31.00 years (range,20-45years). The mean age at pregnancy was 32.76 years (range,22-47years). The mean age of women undergoing excision is similar to that of women getting first pregnancy. 147 (47%) of 312 women were nulliparous. Women of SAB and SPTB with HPV positive before pregnancy (16.22%) were more than women of term delivery (12.18%). Conization to pregnancy interval in case group (mean 17.99 ± 11.03months) were shorter than in control group (mean 18.59 ± 13.04months). The data showed that the majority had a high-grade lesion on histology (CIN2-3 87.18%), and women with SAB and SPTB increased with increasing severity of CIN.

Another nine factors, including the length of cervical cone, the volume of cervical cone, the proportion of the cervical length excised, the proportion of the cervical volume excised, BMI at the end of pregnancy, fertilization method, treatment method, PROM, CIC after excision, showed significant correlation with SAB and SPTB. The dimensions of cervix, cone size and the proportion of cone size varied substantially between individuals: the length of the cervix (range 2.00-4.30cm), the volume of the cervix (range 6.19-54.13cm^3), the length of cervical cone (range 0.50-3.00cm), the volume of cervical cone (range 0.13-19.24cm^3), the proportion of the cervical length excised (range 13.00%-97.00%), the proportion of the cervical volume excised (range 1.00%-95.00%). Cone size in terms of length and volume (absolute values and as percentage of initial cervical length/volume) of case group was greater than of control group. Most of the participants got pregnant by natural fertilization (91.99%). In case group, women with CKC were more than with LEEP (82.43%vs17.57%). And women with CKC in case group were more than in control group (82.43%vs68.49%). Women with PROM in case group were greater than in control group (39.19%vs15.97%). Women with CIC after excision in case group were greater than in control group (22.97%vs4.62%). Data of comparison of risk factors between two groups are presented in Table 1.

Table 1
Comparison of risk factors of spontaneous abortion and spontaneous premature delivery after cervical conization between two groups.

Factors	Case group (n = 74)	Control group (n = 238)	P-value
Age at conization(year)	30.46 ± 4.25	31.16 ± 4.36	0.223
Age at pregnancy(year)	32.64 ± 4.22	32.80 ± 4.44	0.780
Conization to pregnancy interval (month)	17.99 ± 11.03	18.59 ± 13.04	0.718
Menstrual cycle(day)	30.09 ± 4.71	30.13 ± 4.81	0.961
BMI at conization	22.48 ± 3.35	22.21 ± 3.02	0.512
BMI at the end of pregnancy	26.26 ± 4.17	27.34 ± 3.06	0.005
Gravidity	1.57 ± 1.20	1.66 ± 1.33	0.579
Parity	0.62 ± 0.57	0.54 ± 0.56	0.285
Fertilization method			0.030
Natural fertilization	73(98.65)	214(89.92)	
in vitro fertilization	1(1.35)	24(10.08)	
Length of cervical cone(cm)	1.53 ± 0.59	1.25 ± 0.52	< 0.001
Volume of cervical cone(cm^3)	4.93 ± 3.31	3.67 ± 3.23	0.004
Proportion of cervical length excised	0.52 ± 0.22	0.39 ± 0.18	< 0.001
Proportion of cervical volume excised	0.25 ± 0.22	0.14 ± 0.17	< 0.001
PROM			< 0.001
No	45(60.81)	200(84.03)	
Yes	29(39.19)	38(15.97)	
Treatment method			0.020
LEEP	13(17.57)	75(31.51)	
CKC	61(82.43)	163(68.49)	
CIC after excision			< 0.001

*Data: mean ± standard errors ,median ± standard errors ,ratios(%).

BMI, body mass index; AIS, adenocarcinoma in situ; PROM, premature rupture of membranes; LEEP, loop electrical excision procedure; CKC, cold knife conization; CIC, cervical incompetence; CIN, cervical intraepithelial neoplasia; HPV, pregestational maternal human papillomavirus.

Factors	Case group	Control group	P-value
	(n = 74)	(n = 238)	
No	57(77.03)	227(95.38)	
Yes	17(22.97)	11(4.62)	
Grade of lesion			0.061
CIN1	8(10.81)	26(10.92)	
CIN2	10(13.51)	68(28.57)	
CIN3	55(74.32)	139(58.40)	
AIS	0	2(0.84)	
stage A1 of cervical cancer	1(1.35)	3(1.26)	
HPV positive before pregnancy			0.370
No	62(83.78)	209(87.82)	
Yes	12(16.22)	29(12.18)	
*Data: mean ± standard errors ,median ± standard errors ,ratios(%).			
BMI, body mass index; AIS, adenocarcinoma in situ; PROM, premature rupture of membranes; LEEP, loop electrical excision procedure; CKC, cold knife conization; CIC, cervical incompetence; CIN, cervical intraepithelial neoplasia; HPV, pregestational maternal human papillomavirus.			

Univariate analysis of risk factors

We conducted the univariate analysis of the nine risk factors closely related to SAB and SPTB in 312 participants. Of the nine factors, treatment method, the cervical length excised, the cervical volume excised, the proportion of the cervical length excised, the proportion of the cervical volume excised, CIC after excision, PROM were risk factors. BMI at the end of pregnancy and fertilization method were protective factors. (Table 2)

Table 2
Risk factors related to spontaneous abortion and spontaneous premature delivery in 312 participants: univariate analysis.

Variable	regression coefficient	Standard error	Wald2	OR	95% CI	P-value
BMI at the end of pregnancy	-0.128	0.041	9.449	0.88	0.811–0.955	0.002
Treatment method	0.770	0.336	5.252	2.159	1.118–4.170	0.022
Fertilization method	-2.103	1.03	4.17	0.122	0.016–0.919	0.041
Cervical length excised	0.901	0.240	14.096	2.463	1.539–3.943	< 0.001
Proportion of cervical length excised	2.911	0.678	18.414	18.382	4.863–69.485	< 0.001
Cervical volume excised	0.106	0.038	7.878	1.112	1.033–1.198	0.005
Proportion of cervical volume excised	3.303	0.687	23.082	27.189	7.067-104.605	< 0.001
CIC after excision	1.817	0.414	19.235	6.155	2.732–13.864	< 0.001
PROM	1.221	0.297	16.947	3.392	1.896–6.067	< 0.001

Pearson correlation

We conducted the Pearson correlation between cone dimensions and the proportion of cone dimensions and pregnancy duration among participants who underwent cervical excisional treatment (Table 3 and Fig. 1). Data demonstrated significant correlation between cone dimensions and the proportion of cone dimensions ($P < 0.001$). And we found a significant inverse correlation between the cone length ($P = 0.007$, $r = -0.153$), the proportion of the cervical length excised ($P = 0.002$, $r = -0.178$), the proportion of the cervical volume excised ($P < 0.001$, $r = -0.220$) and pregnancy duration respectively, but not with the cone volume ($P = 0.062$).

Table 3
The Pearson correlation between cone length/volume, the proportions of the cone length/volume and pregnancy duration among women who underwent cervical excisional treatment.

Variable		Pregnancy duration	Cervical length excised	Proportion of excised length	Cervical volume excised
Cervical length excised	Correlation coefficient (r)	-0.153	1		
	P value	0.007			
Proportion of excised length	Correlation coefficient (r)	-0.178	0.923	1	
	P value	0.002	< 0.001		
Cervical volume excised	Correlation coefficient (r)	-0.106	0.847	0.780	1
	P value	0.062	< 0.001	< 0.001	
Proportion of excised volume	Correlation coefficient (r)	-0.220	0.727	0.841	0.816
	P value	< 0.001	< 0.001	< 0.001	< 0.001

Comparison of univariate analysis and multivariate logistic regression models

The data of *multivariate logistic regression models* are shown in Table 4 and Table 5. The multivariate logistic regression models reflected that the cervical length excised, the cervical volume excised, the proportion of the cervical length excised, the proportion of the cervical volume excised significantly correlated with SAB and SPTB, respectively ($P < 0.05$). The results of model 2 with the proportion of the cervical length excised and model 3 with the cervical volume excised did not indicate the high goodness of fit (Hosmer–Lemeshow test $P < 0.05$). Compared with model 1 with the cervical length excised, model 4 with the proportion of the cervical volume excised was the model with the better goodness of fit (Hosmer–Lemeshow test $P > 0.05$, Nagelkerke's R-squared 0.286 vs 0.264, Percentage Correct 81.1% vs 79.8%). And the risk of SAB and SPTB increased with the proportion of the cervical volume excised increasing (OR 19.704, 95% CI 4.646–83.568).

Table 4
Comparison of risk factors related to SAB and SPTB between the univariate analysis and four multivariate logistic regression models.

Variable	Univariate	Model 1	Model 2	Model 3	Model 4
Treatment method	0.770(0.240–0.895),0.022	0.201(0.525–2.851),0.641	0.267(0.561–3.038),0.536	0.088(0.409–2.051),0.830	0.236(0.562–2.851),0.569
BMI at the end of pregnancy	-0.128(0.811–0.955),0.002	-0.127(0.805–0.965),0.006	-0.118(0.812–0.972),0.010	-0.126(0.805–0.965),0.006	-0.123(0.807–0.969),0.009
Fertilization method	-2.103(0.016–0.919),0.041	-2.269(0.013–0.843),0.034	-2.382(0.011–0.781),0.029	-2.379(0.011–0.766),0.027	-2.419(0.010–0.767),0.028
CIC after excision	1.817(2.732–13.864), < 0.001	1.725(2.173–14.496), < 0.001	1.716(2.158–14.337), < 0.001	1.770(2.299–14.989), < 0.001	1.734(2.207–14.533), < 0.001
PROM	1.221(1.896–6.067), < 0.001	1.099(1.551–5.803), 0.001	1.064(1.496–5.619),0.002	1.020(1.452–5.294),0.002	1.000(1.399–5.279),0.003
Cervical length excised	0.901(1.539–3.943), < 0.001	0.982(1.423–5.007),0.002			
Proportion of cervical length excised	2.911(4.863–69.485), < 0.001		2.956(3.379-109.306),0.001		
Cervical volume excised	0.106(1.033–1.198),0.005			0.102(1.006–1.218),0.037	
Proportion of cervical volume excised	3.303(7.067-104.605), < 0.001				3.205(4.725-128.656), < 0.001
Nagelkerke's R-Squared		0.264	0.272	0.242	0.286
Hosmer–Lemeshow test P value		0.086	0.041	0.008	0.060
Percentage Correct (%)		79.8	80.4	79.2	81.1

*Data: B(95%CI), P

Table 5
Risk factors related to SAB and SPTB in model 4: multivariate analysis.

Variable	regression coefficient	Standard error	Waldχ^2	OR	95% CI	P value
BMI at the end of pregnancy	-0.120	0.046	6.761	0.887	0.810–0.971	0.009
Proportion of cervical volume excised	2.981	0.737	16.350	19.704	4.646–83.568	< 0.001
Fertilization method	-2.418	1.097	4.857	0.089	0.010–0.765	0.028
CIC after excision	1.734	0.482	12.923	5.662	2.200-14.572	< 0.001
PROM	0.970	0.334	8.441	2.637	1.371–5.072	0.004

Cutoff points and comparison of AUC of cone dimensions

The cutoff points and AUC of cone dimensions are shown by the ROC curves in Fig. 2–5 and Table 6. The cutoff points of the cone length, the cone volume, the proportion of the cervical length excised, the proportion of cervical volume excised were respectively 1.45cm (sensitivity 0.622; specificity 0.622), 2.85cm3 (sensitivity 0.703; specificity 0.538), 48.5% (sensitivity 0.581; specificity 0.672), 19.5% (sensitivity 0.635; specificity 0.655). The AUC of the cone length, the cone volume, the proportion of cervical length excised, the proportion of cervical volume excised were respectively 0.641 (95%CI 0.568–0.714), 0.637 (95%CI 0.567–0.708), 0.659 (95%CI 0.587–0.731), 0.700 (95%CI 0.634–0.765). In addition, we found that there were significant statistical differences in AUC between the proportion of the cervical volume excised and another three dimensions ($P < 0.05$) (Table 7). Therefore, the proportion of the cervical volume excised is the best predictor for SAB and SPTB after cervical conization.

Table 6
Results from ROC analysis of study parameters for the prediction of SAB and SPTB.

Variable	Cutoff	Sensitivity	Specificity	AUC	P value	95% CI
Proportion of cervical volume excised	0.195	0.635	0.655	0.700	< 0.001	0.634–0.765
Proportion of cervical length excised	0.485	0.581	0.672	0.659	< 0.001	0.587–0.731
Length of cervical cone	1.450	0.622	0.622	0.641	< 0.001	0.568–0.714
Volume of cervical cone	2.850	0.703	0.538	0.637	< 0.001	0.567–0.708

Table 7
Comparison of AUC of cone length/volume and the proportion of cone length/volume.

Variable	Z	P value	95%CI
Length of cervical cone – Proportion of cervical volume excised	2.580	0.010	0.014–0.104
Volume of cervical cone - Proportion of cervical volume excised	3.371	< 0.001	0.026–0.099
Proportion of cervical length excised - Proportion of cervical volume excised	2.207	0.027	0.005–0.078
Length of cervical cone - Proportion of cervical length excised	1.332	0.183	−0.008–0.044
Volume of cervical cone - Proportion of cervical length excised	0.944	0.345	−0.023–0.066
Length of cervical cone - Volume of cervical cone	0.176	0.861	−0.037–0.044

Discussion

In the present study, we found that the length/volume of original cervix and the cone length/volume and the proportions of cone length/volume varied substantially between individuals. We confirmed that the length of cervical cone, the volume of cervical cone, the proportion of cervical length excised, the proportion of cervical volume excised significantly correlated SAB and SPTB in multivariate logistic regression models, respectively ($P < 0.05$), but the proportion of the cervical volume excised has the best predictive value for SAB and SPTB (AUC 0.700,95% CI 0.634–0.765). And the risk of SAB and SPTB increased with the proportion of the cervical volume excised increasing (OR 19.704, 95% CI 4.646–83.568). When the proportion of the cervical volume excised is more than19.5% (sensitivity 0.635; specificity 0.655), it means that women are at high risk for SAB and SPTB in subsequent pregnancy.

Our study further complements and extends the relationship between cone dimensions and preterm birth. Nevertheless, we cannot be certain that the observed association is causal. However, even if the association is not causal, our results are of prognostic value to obstetricians[6]. In addition, the dimensions of cervix were measured using two-dimensional transvaginal sonography (2D-TVS). Although MRI is thought to be optimally accurate, both two-dimensional and three-dimensional (3D) transvaginal ultrasounds are reported to be imaging methods with a high accuracy in evaluating cervical volume[16, 17].

Furthermore, the excisional procedures were performed using a standardized technique. The data on cone dimensions relied on retrospective data recorded in histopathology reports of formalin-fixed samples, with limitations. Future research should aim to correlate outcomes with precise prospective cone depth and cervical measurements. Moreover, the retrospective data collected are at known risk of recall bias and incomplete outcome data, which could be a potential limitation. However, the meticulous gathering of data through medical chart review enabled the collection of data involving multiple confounding factors and decreased recall bias.

In line with previously published data[12], the present study indicated that the proportion of the cone volume was the best predictor for SAB and SPTB. And Papoutsis et al. found that cervical regeneration at 6 months after excision was dependent on the proportion of cervical volume excised[16]. And our findings showed that the proportion of the cervix removed and the dimensions of the cervix pretreatment varied substantially, which were also consistent with the previous studies[12]. We confirmed that the proportion of the cervix removed more accurately reflected the effect of treatment on the cervix than the absolute cone dimensions; and identical cone sizes represented different proportions of excision in different patients.

The results from our study demonstrated consistency with previous studies, which found that cone dimensions including cone length or volume were associated with preterm birth[4, 9, 10, 15, 18]. However, we also found a significant negative correlation of pregnancy duration with cone length ($P = 0.007$, $r = -0.153$), but not with cone volume ($P = 0.062$), which was in contrast with Kyrgiou et al.[12],but in line with Carlo et al[15]. In our study, the cone length seemed to play a more important role in preterm labor than the cone volume. In fact, the results of the studies reflected that the effects of cone volume/length on pregnancy duration did not consider the effects of original cervical dimensions.

In fact, whether the safe cone dimensions exist below which the risk of preterm labor is not increased is unclear. We have shown that a woman is at risk for SAB and SPTB after conization when cone volume is more than 2.85cm^3 or more than 19.5% of the initial cervical volume and cone length is more than 1.45cm or more than 48.5% of the initial cervical length, which have covered the optimal cutoff of cone parameters for margin negativity[19].

However, there are some discordant results in other studies, which did not show any relationship between cone volume /depth or conization and preterm birth[14, 20–22]. In fact, the exact pathogenetic link between cervical excisional treatments and risk of prematurity has not yet been fully elucidated. The causes could be mainly explained that removed tissues might significantly influence the restoration of anatomy and function of cervix following surgery and as a result lead to compromise the integrity of the cervical stroma and a lack of effective mechanical support in subsequent pregnancies[3, 5, 10, 23, 24].

Other factors may be also important. Infection with HPV changes normal cervicovaginal flora environment[1]. Immunological factors are altered during the process of the cervical lesions[5]. The recent study reported that CIN itself had a baseline risk for prematurity[4, 18, 25]. These factors play a very important role by promoting the persistence of HPV, thus favouring the development of frequent ascending infections and consequent abortion and prematurity. The recent study suggested that maternal HPV infection may be an upstream cause of preterm delivery that acts through a variety of downstream causes, including preterm premature rupture of membranes (PPROM)[26].

Conclusion

The cervical length/volume excised and the proportions of cervical length/volume excised significantly correlate with SAB and SPTB, respectively. And the proportion of the cervical volume excised is the best predictor for SAB and SPTB after cervical conization. When the proportion of the cervical volume excised is more than 19.5%, treated women are more likely to be in the risk of SAB and SPTB. Assessment of the proportion of the cervical volume excised might help to stratify women at risk who need intensive surveillance when pregnant.

It is important for the clinician to make efforts to remove as little tissue as possible, especially in nulliparous women with a small cervix, without compromising the eradication of the disease. Moreover, there is a need for multicenter studies that would make it possible to explore a “risk score” capable of providing women with personal risk assessments.

Abbreviations

SAB: spontaneous abortion; SPTB: spontaneous preterm birth; BMI: body mass index; CIN: cervical intraepithelial neoplasia; LEEP: loop electrical excision procedure; CKC: cold knife conization; AIS: adenocarcinoma in situ; CIC: cervical incompetence; CIN: cervical intraepithelial neoplasia; HPV: pregestational maternal human papillomavirus; CIC: cervical incompetence; ROC curve: receiver operating characteristic curve; AUC: area under the curve; CI: confidence interval; PROM: premature rupture of membranes; PPROM: preterm premature rupture of membranes.

Declarations

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Authors’ contributions

YHW, WL, and FY conceived the idea. YHW, YJL, and ZMC designed the study. YHW, ZYN, YPL conducted the data acquisition. YHW, YZ, and YHD analyzed and interpreted the data. YHW, and YHD wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Figures

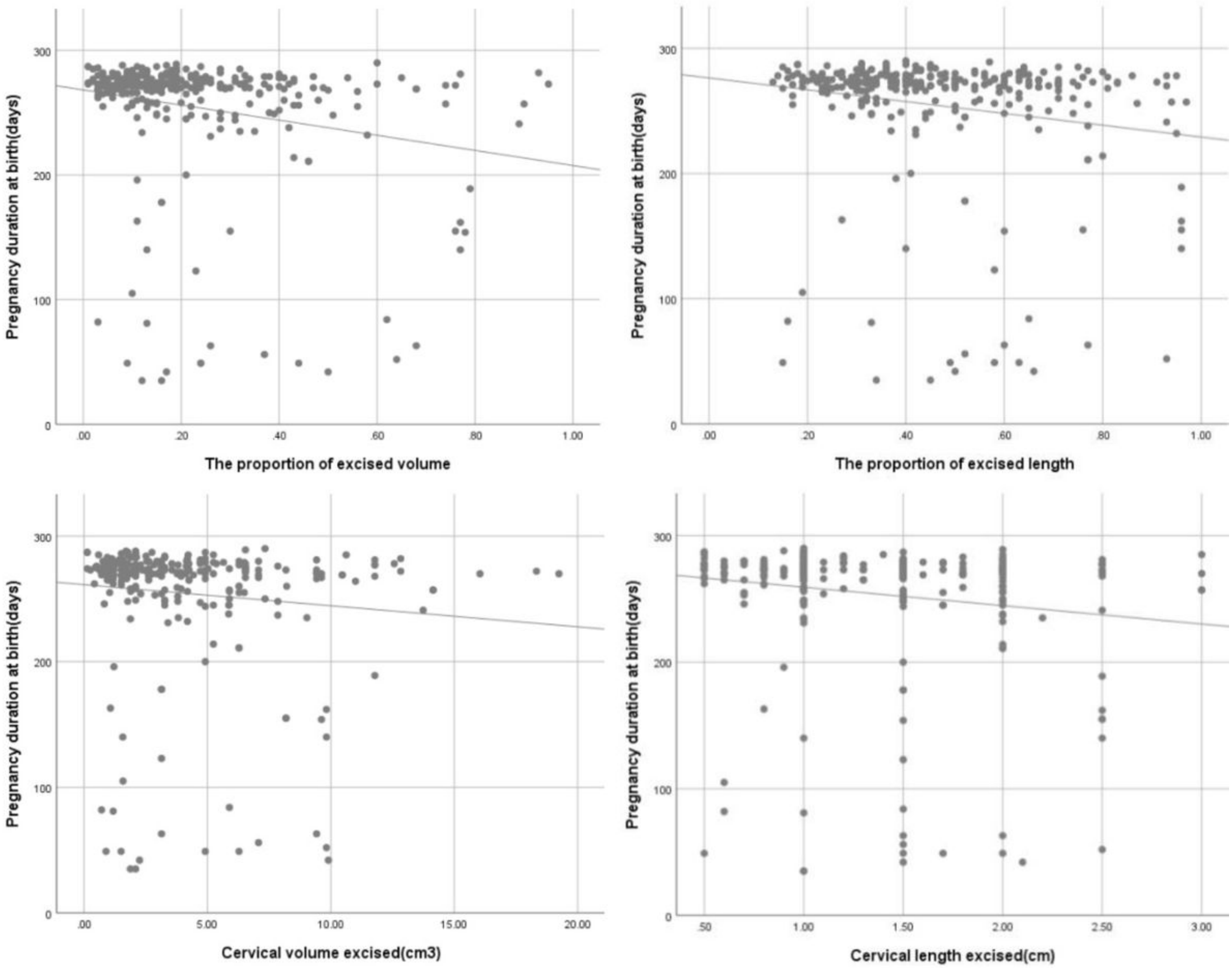

Figure 1

Pearson correlation between cone dimensions, proportions of cone dimensions and pregnancy duration at birth.

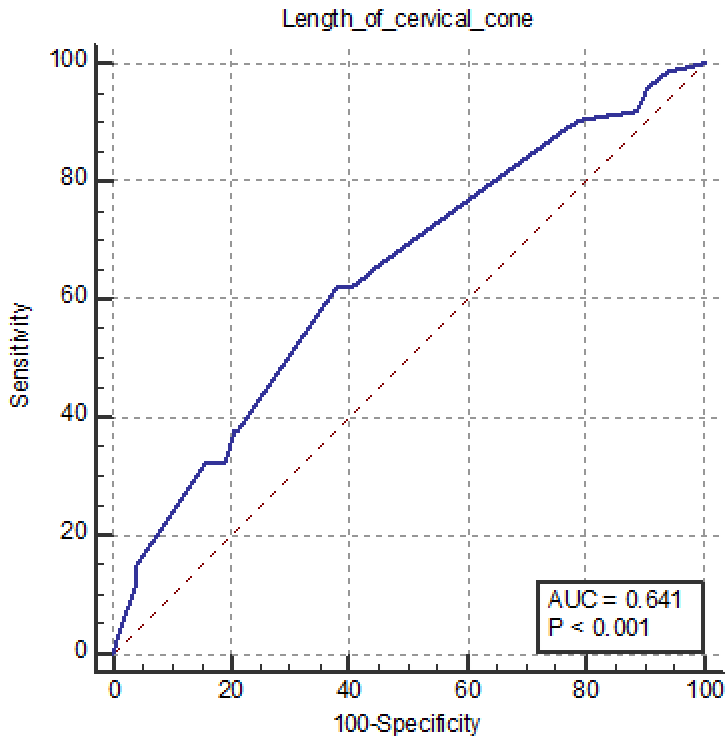

Figure 2

ROC curve for the prediction of SAB and SPTB from cone length of excised cone.

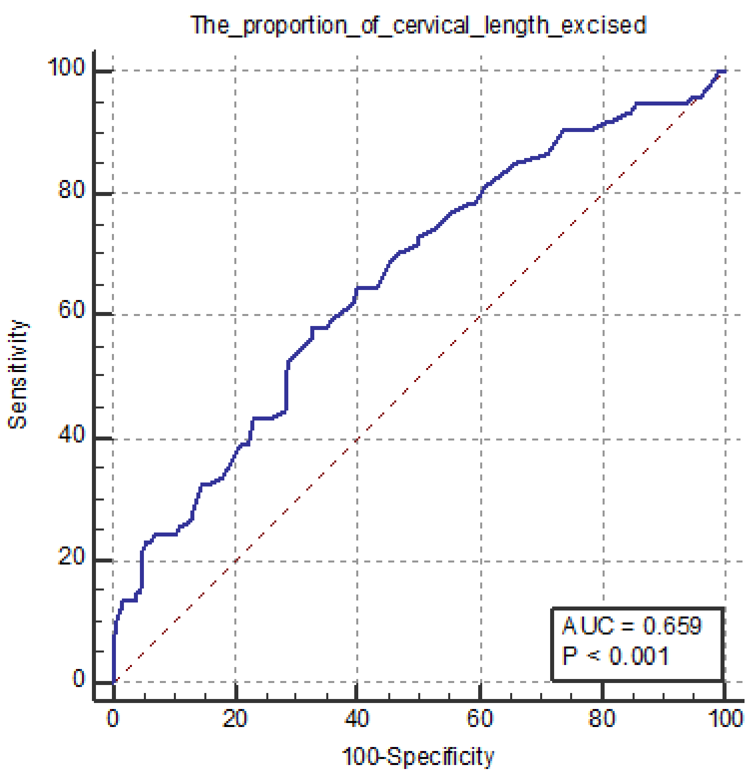

Figure 3

ROC curve for the prediction of SAB and SPTB from the proportion of cervical length excised.

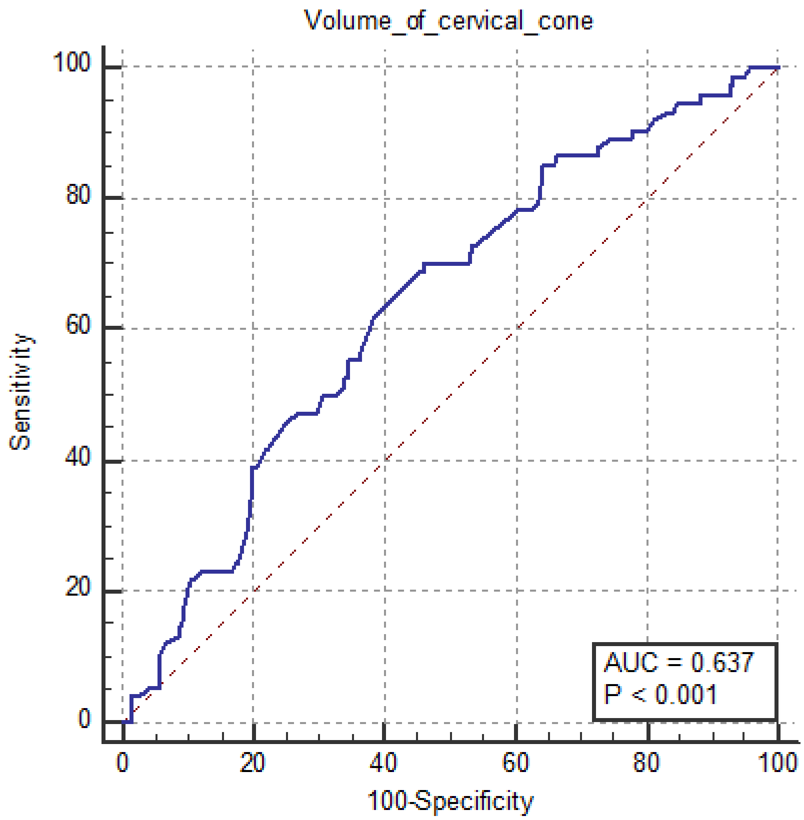

Figure 4

ROC curve for the prediction of SAB and SPTB from cone volume.

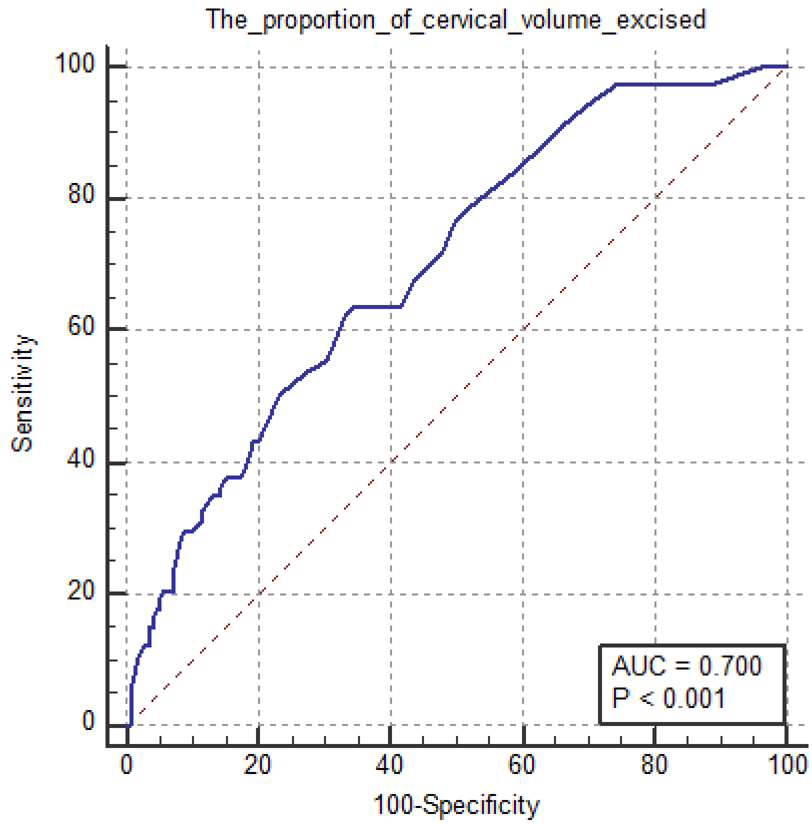

Figure 5

ROC curve for the prediction of SAB and SPTB from the proportion of cervical volume excised.