Thieme

Risk Factors of Preterm Birth in Women After Local Treatment of Cervical Intraepithelial Neoplasia – a Retrospective Cohort Study

Risikofaktoren für eine Frühgeburt bei Frauen nach lokaler Behandlung einer zervikalen intraepithelialen Neoplasie – eine retrospektive Kohortenstudie

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ABSTRACT

Purpose A previous cervical intraepithelial neoplasia is associated with an increased obstetrical risk. It was the aim of the study to identify risk factors of preterm birth in patients with cervical intraepithelial neoplasia in dependence of the treatment modality (excisional vs. ablative).

Methods Women with treated cervical intraepithelial neoplasia and subsequent pregnancy (n = 155) were included in this retrospective study. Methods of treatment were either conization by large loop excision of the transformation zone (LLETZ) or ablative laser vaporization.

Results Of the total population 60.6 % (n = 94) had a conization and 39.4 % (n = 61) a laser vaporization alone. The frequency of preterm birth < 37 weeks was 9.7 % (n = 15) without differences between conization and laser (11.7 vs. 6.7 %, p = 0.407) with an odds ratio (OR) of 1.9 (95 % confidence interval [CI] 0.6–6.2). Preterm birth < 34 weeks was found in 2.6 % (n = 4), of which all had a conization (4.3 vs. 0 %, p = 0.157). Risk factors for preterm birth were repeated cervical intervention (OR 4.7 [95 % CI 1.5–14.3]), especially a combination of conization and laser ablation (OR 14.9 [95 % CI 4.0–55.6]), age at intervention < 30 years (OR 6.0 [95 % CI 1.3–27.4]), a history of preterm birth (OR 4.7 [95 % CI 1.3–17.6]) and age at delivery < 28 years (OR 4.7 [95 % CI 1.5–14.3]).

Conclusion The large loop excision of the transformation zone as a modern, less invasive ablative treatment did not obviously increase the risk of preterm birth compared to laser vaporization. The most important risk factor for preterm delivery was the need of a repeated intervention, especially at younger age. We assume that the persistence or recurrence of the cervical intraepithelial neoplasia following a high-risk human papillomavirus infection is mainly responsible for the observed effect.

ZUSAMMENFASSUNG

Zielsetzung Eine frühere intraepitheliale Neoplasie der Zervix wird mit einem höheren geburtshilflichen Risiko assoziiert. Ziel dieser Studie war es, die Risikofaktoren für eine Frühgeburt bei Patientinnen mit einer zervikalen intraepithelialen Neoplasie in der Anamnese zu identifizieren in Abhängigkeit von der Behandlungsmodalität (Exzision vs. ablative Behandlung).

Methoden In dieser retrospektiven Studie wurden Frauen aufgenommen, die zuvor wegen einer zervikalen intraepithelialen Neoplasie behandelt worden waren und danach schwanger wurden (n = 155). Die Behandlungsmethode bestand entweder aus Konisation mittels Schlingenexzision der Transformationszone (LLETZ) oder ablativer Laservaporisation.

Ergebnisse Von der Gesamtkohorte erhielten 60,6 % (n = 94) eine Konisation und 39,4 % (n = 61) eine Laservaporisation. Die Frequenz der Frühgeburten vor der 37. Schwangerschaftswoche betrug 9,7 % (n = 15). Es gab keinen Unterschied zwischen Konisation und Laserbehandlung (11,7 vs. 6,7 %, p = 0,407) mit einer Odds Ratio (OR) von 1,9 (95 %-Konfidenzintervall [KI] 0,6–6,2). Eine Frühgeburt vor der 34. Schwangerschaftswoche trat bei 2,6 % (n = 4) auf, und alle Betroffenen hatten zuvor eine Konisation erhalten (4,3 vs. 0 %, p = 0,157). Risikofaktoren für eine Frühgeburt waren wiederholte zervikale Prozeduren (OR 4,7 [95 %-KI 1,5–14,3]), vor allem eine Kombination aus Konisation und Laserablation (OR 14,9 [95 %-KI 4,0–55,6]), Alter beim Eingriff < 30 Jahre (OR 6,0 [95 %-KI 1,3–27,4]), Frühgeburt in der Anamnese (OR 4,7 [95 %-KI 1,3–17,6]) sowie Alter bei der Entbindung < 28 Jahre (OR 4,7 [95 %-KI 1,5–14,3]).

Schlussfolgerung Die Schlingenexzision der Transformationszone stellt eine moderne, weniger invasive ablative Behandlung dar, die offenkundig nicht das Risiko einer Frühgeburt erhöht verglichen mit der Laservaporisation. Der wichtigste Risikofaktor für eine frühgeburtliche Entbindung waren wiederholte Prozeduren zur Behandlung von Neoplasien, vor allem in jüngeren Jahren. Wir nehmen an, dass die Persistenz bzw. das Wiederauftreten einer zervikalen intraepithelialen Neoplasie nach einer Infektion mit einem Hochrisikoform des humanen Papillomavirus maßgeblich verantwortlich für die beobachtete Wirkung ist.

Abbreviations

CI	confidence interval
CIN	cervical intraepithelial neoplasia
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
LLETZ	large loop excision of transformation zone
LV	laser vaporization
OR	odds ratio
PTB	preterm birth

Introduction

The treatment of the cervical intraepithelial neoplasia (CIN) by conization has been widely associated with an increased risk of preterm birth (PTB) [1, 2, 3]. The risk rises with the invasiveness of the intervention and was most obvious after performance of cold knife conization [4]. However, considering less invasive and currently preferred methods of excisional treatment like Large Loop excision of Transformation Zone (LLETZ) or Loop Electrical Excision Procedure (LEEP) the association was only weak or indistinct [4, 5, 6, 7]. This coincides with the observation of a greater risk of PTB with an increasing cone depth [5, 8].

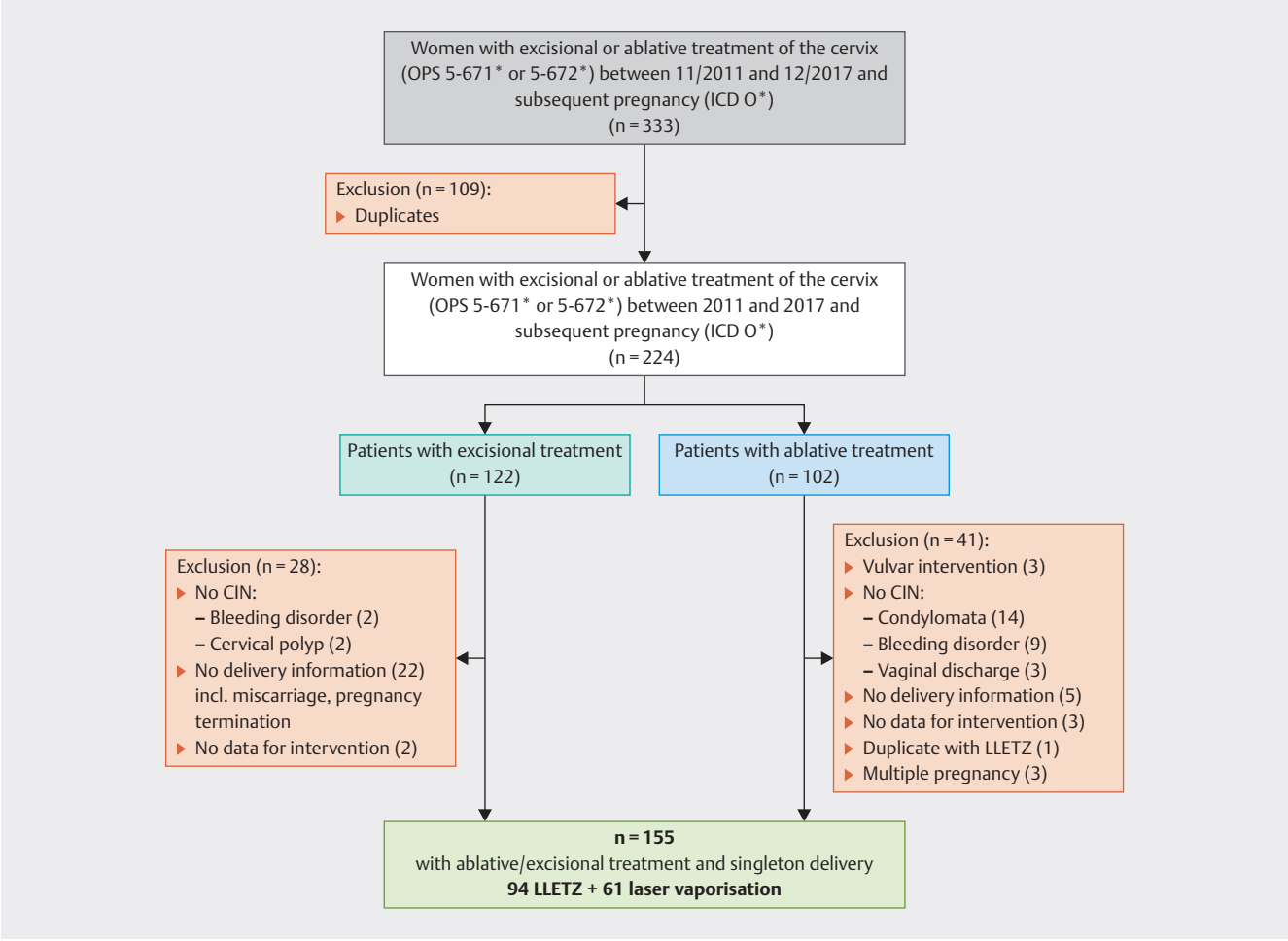
Remarkably, an increased risk of PTB was even observed in women who were treated by minimally invasive laser ablation only and in untreated women with precancerous lesions of the cervix compared to a healthy control group [2]. These results suggest that treatment itself with the removal of tissue is not the only reason for the observed increased obstetric risk. In a recent Cochrane review the observed adverse obstetrics effects were lower if the comparison group consisted of women with CIN without treatment compared to external or internal comparators [3]. In a Swedish population based study, the frequency of PTB was 30% higher in women with abnormal cervical cytology irrespective of treatment compared to healthy women [9]. Similar results were observed in a retrospective Australian cohort study, in which the diagnosis of a precancerous lesion of the cervix resulted in an increased risk of PTB in both treated and untreated women [7]. Consequently, the comparison of women treated for CIN with unaffected women may overestimate the treatment-related effects on risk of PTB and neglect other co-factors which could contribute to the increase in risk.

Human papillomavirus (HPV) infection during the reproductive age is common and usually resolves within one to two years [10]. However, the persistence of the HPV infection, which is necessary for development of cervical dysplasia, may indicate a risk constellation for PTB by its own. Proofing this hypothesis is difficult, because the avoidance of any therapy in cases of persistent or high grade CIN is not justifiable and therefore a direct comparison of pregnancy outcome between treated and untreated women is not feasible. It was the goal of our study, to identify putative risk factors for PTB in a cohort of pregnant women with a history of CIN necessary for treatment. In this retrospective cohort study, we compared the pregnancy outcome between women after excisional cervical treatment by LLETZ and/or ablative treatment by Laser vaporization (LV) only.

Material and Methods

Recruitment of patients

This retrospective, single center cohort study was conducted on a German tertiary perinatal care center. Using the German coding system for medical procedures and the international classification of diseases (10 th revision) we searched for all women with an excisional or ablative intervention on the cervix and a subsequent



▶ **Fig. 1** Flow diagram of patient selection with criterions of exclusion.

pregnancy between November 2011 and December 2017. Only women with a history of CIN and a subsequent singleton pregnancy to at least 20 completed gestational weeks were included. After exclusion of doublettes and inappropriate cases 155 women were suitable for analysis (▶ **Fig. 1**). Pregnancies before cervical interventions were allowed, so that some patients revealed a history of a previous preterm birth or abortion.

Data collection and definitions

Two treatment modalities for CIN were used: LLETZ as excisional and LV as ablative intervention. An additional colposcopically controlled LV of lower stages of CIN in the periphery of the cervix during the LLETZ procedure in the same session was usual and classified as LLETZ. The LV group comprises only interventions with exclusive use of LV and without LLETZ. In contrast, repeated intervention was defined as at minimum two cervical interventions in different sessions following persistence or recurrence of CIN.

For data analysis, we used the following definitions: CIN 2+ comprises all patients with CIN grade 2 and higher. The results of the hybrid capture II test (HC2, Qiagen, Hilden, Germany) allowed the detection of HPV high risk types.

For the approximation of the cone volume (V) we used the following formula for calculation of a cylindrical volume: $V = \pi * r^2 * h$. The radius r corresponds to half of the mean diameter and the height is equal to the depth of the cone. The formula was chosen as the geometry of the thin resection specimen after LLETZ corresponds better to a cylinder than a cone [11].

Gestational age was calculated from the first day of the last menstrual period and was corrected by ultrasound if measurements of the crown-rump-length during the first trimester revealed a difference of seven or more days.

Calculation of birth weight centiles was based on the German perinatal statistic [12]. Perinatal mortality comprises intrauterine demise and neonatal death during the first 28 days after delivery.

Statistical analysis

All data were stored and analyzed using the IBM SPSS statistical package 25 (SPSS Inc. Chicago, IL, USA), Excel 2013 (Microsoft Corporation, Redmond, WA, USA) and the R 4.1.2 and R-Studio statistical software [13, 14]. Testing for differences in continuous variables between groups was done using Student's t-test or Mann-Whitney U-test as appropriate; comparisons of categorical variables between groups were done with Fisher's exact test. Diag-

nostic odd ratios (OR) with 95% CI were given. All P values were obtained using two-sided statistical tests, and values < 0.05 were considered statistically significant.

A logistic regression model was used to assess the independence of specific risk parameters and to compute a combined risk model for preterm birth. The following risk factors for preterm birth were included: repeated cervical intervention, age below 28 years at delivery, age below 30 years at intervention, preterm birth or late abortion in history. Receiver operating characteristics (ROC) curves and the area under the curve (AUC) were computed using the combined risk models. Based on the model with the best test characteristic we developed a risk prediction score. Therefore, the scoring points were weighted relative to the values of the regression coefficients. For the sum score the ROC-AUC was computed and the optimal cut-off value (minimal distance to sensitivity and specificity of 1) was calculated by using the following equation: $(1\text{-sensitivity})^2 + (1\text{-specificity})^2$.

The Ethics Committee of the University of Rostock does not request formal approval for anonymized retrospective analysis of clinical data.

Results

Patient characteristics

Ninety-four of 155 patients (60.6%) received an excisional treatment by LLETZ, 61 patients (39.4%) where treated by LV alone (▶ **Table 1**). The majority of patients (81.3%, n = 126) had only one intervention. Of the remaining women 14.2% (n = 22) had two and 4.5% (n = 7) had three cervical interventions. In case of a repeated intervention (18.7%, n = 29) the following types of interventions were performed: repeated LLETZ in 24.1% (n = 7), repeated LV in 34.5% (n = 10) and a subsequent LV after LLETZ in 41.4% (n = 12). There was no case with LLETZ after LV. The patients with repeated LLETZ had a positive margin of the cone in 71.4% (n = 5/7). Women with ablative treatment were more frequently primiparous (63.9% vs. 46.8%, p = 0.048). As expected, occurrence of high-grade squamous intraepithelial lesion (HSIL) was lower in the LV group (74.1% vs. 96.8%, p < 0.001). No patient received a surgical cerclage and in only one patient, a pessary was vaginally inserted, subsequently resulting in a PTB at 29 weeks of gestation. Sufficient data on progesterone application were missing.

▶**Table 1** Patient characteristics comparing the groups with excisional treatment and ablative treatment.

	All patients	Excisional treatment (LLETZ)	Ablative treatment (Laser vaporisation)	P value
	N = 155	N = 94 (60.6%)	N = 61 (39.4%)	
Maternal age at intervention, years	29 (26–32)	32 (28–34)	31 (28–33)	0.285
Maternal age at delivery, years	31 (28–34)	29.5 (26–32)	28 (26–31)	0.275
Interval between intervention and delivery, years	2 (1–3)	2 (1–3)	2 (1–3)	0.877
Pregravid body mass index, kg/m^2	22.9 (20.3–26.5)	23.2 (20.4–27.5)	22.5 (20.3–24.2)	0.201
Obesity (BMI ≥ 30 kg/m^2)	20 (12.9%)	15 (16.0%)	5 (8.2%)	0.221
Gravidity, n	2 (1–3)	2 (1–3)	1 (1–2)	0.010
Parity, n	1 (1–2)	2 (1–2)	1 (1–2)	0.027
Primiparous women, n	83 (53.5%)	44 (46.8%)	39 (63.9%)	0.048
History of preterm birth or abortion > 16 weeks before intervention, n	14 (9.0%)	9 (9.6%)	5 (8.2%)	1.000
Nicotine abuse, n	18 (11.6%)	12 (12.8%)	6 (9.84%)	0.620
Number of interventions, n	1 (1–1)	1 (1–1)	1(1–1)	0.483
Assisted reproductive technique, n	7 (4.5%)	6 (6.4%)	1 (1.6%)	0.246
HPV high risk	130 (90.9%)	78 (92.9)	52 (88.1)	0.384
HSIL	134 (88.2%)	91 (96.8%)	43 (74.1%)	< 0.001
Gestational age at delivery, weeks	39 (38–40)	39 (38–40)	39 (38–40)	0.398
Preterm birth < 37 weeks, n	15 (9.7%)	11 (11.7%)	4 (6.7%)	0.407
Preterm birth < 34 weeks, n	4 (2.6%)	4 (4.3%)	0 (0.0%)	0.157
Birth weigth, g	3385 (3082–3730)	3430 (3152–3767)	3380 (3020–3720)	0.217
Birth weigth, percentile	60.5 (32–82.5)	63 (33–81)	50 (24–83)	0.206
SGA, n	8 (5.2%)	4 (4.3%)	4 (6.6%)	0.713
Caesarean sectio, n	42 (27.1)	25 (26.6%)	17 (27.9%)	0.856

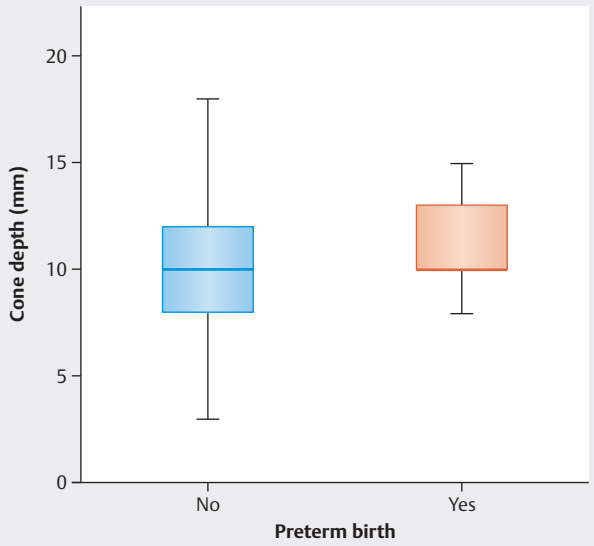
▶**Table 2** Patient characteristics comparing the groups with term birth and preterm birth.

	Term birth	Preterm birth	P value
	N = 140 (90.3%)	N = 15 (9.7%)	
Maternal age at intervention, years	29 (26–32)	27 (24–29)	0.043
Maternal age at delivery, years	31.5 (28–34)	29 (26–34)	0.108
Interval between intervention and delivery, years	2 (1–3)	2 (1–3)	0.459
Pregravid body mass index, kg/m^2	22.9 (20.4–26.9)	22 (20–25)	0.404
Obesity (BMI ≥ 30 kg/m^2)	20 (14.3%)	0 (0.0%)	0.220
Gravidity, n	2 (1–3)	3 (1–5)	0.047
Parity, n	1 (1–2)	1 (1–4)	0.176
Primiparous women, n	75 (53.6%)	8 (53.3%)	1.000
History of preterm birth or abortion > 16 weeks before intervention, n	10 (7.1%)	4 (26.7%)	0.032
Nicotine abuse, n	17 (12.1%)	1 (6.7%)	1.000
LLETZ, n	83 (59.3%)	11 (73.3%)	0.407
Number of interventions, n	1 (1–1)	1 (1–2.5)	0.001
Repeated cervical intervention, n	22 (15.7%)	7 (46.7%)	0.011
Cone depth, mm	10 (8–12)	10 (10–12.5)	0.278
Cone depth ≥ 10 mm, n	42 (53.2%)	8 (80.0%)	0.176
Cone diameter, mm	16.5 (13.5–20.0)	17.8 (13.9–20.0)	0.603
Cone volume, cm^3	1.9 (1.3–2.9)	2.5 (1.7–3.1)	0.302
Cone volume > 3 cm^3, n	80 (57.1%)	8 (53.3%)	0.790
Assisted reproductive technique, n	5 (3.6%)	2 (13.3%)	0.138
HPV high risk	119 (91.5%)	11 (84.6%)	0.335
HSIL	120 (87.6%)	17 (93.3%)	1.000
Gestational age at delivery, weeks	40 (39–40)	35 (32–36)	< 0.001
5'-APGAR	10 (9–10)	9 (9–10)	0.328
Birth weigth, g	3440 (3160–3813)	2495 (1900–2640)	0.217
Birth weigth, percentile	60.5 (32–81.5)	60.5 (28–78.25)	0.206
SGA, n	8 (5.7%)	0 (0.0%)	1.000
Caesarean section, n	36 (25.7%)	6 (60%)	0.237

Pregnancy outcome and risk factors for preterm birth

PTB with delivery occurred in 9.7% (n = 15) below 37 weeks and in 2.6% (n = 4) below 34 weeks (▶ **Table 2**). Neither gestational age at delivery nor the frequency of PTB differed significantly between groups (▶ **Table 1**). In direct comparison, LLETZ revealed a non-significant trend to a higher proportion of PTB (11.7 vs. 6.7%, p = 0.407 for delivery < 37 weeks and 4.3% vs. 0%, p = 0.157 for delivery < 34 weeks).

The metric of the cone was available in 94.7% (89/95): 56.2% had a cone depth ≥ 10 mm and 22.5% ≥ 12 mm. A cone volume ≥ 3 cm^3 applied to 24.7% of patients. Neither median cone depth nor estimated cone volume differed between preterm and term birth groups (▶ **Table 2**, ▶ **Fig. 2**). Differences in women with and without preterm birth below 37 weeks' gestation are summarized in ▶ **Table 3** and ▶ **Fig. 3**. Repeated interventions were observed in 46.7% (n = 7/15) of patients with PTB compared to 15.7% (n = 22/140, p = 0.009) with delivery at term. The proportion of PTB increased with the number of interventions: 6.3% with one, 13.6% with two and 57.1% with three interventions (p = 0.001). Risk of PTB was 24.1% if more than one intervention was performed. Interestingly, none of the patients with repeated LLETZ (n = 0/7) delivered preterm compared to six patients (n = 6/12, 50.0%) with LV after LLETZ and one patient (n = 1/10, 10%) with repeated LV. Additionally, a history of preterm birth or late miscarriage before cervical intervention was associated with an increased risk of PTB (OR 4.7 [95% CI 1.3–17.6], p = 0.020). Risk of PTB was also increased in younger women regarding the age at intervention as well as delivery (▶ **Table 3**).



▶ **Fig. 2** Cone depth and preterm birth. The boxplot diagram represents only women after LLETZ conisation with known cone depth (n = 89) without difference between preterm birth (n = 10) and term birth (n = 79, p = 0.278).

Multiple Regression analysis with development of a combined risk model

For better prediction of PTB we developed a combined risk model by multiple regression analysis. The risk factors age at intervention and age at delivery were transformed in a binary variable after definition of the optimal cut-off by ROC-analysis. The first model included the following independent parameters: repeated intervention, history of PTB, age below 30 years at intervention, age below 28 years at delivery (▶ **Table 4**). The variable gravidity was dependent on history of PTB and BMI was neither predictive nor improved the model. Both parameters were excluded from the model.

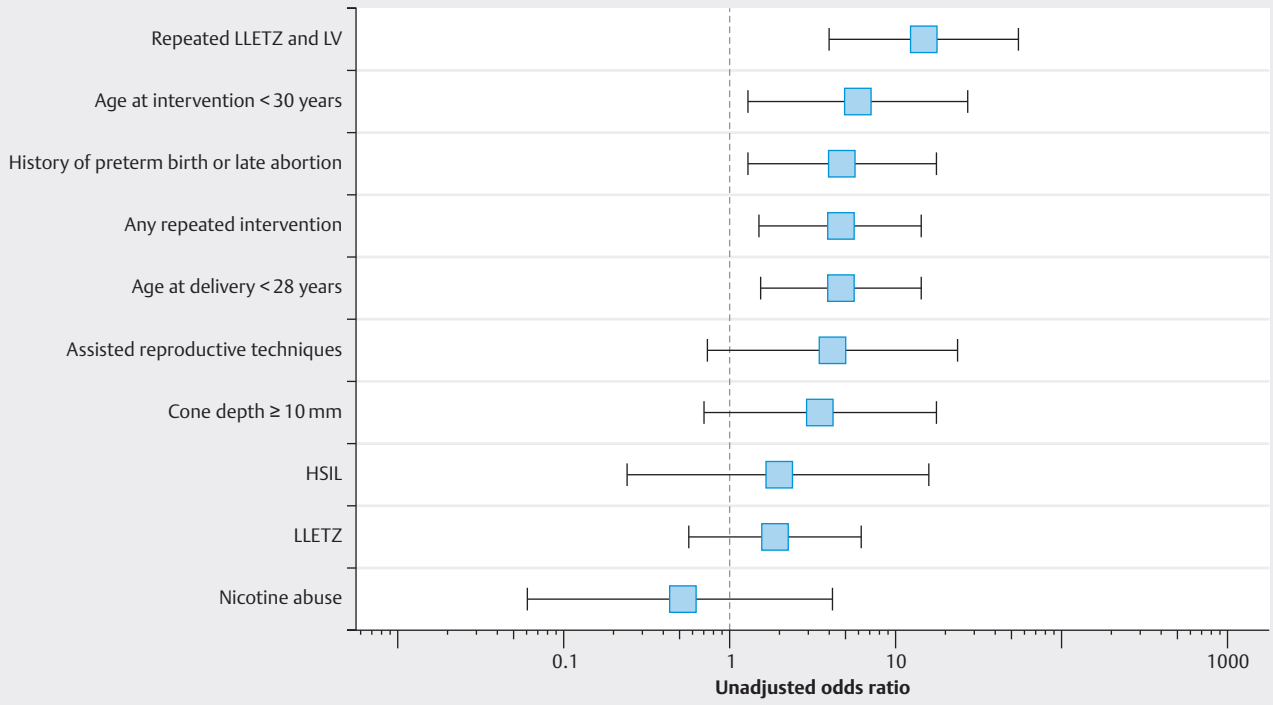
In the second model the parameter of any repeated intervention was replaced by repeated intervention with LLETZ and LV (▶ **Table 4**). The ROC-AUC of the combined model 1 was 0.83 (95% CI 0.71–0.95, p < 0.001). Model 2 performed marginally better with AUC 0.85 (95% CI 0.74–0.97, p < 0.001). Subsequently, we developed a risk score. Scoring points were weighted by the regression coefficients of model 2: Repeated intervention with LV after LLETZ – 3 points, age at intervention < 30 years – 2 points, age at delivery < 28 years – 1 point, previous preterm birth – 1 point. The sum of the scoring point resulted in an AUC of 0.86 (95% CI 0.74–0.98, p < 0.001) with an optimal cut-off value of four points (**Fig. S1**). The test characteristics of the combined score are presented in ▶ **Table 5**.

Discussion

Numerous studies left no doubt as to the increased obstetrical risks of patients with a history of treated CIN. A recent meta-analysis of the Cochrane library with inclusion of 59 studies and more than five million participants indicated an increased risk for PTB below 37 weeks with a risk ratio (RR) of 1.75 (95% CI 1.57–1.96) [3]. However, several factors contribute to the risk estimation. On the one hand the risk depends on the chosen procedure and was higher in excisional compared to ablative treatments. The risk increases with the invasiveness of the surgical procedure and was lowest in the group of a cone depth below 10–12 mm (RR 1.54 [95% CI 1.09–2.18]). Risk estimation in dependence of the cone volume revealed similar results. Laser vaporization, a method of minimal invasiveness, was even not associated with an increase of risk (RR 1.04 [95% CI 0.86–1.26]) [3]. The findings of our study were comparable, even if the study size was insufficient for reaching the level of significance. With higher invasiveness of therapy, we found a trend to an increased proportion of PTB with a number needed to harm of 20 comparing LLETZ ± LV with LV alone. Depth and volume of the LLETZ specimens of our cohort belong mainly to the low risk category (< 12 mm, < 3 cm^3).

▶ **Table 3** Risk factors of preterm birth.

Risk factor	% with preterm birth in exposed group	% with preterm birth in non-exposed group	Unadjusted OR (95% CI)	P value
Repeated LLETZ + LV	50.0%	6.3%	14.9 (4.0–55.6)	< 0.001
Age at intervention < 30 years	15.1%	2.9%	6.0 (1.3–27.4)	0.022
Age at delivery < 28 years	24.1%	6.3%	4.7 (1.5–14.3)	0.006
Any repeated intervention	24.1%	6.3%	4.7 (1.5–14.3)	0.006
History of PTB or late abortion	28.6%	7.8%	4.7 (1.3–17.6)	0.02
ART	28.6%	8.8%	4.2 (0.7–23.6)	0.108
Cone depth ≥ 10 mm	16.0%	5.1%	3.5 (0.7–17.7)	0.125
HSIL	10.4%	5.6%	2.0 (0.2–16.1)	0.521
LLETZ	73.3%	59.3%	1.9 (0.6–6.2)	0.296
Nicotin abuse	5.6%	10.2%	0.5 (0.06–4.2)	0.536



▶ **Fig. 3** Risk factors of preterm birth. The Forrest plot shows the crude odds ratios (squares) with 95 % confidence intervals (whiskers). The dashed line marks the one on x-axis.

▶**Table 4** Combined risk models of preterm birth with adjusted odds ratio and ROC-AUC.

	Model 1			Model 2			
Risk factor	**Coefficient of regression**	**Adjusted OR (95 % CI)**	**P value**	**Coefficient of regression**	**Adjusted OR (95 % CI)**	**P value**	**Risk score**
Any repeated intervention	1.9	6.5 (1.7–25.1)	0.006				
Repeated LLETZ + LV				3.1	22.0 (3.8–129.0)	0.001	3
Age at intervention < 30 years	1.6	4.9 (0.8–29.0)	0.078	1.9	6.5 (0.9–47.9)	0.066	2
Age at delivery < 28 years	1.5	4.3 (1.1–17.7)	0.041	1.2	3.4 (0.8–14.5)	0.093	1
History of PTB or late abortion	1.5	4.5 (0.9–22.5)	0.067	1.6	4.9 (0.9–26.9)	0.065	1
		ROC-AUC (95 % CI)			ROC-AUC (95 % CI)		
		0.83 (0.71–0.95)	< 0.001		0.85 (0.74–0.97)	< 0.001	

▶**Table 5** Test Characteristics of the risk score based on predictive model 2. A sum score ≥ 4 points was assumed as test positive.

	Sensitivity	**Specificity**	**PPV**	**NPV**	**pos. LR**	**neg. LR**	**Accuracy**	**OR (95 % CI)**	**P value**
Sum score ≥ 4 points	0.67	0.99	0.91	0.97	93	0.34	0.96	278 (29.6–2163)	< 0.001

At least as important for the risk assessment is the choice of the comparison group [5]. Due to the lack of randomized controlled trials, it is necessary to choose an appropriate comparator. Lowest increase of risk for PTB was observed if women with dysplasia and without treatment were used as comparison group (RR 1.27 [95% CI 1.14–1.41]). However, this comparison group of the meta-analysis comprises a heterogeneous spectrum of patients, whose diagnosis was partly based on colposcopic findings alone. It suggests that the group contains a high proportion of transient HPV infection and low-grade dysplasia with spontaneous remission. In contrast to high-grade dysplasia, low-grade dysplasia was not associated with an increased risk of PTB [15]. A comparison with patients having an untreated high-grade squamous lesion (HSIL) seemed to be more suitable. In this subgroup analysis of the Cochrane meta-analysis, the cervical treatment did not result in an increased risk of PTB (RR 1.37 [95% CI 0.85–2.19])[3]. However, the analysis comprised only three studies with 742 untreated and 3022 treated participants [16, 17, 18]. A similar trend was observed, when the cohorts of the untreated HSIL patients were compared to the general healthy population (RR 1.4 [95% CI 0.94–2.1]). These data suggest an additional role of a persistent high-risk HPV infection for the increase of PTB risk. The results of a recent prospective study supported this hypothesis. In the Canadian HERITAGE study 899 pregnant women were tested on vaginal HPV DNA [19]. A persistent infection with the high-risk HPV types 16 and 18 during pregnancy was, independent of cervical treatment, associated with an increased risk of PTB (aOR 3.72 [95% CI 1.47–9.39]). Both HPV persistence and PTB share some risk factors like an inflammatory vaginal milieu due to bacterial vaginosis, aerobic vaginitis and cervicitis following infection with chlamydia trachomatis [10, 20, 21, 22, 23, 24, 25, 26]. Therefore, it remains unclear if the HPV infection is directly causal for the increased risk of PTB or if it is only an indicator for a high-risk milieu. In our study, a history of repeated cervical intervention obviously revealed a higher impact on risk of PTB as the type of intervention itself. It should be noticed that the risk of HPV infection as well as the development of a high-grade cervical dysplasia can be sufficiently reduced by vaccination. Vaccination after surgical intervention may also decrease the risk of a persistent HPV infection [27]. Interestingly, the increase of risk did not result from a higher invasiveness of the method of intervention, because LV in combination with LLETZ and not the repeated LLETZ gave rise to our observation. Patients with repeated intervention by LLETZ and LV had the greatest risk for PTB. Unfortunately, our data lack the information about the time interval between interventions. Nevertheless, we interpreted the results as follows: patients got a repeated LLETZ mainly because of residual disease after the first intervention whereas the combination of LLETZ and LV primary resulted from the persistence or recurrence of a HPV-associated dysplasia. Consequently, a persistence of high-risk HPV infection seemed to be associated with an increased risk of PTB. Younger age at intervention and delivery were further risk factors. In combination with a HPV induced dysplasia the younger age may indicate a susceptible subgroup of women with faster progression. It remains hypothetic if younger women with CIN represent a subgroup with a disturbed proinflammatory or immunodeficient milieu. Finally, a personal history of PTB was a risk factor in our analysis, which should be independent from intervention indicating an increased basal risk.

For an optimal estimation of risk factors, the characteristics of the comparison group should be as similar as possible to the treatment group for minimizing the influence of possible confounders. Usually there is an indication for treatment in patients with persistent high-grade cervical dysplasia following a high-risk HPV infection. Using untreated patients as a comparator is hardly possible. As LV did not or did only marginally increase the risk of PTB, we used this mode of minimally invasive intervention as comparator. The resulting homogeneity of the study population's characteristics is a strength of our study, because it minimized the risk of a selection bias. However, the small size of our study population limited the power of our study. Some well-established risk factors did not reach the level of significance even the observed effect size was comparable to others [3]. Nevertheless, the study size was sufficient to verify the importance of repeated interventions as an independent risk factor for PTB. The developed risk score by combining the four significant risk factors demonstrated considerable test characteristics and could be helpful for simple risk estimation in the clinical situation. However, the predictive performance of the score needs to be proofed in the future.

Conclusion

Although the exact connection between cervical dysplasia and preterm birth is unknown until today, a single treatment effect can be excluded. Within the present study, it was possible to confirm the impact of a repeated intervention on PTB risk, which was of greater relevance than the performance of a contemporary excisional treatment like LLETZ compared to ablative LV. We hypothesize that the persistence of a high-risk HPV infection gave rise to this observation.

Author Contributions

- Johannes Stubert – manuscript writing, statistical analysis, development of the study concept.
- Elisa Stratmann – Data collection, statistical analysis, proof reading.
- Bernd Gerber – development of the study concept, proof reading.
- Ellen Mann – proof reading, development of the study concept.

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Key Message

Repeated cervical intervention revealed a greater impact on the risk of preterm birth than a single performance of a minimally invasive treatment method like large loop excision of the transformation zone (LLETZ) in comparison to ablative laser vaporization.

Conflict of Interest

The authors declare that they have no conflict of interest.

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