Original Investigation

Factors Affecting Obstetric Outcomes in Patients Who Underwent Cold-Knife and Loop Electrosurgical Excision Procedure Conization Due to CIN 2 or CIN 3

Obut et al. LEEP vs Cold-Knife Conization: Obstetric Outcomes

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Abstract

Objective: To determine factors affecting obstetric outcomes in pregnancies after conization by loop electrosurgical excision procedure (LEEP) or cold-knife conization (CKC) due to cervical intraepithelial neoplasia (CIN).

Material and Methods: The maternal and clinical characteristics and obstetric outcomes of CKC, LEEP and control groups were evaluated and compared. Risk factors for adverse pregnancy outcomes were evaluated using multiple logistic regression analyses.

Results: The incidence of preterm delivery, PPROM, low APGAR scores, fetal mortality, and late-period spontaneous abortus was highest in patients who underwent CKC (p<0.05). Cone depth of CKC was longer than LEEP (p=0.025). Cervical length (CL) at pregnancy was CKC<LEEP<controls (p=0.003). Shorter CL at pregnancy and time from conization to pregnancy (t-CP) was correlated with a high incidence of preterm delivery and PPROM (p<0.05). To predict preterm delivery, t-CP <14 months had 63.16% sensitivity and 77.42% specificity (AUC=0.714, 95% CI: [0.603-0.809]; p=0.005), and CL at pregnancy <31 mm had 65% sensitivity and 71.78% specificity (AUC=0.731, 95% CI: [0.675-0.782]; p<0.001). To predict PPROM, t-CP <15 months had 85.71% sensitivity and 65.22% specificity (AUC=0.730, 95% CI: [0.603-0.809]; p=0.024), and CL <32 mm had 72.73% sensitivity and 61.89% spcificity (AUC=0.685, 95% CI: [0.675-0.782,p=0.007).

Conclusion: Compared with CKC, LEEP has shorter cone depth and fewer adverse pregnancy outcomes. The t-CP<14 months was a risk for preterm delivery and <15 months was a risk for PPROM. CL at pregnancy <31 mm was a risk for preterm delivery and <32 mm was a risk for PPROM.

Keywords: Cervical intraepithelial neoplasia; conization; cold-knife conization; loop electrosurgical excision procedure; obstetric outcome

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Introduction

Cervical cancer screening and follow-up treatment have been implemented in routine healthcare. As a result, most cases are detected and treated in the pre-malignant phase, known as cervical intraepithelial neoplasia (CIN). Thus, the incidence of cervical cancer has been significantly decreased from 14.8 per 100,000 in 1975 to 6.6 per 100,000 in 2013 (1, 2). The majority of CIN 2 (peaking at the age of 25 to 29 years) and CIN 3 (peaking at the age of 25 to 40 years) occur in childbearing age (3). Cold-knife conization (CKC) and loop electrosurgical excision procedure (LEEP) conization are both excisional procedures, the most accepted and used in the treatment of CIN 2 and 3. However, both CIN and conization alter the morphology of the cervix, which holds the fetus in the uterine cavity. Accordingly, adverse pregnancy outcomes in patients with CIN 2 and CIN 3 who underwent excisional procedures have been reported in previous studies, including late pregnancy loss due to cervical insufficiency, preterm birth, preterm premature rupture of membranes (PPROM), premature rupture of membranes (PROM), increased fetal mortality and second-trimester abortion (4-6). However, some studies attributed these adverse pregnancy outcomes to inherited risks because these patients also have low socioeconomic status and income, advanced maternal age, and high smoking rates (7). Also, one study affirmed that the risk of preterm delivery in these patients was not due to conization but because of CIN (8). In addition, there is a conflict regarding pregnancy outcomes between studies in respect to the effect of the type of cervical excision procedures (CKC or LEEP) performed, the depth and volume of excised tissue, remaining cervical length, and the time elapsed from the procedure on adverse pregnancy outcomes (4-6,9,10). Based on these findings, it is clear that there is a necessity to bring a clarity on these issues. Further studies will allow to develop strategies for optimizing subsequent pregnancy results after conization.
This study aimed to evaluate factors affecting pregnancy outcomes in patients with CIN 2 or CIN 3 who underwent LEEP or CKC.

Material and Methods

This study is single centred and evaluates the data of singleton pregnancies that reached 16 gestational weeks after conization due to CIN 2 or CIN 3 between January 2010 and July 2020 retrospectively.
The inclusion criteria were patients with singleton fetuses, pathologic diagnoses as CIN 2 or CIN 3, subsequent pregnancy after CKC or LEEP, and reaching at least 16 gestational weeks. The exclusion criteria were patients who aborted before 16 gestational weeks because measuring the cervical length before this week is problematic and also the relation of spontaneous abortion due to cervical insufficiency is weak (11), patients' known major risk factor for preterm delivery including history of preterm delivery and having multifetal pregnancies, history of repeated conization or ablative treatments, and those with missing data. We documented the maternal age, body mass index (BMI), medico-surgical and obstetric history, smoking habits, gravidity, parity, pathologic diagnoses, times and types of conization, depth and volume of conization specimens, length of cervix measured between the 16^{th} and 24^{th} gestational weeks, weeks of spontaneous abortion and delivery, time interval between conization, and pregnancy and fetal outcomes. The cases in control group was

selected among those had no symptoms such as bledding, uterine contractions, age-matched and cervical length measured as a part of ours clinical routine during routine detailed fetal anatomic evaluation.

Deliveries occurring between the 24th and 37th gestational weeks were defined as preterm deliveries. PPROM was defined as the loss of the integrity of membranes before labor began in pregnancies before 37 gestational weeks, PROM was defined as the loss of the integrity of membranes before labor began in pregnancies after 37 gestational weeks (12). Late spontaneous abortion was defined as abortion occurring between 16th and $23^{0/6}$ gestational weeks. Cervical length measurements were obtained using transvaginal ultrasonography after voiding between the 16th and 24th gestational weeks.

CKC was performed in the operating room and all patients were treated by experienced gynecologic oncologists who have perfomed at least 60 conization per year. Under spinal anesthesia, a surgical margin of 2 mm was created using a scalpel, and interrupted vertical sutures with Dexon-1 were used for hemostasis. All LEEPs were performed by experienced gynecologic oncologists using the same technique; first, Lugol iodine was applied and then a 2% lidocaine-containing solution. Cone size was based on loop dimension: small, ≤10×10 mm; middle-sized, 15×12 mm, and the current was set to cut and coagulate.

The volume of the elliptical cone = (D.d.ϖ / 4) X h / 3 h: height of the cone; D: major axis of the ellipse; d: minor axis of the ellipse (ϖ=2.622).

The primary outcomes of the study were preterm birth (between 24-36 gestational weeks), PPROM, the secondary outcome was spontaneous abortion (between 16-24 gestational weeks) and fetal mortality.

Statistical Analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of data distribution. Appropriate tests were selected according to the results. Continuous variables that satisfied the assumption of normal distribution were compared using Student's t-test and the others by using the Mann-Whitney U test among categories of groups such as LEEP+CKC and controls. Homogeneities of variances were tested using the Levene test. For comparisons of more than two independent groups, one-way analysis of variance (ANOVA) or the Kruskal-Wallis tests were used. Mean±standard deviation and median (range) are given as descriptive statistics for these variables. The differences in proportions between groups were compared using using the Chi-Square or Fisher's exact tests, where appropriate, and the results were summarized using column percentages with frequency distributions. To define independent risk factors of outcome variables such as LEEP and CKC, we ran multiple logistic regression (LR) analyses and odds ratios with their confidence intervals were calculated. Correlations between variables were examined against the multicollinearity problem and a candidate model was arranged accordingly. Variance inflation factor (VIF) and tolerance values and model fit statistics were also found appropriate and multiple logistic regression was used with the backward LR method. P values of less than 0.05 were considered statistically significant. The IBM SPSS Statistics for Windows, Version 26.0. (2) package was used for all statistical analyses.

Results

The data of 1069 pregnant women who underwent conization due to CIN 2 and CIN 3 were evaluated. Among them, 598 were CKC and 471 were LEEP. Seventy-two patients who underwent CKC and 45 patients who underwent LEEP became pregnant. Twenty-one women who underwent CKC and 15 who underwent LEEP were excluded due to histories of preterm delivery, early pregnancy losses, and losses to follow-up. As a result, 51 pregnancies with a history of CKC and 30 with a history of LEEP were included in the study (Figure 1).

The basic maternal characteristics including maternal age at pregnancy, BMI, gravidity, parity, method of conception, and rates of smoking of all groups showed no differences

(p>0.05). The incidence of complications such as diabetes, hypertension, preeclampsia, oligohydramnios, polyhydramnios, and placenta previa of all groups was similar (p>0.05). Also, gestational weeks at the time of cervical length measurements of all groups were not different (p>0.05). Accordingly, the baseline characteristics of patients in each group were comparable. To minimize the effect of factors on obstetric outcomes, maternal age when conization was performed, time from conization to last menstrual period, and rates of CIN 2 and CIN 3 were compared between the CKC and LEEP groups, and no significant difference was found between them (p>0.05) (Table 1 and 2). Thus, the CKC and LEEP groups were comparable.
Although the mean cone volume by CKC was greater (5.59±5.28 cm^3) than in LEEP (2.96±3.14 cm^3), the difference was not statistically significant. The depth of tissue was greater in the CKC group than in the LEEP group (p=0.025). The calculated length of cervix was CKC=LEEP<controls (p=0.003) (Table 1). Although conization was not seen as a factor affecting the total duration of pregnancy (p=0.294) (Table 1), the number of preterm deliveries was higher in the CKC and LEEP groups than in the control group (p=0.014). When we analysed the reason of preterm delivery, five (38%) patients in CKC group and one (16%) in LEEP group were due to PPROM (Table 2). Pregnancies with a history of CKC were more likely to be complicated by PPROM and low 1st and 5th minute APGAR scores than pragnancies with a history of LEEP and the controls (p=0.007, p=0.015 and p=0.001, respectively) (Table 1, 2). The incidence of low 1st and 5th min APGAR scores was more common in preterm and PPROM cases, which was the main reason for the difference between the CKC and LEEP groups and the control group. The rate of overall mortality, which included late spontaneous abortion and fetal mortality, in the CKC group was also higher than in the LEEP and control groups (p=0.004) (Table 2).
We evaluated the effect parameters such as cone volume and depth, time elapsed from conization to pregnancy, cervical length, smoking, and type of CIN (CIN 2 CIN 3) on adverse pregnancy outcomes including preterm delivery, PPROM, PROM, and fetal mortality. The time from conization to pregnancy in patients with PPROM and preterm delivery were significantly shorter than in those who delivered at term and without PPROM (p=0.005 and p=0.046, respectively). A shortened cervix was associated with preterm delivery, PPROM, and fetal mortality (p<0.001, p=0.037, and p=0.005). As the volume of excised tissue increased, the rate of fetal mortality also increased (p=0.019) (Table 3). Using the receiver operating characteristics (ROC) curve, a cervical length under 31 mm and time from conization to pregnancy under 14 months was observed to be the most relevant value for the prediction of preterm delivery, with 63.16% sensitivity and 77.42% specificity (AUC=0.714, 95% CI: [0.603-0.809]; p=0.005), and <31 mm had 65% sensitivity and 71.78% specificity (AUC= 0.731, 95% CI: [0.675-0.782]; p<0.001), respectively (Figure 2). For the prediction of PPROM, time from conization to pregnancy of <15 months had 85.71% sensitivity and 65.22% specificity (AUC 0.730, 95% CI: [0.603-0.809]; p=0.024), and cervical length of <32 mm had 72.73% sensitivity and 61.89% specificity (AUC 0.685, 95% CI: [0.675-0.782]; p=0.007], (Figure 3).
Table 4 shows the results of multivariate logistic regression that included the risk of admission to the neonatal intensive care unit, PPROM, delivery mode, preterm delivery, cervical length, and low APGAR 1st and 5th-minute scores. According to the final model, PPROM and cervical length were found as significant (p=0.024 and p=0.048, respectively); patients with PPROM were 4.3 times more likely to be in conization group. For each one millimetre shortening of the cervix, the likelihood of PPROM was increased 1.01 times.

Discussion

This study aimed to focus on obstetric outcomes and affecting factors in subsequent pregnancies after conization due to CIN. The one difficulty in evaluating factors affecting obstetric outcomes is that there are numerous potential factors. The well-known risk factors of adverse obstetric outcomes are increased maternal age, smoking, multifetal gestation, and obstetric complications including polyhydramnios, hypertension, and preeclampsia, which were similar between all groups in our study. Also, we did not include patients with a history of preterm delivery and multifetal gestation. Moreover, obstetric complications including gestational diabetes mellitus, hypertension, preeclampsia, polyhydramnios, oligohydramnios, and placenta previa were similar in all groups of this study. The majority of studies in the literature compared conization groups and control groups, meaning that the control and conization groups were different in respect to the history of preterm delivery. Thus, the outcomes of these studies are debatable. In this respect, the present study is valuable.

The outcomes of this study can be summarized as cone volume revealed either by CKC or LEEP was similar; however, cone depth in CKC was longer. CKC was related to a higher incidence of preterm delivery, PPROM, low 1st and 5th minute APGAR scores, fetal mortality, and late spontaneous abortion. When we evaluated factors that affected preterm delivery and PPROM, shorter cervical length and less time elapsed from conization to pregnancy were correlated instead of cone volume and depth. Cone volume was correlated with overall fetal mortality including late spontaneous abortion and fetal mortality.

As a structure that holds the fetus in the uterine cavity and protects the fetus both anatomically and by secreting cervical mucus, which contains several antimicrobial agents and forms a mucus plug, the cervix is the main affected tissue by CIN and conization. Thus, many studies focused on cervical changes and their relationship with adverse pregnancy outcomes (6,9,13,14). Some studies found that pregnancies with a history of CIN had an increased risk for PPROM or preterm delivery (15). In contrast, other studies found that these risks were not because of CIN but because of inherited adverse obstetrics risks such as increased maternal age, smoking, lifestyle or socioeconomic status (8, 16). In this study, we evaluated the effect of having CIN 2 or CIN 3 on pregnancy outcomes and we found that they did not affect adverse pregnancy outcomes.

It is known that some bacteria such as Bacteroides fragilis and group B streptococcus can cause PPROM or preterm delivery by secreting phospholipase or proteolytic enzymes (17). Conization alters the cervical tissue anatomically, physiologically, and histologically. As a result of conization, the internal orifice of the cervical canal can be damaged and the cervical gland, which secretes mucus with a protective effect against ascending infectious agents, can be destroyed (11). LEEP and CKC are both effective, safe methods and have similar rates of recurrence in the treatment of CIN (18). LEEP controls the maximum size of the cone; however, cone biopsy by CKC can either be too large or too deep (6). In our study, although the mean cone volume revealed from CKC (5.59±5.28 cm^3) and LEEP (2.96±3.14 cm^3) were similar (p=0.061), and the cone depth in CKC (1.11±0.39 mm) was longer than in LEEP (0.96±0.35 mm) (p=0.025). Considering the damage of the cervical canal and the secretory function of cervical glands, cone biopsy depth is more important than cone volume. The other evidence that supports this opinion is that although cervical cerclage supports the cervix mechanically, it is not effective in pregnancies with a history of conization (14,19). Recently, Liverani et al. reported that cone depth was correlated with preterm delivery in pregnancies after conization due to CIN, but not cone volume (13). Liu et al. conducted a prospective randomized controlled study comparing 124 pregnancies with a history of LEEP and 120 pregnancies with a history of CKC and they found that compared with LEEP, cone biopsy depth by CKC was deeper and in parallel with the incidence of preterm delivery, and PPROM was more common with CKC compared with LEEP. However, they did not note the cone volumes (6). Although studies found a similar incidence of preterm delivery and PPROM between CKC and LEEP, a link was reported between cone depth and preterm delivery

(9,10). This disparity might result from different cone sample sizes, depths, and diameters, and times elapsed from conization to pregnancy.

It has been shown the cervical tissue is highly regenerable. As expected, deeper and wider wounds to the cervix require more time. Accordingly, a study that investigated the minimum time that should elapse from conization to pregnancy found the time for CKC was 9 months and LEEP was 6 months, which is compatible with the volume and depth of excised tissue (11). In this line, a study found that immediate pregnancy after LEEP increases the risk of preterm delivery (20). Accordingly, in our study, the time from conization to pregnancy was significantly shorter in those with preterm delivery and PPROM compared with those without ($p<0.05$). In this study, using ROC analysis in patients who underwent conization, the time from conization to pregnancy under 14 months was a risk for preterm delivery and under 15 months was a risk for PPROM. This time was longer than those reported in a previous study (11). Although pregnancy outcomes improved over time, this should be balanced by the fact that the patients who undergo conization due to CIN are older than the general pregnant population and advanced age in women is related to low fertility rates and poorer pregnancy outcomes. Thus, recommendations for the optimal time that should elapse from conization to pregnancy must consider the patient's age, cone depth, and the desired number of children. Further studies are needed in this regard.

The relationship between cervical length and preterm delivery has been well established in obstetric care. However, there is no consensus on the exact length, ranging from 15 mm to 30 mm. Some authors accept 25 mm for those with a history of preterm delivery and 20 mm for those without a history of preterm delivery (21,22). In this study, for patients who underwent conization, using ROC analysis, cervical length under 31 mm was a risk for preterm delivery and under 32 mm was a risk for PPROM. These differences between conization and non-conization cases may result from altering the physiologic and histologic nature of cervical tissue by conization.

Study Limitations

The limitation of this study is that although the patients had good documentation, there is a possibility of missing patients, which creates selection bias due to the nature of the retrospective analysis.

Conclusion

CKC causes deeper cone depth and shorter cervical length. The incidence of PPROM, preterm delivery, low APGAR scores, and fetal mortality are higher in patients with a history of CKC. The time from conization to pregnancy and cervical length at pregnancy are determinant factors for preterm delivery and PPROM. Cervical length at pregnancy under 31 mm was a risk for preterm delivery and under 32 mm was a risk for PPROM. It is important to consider these when advising patients about the optimal time to become pregnant because the time from conization to pregnancy under 14 months was a risk for preterm delivery and 15 mm was a risk for PPROM. Strategies that regulate the vaginal microbiota and prevent infectious morbidity is also reasonable because one of the most prevalent complications of pregnancies with conization is PPROM. However, future randomized controlled studies are needed before suggesting these.

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Table 1. Comparison of the groups regard fetal and maternal characteristics

	CKC		**LEEP**		**Control**		**p**
	Mean ± S.D	**Median (Range)**	**Mean ± S.D**	**Median (Range)**	**Mean ± S.D**	**Median (Range)**	
Maternal age at conisation (years)	31.61±3.97	32(18)	31.53±4.21	32(16)	NA	NA	0.875*
Maternal age at delivery (years)	34.12±3.54	34(19)	34.57±3.11	34.5(12)	33.86±3.97	34(20)	0.620+
BMI (kg/m^2)	27.82±3.72	27(17)	28.07±3.05	28(12)	27.24±4.59	26.79(26.7)	0.236
Gravidity	3.49±1.63	3(9)	3.2±1.37	3(5)	3.69±2.15	3(19)	0.614
Parity	1.78±1.15	2(5)	1.47±1.11	2(4)	1.82±1.21	2(5)	0.405
Volume of cone (cm^3)	5.59±5.28	4.39(18.71)	2.96±3.14	2.43 (11.64)	NA	NA	0.061*
Dept of cone (cm)	1.11±0.39	1(1.7)	0.96±0.35	0.8 (1.2)	NA	NA	**0.025***
Time from conisation to delivery (month)	30.12±18.00	24(72)	36.33±31.32	2 (8)	NA	NA	0.960*
Time from conisation to LMP (month)	22.47±14.88	18 (57)	28.27±28.34	17.5 (91)	NA	NA	0.984*
Cervical length (mm)	32.12±5.56	32 (28)[a]	32.97±3.92	32 (14)[a]	34.91±6.37	36 (30)[b]	**0.003**
Pregnancy weeks at cervical length measurement	18.43±2.69	17 (8)	17.87±2.45	17 (8)	17.8±2.14	17 (10)	0.582
Duration of pregnancy (days)	254.43±41.23	266 (241)	262.13±29.3	270.5 (151)	260.99±26.85	266.0 (175)	0.294
Apgar 1'	8.5±1.56[a]	9 (9)	8.83±0.54[b]	9 (2)	8.88±0.53[b]	9 (3)	**0.015+**
Apgar 5'	9.46±1.64[a]	10 (10)	9.93±0.26[b]	10 (1)	9.89±0.52[b]	10 (3)	**0.001+**

P<0.05 means there is significantly statistical difference between groups.
*p values from Mann Whitney U test; + p values from ANOVA and all others from Kruskal Wallis test a,b,ab
Medians or means with the same indices are the same, with different indices are statistically different from each other.
CKC: Cold knife conization, LEEP: Loop electrosurgical excision procedure, BMI: Body mass index, LMP: Last menstrual period, cm: centimeter, mm: milimeter

Table 2. Comparison of the groups according to maternal characteristics and obstetric outcomes

		CKC		LEEP		Control		p
		n	%	n	%	n	%	
CIN	CIN 2	21	41.18	19	63.33	-	-	0.068
	CIN 3	30	58.82	11	36.67	-	-	
Method conception	Spontaneous	48	94.12	28	93.33	191	95.50	0.574*
	IUI	1	1.96	0	0.00	4	2.00	
	IVF	2	3.92	2	6.67	5	2.50	
Smoking	No	29	56.86	23	76.67	134	67.00	0.173
	Yes	22	43.14	7	23.33	66	33.00	
Preterm Delivery	No	38	74.51	24	80.00	179	89.50	**0.014**
	Yes	13	25.49	6	20.00	21	10.50	
Mode of delivery	VD	24	47.06	12	40.00	110	55.00	0.096*
	C/S	24	47.06	17	56.67	88	44.00	
	Abortus	3	5.88	1	3.33	2	1.00	
PPROM	No	45	88.23	28	93.33	196	98.00	**0.007***
	Yes	6	11.76	2	6.66	4	2.00	
PROM	No	48	94.12	27	90.00	194	97.00	0.126*
	Yes	3	5.88	3	10.00	6	3.00	
HT	No	48	94.10	26	86.70	185	92.50	0.450*
	Yes	3	5.90	4	13.30	15	7.50	
Placenta Previa	No	49	96.08	30	100.00	195	97.50	0.683*
	Yes	2	3.92	0	0.00	5	2.50	
Preeclampsia	No	50	98.04	26	86.67	189	94.50	0.123*
	Yes	1	1.96	4	13.33	11	5.50	
GDM	No	47	92.16	28	93.33	182	91.00	1.000*
	Yes	4	7.84	2	6.67	18	9.00	
Oligohydramnios	No	47	92.20	29	96.67	196	98.00	0.075*
	Yes	4	7.80	1	3.33	4	2.00	
Polyhydramnios	No	50	98.04	27	90.00	194	97.00	0.108*
	Yes	1	1.96	3	10.00	6	3.00	
IUGR	No	47	92.16	27	90.00	177	88.50	0.746
	Yes	4	7.84	3	10.00	23	11.50	
Gender	Female	23	45.10	15	50.00	99	49.50	0.845
	Male	28	54.90	15	50.00	101	50.50	
NICU admission	No	42	82.35	26	86.66	184	92.90	0.067*
	Yes	9	17.64	4	13.33	14	7.10	
RBC Tx	No	49	96.10	30	100.00	192	96.00	0.761*
	Yes	2	3.90	0	0.00	8	4.00	
Foetal	No	46	90.2	28	93.30	198	99.00	**0.004**

Mortality	Yes	5	9.80	2	6.70	2	1.00	
	Abortus	3	5.88	1	3.33	2	0.00	

P<0.05 means there is significantly statistical difference between groups. CKC: Cold knife conization, LEEP Loop electrosurgical excision procedure, CIN: Cervical intraepithelial neoplasia, IUI: Intrauterine insemination, IVF: In-vitro fertilization, VD: Vaginal delivery, C/S: Cesarean section, NICU: Neonatal intensive care unit, PPROM: Preterm premature rupture of membranes, PROM: Premature rupture of membranes, HT: Hypertension, GDM: Gestational diabetes mellitus, IUGR: Intrauterine growth restriction, RBC: Red blood cell, Tx: Transfusion

Table 3. Effect of some parameter on pregnancy outcomes

			Volume of cone (cm^3)	Depth of cone (mm)	Time from conization to pregnancy (months)	Cervical length (mm)	Smoking (no)	Smoking (yes)	CIN2	CIN3
Preterm Delivery	**No**	**Mean**	4.14	1.06	27.76	34.92	160 (86.02)	81 (85.26)	32 (80.00)	30 (73.17)
		S.D	4.22	0.40	22.43	5.75				
		Median	2.58	0.80	23.00	35.00				
		Range	18.76	1.70	91.00	32.00				
	Yes	**Mean**	6.15	1.02	14.37	29.80	26 (13.98)	14 (14.74)	8 (20.00)	11 (26.83)
		S.D	6.08	0.30	9.67	6.43				
		Median	2.73	0.80	10.00	29.50				
		Range	18.40	0.90	31.00	29.00				
P			0.210	0.995	**0.005**	**<0.001**	0.863		0.601	
PPROM	**No**	**Mean**	4.53	1.06	25.58	34.44	174 (96.13)	91 (95.79)	34 (89.47)	35 (92.11)
		S.D	4.74	0.39	21.50	6.10				
		Median	2.64	0.80	18.00	35.00				
		Range	18.76	1.70	91.00	32.00				
	Yes	**Mean**	5.80	0.96	12.71	30.27	7 (3.87)	4 (4.21)	4 (10.53)	3 (7.89)
		S.D	5.72	0.26	9.83	5.78				
		Median	2.73	0.80	9.00	31.00				
		Range	14.91	0.70	28.00	20.00				
P			0.403	0.685	**0.046**	**0.037**	1.000*		1.000*	
PROM	**No**	**Mean**	4.82	1.06	24.43	34.28	179 (96.24)	90 (94.74)	36 (90.00)	39 (95.12)
		S.D	4.83	0.39	21.71	6.15				
		Median	2.76	0.80	17.00	35.00				
		Range	18.71	1.70	91.00	32.00				
	Yes	**Mean**	2.05	0.98	27.00	32.33	7 (3.76)	5 (5.26)	4 (10.00)	2 (4.88)
		S.D	2.96	0.27	3.58	4.85				
		Median	0.85	0.90	27.00	32.00				
		Range	7.77	0.70	10.00	14.00				
P			0.069	0.929	0.100	0.202	0.547*		0.432*	
Foetal Mortality	**No**	**Mean**	4.19	1.03	25.26	34.40	180 (96.72)	92 (96.84)	36 (90.00)	38 (92.68)
		S.D	4.39	0.37	21.22	6.00				
		Median	2.52	0.80	18.00	35.00				
		Range	18.76	1.70	91.00	30.00				
	Yes	**Mean**	9.10	1.27	17.86	27.89	6 (3.23)	3 (3.16)	4 (10.00)	3 (7.32)
		S.D	6.46	0.39	17.16	6.25				
		Median	8.48	1.50	9.00	30.00				
		Range	16.17	0.90	48.00	21.00				
P			**0.019**	0.069	0.198	**0.005**	1.000*		0.712*	

*Fisher's exact p value and all others from Mann Whitney U test, P<0.05 means there is significantly statistical difference between groups. S.D, standard deviation; CIN, cervical intraepithelial neoplasia;

PPROM, preterm premature rupture of membranes; PROM, premature rupture of membranes;cm,centimeter; mm, milimeter.

Table 4. Multiple Logistic Regression Analysis results to identify risk factors for being conization

Variables	B	Standard Error	P	Exp (B) O.R.	O.R. Lower Limit	O.R. Upper Limit
PPROM	1.472	0.652	0.024	4.357	1.214	15.643
Cervical length	-0.046	0.024	0.048	0.988	1.000	1.101

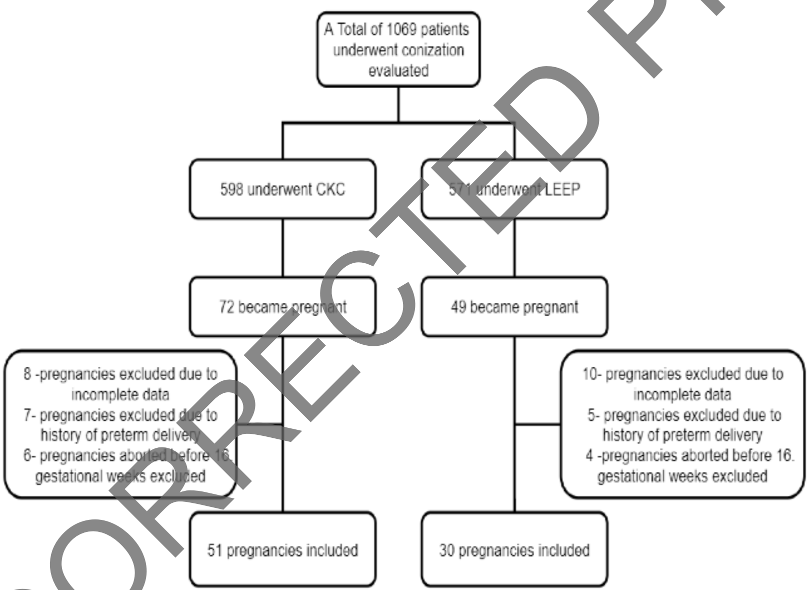

Figure 1. Descripsion of the study cohort

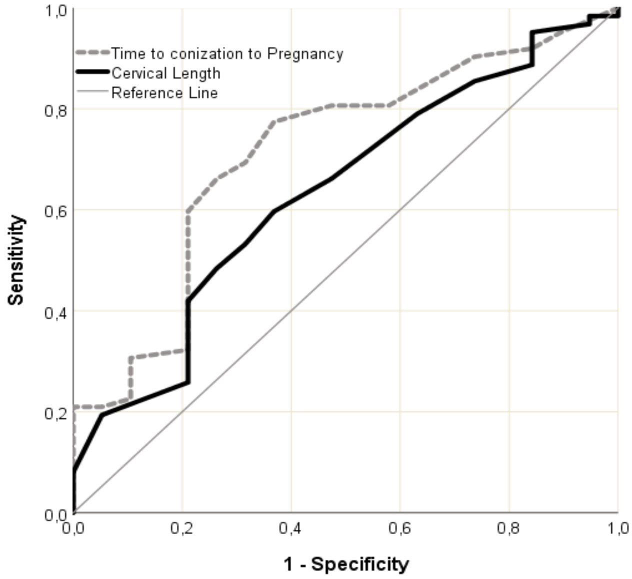

Figure 2. ROC analysis of cervical length and time from conization to pregnancy and preterm delivery

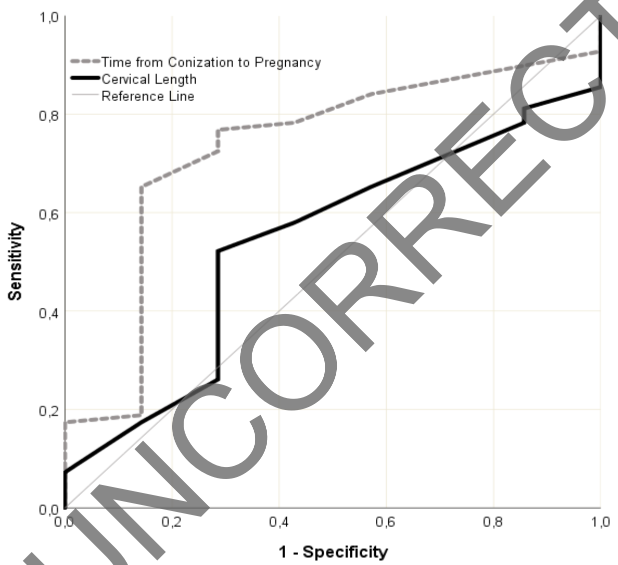

Figure 3. ROC analysis of cervical length and time from conization to pregnancy and PPROM