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Original Article

Obstetrics and Gynaecology Section

Cervical Conization and the Risk of Preterm Birth: A Population-Based Multicentric Trial of Turkish Cohort

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ABSTRACT

Introduction: Cold Knife Conization (CKC) is one of the most effective methods for the treatment of Cervical Intraepithelial Neoplasia (CIN). Some studies showed a relation between preterm birth and the treatment of CIN; on the other hand, other studies do not show such a relationship.

Aim: The present study was conducted with the aim to investigate the pregnancy outcomes of Turkish women regarding demographic characteristics, obstetric history, removed tissue, and residual cervical length after CKC and to determine the effect of removed cervical tissue volume and height on preterm birth.

Materials and Methods: This study was a population-based, multicenter trial that was conducted on singleton pregnancies between January 2007 and December 2013. The control group comprised of 38,892 patients who gave birth during this period. On the other hand, patients who conceived after CKC during this period were invited to the hospital and included in the case group (n=20). The course of pregnancy following CKC was studied. Preterm birth rates, risk factors for preterm birth, conisation age, cervical smear and colposcopic biopsy results and the volume and height of the removed cervical tissue of those patients were evaluated.

Results: There was no statistically significant difference in preterm birth rates between the case and the control groups. None of our cases had any identified preterm birth risk factor except for one case. The average height of removed cervical tissue was 12.6±5.4 mm and the average length of the residual cervix after birth was 28.7±4.3 mm.

Conclusion: Removal of cervical tissue of 12.6±5.4 mm in height and 2.35±2.27 cm^3 in volume will not increase the risk of preterm birth of women who do not have any other preterm birth risk factors. If there is no other preterm birth risk factors, term birth is most probably possible after conisation.

Keywords: Cervical intraepithelial neoplasia, Cold conisation, Preterm birth risk factors, Term birth

INTRODUCTION

Early detection and treatment of CIN is important for the prevention of cervical cancer. CKC is one of the most effective methods for the treatment of CIN. Accurate evaluation of the surgical margins is the major advantage of this procedure. Laser conization, Large Loop Excision of the Transformation Zone (LLETZ) and Loop Electrosurgical Excision Procedure (LEEP) are other methods that remove different volumes of tissue and have less risk of bleeding [1,2].

Some studies show a relation between preterm birth and the treatment of CIN [1,2]; on the other hand, other studies do not show any such relationship [3,4]. If all miscarriages or just first trimester losses are considered, some of the previous studies showed no significant difference between the treated and untreated groups [3,4]. If only the second trimester losses are considered, some studies reported significant differences between the treated and untreated groups [2,5,6], and some other studies did not [7-9].

Preterm birth is a complex condition and influenced by many factors. Stress-induced maternal or foetal hypothalamic-pituitary-adrenal axis activation, decidual- chorioamniotic or systemic inflammation, decidual haemorrhage and uterine distension (multifoetal pregnancy, polyhydramnios, uterine anomalies) are thought to be four main trigger mechanisms [10]. Preterm birth history is one of the most important risk factor that increases the risk of preterm birth [11]. Although, risk factors can not be specified in most of the cases, other risk factors are Premature Rupture Of Membranes (PROM), preterm uterine contractions, ethnicity, smoking, Body Mass Index (BMI)≤ 19.8kg/cm^2, the intervals between pregnancies being shorter than 18 months. While investigating the preterm birth after CKC or LEEP, identification of patients with previously mentioned risk factors and exclusion from the study is essential for reliable results. The presence of risk factors that give rise to preterm birth reduces the reliability of the study and will lead to misinterpretation. There is only one study in the literature that assess but do not exclude these factors [12]. There are also a few number of studies considering the volume and depth of the removed cervical tissue and all surgical techniques are evaluated altogether in most of the studies which makes the groups heterogeneous [1,12,13].

The cervix has a bell-shaped curve and stable in length (35 mm-50th centile) between 14-28 weeks of gestational age [14,15]. Cervical insufficiency is one of the causes of preterm birth and it is defined as recurrent pregnancy loss/birth due to painless cervical dilatation in the second trimester. To determine second trimester loss/birth after conisation as a result of cervical insufficiency, it must be characterized by painless dilatation. This has not been questioned in the previous studies reporting the preterm birth as a result of conisation [5,16]. Although some of the losses in the second trimester depend on cervical structural weakness; decidual inflammation, infection, haemorrhage or uterine overdistention are the other major reasons [10].

A short cervix is defined as a cervical length of less than 20 mm (women without preterm birth history) or 25 mm (women with preterm birth history) measured by transvaginal ultrasound between 16-28 weeks of gestation [14,17,18]. The origin of the idea of preterm birth after conisation comes from the belief that cervical shortening is equal to the amount of removed cervical tissue length. However, cervical competence may be much more related to residual cervical length than amount of removed tissue. Determination of residual cervical length after conisation will give information about the risks of premature birth and cervical insufficiency.

In our study, we aimed to investigate the pregnancy outcomes of Turkish women regarding demographic characteristics, obstetric history, removed tissue, and residual cervical length after CKC and to determine the effect of removed cervical tissue volume and height on preterm birth.

MATERIALS AND METHODS

This study was a population-based, multicenter trial that was conducted on singleton pregnancies. Written and electronic medical records of obstetric and pathology clinics of two main hospitals in Istanbul (Haseki Education and Research Hospital and Suleymaniye Maternity and Women's Disease Education and Research Hospital) between January 2007 and December 2013 were evaluated. The study was approved by local ethics committee.

Data including gestational age at delivery, gestational age at termination and preterm birth rates of 38,892 patients who gave birth during this period (Jan 2007- Dec 2013) were evaluated as the control group. Deliveries between 20-37 weeks of gestation were considered as preterm birth. Elective abortions (≤10 weeks), spontaneous foetal losses (earlier or later than 10 weeks) were categorized into different groups. On the other hand, patients who conceived after CKC during the same period (Jan 2007- Dec 2013) were considered as the case group (n = 20). All of the patients gave informed consent.

Cervical length measurements were obtained by transvaginal ultrasonography after voiding [19]. The course of pregnancy following CKC was evaluated. Risk factors for preterm birth (history of preterm birth, having hypertension, presence of cervical insufficiency, having a high body mass index, gestational diabetes mellitus, urogenital infections, recurrent foetal losses, premature rupture of membranes, polyhydramnios, abruption placentae, placental insertion abnormalities) were assessed. Obstetric history (gravidity, parity, abortion, ectopic pregnancy) smoking habit, the time elapsed between conisation and pregnancy, the presence of congenital malformation, gestational age at delivery, foetal birth weight, birth complications were identified. Conization age, cervical smear and colposcopic biopsy results and the dimensions of the removed cervical tissue of those patients were identified from the database of pathology clinic. Volume of the removed tissue was calculated as –

The volume of elliptical cone = (D.d.ϖ / 4) X h / 3

h: height of the cone; D: major axis of ellipse; d: minor axis of elipse.

STATISTICAL ANALYSIS

Statistical analysis was done by computer software SPSS version 16.0 (SPSS Inc. Chicago, IL, USA). Results were given as mean±standard deviation. We used Odds Ratio (OR) to estimate associations of preterm birth with cervical conisation. OR and their 95% CI were computed. p value < 0.05 was considered statistically significant.

RESULTS

Among the 20 patients in the case group, the preterm birth risk factors and demographic features were assessed: Preterm birth in previous pregnancies (n=1), PROM (n=0), Gestational Hypertension (GH)(n=0), Gestational Diabetes Mellitus (GDM) (n=0), urogenital infections during pregnancy (n=0), smoking (n=0), gravidity (2.3±1.6), parity (2.0±1.2), abortion (n =0), mean conisation age of the patients (31.1±5.2), mean maternal age when the pregnany was diagnosed (33.4±4.6), mean foetal birth weight (gm) (3209±508), the time elapsed between conisation- pregnancy (years) (2.3±0.9) and BMI (26.0±3.3). For the control group, patients with GH, GDM, urogenital infections during pregnancy and who smoke were excluded. Their mean gravidity was 2.5±1.9, parity-2.3±1.3 and mean age when the pregnancy was diagnosed-28.1±3.8 years.

The cervical smear results were Atypical Squamous Cells of Undetermined Significance (ASCUS) (2;10%), Low-Grade Squamous Intraepithelial Lesion (LGSIL) (11;55%), High-Grade Squamous Intraepithelial Lesion (HGSIL) (7;35%). The cervical biopsy results were CIN 1 (3;15%), CIN 2 (10;50%), CIN 3 (7;35%).

Only one woman had a preterm delivery history at 34 weeks of gestation. She was the only patient who gave preterm birth after CKC. The remaining patients had no known risk factors for preterm birth. Comparison of preterm birth rates of women who became pregnant after CKC and the control group are shown in [Table/Fig-1].

The average height of removed cervical tissue in the case group was 12.6±5.4 mm. The average length of the residual cervix after birth was 28.7±4.3 mm.

Comparison of pre-conisation cervical length by conisation height and cervical length after birth is shown in [Table/Fig-2]. The average volume of cervical tissue removed was 2.35±2.27 cm^3.

	Conization Group	Control Group	Odds ratio (95%CI)	p-value
	n (%)	n (%)		
Total	20 (100)	38872 (100)		
Birth week <37	1 (5)	501 (1.29)	4.03 (0.53-30.17)	0.174
Birth week <34	0 (0)	432 (1.11)	2.16 (0.13-35.90)	0.589
Birth week <28 (>20)	0 (0)	91 (0.23)	10.33 (0.62-172.21)	0.103
Ectopic Pregnancy	1 (5)	196 (0.50)	10.38 (1.38-77.96)	0.022
Termination of pregnancy ≤10* wks	2 (10)	-	-	-
Termination of pregnancy ≤10** wks	1 (5)	4016 (10.33)	0.45 (0.06-3.41)	0.445
Termination of pregnancy >10 wks	2 (10)	962 (2.47)	4.37 (1.01-18.89)	0.047

[Table/Fig-1]: Comparison of preterm birthrates of women who became pregnant after CKC and the control group.
*Elective abortions ≤10 weeks, **spontaneous foetal losses earlier than 10 weeks

		CLAB	Calculated CL (Pre-Conization)
CH (mm)	12.6	28.7	41.3*
1/3 CH (mm)	4.2		32.9**

[Table/Fig-2]: Calculation of pre-conisation cervical length by conisation height and cervical length after birth.
CH: Conization height (removed tissue height), CLAB: Cervical length after birth
*CH+CLAB **1/3CH+CLAB

DISCUSSION

Exclusion of previously proven risk factors leading to preterm birth is crucial while investigating the influence of a factor in preterm birth. Exclusion criteria have not been well established in the studies assessing the relation between conisation and preterm birth. Instead, statistical methods were used in a limited number of studies for the assessment of the influence of factors that may cause preterm birth [2,6,12,16]. The results were affected by the density of risk factors in the study group. Armarnik S et al., investigated the risk factors in women who had undergone conisation with those who had not. Although there was statistically significant difference between the two groups in terms of adverse obstetric history, a clear association was reported between conisation and preterm birth in the conclusion of the study [6].

The study conducted by Simoens C et al., was a rare study assessing the risk factors in pregnant women with a history of CIN treatment and pregnant women without a history of CIN treatment but the groups were not homogenous in terms of risk factors. Although the control group was twice as large as the case group, the number of patients with positive risk factors was nearly the same. Risk groups reached statistical significance with the presence of only one single

positive case (p = 0.04) (preterm birth history and urogenital infection in the first trimester). Patients who had gestational hypertension as a risk factor also differed significantly in both groups [12]. Andia D et al., reported no significant difference in terms of preterm birth rate for the pregnancies before and after the conisation for the same women. They concluded that conisation did not increase this risk. They expressed that preterm birth risk factors often present in women requiring conisation. Therefore, increased preterm birth rate was detected in women who underwent conisation compared to women who did not [20].

In our study, none of our cases had an identified preterm birth risk factor except for one case. (Only one woman had a history of preterm delivery and gave preterm birth). Preterm birth rates of women giving birth after CKC were compared with the patients who gave birth during this seven year- period. There was no statistically significant difference in preterm birth rates between the case and the control groups. We concluded that the absence of the preterm birth risk factors is one of the most important cause of the high percentage of term births after conisation.

Second trimester loss after conisation due to painless cervical dilatation has never been reported (cervical insufficiency). Occurance of the foetal losses in the second trimester was considered satisfactory. Any other aetiology than the cervical insufficiency in those patients might be the reason of preterm birth for those patients [10]. Armarnik S et al., could not show a benefit of prophylactic cerclage application [6]. The main reason for such a claim may be the inability to determine the risk factors other than cervical insufficiency for second trimester foetal losses. If the only mechanism that causes preterm delivery was cervical shortening and loss of cervical tissue, a significant proportion of patients would be expected to benefit from cervical cerclage [21].

Patients without a history of preterm birth and having a cervical length less than 20 mm between 16-28 weeks of gestation are considered to have a short cervix [15,17,18]. Preterm births can be expected in patients with deep cervical conisation (>15 mm) and in patients with residual cervical tissue lesser than 20 mm [2,12]. If so, there should be different preterm birth aetiologies in patients of whom the height of cervical tissue removed was lesser than 15 mm and with an adequate residual cervical length. Increased susceptibility to uteroplacental infection due to impaired tissue integrity and mechanical barriers may be a cause in such women. Neural or connective tissue damage in this region due to tissue trauma may also lead to early onset of labour. Well-designed studies are needed on these issues. In our study; the average height of removed cervical tissue was 12.6±5.4 mm and the average length of residual cervical tissue after birth was 28.7±4.3 mm.

Extracted conical cervical tissue volume is equal to the 1/3rd of the height of a cylinder having the same base diameter V cone=1/3 x Vcylinder. Mean cervical length achieved by summing actual height of removed conic tissue and height of residual cervical length is shown in [Table/Fig-2]. The actual amount of cervical shortening after conisation is determined by comparison of cervical length before the conisation and after the healing period. Determination of conisation height would be one of the most important criteria for prevention of premature birth.

Average volume of cervical tissue removed was 5.53±1.29 cm^3 by Sozen H et al., [13]. A limitation of this study is same sensitivity ratio (100%) was given for quite different volumes (0.59-3.99). In our study, the average volume of cervical tissue removed was 2.35±2.27 cm^3. This volume is a reliable value for patients who do not have preterm birth risk factors. However, only one patient who had a preterm birth risk factor (history of preterm birth) had a 0.86 cm^3 removed tissue volume and had 10 mm height of the cone. Further studies are needed to calculate preterm birth risk according to removed tissue volume in the presence of preterm birth risk factors.

In several studies, it is reported that cervical length measured 40 mm at the beginning of pregnancy remains stable until 14-28 weeks (35 mm-12.5% shortening) [14,22-24]. The average cervical length of our patients who underwent cervical conisation was 28.7 mm. If these values were shortened at the same rate between 14-28 weeks (3.5 mm-12.5%), the cervical length would be 25.2 mm. This value would also be above the cut-off value for a short cervical length in women without a prior history of preterm birth (20 mm).

When the proportion of the removed cervical tissue was considered, actual cervical shortening was about one-third of the height of cervical tissue removed. Cervical measurement prior to conisation has utmost importance. Contribution to actual shortening and preterm labour risk may be more clearly identified by comparison of cervical height after healing. Removing cervical tissue 12.6±5.4 mm in height and 2.35±2.27 cm^3 in volume will not increase the risk of preterm birth of women especially who do not have any other preterm birth risk factors. Further studies with homogenous groups are needed to determine how conisation would increase the risk of preterm birth in women with preterm birth risk factors.

The guidelines continue to recommend aggressive treatment for patients with high-grade dysplasia who are at significant risk for the progression of disease [25]. If removing cervical tissue greater than the determined cut-off values is necessary, antenatal follow ups of pregnant women should be strict for preterm birth risk.

CONCLUSION

CKC procedure performed according to given conisation height and volume does not increase the risk of preterm birth. Women who want to concieve and need to be treated agressively should be informed about preterm birth risk. Pregnancy must be closely monitored with cervical length measurements.

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