Effects of loop electrosurgical excision procedure or cold knife conization on pregnancy outcomes

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Summary

Purpose: To explore the effects of cervical loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) on pregnancy outcomes. *Materials and Methods:* Patients with cervical intraepithelial neoplasia (CIN) who wanted to become pregnant and received LEEP or CKC were considered as the treatment groups. Women who wanted to become pregnant and only underwent colposcopic biopsy without any treatments were considered as the control group. The pregnancy outcomes were observed and compared in the three groups. *Results:* Premature delivery rate was higher ($p = 0.048$) in the CKC group (14 / 36, 38.88%) than in control group (14 / 68, 20.5%) with a odds ratio (OR) of 2.455 (1.007 - 5.985); and premature delivery was related to cone depth, OR was significantly increased when the cone depth was more than 15 mm. There was no significant difference in premature delivery between LEEP (10 / 48, 20.83%) and the control groups. The average gestational weeks were shorter ($p = 0.049$) in the CKC group (36.9 ± 2.4) than in the control group (37.8 ± 2.6), but similar in LEEP (38.1 ± 2.4) and control groups. There were no significant differences in cesarean sections between the three groups. The ratio of neonatal birth weight less than 2,500 g was significantly higher ($p = 0.005$) in the CKC group (15/36) than in the control group (10/68), but similar in the LEEP and control groups. *Conclusion:* Compared with CKC, LEEP is relatively safe. LEEP should be a priority in the treatment of patients with CIN who want to become pregnant.

Key words: Conization of cervix; Cervical loop electrosurgical excision procedure; Cervical cold knife conization; Cervical intraepithelial neoplasia; Pregnancy outcomes.

Introduction

Cervical intraepithelial neoplasia (CIN) is a group of pre-cancerous lesions closely related to invasive cervical cancer. In recent years, with the development of cervical screening technology, many patients with CIN have been identified in time and most of these patients are at a childbearing age and want to become pregnant. At present, loop electrosurgical excision procedure (LEEP) and cold knife (CKC) conization are commonly used in the treatment of CIN. A great deal of attention has been paid to the effects of surgical procedures on pregnancy outcomes. There have been different reports regarding the effects of cervical conization on pregnancy outcomes. Most studies from China have described that LEEP and CKC have no adverse effects on pregnancy outcomes, but these studies are retrospective analyses with small-scale cases and without controls [1, 2]. Foreign large-scale, multi-centric case-control analyses and meta-analyses have indicated that LEEP and CKC have certain adverse effects on pregnancy outcomes [3-5], however, the latter have not been compared between LEEP and CKC. In this study, a contract analysis of pregnancy outcomes was performed in 84 patients who became pregnant after LEEP (48 patients) or CKC (36 patients) and 68 women who became pregnant after only colposcopic biopsy between January 2005 and January 2009 in this Hospital.

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Materials and Methods

All study methods were approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All the subjects enrolled into the study gave written formal consent to participate.

The patients who were diagnosed with CIN by colposcopic biopsy and postoperative pathology, who underwent LEEP or CKC, and who wanted to become pregnant between January 2005 and January 2009 were enrolled in this Hospital study. All patients had no histories of infertility and recurrent miscarriage, no evidence of premature delivery, and no smoking habits. They were followed for two years. There were 48 patients who became pregnant after LEEP with a mean age of 29.8 ± 5.1 years (range 20 - 39). Of the 48 patients, 12 had CIN I, 23 had CIN II, and 13 had CIN III. There were 36 patients who became pregnant after CKC with a mean age of 31.8 ± 3.8 years (range 22 - 38). Of the 36 patients, 11 had CIN II and 25 had CIN III. At the corresponding time period, 68 women aged 31.0 ± 4.0 years (range 21 - 39) who became pregnant after exclusion of CIN II or above CIN II by colposcopic biopsy and did not receive any surgical procedures, served as the control group. These women also had no histories of infertility and recurrent miscarriage, no evidence of premature delivery, and no smoking habits. They were followed for two years.

LEEP or CKC was performed by the same three surgical experts three to seven days after menstruation. The extent of cervical lesions was observed with compound iodine solution. Circumcision or conization was performed from 2 - 5 mm outside the iodine-unstained extent with an excision depth of 6 - 22 mm. The excisional tissue was marked for localization and the cone height was recorded, followed by pathological examination. Electric coagulation or transfixion was used to stop bleeding on the postoperative wound surface. The vagina was filled with gauze which was removed 24 hours later. Antibiotics were

routinely used to prevent infection. If the endovaginal examination was normal at three to six months postoperatively, the patients were permitted to consider pregnancy. The time, status, and outcomes of pregnancy were recorded. In the control group, the time, status, and outcomes of pregnancy after colposcopic biopsy were also recorded. The subjects who had postoperative infertility, early pregnancy abortion, ectopic pregnancy, multiple-time conization or positive incisal edge were excluded from this study.

Statistical treatment was performed with the SPSS 17.0 software. The chi-squared (χ^2) test was used in numeration data. Logistic regression analysis was used in premature delivery-related factor analysis.

Results

There were no statistical differences between the treatment groups and control group with regards to age, gravidity, and premature delivery-related complications including placenta previa, pre-eclampsia, pregnancy associated with diabetes, and bigeminal pregnancy (Table 1).

In the two treatment groups, there was no abortion during the second trimester. In the LEEP group, premature delivery occurred in ten patients with a premature delivery rate of 20.83%. Of the ten patients, four had preterm premature rupture of the membrane (PPROM), and two had premature delivery before the 34th gestational week. Term-delivery occurred in 38 patients in the LEEP group. In the 38 patients, the gestational week was ≥ 37 weeks and < 38 weeks in ten patients, ≥ 38 weeks and < 39 weeks in eight patients, ≥ 39 weeks and < 40 weeks in ten patients, and ≥ 40 weeks and < 42 weeks in ten patients. No post-term pregnancy occurred and the average gestational week was (38.1 ± 2.4) weeks in LEEP group. In the CKC group, premature delivery occurred in 14 patients with a premature delivery rate of 38.88%. Of the 14 patients, five had PPROM, and three had premature delivery before the 34th gestational week. Term-delivery occurred in the 22 patients in the CKC group. In 22 patients the gestational week was ≥ 37 weeks and < 38 weeks in six patients, ≥ 38 weeks and < 39 weeks in eight patients, ≥ 39 weeks and < 40 weeks in six patients, and ≥ 40 weeks and < 42 weeks in two patients. No post-term pregnancy occurred and the average gestational week was 36.9 ± 2.4 weeks in the CKC group. In the control group, premature delivery occurred in 14 women with a premature delivery rate of 20.59%. Of the 14 women, six had PPROM and one of the six PPROM occurred during the second trimester, and three had premature delivery before the 34th gestational week. Term-delivery occurred in 54 women in the control group. In 54 women, the gestational week was ≥ 37 weeks and < 38 weeks in 13 patients, ≥ 38 weeks and < 39 weeks in 14 patients, ≥ 39 weeks and < 40 weeks in 16 patients, and ≥ 40 weeks and < 42 weeks in 11 patients. No post-term pregnancy occurred and the average gestational week was (37.8 ± 2.6) weeks in the control group. The results are shown in Figure 1 and in Table 2. The premature delivery rate was higher in the CKC group than in the control group ($p = 0.048$) with a odds ratio (OR) of 2.455 (1.007 - 5.985). The average gestational week was lower in the CKC group than in the control group ($p = 0.049$).

The constituent ratios of the gestational week in LEEP, CKC, and control groups are shown in Figure 1. It can be seen from Figure 1 that the constituent ratios of gestational week are similar in the LEEP and control groups; but less than 37 gestational weeks was significantly greater ($p < 0.05$) in the CKC group (14/36) than in the control group (14/68), and 40-42 gestational weeks was less in CKC group (2/36) than in the control group (11/68) without statistical significance ($p = 0.211$).

Premature delivery-related factors including cone depth, cone area, and lesion severity were analyzed. Premature delivery was strongly related to cone depth (Table 3).

Further analysis indicated that less than 10 mm cone depth scarcely increased the risk of premature delivery; a 15 mm cone depth had an OR of 1.259 and more than 15 mm cone depth markedly increased OR (Figure 2).

Table 1. — *Comparison of the general data between treatment groups and control group*.

	LEEP group n = 48	CKC group n = 36	Control group n = 68	Test statistics and p values
Age (years)	29.8 ± 5.1	31.8 ± 3.8	31.0 ± 4.0	$\chi^2 = 0.651$, $p < 0.862$
Primiparity	36	26	48	$\chi^2 = 0.276$, $p < 0.871$
Complications	9	8	14	$\chi^2 = 0.156$, $p < 0.925$
Placenta previa	2	2	4	
Pre-eclampsia	3	2	4	
Diabetes	2	2	3	
Bigeminal pregnancy	2	2	3	

Table 3. — *Logistic analysis of premature delivery-related factors*.

	B	S.E.	Wald	df	Sig.	Exp (B)
CIN severity			5.098	2	0.078	
CIN (I)	- 2.861	1.427	4.019	1	0.045	0.057
CIN (II)	- 1.048	0.826	2.904	1	0.088	0.245
Excision depth	0.682	0.163	17.604	1	0.000*	1.979
Excision area	0.929	0.780	1.420	1	0.233	0.549

B = coefficient; S.E. = standard error; Wald = Chi-square value; df = degree of freedom; Sig. = p value; Exp (B) = OR value. * indicates statistical significance.

Table 2. — *Gestational weeks and hazard ratios in each group*.

Gestational weeks	LEEP group N=48	CKC group n = 36	Control group n = 68	OR values 95% CI LEEP group	CKC group
< 37 weeks	10 (20.83%)	14 (38.89%)*	14 (20.58%)	1.015 (0.408 ~ 2.525)	2.455 (1.007 ~ 5.985)
< 34 weeks	2 (4.16%)	3 (8.57%)	4 (5.88%)	0.696 (0.122 ~ 3.960)	1.455 (0.307 ~ 6.886)
PPROM	4 (8.33%)	5 (13.89%)	6 (8.82%)	0.939 (0.250 ~ 3.527)	1.667 (0.472 ~ 5.892)

* indicates $p < 0.05$ compared with the control group. PPROM: preterm premature rupture of membrane.

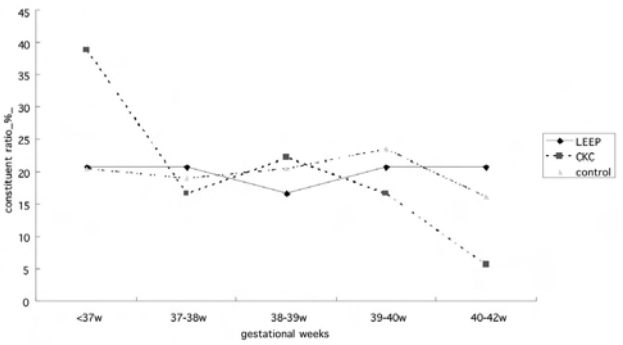

Figure 1. — The constituent ratios of gestational weeks in LEEP, CKC, and control groups.

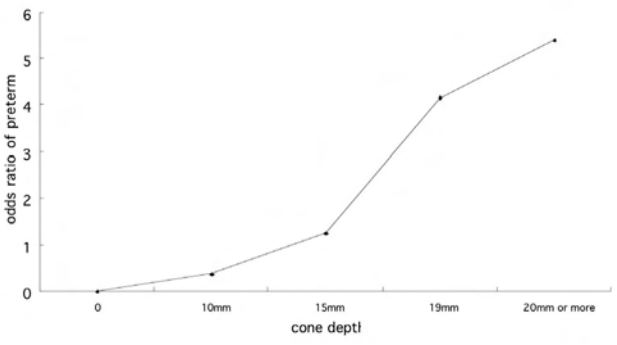

Figure 2. — Relation between cone depth and odds ratio of premature delivery.

In 48 patients of the LEEP group, 20 experienced vaginal delivery with normal birth process and without precipitate delivery and prolonged labour and 28 patients underwent cesarean section with indications including social factors in eight patients, intra-uterine asphyxia in two patients, breech position in two patients, cephalopelvic disproportion in one patient, gestation period complications in nine patients, and no per vagina trial labor after LEEP in six patients. In the 36 patients of the CKC group, 16 patients experienced vaginal delivery with normal birth process and without precipitate delivery and prolonged labor and 20 patients underwent cesarean section with indications including social factors in five patients, intra-uterine asphyxia in two patients, breech position in one patient, prolonged active phase in one patient, gestation period complications in six patients, and no per vagina trial labor after LEEP in five patients. In 68 women of the control group, 29 of them experienced vaginal delivery with normal birth process and without precipitated delivery and prolonged labor; 39 women underwent cesarean section with indications including social factors in 13 women, intra-uterine asphyxia in six women, breech position in two woman, horizontal position in one woman, cephalopelvic disproportion in two women, oligohydramnios in three women, persistent occipitoposterior position in one woman, and gestational complications in 11 women. There were no significant differences in the cesarean section rate between the three groups ($\chi^2 = 0.065$, $p = 0.968$).

In the LEEP group, the average birth weight was 3,350 g (range 1,450 - 3,850), the birth weight was less than 2,500 g in nine neonates, there was no macrosomia, and one minute Apgar score was more than 7 in all neonates. In the CKC group, the average birth weight was 2,950 g (range 1,050 - 3,800), the birth weight was less than 2,500 g in 15 neonates, there was no macrosomia, one minute Apgar score was less than 7 in two neonates, and in other neonates one minute Apgar score was more than 7. In the control group, the average birth weight was 3,450 g (range 650 - 4,200), the birth weight was less than 2,500 g in ten neonates, three neonates were macrosomia, a mid-trimester neonate died, one minute Apgar score was less than 7 in three neonates, and in other neonates one minute Apgar score was more than 7. The neonates with a birth weight of less than 2,500 g was significantly greater in the CKC group than in the control group ($\chi^2 = 7.952$, $p = 0.005$).

Discussion

CIN has become a common disease in women of childbearing age. Conization is often used to treat CIN and it mainly includes LEEP and CKC. Whether conization has adverse effects on pregnancy has been a concern of patients and doctors. With LEEP, high-frequency electric waves allow tissue to produce impedance, then oscillation produces high temperatures which leads to intracellular water evaporation, followed by cell rupture and tissue separation. LEEP is a common and effective method for treatment of CIN because it has some advantages including little radiation on surrounding tissue, little bleeding, simple procedures, minimal invasion, shorter operative time, and low cost. With CKC, cervical lesions were removed with a cryo-scalpel, the excisional extent and depth may be controlled, and there is no electrical damage on surrounding tissue. Connective tissue, smooth muscle, blood vessels, and elastic fibers comprise the cervix which plays an important role in pregnancy and delivery. Excessive tissue excision may lead to loose cervix or cervical incompetence which is likely to result in higher premature birth and abortion. Partial removal of cervical tissue may affect its function, especially on subsequent pregnancy [6]. In the present study, pregnant women who underwent colposcopic biopsy but did not receive any treatment, were considered the control to observe the effects of LEEP or CKC on pregnancy outcomes. The results in this study indicated that compared with the control group, premature delivery rate was significantly increased with OR of 2.455 (1.007 - 5.985), gestational week was significantly shorter, and neonates weighing less than 2,500 g were significantly increased; but there were no significant differences in uterine-incision delivery rate and neonatal asphyxia in the CKC group. A Chinese study has reported that CKC has no adverse effects on pregnancy [3]. This may be related to case number and inclusion criteria. The results in the present study are similar to those of most foreign studies

[6] regarding that CKC has adverse effects on pregnancy, such as increased premature birth risk and the rate of low birth weight infants. However, this study indicated that LEEP results were different from CKC. Compared with the control group, LEEP had no adverse effects on postoperative pregnancy. This may be related to less number of cases. Chinese studies in essence indicate that LEEP has no adverse effects on postoperative pregnancy [7], which is different from foreign studies [8-10]. Is this phenomenon perhaps related to race? The results suggest that LEEP may be safer than CKC and patients with CIN who desire to become pregnant should undergo LEEP as much as possible instead of CKC.

The authors further analyzed premature delivery-related factors after conization. Among lesion severity, and cone depth and area, premature delivery was strongly related to cone depth, which is consistent with the results reported by Noehr *et al*. [3, 6]. It was also found that less than 10 mm cone depth scarcely increased the risk of premature delivery; a 15 mm cone depth had a OR of 1.259, and more than 15 mm cone depth markedly increased OR. Grane [11] has described that less than 10 mm cone depth has no marked effects on pregnancy. Houlard *et al*. [12] have reported that with LEEP, when the excision depth is more than 20 mm, the incidence of postoperative cervical stenosis is significantly increased. Sadler *et al*. [13] have found that when the cone depth is more than or equal to 17 mm, the incidence of PROM is more than three times the incidence in the control group. However, there is also a report that cone depth is not related to premature delivery [14]. The results in the present study suggest that under the condition to ensure adequate removal of the lesion, the cone depth should be controlled within 15 mm, which may help to decrease the risk of premature delivery.

For LEEP or CKC, their effects on pregnancy also including postoperative cervical stenosis, infertility caused by postoperative pelvic infection, and ectopic pregnancy, remain to be further studied.

In summary, this study suggests that CKC may have certain adverse effects on postoperative pregnancy and pregnancy after LEEP is relatively safe; under the condition to ensure adequate removal of the lesion, the cone depth should be controlled within 15 mm, which may help to decrease the risk of premature delivery. The limitations of this study include less case number, shorter follow-up time, and more pregnancy-related factors. Large-scale studies will be performed in the future.

References

[1] De-ying Qian, Ren-hai Zeng, Dan-hua Hong, Jian-min Cen: "Pregnancy and delivery outcomes after loop electrosurgical excision procedure of cervical intraepithelial neoplasia". *Chin. J. Obstet. Gynecol.,* 2004, *39*, 326.

[2] Hao-jie He, Ling-ya Pan, Hui-fang Huang, Jing-he Lang: "Clinical analysis of the effect of cervical conization on fertility and pregnancy outcomes". *Chin. J. Obstet. Gynecol.,* 2007, *42*, 515.

[3] Noehr B., Jensen A., Frederiksen K., Tabor A., Kjaer S.K.: "Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous". *Preterm Delivery Obstet. Gynecol*., 2009, *114,* 1232.

[4] Arbyn M., Kyrgiou M., Simoens C., Raifu A.O., Koliopoulos G., Martin-Hirsch P. *et al*.: "Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis". *BMJ,* 2008, *337,* a1284.

[5] Sjøborg K.D., Vistad I., Myhr S.S., Svenningsen R., Herzog C., Kloster-Jensen A. *et al*.: "Pregnancy outcome after cervical cone excision: a case-control study". *Acta Obstet. Gynecol. Scand*., 2007, *86*, 423.

[6] Kyrgiou M., Koliopoulos G., Martin-Hirsch P., Arbyn M., Prendiville W., Paraskevaidis E.: "Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis". *Lancet,* 2006, *367,* 489.

[7] Xue-jie Zhu, Yun-fei Zheng, Xue-qiong Zhu, Jia-na Mao, Bo-zhong Xu: "The effect of loop electrosurgical excision on pregnancy during and mode of delivery". *J. Pract. Obstet. Gynecol.,* 2008, *24,* 109.

[8] Nφhr B., Tabor A., Frederiksen K., Kjaer S.K.: "Loop electrosurgical excision of the cervix and the subsequent risk of preterm delivery". *Acta Obstet. Gynecol. Scand*., 2007, *86*, 596.

[9] Samson S.L., Bentley J.R., Fahey T.J., Mckay D.J., Gill G.H.: "The effect of loop electrosurgical excisional procedure on future pregnancy outcome". *Obstet. Gynecol*., 2005, *105*, 325.

[10] Jakobsson M., Gissler M., Paavonen J., Tapper A.M.: "Loop electrosurgical excision procedure and the risk for preterm birth". *Obstet. Gynecol.,* 2009, *114*, 504.

[11] Crane J.M.: "Pregnancy outcome after loop electro surgical excision procedure: a systematic review". *Obstet. Gynecol.,* 2003, *102,* 1058.

[12] Houlard S., Perrotin F., Fourquet F., Marret H., Lansac J., Body G.: "Risk factors for cervical stenosis after laser cone biopsy". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 2002, *104,* 144.

[13] Sadler L., Saftlas A., Wang W., Exeter M., Whittaker J., McCowan L.: "Treatment for cervical intraepithelial neoplasia and risk of preterm delivery". *JAMA*, 2004, *291,* 2100.

[14] Mathevet P., Chemali E., Roy M., Dargent D.: "Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 2003, *106*, 214.

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