General Section

Pregnancy outcome after treatment of cervical intraepithelial neoplasia by the loop electrosurgical excision procedure and cold knife conization

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Summary

Purpose of investigation: The aim of this study was to evaluate the effect of LEEP and cold-knife conization on the outcome of subsequent pregnancy in a tertiary public hospital. *Methods:* One hundred and ninety-nine patients met the inclusion criteria (age between 18 and 45 years old). Cold-knife conization, LEEP, and both (conization and LEEP) were performed in 102 (51.3%), 95 (47.7%) and two (1%) women, respectively. Average ages were respectively, 33 ± 7.3; 25 ± 6.73 and 30 ± 2.8. *Results:* Pregnancies occurred 2.6 and 4.8 years after LEEP and conization, respectively. Miscarriages and preterm pregnancies were more frequent in conization cases versus LEEP, 26% and 5.2%, 23% and 5.5%, respectively. *Conclusion:* If patients express a desire for pregnancy, LEEP should be the procedure of choice.

Key words: : Cervical intraepithelial neoplasia; Conization; Loop electrosurgical excision procedure; Pregnancy, outcome.

Introduction

The most common treatment of cervical intraepithelial neoplasia is the loop electrosurgical excision procedure (LEEP) and cold-knife conization. LEEP requires local anesthesia, whereas cold-knife conization requires hospitalization and general or spinal anesthesia [1-2]. Hemorrhage is a main intra- and early postoperative complication, and cervical stenosis is more frequent in cold-knife conization than LEEP [1-3].

Today pregnancy has become a late event in many women's lives. Thus, a desire for pregnancy after CIN treatment is a relatively common solicitation. In terms of pregnancy outcome, cryosurgery and laser have been found to be safer procedures, but they destroy the tissue making it unavailable for further histological examination. This is important for treatment because an invasive lesion is not diagnostic, and an important marker of recurrence, CIN in surgical margins, is not evaluated. Thus, LEEP and cold-knife conization are illegible treatment for CIN.

Previous studies on pregnancy outcome after treatment of CIN have shown conflicting results. Cold-knife conization [4, 5], and laser [6, 7] are associated with preterm delivery and low birthweight. The effect of LEEP in pregnancy results also showed discordant data [8-12]. Nonetheless, one study affirms that diagnosis of precancerous changes in the cervix, regardless of the treatment, was associated with increased risk of preterm birth and that the preferential use of ablative treatment should be given [12].

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Contradictory results on pregnancy outcome have been described after LEEP and cold-knife conization. The aim of this study was to evaluate the effect of LEEP and cold-knife conization on the outcome of subsequent pregnancy in a tertiary public hospital.

Patients and Methods

Patients

A retrospective study was conducted on surgical specimens of women submitted to LEEP and cold-knife conization due to CIN, from 1 January 1981 to 31 December 2004, in the Gynecologic and Obstetrics outpatient service of our Institution (Research Institute of Oncology - IPON/UFTM). The project was approved by the Research Ethics Committee of UFTM.

A total of 338 women were referred because of the presence of CIN I-III in a biopsy specimen. One hundred and ninety-nine patients met the inclusion criteria (age between 18 and 45 years old). Patients submitted to hysterectomy or proposed bilateral tubal ligature for sterilization were excluded. All patients were previously submitted to both triple collection of material for cytological examination and colposcopically directed biopsies. Cold-knife conization, LEEP, and both (conization and LEEP) were performed in 102 (51.3%), 95 (47.7%) and two (1%) women, respectively. Average age was respectively, 33 ± 7.3, 25 ± 6.7, and 30 ± 2.8.

LEEP, conization and hysterectomy management, and follow-up criteria for LEEP, conization and hysterectomy were performed by residents supervised by board-certified attending obstetrician-gynecologists. LEEP was performed in women with the LEEP WEM machine, using a power setting of 50 W. After application of Lugol iodine, cervical anesthesia was performed with 2% lidocaine containing a solution of 1:1000 epinephrine (4-6 ml, approximately 1 ml per cervical quadrant). Loop size was 10 mm x 10 mm, and current was blended to cut and coagulate. After the procedure, all cases underwent roller ball coagulation (50 W) with the aim of hemostasis. The main

criteria for LEEP in the majority of cases were small lesions, visible squamocolumnar junction (SCJ), and desire for future pregnancy.

Cold-knife conization was performed on patients in the operating room after spinal anesthesia. After Schiller's test, a surgical margin of 2 mm was done by bistury and the cone specimen was extipated. A hysterometer was placed in the endocervix and at least 1 cm of endocervix from the internal cavity was left. The sturmdorf procedure was performed.

Follow-up criteria after the above procedures consisted of cytology and colposcopy each six months for five years, and after annually. The minimum time of follow-up was 16 months. The presence of CIN I-III confirmed by colposcopically directed biopsies was considered as recurrence. The median time of patient follow-up for diagnosis of pregnancy ranged from one to 23 years (median 10 years).

Cytohistological techniques and colposcopy

The cytological material was processed by Papanicolaou's technique and reading was performed by trained cytologists. Biopsies were guided by colposcopic exams carried out by residents under teaching supervision, and the material was fixed in 4% formaldehyde. Colposcopy was considered unsatisfactory when the SCJ was not visible. There was no standard number of histological cuts for each biopsy, varying from 1-10 successive cuts as judged necessary by the pathologist for each case.

Cone biopsy specimens were marked with sewing thread at the 12 o'clock position. Hysterectomy and cone biopsy specimens were fixed in 4% formaldehyde. The cone biopsy or uterine cervix were cut into pieces of about 1 mm in thickness, perpendicular to the surface of the endocervical mucosa and the material was processed for inclusion in paraffin. One histological cut of each block was stained with hematoxylin-eosin. Additional cuts were made when necessary.

Statistical analysis

Comparisons between groups were made with the chi-square test with Yates' correction or the Fisher's exact test, depending on the conditions of validity of the chi-square test. The differences were considered significant with $p < 0.05$.

Results

One hundred and ninety-nine patients met inclusion criteria and were evaluated (102, 95, and two were submitted to cold-knife conization, LEEP, and LEEP and cold knife conization, respectively). Histological results of CIN I, II and III were found in one, 25, and 76 cases of the LEEP procedure; 0, 2, and 93 in the cold-knife conization. The two cases of CIN III in patients undergoing LEEP and conization, first had CIN I with recurrence after LEEP.

Table 1 shows the frequency of full-term pregnancy and miscarriages in patients who underwent conization and LEEP. Miscarriages were most frequent in conization cases. Preterm pregnancy was more frequent in conization cases (Table 2). Pregnancies occurred 3.5 ± 3.09 and 3 ± 3.9 years after LEEP and conization, respectively.

Discussion

This study was conducted in a tertiary service of gynecology and obstetrics that examines pregnancy outcomes following histological diagnoses and treatment for CIN, thus, the same group of physicians are involved. The aim of this study was to compare pregnancy outcome after conization and/or LEEP for CIN in our service where a standard treatment is utilized and the median age of patients is similar. The results showed that miscarriages occurred more frequently in patients with previous conization than in patients who underwent LEEP.

Table 1. — *Total number of full-tem pregnancies and miscarriages in patients submitted to conization and/or LEEP.*

	Full term pregnancy		Miscarried		
	n	%	n	%	
LEEP (n = 95)	18	18.9	1	1	(5.2)
Conization (n = 102)	17	16.6	6	5.8	(26)
LEEP and conization (n = 2)	1	50	0	0	(0)

( ): % in relation to number of pregnancies. X^2 test: p = 0.0240.

Table 2. — *Distribution of preterm birth and low birthweight in patients undergoing conization and/or LEEP.*

	Preterm pregnancy		Low birth-weight	
	n	%	n	%
LEEP (n = 18)	1	5.5	2	11.1
Conization (n = 17)	4	23.5	2	11.7
LEEP and conization (n = 1)	–	–	–	–

X^2 test: p = not significant.

Preterm birth was more frequently found in patients treated for CIN (standardized prevalence ratio 2.0, 95% CI 1.8-2.3) but also in untreated patients (standardized prevalence ratio 1.5, 95% CI 1.4-1.7) than the general population, suggesting that the treatment is not the only factor that plays a role in increased risks for preterm patients [12]. In other studies on untreated patients, preterm birth was reported in 10.7 to 12.2% [10], but none has been compared with the general population. In our series, a 13.8% prevalence was found (5 out of 36 pregnancies > 20 weeks).

Our results showed that preterm birth is a more frequent event in patients submitted to conization than LEEP (23.5 vs 5.5%). Inconsistent findings on the association between conization and preterm birth have been shown in previous studies. A retrospective analysis showed that after conization women had an increased odds ratio of preterm birth after adjusting for maternal smoking, race, parity, marital status and history of induced terminations (OR 1.6, 95% CI 1.2-2.0) [13].

Conization is the most cumulative experience in the treatment of CIN, thus the possible data on its influence in fertility is insufficient for a definitive conclusion [14]. Delivery before 37 weeks and a birthweight lower than 2,500 g had a relative risk, respectively, of 3.4 and 2.5 compared to a control group [15]. An increased rate of induced abortion and a significantly higher risk of preterm delivery in a group that had undergone conization (OR 4.13, 95% CI 2.53-6.75) were found in another study [5, 16]. Cone height is an important point to discuss. One study showed that a cone height of at least 10 mm is an independent risk factor for the duration of pregnancy, and for the occurrence of preterm delivery in

a subsequent pregnancy [16]. In our study, we performed conization with a hysterometer and at least l cm of endocervix was left. However with this practice miscarriages were more common than for the LEEP procedure.

Although the number of LEEP being performed has increased, the data regarding pregnancy outcome is more scant than for conization data [14]. A study in Norway demonstrated that LEEP in women with CIN did not significantly increase the risk of preterm birth or low birthweight in subsequent pregnancies in comparison with controls, nevertheless, the size of the electrosurgical loop was relatively large [11]. Apparently, the maximum diameter of loop that will not affect pregnancy outcome is 18 mm [11, 17], but a loop diameter of 25 mm is correlated with increased risk of preterm birth and low birthweight [11, 16, 18]. We used a loop of 1 x 1 cm. The small diameters of loop that we utilized explain the low finding of miscarriages in comparison with conization. Nevertheless, when we used this type of loop, more than two fragments of cone specimen were removed, which can be a problem for accurate histological studies, but the fragments were small and could explain the low rate of miscarriages in our results.

One review showed all excisional procedures to treat CIN present similar pregnancy-related morbidity without apparent neonatal morbidity [19]. Another study demonstrated that the diagnosis of precancerous changes in the cervix (regardless of the treatment) was associated with an increased risk of preterm birth. The results showed that both treated and untreated women were at a significantly increased risk for preterm birth compared with those in the general population: treated - standardized prevalence ratio (SPR) 2.0, 95% CI 1.8-2.3 and untreated - SPR 1.5, 95% CI 1.4-1.7. Within the cohort, the treated women were significantly more likely to give birth preterm (adjusted OR 1.23, 95% CI 1.01-1.51). Cone biopsy, LEEP and diathermy were associated with preterm birth. After adjusting for possible confounding factors, only diathermy remained significant (adjusted OR 1.72, 95% CI 1.36-2.17). Women treated using laser ablation were not at an increased risk for preterm birth (adjusted OR 1.1, 95% CI 0.8-1.4), but consideration should be given to the preferential use of ablative treatments [12].

Conization and LEEP are safe procedures for CIN treatment. Histological study of the specimen is important to exclude invasion [1, 2]. Expectant observation is conducted in pregnant women with CIN, but a surgical procedure is indicated in non pregnant women. In our point of view, histological study is important and the procedures must be preferable to others that do not permit histological analysis. Taken together, our results showed that the frequency of miscarriages is minor in women who undergo LEEP. Thus, if patients express a desire for pregnancy, LEEP should be the procedure of choice.

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