Loop electrosurgical excision procedure and risk of miscarriage

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Objective: To evaluate the risk of miscarriage in the subsequent pregnancy after a loop electrosurgical excision procedure (LEEP), also considering time elapsed from LEEP to pregnancy.
Design: Multicenter, retrospective cohort study.
Setting: Tertiary care university hospitals.
Patient(s): Women who had undergone LEEP from January 2000 to December 2011. Women with histologic assessment of low-grade cervical dysplasia, not requiring subsequent surgical treatment, constituted the control group.
Intervention(s): None.
Main Outcome Measure(s): The first pregnancy after the procedure was evaluated, and only women with singleton spontaneous pregnancies were considered. Women with time intervals of <12 months and women with intervals of ≥ 12 months or more from LEEP to pregnancy were then compared, to identify adjusted odds ratios for miscarriage.
Result(s): In women previously treated with LEEP, a total of 116 cases of miscarriage (18.1%) was reported. The mean time interval from LEEP to pregnancy for women with miscarriage compared with women without miscarriage was significantly shorter (25.1 ± 11.7 months vs. 30.1 ± 13.3 months). A higher rate of miscarriage in women with a LEEP-to-pregnancy interval of <12 months compared with controls emerged (28.2% vs. 13.4%; adjusted odds ratio 2.60, 95% confidence interval 1.57–4.3). No significant difference in the rate of miscarriage in women with a LEEP-to-pregnancy interval of ≥ 12 months compared with controls emerged.
Conclusion(s): Women with a time interval from LEEP to pregnancy of <12 months are at increased risk for miscarriage. (Fertil Steril® 2015;103:1043–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Loop electrosurgical excision procedure, LEEP, miscarriage

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Cervical intraepithelial neoplasia (CIN) is a potential precancerous lesion in the cervical epithelium and, although it can occur at any age, the peak incidence is in women aged 25–35 years (1). Even considering the growing incidence of human papillomavirus–related lesions in reproductive-age women, cervical excision procedures for diagnosis and treatment of cervical dysplasia are becoming increasingly common (2). Furthermore, in the last decades we have seen a continuous trend of delayed childbearing, which results in an increased proportion of women diagnosed with CIN and subsequently treated before their first pregnancy (3). A variety of procedures have been used to treat CIN, including cold-knife conization, cryotherapy, laser, and loop electrosurgical excision procedure (LEEP). This technique was introduced in 1989 and is the most common cervical excision procedure currently used worldwide (4–6). The LEEP can be performed under local anaesthesia on an outpatient basis, resulting in a relatively inexpensive surgery, easy and quick to perform, and the tissue sample can be effectively used for histologic evaluation (7–9). However, the surgical removal of a portion of the cervix theoretically leaves future pregnancies at higher risk for complications related to cervical integrity (10, 11); thus, women with a history of excisional cervical surgery are generally considered to be at increased risk of adverse obstetric events, such as preterm birth. Virtually, the structural

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changes of the cervix, and the process of inflammation and subsequent healing and remodelling of the cervical tissue after the excision procedure, could determine an increased risk of miscarriage in these women.

Although the effect of cervical excision procedures on the risk of preterm birth has been investigated to an extent in the literature, data on the effect of LEEP on the risk of miscarriage are lacking.

The aim of the present study was to evaluate whether LEEP, performed under colposcopic guidance, could determine an increased risk of miscarriage in the subsequent pregnancy, also considering the time elapsed from LEEP to pregnancy.

MATERIALS AND METHODS

This was a multicenter, retrospective cohort study performed at the Gynecologic Section, Woman's Health Sciences Department, Polytechnic University of Marche, Hospital G. Salesi, Ancona, Italy and the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda–Ospedale Maggiore Policlinico, University of Milan, Italy. Women who had undergone LEEP in one of these centers between January 2000 and December 2011 and who subsequently became pregnant were included in the analysis. The first pregnancy after LEEP was analysed, and only women with singleton spontaneous pregnancies were considered. Women who underwent LEEP or any other cervical excisional or ablative procedure before pregnancy at other institutions and women who underwent two or more LEEPs before pregnancy were excluded. Multiple pregnancies and pregnancies obtained with IVF techniques were also excluded.

Women who had undergone colposcopy at our institutions for atypical squamous cells of undetermined significance on Papanicolaou smear during the study period (with histologic assessment of low-grade cervical dysplasia not requiring subsequent excisional or ablative procedure), fulfilling the study inclusion criteria (singleton spontaneous pregnancy after the colposcopy and no previous cervical excisional or ablative procedures) were considered as the "control group."

Women with a known HIV infection were not included in the analysis. Moreover, all women with histologic diagnosis of cervical dysplasia (both in the study cohort and in the control group), and with unknown HIV status, were routinely screened for HIV infection.

Patients were identified by searching our clinical databases, and the medical records of women fulfilling the study inclusion criteria were retrospectively analyzed in an observational cohort study (II-2 Canadian Task Force Classification of Study Design). Data obtained included information regarding pertinent medical and surgical history, sociodemographic characteristics, and the outcome of the first pregnancy after the procedure. Trained obstetric research nurses conducted structured, closed-ended telephone interviews to complete demographic and obstetric data unavailable in the medical records.

All the LEEPs were performed within the Colposcopy Units in an outpatient setting under local anaesthesia. Diathermy loops were chosen according to the area of cervical tissue to remove and location of the cervical transformation zone. All excisions were performed under strict colposcopic guidance, using 1.5–2.0-cm rounded loops. Information on loop size, volume, and length of the cone specimen were recorded; in particular the longitudinal diameter (a), transverse diameter (b), and length (c) of the cone specimen were recorded. The specimen obtained after LEEP is much more similar to a triaxial hemiellipsoid rather than a circular cone, because the parameters a, b, and c are often unequal, so the volume of the surgical specimen obtained after LEEP was calculated using the hemiellipsoid formula as described by Phadnis et al. [12]: $1/2 \times 4/3 \times \pi \times a/2 \times b/2 \times c$ (because the length of the specimen is a radius of the ellipsoid rather than a diameter).

Miscarriage was defined as a spontaneous pregnancy loss after ultrasound identification of pregnancy (with evidence of embryonic cardiac activity) and before 24 weeks of pregnancy. Miscarriage was also classified as early (before 12 weeks of gestation) or late (12–24 weeks of gestation) [13]. Induced abortions were excluded.

Patients were then subdivided into two groups according to time elapsed from LEEP to pregnancy (<12 months and ≥ 12 months). The 12-month time interval was chosen on the basis of results from previous studies [14, 15]. To identify the time interval from LEEP to pregnancy, the last menstrual period of each woman was identified as the starting point of the pregnancy itself.

Statistical analysis was performed using IBM SPSS version 22.0. The Student t test, χ^2 testing, Fisher exact test, and analysis of variance were used for categorical or continuous variables, as appropriate. Probability $<.05$ was considered as statistically significant. Associations were expressed with 95% confidence intervals (CIs). Multivariable logistic regression was used to adjust for confounding factors identified through the results of the univariable and stratified analyses.

The approval of the local ethics committee of each center was obtained to collect data routinely.

RESULTS

During the study period, a total of 1,480 reproductive-age women were diagnosed with high-grade CIN and subsequently were treated with LEEP. Among them, 640 women (43.2%) fulfilling the study inclusion criteria had a subsequent pregnancy and were included in the analysis. The time interval from LEEP to pregnancy was <12 months for 142 women (22.2%) and ≥ 12 months for 498 women (77.8%). In the same period, 1,310 reproductive-age women had undergone colposcopy at our institutions for atypical squamous cells of undetermined significance on Papanicolaou smear. Among them, 398 women (30.4%) fulfilling the study inclusion criteria (singleton spontaneous pregnancy after the colposcopy and no previous cervical excisional or ablative procedures) had a histologic assessment of low-grade cervical dysplasia (CIN 1) not requiring a subsequent excision or ablative procedure and constituted the "control group."

To complete the collection of demographic and obstetric data unavailable in the medical records, telephone interviews