Loop electrosurgical excision procedure and risk of miscarriage

Andrea Ciavattini, M.D.,[a] Nicolò Clemente, M.D.,[a] Giovanni Delli Carpini, M.D.,[a] Chiara Gentili, M.D.,[a] Jacopo Di Giuseppe, M.D.,[a] Pamela Barbadoro, M.D.,[b] Emilia Prospero, M.D.,[b] and Carlo Antonio Liverani, M.D.[c]

[a] Gynecologic Section, Woman's Health Sciences Department, and [b] Department of Biomedical Science and Public Health, Polytechnic University of Marche, Ancona, Italy; and [c] 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, Milan, Italy

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

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/ciavattinia-loop-electrosurgical-excision-procedure-miscarriage/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

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

Received August 27, 2014; revised November 14, 2014; accepted December 11, 2014; published online January 23, 2015.
A.C. has nothing to disclose. N.C. has nothing to disclose. G.D.C. has nothing to disclose. C.G. has nothing to disclose. J.D.G. has nothing to disclose. P.B. has nothing to disclose. E.P. has nothing to disclose. C.A.L. has nothing to disclose.
Reprint requests to: Andrea Ciavattini, M.D., Gynecologic Section, Woman's Health Sciences Department, Polytechnic University of Marche, Via F. Corridoni 11, 60123 Ancona, Italy (E-mail: ciavattini.a@libero.it).

Fertility and Sterility® Vol. 103, No. 4, April 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.12.112

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

were necessary in 84 women of the study group and 63 of the control group (13.1% and 15.8%, respectively).

The baseline clinical and demographic characteristics of women who got pregnant within 12 months since LEEP were similar to those of women who got pregnant at ≥12 months and to those of women of the control group (Table 1).

A serologic test for HIV in the 12 months before the procedure was requested, and women with known HIV infection were not included in the analysis. Moreover, 100 women of the study cohort and 82 women of the control group (15.6% and 20.6%, respectively) with unknown HIV status were screened for HIV infection. None of them were HIV positive. Furthermore, only three women of the study cohort had signs or symptoms of lower genital tract infection in the 3 months before the procedure. A vaginal swab was collected in these symptomatic women, and bacterial vaginosis was detected. An appropriate therapy was performed (with subsequent negative vaginal swab) before the LEEP. None of these women had a miscarriage in the subsequent pregnancy. In the 640 women treated with LEEP and who subsequently got pregnant the overall median volume of the cervical specimen removed was 2.4 cm^3 (mean 2.2 cm^3; range 0.4–2.8 cm^3); the median length was 1.2 cm (mean 1.2 cm; range 0.4–2.8 cm). The mean volume and length of the cervical specimens of women who got pregnant within 12 months since LEEP were similar to those of women who got pregnant at ≥12 months (Table 1).

In the entire study population of women previously treated with LEEP, a total of 116 cases of miscarriage (18.1%) was reported. Specifically, 95 cases of early miscarriage and 21 cases of late miscarriage were found. Among the 21 women with late miscarriage, three cases (14.3%) were attributed to cervical insufficiency. In the 116 women with miscarriage, compared with the remaining 524 women previously treated with LEEP, no significant difference in the mean cone volume and length was found (2.1 cm^3 ± 1.6 vs. 2.3 cm^3 ± 2.0 [P=.3] and 1.2 cm ± 0.8 vs. 1.3 cm ± 1.0 [P=.3], respectively).

In the 398 women of the control group, a total of 51 cases of miscarriage (12.8%) was reported; specifically, 41 cases of early miscarriage and 10 cases of late miscarriage were found. Among the 10 women with late miscarriage, one case (10%) was attributed to cervical insufficiency.

To identify the time interval from colposcopy to pregnancy in the control group, the date of colposcopy (with bioptic assessment of low-grade cervical dysplasia) was assumed as the "starting point." The mean time from colposcopy to pregnancy was 27.7 ± 11.8 months (range, 4–50 months). The time interval from colposcopy to pregnancy was <12 months for 82 women (20.6%) and ≥12 months for 316 women (79.4%).

In the control group, no difference in the rate of miscarriage in women with a time interval of <12 months compared with women with a time interval of ≥12 months emerged (13.4% vs. 12.7%; P=1.0).

In the women previously treated with LEEP, compared with controls, an overall higher rate of miscarriage emerged (18.1% vs. 12.8%; adjusted odds ratio [OR] 1.78, 95% CI 1.24–2.95, P=.003).

The mean time from LEEP to pregnancy for the entire study cohort was 29.2 ± 13.2 months (range, 2–61 months). In women with miscarriage, the mean time interval from LEEP to pregnancy was significantly shorter compared with women without miscarriage (25.1 ± 11.7 months vs. 30.1 ± 13.3 months; P<.001). The LEEP-to-pregnancy time interval in women with early miscarriage compared with women without miscarriage was significantly shorter (24.5 ± 11.4 months vs. 30.1 ± 13.3 months; P<.001). No difference was found in the LEEP-to-pregnancy time interval for women with late miscarriage compared with women without miscarriage (27.9 ± 12.2 months vs. 30.1 ± 13.3 months; P=.5). A higher rate of miscarriage was reported in women with a LEEP-to-pregnancy interval of <12 months compared with women with a LEEP-to-pregnancy interval of ≥12 months (28.2% vs. 15.3%; OR 2.18, 95% CI 1.40–3.38, P<.001). A logistic regression adjusted for age, nulliparity, previous miscarriage, smoking, and body mass index (BMI) was performed (Table 2).

Furthermore, the rate of miscarriage was significantly higher in women with a time interval from LEEP to pregnancy of <12 months compared with women with a colposcopy-to-pregnancy time of <12 months (28.2% vs. 13.4%; adjusted OR 2.60, 95% CI 1.57–4.3, P<.001). Conversely, in women with a LEEP-to-pregnancy time interval of ≥12 months compared with women with a colposcopy-to-pregnancy time of ≥12 months, no significant difference in the rate of

TABLE 1

Baseline characteristics of the study cohort.

Characteristic	LEEP-to-pregnancy interval: <12 mo (n = 142)	LEEP-to-pregnancy interval: ≥12 mo (n = 498)	Control group (n = 398)	*P* value
Age (y)	35.5 ± 3.8	35 ± 4.9	35 ± 5.3	.4
Nulliparity	51 (35.9)	212 (42.6)	190 (47.7)	.1
Previous miscarriage	22 (15.5)	62 (12.4)	75 (18.8)	.1
Smoking	9 (6.3)	29 (5.8)	66 (16.6)	.2
BMI (kg/m^2)	23.9 ± 2.3	24.1 ± 2	24.3 ± 1.5	.2
Length of the cervical specimen (cm)	1.3 ± 0.6	1.2 ± 0.8	–	.2
Volume of the cervical specimen (cm^3)	2.1 ± 1.5	2.3 ± 1.4	–	.1

Note: Data are mean ± SD or n (%) unless otherwise specified.

Ciavattini. Risk of miscarriage after LEEP. Fertil Steril 2015.

TABLE 2

Risk of spontaneous miscarriage for women with time interval of < 12 months compared with ≥12 months from LEEP to pregnancy.

	LEEP-to-pregnancy interval				
Outcome	**< 12 mo (n = 142)**	**≥12 mo (n = 498)**	**OR (95% CI)**	**Adjusted OR (95% CI)[a]**	***P* value**
Miscarriage (<24 wk of gestation)	40 (28.2)	76 (15.3)	2.18 (1.40–3.38)	2.28 (1.36–3.56)	<.001
Early miscarriage (<12 wk of gestation)	34 (23.9)	61 (12.2)	2.26 (1.41–3.61)	2.43 (1.50–3.93)	<.001
Late miscarriage (12–24 wk of gestation)	6 (4.2)	15 (3.0)	1.42 (0.54–3.73)	1.36 (0.51–3.60)	.54

[a] Adjusted for age, nulliparity, previous spontaneous abortion, smoking, and BMI.

Ciavattini. Risk of miscarriage after LEEP. Fertil Steril 2015.

miscarriage was found (15.3% vs. 12.7%; adjusted OR 0.94, 95% CI 0.47–1.91, *P*=.87). Moreover, in women with a LEEP-to-pregnancy interval of <12 months compared with women with a colposcopy-to-pregnancy time of <12 months, the rate of early miscarriage was significantly higher (23.9% vs. 11%; *P*=.03), whereas the rate of late miscarriage was similar (4.2% vs. 1.2%; *P*=.4). In women with a LEEP-to-pregnancy interval of ≥12 months compared with women with a colposcopy-to-pregnancy time of ≥12 months, the rates of early and late miscarriage were similar (12.2% vs. 10.1% [*P*=.4] and 3.0% vs. 2.5% [*P*=.8], respectively).

In secondary analyses, women were further stratified into interval strata: <6 months from LEEP to pregnancy, 6–11 months, and 12–23 months, and they were compared with women with a LEEP-to-pregnancy interval of ≥24 months, considered as reference. A significantly higher risk for miscarriage in women with a time interval of 6–11 months emerged (Table 3).

DISCUSSION

Women with a history of excisional cervical surgery are generally considered to be at increased risk of adverse pregnancy outcomes because of the potential loss of cervical integrity due to the procedure. The depth of tissue removed with the conization seems to be an important risk factor, and the majority of the studies indicate an increased risk of adverse pregnancy outcomes, such as preterm delivery, related to the length of tissue removed (1, 11, 16–19). Moreover, considering the physiologic process of healing and remodelling of the cervix after a surgical procedure, it seems to be biologically plausible that the time elapsed from LEEP to pregnancy is another important risk factor for obstetric complications.

Previous studies analysed the correlation between the time interval from LEEP to pregnancy and pregnancy complications, with most relating to preterm delivery, with conflicting results (14, 15, 20–24). Although the effect of LEEP on risk of preterm birth has been investigated to an extent in the literature, data on the effect of cervical procedures on the risk of miscarriage are lacking.

Only few studies analyzed the correlation between LEEP and miscarriage, and previous published data are conflicting. In 1979 Weber and Obel (25) reported higher rates of miscarriage in women with a history of conization compared with women in an age-matched control group (20.4% vs. 9.0%). Other authors did not find such a correlation between LEEP and miscarriage in the subsequent pregnancy (26, 27). In 2004, in a retrospective case–control study, Tan et al. (26) reported similar rates of miscarriage in women with a history of LEEP compared with women in the control group (11.8% vs. 9.2%; *P*=.53). Similarly, in a recent case–control study by Frega et al. (27) for 475 pregnant women who previously underwent LEEP compared with 441 untreated women, a similar rate of miscarriage was reported (14.5% vs. 14.1%). Furthermore, to our knowledge, only one study analyzed the correlation between the time elapsed from LEEP to pregnancy and the risk of miscarriage in the subsequent pregnancy, reporting an increased risk in women with a time interval between LEEP and pregnancy of <12 months (15).

With more than 10 years of data, this multicenter cohort study detected a large number of pregnancies after LEEP. Furthermore, all the excisional procedures were performed in the Colposcopy Units of our institutions, with a

TABLE 3

Rates of miscarriage stratified by time interval from LEEP to pregnancy.

	LEEP-to-pregnancy interval (mo)				
Outcome	**< 6 mo**	**6–11 mo**	**12–23 mo**	**≥24 mo**	***P* value**
No miscarriage	4 (80)	74 (71.1)	79 (87.8)	367 (83.2)	.01
Miscarriage	1 (20)	30 (28.9)	11 (12.2)	74 (16.8)	.01
OR (95% CI)	1.24 (0.14–11.25)	2.01 (1.22–3.28)	0.69 (0.35–1.36)	Reference	–

Note: Data are n (%) unless otherwise specified.

Ciavattini. Risk of miscarriage after LEEP. Fertil Steril 2015.

standardized technique, by physicians with particular expertise in lower genital tract disease. In addition, the meticulous gathering of data through medical chart review enabled the collection of data involving multiple confounding factors, which allowed us to adjust the analysis for potential confounders.

In this study a higher rate of miscarriage in women previously treated with LEEP compared with controls was found. In particular, a significantly higher rate of miscarriage in women with a time interval from LEEP to pregnancy of <12 months emerged. As already pointed out by Conner et al. (15), the exact mechanism that would lead to miscarriage after LEEP is unknown but may be related to structural changes of the cervix. Another possible mechanism could be related to the process of inflammation and subsequent healing and remodelling of the cervical tissue after the excisional procedure. These hypotheses could explain the higher risk of miscarriage when a short time interval from LEEP to pregnancy occurred. However the exact pathogenesis of early and late miscarriage after LEEP is far from understood and deserves further study.

The human papillomavirus (HPV) status in women treated with LEEP could potentially influence the risk of miscarriage. Some studies have described high rate of HPV infection in placenta and spontaneous abortion products (28, 29), and early experimental evidence with murine models suggested that HPV could affect the survival or apoptosis of embryos (30, 31). Moreover, clinical studies have found HPV DNA in the amniotic fluid and peripheral blood, supporting the ascending infection and possibly the transplacental transmission hypotheses (32, 33).

The time elapsed from LEEP to pregnancy could have a role in determining the risk of miscarriage because it is well known that LEEP can gradually eliminate HPV infection (34), with a persistent infection rate of 44.6% and 2.1% after 3 and 12 months from the procedure, respectively (35). Epidemiologic evidence on the role of HPV in miscarriage, however, is still scarce, and in a recent case control study by Conde-Ferraez et al. (36) HPV infection seemed to be not significantly associated with miscarriage.

In this study we were not able to analyze the posttreatment HPV status of each woman. However, the possible correlation between HPV status after LEEP and the risk of miscarriage is interesting and deserves further study. To eliminate other potential confounders, women with a known HIV infection were not included in the analysis. Moreover, all women with a 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. None of them were HIV positive. Furthermore, only three women of the study cohort had signs or symptoms of lower genital tract infection in the 3 months before the procedure. A vaginal swab was collected in these symptomatic women, and bacterial vaginosis was detected. An appropriate therapy was performed (with subsequent negative vaginal swab) before the LEEP. None of them had a miscarriage in the subsequent pregnancies.

In conclusion, a significantly higher rate of miscarriage in women with a time interval from LEEP to pregnancy of <12 months emerged. In women with a LEEP-to-pregnancy time of <6 months, only a slightly increased risk of miscarriage was found, but this statistically insignificant result could be due to the small number of cases: only five women got pregnant within 6 months from LEEP, and only one case of miscarriage was reported. Conversely, with a time interval of ≥ 12 months, the risk of miscarriage seems to be similar to that of controls.

The findings of this study could potentially provide health practitioners with evidenced-based data to counsel women regarding the optimal timing of pregnancy after LEEP to reduce the risk of miscarriage. It is the authors' opinion that a time interval of ≥ 12 months after LEEP seems to be appropriate.

REFERENCES

1. Noehr B, Jensen A, Frederiksen K, Tabor A, Kjaer SK. Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery. Obstet Gynecol 2009;114:1232–8.
2. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol 2013;121:829–46.
3. Sopracordevole F, Chiossi G, Barbero M, Cristoforoni P, Ghiringhello B, Frega A, et al. Surgical approach and long-term clinical outcome in women with microinvasive cervical cancer. Anticancer Res 2014;34:4345–9.
4. Duggan BD, Felix JC, Muderspach LI, Gebhardt JA, Groshen S, Morrow CP, et al. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. Am J Obstet Gynecol 1999;180:276–82.
5. Kleinberg MJ, Straughn JM Jr, Stringer JS, Partridge EE. A cost-effectiveness analysis of management strategies for cervical intraepithelial neoplasia grades 2 and 3. Am J Obstet Gynecol 2003;188:1186–8.
6. Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. Gynecol Oncol 1994;54:175–9.
7. Prendiville W, Cullimore J, Norman S. Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. Br J Obstet Gynaecol 1989;96:1054–60.
8. Prendiville W. Large loop excision of the transformation zone. Clin Obstet Gynecol 1995;38:622–39.
9. Wright TC Jr, Richart RM. Loop excision of the uterine cervix. Curr Opin Obstet Gynecol 1995;7:30–4.
10. Crane JM. Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. Obstet Gynecol 2003;102:1058–62.
11. 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;367:489–98.
12. Phadnis SV, Atilade A, Young MP, Evans H, Walker PG. The volume perspective: a comparison of two excisional treatments for cervical intraepithelial neoplasia (laser versus LLETZ). BJOG 2010;117:615–9.
13. Farquharson RG, Jauniaux E, Exalto N. ESHRE Special Interest Group for Early Pregnancy (SIGEP). Updated and revised nomenclature for description of early pregnancy events. Hum Reprod 2005;20:3008–11.
14. Himes KP, Simhan HN. Time from cervical conization to pregnancy and preterm birth. Obstet Gynecol 2007;109:314–9.
15. Conner SN, Cahill AG, Tuuli MG, Stamilio DM, Odibo AO, Roehl KA, et al. Interval from loop electrosurgical excision procedure to pregnancy and pregnancy outcomes. Obstet Gynecol 2013;122:1154–9.
16. Leiman G, Harrison NA, Rubin A. Pregnancy following conization of the cervix—complications related to cone size. Am J Obstet Gynecol 1980;136:14–8.
17. Luesley DM, McCrum A, Terry PB, Wade-Evans T, Nicholson HO, Mylotte MJ, et al. Complications of cone biopsy related to the dimensions of the cone

and the influence of prior colposcopic assessment. Br J Obstet Gynaecol 1985;92:158–64.
18. Raio L, Ghezzi F, Di Naro E, Gomez R, Lüscher KP. Duration of pregnancy after carbon dioxide laser conization of the cervix: influence of cone height. Obstet Gynecol 1997;90:978–82.
19. Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2007;109:309–13.
20. Kristensen J, Langhoff-Roos J, Kristensen FB. Increased risk of preterm birth in women with cervical conization. Obstet Gynecol 1993;81:1005–8.
21. Andía D, Mozo de Rosales F, Villasante A, Rivero B, Díez J, Pérez C. Pregnancy outcome in patients treated with cervical conization for cervical intraepithelial neoplasia. Int J Gynaecol Obstet 2011;112:225–8.
22. Forsmo S, Hansen MH, Jacobsen BK, Oian P. Pregnancy outcome after laser surgery for cervical intraepithelial neoplasia. Acta Obstet Gynecol Scand 1996;75:139–43.
23. Ortoft G, Henriksen T, Hansen E, Petersen L. After conisation of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy. BJOG 2010;117:258–67.
24. Heinonen A, Gissler M, Riska A, Paavonen J, Tapper AM, Jakobsson M. Loop electrosurgical excision procedure and the risk for preterm delivery. Obstet Gynecol 2013;121:1063–8.
25. Weber T, Obel EB. Pregnancy complications following conization of the uterine cervix (II). Acta Obstet Gynecol Scand 1979;58:347–51.
26. Tan L, Pepra E, Haloob RK. The outcome of pregnancy after large loop excision of the transformation zone of the cervix. J Obstet Gynaecol 2004;24:25–7.
27. Frega A, Sesti F, De Sanctis L, Pacchiarotti A, Votano S, Biamonti A, et al. Pregnancy outcome after loop electrosurgical excision procedure for cervical intraepithelial neoplasia. Int J Gynaecol Obstet 2013;122:145–9.
28. Srinivas SK, Ma Y, Sammel MD, Chou D, McGrath C, Parry S, et al. Placental inflammation and viral infection are implicated in second trimester pregnancy loss. Am J Obstet Gynecol 2006;195:797–802.
29. Hermonat PL, Han L, Wendel PJ, Quirk JG, Stern S, Lowery CL, et al. Human papillomavirus is more prevalent in first trimester spontaneously aborted products of conception compared to elective specimens. Virus Genes 1997;14:13–7.
30. Calinisan JH, Chan SR, King A, Chan PJ. Human papillomavirus and blastocyst apoptosis. J Assist Reprod Genet 2002;19:132–6.
31. Henneberg AA, Patton WC, Jacobson JD, Chan PJ. Human papillomavirus DNA exposure and embryo survival is stage-specific. J Assist Reprod Genet 2006;23:255–9.
32. Armbruster-Moraes E, Ioshimoto LM, Leão E, Zugaib M. Presence of human papillomavirus DNA in amniotic fluids of pregnant women with cervical lesions. Gynecol Oncol 1994;54:152–8.
33. Favre M, Majewski S, De Jesus N, Malejczyk M, Orth G, Jablonska S. A possible vertical transmission of human papillomavirus genotypes associated with epidermodysplasia verruciformis. J Invest Dermatol 1998;111:333–6.
34. Kim YT, Lee JM, Hur SY, Cho CH, Kim YT, Kim SC, et al. Clearance of human papillomavirus infection after successful conization in patients with cervical intraepithelial neoplasia. Int J Cancer 2010;126:1903–9.
35. Du R, Meng W, Chen ZF, Zhang Y, Chen SY, Ding Y. Post-treatment human papillomavirus status and recurrence rates in patients treated with loop electrosurgical excision procedure conization for cervical intraepithelial neoplasia. Eur J Gynaecol Oncol 2013;34:548–51.
36. Conde-Ferráez L, Chan May Ade A, Carrillo-Martínez JR, Ayora-Talavera G, González-Losa Mdel R. Human papillomavirus infection and spontaneous abortion: a case-control study performed in Mexico. Eur J Obstet Gynecol Reprod Biol 2013;170:468–73.