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# Impact of Age at Conization on Obstetrical Outcome: A Case-Control Study

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**Objective:** The aim of the study was to assess whether an age younger than 25 years at conization affected future pregnancy outcome as an independent factor.

**Materials and Methods:** A retrospective study of 115 women who underwent both loop electrosurgical excision procedure (LEEP) and subsequent pregnancy follow-up in a referral center was conducted. Two groups were considered: patients younger than 25 years at the time of LEEP (n = 42) and 25 years or older (n = 73). Analyzed data were occurrence of preterm adverse obstetrical event and, specifically, preterm labor (PL) and preterm rupture of membranes; stratification based on term of occurrence was performed: less than 37 weeks of amenorrhea (WA), less than 34 WA, and less than 26 WA.

**Results:** Patients characteristics were comparable in terms of excised specimen thickness and pathological analysis, as well as for tobacco intoxication during pregnancy. Although there was no difference of term at delivery or total number of preterm adverse obstetrical events, we found a significant increase of events (19% vs 4.1%) and PL (19% vs 0%) before 26 WA in the group of patients younger than 25 years. After adjusting for excised specimen thickness, the same results were found for thickness of 15 mm or less (respectively, 16.7% vs 3.3% and 16.7% vs 0%). For thickness of greater than 15 mm, only ratio of PL before 26 WA was higher in the group of patients younger than 25 years (33.3% vs 0%).

**Conclusions:** Age younger than 25 years at the time of LEEP seems to be is associated with a more frequent occurrence of extremely early preterm adverse obstetrical events, particularly PL.

**Key Words:** LEEP, conization, preterm labor, younger women

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Loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN) has been shown to be associated with an increased risk of preterm delivery by inducing preterm labor (PL) and preterm rupture of membranes (PROM).[1,2] This especially seems to be the case for greater excision specimen thicknesses.[3] In that respect, cone sizes are limited to the minimum required to obtain negative margins, even more so when a younger patient is concerned. Indeed, this specific age group presents the particular feature of often being nulliparous and having a longer time span for potential recurrence and, therefore, iterative LEEP. In France, systematic cervical screening for asymptomatic women begins at the age of 25 years, but some practitioners choose to start PAP smear testing at an earlier age. This automatically leads to accidental high-grade CIN detections and subsequently to invasive surgical treatments. Nevertheless, younger women also bear distinct cervical anatomic characteristics, notably a shorter and growing cervix on which specific consequences of conization have yet to be studied.[4–6] It is in that context that this study was conducted, with the aim of evaluating whether an age of younger than 25 years at the time of LEEP was an independent factor for occurrence of preterm adverse obstetrical events.

## MATERIALS AND METHODS

We conducted a retrospective observational study between January 2008 and December 2015 in a French colposcopic referral academic hospital. The maternity ward attached to the colposcopy clinic was also the obstetrical referral center for the region and carried out approximately 2500 deliveries per year. The institutional board of the hospital approved all research linked to the study.

We recruited all patients who underwent LEEP during the studied period and subsequently delivered in our institution. This only concerned the immediate after pregnancy: patients having delivered in our institution after having delivered elsewhere after LEEP were excluded. Early miscarriages (<14 weeks of amenorrhea [WA]) were also excluded.

All patients were managed according to a multidisciplinary decision, based on French guidelines at the time of diagnosis. Loop electrosurgical excision procedure was only performed after colposcopic assessment, and indications were of 2 types: biopsy-proven high-grade CIN and persistent PAP smear abnormality. For the latter surgical indication, LEEP was performed as a diagnostic excision procedure after 18-month persistent low-grade squamous intraepithelial lesion or atypical squamous cells of undetermined significance PAP smear result or a 12-month persistent high-grade squamous intraepithelial lesion or atypical squamous cells–cannot exclude HSIL (high-grade squamous intraepithelial lesion) PAP smear result, associated with a normal colposcopy. These were excluded from the study: iterative LEEP and missing LEEP or obstetrical data (see Figure 1). Data were collected through our institution's centralized medical computerized record.

### Patients and Surgeons

The following individual characteristics were recorded: age at LEEP, parity before procedure, tobacco intoxication during pregnancy, period between LEEP and conception (in months), final pathological conization conclusions, and excised specimen thickness (measured after formalin fixation). Analyzed obstetrical variables were the following: term (in WA) and mode of delivery (vaginal or cesarean section), occurrence and term of occurrence of obstetrical events associated with LEEP, namely, PL and PROM. Late miscarriages (≥14 WA) were also recorded.

Subjects were divided into 2 groups depending on whether age at LEEP was strictly younger than 25 years of age or older. Cutoff age was chosen on the basis of French recommendations stipulating that PAP-smear testing should not begin before the age of 25 years in the case of an asymptomatic patient.

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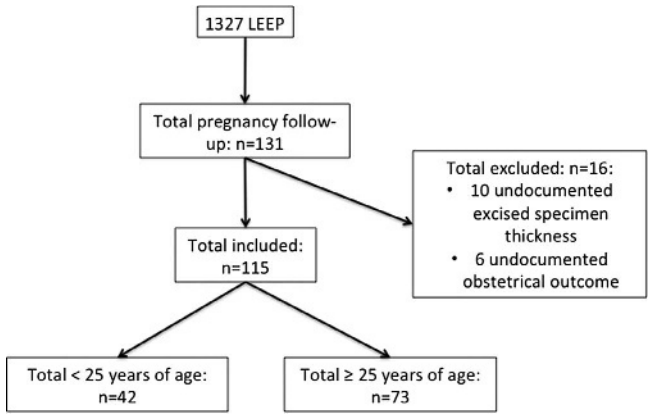


**FIGURE 1.** Flow chart.

Preterm labor was defined by uterine contractions associated with cervical modifications before 37 WA and PROM by the spontaneous rupture of membranes before 37 WA. Both obstetrical complications were stratified into 2 groups according to term of occurrence: strictly less than 34 and 26 WA. Finally, obstetrical morbidity was presented into 2 categories according to excised specimen thickness: 15 mm or less or greater. Cutoff thickness was chosen on the basis of what most authors describe as the limit where morbidity starts to become significantly augmented.[3,7]

Surgeons were all experienced senior practitioners, with regular practice of routine colposcopy and LEEP. All procedures were performed in a specific surgical ward, under local, locoregional, or general anesthesia depending on patient's profile, and using a semicircular electrosurgical loop. A systematic colposcopy was performed immediately before surgery, and depending on the surgeon's habits, LEEP was performed under direct colposcopic vision.

## Statistical Analysis

A descriptive statistical analysis was performed to describe the cohort. Time intervals were expressed in weeks or months, rounded to the nearest whole number. Qualitative variables were expressed as "n (%)" and quantitative variables were expressed as mean (SD). $\chi^2$ and Fisher exact tests were used to compare qualitative variables, with a significance threshold set up at $p$ values of less than .05.

## RESULTS

A total of 115 patients were included in the study: 73 were at least the age of 25 years and 42 were younger than 25 years (Figure 1). General patients' characteristics are illustrated in Table 1. Parity was significantly lower, and period between LEEP and conception was higher in the younger age group. Tobacco intoxication during pregnancy was not different in the 2 groups.

As shown in Table 2, there was no difference between the 2 groups regarding final pathological result, excised specimen thickness, and term or mode of delivery. The total numbers of obstetrical events and late miscarriages were not different in the 2 groups, but ratio of events (19% vs 4.1%, $p < .05$) and PL (19% vs 0%, $p < .05$) occurring before 26 WA were significantly higher in the younger age group.

When comparing the 2 age groups after stratification on excised specimen thickness (≤15 or >15 mm), a statistical difference was observed with a higher rate of obstetrical events and PL before 26 WA in younger patients for thickness of 15 mm or less (respectively, 16.7% vs 3.3% and 16.7% vs 0%, $p < .05$). The same results regarding PL before 26 WA were observed in younger patients for thickness of greater than 15 mm (33.3% vs 0%, $p < .05$; see Table 3).

## DISCUSSION

Our work's main goal was to determine whether age younger than 25 years at the time of LEEP was an independent factor for occurrence of preterm adverse obstetrical events. Our results showed identical ratios of obstetrical events in both groups but a significantly higher rate of PL at an extremely early term (<26 WA). This was the case regardless of excision specimen thickness. Potential cofounders, such as a shorter period between LEEP and conception as well as tobacco intoxication, did not apply to our cohort.[8,9] In our series, these observations were not linked to lower global delivery term or higher late miscarriages frequency, but it can be anticipated that the augmented rates of PL implied greater usage of tocolytic drugs, maternal and neonatal hospital admissions, induced maternal stress, and, all in all, higher medical expense.

It could be argued that our observations may be explained by lower compliance with follow-up after LEEP in the case of younger patients. Indeed, during pregnancy, this could result in delayed

**TABLE 1.** Included Patients' Characteristics

| | Patients Aged <25 y (n = 42) | Patients Aged ≥25 y (n = 73) | 95% CI | *p* |
|---|---|---|---|---|
| Mean (SE) age at LEEP, y | 23.0 (1.4) | 30.7 (3.4) | — | <.05* |
| Mean (SE) parity at LEEP, n (%) | 0.3 (0.5) | 1.3 (1.2) | — | <.05* |
| Mean (SE) period LEEP—conception, mo | 28.3 (18.3) | 20.3 (16.3) | 1.2 to 14.8 | <.05* |
| Tobacco intoxication during pregnancy, n (%) | 28 (66.7) | 36 (49.3) | — | .07 |

SE indicates standard error; LEEP, loop electrosurgical excision procedure.

*Indicates significant difference.

**TABLE 2.** Conization and Obstetrical Characteristics

| | Patients Aged <25 y (n = 42) | Patients Aged ≥25 y (n = 73) | 95% CI | *p* |
|---|---|---|---|---|
| Final pathological conclusion, n (%) | | | | |
| LG CIN | 10 (23.8) | 10 (13.7) | — | .09 |
| HG CIN | 32 (76.2) | 63 (86.3) | — | .17 |
| Mean (SE) excised specimen thickness, mm (%) | 10.2 (5.2) | 11.4 (5.0) | 0.2 to 1.1 | .24 |
| ≤15 | 36 (85.7) | 61 (83.6) | — | .76 |
| ≥20 | 4 (9.5) | 7 (9.6) | — | .99 |
| Mean (SE) term of delivery, WA | 36.8 (5.4) | 37.4 (4.3) | −2.6 to 1.3 | .52 |
| Mode of delivery, n (%) | | | | |
| Cesarean section | 2 (4.8) | 11 (15.1) | — | .09 |
| Vaginal delivery | 40 (95.2) | 62 (84.9) | — | |
| Obstetrical events, WA, n (%) | | | | |
| <37 | 12 (28.6) | 21 (28.8) | — | .98 |
| <34 | 10 (23.8) | 15 (20.1) | — | .68 |
| <26 | 8 (19.0) | 3 (4.1) | — | <.05* |
| Preterm labor, WA, n (%) | 10 (23.1) | 14 (19.2) | — | .56 |
| <34 | 10 (23.1) | 11 (15.1) | — | .24 |
| <26 | 8 (19.0) | 0 | — | <.05* |
| Premature rupture of membranes, WA, n (%) | 2 (4.8) | 7 (9.6) | — | .35 |
| <34 | 0 | 4 (5.5) | — | .12 |
| <26 | 0 | 3 (4.1) | — | .18 |
| Late miscarriages, n (%) | 2 (4.8) | 2 (2.7) | — | .57 |

LG indicates low-grade; CIN, intraepithelial neoplasia, HG, high-grade; SE, standard error; WA, weeks of amenorrhea.
*Indicates significant difference.

detection (and thus prevention) of LEEP-induced morbidity such as cervical incompetence. The question has been in part addressed by Campbell and Lara-Torre[10] who conducted a retrospective review of 210 adolescent patients (defined as women aged 12–21 years) who underwent management for abnormal cytological or histological cervical results. The authors concluded to an absence of difference in compliance with follow-up, regardless of severity of disease or surgical intervention. Regarding obstetrical follow-up, although the current literature clearly shows lower quality of prenatal care in terms of numbers of consultations and ultrasounds among pregnant adolescents, no study has ever proved that this also was the case for young adults such as the women composing our younger age group (the youngest patients being 18 years).[11,12]

Surgical treatment of CIN by LEEP is known to be responsible for PL and PROM.[1,13] Cervical incompetence seems to be the primary mechanism and is essentially linked to excised specimen thickness. Thickness threshold for occurrence of preterm adverse

**TABLE 3.** Obstetrical Morbidity According to Excised Cervical Specimen Thickness

| | Excised Thickness ≤15 mm | | | | Excised Thickness >15 mm | | | |
|---|---|---|---|---|---|---|---|---|
| | Age, <25 y (n = 36) | Age, ≥25 y (n = 61) | 95% CI | *p* | Age, <25 y (n = 6) | Age, ≥25 y (n = 12) | 95% CI | *p* |
| Mean (SE) term of delivery, WA | 37.3 (4.9) | 37.5 (4.1) | −2.1 to 1.7 | .83 | 33.7 (7.6) | 36.9 (5.5) | −11.3 to 4.8 | .38 |
| Obstetrical events, WA, n (%) | | | | | | | | |
| <37 | 10 (27.8) | 18 (29.5) | — | .86 | 2 (33.3) | 3 (25.0) | — | .71 |
| <34 | 8 (22.2) | 13 (21.3) | — | .92 | 2 (33.3) | 2 (16.7) | — | .42 |
| <26 | 6 (16.7) | 2 (3.3) | — | <.05* | 2 (33.3) | 1 (8.3) | — | .18 |
| Preterm labor, WA, n (%) | 8 (22.2) | 13 (21.3) | — | .92 | 2 (33.3) | 1 (8.3) | — | .18 |
| <34 | 8 (22.2) | 10 (16.4) | — | .48 | 2 (33.3) | 1 (8.3) | — | .18 |
| <26 | 6 (16.7) | 0 | — | <.05* | 2 (33.3) | 0 | — | .05* |
| Premature rupture of membranes, WA, n (%) | 2 (5.6) | 5 (8.2) | — | .63 | 0 | 2 (16.7) | — | .29 |
| <34 | 0 | 3 (4.9) | — | .18 | 0 | 1 (8.3) | — | .47 |
| <26 | 0 | 2 (3.3) | — | .27 | 0 | 1 (8.3) | — | .47 |

SE indicates standard error; WA, weeks of amenorrhea.
*Indicates significant difference.

obstetrical events is variable according to authors and has been estimated by Berretta et al.[3] at 15 mm. Jakobsson et al.[7] added an extra 20% risk after each additional millimeter. For others, the limit is estimated at as low as 10 mm.[14] Cervical incompetence after conization seems to be the result of an anatomic shortening of the gravid cervix. Indeed, as shown by several studies, women with a previous cervical excisional procedure have shorter midtrimester cervical lengths.[15,16] Of a cohort of 6669 patients, Miller and Grobman[17] reported shorter mean cervical length when a previous history of conization was present (42[9]mm vs 45[9]mm, $p < .05$), associated with a higher risk of PL. The fact that previous conization has clear and definitive anatomic repercussions in terms of cervical length during pregnancy probably explains why younger patients are more at risk of developing extremely early preterm adverse events as the ones highlighted in our series. Indeed, as reported by D'Agostini et al.,[4] the cervix is a growing organ, and its length during pregnancy is significantly shorter in younger women, with an average difference at midgestation of 5 mm when comparing primigravidae adolescents younger than 16 years and adults. Although it is unclear exactly when the cervix ends its evolution, it is probable that an early distal amputation permanently alters its growth potential, clinically translating, during pregnancy, into cervical incompetence.

Our findings prompt important practical implications and also constitute a strong argument to limit surgical intervention in younger patients, especially because this fringe of the population presents a higher propensity for spontaneous CIN regression.[18] Morrison et al.[19] estimated the latter at 72% for high-grade CIN in younger women versus 47% for patients 40 years or older. Progression to grade 3 from CIN 2 has also been found significantly inferior, as outlined by another recent prospective work studying women aged 13 to 24 years and estimated at 2% per year in comparison with 21% in older patients.[20,21] With specific and more favorable natural evolution, associated with higher risk of extremely early PL in the case of surgical treatment, we believe that CIN in younger patients should be managed conservatively, on the sole condition of a guaranteed rigorous follow-up. Our evidence also argues not to begin systematic PAP smear too early. Indeed, with a higher rate of positive cytologies in younger populations, unnecessary testing may induce unneeded CIN detections, which would have otherwise spontaneously regressed, and, a fortiori, conizations and subsequently, as we have reported, higher obstetrical morbidity.[22,23]

In case of previous LEEP history, certain authors recommend specific ultrasound follow-up during pregnancy, with an estimation of cervical length; this type of monitoring presents the advantage of a high reproducibility among asymptomatic patients with a high PL risk.[24,25] Two prospective studies conducted among parturients with a history of LEEP reported that a cervical length measured at less than 25 mm before 24 WA increased risk of PL by a factor of 2.91 and 4.95, respectively.[16,26] These studies were conducted regardless of age at conization, and further proof should be obtained regarding patients younger than 25 years before drawing conclusions, but the high rates of PL before 26 WA in our series suggest that an early cervical length ultrasonic assessment during pregnancy could allow better prevention of potential adverse events, with the possibility of anticipated cerclage in the case of shortened cervix.

Our retrospective study presented certain limitations that should be outlined. First of all, we only included patients who chose to have their obstetrical follow-up in our institution, probably in part due to PL fear. This suggests potentially more observant patients and therefore renders extrapolation of our results to the general LEEP population hazardous. Nevertheless, if anything, our results on higher early preterm obstetrical events in younger patients are underestimated and are probably higher in the general, potentially less observant, population. The second limitation was the retrospective collection of our data. Indeed, one could wonder about the 2 groups' comparability. We have addressed this question by analyzing most implicated factors regarding adverse obstetrical events for patients with a history of LEEP, which are excision specimen thickness and tobacco intoxication.[19] These confounding factors were not different in the 2 age groups, which limited major selection bias, even though others might exist.

To our knowledge, this is the first study proving the existence of an association between a younger age at LEEP and extremely early preterm adverse obstetrical events. Others are needed to corroborate our results, notably prospective series comparing cervical lengths of younger and older parturients after LEEP.

## CONCLUSIONS

Patients younger than 25 years at the time of LEEP present higher ratios of extremely early preterm adverse obstetrical events, particularly PL. Our results indicate the existence of an association between a younger age at LEEP and subsequent obstetrical morbidity; this supports conservative CIN management for younger patients, as well as meticulous obstetrical follow-up for succeeding pregnancies. Other prospective studies are needed to corroborate our observations.

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