CONTEMPORARY OB/GYN

Is it safe to perform LEEP on a patient before she gets pregnant?

A recent study suggests it may not be. Our analysis puts the new data into context and provides clinicians with the practical implications.

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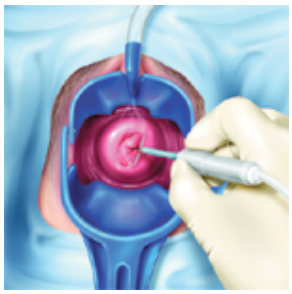

If a patient with cervical intraepithelial neoplasia (CIN) came to you prior to the 1980s, chances are you may have done cold knife surgical conization to treat her condition. But since then, outpatient excisional treatments by laser conization and loop electrosurgical excision procedure (LEEP), and ablative treatments by laser, cryotherapy and diathermy have become popular.

LEEP, the current treatment of choice worldwide, is easy to perform, inexpensive, as effective as earlier or alternative methods, and provides a surgical specimen to exclude malignancy. The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines recommend LEEP (among other approaches) for the treatment of CIN2 and CIN3, and for CIN1 under some circumstances.[1]

Since LEEP is widely used, most recent studies evaluating the effects of treatment on reproductive outcomes have concentrated on it. Our purpose here is to take a closer look at the research to determine just how safe the procedure is with regard to pregnancy, and to discuss the research on this issue that we recently published in *JAMA*. [2]

Why a new investigation was needed

There are fewer than 20 published studies on adverse reproductive events following LEEP and they are either case series or cohort studies. Most concentrate on the risk of preterm delivery, while very few provide data on the potential effect of LEEP on infertility and mid-trimester abortion. Many studies are small and thus inadequately powered to address most outcomes. The comparison groups in all of the cohort studies addressing preterm birth other than ours[2] have been the general obstetric population, matched to treated patients on factors such as age, parity, ethnicity, smoking, social class, height, multiple pregnancy, history of previous preterm birth, and hospital of birth.

The comparison group in our study consisted of women evaluated but not treated at the colposcopy clinic where the treated group received therapy. We believe this comparison group allowed us to obtain a more accurate estimate of relative risk by minimizing the chance of confounding, when evaluated against comparison groups of general obstetric patients, who share fewer risk factors with LEEP-treated women (e.g., smoking, sexually transmitted infections). The presence of confounding due to shared risk factors would exaggerate the size of the adverse effects of LEEP on preterm birth. Of course, the corollary of this is that if no effect is seen, it is probable that none exists.

Measurement of treatment and outcome variables has also been inconsistent and sometimes inadequately described in the published studies. For example, studies of preterm birth have not always separated medically-induced preterm births from spontaneous preterm births or spontaneous preterm births into those

caused by preterm premature rupture of the membranes (pPROM) or the spontaneous onset of labor. That's important first because it may not be plausible to propose that LEEP directly increases iatrogenic preterm birth (although it may, due to the shared risk factors for poor obstetric outcome).

Second, if LEEP does increase the risk of preterm birth, it's plausible that the mechanism may be an increase in spontaneous preterm labor or an increase in pPROM. Currently, the pathophysiology of spontaneous preterm birth remains unclear in general, not only as a result of any adverse effect of LEEP. In the few studies providing data on depth of tissue excised, there is a large range in mean depth, which is likely to impact the variability of treatment effects on pregnancy outcomes (Table 1).

Table 1 LEEP and risk of preterm delivery

A closer look at the research

The effect of LEEP on infertility is addressed in only two comparative studies.[3,4] One of these found no difference in time to pregnancy among 76 women who became pregnant and 66 control pregnancies from 250 women followed at 3 to 4 years among an initial cohort of 1,000 women treated by LEEP.[3] The other found 11 of 12 treated women who desired pregnancy achieved it along with 17 of 17 untreated controls.[4]

Data on mid-trimester pregnancy loss following LEEP are given for treated women in three studies but not for controls.[5-7] Comparative data, however, were given by only one small study.[8]

There are 10 cohort studies published in the English literature on the effect of LEEP on preterm birth (Table 1). As the majority of studies provide rates as a percentage of pregnancies delivering after 20 weeks, rates from some studies have been recalculated to allow comparison. [None of the small studies prior to 2003 reported a significant increase in risk of preterm birth; however, a meta-analysis, which pooled data from these same small observational studies, reported a summary odds ratio for preterm birth of 1.81 for women treated by LEEP,] compared to non-treated comparison groups, and an odds ratio of 2.53 when the three studies matched for smoking status were included.[9]

To date, only three studies have been designed to estimate the relative risk of spontaneous preterm birth (excluding medically indicated preterm birth) following LEEP[2,10,11] ; similarly, just three report data on the risk of pPROM.[2,11,12] The largest and most recent studies, our own and that by Samson,[11] both show a significant association between LEEP and spontaneous (non-medically indicated) preterm birth and with pPROM. Our study exemplifies the importance of separating spontaneous and medically indicated preterm birth. The rate of iatrogenic preterm birth in controls was higher in the untreated comparison group at 5.2% compared to 2.9% among the treated group, masking the significant effect of treatment on spontaneous preterm birth. In addition, we found an increase in pPROM leading to preterm birth, but no increase in spontaneous preterm labor leading to preterm birth, whereas Samson[11] reported an increased risk for both of these described pathways to preterm birth following LEEP. The magnitude of risk reported in Samson's study is greater than in ours; but this may be a result of confounding due to use of different comparison groups and multivariate analysis in our study to adjust for known potential confounders.

Some studies have reported data on size and/or number of LEEP biopsies in an attempt to establish whether the removal of more cervical tissue results in a greater risk; these provide conflicting data. The analyses are also based on rather crude retrospective pathological measurements. The analyses in our study combined height data for laser conization and LEEP specimens. We found a significant increasing risk for total preterm birth and pPROM with increasing depth of tissue excised. Samson reports no association between spontaneous preterm birth and mean depth or diameter of LEEP, number of passes, whether there was an endocervical pass, or number of LEEPs. They did report a significant increase in preterm birth among women treated with a combination of procedures. One research team reported an increase in total preterm birth among women treated with a 25 mm loop compared to controls.[7]

With the exception of our report, all of the studies listed in our table report caesarean section rates for treated and comparison groups and all studies prior to 2003 reported length of labor. No significant differences were found in caesarean section rate, length of first or second stage of labor or precipitate labor (labor less than 2 hours duration) in any study reporting these outcomes.

What's the take-home message for clinicians?

With all this research in mind, there are inadequate data to make a definitive case regarding the effect of LEEP on infertility and mid-trimester abortion. However [LEEP probably increases the risk of spontaneous preterm birth and, although the data are limited, the risk is apparently greater with larger LEEPs. Given this finding, and in the absence of data, it is plausible that LEEP might increase the risk of mid-trimester pregnancy loss.] It's unlikely, however, that LEEP has any impact on the progress of labor.

Future studies should more accurately assess the amount of tissue excised at LEEP to confirm the existence of a dose response relationship and identify those women who are at greatest risk of preterm birth following treatment. Further work is also needed to explore the mechanisms by which LEEP might increase the risk of spontaneous preterm birth.

But given that there probably is an increase in the risk of preterm birth following LEEP, we suggest a conservative approach to management of CIN in young women. "See and treat" protocols are best avoided, although it is recognized that failure to prevent cervical cancer must be weighed against the risk of adverse pregnancy outcome.

Guidelines for the management of abnormal cytology should reflect the high rates of regression of squamous intraepithelial lesions (SIL) described in recent natural history studies.[13,14] One investigator concluded from her study of regression of low-grade SIL (LSIL) in young women that colposcopy is unwarranted for the first LSIL cytology in young women as LSIL is almost always benign in this group.[13] The majority will regress by 1 year and almost all will regress by 3 years. Another recent natural history study supports this conclusion and shows that regression of high-grade SIL (HSIL) cytology occurs in the majority of cases.[14]

If treatment is required in women who have not completed their families and colposcopic examination is satisfactory, ablative methods, such as cryotherapy and laser ablation, where the volume/depth of tissue destruction is less, may be less harmful as first-line management.

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