**Adverse Obstetric Outcomes After Local Treatment for Cervical Preinvasive and Early Invasive Disease According to Cone Depth: Systematic Review and Meta-analysis**

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**ABSTRACT**

Local cervical treatment for preinvasive cervical disease such as cervical intraepithelial neoplasia (CIN) has been associated with an increased risk of preterm birth, perinatal morbidity, and mortality in a later pregnancy. This meta-analysis aimed to investigate the impact of treatment for cervical preinvasive and early invasive disease on obstetric outcomes and to see how this risk could be modified by the cone depth and comparison group. The CENTRAL, MEDLINE, and EMBASE databases were searched for reports published between 1948 and 2016. All reports on obstetric outcomes (over 24 weeks’ gestation) in women who had earlier received local cervical treatment for CIN or for early invasive cervical cancer compared with outcomes in women with no treatment history were included in the study. The maternal outcomes assessed included overall (<37 weeks’ gestation), severe (<32–34 weeks’ gestation), and extreme (<28–30 weeks’ gestation) prematurity (all preterm birth, iatrogenic and spontaneous). The neonatal outcomes assessed included low birth weight (<2500, <2000, <1500, and <1000 g), admission to the neonatal intensive unit, perinatal mortality, stillbirth, and Apgar score. The risk ratios and 95% confidence intervals (CIs) for each reported outcome in the treated versus untreated group were calculated.

The risk of preterm birth significantly increased after cervical treatment (overall prematurity: relative risk (RR), 1.78; 95% CI, 1.60–1.98; severe prematurity: RR, 2.40; 95% CI, 1.92–2.99; extreme prematurity: RR, 2.54; 95% CI, 1.77–3.63). The magnitude of the effect of treatment was found to be greater for excision than ablation. The risk increased gradually with increasing cone depth and cone volume ([cone depth ≤10–12 mm: RR, 1.54; 95% CI, 1.09–2.18; ≥10–12 mm: RR, 1.93; 95% CI, 1.62–2.31; ≥15–17 mm: RR, 2.77; 95% CI, 1.95–3.93; ≥20 mm : RR, 4.91; 95% CI, 2.06–11.68];[cone volume ≤6 mL: RR, 2.25; 95% CI, 1.09–4.66; ≥6 mL: RR, 13.9; 95% CI, 5.09–37.98]). Cervical treatment (excisional or ablative) was correlated to a significant increase in adverse neonatal outcomes, including low birth weight (<2500 g: RR, 1.81; 95% CI, 1.58–2.07; <1500 g: RR, 3.00; 95% CI, 1.54–5.85), admission to a neonatal intensive unit (RR, 1.45; 95% CI, 1.16–1.81), and perinatal mortality (RR, 1.51; 95% CI, 1.13–2.03). Significant heterogeneity was observed between studies for perinatal mortality (P = 0.04, I2 = 36%). The study concluded that women with CIN had a higher baseline risk of preterm birth, that local cervical treatment for preinvasive or early invasive disease further augmented the risk, and that the risk of preterm birth increased with increasing cone depth.

**EDITORIAL COMMENT**

(Preterm birth remains a tremendous public health problem and is the most common cause of neonatal mortality. It is responsible for 27% of neonatal deaths worldwide, comprising more than 1 million deaths annually (Lancet 2012;379(9832):2162). Previous cervical surgery, involving excisional procedures used to treat cervical dysplasia, is considered a risk factor for preterm birth.

Women who have undergone loop electrosurgical excision procedures (LEEPs) are usually followed closely in pregnancy with serial ultrasounds to measure cervical length. If the cervix appears shortened, it is unclear whether standard treatments for short cervix are effective, but such women are often treated with vaginal progesterone, activity restriction, and/or cervical cerclage.

This abstracted article is a systematic review and meta-analysis of the risk of preterm birth and other adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth. The authors were interested in whether the reported increased risk of preterm birth is attributable to the procedure itself, the physical removal of part of the cervix and how much cervix is excised, or primarily to other risk factors associated with cervical dysplasia. The literature in this area is conflicting, in part because investigators have used different control groups. This meta-analysis included studies of women who underwent cold knife cone, laser cone, other excisional procedures, large loop excision, and other ablation procedures. They found that compared with women who had no treatment those who underwent these procedures had increased risk of pretermdelivery and that the greater this risk, the larger the depth of excision. Relative risks for delivery at less than 37 weeks were 2.70 (95% CI, 2.14–3.40) for cold knife conization, 2.11 (95% CI, 1.26–3.54) for laser conization, 2.02 (95% CI, 1.60–2.55) for excision not otherwise specified, 1.56 (95% CI, 1.36–1.79) for large loop excision of the transformation zone, and 1.46 (95%CI, 1.27-1.66) for ablation not otherwise specified. The authors also found that the risk of preterm birth was increased in women with CIN but no treatment (5.9% vs 5.6%; RR, 1.24 (95% CI, 1.14–1.35). The association of LEEP and other procedures for treatment of CIN with preterm delivery is made somewhat clearer by this study, which found a consistent association that was increased with increasing cone depth. Whether small excisional procedures increased the risk beyond the increase seen with untreated CIN was unclear, although any such increased risk appears to be small. Other studies have reported similar outcomes, finding that LEEP appears to be safer than cold knife cone biopsy (Gynecol Obstet Invest. April 16, 2014) and that the volume of the excised tissue is associated with risk of preterm birth (BJOG. 2012;119(6):685–691). There is a couple of other interesting points about this article that have less to do with the content and more to do with the conduct of research and approach of this journal. The first is that they specifically discuss patient involvement, a topic of great interest to funding agencies, researchers, and patient advocates. In a section entitled “Patient Involvement,” the authors note that patients and the wider public were involved from the outset through informal interviews and patient advocate representative bodies. They point out that the research questions and outcomes were developed at least in part based on patient input and further discuss how the results will be disseminated to a lay audience; these are interesting points to make. Furthermore, they note that it was difficult in this meta-analysis to pool data, given different inclusion and exclusion criteria, as well as different outcome

measures. They encourage use of outcomes based on the CROWN initiative, which seeks to develop a core set of outcome measures to be used by researchers and required by journals, so that data can be more easily compared and pooled. Like all the complex factors associated with preterm birth, the relationship between cervical dysplasia and excisional procedures is complex. However, it seems that the question before us is not whether women who have had a LEEP procedure are at high risk—they do appear to be and should probably be monitored more closely. I think the question that remains is whether women with cervical dysplasia who have not had an excisional procedure are also at high risk and should be monitored more closely. It seems that that should at least be considered when assessing patient risk factors and choosing a prenatal care strategy. These women may have particular socioeconomic factors that put them at risk of cervical dysplasia as well as preterm birth. Surgeons caring for reproductive-aged women with cervical dysplasia should consider treatments that minimize the volume of cervical tissue removed, and obstetricians caring for women with a history of cervical dysplasia should consider this a potential risk factor regardless of prior treatment. The optimal intervention remains to be determined.—MEN)