

Title: Preterm Birth and Surgical Treatment of the Uterine Cervix.

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**Abstract:**

Cervical cancer is the second most common cancer among women globally. Most, probably all cases, arise through a precursor, cervical intraepithelial neoplasia (CIN). Effective cytological screening programmes and surgical treatments of precancerous lesions have dramatically reduced its prevalence and related mortality. Although these treatments are effective, they may have adverse effects on future fertility and pregnancy outcomes. The aim of this study was to evaluate the effects of surgical treatment of the uterine cervix on pregnancy and fertility outcomes, with the focus particularly on preterm birth. The general preterm birth rates and risk factors during 1987-2005 were studied. Long-term mortality rates of the treated women were studied.

In this study, information from The Medical Birth Register (MBR), The Hospital Discharge Register (HDR), The Cause-of-Death Register (CDR), and hospital records were used. Treatments were performed during 1987-2003 and subsequent deliveries, IVF treatments and deaths were analyzed. Preterm births were further divided into moderately preterm (from 32 to 36 gestational weeks), very preterm (from 28 to 31 gestational weeks) and extremely preterm (less than 28 gestational weeks) subgroups.

The general preterm birth rate in Finland was relatively stable, varying from 5.1% to 5.4% during the study period (1987 to 2005), although the proportion of extremely preterm births had decreased substantially by 12%, from 0.39% to 0.34%. The main risk factor as regards preterm birth was multiplicity, followed by elective delivery (induction of delivery or elective cesarean section), primiparity, *in vitro* fertilization treatment, maternal smoking and advanced maternal age.

The risk of preterm birth and low birth weight was increased after any cervical surgical treatment; after conization the risk of preterm birth was almost two-fold (RR 1.99, 95% CI 1.81-2.20). In the conization group the risk was the highest for very preterm birth (28-31 gestational weeks) and it was also high for extremely preterm birth (less than 28 weeks). In this group the perinatal mortality was also increased. In subgroup analysis, laser ablation was not associated with preterm birth. When comparing deliveries before and after Loop conization, we found that the risk of preterm birth was increased 1.94-fold (95% CI 1.10-3.40). Adjusting for age, parity, or both did not affect our results. Large or repeat cones increased the risk of preterm birth when compared with smaller cones, suggesting that the size of the removed cone plays a role. This was corroborated by the finding that repeat treatment increased the risk as much as five-fold when compared with the background preterm birth rate.

We found that the proportion of IVF deliveries (1.6% vs. 1.5%) was not increased after treatment for CIN when adjusted for year of delivery, maternal age, or parity. Those women who received both treatment for CIN and IVF treatment were older and more often primiparous, which explained the increased risk of preterm birth.

We also found that mortality rates were 17% higher among women previously treated for CIN. This excess mortality was particularly seen as regards increased general disease mortality and alcohol poisoning (by 13%), suicide (by 67%) and injury death (by 31%). The risk of cervical cancer was high, as expected (SMR 7.69, 95% CI 4.23-11.15). Women treated for CIN and having a subsequent delivery had decreased general mortality rate (by -22%), and decreased disease mortality (by -37%). However, those with preterm birth had increased general mortality (SMR 2.51, 95% CI 1.24-3.78), as a result of cardiovascular diseases, alcohol-related causes, and injuries.

In conclusion, the general preterm birth rate has not increased in Finland, as in many other developed countries. The rate of extremely preterm births has even decreased. While other risk factors of preterm birth, such as multiplicity and smoking during pregnancy have decreased, surgical treatments of the uterine cervix have become more important risk factors as regards preterm birth. Cervical conization is a predisposing factor as regards preterm birth, low birth weight and even perinatal mortality. The most frequently used treatment modality, Loop conization, is also associated with the increased risk of preterm birth. Treatments should be tailored individually; low-grade lesions should not be treated at all among young women. The first treatment should be curative, because repeat treatments are especially harmful. The proportion of IVF deliveries was not increased after treatment for CIN, suggesting that current treatment modalities do not strongly impair fertility. The long-term risk of cervical cancer remains high even after many years post-treatment; therefore careful surveillance is necessary. In addition, accidental deaths and deaths from injury were common among treated women, suggesting risk-taking behavior of these women. Preterm birth seems to be associated with extremely high mortality rates, due to cardiovascular, alcohol-related and injury deaths. These women could benefit from health counseling, for example encouragement in quitting smoking.