Treatment for cervical intraepithelial neoplasia and subsequent IVF deliveries

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BACKGROUND: The aim was to study whether the treatment of cervical intraepithelial neoplasia (CIN) is associated with a subsequent increase in the use of IVF to achieve deliveries and whether women with cervical treatment and IVF have increased rates of preterm delivery. METHODS: This was a register-based retrospective cohort (n = 822 183 deliveries) study from Finland whose main outcome measures were the rates of IVF and preterm deliveries in different CIN treatment groups. RESULTS: Of all deliveries in Finland, 1.5% (12 240) resulted from IVF treatment. This proportion was 1.6% for women who had undergone any cervical procedure [n = 150, risk ratio (RR): 1.21, confidence interval (CI): 1.04–1.42]. The risk for IVF was not increased after cervical conization, whether by loop or laser (1.6%), or ablation (1.8%). An increased number of IVF deliveries (2.7%) was observed following other excisional treatments, even when adjusted for year of delivery (RR: 1.83, CI: 1.16–2.89) or parity (RR: 1.95, CI: 1.25–3.04). Although women who had undergone any cervical procedure and IVF appeared to have an increased relative risk for preterm delivery (3.42-fold, CI: 2.18–5.37) when compared with women with neither, this was explained by maternal age and parity. CONCLUSIONS: The proportion of IVF deliveries was not increased after cervical conization or ablation. This is reassuring for young women who undergo such treatments.

Keywords: treatment for CIN; conization; subfertility; IVF; preterm delivery

Introduction

We have previously demonstrated that any cervical surgical treatment is associated with preterm delivery (Jakobsson et al., 2007) and that IVF treatment is a risk factor for preterm delivery even in singleton pregnancies (Poikkeus et al., 2007; Jakobsson et al., 2008). Women with preterm delivery and subfertility seem to share some common risk factors, such as infection. Subfertile women may have had more infections leading to tubal damage and tubal infertility and are more likely to have human papillomavirus (HPV)-related atypia compared with the general population (van Hamont et al., 2006). Cervical treatment for cervical intraepithelial neoplasia (CIN) can cause cervical stenosis and amucorrea (Hammond and Edmonds, 1990) impairing fertility. However, the association between treatment for CIN and subfertility has not been systematically studied.

In this study, we wanted to find out whether treatment for CIN predisposes to subfertility—measured by the number of IVF deliveries—and whether IVF further increases the risk for prematurity among women treated for CIN.

Materials and Methods

We used Hospital Discharge Register (HDR) data to identify fertile women aged 15–49 who underwent treatment for CIN during 1986–2003. These cases were linked to the Finnish Medical Birth Register (MBR) for 1991–2004 to identify all subsequent spontaneous and IVF deliveries. Both registers are held by STAKES (National Research and Development Centre for Welfare and Health), and cover the whole population, including hospital care and deliveries in the private sector. Women’s unique identification number, which exists in both registers, was used as the linkage key. The data linkage between the MBR and HDR was performed after the register-keeping organization, STAKES, had provided authorization, as required by legislation.

The HDR collects information on all inpatient episodes in healthcare facilities. According to the latest data quality study from the late 1980s, a total of 95% of hospitalizations were registered and 97% of main diagnoses concerning pregnancy, delivery and puerperium were correctly reported at the three-digit ICD code level (Keskima¨ki and Aro, 1991). Increased use of electronic patient records in hospitals has further improved the completeness and validity of the HDR (Gissler and Haukka, 2004). Since 1994, the HDR includes all day surgical procedures, and since 1998 all hospital outpatient visits. The extension of registration resulted from changes in clinical practice, and since early 1990s cervical procedures have mainly been done in outpatient settings. The medical procedures performed in the hospitals were identified by using surgical procedure codes, i.e. in 1986–1996 based on the national classification of Finnish Hospital League and since 1996 on the Finnish version of the Nordic Classification on Surgical Procedures.
The MBR collects baseline data on healthcare and interventions during pregnancy. Data are collected from all delivery units in Finland. Less than 0.1% of all newborns are missing from the MBR, but this information is routinely obtained from the Central Population Register and the cause-of-death statistics kept by Statistics Finland. Data are checked by STAKES, and seemingly incorrect information is returned for checking. For most variables, the data corresponds well with information in hospital records (Gissler and Shelley, 2002). Information on IVF deliveries in the MBR was only available from 1991 onwards. However, only 170 IVF children were born in 2002. We also analysed the data by adjusting separately for year of delivery, maternal age and parity using the logistic regression analysis. Separate analyses were performed for first deliveries only (n = 483 989 women and 126 deliveries).

### Results

The study material consisted of 822 183 deliveries during 1991–2004, of which 8295 deliveries followed cervical treatment (Table I). Of all deliveries, 1.5% (12 240) resulted from IVF treatment. This proportion was 1.6% for women with any cervical procedure (n = 150, RR: 1.21, CI: 1.04–1.42). In the conization group, 1.6% (n = 70, RR: 1.10, CI: 0.87–1.39) had IVF treatment. The corresponding figures in the ablation group and in the other excisional treatments group were 1.8% (n = 61, RR: 1.23, CI: 0.96–1.58) and 2.7% (n = 19, RR: 1.82, CI: 1.15–2.87), respectively. When adjusting by year of delivery (RR: 1.04, CI: 0.87–1.24), maternal age (RR: 1.05, CI: 0.89–1.26) or parity (RR: 1.05, CI: 0.87–1.29), the IVF delivery rates among women with any cervical procedure became non-significant (Table I). The same was true for the conization and ablation groups. An increase in the number of IVF deliveries was, however, observed in the other excisional treatments group when adjusting for year of delivery (RR: 1.83, CI: 1.16–2.89) or parity (RR: 1.95, CI: 1.25–3.04) (Table I).

We also analysed the first deliveries only, and the results were similar to the whole group and all deliveries. For the first deliveries, the IVF rate was 2.0%. For women with conization, the rate was 1.9% (RR: 0.95, CI: 0.74–1.23), for women with ablation, 0.9% (RR: 0.89, CI: 0.67–1.18), and for women with any other excisional procedure, 1.2% (RR: 1.10, CI: 0.87–1.42).

### Table I. IVF by previous cervical procedures, Finland 1991–2004 (all deliveries).

<table>
<thead>
<tr>
<th></th>
<th>No cervical procedure</th>
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<tr>
<td></td>
<td></td>
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<td>Conization</td>
<td>Ablation</td>
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<tr>
<td>Deliveries</td>
<td>822 183 (100%)</td>
<td>8295 (1.0%)</td>
<td>4259 (51.3%)</td>
<td>3335 (40.2%)</td>
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<td>IVF</td>
<td>12 240 (1.5%)</td>
<td>150 (1.6%)</td>
<td>110 (0.87–1.39)</td>
<td>123 (0.96–1.58)</td>
</tr>
<tr>
<td>Unadjusted, RR</td>
<td>1.21 (1.04–1.42)*</td>
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<td>10.04 (2.00)</td>
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<tr>
<td>Year of delivery, %</td>
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<td>1991–1995</td>
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<td>0.6</td>
<td>0.5</td>
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<td>2001–2004</td>
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<td>1.9</td>
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<td>1.3</td>
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<tr>
<td>Adjusted RR (95% CI)</td>
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<td>1.04 (0.87–1.24)</td>
<td>0.88 (0.68–1.15)</td>
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<td>2.5</td>
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<td>&gt; 40</td>
<td>4.1</td>
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<td>3.9</td>
<td>5.5</td>
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<tr>
<td>Adjusted for maternal age</td>
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<td>1.7</td>
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<tr>
<td>Adjusted RR (95% CI)</td>
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<td>1.05 (0.89–1.26)</td>
<td>0.91 (0.70–1.18)</td>
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<td>Parity, %</td>
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<td>0.4</td>
<td>—</td>
<td>1.6</td>
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<td>Adjusted for parity</td>
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<td>1.5</td>
<td>1.4</td>
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<tr>
<td>Adjusted RR (95% CI)</td>
<td></td>
<td></td>
<td>1.04 (0.88–1.24)</td>
<td>1.01 (0.79–1.29)</td>
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*p < 0.01; **p < 0.001; RR (95% CI), risk ratio (95% confidence interval). 1Cervical amputation, other cervical excisions.
ablation 2.3% (RR: 1.14 CI: 0.86–1.49) and for women with other excisional treatments 4.5% (RR: 2.26; CI: 1.40–3.36).

We also analysed associations between preterm delivery, cervical treatment and IVF (Table II). Our database included 691 (8.4%) singleton preterm deliveries after any cervical treatment. Among women with any cervical treatment and IVF, the preterm delivery rate was 15.5% (16 deliveries). Compared with women with any cervical treatment and IVF, the rate was 8.3% among women with any cervical treatment and no IVF (675 deliveries, \( P = 0.008 \).) Corresponding rates among untreated women with IVF or without IVF were 8.2% (800 deliveries, \( P = 0.007 \)) and 4.5% (36 307 deliveries, \( P < 0.001 \)). Thus, the risk for preterm delivery was 1.89-fold among women with cervical treatment and IVF (RR: 1.89, CI: 1.20–2.98) when compared with women with IVF but without cervical treatment. Among women with cervical treatment but no IVF, the risk was 1.82-fold (RR: 1.82, CI: 1.69–1.96) when compared with women with neither. (Table II). For those women who had both cervical treatment and IVF, the risk for preterm delivery was 3.4-fold (RR: 3.42, CI: 2.18–5.37) when compared with women with no cervical treatment and no IVF. This risk, however, disappeared when adjusted for age and parity (RR: 1.47, CI: 0.71–3.01).

**Discussion**

Our large register study showed that IVF deliveries were not increased after cervical conization or ablation. This is reassuring and suggests that such treatments are not strongly linked to subfertility. We found an increased risk for IVF deliveries after other excisional treatments (such as amputation of the cervix). Although this was only a small subgroup in our study, it suggests that only major cervical procedures affect cervical function. Since we only had information on the successful IVF treatments, our results cannot be generalized to the whole population of subfertile women.

The risk for preterm delivery was increased after any treatment for CIN, as reported previously (Kyrgiou et al., 2006; Jakobsson et al., 2007). Not surprisingly, women with cervical and IVF treatments had higher preterm delivery rates, although maternal characteristics, age and parity, explained the observed increased risk. Primiparity and extremities of maternal age are known risk factors for preterm delivery (Shennan and Bewley., 2006; Goldenberg et al., 2008).

We used population-based data covering practically all deliveries in Finland. The register data have been proven to be of high quality and feasible for evaluation of healthcare practices (Gissler and Shelley, 2002). In general, register data have no reporting bias, recall bias or participation bias. Although some procedures before 1998 may have been performed in settings not captured by the database, the numbers are small. Only few procedures were performed in private clinics. These few missing cases are unlikely to change our results.

The MBR has collected information on IVF and other assisted reproduction since October 1990. Only 170 IVF children were born before 1991 (0.3% of all deliveries in 1984–1990). It has been suggested that information on IVF in the Finnish MBR may not be complete due to the use of private services and social stigma related to infertility and its treatment (Gissler et al., 2004). However, it is unlikely that information on IVF would be biased by previous medical conditions such as treatment for CIN.

We were able to adjust our outcomes for maternal age, parity and delivery year, which are the most important confounding factors. Unfortunately, we had no information on mothers’ socio-economic position. It is, however, difficult to define such status for young women many of whom are either students or stay at home. It has been shown that low socio-economic position is associated with increased risk for CIN (Castellsague et al., 2002) and also for preterm delivery (Gissler et al., 2003; Björk et al., 2008), so it is possible that women in our population had lower socio-economic position. However, in the use of IVF services, socio-economic position plays only a minor role in Finland (Klemetti et al., 2005).

Our results are in line with previous studies, including a recent systematic review and meta-analysis (Kyrgiou et al., 2006). It should be noted that our data included women with successful IVF treatment and IVF deliveries. We did not have information about any women who had IVF treatment but did not conceive or had an adverse pregnancy outcome

| Table II. Preterm delivery rates by cervical treatment and IVF (singleton deliveries only). |
|---------------------------------|--------------------------|--------------------------|--------------------------|
|                                  | All preterm, n (%)       | No cervical treatment (n = 37 107) | Total (n = 37 798) |
|                                  | IVF                      | No IVF                   | IVF                      | No IVF                   | IVF                      | No IVF                   |
| All preterm, n (%)               | 16 (15.5)                | 675 (8.3)*               | 800 (8.2)*               | 36 307 (4.5)**           | 37 798 (4.6)            |
| Total deliveries, n              | 103                      | 8158                     | 9746                     | 799 888                  | 817 895                 |
| Risk for preterm delivery, RR (95% CI) | 1.89 (1.20–2.98) | 1.82 (1.69–1.96) | 1.00                     | 1.00                     | 1.00                     |
|                                  | 1.88 (1.19–2.96)         | 1.00                     | 1.00                     | 1.00                     | 1.00                     |
|                                  | 3.43 (2.18–5.37)         | 1.00                     | 1.00                     | 1.00                     | 1.00                     |
| Total, %                        | 15.5                     | 8.2                      | 8.2                      | 4.6                      | 4.6                      |
| Adjusted for age, %             | 11.4                     | 8.2                      | 7.9                      | 4.5                      | 4.6                      |
| RR (95% CI)                     | 1.37 (0.80–2.37)         | 1.00                     | 0.95 (0.86–1.06)         | 0.55 (0.51–0.59)         |
| Adjusted for parity, %          | 11.8                     | 8.2                      | 8.2                      | 4.5                      | 4.6                      |
| RR (95% CI)                     | 1.43 (0.84–2.44)         | 1.00                     | 1.00 (0.90–1.10)         | 0.55 (0.51–0.59)         |
| Adjusted for age and parity, %  | 6.7                      | 8.3                      | 7.9                      | 4.6                      | 4.6                      |
| RR (95% CI)                     | 0.81 (0.39–1.67)         | 1.00                     | 0.95 (0.86–1.05)         | 0.55 (0.51–0.59)         |

*P < 0.01; **P < 0.001 compared with women with any cervical treatment and IVF; RR (95% CI), risk ratio (95% confidence interval).
before 22 weeks of pregnancy. This is a limitation of our study. Therefore, we cannot draw conclusions about the impact of cervical treatment on subfertility, but rather on its impact on successful treatment of infertility by IVF which are not same end-points. It has been shown that women with HPV infection (i.e. CIN) undergoing IVF treatment have decreased pregnancy rates (Spandorfer et al., 2006) which may affect our conclusions. Finally, our data did not include information on women who had other infertility treatments such as intrauterine insemination or ovulation induction. It is possible that this caused bias in our study and therefore our results cannot be generalized to the wider population of subfertile women.

Theoretically, there are at least two potential mechanisms for infertility after cervical treatment. The first is cervical stenosis, which could prevent sperm from entering the uterine cavity. Second, all treatment modalities destroy mucus-secreting glands of the cervix which might predispose to subfertility. Furthermore, it is important to notice that HPV infection causing CIN may also be a risk marker for other sexually transmitted infections, leading to ascending infection and ultimately resulting in tubal damage.

Any surgical treatment for CIN increases the risk for preterm delivery (Kyrgiou et al., 2006; Jakobsson et al., 2007). IVF treatment also increases the risk for preterm delivery (Poikkeus et al., 2007; Jakobsson et al., 2008). Having surgical treatment for CIN combined with IVF, the risk for preterm delivery was 3-fold, but adjustment for background factors explained the excess risk. Women with CIN requiring surgical cervical treatment are generally young. Our results are reassuring, suggesting that current treatment modalities do not strongly impair their future fertility.

Acknowledgements
Medical writer: Mark Philips, language reviser at STAKES.

Funding
This study was supported by Clinical Graduate School in Pediatrics and Obstetrics/Gynecology, University of Helsinki and a grant from the Research Foundation of the University of Helsinki, Finland. STAKES covered the expenses for data linkages and analyses.