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Excisional treatments of the cervix and effect on subsequent fertility: a retrospective cohort study

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ABSTRACT

Objective: Concerns exist regarding the impact of excisional treatments for cervical intraepithelial neoplasia (CIN) on subsequent pregnancy outcome yet few studies have addressed fertility following surgery.

Study design: Retrospective cohort study. Set in the colposcopy service of National Maternity Hospital. A postal questionnaire was sent to 3590 women of reproductive age who attended colposcopy from 2001 to 2007; 1795 of these had at least one excisional treatment (surgical group) and 1795 had no treatment (non-surgical group). Records were reviewed to confirm the clinical details and volume of tissue excised. The main outcome measures were pregnancy and fertility rates as well as time to conception correlated with volume of tissue excised. Students' *t*-test, Mann–Whitney *U*-test, spearman correlation and Kruskal–Wallis tests were used during the analysis.

Results: 1355 Women (37.7%) responded. 537 Women had no treatment and 818 had at least one excision. A subsequent pregnancy was reported in 730 women (434 surgical and 296 non-surgical groups). No difference was detected between the groups in the reported pregnancy rates ($p = 0.56$), the time to conception ($p = 0.37$) or fertility problems ($p = 0.89$). The volume of the excision did not affect fertility rates or time to conception. There were fewer pregnancies in women following a cold knife cone or more than one LLETZ treatment-significant surgery, ($p = 0.004$) but no difference in their reported time to conception ($p = 0.54$).

Conclusions: One excisional treatment for CIN does not appear to affect subsequent fertility. Our study showed no delay in conception and no increased risk of problems conceiving in this group, even when controlling for the volume and depth of tissue removed. Women should be reassured by these results. Further work is required to evaluate the effect of cold knife cone biopsy and repeated LLETZ procedures on subsequent fertility.

Introduction

Large loop excision of the transformation zone (LLETZ) or loop electrosurgical excision procedure (LEEP) is currently the most widely practised treatment for cervical intra-epithelial neoplasia (CIN) [1]. The obstetric impact of this procedure has been a source of concern with particular reference to preterm birth [1–7].The most recent systematic review and meta-analysis by Bruinsma et al. reported a significantly increased risk (RR 2.19) of preterm birth with excisional treatments for CIN [7]. Castanon et al. in their large study involving over 18,000 women refuted this however, reporting that the risk was substantially less than that reported in other studies [5]. Most studies, including Castanon's, implicate the depth or size of the treatment with the subsequent risk of preterm delivery. LLETZ treatments and LLETZ specimens are a very heterogeneous group [8,9]. It has been reported that the height (or depth) and volume of the specimens can predict the relative risk of pregnancy related morbidity [2,10–12]. Excisions greater than 1.2 cm and larger than 6 cm^3 are reported to carry a three times greater risk of preterm labor [10].

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Despite the fact that LLETZ treatment can produce anatomical changes which could affect fertility, surprisingly few studies have focussed on the subsequent fertility of women undergoing excisional treatments to the cervix [13–16]. Possible effects of surgery include cervical stenosis which can prevent sperm entry, secondary infection leading to ascending infection and tubal damage, as well as changes in the physical characteristics of cervical mucus [14]. As with obstetric morbidity, the size of the specimen removed must be considered when assessing any possible impact on a woman's fertility.

The aims of this study were to examine whether cervical surgery/type of surgery/repeat surgery, has an impact on subsequent fertility and to assess whether the size of the specimen removed influences subsequent fertility.

Materials and methods

This was a retrospective cohort study with institutional ethical approval of women aged 24 to 40 years, who attended the colposcopy services in the National Maternity Hospital between 2001 and 2007. The exposed cohort included women, who had cervical surgery, either LLETZ or cold knife cone (CKC), and the non-exposed cohort, were women who had attended colposcopy but who had not had surgery. The Mediscan database in the colposcopy clinic was used to identify both the exposed and un-exposed cohorts. Those who had a CKC were identified by accessing pathology records for CKCs for the specified years. The surgical group were picked randomly from the Mediscan database and were divided into three age groups; less than 25 years, 26 to 35 years, 36 to 42 years (age at time of surgery). Then the non-surgical group attending during the same time period were matched to the age of the surgical group.

The number of surgeries the woman had, the type of surgery, the volume of cervix removed and the degree of abnormality were determined by accessing clinical and pathology records.

To adequately power this study it was estimated that it would be necessary to have approximately 700 women in each group to identify a 5% difference between the groups. It was conservatively estimated that 10% of women have fertility problems and that a finding of 15% in women post cervical surgery would indicate a clinically significant difference. With an estimated response rate of 50%, it would be necessary to recruit approximately 1500 women in each group.

Women were contacted by post and invited to complete a questionnaire relating to their contraceptive and fertility histories. (see Attachment 1 in Appendix A)

Women were deemed to have been exposed to pregnancy if they answered that they had become pregnant or if they could potentially have become pregnant but did not. Women who answered yes to any of the following questions were deemed to have a problem conceiving: Trying to get pregnant but with no success; diagnosed with a fertility problem; not avoiding pregnancy—but it just never happened (see Attachment 1 in Appendix A).

Measurements

The volume of the specimen was calculated as a three-dimensional truncated cone, using the formula: $1/2 \times 4/3 \times \pi \times a/2 \times b/2 \times c$ (where a = transverse diameter, b = longitudinal diameter and c = depth of the specimen). Only specimens that were removed in one piece were analyzed for correlation studies.

Statistics

Results were analyzed using SPSS 20, using Pearson's chi square test, the Students' t-test, Mann–Whitney U-test, spearman correlation and Kruskal–Wallis test. To perform partial correlations, the data was ranked and then analyzed. Missing data was excluded pairs wise. Logistic regression was used to predict the likelihood of a woman reporting a perceived difficulty conceiving.

Results

3590 Women were sent a postal questionnaire. 1795 Women had had cervical surgery (1729 LLETZ and 66 cone biopsies) and 1795 women had not had surgery. 1355 Women completed the questionnaires, giving a response rate of 37.7% (1355/3590). Of those who responded, 759 had a history of one previous LLETZ, 37 had a CKC, 22 had more than one LLETZ (total 818 had surgery) and 537 women had no history of cervical surgery. The 59 women who had either a CKC or more than one surgery to their cervix were analyzed separately.

Women with one LLETZ only (N = 759) compared with non-surgical group (N = 537)

Tables I and II outline the fertility history of the surgical and non-surgical groups. Similar numbers of women were exposed to pregnancy in the two groups—64.6% (491/759) versus 61.8% (330/534), $p = 0.26$. Of women exposed to pregnancy, there was no statistically significant difference in the number of women who conceived—88.4% (434/491) of women in the surgical group and 89.7% (296/330) in the non-surgical group ($p = 0.56$).

Of women who conceived, similar proportions reported no difficulty conceiving—82.8% (352/425) versus 80.8% (236/292), $p = 0.49$. 17.2% Of women in the surgical group (73/425) and 19.2% (56/292) in the non-surgical group reported a fertility issue and similar numbers in each group had fertility treatment—7.7% (33/426) and 8.5% (24/283), $p = 0.72$.

Of those women exposed to pregnancy, 7.7% (38/491) in the surgical group and 6.1% (20/330) in the non-surgical group reported difficulty conceiving and failed to conceive. If those who were not avoiding pregnancy but who did not conceive are added to those with a fertility problem, 57 in the surgical group versus 34 in the non-surgical group could have conceived but did not ($p = 0.56$). This gives an approximate rate of subfertility (failure to conceive) of 11.6% in the surgical group and 10.3% in the non-surgical group (potentially could have gotten pregnant but did not/total number exposed to pregnancy).

The reported time taken to conceive (TTC) was not significantly different between the two groups—7.76 months for the surgical group versus 8.43 months for the non-surgical group (Mann Whitney U-test for medians, $p = 0.37$). No correlation was found between TTC and volume of cervix removed (Spearman rho = 0.02, $p = 0.69$) or with depth of cervix removed (Spearman rho = 0.03, $p = 0.52$). A Kruskal–Wallis Test revealed no statistically significant difference in reported time to conceive across three different volume groups—less than 3 cm^3, 3 to 6 cm^3 and greater than 6 cm^3 ($N = 329$, $p = 0.51$).

When age at surgery or colposcopy was controlled for, there was still no correlation found between TTC and volume of cervix removed (partial correlation, ranked, $p = 0.96$). This was also observed for depth (partial correlation, ranked, $p = 0.93$). Also, there was no difference in depth (Mann–Whitney U-test, $p = 0.85$) or volume (Mann–Whitney U test, $p = 0.74$) of the tissue excised in women who got pregnant compared to those who were trying and did not.

There was no difference between the groups with regards to reporting whether a cause was found for their fertility problems—46 in the surgical group compared with 32 in the non-surgical group ($p = 0.63$) but three of the women in the surgical group cited