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ORIGINAL ARTICLE

Large loop excision of the transformation zone and preterm delivery over a decade in a major women's hospital

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Abstract

Background The success of cervical screening relies on assessment and treatment of pre-malignant disease. Large loop excision of the transformation zone (LLETZ) has been the mainstay of treatment for cervical intraepithelial neoplasia (CIN). Preterm delivery (PTD) in subsequent pregnancy is a long-term complication of the intervention.

Aims To describe the characteristics of women who had LLETZ treatment(s) followed by PTD in the Rotunda Hospital over a 10-year period.

Methods The pathology and the obstetric databases were searched to identify women who had LLETZ followed by PTD from 1 January 2007–31 December 2016. Details including gestation at delivery, depth of LLETZ and grade of CIN were extracted. Exclusion criteria included multiple pregnancy, and deliveries due to current pregnancy indications.

Results There were 97 women eligible for inclusion. Mean gestation at delivery was 33^{+2} weeks. CIN 1 was diagnosed in 16, CIN 2 in 24, CIN 3 in 53, and four were negative for CIN. No microinvasive or invasive disease was identified. The average depth of excision was 9.9 mm, 11.4 mm and 8.5 mm for CIN 1, 2 and 3, respectively. The difference in depth between excisions with CIN 2 and 3 was significant ($p = 0.019$).

Conclusions Despite having a lower mean depth of excision, women with CIN 3 comprised the majority of those who experienced PTD, suggesting that factors other than mechanical weakness are implicated in PTD for these women. This is in keeping with recent suggestions that the common denominator in high grade CIN and PTD is an altered vaginal microbiome.

Keywords Large loop excision of the transformation zone (LLETZ) · Preterm delivery

Introduction

Cervical cytology screening aims to reduce the incidence of cervical cancer by detecting abnormalities associated with preinvasive disease of the cervix, and women of reproductive age comprise a significant proportion of those eligible for screening [1]. Women with abnormal cytology are triaged according to the severity of abnormality and colposcopic assessment is performed where indicated [1]. The mainstay of treatment for high-grade cervical intraepithelial neoplasia (CIN) is large loop excision of the transformation zone (LLETZ), i.e. colposcopically directed excision of the area of abnormality, usually following histological confirmation of the grade of abnormality by an initial biopsy.

Preterm delivery (PTD) in subsequent pregnancies is a recognised risk for women who have undergone excisional treatment of CIN [2]. Previous reports have found that the volume of excised cervical tissue is more important than grade of CIN with regard to the risk of PTD [3]. The aim of this retrospective study was to describe the characteristics of women who experienced PTD following LLETZ over a 10-year period in the Rotunda Hospital.

Materials and methods

The Rotunda Hospital is a major women's hospital in Dublin. It is a university teaching hospital that provides both gynaecological and obstetric services and, in terms of deliveries, is one of the busiest maternity units in Europe [4]. The colposcopy service in the hospital is one of a network of 15

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centres in Ireland recognised by CervicalCheck, the National Cervical Screening Programme, as a referral centre for provision of colposcopy services following positive cervical screening [4]. Staff performing LLETZ treatment in the clinic are accredited by the British Society for Colposcopy and Cervical Pathology. Women are referred to the hospital's colposcopy service from a catchment area ranging from inner city Dublin to rural areas surrounding the city, making the population representative of the national population [4]. By way of illustration, there were a total of 5662 attendances at the colposcopy clinic in 2016, comprised of 1805 new referrals and 3857 returning women [4].

In addition to its gynaecological services, the hospital is a national referral centre for both high-risk pregnancies and neonates. The neonatal unit provides advanced care beginning at the threshold of viability [4].

When the study commenced the prospectively maintained histopathology laboratory database and the obstetric database were searched concurrently to identify women aged 18–45 years who underwent LLETZ treatment and women who experienced PTD, respectively, over the 10-year period 1 January 2007–31 December 2016. PTD was defined as delivery at < 37 weeks' gestation. Pathological and obstetric data were gathered including depth of LLETZ, grade of CIN, gestation at delivery and maternal characteristics. In women who had more than one LLETZ, the depths of excision were combined to determine the cumulative depth of excision. The records of women who experienced PTD were examined and deliveries deemed secondary to antenatal complications such as severe pre-eclampsia were excluded from the final analysis. Women who had twin (or higher order) pregnancies were also excluded. Data were entered and analysed using a spreadsheet programme (Microsoft Excel 2016, Microsoft Corporation, Redmond, WA, USA). The Hospital's Research Ethics Committee approved the study (reference RAG-2016-019). A p value < 0.05 was considered significant.

Results

There were 4576 LLETZ treatments performed over the study period and 6009 PTDs. There were 97 women who had LLETZ treatment followed by PTD eligible for inclusion in the study and their characteristics are shown in Table 1. Mean gestation at delivery for these 97 women was 33^{+2} weeks. Of the 97 women, CIN 1 was diagnosed in 16, CIN 2 in 24, CIN 3 in 53, and LLETZ specimens of four women were negative for CIN. No microinvasive or invasive disease was identified. The average depth of excision was 9.9 mm, 11.4 mm and 8.5 mm for CIN 1, 2 and 3, respectively, with the difference in depth of excision between CIN 2 and CIN 3 being significant ($p = 0.019$; Table 2).

Table 1 Characteristics of eligible women who experienced preterm delivery following LLETZ[a] in the Rotunda Hospital, 2007–2016 ($n = 97$)

Characteristic	Value
Mean gestation at delivery, weeks (range)	33^{+2} (19—36)
Mean birthweight, g (range)	2160 (320—3490)
Mean age, years (range)	32 (26—41)
Single LLETZ treatment, *n* (%)	83 (85.6)
Complete excision status, *n* (%)	44 (45.4)
Depth > 10 mm, *n* (%)	46 (47.4)
CIN[b] 1/negative, *n* (%)	20 (20.6)
CIN 2, *n* (%)	24 (24.7)
CIN 3, *n* (%)	53 (54.6)
Invasive disease, *n* (%)	0 (0)

[a] Large loop excision of the transformation zone

[b] Cervical intraepithelial neoplasia

Discussion

In this large sample spanning a decade in a major women's hospital, 97 women experienced PTD after LLETZ. While women with CIN 2 had the deepest excision, women with CIN 3 comprised the majority of those who experienced PTD.

This study has strengths. The delivery and histopathology laboratory databases from which data were extracted are prospectively maintained and reliable. Women attending the hospital are representative of the national population, making our findings relevant for all Irish women. The hospital colposcopy clinic is accredited by the National Cervical Screening Programme and subject to regular audit and quality control. A weakness of the study is its retrospective nature, which meant that we were unable to determine with certainty whether women who underwent LLETZ in the Rotunda experienced PTD in another hospital. However, the catchment area for the colposcopy service is the same as that for obstetric care and while women are free to attend the antenatal booking clinic in any maternity unit in the State, the usual practice is that women attend a hospital to which they are geographically close and with which they are familiar.

Table 2 Comparison of mean depths of excision according to grade of cervical intraepithelial neoplasia (CIN) in women who experienced preterm delivery after LLETZ[a] treatment in the Rotunda Hospital, 2007–2016

	Mean depth (mm)	0.95 confidence internal	p
CIN 1	9.9	± 3.1	
			0.211
CIN 2	11.4	± 2.4	
			0.019
CIN 3	8.5	± 1.3	

[a] Large loop excision of the transformation zone

The association between LLETZ and subsequent PTD has previously been described [2, 3]. A study in another women's hospital in Dublin conducted between 1999–2002 found that cervical excisions of a depth greater than 12 mm carried a three-fold greater risk of PTD [3]. The study did not identify any association between grade of CIN and PTD in the 25 women who delivered at < 37 weeks' gestation.

Infection with high-risk subtypes of the human papilloma virus (HPV) is recognised as the cause of CIN and, in turn, cervical cancer [5]. There is evidence that a disordered vaginal microbiome such as that found in bacterial vaginosis is associated with HPV infection and with PTD [6]. This opens the possibility that the increased risk of PTD seen in association with LLETZ treatment may not simply be caused by mechanical weakness owing to removal of cervical tissue. An abnormal vaginal microbiome may be the common denominator in HPV infection with high grade CIN and PTD [6]. The findings we report here, where women with CIN 3 had a lower mean depth of excision yet comprised the majority of those who experienced preterm delivery would also suggest that removal of cervical tissue is not the only factor in the increased rates of PTD following LLETZ treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Hospital's Research Ethics Committee approved the study (reference RAG-2016-019). As a retrospective study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

References

1. National Screening Programme. Cervical screening management recommendations explanatory guide. National Screening Programme, 2016. https://www.cervicalcheck.ie/_fileupload/Health-professionals/HPPublications/CS-PUB-LAB-1%20Cervical%20Screening%20Management%20Recommendations%20Explanatory%20Guide.pdf. Accessed 8 February 2018
2. Kyrgiou M, Athanasiou A, Kalliala IEJ, et al. (2017) Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. Cochrane Database Syst Rev; 11: art. no. CD012847
3. Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, Arbyn M, Prendiville W (2012) The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. BJOG 119:685–691
4. Rotunda Hospital (2017) Annual Clinical Report 2016. Rotunda Hospital
5. Baird PJ (1983) Serological evidence for the association of papillomavirus and cervical neoplasia. Lancet 322:17–18
6. Lee JE, Lee S, Lee H, Song YM, Lee K, Han MJ, Sung J, Ko GP (2013) Association of the vaginal microbiota with human papillomavirus infection in a Korean twin cohort. PLoS One 8:e63514