Is Endocervical Crypt Involvement by CIN A Newly Identified Risk Factor for Disease Recurrence Following Cervical Treatment? - ©

Dimitrios Papoutsis*

Dimitrios Papoutsis, MD, PhD, Department of Obstetrics and Gynaecology, Shrewsbury and Telford Hospitals NHS Trust, Apley Castle, Grainger Drive, Telford, TF16TF, United Kingdom.

*Address for Correspondence: Dimitrios Papoutsis*. Address: Dimitrios Papoutsis, Shrewsbury and Telford Hospitals NHS Trust, Apley Castle, Grainger Drive, Telford, TF16TF, United Kingdom. Tel.: (+44) 01952 641222; E-mail: dimitrios.papoutsis@nhs.net

Submitted: 10 December 2015; Approved: 28 December 2015; Published: 31 December 2015

Citation this article: Papoutsis D. Is Endocervical Crypt Involvement by CIN A Newly Identified Risk Factor for Disease Recurrence Following Cervical Treatment ?. SRL Reprod Med Gynecol. 2015;1(1): 005-008.

Copyright: © 2015 Papoutsis D. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
SUMMARY

There is evidence suggesting that endocervical crypt involvement by cervical intraepithelial neoplasia (CIN) is a risk factor for disease recurrence following excisional and ablative cervical treatment. Even though the rates of crypt involvement by CIN in cervical tissue vary greatly between 15-58%, it has been demonstrated that the presence of this risk factor increases almost two-fold the risk of recurrence following treatment. It is speculated that crypt involvement may represent a deeper and multifocal lesion with a more aggressive potential of CIN and therefore more extensive treatment and a closer case follow-up may be needed. More research is necessary to show whether ‘hidden’ high-risk-human papilloma virus (HPV) strains deep in the crypts could be the most likely explanation for the increased risk of disease recurrence after treatment.

EDITORIAL

There are literature reports that women treated for cervical intraepithelial neoplasia (CIN) are still at an increased risk of developing CIN and cervical carcinoma for a time period of up to 10 years following their treatment in comparison to unaffected women who have up to date and normal cervical cytology screening tests [1]. It has been estimated that women will develop high-grade recurrence in the range of 5 to 25% despite cervical treatment, with 80% of these cases presenting within the first two years of follow-up [2-5]. National Health Service-Cervical Screening Programme (NHS-CSP) guidelines in the United Kingdom have clearly reported on certain risk factors for recurrence that render repeat cervical treatment such as women over the age of 50 years old who have CIN3 extending to the deep or lateral margins of excision [6]. Other risk factors identified in the literature as predictive of disease recurrence except for age and margin status involve the depth of excision, the severity and size of lesion [7,8]. There is recently an emerging body of evidence suggesting that endocervical crypt involvement by high-grade CIN on cervical tissue may represent an additional risk factor for disease recurrence [9-15]. In this editorial a critical appraisal of the existing evidence will be presented along with the clinical implications to the patients’ treatment and follow-up of this newly identified risk factor.

It is known that the ectocervix is lined by a squamous epithelium that is non-keratinised and pluristratified, whereas the endocervix is covered by the columnar epithelium which is monostratified. Within the endocervical canal there are multiple foldings and invaginations of the glandular epithelium into the stroma of the cervix thus forming the endocervical crypts. These crypts are lined by endocervical cells the cytoplasm of which contains mucin but they are not ‘true’ glands as there is no duct leading to acini. The area between the original squamous epithelium and the glandular epithelium undergoing squamous metaplasia is known as the transformation zone where the CIN lesions develop and affect the epithelium both at the surface and also at the crypts. Histological assessment of the depth of crypt involvement by CIN 3 has shown a mean depth of 1-2 mm with a maximum of 5.22 mm [16-17]. For this reason the NHS-CSP guidelines have recommended that excisional techniques should remove tissue to a depth of greater than 7 mm when the lesion is ectocervical. The NHS-CSP guidelines further report that extensive involvement of the endocervical crypts by CIN represents a variant of CIN3 that is more likely than others to be associated with early invasion and they require that the presence of crypt involvement always be reported [18].

There are studies reporting that crypt involvement by CIN is a significant independent predictor of CIN disease recurrence [9-15]. In these studies women were offered cervical treatment in the form of either excision or ablation. The high-grade recurrence rate ranged between 3.5% to 14.5% with an almost two-to-three-fold increase in the overall disease recurrence for women who had crypt involvement when compared to those without. The theoretical explanations provided were that crypt involvement by CIN may represent a deeper or multifocal lesion with more aggressive potential of CIN associated with high-risk HPV strains. The findings from these studies lend support to the theory that residual CIN or ‘hidden CIN’ deep in the crypts may play a role in CIN recurrence even in cases with ‘presumed’ complete excision [11].

One of the early reports on the effect of crypt involvement on the cure rates of women treated for CIN is from Savage et al in 1982 [19]. In this initial study, n=160 women underwent cryosurgery cervical treatment and were followed up for five years demonstrating a failure rate of 16.3% (n=23). They found that endocervical crypt involvement by CIN involved 39.4% (n=63) of patients and was a risk factor for treatment failure resulting in an almost two-fold increase in the recurrence risk. The authors hypothesized that neoplastic tissue harbored within the endocervical glands may in some way be protected against cryosurgical destruction and may remain undetectable by cytological studies and might possibly progress to cervical carcinoma over a number of years.

Two other research groups have also investigated the role of crypt involvement in disease recurrence following cold-knife conisation (CKC) treatment. The first research group of Demopoulos et al in 1991, investigated n=341 women undergoing CKC treatment and who were followed up for five years [14]. Crypt involvement in cervical tissue involved 31.1% (n=106) of women. They found that 5.2% (n=18) had CIN2-3 histological recurrence in their cohort with an almost two-fold increase in CIN3 recurrence rates in those women with crypt involvement when compared to those without (23.6% versus 11.3%). The second research group of Meng et al in 2007, looked into n=266 women who underwent CKC treatment for high-grade CIN and had negative excision margins [12]. These women were followed up for a median of 46 months and the CIN histological recurrence rate was 8.6% (n=23). They found that 17.5% of women with crypt involvement recurred in comparison to 6.0% of women without crypt involvement. They concluded that women with crypt involvement by high-grade CIN should have a closer follow-up after cervical treatment.

There are further reports of crypt involvement on disease recurrence in cases of patients undergoing large loop excision of the transformation zone (LLETZ) that highlight its potential role as a risk factor for treatment failure. In the report of Livasy et al in 1999, data was retrospectively collected for n=248 women who underwent LLETZ treatment and had CIN3 on cone histology [13]. They found crypt involvement by CIN3 in 58.1% (n=144) of cone specimens. They estimated that the high-grade cytology recurrence in the cohort of women who were followed up for six years was 14.5% (n=36). The authors showed that CIN3 involving endocervical glands was a significant predictor of recurrence even with negative excision margins resulting in a two-fold increase in the risk (20% versus 9%). They concluded that crypt involvement by high-grade CIN is indicative of a larger or multifocal lesion that is more difficult to eradicate. They stressed the importance of including in the surgical pathology reports the presence or absence of endocervical crypt
in 2015, it was found that a pretreatment punch biopsy Papoutsis et al coagulation treatment [9,10].

On pretreatment cervical punch biopsy in 9.7% (n=54) of women. They detected endocervical crypt involvement by CIN2-3 during the entire follow-up period overall cytology recurrence occurred in 2.7% (n=15) of women. The only factor that was found to be significantly associated with high-grade cytology recurrence and a trend for a four-fold increased risk of high-grade cytology recurrence.

In conclusion, current evidence suggests that when there is crypt involvement by CIN, either in the form of a pretreatment cervical biopsy or in the form of cervical tissue following excisional treatment, then there is an increased risk of disease recurrence. Future research is necessary to show whether these patients with endocervical crypt involvement are hrHPV-positive following excisional and ablative cervical treatment, and whether ‘hidden’ hr-HPV strains deep in the crypts could be the most likely explanation for the increased disease recurrence at follow-up.

REFERENCES


