International Journal of
Reproductive Medicine & Gynecology

Editorial

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.

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

involvement as this information might influence patient management and case follow-up.

In the report of *Kodampur et al* in 2013, n=309 women having had LLETZ treatment with CIN2-3 on LLETZ specimen and negative excision margins were included and were followed up for seven years [11]. In the total cohort, the CIN2-3 histological recurrence rate was 3.5% (n=11) and the crypt involvement rate was 37.9% (n=117). It was found that the odds ratio for disease recurrence following the first LLETZ treatment and therefore for repeat treatment with crypt involvement was 2.67. The authors concluded that crypt involvement might make the CIN lesions more aggressive with higher chances of recurrence or it might be that the volumes of the lesions in the crypts are bigger. They also speculated that crypt involvement may be associated with high-risk human papilloma virus (hr-HPV) strains. They suggested that patients with crypt involvement should remain under close follow-up for at least 10 years.

In the report of *Papoutsis et al* in 2015, n=526 women were included having had LLETZ treatment and were followed up for three years [9]. The high-grade cytology recurrence rate over the follow-up period was 2.1% (n=11) and the rate of women with crypt involvement was 31% (n=163). Crypt involvement was not a predictor of recurrence in the total sample with all grades of CIN in the cone specimen included. However, in the subgroup of women with CIN2-3 on pretreatment punch biopsy and with crypt involvement on the cone specimen in comparison to those without, there was a three-fold increased risk for overall cytology recurrence and a trend for a four-fold increased risk of high-grade cytology recurrence.

On review of the literature, the only report on the effect of crypt involvement on the treatment failure following cold-coagulation cervical treatment is that of *Papoutsis et al* in 2015 [10]. The authors included n=559 women that were followed up over a ten year period. They detected endocervical crypt involvement by CIN2-3 on pretreatment cervical punch biopsy in 9.7% (n=54) of women. During the entire follow-up period overall cytology recurrence occurred in 22% (n=123) and high-grade 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 was crypt involvement on pretreatment cervical punch biopsy resulting in an almost four-fold increased risk.

There are three reports so far on the predictive value of the finding of crypt involvement by high-grade CIN on a pretreatment cervical biopsy for disease recurrence. In the study of *Rasbridge et al* in 1990, even though it was a small case-control study (n=23) the authors concluded that there was an increased risk for CIN3 recurrence if the pretreatment cervical punch biopsy showed crypt involvement and CIN3 on histology even when the cone specimen after treatment had negative excision margins [15]. In the studies of *Papoutsis et al* in 2015, it was found that a pretreatment punch biopsy showing crypt involvement by CIN2-3 was indicative of women at risk for abnormal cytology both after LLETZ excision and cold-coagulation treatment [9,10].

There are certain limitations to all of the previously described studies. First, the retrospective nature of the data collection poses a selection bias that is always inherent to these study types. Second, the differences in the recurrence rates most likely reflect variable study designs with different definitions of recurrence as they may be based on cytology-only testing, on pathology-only testing or combined pathology/cytology testing [7]. Moreover, there is a wide variation in the rates of crypt involvement reported ranging from 15% to 58% [9-15]. Given the fact that endocervical crypts may traverse to a maximum depth of 5.22 mm from the surface of the cervix and shallow biopsies may fail to detect CIN3, perhaps if more patients had a punch biopsy taken and biopsies were deeper, then maybe the percentage of crypt involvement would have been higher [16,17,20].

The overall recommendations from these studies are that women with endocervical crypt involvement should probably receive a closer follow-up after treatment or should even have more extensive local treatment [9-15]. In the study of *Papoutsis et al*, the risk of overall and high-grade cytology recurrence was significantly reduced if more than 1.9 cm3 of cervical tissue was removed at the first LLETZ treatment [9]. This supports what other studies in the literature have contemplated but did not quantify that crypt involvement may represent a multifocal or deeper CIN lesion and perhaps more extensive treatment may be needed [14,15]. Nevertheless, the authors comment that precise estimation of the excised tissue volume removed during LLETZ treatment is technically difficult. Moreover, removing more cervical tissue during excision increases the risk of preterm delivery in a subsequent pregnancy [21,22].

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

1. Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. See comment in PubMed Commons below Lancet. 1997; 349: 978-980.
2. Kocken M, Helmerhorst TJ, Berkhof J, Louwers JA, Nobbenhuis MA, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. Lancet Oncol 2011;12:441-50.
3. van Hamont D, van Ham MA, Struik-van der Zanden PH, Keijser KG, Bulten J, et al. Long-term follow-up after large-loop excision of the transformation zone: Evaluation of 22 years treatment of high-grade cervical intraepithelial neoplasia. Int J Gynecol Cancer 2006;16:615-619.
4. Paraskevaidis E, Jandial L, Mann EM, Fisher PM, Kitchener HC. Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol. See comment in PubMed Commons below Obstet Gynecol. 1991; 78: 80-83.
5. Kitchener HC, Walker PG, Nelson L, Hadwin R, Patnick J, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. See comment in PubMed Commons below BJOG. 2008; 115: 1001-1007.
6. Luesley D, Leeson S (2010) Colposcopy and programme management. Guidelines for the NHS cervical screening programme. Second edition, Sheffield, England: NHSCSP Publication No. 20.
7. Ang C, Mukhopadhyay A, Burnley C, Faulkner K, Cross P, et al. Histological recurrence and depth of loop treatment of the cervix in women of reproductive age: incomplete excision versus adverse pregnancy outcome. See comment in PubMed Commons below BJOG. 2011; 118: 685-692.
8. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. See comment in PubMed Commons below Lancet Oncol. 2007; 8: 985-993.
9. Papoutsis D, Panikkar J, Underwood M, Blundell S, Sahu B, et al. Endocervical Crypt Involvement by CIN2-3 as a Predictor of Cytology Recurrence After

Excisional Cervical Treatment. See comment in PubMed Commons below J Low Genit Tract Dis. 2015; 19: 311-318.

10. Papoutsis D, Underwood M, Parry-Smith W, Panikkar J. Risk factors for treatment failure following cold coagulation cervical treatment for CIN pathology: a cohort-based study. See comment in PubMed Commons below Arch Gynecol Obstet. 2015; 292: 1329-1337.

11. Kodampur M, Kopeika J, Mehra G, Pepera T, Menon P. Endocervical crypt involvement by high-grade cervical intraepithelial neoplasia after large loop excision of transformation zone: do we need a different follow-up strategy? J Obstet Gynaecol Res 2013;39:280-6.

12. Meng QW, Qin ZH, Mao Y, Zhao XD. [Prognostic factors of cervical high-grade squamous intraepithelial lesions treated by cold knife conization with negative margin]. See comment in PubMed Commons below Zhonghua Fu Chan Ke Za Zhi. 2007; 42: 457-459.

13. Livasy CA, Maygarden SJ, Rajaratnam CT, Novotny DB. Predictors of recurrent dysplasia after a cervical loop electrocautery excision procedure for CIN-3: a study of margin, endocervical gland, and quadrant involvement. See comment in PubMed Commons below Mod Pathol. 1999; 12: 233-238.

14. Demopoulos RI, Horowitz LF, Vamvakas EC. Endocervical gland involvement by cervical intraepithelial neoplasia grade III. Predictive value for residual and/or recurrent disease. See comment in PubMed Commons below Cancer. 1991; 68: 1932-1936.

15. Rasbridge SA, Jenkins D, Tay SK. A histological and immunohistological study of cervical intraepithelial neoplasia in relation to recurrence after local treatment. See comment in PubMed Commons below Br J Obstet Gynaecol. 1990; 97: 245-250.

16. Anderson MC, Hartley RB. Cervical crypt involvement by intraepithelial neoplasia. See comment in PubMed Commons below Obstet Gynecol. 1980; 55: 546-550.

17. Boonstra H, Aalders JG, Koudstaal J, Oosterhuis JW, Janssens J. Minimum extension and appropriate topographic position of tissue destruction for treatment of cervical intraepithelial neoplasia. See comment in PubMed Commons below Obstet Gynecol. 1990; 75: 227-231.

18. NHS cervical screening programme (2012). Histopathology reporting in cervical screening-an integrated approach. Second edition, Sheffield, England: NHSCSP Publication No. 10.

19. Savage EW, Matlock DL, Salem FA, Charles EH. The effect of endocervical gland involvement on the cure rates of patients with cervical intraepithelial neoplasia undergoing cryosurgery. Gynecol Oncol 1982; 14:194-8.

20. Byrom J, Douce G, Jones PW, Tucker H, Millinship J, et al. Should punch biopsies be used when high-grade disease is suspected at initial colposcopic assessment? A prospective study. Int J Gynecol Cancer 2006;16:253-6.

21. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. See comment in PubMed Commons below Lancet. 2006; 367: 489-498.

22. Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, et al; PaCT Study Group. Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. BMJ 2014;349:g6223.