European Journal of Obstetrics & Gynecology and Reproductive Biology 211 (2017) 194–198

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Influence of high risk HPV genotype on colposcopic performance: A large prospective study demonstrates improved detection of disease with ZedScan *I*, particularly in non-HPV 16 patients

Madeleine C. Macdonald[a,*], Brian H. Brown[b], Rachel E. Lyon[a], T. Jamie Healey[c], Julia E. Palmer[a], John A. Tidy[a]

[a] Colposcopy Clinic, Jessop Hospital Wing, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[b] Medical Physics, University of Sheffield, Sheffield, UK
[c] Medical Physics, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

ARTICLE INFO

Article history:
Received 5 August 2016
Received in revised form 18 January 2017
Accepted 16 February 2017
Available online xxx

Keywords:
Electrical impedance spectroscopy
ZedScan
hrHPV genotype
High-grade CIN

ABSTRACT

Objective: To assess the influence of high-risk Human Papilloma Virus (hrHPV) genotyping on the detection of high-grade disease (CIN2+) using colposcopic impression both with and without electrical impedance spectroscopy (ZedScan *I*) as an adjunct.
Study design: A prospective cohort of women with a known hrHPV genotype referred to a single colposcopy service.
Results: 839 women underwent colposcopy and ZedScan *I* examination. 613 women were referred with abnormal cytology; 411 (67%) with low-grade dyskaryosis (67%) and 202 (33%) with high-grade dyskaryosis. 187 were referred with persistent hrHPV but negative cytology. 35 were attended for follow up and 4 for a clinical indication. 159 (19%) women were positive for HPV16 only; 54 (6%) with HPV18 only, 443 (53%) women were positive for hrHPV other types (HPV O). 183 (22%) were positive for multiple hrHPV genotypes. CIN2+ was present in 170 (84.2%) of high-grade and 69 (16.7%) of low-grade cytology referrals. Colposcopy was better at detecting HPV16 associated CIN2+ than that associated with HPV18 or HPV O (86.9% vs 79.7%, $p = 0.0191$). ZedScan *I* increased the detection of CIN2+ from 85.6% to 96% irrespective of hrHPV genotype status ($p < 0.0001$).
Conclusion: The use of an electrical impedance spectroscopic device (ZedScan *I*) increases detection of CIN2+ irrespective of hrHPV genotype.

Introduction

It is widely accepted that the vast majority of invasive cervical cancers are caused by persistent high-risk Human Papilloma Virus (hrHPV) infections [1,2]. There is also little doubt that well organised cervical screening programmes have significantly reduced rates of cervical cancer by the detection and treatment of high-grade cervical intraepithelial neoplasia (CIN2/3 or HSIL) [3]. Colposcopy and directed biopsy are integral to diagnosing high-grade disease [4] however, colposcopy is highly subjective with a specificity for the detection of high-grade CIN lesions of between 32 and 92% [5]. More recently some studies have demonstrated at least 19–37% of CIN2 or worse is diagnosed on biopsies taken at random from areas of the cervix not identified by acetowhite changes, suggesting not all high-grade lesions may become obvious and small lesions may be easily missed by the colposcopist [4,6,7].

High-risk HPV screening is significantly more sensitive than cytology alone at predicting high-grade disease [8,9]. HPV genotyping; identification of high-risk types (HPV16 and HPV18 in particular) may further improve risk assessment for high-grade disease thus enabling screening programmes to triage women with low-grade cervical cytology to colposcopy or return to routine recall [10,11]. The English Cervical Screening Programme is currently evaluating primary HPV screening at six sites in England [12]. Sheffield is one of these sites.

There is conflicting evidence regarding the role of hrHPV genotype, its effect on colposcopic impression and detection of high-grade disease, with some authors reporting increased detection of abnormalities at colposcopy in the presence of

* Corresponding author at: Department of Gynaecological Oncology, Royal Hallamshire Hospital, Glossop Rd, Sheffield, S10 2JF, UK.
E-mail addresses: madeleine.macdonald@sth.nhs.uk, maddy@doctors.org.uk (M.C. Macdonald).

http://dx.doi.org/10.1016/j.ejogrb.2017.02.020
0301-2115/

HPV16 [13], while others have found no effect on colposcopic impression [14]. As aforementioned the ability of colposcopy to identify high-grade lesions may be dependent on changes to the cervical epithelium after the application of acetic acid and so some high-grade lesions may be missed at colposcopy [15,16]. ZedScan *I* is a handheld CE marked device measuring electrical impedance spectroscopy to differentiate between tissues. The prototype of ZedScan *I* has been shown to improve colposcopic performance by aiding the detection of high-grade CIN independent of the effect of acetic acid on cervical tissue [17]. ZedScan *I* was introduced into routine clinical use in Sheffield in December 2013 to provide the colposcopy team with additional information to support more effective patient management.

This study aims to use one population of women to assess the influence of hrHPV genotyping on the detection of high-grade disease (CIN2+) using colposcopic impression both with and without electrical impedance spectroscopy (ZedScan *I*) as an adjunct.

Materials and methods

A prospective cohort study of women undergoing colposcopy and ZedScan *I* assessment in the Jessop Wing Colposcopy Unit, Sheffield, UK from 1st January 2014 and 31st December 2015 was performed. Five BSCCP accredited colposcopists undertook the examinations. Women who had an adequate colposcopic examination with type 1 and type 2 transformation zones, as per IFCPC terminology, were included in the study, to permit direct comparison between colposcopic impression and EIS readings [18].

All cytology specimens were processed by means of *SurePath*® and the *Roche Cobas 4800* system was used for hrHPV genotyping (this system tests for 14 hrHPV genotypes; 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). ZedScan *I* colposcopic examinations were carried out according to the manufacturer's protocol. Biopsies and treatments (large loop excision of the transformation zone (LLETZ)) were undertaken based on colposcopic impression and ZedScan *I* results. Random biopsies of normal cervical transformation zone and endocervical curettage were not performed as per local and national guidance [19]. All cervical biopsies and LLETZ specimens were reviewed by specialist gynaecological histopathologists.

Data was collected prospectively on referral indication, hrHPV genotype, final histological diagnosis from direct punch biopsy or LLETZ and entered onto a *Microsoft Excel* ™ database, with Fisher's exact test and Chi squared tests were used to analyse any significant differences between the groups.

The study was performed in the context of a service evaluation and therefore ethical approval was not required.

Results

In total 839 women with a known HPV genotype attended the colposcopy clinic and underwent an adequate colposcopic examination and ZedScan *I* assessment. The mean age of the women referred was 32.9 years (range 20.3–66.1 years). Overall 613 (73%) women were referred with abnormal cytology; 411 with low-grade dyskaryosis (67%) and 202 with high-grade dyskaryosis (33%). A further 187 (22%) were referred with persistent hrHPV but negative cytology (present on two screenings 12 months apart). In addition, there was a small number of women attending for follow up (35), and four who were seen due to a clinical indication. A total of 159 women (19%) were HPV16 positive only; 54 (6%) HPV18 only and 626 women (75%) were positive for hrHPV other (HPV O, comprising of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) with or without HPV16 or 18 (Fig. 1).

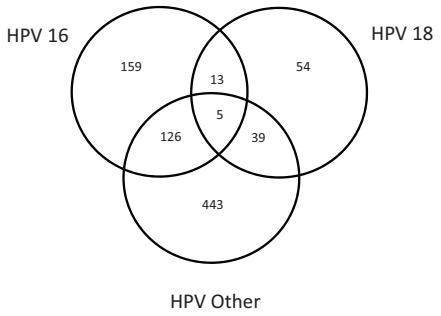

Fig. 1. hrHPV genotype of women referred to the Jessop Wing Colposcopy Unit, Sheffield UK.

Within the cohort of women studied 265 were found to have CIN2+ (31.6%). The incidence of CIN2+ in women referred with high-grade and low-grade cytology was 84.2% (170) and 16.7% (69) respectively (Table 1) and for the women referred with persistent hrHPV positive/cytology negative the incidence of CIN2+ was 9.6% [19]. A further eight cases of high-grade disease were found in the group of women referred with clinical indications and those under follow up for previous CIN.

Women referred with HPV16 genotype

In total 303 women were referred with HPV16, either as a single infection (159), or multiple infections with other hrHPV genotypes (144); 99 (32.7%) had high-grade and 108 (35.6%) low-grade cytology; 82 (27.1%) had negative cytology and 14 were seen for follow up or a clinical indication. Biopsy-proven CIN2+ was identified in 137 (45.2%) women; 92.2% of women referred with high-grade cytology had CIN2+ whereas 28.7% referred with low-grade cytology had CIN2+. The incidence of CIN2+ in women with HPV16 co-infected with HPV18 was 55.6%, and 51.1% in those co-infected with HPV O.

Women referred with HPV18 genotype

A total of 111 women were positive for HPV18 either as a single infection (54) or multiple infections with other hrHPV genotypes (57); 32 (28.8%) were referred with high-grade and 38 (34.2%) with low-grade cytology; 38 (34.2%) had negative cytology and 3 were on follow up or seen for a clinical indication. Biopsy-proven CIN2+ was identified in 35 (31.5%) women; 84.4% of women referred with high-grade cytology had CIN2+ whereas for women with low-grade cytology, 13.2% had CIN2+. The incidence of CIN2+ in those women who also had HPV16 is described above (55.6%) and for those co-infected with HPV O the incidence was 28.2%.

Table 1
High-grade disease detected according to referral cytology and hrHPV genotype status.

	High-grade cytology n = (%)	Low-grade cytology n = (%)
hrHPV ge notype		
HPV 16 only n = 159	42 (89.4%)	12 (23.1%)
HPV 18 only n = 54	10 (83.3%)	1 (6.7%)
HPV O only n = 443	61 (75.3%)	34 (12.7%)
HPV 16 + HPV 18 n = 13	6 (85.7%)	1 (33.3%)
HPV 18 + HPV O n = 39	8 (80.0%)	3 (15.8%)
HPV O ± HPV 16 ± HPV 18 n = 131	43 (95.6%)	18 (34.0%)