Folate receptor-mediated cervical staining as an adjunct to colposcopy which can improve the diagnostic accuracy of detecting high grade squamous intraepithelial lesions

Wojciech Homola, Michal Pomorski, Aleksandra Zimmer, Pawel Baranski, Mariusz Zimmer

2nd Department and Clinic of Gynaecology, Obstetrics and Neonatology, Wroclaw Medical University, Wroclaw, Poland

ABSTRACT

Objectives: Cervical cancer is rated fourth in terms of incidence and cancer-related mortality in women. Cytology-based screening programs and colposcopy provided insufficient rates of detecting cervical intraepithelial neoplasia (CIN) prompting researchers to develop new tools. The aim of this study was to evaluate whether folate receptor-mediated staining is useful in detecting CIN2+ during gynecological examination with colposcopy.

Material and methods: In total 96 women with abnormal cytology findings were enrolled. The study was conducted on the Polish population. The diagnostic process consisted of colposcopy, receptor-mediated diagnosis (FRD), and histopathology examination. All women were subjected to the same diagnostic procedure.

Results: The patient mean age of 96 women was 38 ± 14.5 years. On colposcopy, high-grade lesions were detected in 83 women. The FRD gave positive results in 63 women. Histopathology revealed 1 case of carcinoma plano epithelial akeratodes, 21 cases of high-grade squamous intraepithelial lesions, 13 cases of low-grade squamous intraepithelial lesions. A total of 61 cases presented no pathology. FRD as an adjunct to colposcopy gave the following test results in detecting CIN2+ lesions: sensitivity — 94.29%, specificity — 46.67%, PPV — 50.77%, NPV — 93.33%, and accuracy — 64.21%. Using both techniques provided better results than using each of the tests alone.

Conclusions: FRD is a promising test for the diagnosing CIN2+ cervical pathologies because it can increase the probability of detecting CIN2+ without any additional burden posed on patients. Further studies should be conducted on large and various populations to complement current evidence.

Key words: cervical neoplasia; cervical cancer; folate receptor-mediated cervical staining; FRD

INTRODUCTION

Cervical cancer is a considerable problem for women's health. The estimated number of new cancer cases reached 569,800, and the estimated number of deaths was 311,400 in 2018 worldwide, which placed cervical cancer at the fourth position in terms of incidence and cancer-related mortality in women [1]. Increasing awareness and introduction of screening programs allowed to decrease morbidity and mortality rates due to cervical cancer [2]. In high-income countries, indices for cervical cancer are much lower than in low-income countries. For this reason, cervical screening is one out of three elements of the WHO global strategy towards eliminating cervical cancer worldwide as a public health problem [3].

Currently, many screening programs are based on cytology [4]. However, this method is considered to be of insufficient and differentiated accuracy. An 11-year retrospective analysis of 999 cases published by Kang et al. reported a sensitivity of 97.14% and specificity of 85.58% for detecting high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma (SCC) [5]. But the study by Wojciech et al. [6] on patients with histologically confirmed cervical intraepithelial neoplasia (CIN) showed a sensitivity of 58.02% and specificity of 63.28% in detecting CIN. For this reason, other noninvasive methods such as based on electrical impedance spectroscopy, folic acid receptor-mediated diagnosis (FRD) method, or those employing arti-
In the overall assessment, the case was considered to be negative for High-Grade Squamous Intraepithelial Lesions (HG-SIL) when the result of colposcopy was normal without any acetowhiteness changes or any worse abnormalities; the FRD staining was brown or green, and histopathology samples were negative for HG-SIL (below CIN II).

Collected data were statistically analyzed. Categorical variables were presented as numbers and percentages, while continuous data were presented as means with a standard deviation. Results between the two diagnostic methods (classical colposcopy and colposcopy + FRD staining) were compared with the Fisher's exact test. To evaluate diagnostic tests, the following results were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

RESULTS

Overall, 96 women were eligible for the study. The patient population mean age was 38 years old with an SD of 14.5 and range from 24 to 86 years. All study participants had abnormal cytology results which are summarized in Table 1. On colposcopy, high-grade lesions were detected in 83 women. The FRD gave positive results in 63 women. Table 2 shows the results of the histopathological examination.

Positive and negative results of colposcopy, FRD and histopathology (Tab. 3) were used to calculate sensitivity, PPV, NPV, and accuracy (Tab. 4).

Table 1. Cytology results of referred women (n = 96)

<table>
<thead>
<tr>
<th>Cytology diagnosis</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Squamous cell carcinoma (SCC)</td>
<td>1</td>
</tr>
<tr>
<td>2. Atypical squamous cells cannot exclude HSIL (ASC-H)</td>
<td>14</td>
</tr>
<tr>
<td>3. AGC-US</td>
<td>6</td>
</tr>
<tr>
<td>4. Atypical squamous cells of undetermined significance (ASC-US)</td>
<td>18</td>
</tr>
<tr>
<td>5. High-grade squamous intraepithelial lesion (HSIL)</td>
<td>15</td>
</tr>
<tr>
<td>6. AIS</td>
<td>1</td>
</tr>
<tr>
<td>7. Low-grade squamous intraepithelial lesions (LSIL)</td>
<td>36</td>
</tr>
<tr>
<td>8. Negative for intraepithelial lesion or malignancy (NILM)</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. Histopathological results of the study group (n = 96)

<table>
<thead>
<tr>
<th>Lp.</th>
<th>Histological diagnosis</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Carcinoma plano epithelial akeratodes (G1)</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
<td>21</td>
</tr>
<tr>
<td>4.</td>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>13</td>
</tr>
<tr>
<td>5.</td>
<td>Normal</td>
<td>61</td>
</tr>
</tbody>
</table>
in normal human lung tissue. Liu et al. [13] investigated the expression of FRα and the role of FRα in the regulation of the ERK signaling pathway. They found that FRα expression was progressively increasing along with the progression of cervical lesions. In squamous cell carcinoma of the cervix, expression of proteins of ERK signaling pathway correlated with the expression of FRα. They concluded that expression of FRα is associated with the progression of cervical cancer and can regulate cervical cancer cells growth.

Since the discovery of the link between FR and cervical cancer, evidence on the potential role of FR in the detection of cervical metaplasia is growing rapidly. Several studies conducted in the real clinical practice settings were published recently. Lu et al. [14] conducted a study on 169 women and compared the results of FRD and cytology testing. They reported a sensitivity of 71.93%, specificity of 66.07%, PPV of 51.90%, and NPV of 82.22% of FRD in the diagnosis of cervical cancer and considered this result to be comparable to cytology. Li et al. [15] conducted the largest study up until now. They recruited 14,344 women from rural areas of China. In detecting CIN2+, FRD showed a sensitivity of 85.7%, specificity of 76.4%, PPV of 61.3%, and NPV of 92.5%. Authors concluded that FRD had a moderate agreement with cytology in detecting atypical squamous cells, was unable to exclude high-grade intraepithelial lesions, but was more sensitive than cytology. Xiao et al. [16] examined 404 women using FRD to screen them for high-grade cervical lesions. They found that the sensitivity of FRD in detecting CIN2+ was 80.00%, specificity was 51.92%, PPV was 24.19% and NPV 93.12%. Dai et al. [17] included 216 women and subjected to FRD, human papillomavirus testing and ThinPrep cytology test. They reported the following test results for FRD: sensitivity — 80.41%, specificity — 68.29%, PPV — 60%, NPV — 85.5%. They concluded that FRD had significantly higher specificity than HPV testing and TCT, but no differences were noted in specificity. The recent study of Zhao et al. [18] recruited 1,504 patients with abnormal cytology and/or positive human papillomavirus (HPV) testing at primary screening. In this study, the sensitivity of FRD was 77.72% and specificity of FRD was 60.02%. It is worth noting that the rate of detection of pathological lesions increased with the greater severity of the disease. FRD detected 45.45% of CIN1, 66.93% of CIN2, 84.44% of CIN3, and 98% of carcinomas.

The results of our study are in line with the above-discussed reports from the literature. The advantage of our study lies in the evaluation of the benefit of FRD as an added value to the standard of care diagnosis in our institution, while most studies focus on presenting results of FRD alone in comparison to other diagnostic methods. Nevertheless, further studies should be conducted to further investigate the usefulness of FRD in detecting CIN2+ in clinical practice.
settings. FRD is a simple technique with a rapid result which should be considered when adding this examination to the current standard of care.

**CONCLUSIONS**

FRD is a promising test for the diagnosing CIN2+ cervical pathologies because it can increase the probability of detecting CIN2+ without any additional burden posed on patients. Further studies should be conducted on large and various populations to complement current evidence.

**REFERENCES**