

Research Article

Visual Inspection of Acetic Acid (VIA) as a Promising Standard for Cervical Cancer Screening***Inspeksi Visual dengan Asam Asetat (IVA) sebagai Standar Metode Skrining Kanker Serviks yang Menjanjikan*****Tofan W Utami¹, Laila Nuranna¹, Marendra Mahathir¹, Alexander AW Peters², Gert J Fleuren³, Michelle Osse³, Sigit Purbadi¹***¹Department of Obstetrics and Gynecology
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The Netherlands***Abstract****Objective:** To evaluate the "false negative" of VIA in our study population compared to HPV DNA test as the reference test or gold standard.**Method:** We processed the cervical swab from 1,279 patients with negative VIA and detected the HPV DNA by using INNO-Lipa HPV DNA test.**Result:** From 1,279 women with negative VIA, 65 samples were excluded because of incomplete data and duplicate examination. From the remaining 1,214 women with negative VIA, 39 samples were confirmed to be positive for HPV DNA by both PCR and hybridization, leading to a "false negative" result of 3.21%.**Conclusion:** This study shows VIA as a very effective method for cervical cancer screening. VIA gives an excellent result, particularly for ectocervix, with minimal cost. Therefore, it is very suitable to be used as cervical cancer screening in developing countries like Indonesia.

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Keywords: cervical cancer, HPV DNA, negative VIA, screening, VIA**Abstrak****Tujuan:** Untuk mengevaluasi "negatif palsu" IVA dibandingkan dengan tes DNA HPV sebagai pemeriksaan standar referensi dan baku emas.**Metode:** Terdapat 1.279 subjek dengan IVA negatif yang memenuhi kriteria inklusi. Hasil negatif tersebut dibandingkan dengan pemeriksaan baku yaitu tes DNA HPV INNO-Lipa.**Hasil:** Dari 1.279 pasien dengan IVA negatif, sebanyak 65 sampel dieksklusi karena data yang tidak lengkap dan pemeriksaan duplikat. Di antara 1.214 sampel yang tersisa, ditemukan 39 sampel positif setelah dibandingkan dengan tes DNA HPV baik PCR maupun hibridisasi. Berdasarkan temuan ini, didapatkan hasil negatif palsu IVA sebanyak 3,21%.**Kesimpulan:** Studi ini menunjukkan bahwa IVA merupakan metode skrining yang sangat efektif. Dengan biaya yang minimal, IVA memberikan hasil yang sangat baik pada fase skrining terutama untuk ekto-serviks. IVA sangat sesuai diterapkan sebagai metode skrining kanker serviks di negara-negara berkembang seperti Indonesia.

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Kata kunci: DNA HPV, IVA, IVA negatif, kanker serviks, skrining**Correspondence:** Tofan W Utami. Department of Obstetrics and Gynecology, Faculty of Medicine University of Indonesia, Jakarta. Telephone: 0818859585, Email: tofanwidya@yahoo.com**INTRODUCTION**

It is estimated that about 529,828 women are diagnosed with cervical cancer globally, of which 275,128 died due to this condition.^{1,2} Approximately 85 % of those cases occur in developing countries. Based on World Health Statistics in 2010, the incidence of cervical cancer in Indonesia was 100 per 100,000 people with approximately 200,000 new cases diagnosed annually. About 70% of cervical cancer cases were already at an advanced stage upon diagnosis.^{2,3}

In 2007, 3,112 cases of cervical cancer were reported, contributing to 75% of all gynecologic cancer cases. Based on the cancer staging, it was found that among all the cases 439 were at stage I (14.1%); 1,104 cases were at stage II (35.4%); 1,392 cases were at stage III (44.7%) and 117 cases were at stage IV (5,7%). Five year survival rate for stage I, II, III and IV were 50%, 40%, 20% and 0%, respectively.⁴

Cervical cancer is a condition that could potentially be prevented.⁵ However, due to the lack of

effective screening methods, preventive measures are difficult to carry out. Several methods are recognized for early detection of the disease. One of them is Pap test, which is a cytology test considered to be effective as a screening method. Nonetheless, the cost of this test is considered high and requires trained medical personnel to perform the test. Another detection method is HPV DNA testing. It is considered superior to other methods, as it can detect pre-cancerous lesions 30%-100% more accurately compared to Pap test. However, this is not a cost effective test making it inappropriate as a screening method.⁶ Another method that can detect cervical cancer in its early stage is visual inspection with acetic acid (VIA). This is a low cost test and is easy to perform in settings with limited health facilities. This test is a simple test with a sensitivity and specificity comparable to Pap test. Therefore, VIA is appropriate to be used in Indonesia for cervical cancer screening.

Various controversies exist on the ability of VIA method as an effective method that can be widely applied in Indonesia. If a large proportion of subjects with negative VIA turned out to have HPV infection, then VIA method may not be appropriate for cervical cancer screening. In order to achieve the target of an ideal screening coverage rate of 80%, it would require a screening method that is simple with low cost, but has a high accuracy. In this study, we evaluated VIA accuracy by involving a large number of subjects among the population of Jakarta, Indonesia. The aim of this study is to provide a strong rationalization for recommending VIA as a standard method of screening in Indonesia, which can subsequently be used as a national program.

METHODS

This study is a cross sectional study. It was conducted from January 2012 to May 2013 at the obstetrics and gynecology clinic in Dr. Cipto Mangunkusumo hospital, primary health centers, and other health facilities that are included in the "See and Treat" Female Cancer Programme (FCP) in Jakarta as well as at the Department of Gynecology and Department of Pathology, Leids Universitair Medisch Centrum (LUMC), The Netherlands. We included subjects who agreed to participate in this study, married, aged 20-50 years, resides permanently in Jakarta and had negative result from VIA test. In total, 1,279 subjects were suitable for in-

clusion into the study. We processed the cervical swab of all subjects and detected the HPV DNA by using PCR and electrophoresis test by INNO-Lipa.

RESULTS

Our youngest subject was aged 31 years old and the oldest was 50 years old, with a mean age of 40.9 years old. The first marriage is considered as the first sexual contact, which was relatively young, just a little over 20 years old. Based on marital status, most of our subjects were married once (88.2%). Considering the partners' marital status, almost all were married once (92.6%). Almost all subjects did not smoke (94.3%). Based on the baseline characteristics, the subjects in this study had a low risk for HPV infection. Characteristic of subjects are shown in Table 1.

Table 1. Baseline Characteristics

Variable	Description
Age (years)	40.9 9.28
Age at first marriage (years)	22.0 4.31
Marital status	
Married once	1054 (88.2%)
Married more than once	75 (6.3%)
Widow	65 (5.5%)
Marital status of partner	
Married once	1060 (92.6%)
Married more than once	84 (7.4%)
Parity	2.3 1.57
Smoking habit	
Smoke	69 (5.7%)
Do not smoke	1145 (94.3%)

Table 2. HPV DNA Test Results

Variable	n	%
HPV DNA (+)	39	3.21
HPV DNA (-)	1175	96.79
HR-HPV	13	68.42
Non HR-HPV	5	26.32
HPV-X	1	5.26
Single infection	22	56.41
Multiple infection	17	43.59

HR-HPV = high-risk HPV

The prevalence of HPV infection in subjects with negative VIA obtained in this study was 3.21%, which was very low compared to other studies on the prevalence of HPV in the screened population. If the HPV DNA test is used as a reference standard, this percentage can be considered as "false negative". HPV DNA test results are presented in table 2.

DISCUSSION

The prevalence of HPV infection obtained from this study is relatively low at 3.21% compared to the prevalence of HPV infection acquired from previous studies that have been conducted in asymptomatic reproductive age female population ranging from 5%-40%.⁷

Existing studies suggest that the majority of sexually active women will have HPV infection throughout their life, of which 75% will be infected by more than one type of HPV.⁸ Clifford et al reported the proportion of HPV infection in cytologically normal women aged 15-74 years from 11 countries (Nigeria, India, Vietnam, Thailand, Korea, Colombia, Argentina, Chile, The Netherlands, Italy, and Spain). The range of HPV infection in cytologically normal women was reported to range between 1.4% in Spain to 25.6% in Nigeria.⁹ Molano et al¹⁰ reported the prevalence of HPV in 1,859 subjects with normal cytology was 14.8%, while Bennani et al¹¹ reported a very high rate, which was 42.5%. HPV prevalence in cytologically normal women in Honduras as reported by Tabora et al was even as high as 51%.¹² Compared to these studies, the 3.21% found in our study is relatively low, allowing us to conclude that VIA can provide results comparable to or maybe even better than cytology. Bellinson et al in a study of 1,997 women in China concluded that the sensitivity of VIA is equal to or better than conventional cytology.¹³

From research conducted by Vet et al in the period of October 2004-February 2006 in Indonesia to 2,686 women aged 15-70 years in Jakarta, Tasikmalaya, and Bali, the overall prevalence of HPV was 11.4%. This figure is higher than that obtained from this study, because of the different population. Our study was done on subjects who had prior screening (VIA negative), while Vet et al conducted research in the general population who has not been screened.¹⁴ In another study conducted in the United States on a sample of 1,921 women aged 14-59 years, the overall prevalence of HPV was 26.8%.¹⁵

CONCLUSION

The prevalence of HPV infection in VIA negative women in this study was 3.21%. Based on our study results, we support VIA as a very effective method for cervical cancer screening. VIA provides excellent results with minimal cost. Therefore, it is very suitable to be used for cervical cancer screening in developing countries like Indonesia with the aim of eventually decreasing the incidence of cervical cancer.

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