10.5005/jp-journals-10032-1136

RESEARCH ARTICLE

Gynocular™ as a Field Colposcope: Real-life Experiences from a VIA and HPV DNA-based Cervical Cancer Screening Program in Rural India

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ABSTRACT

Introduction: Gynocular™ is a battery-operated, portable field colposcope with three-step magnification and green filter. The present study was conducted in a community setting to evaluate accuracy and also asess the advantages and limitations of Gynocular™ as a field colposcope.

Materials and methods: Women between 30 and 60 years were screened in the rural clinics in India using visual inspection on acetic acid (VIA) and human papillomavirus deoxyribonucleic acid (HPV DNA) test performed by trained health workers. Women positive on either test had evaluation by Gynocular™ by cervical punch biopsy irrespective of their Gynocular™ findings. A total of 12,727 women were screened using both VIA and hybrid capture 2 (HC2) test from April 2014 to February 2016.

Result: A total of 1,021 women positive on either VIA or HC2 test were examined by Gynocular™. A total number of 231 cases of cervical intraepithelial neoplasm 1 (CIN1), 23 cases of CIN2, 13 cases of CIN3, and 7 cases of invasive cancers were detected on histology. The sensitivity and specificity of Gynocular™ at Swede Score (SS) ≥ 5 were 97.7% [95% confidence interval (CI): 87.7–99.9%] and 78.6% (95% CI: 75.9–81.2%) respectively. Raising the threshold to ≥6 resulted in drop in the sensitivity to 93.0% (95% CI: 80.9–98.5%), but a large improvement in specificity at 94.5% (95% CI: 92.8–95.8%).

Conclusion: There is a great need for a technically less demanding and inexpensive colposcope to be used for programs in low- and middle-income countries (LMICs). The portability of the device, long battery back-up and ability to capture images using mobile phone are the advantages for using this device in field settings.

Keywords: Field colposcope in cervical cancer screening, Gynocular™ in cervical cancer screening, Portable colposcope.

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How to cite this article: Banerjee D, Taghavi K, Mandal R, Rohner E, Mittal S, Maji T. Gynocular™ as a Field Colposcope: Real-life Experiences from a VIA and HPV DNA-based Cervical Cancer Screening Program in Rural India. J South Asian Feder Menopause Soc 2018;6(1):52-56.

Source of support: Nil

Conflict of interest: None

Date of received: 10 January 2018

Date of acceptance: 27 January 2018

Date of publication: August 2018

INTRODUCTION

Cervical cancer is a major cause of cancer-related deaths in females, especially in LMICs.[1] Cervical cancer is caused by a double-stranded DNA virus. With its long preinvasive stage, cervical cancer is amenable to prevention and cure is possible through early detection and management of pre cancers and early-stage cancer, thus making it one of the few cancers which fulfils all the criteria as a preventable disease. It is possible to arrest further progression to the invasive stage if the disease is detected in its preinvasive or microinvasive stage.

In high-income countries, cervical cancer is well controlled with established cytology-based screening program.[2] However, such resource-intense screening programs are difficult to implement and maintain in low-resource set-up due to poor infrastructure, lack of awareness about the disease, and shortage of trained manpower in remote places.[3] With introduction of non-cytological tests like VIA and HPV DNA test, there is a paradigm shift in the early detection and treatment of cervical neoplasias.[4] Based on these new screening tests, management algorithms for screening positive women have also been modified and recommended.[5] The main objectives of these screening test and the management algorithms are to limit the number of visits to health facilities and to ensure better compliance with treatment for women with cervical lesions. This is most relevant in low-resource settings, where women must overcome huge social and economic barriers to reach screening or treatment clinics and are likely to have only a once-in-a-lifetime opportunity to access services.

Fig. 1: Gynocular™ device

The standard of care for cytology-based programs in high-resource countries has been colposcopic verification and exact localization of disease in screen-positive women.[6] However, facilities for colposcopy are limited in low-resource settings because the specialized and expensive equipment is difficult to procure and maintain, the training requirements for the providers are high, and the necessary histopathology services are rarely available.[7] In addition to the demanding logistics, colposcopy in noncytology-based programs are more challenging, as the colposcopist will miss the option of reliability on the cytology result to diagnose the morphological abnormality.[8]

The Gynocular™ is a United States Food and Drug Administration-approved portable, battery-operated, handheld instrument measuring 50 × 33 × 166 mm with all features of a colposcope, i.e., illumination, green filter and three-step magnification (Fig. 1). The device can be mounted on a tripod stand using an adapter. When attached to a smart phone, one can capture images and store them online in a cloud called Triage to Diagnosis (T2D) software.

We performed a community-based study to assess the accuracy of Gynocular™ in detecting cervical precancers and cancers. The study also evaluated the advantages and challenges of using the Gynocular™ in clinical practice.

MATERIALS AND METHODS

This cross-sectional community-based study was a part of a rural community-based demonstration project conducted by the Department of Gynecological Oncology, Chittaranjan National Cancer Institute (CNCI), Kolkata, India, between April 2014 and February 2016. Women aged between 30 and 60 years were invited to participate in the study. Women with previous treatment for cervical neoplasias, pregnant women, and women who did not consent were excluded from the study. The inclusion criteria were women aged between 30 and 60 years without debilitating illness and having an intact uterus. After signing informed consent, all women were screened by VIA and the majority of women were screened by both by VIA and HC2 test (QIAGEN™, Gaithersburg, USA). The HC2 test detects 13 high-risk oncogenic HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) in the tested samples.[9] Trained health workers with appropriate aseptic measures first collected cervical swab for HPV testing and then performed VIA. The VIA was performed according to the World Health Organization (WHO) VIA manual on cervical cancer screening guidelines.[10] All VIA-positive women were examined with a Gynocular™ followed by biopsy on the same day as VIA was performed. The HC2-positive women who did not have Gynocular™ examination at the initial visit (since they were VIA-negative) were recalled to the community-based clinic on a later date upon confirmation of HC2 positivity for Gynocular™ examination followed by biopsy.

The Gynocular™ examination was performed by four trained gynecologists with more than 5 years of experience. The examination was performed following the same steps necessary to perform colposcopy—visualization of cervix after applying normal saline, examination of cervix with green filter, examination after applying 5% acetic acid for 1 minute, and examination after applying 5% Lugol's iodine. The magnifications (5×, 8×, and 12×) were used as and when required. The findings of Gynocular™ examination were documented using SS and International Federation for Cervical Pathology and Colposcopy (IFCPC) 2011 colposcopy terminology.[11] Both SS and IFCPC colposcopy terminology have been validated in colposcopy practice by several studies and based on these studies, biopsy and/or treatment is recommended.[11-13] Several studies suggested that SS at the cut-off value of 6 or higher indicates a high-grade lesion.[14] All women recruited in the current study received a cervical biopsy irrespective of their Gynocular™ findings. In case of normal Gynocular™ examination, at least one small punch biopsy was obtained from 12 o'clock position. Images were captured using Samsung Galaxy S3 smart phone and were stored in an online cloud using the T2D software application.

The formalin-fixed biopsy specimens were processed and interpreted at CNCI. The clinical information regarding age, Gynocular™ findings, and HPV status was provided to the pathologists. The histopathology findings were graded as normal, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesion, adenocarcinoma *in situ*, microinvasive carcinoma, squamous cell carcinoma, and adenocarcinoma.

The records of the screened women were maintained in a database prepared with EPI-INFO™ software,

version 7 (Centers for Disease Control and Prevention, Atlanta, USA). Statistical analysis was carried out using STATA 12 software. The cervical biopsies were considered as "gold standard" method for diagnosis and the histology reports were therefore, regarded as final diagnosis in all participants. The test accuracies [sensitivity, specificity, positive and negative likelihood ratios, and positive (PPV) and negative predictive values (NPV)] along with 95% CI were calculated after excluding a few cases who refused biopsy or had inconclusive biopsy report. Receiver operating characteristic (ROC) analysis was used to identify the optimal SS cut-off for discriminating between women with normal or low-grade lesions and those with CIN2+ during Gynocular™ examination. The curve was estimated with a parametric approach using a binomial model.

The study was approved by the CNCI Human Research Ethics Committee vide their approval no. 4.311/27/2014.

RESULTS

A total of 12,727 women were screened by VIA and HC2 test. Due to nonavailability of HC2 kit, 180 women recruited in the study were VIA-positive only as HC2 test was not performed. VIA was positive in 5.6% (n = 712/12727) and HC2 in 4.8% (n = 602/12547) of women. Totally, 1,021 women positive on either of the tests were examined by Gynocular™. Of the 1,021 screen-positive women, 37 women were excluded because they either refused (n = 1) or had inconclusive biopsy report (n = 36). The 37 women who were excluded had either normal or miscellaneous findings upon Gynocular™ examination. Totally 984 histology proven cases with diagnostic verification by Gynocular™ were taken for final data analysis. The sociodemographic characteristics of the participants recruited in the study are described in (Table 1). A total number of 231 cases of CIN1, 23 cases of CIN2, 13 cases of CIN3, and 7 cases of invasive cancers were detected on histology (Table 2).

The sensitivity and specificity estimates were derived for Gynocular™ examination and using two cut-off values on SS (Table 3). The sensitivity and specificity of Gynocular™ at SS ≥ 5 was 97.7% (95% CI 87.7–99.9%) and 78.6% (95% CI 75.9–81.2%) respectively. The PPV and NPV at SS ≥ 5 were 17.3% (95% CI 12.7–22.6%) and 99.9% (95% CI 99.3–100%) respectively. Raising the threshold to ≥6 resulted in drop in the sensitivity to 93.0% (95% CI 80.9–98.5%), but a large improvement in specificity at 94.5% (95% CI 92.8–95.8%). The estimated PPV and NPV at SS ≥ 6 were 43.5% (95% CI 33.2–54.2%) and 99.7% (95% CI 99.0–99.9%) respectively. The ROC curve (Graph 1) shows the diagnostic performance of the Gynocular examination with varying SS cut-offs. We observed that the optimum combination of high sensitivity and specificity could be achieved at the cut-off score of ≥6. In the interim analysis done on first 684 subjects recruited in the same study, the optimum cut-off of SS was 5 instead of 6. This can be explained by the more availability of senior colposcopists, and also increased experience of the physicians performing the Gynocular™ examination was useful in more precise examination of the cervix by the Gynocular™.

Table 1: Baseline characteristics of the study participants

Age (years)	*Number*
30–39	562 (57.11%)
40–49	279 (28.35%)
50–60	137 (13.92%)
Age at marriage (years)	
<20	539 (54.77%)
20–30	388 (39.43%)
>30	57 (5.79%)
Menopause achieved	
Yes	236 (23.98%)
No	748 (76.01%)
Education	
Nil	69 (7.01%)
Primary	385 (39.12%)
Secondary	420 (42.68%)
Graduate	101 (10.26%)
Postgraduate	9 (0.91%)

DISCUSSION

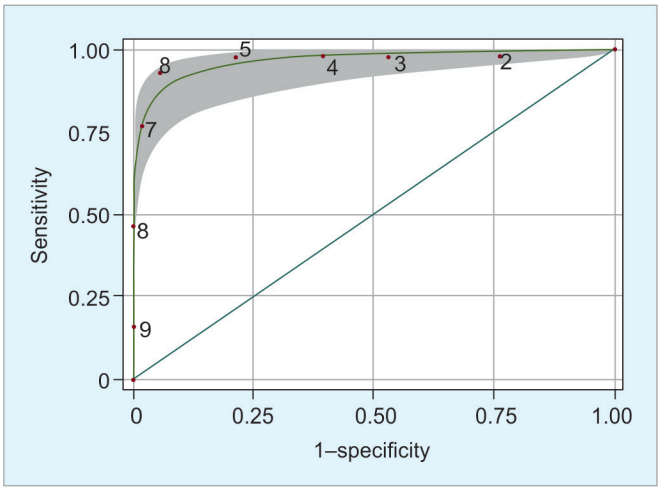
Colposcopy plays a key role to triage screen-positive women for guided biopsy and treatment.[15,16] But availability of this high-end technical instrument is limited in resource-constrained settings. With advancements in medical technology, the logistic disadvantages of the standard colposcopes can be overcome by simplified, portable

Table 2: Relationship between histology diagnosis and Gynocular™ SS

	Histology						
SS	*Normal*	*CIN1*	*CIN2 + CIN3*	*Invasive cancer*	*Not done*	*Inconclusive*	*Total*
<5	587	153	1	0	36	0	777 (100%)
5–6	114	69	9	0	0	1	193 (100%)
>6	9	9	26	7	0	0	51 (100%)
Total	710	231	36	7	36	1	1021 (100%)

Table 3: The sensitivity and specificity estimates for Gynocular™ examination using two cut-off values on SS

	SS	
Prevalence	*≥5*	*≥6*
Sensitivity	97.7% (95% CI 87.7–99.9)	93.0% (95% CI 80.9–98.5)
Specificity	78.6% (95% CI 75.9–81.2)	94.5% (95% CI 92.8–95.8)
+ Likelihood ratio	4.57 (95% CI 4.01–5.21)	16.8 (95% CI 12.8–22.2)
−Likelihood ratio	0.030 (95% CI 0.004–0.205)	0.074 (95% CI 0.025–0.22)
PPV	17.3% (95% CI 12.7–22.6)	43.5% (95% CI 33.2–54.2)
NPV	99.9% (95% CI 99.3–100)	99.7% (95% CI 99.0–99.9)



Graph 1: Estimated ROC curve of Gynocular™ examination in detection of CIN2+ lesions at different SS cut-off levels. The gray area represents the 95% CI of the estimated ROC curve; the diamonds indicate the test performance at a given SS cut-off

devices like the Gynocular™ which are available at lower cost. Linkage between screening and treatment has to be completed with minimum number of visits. Preferably, screening and treatment could even be completed within one visit, as proposed by the so-called "screen and treat" strategy as recommended by the WHO.[17]

The major limitation of the "screen and treat" strategy is overtreatment.[18] The PPV of VIA or HPV test does not exceed 10%.[19] Therefore, a triaging strategy that is accurate, logistically feasible, and inexpensive in the context of primary care settings in the LMICs is very much required for VIA- or HPV-based screening, and Gynocular™ fits the requirements. Our study shows that the accuracy of the Gynocular™ in identifying the benign or low-grade lesions is high also when performed in the field settings. Hence, using the Gynocular™ and a SS cut-off of ≥6 to decide on immediate treatment will minimize overtreatment for women who screened positive with VIA and/or HC2 testing. On the contrary, the SS cut-off of ≥6 also had a high sensitivity, indicating that there is very little possibility to miss the high-grade lesions. The magnification and the bright illumination can help the providers identify the squamocolumnar junction better, which will improve their capacity to select the cases eligible for ablative treatment correctly.

The biggest advantage of the Gynocular™ is its transportability while maintaining almost comparable features with the standard colposcopes. The ability of Gynocular™ to capture images on a cell phone allows obtaining opinions from experts who are not on site, and thereby facilitates continuous education to improve further skills. The stored images can be used for further training and quality assurance of the program. The limitations of using the Gynocular™ in this study were:

- Monocular optics
- Manual focusing
- Fixity of the device on the tripod stand
- Using the smart phone application requires some training, especially for persons less skilled in internet applications

A limitation of our study is that we have not used a randomized design to compare the device with colposcopy. Since application of Lugol's iodine takes hours to fade, it was difficult to perform both Gynocular™ and conventional colposcope in the same sitting. We did not compare Gynocular™ examination with standard colposcopy.

In the near future, using Gynocular™ as a triaging tool for women who screened positive for VIA and HC2 testing in resource-limited settings seems to be a feasible approach. The SS is useful in interpretation of changes seen on cervix during examination and can be used to categorize cervical abnormalities. Gynocular™ features, such as image capture and cloud storage yield new opportunities for telemedicine. For example, interpretation of the images by expert colposcopists who are not on site becomes possible and might be used to inform patient outcomes. In the era of technical advancements, Gynocular™ has opened up the options of new-generation devices and techniques which can be utilized according to the accessibility, affordability, and also feasibility of the health care system.

ACKNOWLEDGMENTS

The Gynocular™ instrument used in the study was donated free of charges to the project by Elisabeth Wikstrom Shemer, Founder of the Gynocular Device, Sweden. However, they did not have any role in preparing the project protocol, conduct of the study, or analysis and preparation of manuscript.

Dr Partha Basu, Screening Division, International Agency for Research on Cancer, Lyon, France, was

initially part of the project as Head, Department of Gynecological Oncology, Chittaranjan National Cancer Institute, Kolkata, and has contributed significantly in conceptualizing and implementing the project.

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