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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Abstract

Objectives Evaluation of the performance of VIA trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurse and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy and detect cervical lesions as accurate as doctors by using the Swede score method. Also, there was no difference using the Gynocular or stationary colposcope. Swede score by the Gynocular performed by nurses could offer a highly accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. However, considering the large sample size we consider the risk nondifferential.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no differences in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a very good specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled up by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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Competing interests and funding statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertice. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Concious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Contributions

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC,

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QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Data sharing statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer.

Transparancy Declaration

I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year 490 000 women are diagnosed with cervical cancer and 273 000 die from the disease.[1] In Bangladesh, 17,686 new cases of cervical cancer are discovered yearly and each year 10,364 women die from the disease.[2] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability.[3 4] According to the WHOs projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[5] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[6] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most common approach.[7 8 9] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[7 8 9 10]

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The role of colposcopy, is to visually assess size and extent of cervical lesion with strong illumination and magnification, and to select the most abnormal lesions for biopsy. [11] In low-resource settings, colposcopy is often used to assess the severity of the lesion as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[12]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[12 13 14 15 16] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure. [12 14 15 16]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors,[17 18 19] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[14 15 16]

The aim of this study was to evaluate accuracy in detection of cervical lesions by VIA trained nurses trained for colposcopy, using the Swede score colposcopy method, as compared to doctors by stationary colposcope and the Gynocular, using final histopathological result from cervical biopsies as gold standard.

METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using

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biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst them approximately 5% are VIA positive.[7] The opportunistic VIA screening programme in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh.[20 21 22] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[20 21 22] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[7 9]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. All women in the study were also examined by one of the six colposcopy specialists. The colposcopy specialists were

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physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7]

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH & Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[23] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points.[13 14 15 16]A self-holding nonlubricated speculum was applied into the vagina and the cervix was visualized.

The nurse started the examination with inspection of cervical vessel patterns as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel pattern with both instruments as randomized. The cervix was then wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution,

and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. All the scores were immediate recorded by the study nurse. The examination was completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4.[13 15 16] The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[24]

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Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular. The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

The Gynocular (Gynius AB, Stockholm, Sweden) has similar specifications to traditional colposcopes[15 16] and is small handheld battery-driven colposcope measuring 50 x 33 x 166 mm with 300 mm focal distance and three magnifications: 5x, 8x and 12x.[15 16] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non invasive medical diagnostic class I tool, CE marked and FDA pending.

Statistical Analysis

All statistical analyses have been performed using R version 2.14.[25] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope.[13 14 15 16] Detection rates of CIN 1, CIN 2, CIN 3, CIN 3+(invasive cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were

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calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of doctor's Swede scores between 4 and 10 and nurses Swede scores between 1 and 10. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of ROC curves between nurses and doctors were performed on a subset of women with Swede scores ≥4 for both nurses and doctors. The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. With an expected rate of 2.5 % in naïve women and 7.5% in VIA positive women, a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the parameter estimates. Thus the aim was to include a total of approximately 1000 women.

RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (58.2 %) women, Swede score was <4 and no biopsy taken.

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When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 66.1% (95% CI 58.9 - 72.8%) for CIN2+ and gynocular had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4% for CIN2+ (table 2). For doctors, using the colposcope and a cuf-off values of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) and for the Gynocular the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) for detecting CIN2+ (table 3).

The sensitivity decreased while specificity increased with increased Swede score, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3).

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that nurses trained on VIA for 2 weeks in colposcopy in a low-resource setting, were equally good in detecting CIN2+ lesions as accredited colposcopists. Also, there were no significant

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differences using the Gynocular and the standard colposcope in detecting cervical lesions confirmed by a high agreement of Swedes scores and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[23] Another strength is that all the biopsies were analyzed in single-site laboratory.

The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. However, considering the large sample size we consider the risk nondifferential.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year.[27 28 29] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [28 29] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap.[28 29]

The task-shifting could also be applied to colposcopy since 273 000 women die from cervical cancer eash year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse colposcopists are an well-established resource within colposcopy,[17 18 19] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

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Bowring et al.[14] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[13 14] and low-resource settings.[15 16]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested that Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. [14 15 16] Thus, it is interesting to note that Swede score directed punch biopsies were more accurate than cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and Bangladesh.[15 16] In a multi-center randomized controlled trial, direct colposcopy identified more cervical lesions than repeat cytology[30] and a studies from Nigeria and Bangladesh concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[21 31]

A recent trial from Bangladesh concluded that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[22] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[32] VIA camps had a synergistic effect on the community, as women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[32] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future

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approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment. Improvement of patients' knowledge and proper counselling should be important component of this protocol.

Women would then not have to accept treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings. Sankaranarayanan et al revealed that adequately trained nurses can be used to deliver colposcopy and cryotherapy services and are important, reliable, and efficient alternate human resources.[33] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should evaluate the effectiveness of VIA screening and direct colposcopy evaluation and treatment in low-resource settings.

Conclusion

In summary, a colposcopy examination by a colposcopy trained VIA nurse or doctor, using the Gynocular or stationary colposcope utilizing the Swede score colposcopy scoring system, are equally good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams for detection of cervical high-grade lesions.

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Ethical approval

This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

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Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

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Contributorship Statement

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing Interests

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertice. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Concious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Data Sharing Statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer at elisabeth@gynocular.com

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.8)	13 (2.5)
Chronic cervicitis		23 (5.8)	82 (15.7)
CIN1		19 (4.8)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
CIN3+		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		342 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels (*nurses*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
1	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
1	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels *(doctors).*

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
5	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
5	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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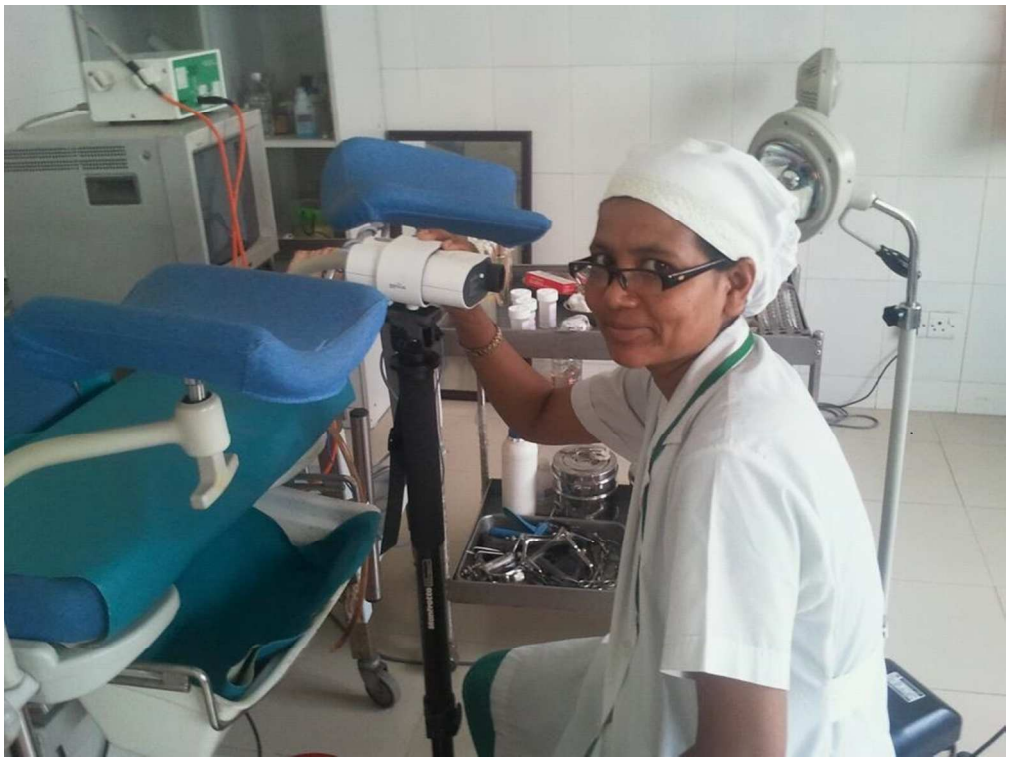

Colposcopy trained VIA nurse with Gynocular
254x190mm (96 x 96 DPI)

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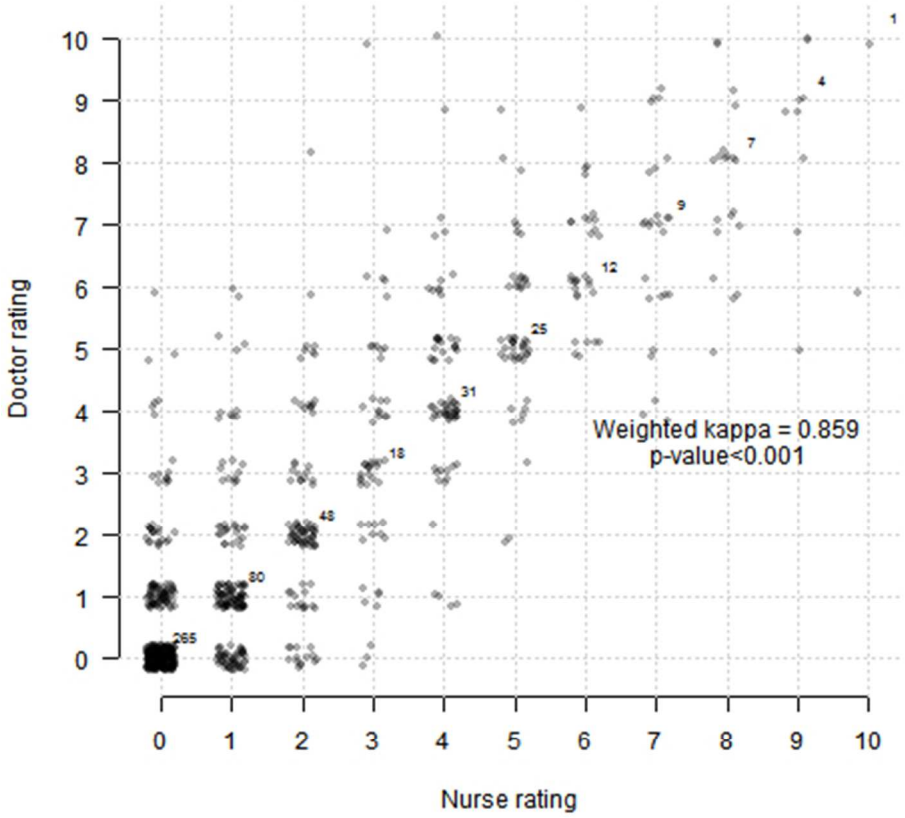

Agreement between nurses and doctors using Gynocular (500 out of 919 with exact same result (54.4 %)).
169x169mm (72 x 72 DPI)

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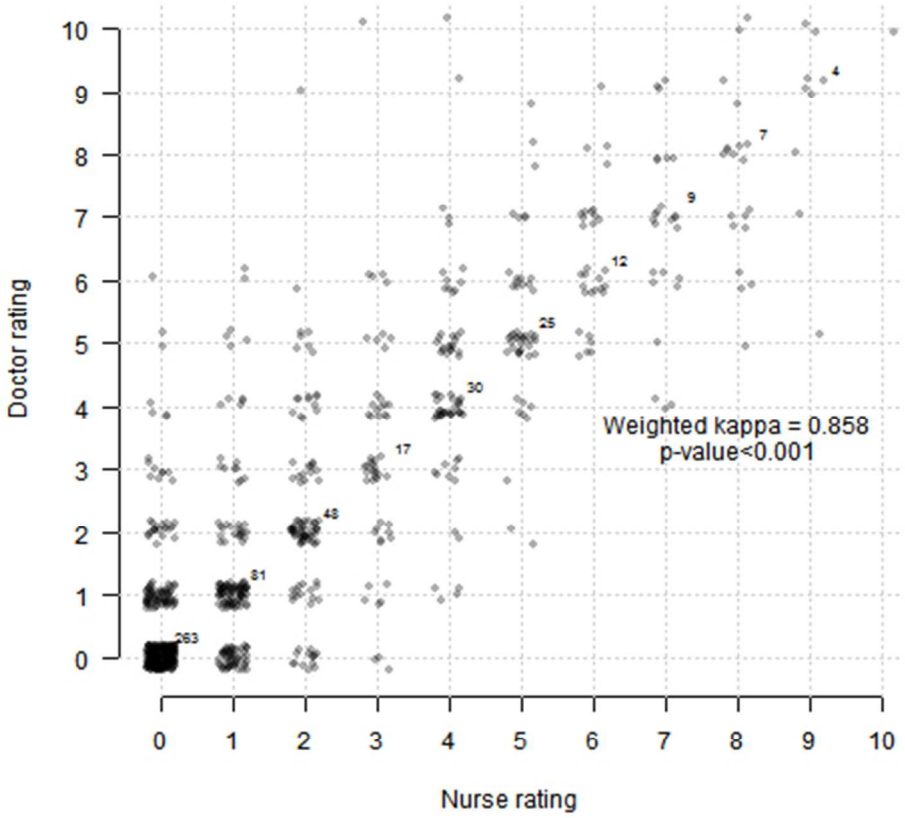

Agreement between nurses and doctors using coploscope (497 out of 918 with exact same result (54.1 %).
169x169mm (72 x 72 DPI)

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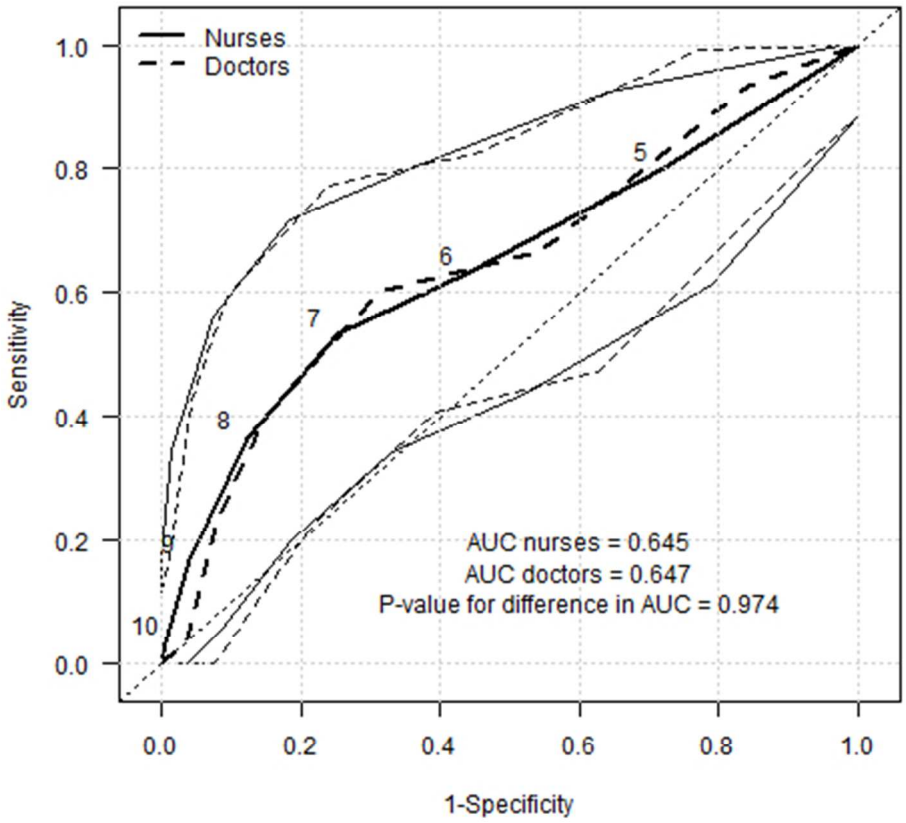

ROC curves for predicting a positive biopsy result (CIN2+), using Gynocular.
169x169mm (72 x 72 DPI)

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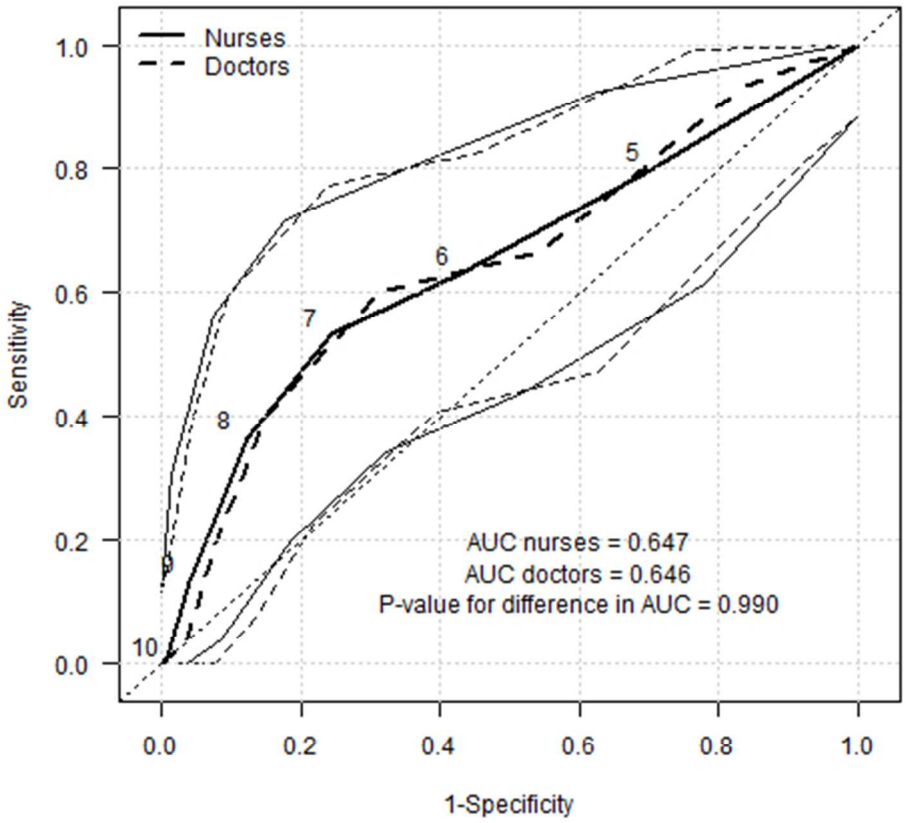

ROC curves for predicting a positive biopsy result (CIN2+), using colposcope.
169x169mm (72 x 72 DPI)

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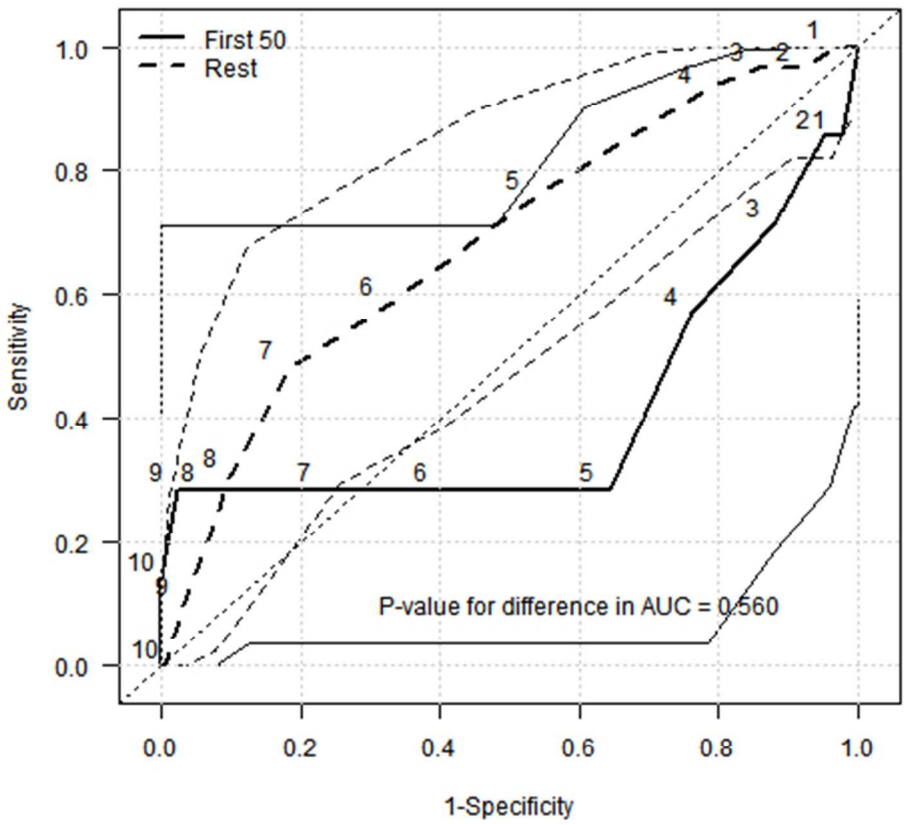

ROC curves for predicting a positive biopsy result (CIN2+) using Gynocular (Nurses first 50 vs rest).
169x169mm (72 x 72 DPI)

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Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	167-169
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	182-187
Interventions	Interventions intended for each group	197-223
Objective	Specific objective or hypothesis	158-161
Outcome	Clearly defined primary outcome for this report	167-169
Randomization	How participants were allocated to interventions	201-202
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Not applicable
Results		
Numbers randomized	Number of participants randomized to each group	206
Recruitment	Trial status	Completed
Numbers analysed	Number of participants analysed in each group	All
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	268-297
Harms	Important adverse events or side effects	None
Conclusions	General interpretation of the results	376-281
Trial registration	Registration number and name of trial register	228-230
Funding	Source of funding	108-110

**this item is specific to conference abstracts*

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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Global health, Medical education and training, Diagnostics
Keywords:	Colposcopy < GYNAECOLOGY, GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Abstract

Objectives Evaluation of the performance of VIA (Visual inspection with acetic acid) trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular, as compared to doctors.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. Swede score grade cervical acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurses and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy. There was no significant differences compared to doctors in detecting cervical lesions by stationary colposcope or the Gynocular using the Swede score system. Swede score by the Gynocular performed by nurses could offer a highly accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. Other study designs were considered, but would have been difficult to implement in a low-resource setting, where many poor women might never come back again to the colposcopy clinic. Also, blinding of which instrument that was used was not possible, due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we consider the risk of bias reduced.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no evidence of statistically significant differences for nurses or doctors in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a high specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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Competing interests and funding statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Conscious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Contributions

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

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Data sharing statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer.

Transparancy Declaration

I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year, 528 000 women are diagnosed with cervical cancer worldwide and 266 000 die from the disease.[1] A majority (87%) of women diagnosed with cervical cancer live in less developed regions of the world.[1] Mortality varies highly, ranging from less than 2 per 100 000 in developed regions to more than 20 per 100 000 areas such as Melanesia, Middle and Eastern Africa.[1]

In Bangladesh, 11 956 new cases of cervical cancer are discovered yearly and each year 6 582 women die from the disease.[1] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability. [2 3] According to the IARC's projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[4] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[5] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most

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common approach.[6 7 8] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[6 7 8 9]

The role of colposcopy, is to visually assess size and extent of cervical lesions with strong illumination and magnification, and to select the most abnormal lesions for biopsy.[10] In low-resource settings, colposcopy is often used to assess the severity of the lesion in VIA positive women as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[11]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[11 12 13 14 15] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure.[11 12 14 15]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors,[16 17 18] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[13 14 15] By using the Swede score systematic colposcopy method, the findings of the colposcopic findings of the cervix[12 13] can be organized and scored in a structured manner.[12 13] The Swede score differ from other cervical scoring systems by adding the lesion size as a variable.[12 13]

The main aim of this study was to evaluate if nurse led Swede score colposcopy in a low resource setting, had a similar performance to a doctor Swede score colposcopy in detecting cervical lesions. The second aim of the study was to evaluate if a nurse or doctor Gynocular colposcopy had similar performances as compared to a stationary colposcopy in detecting cervical lesions. The third aim of the study was to evaluate if nurse led Swede score colposcopy could be a future option for detection of cervical lesions in low resource settings.

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METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst them approximately 5% are VIA positive.[6] The opportunistic VIA screening programme in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh. [18 19 20] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[18 19 20] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[6 8]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

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In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. The colposcopy specialists were accredited physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7] All women in the study were examined by one of the two nurses and one of the six colposcopy specialists and both by the stationary colposcope and the Gynocular.

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH & Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[22] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points. [12 13 14 15]

A self-holding non-lubricated speculum was applied into the vagina and the cervix was visualized. The nurse started the examination with inspection of cervical vessels of mosaic pattern, punctuation, atypical vessels or absence of vessels as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel patterns with both instruments as randomized. This procedure slightly differs from the original Swede score[12], where vessels are inspected after acetic acid application of the cervix. However, after application of acetic acid, the whitening effect on the cervix slowly fades. Therefore

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we chose to first inspect the vessel pattern, and then applicate the acetic acid to ensure both nurses and doctors would have enough time to accurately estimate the acetowhitening effect before fading. Thus, the cervix was wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution, and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. The results from the examinations were reported from the nurses and the doctors to the study nurse in a separate location. The other examiners could not overhear the reports and they could not see the results of the previous examiner. The nurses and the doctors were also not allowed to communicate the patient's examination results. The examination was completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4, [12 13 15] as doctors using the Swede score has been validated and biopsy recommended when Swede score of 6 and above, [12 13] and this study aimed to validate nurse colposcopist's Swede scoring in a low resource setting (which has not been validated before). The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[23]

Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cervical cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular.

The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

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The Gynocular (Gynius AB, Stockholm, Sweden) is a high resolution monocular colposcope with similar specifications to stationary colposcopes, [14 15] The Gynocular is small, handheld, battery-driven, measuring 50 x 33 x 166 mm with 300 mm focal distance, and three magnifications: 5x, 8x and 12x.[14 15] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non-invasive medical diagnostic class I tool, CE marked and FDA approved.

Statistical Analysis

All statistical analyses have been performed using R version 2.14.[24] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope. [12 13 14 15] Detection rates of CIN 1, CIN 2, CIN 3, ICC (invasive cervical cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of Swede scores between 4 and 10 for doctors and 0 and 10 for nurses. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. With an expected rate of 2.5 % in naïve women and

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7.5% in VIA positive women, a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the nurses colposcopists accuracy and Swede scoring compared to doctors[12 13]. Thus the aim was to include a total of approximately 1000 women.

In a retrospective power analysis based on the results from the present study, we estimated that approximately 1500 biopsies would have been needed (as compared to the 228 biopsies with in women with Swede score above 4 in this study) for 80 % power to detect a difference of 0.05 in AUC of the ROC curves at 5 % significance level.

RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. 256 women had a Swede score of at least 4 by a doctor and of them 228 had a biopsy, and 28 refused biopsy (excluded from ROC analyses). 59 biopsies were taken outside research protocol (excluded from ROC analyses). 27 VIA positive women had CIN2+ and 5 screening naïve women had CIN2+. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (57.4%) women, Swede score was <4 and no biopsy taken.

When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

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Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, Gynocular by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4%) for CIN2+ and stationary colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 66.1.6% (95% CI 58.9 - 72.8% for CIN2+ (table 2). For doctors, using the Gynocular and a cut-off value of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) and for the stationary colposcope the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) for detecting CIN2+ (table 3). The sensitivity decreased while specificity increased with increased Swede score for CIN2+, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3). A Swede scores of eight and above had high specificity for CIN2+ lesions (table 2 and table3).

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that VIA nurses trained in colposcopy in a low resource setting, detect high grade cervical lesions as good as specialized doctors using the Swede score systematic colposcopy system. Also, there were no significant differences for the nurses or the doctors using the Gynocular and the standard colposcope in detecting cervical lesions, confirmed by a high agreement of Swedes scores

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and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[22] Other strengths are that all the biopsies were analyzed in a single-site laboratory, and the large number of included women were all examined in a single center.

The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. However, the Swede score has already been validated in Sweden and in the United Kingdom [12 13] and a cervical biopsy was recommended when a Swede score of 6 and above. The Swede score has also been used previous Gynocular studies in other low resource settings.[14 15] In our study, we lowered the Swede score biopsy threshold to 4, as we worked in a low resource setting with limited resources for follow-up and call back service of the included women. Interestingly, even when lowering the threshold for biopsy, we found few VIA women positive women with a CIN2+ lesion, results similar to our previous studies.[14 15] In screening naïve women, it was even more uncommon with CIN2+. It was reassuring to note that these women were detected by both nurses and doctors.

The cross-over design was chosen to lessen possible observer variability, but may also have influenced the scoring of the second instrument. Other study designs were evaluated, but would have been difficult to implement in a low-resource setting, where many poor women may never come back again to the colposcopy clinic. Also, blinding of which instrument used was not possible due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we reduced the risk of the second examination's possible influence of cervical impression to affect the statistical calculations. Further, the inclusion of postmenopausal women and

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possible breastfeeding women, could have affected the results, as Swede score has not been validated on postmenopausal women and breast feeding women.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year. [26 27 28] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [27 28] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap. [27 28]

The task-shifting could also be applied to colposcopy since 266 000 women die from cervical cancer each year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse colposcopists are an well-established resource within colposcopy, [16 17 18] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

Bowring et al.[13] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse colposcopist Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[11 12] and low-resource settings.[13 14]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested[13 14 15] that the Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. Thus, it is interesting to note that Swede score directed punch biopsies in women with a score of 4 and above, were more accurate than cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and

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Bangladesh.[14 15] Moreover, in a multi-center randomized controlled trial,[29] direct colposcopy identified more cervical lesions than repeat cytology and a studies from Bangladesh and Nigeria[20 30] concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[20 30]

A recent trial from Bangladesh summarised that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[21] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[31] VIA camps had a synergistic effect on the community, as women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[32] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment and further research on nurse led Swede score colposcopy in low resource settings is needed. Improvement of patients' knowledge and proper counselling should be important component of this protocol. Women would then not have to accept treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings, and to promote and evaluate such programs in adequately powered research studies. Sankaranarayanan et al showed previously that adequately trained nurses can be used to deliver colposcopy and cryotherapy services and are important, reliable, and efficient alternate human

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resources.[32] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should further evaluate VIA screening and direct colposcopy in low-resource settings.

Conclusion

In summary, a Swede score colposcopy examination by a nurse or doctor colposcopist, using the Gynocular or stationary colposcope, is equally good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams a tool for early detection of cervical high-grade lesions. This method should be further explored and evaluated

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Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

Ethical approval

This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

Contributorship statement

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project. EWS and NA designed the study. NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing interests

EWS is the inventor of the Gynococular. EWS and IS are shareholders in Gynius.

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Data sharing

The dataset is available on request from the corresponding author:

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.7)	13 (2.5)
Chronic cervicitis		23 (5.7)	82 (15.7)
CIN1		19 (4.7)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
CIN3+		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		343 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) (*nurses, n = 228*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
≥9 vs <9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
≥6 vs <6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
≥5 vs <5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
≥4 vs <4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
≥3 vs <3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
≥9 vs <9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
≥6 vs <6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
≥5 vs <5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
≥4 vs <4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
≥3 vs <3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer *(doctors, n = 228).*

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
≥6 vs <6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
≥6 vs <6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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Figure Legends

Figure 1

The Gynocular with tripod mounting clip that screws into any standard tripod

Figure 2

Cross tabulation of Swede score's by Gynocular of nurses and doctors with Kappa.

Figure 3

Cross tabulation of Swede score's by stationary colposcope of nurses and doctors.

Figure 4

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by Gynocuar and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 5

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by stationary colposcope and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 6

ROC curves for predicting a positive biopsy result CIN2+(CIN 2, CIN 3 and invasive cervical cancer) using Gynocular (Nurses first 50 vs rest).

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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Abstract

Objectives Evaluation of the performance of VIA (Visual inspection with acetic acid) trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular, as compared to doctors.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. Swede score grade cervical acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurses and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy. There was no significant differences compared to doctors in detecting cervical lesions by stationary colposcope or the Gynocular using the Swede score system. Swede score by the Gynocular performed by nurses could offer a highly accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. Other study designs were considered, but would have been difficult to implement in a low-resource setting, where many poor women might never come back again to the colposcopy clinic. Also, blinding of which instrument that was used was not possible, due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we consider the risk of bias reduced.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no evidence of statistically significant differences for nurses or doctors in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a high specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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Competing interests and funding statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Conscious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Contributions

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

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Data sharing statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer.

Transparancy Declaration

I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year, 528 000 women are diagnosed with cervical cancer worldwide and 266 000 die from the disease.[1] A majority (87%) of women diagnosed with cervical cancer live in less developed regions of the world.[1] Mortality varies highly, ranging from less than 2 per 100 000 in developed regions to more than 20 per 100 000 areas such as Melanesia, Middle and Eastern Africa.[1]

In Bangladesh, 11 956 new cases of cervical cancer are discovered yearly and each year 6 582 women die from the disease.[1] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability. [2 3] According to the IARC's projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[4] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[5] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most

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common approach.[6 7 8] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[6 7 8 9]

The role of colposcopy, is to visually assess size and extent of cervical lesions with strong illumination and magnification, and to select the most abnormal lesions for biopsy.[10] In low-resource settings, colposcopy is often used to assess the severity of the lesion in VIA positive women as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[11]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[11 12 13 14 15] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure.[11 12 14 15]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors,[16 17 18] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[13 14 15] By using the Swede score systematic colposcopy method, the findings of the colposcopic findings of the cervix[12 13] can be organized and scored in a structured manner.[12 13] The Swede score differ from other cervical scoring systems by adding the lesion size as a variable.[12 13]

The main aim of this study was to evaluate if nurse led Swede score colposcopy in a low resource setting, had a similar performance to a doctor Swede score colposcopy in detecting cervical lesions. The second aim of the study was to evaluate if a nurse or doctor Gynocular colposcopy had similar performances as compared to a stationary colposcopy in detecting cervical lesions. The third aim of the study was to evaluate if nurse led Swede score colposcopy could be a future option for detection of cervical lesions in low resource settings.

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METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst them approximately 5% are VIA positive.[6] The opportunistic VIA screening programme in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh. [18 19 20] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[18 19 20] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[6 8]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

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In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. The colposcopy specialists were accredited physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7] All women in the study were examined by one of the two nurses and one of the six colposcopy specialists and both by the stationary colposcope and the Gynocular.

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH & Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[22] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points. [12 13 14 15]

A self-holding non-lubricated speculum was applied into the vagina and the cervix was visualized. The nurse started the examination with inspection of cervical vessels of mosaic pattern, punctuation, atypical vessels or absence of vessels as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel patterns with both instruments as randomized. This procedure slightly differs from the original Swede score[12], where vessels are inspected after acetic acid application of the cervix. However, after application of acetic acid, the whitening effect on the cervix slowly fades. Therefore

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we chose to first inspect the vessel pattern, and then applicate the acetic acid to ensure both nurses and doctors would have enough time to accurately estimate the acetowhitening effect before fading. Thus, the cervix was wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution, and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. The results from the examinations were reported from the nurses and the doctors to the study nurse in a separate location. The other examiners could not overhear the reports and they could not see the results of the previous examiner. The nurses and the doctors were also not allowed to communicate the patient's examination results. The examination was completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4, [12 13 15] as doctors using the Swede score has been validated and biopsy recommended when Swede score of 6 and above, [12 13] and this study aimed to validate nurse colposcopist's Swede scoring in a low resource setting (which has not been validated before). The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[23]

Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cervical cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular.

The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

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The Gynocular (Gynius AB, Stockholm, Sweden) is a high resolution monocular colposcope with similar specifications to stationary colposcopes, [14 15] The Gynocular is small, handheld, battery-driven, measuring 50 x 33 x 166 mm with 300 mm focal distance, and three magnifications: 5x, 8x and 12x.[14 15] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non-invasive medical diagnostic class I tool, CE marked and FDA approved.

Statistical Analysis

All statistical analyses have been performed using R version 2.14.[24] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope. [12 13 14 15] Detection rates of CIN 1, CIN 2, CIN 3, ICC (invasive cervical cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of Swede scores between 4 and 10 for doctors and 0 and 10 for nurses. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. With an expected rate of 2.5 % in naïve women and

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7.5% in VIA positive women, a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the nurses colposcopists accuracy and Swede scoring compared to doctors[12 13]. Thus the aim was to include a total of approximately 1000 women.

In a retrospective power analysis based on the results from the present study, we estimated that approximately 1500 biopsies would have been needed (as compared to the 228 biopsies with in women with Swede score above 4 in this study) for 80 % power to detect a difference of 0.05 in AUC of the ROC curves at 5 % significance level.

RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. 256 women had a Swede score of at least 4 by a doctor and of them 228 had a biopsy, and 28 refused biopsy (excluded from ROC analyses). 59 biopsies were taken outside research protocol (excluded from ROC analyses). 27 VIA positive women had CIN2+ and 5 screening naïve women had CIN2+. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (57.4%) women, Swede score was <4 and no biopsy taken.

When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

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Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, Gynocular by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4%) for CIN2+ and stationary colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 66.1.6% (95% CI 58.9 - 72.8% for CIN2+ (table 2). For doctors, using the Gynocular and a cut-off value of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) and for the stationary colposcope the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) for detecting CIN2+ (table 3). The sensitivity decreased while specificity increased with increased Swede score for CIN2+, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3). A Swede scores of eight and above had high specificity for CIN2+ lesions (table 2 and table3)

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that VIA nurses trained in colposcopy in a low resource setting, detect high grade cervical lesions as good as specialized doctors using the Swede score systematic colposcopy system. Also, there were no significant differences for the nurses or the doctors using the Gynocular and the standard colposcope in detecting cervical lesions, confirmed by a high agreement of Swedes scores

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and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[22] Other strengths are that all the biopsies were analyzed in a single-site laboratory, and the large number of included women were all examined in a single center.

The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. However, the Swede score has already been validated in Sweden and in the United Kingdom [12 13] and a cervical biopsy was recommended when a Swede score of 6 and above. The Swede score has also been used previous Gynocular studies in other low resource settings.[14 15] In our study, we lowered the Swede score biopsy threshold to 4, as we worked in a low resource setting with limited resources for follow-up and call back service of the included women. Interestingly, even when lowering the threshold for biopsy, we found few VIA women positive women with a CIN2+ lesion, results similar to our previous studies.[14 15] In screening naïve women, it was even more uncommon with CIN2+. It was reassuring to note that these women were detected by both nurses and doctors.

The cross-over design was chosen to lessen possible observer variability, but may also have influenced the scoring of the second instrument. Other study designs were evaluated, but would have been difficult to implement in a low-resource setting, where many poor women may never come back again to the colposcopy clinic. Also, blinding of which instrument used was not possible due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we reduced the risk of the second examination's possible influence of cervical impression to affect the statistical calculations. Further, the inclusion of postmenopausal women and

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possible breastfeeding women, could have affected the results, as Swede score has not been validated on postmenopausal women and breast feeding women.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year. [26 27 28] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [27 28] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap. [27 28]

The task-shifting could also be applied to colposcopy since 266 000 women die from cervical cancer each year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse colposcopists are an well-established resource within colposcopy, [16 17 18] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

Bowring et al.[13] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse colposcopist Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[11 12] and low-resource settings.[13 14]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested[13 14 15] that the Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. Thus, it is interesting to note that Swede score directed punch biopsies in women with a score of 4 and above, were more accurate than cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and

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Bangladesh.[14 15] Moreover, in a multi-center randomized controlled trial,[29] direct colposcopy identified more cervical lesions than repeat cytology and a studies from Bangladesh and Nigeria[20 30] concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[20 30]

A recent trial from Bangladesh summarised that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[21] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[31] VIA camps had a synergistic effect on the community, as women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[32] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment and further research on nurse led Swede score colposcopy in low resource settings is needed. Improvement of patients' knowledge and proper counselling should be important component of this protocol. Women would then not have to accept treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings, and to promote and evaluate such programs in adequately powered research studies. Sankaranarayanan et al showed previously that adequately trained nurses can be used to deliver colposcopy and cryotherapy services and are important, reliable, and efficient alternate human

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resources.[32] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should further evaluate VIA screening and direct colposcopy in low-resource settings.

Conclusion

In summary, a Swede score colposcopy examination by a nurse or doctor colposcopist, using the Gynocular or stationary colposcope, is equally good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams a tool for early detection of cervical high-grade lesions. This method should be further explored and evaluated

Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

Ethical approval

This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

Contributorship statement

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project. EWS and NA designed the study. NA, JSR, MAC, QK, RA, MT and EWS provided

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gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing interests

EWS is the inventor of the Gynococular. EWS and IS are shareholders in Gynius.

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Data sharing

The dataset is available on request from the corresponding author:

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Figure Legends

Figure 1

The Gynocular with tripod mounting clip that screws into any standard tripod

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Figure 2

Cross tabulation of Swede score's by Gynocular of nurses and doctors with Kappa.

Figure 3

Cross tabulation of Swede score's by stationary colposcope of nurses and doctors.

Figure 4

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by Gynocuar and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 5

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by stationary colposcope and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 6

ROC curves for predicting a positive biopsy result CIN2+(CIN 2, CIN 3 and invasive cervical cancer) using Gynocular (Nurses first 50 vs rest).

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.7)	13 (2.5)
Chronic cervicitis		23 (5.7)	82 (15.7)
CIN1		19 (4.7)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
CIN3+		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		343 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) (*nurses, n = 228*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
≥9 vs <9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
≥6 vs <6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
≥5 vs <5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
≥4 vs <4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
≥3 vs <3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
≥9 vs <9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
≥6 vs <6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
≥5 vs <5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
≥4 vs <4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
≥3 vs <3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer *(doctors, n = 228)*.

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
≥6 vs <6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
≥6 vs <6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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The Gynocular with tripod mounting clip that screws into any standard camera tripod
90x134mm (300 x 300 DPI)

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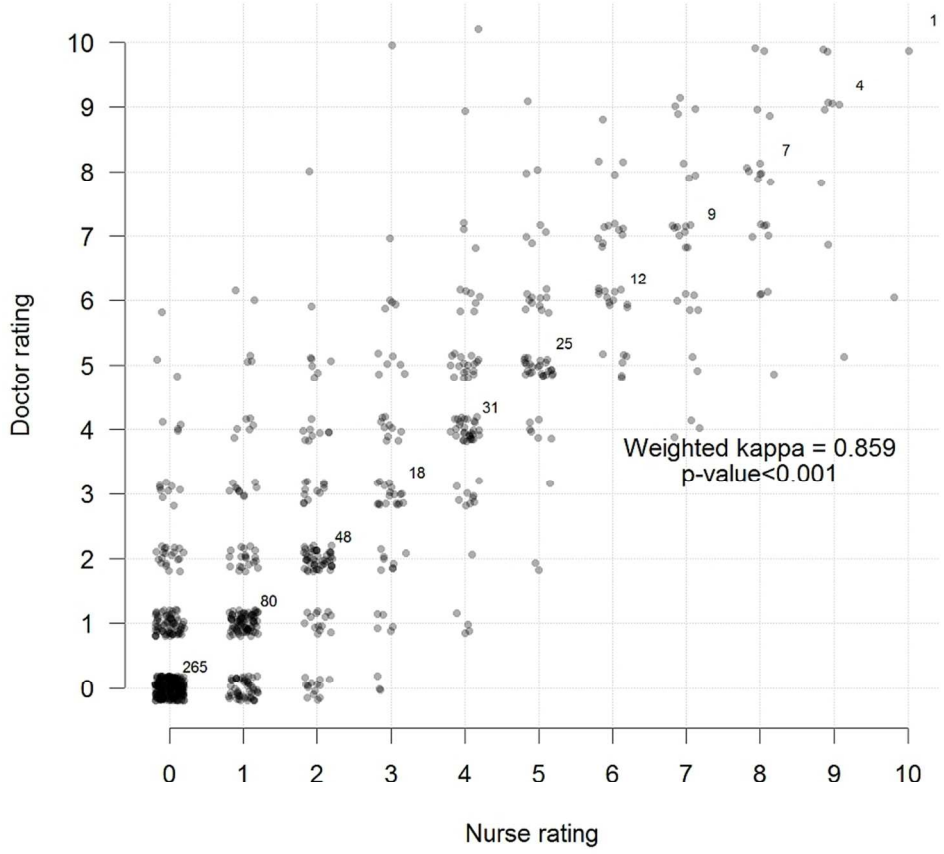

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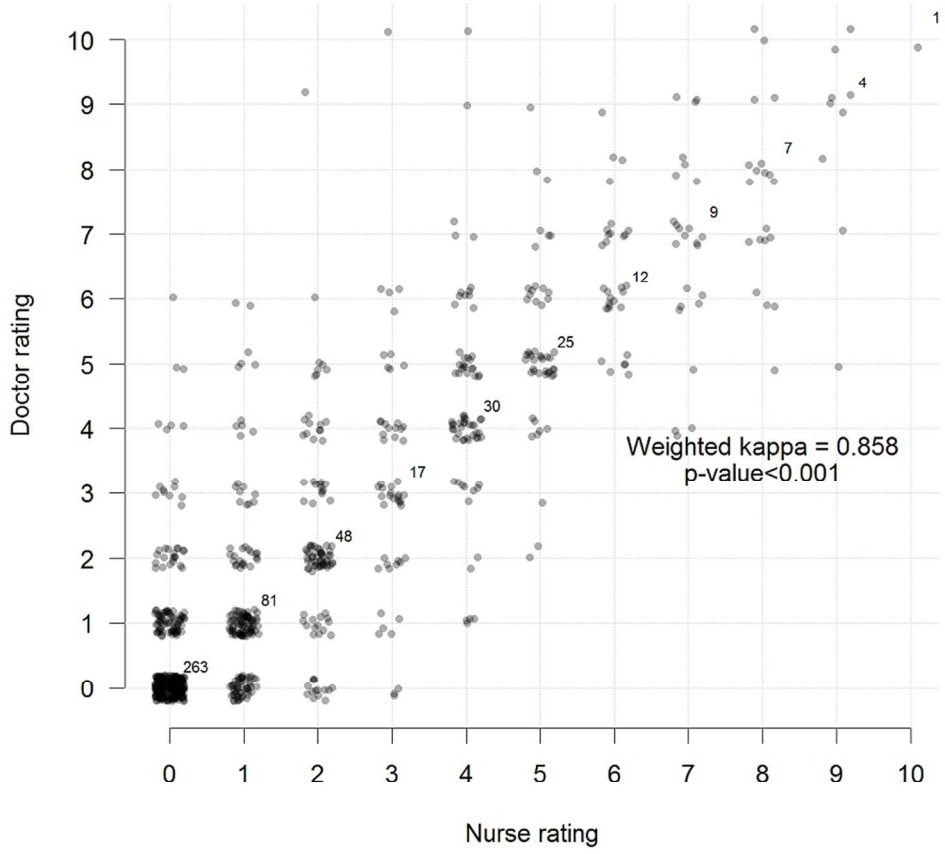

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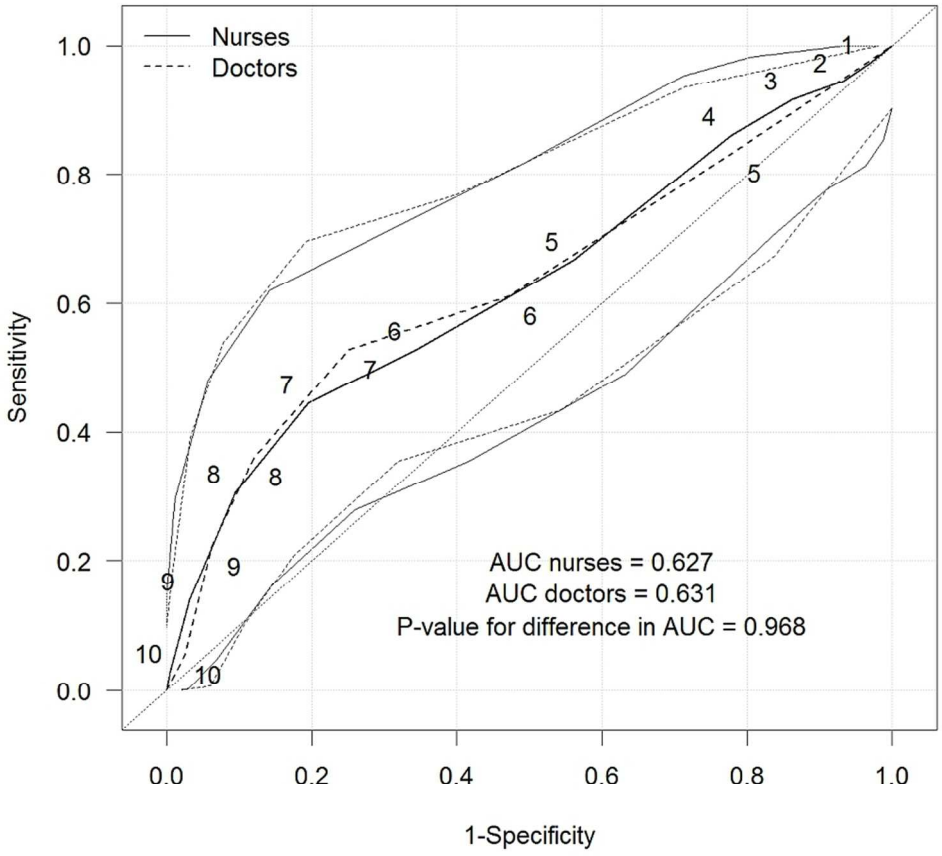

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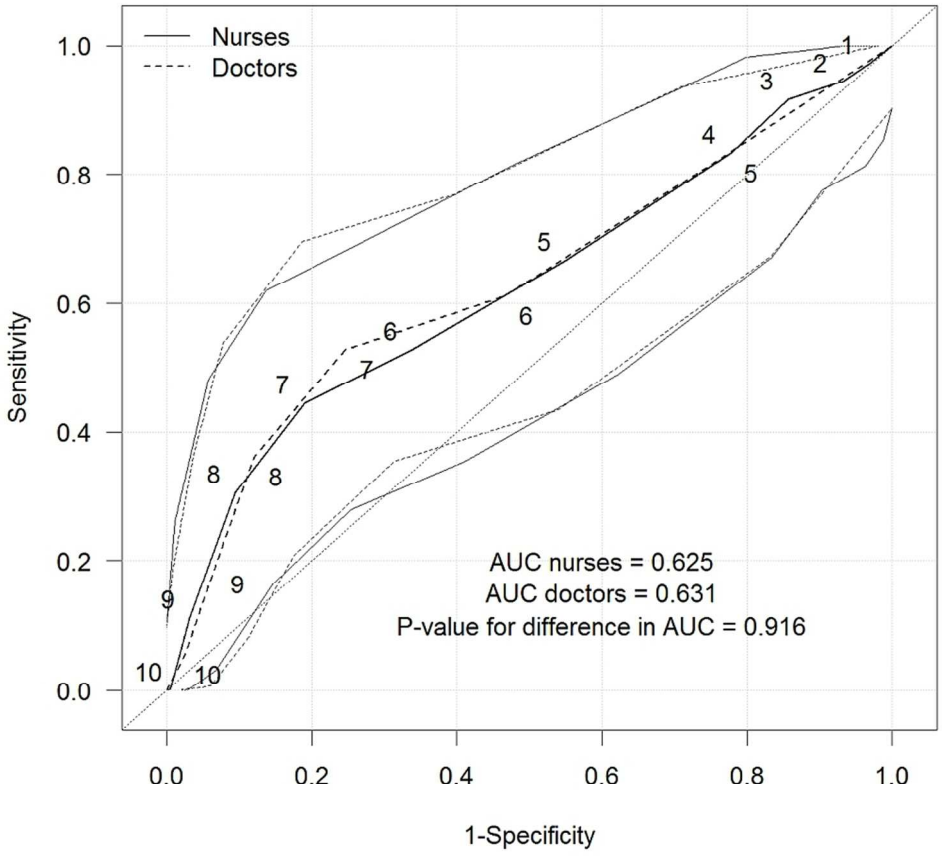

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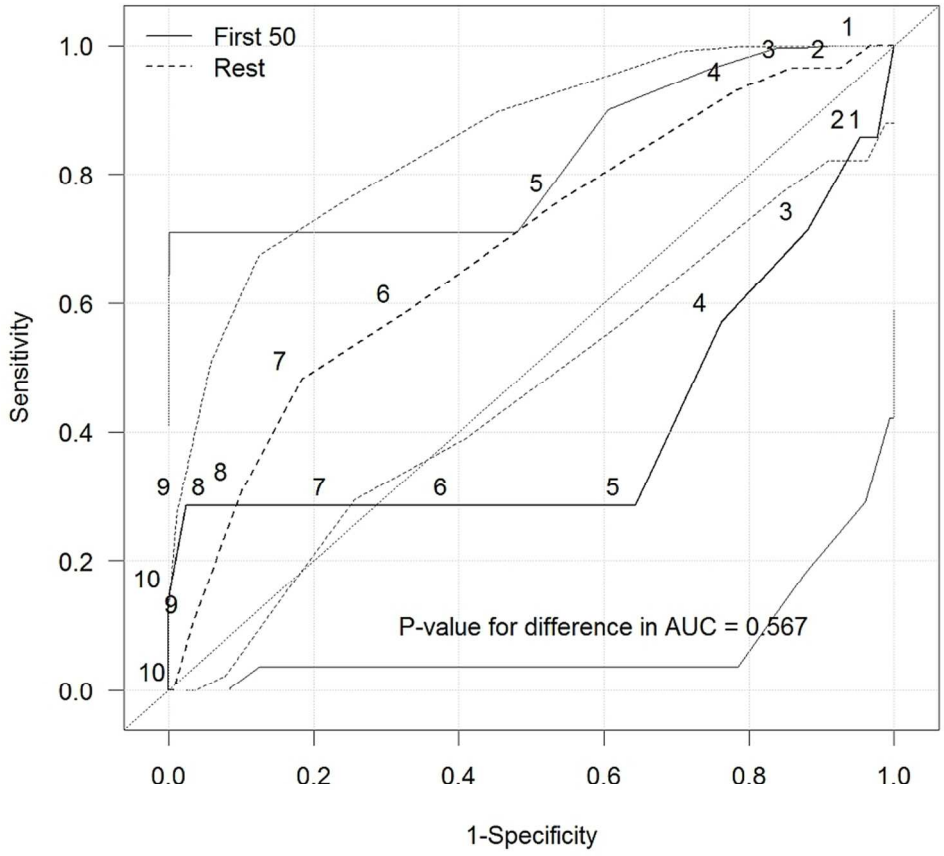

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Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	167-169
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	182-187
Interventions	Interventions intended for each group	197-223
Objective	Specific objective or hypothesis	158-161
Outcome	Clearly defined primary outcome for this report	167-169
Randomization	How participants were allocated to interventions	201-202
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Not applicable
Results		
Numbers randomized	Number of participants randomized to each group	206
Recruitment	Trial status	Completed
Numbers analysed	Number of participants analysed in each group	All
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	268-297
Harms	Important adverse events or side effects	None
Conclusions	General interpretation of the results	376-281
Trial registration	Registration number and name of trial register	228-230
Funding	Source of funding	108-110

**this item is specific to conference abstracts*

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BMJ Open

Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Global health, Medical education and training, Diagnostics
Keywords:	Colposcopy < GYNAECOLOGY, GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Abstract

Objectives Evaluation of the performance of VIA (Visual inspection with acetic acid) trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular, as compared to doctors.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. Swede score grade cervical acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurses and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy. There was no significant differences compared to doctors in detecting cervical lesions by stationary colposcope or the Gynocular using the Swede score system. Swede score by the Gynocular performed by nurses could offer an accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. Other study designs were considered, but would have been difficult to implement in a low-resource setting, where many poor women might never come back again to the colposcopy clinic. Also, blinding of which instrument that was used was not possible, due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we consider the risk of bias reduced.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no evidence of statistically significant differences for nurses or doctors in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a high specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year, 528 000 women are diagnosed with cervical cancer worldwide and 266 000 die from the disease.[1] A majority (87%) of women diagnosed with cervical cancer live in less developed regions of the world.[1] Mortality varies highly, ranging from less than 2 per 100 000 in developed regions to more than 20 per 100 000 areas such as Melanesia, Middle and Eastern Africa.[1]

In Bangladesh, 11 956 new cases of cervical cancer are discovered yearly and each year 6 582 women die from the disease.[1] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability. [2 3] According to the IARC's projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[4] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[5] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most common approach. [6 7 8] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[6 7 8 9]

The role of colposcopy, is to visually assess size and extent of cervical lesions with strong illumination and magnification, and to select the most abnormal lesions for biopsy. [10] In low-resource settings, colposcopy is often used to assess the severity of the lesion in VIA positive women as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[11]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[11 12 13 14 15] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are

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reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure. [11 12 14 15]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors, [16 17 18] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[13 14 15] By using the Swede score systematic colposcopy method, the findings of the colposcopic findings of the cervix[12 13] can be organized and scored in a structured manner.[12 13] The Swede score differ from other cervical scoring systems by adding the lesion size as a variable.[12 13]

The main aim of this study was to evaluate if nurse led Swede score colposcopy in a low resource setting, had a similar performance to a doctor Swede score colposcopy in detecting cervical lesions. The second aim of the study was to evaluate if a nurse or doctor Gynocular colposcopy had similar performances as compared to a stationary colposcopy in detecting cervical lesions. The third aim of the study was to evaluate if nurse led Swede score colposcopy could be a future option for detection of cervical lesions in low resource settings.

METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst those who have been screened, approximately 4.8% were VIA positive. [6] The opportunistic VIA screening programme

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in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh. [18 19 20] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[18 19 20] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[6 8]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. The colposcopy specialists were accredited physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7] All women in the study were examined by one of the two nurses and one of the six colposcopy specialists and both by the stationary colposcope and the Gynocular.

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH &

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Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[22] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points. [12 13 14 15]

A self-holding non-lubricated speculum was applied into the vagina and the cervix was visualized. The nurse started the examination with inspection of cervical vessels of mosaic pattern, punctuation, atypical vessels or absence of vessels as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel patterns with both instruments as randomized. This procedure slightly differs from the original Swede score[12], where vessels are inspected after acetic acid application of the cervix. However, after application of acetic acid, the whitening effect on the cervix slowly fades. Therefore we chose to first inspect the vessel pattern, and then applicate the acetic acid to ensure both nurses and doctors would have enough time to accurately estimate the acetowhitening effect before fading. Thus, the cervix was wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution, and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. The results from the examinations were reported from the nurses and the doctors to the study nurse in a separate location. The other examiners could not overhear the reports and they could not see the results of the previous examiner. The nurses and the doctors were also not allowed to communicate the patient's examination results. The examination was

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completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4, [12 13 15] as doctors using the Swede score has been validated and biopsy recommended when Swede score of 6 and above, [12 13] and this study aimed to validate nurse colposcopist's Swede scoring in a low resource setting (which has not been validated before). The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[23]

Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cervical cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular. The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

The Gynocular (Gynius AB, Stockholm, Sweden) is a high resolution monocular colposcope with similar specifications to stationary colposcopes, [14 15] The Gynocular is small, handheld, battery-driven, measuring 50 x 33 x 166 mm with 300 mm focal distance, and three magnifications: 5x, 8x and 12x.[14] [15] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non-invasive medical diagnostic class I tool, CE marked and FDA approved.

Statistical Analysis

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All statistical analyses have been performed using R version 2.14.[24] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope. [12 13 14 15] Detection rates of CIN 1, CIN 2, CIN 3, ICC (invasive cervical cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of Swede scores between 4 and 10 for doctors and 0 and 10 for nurses. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. In Bangladesh, there are no published data on CIN2+ in previously unscreened population verified by cytology, colposcopy and biopsy, only of CIN2+ in VIA positive women. However, data from India show a rate of 2.7% CIN2+ in unscreened women.[27] Thus, we assumed a similar rate in Bangladesh with an expected rate of CIN2+ of 2.5 % in naïve women and 7.5% in VIA positive women as a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the nurses colposcopists accuracy and Swede scoring compared to doctors[12 13]. Thus the aim was to include a total of approximately 1000 women.

In a retrospective power analysis based on the results from the present study, we estimated that approximately 1500 biopsies would have been needed (as compared to the 228 biopsies with in women with Swede score above 4 in this study) for 80 % power to detect a difference of 0.05 in AUC of the ROC curves at 5 % significance level.

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RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. 256 women had a Swede score of at least 4 by a doctor and of them 228 had a biopsy, and 28 refused biopsy (excluded from ROC analyses). 59 biopsies were taken outside research protocol (excluded from ROC analyses). 27 VIA positive women had CIN2+ and 5 screening naïve women had CIN2+. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (57.4%) women, Swede score was <4 and no biopsy taken.

When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, Gynocular by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4%) for CIN2+ and stationary colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of

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66.1.6% (95% CI 58.9 - 72.8% for CIN2+ (table 2). For doctors, using the Gynocular and a cut-off value of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) and for the stationary colposcope the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) for detecting CIN2+ (table 3). The sensitivity decreased while specificity increased with increased Swede score for CIN2+, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3). A Swede scores of eight and above had high specificity for CIN2+ lesions (table 2 and table3)

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that VIA nurses trained in colposcopy in a low resource setting, detect high grade cervical lesions as similarly good as specialized doctors using the Swede score systematic colposcopy system. Also, there were no significant differences for the nurses or the doctors using the Gynocular and the standard colposcope in detecting cervical lesions, confirmed by a high agreement of Swedes scores and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[22] Other strengths are that all the biopsies were analyzed in a single-site laboratory, and the large number of included women were all examined in a single center.

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The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. However, the Swede score has already been validated in Sweden and in the United Kingdom [12 13] and a cervical biopsy was recommended when a Swede score of 6 and above. The Swede score has also been used previous Gynocular studies in other low resource settings.[14 15] In our study, we lowered the Swede score biopsy threshold to 4, as we worked in a low resource setting with limited resources for follow-up and call back service of the included women. Interestingly, even when lowering the threshold for biopsy, we found few VIA women positive women with a CIN2+ lesion, results similar to our previous studies.[14 15] In screening naïve women, it was even more uncommon with CIN2+. It was reassuring to note that these women were detected by both nurses and doctors.

The cross-over design was chosen to lessen possible observer variability, but may also have influenced the scoring of the second instrument. Other study designs were evaluated, but would have been difficult to implement in a low-resource setting, where many poor women may never come back again to the colposcopy clinic. Also, blinding of which instrument used was not possible due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we reduced the risk of the second examination's possible influence of cervical impression to affect the statistical calculations. Further, the inclusion of postmenopausal women and possible breastfeeding women, could have affected the results, as Swede score has not been validated on postmenopausal women and breast feeding women.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year. [28 29 30] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [27 28] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap. [27 28]

The task-shifting could also be applied to colposcopy since 266 000 women die from cervical cancer each year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse

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colposcopists are an well-established resource within colposcopy, [16 17 18] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

Bowring et al.[13] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse colposcopist Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[11 12] and low-resource settings.[13 14]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested[13 14 15] that the Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. Thus, it is interesting to note that Swede score directed punch biopsies in women with a score of 4 and above, were more accurate than cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and Bangladesh.[14 15] Moreover, in a multi-center randomized controlled trial,[30] direct colposcopy identified more cervical lesions than repeat cytology and a studies from Bangladesh and Nigeria[20 31] concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[20 31]

A recent trial from Bangladesh summarised that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[21] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[32] VIA camps had a synergistic effect on the community, as

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women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[33] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment and further research on nurse led Swede score colposcopy in low resource settings and learning curve is needed. Improvement of patients' knowledge and proper counselling should be important component of this protocol. Women would then not have to accept treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings, and to promote and evaluate such programs in adequately powered research studies. Sankaranarayanan et al showed previously that adequately trained nurses can be used to deliver colposcopy and cryotherapy services and are important, reliable, and efficient alternate human resources.[32] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should further evaluate VIA screening and direct colposcopy in low-resource settings.

Conclusion

In summary, a Swede score colposcopy examination by a nurse or doctor colposcopist, using the Gynocular or stationary colposcope, is similary good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams a tool for early detection of cervical high-grade lesions. Nurse-

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colposcopy in low resource setting with the Gynocular and the Swede score should be further explored and evaluated

Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

Ethical approval

This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

Contributorship statement

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project. EWS and NA designed the study. NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing interests

EWS is the inventor of the Gynococular. EWS and IS are shareholders in Gynius.

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previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received financial support for study support in Bangladesh. H&M Conscious Foundation and Gynius AB funded the research project.

Data sharing

The dataset is available on request from the corresponding author:

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Transparancy Declaration

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I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

Figure Legends

Figure 1

The Gynocular with tripod mounting clip that screws into any standard tripod

Figure 2

Cross tabulation of Swede score's by Gynocular of nurses and doctors with Kappa.

Figure 3

Cross tabulation of Swede score's by stationary colposcope of nurses and doctors.

Figure 4

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by Gynocuar and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 5

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by stationary colposcope and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 6

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ROC curves for predicting a positive biopsy result CIN2+(CIN 2, CIN 3 and invasive cervical cancer) using Gynocular (Nurses first 50 vs rest).

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.7)	13 (2.5)
Chronic cervicitis		23 (5.7)	82 (15.7)
CIN1		19 (4.7)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
ICC		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		343 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) (*nurses, n = 228*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
≥9 vs <9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
≥6 vs <6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
≥5 vs <5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
≥4 vs <4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
≥3 vs <3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
≥9 vs <9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
≥6 vs <6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
≥5 vs <5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
≥4 vs <4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
≥3 vs <3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer *(doctors, n = 228).*

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
≥6 vs <6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
≥6 vs <6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Abstract

Objectives Evaluation of the performance of VIA (Visual inspection with acetic acid) trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular, as compared to doctors.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. Swede score grade cervical acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurses and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy. There was no significant differences compared to doctors in detecting cervical lesions by stationary colposcope or the Gynocular using the Swede score system. Swede score by the Gynocular performed by nurses could offer an accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. Other study designs were considered, but would have been difficult to implement in a low-resource setting, where many poor women might never come back again to the colposcopy clinic. Also, blinding of which instrument that was used was not possible, due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we consider the risk of bias reduced.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no evidence of statistically significant differences for nurses or doctors in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a high specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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Competing interests and funding statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Conscious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Contributions

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

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Data sharing statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer.

Transparancy Declaration

I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year, 528 000 women are diagnosed with cervical cancer worldwide and 266 000 die from the disease.[1] A majority (87%) of women diagnosed with cervical cancer live in less developed regions of the world.[1] Mortality varies highly, ranging from less than 2 per 100 000 in developed regions to more than 20 per 100 000 areas such as Melanesia, Middle and Eastern Africa.[1]

In Bangladesh, 11 956 new cases of cervical cancer are discovered yearly and each year 6 582 women die from the disease.[1] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability. [2 3] According to the IARC's projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[4] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[5] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most

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common approach.[6 7 8] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[6 7 8 9]

The role of colposcopy, is to visually assess size and extent of cervical lesions with strong illumination and magnification, and to select the most abnormal lesions for biopsy.[10] In low-resource settings, colposcopy is often used to assess the severity of the lesion in VIA positive women as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[11]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[11 12 13 14 15] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure.[11 12 14 15]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors,[16 17 18] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[13 14 15] By using the Swede score systematic colposcopy method, the findings of the colposcopic findings of the cervix[12 13] can be organized and scored in a structured manner.[12 13] The Swede score differ from other cervical scoring systems by adding the lesion size as a variable.[12 13]

The main aim of this study was to evaluate if nurse led Swede score colposcopy in a low resource setting, had a similar performance to a doctor Swede score colposcopy in detecting cervical lesions. The second aim of the study was to evaluate if a nurse or doctor Gynocular colposcopy had similar performances as compared to a stationary colposcopy in detecting cervical lesions. The third aim of the study was to evaluate if nurse led Swede score colposcopy could be a future option for detection of cervical lesions in low resource settings.

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METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst those who have been screened, approximately 4.8% were VIA positive. [6] The opportunistic VIA screening programme in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh. [18 19 20] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[18 19 20] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[6 8]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

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In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. The colposcopy specialists were accredited physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7] All women in the study were examined by one of the two nurses and one of the six colposcopy specialists and both by the stationary colposcope and the Gynocular.

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH & Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[22] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points. [12 13 14 15]

A self-holding non-lubricated speculum was applied into the vagina and the cervix was visualized. The nurse started the examination with inspection of cervical vessels of mosaic pattern, punctuation, atypical vessels or absence of vessels as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel patterns with both instruments as randomized. This procedure slightly differs from the original Swede score[12], where vessels are inspected after acetic acid application of the cervix. However, after application of acetic acid, the whitening effect on the cervix slowly fades. Therefore

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we chose to first inspect the vessel pattern, and then applicate the acetic acid to ensure both nurses and doctors would have enough time to accurately estimate the acetowhitening effect before fading. Thus, the cervix was wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution, and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. The results from the examinations were reported from the nurses and the doctors to the study nurse in a separate location. The other examiners could not overhear the reports and they could not see the results of the previous examiner. The nurses and the doctors were also not allowed to communicate the patient's examination results. The examination was completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4, [12 13 15] as doctors using the Swede score has been validated and biopsy recommended when Swede score of 6 and above, [12 13] and this study aimed to validate nurse colposcopist's Swede scoring in a low resource setting (which has not been validated before). The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[23]

Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cervical cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular.

The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

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The Gynocular (Gynius AB, Stockholm, Sweden) is a high resolution monocular colposcope with similar specifications to stationary colposcopes, [14 15] The Gynocular is small, handheld, battery-driven, measuring 50 x 33 x 166 mm with 300 mm focal distance, and three magnifications: 5x, 8x and 12x.[14 15] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non-invasive medical diagnostic class I tool, CE marked and FDA approved.

Statistical Analysis

All statistical analyses have been performed using R version 2.14.[24] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope. [12 13 14 15] Detection rates of CIN 1, CIN 2, CIN 3, ICC (invasive cervical cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of Swede scores between 4 and 10 for doctors and 0 and 10 for nurses. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. In Bangladesh, there are no published data on CIN2+ in previously unscreened population verified by cytology, colposcopy and biopsy, only of CIN2+ in VIA

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positive women. However, data from India show a rate of 2.7% CIN2+ in unscreened women.[27] Thus, we assumed a similar rate in Bangladesh with an expected rate of CIN2+ of 2.5 % in naïve women and 7.5% in VIA positive women as a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the nurses colposcopists accuracy and Swede scoring compared to doctors[12 13]. Thus the aim was to include a total of approximately 1000 women.

In a retrospective power analysis based on the results from the present study, we estimated that approximately 1500 biopsies would have been needed (as compared to the 228 biopsies with in women with Swede score above 4 in this study) for 80 % power to detect a difference of 0.05 in AUC of the ROC curves at 5 % significance level.

RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. 256 women had a Swede score of at least 4 by a doctor and of them 228 had a biopsy, and 28 refused biopsy (excluded from ROC analyses). 59 biopsies were taken outside research protocol (excluded from ROC analyses). 27 VIA positive women had CIN2+ and 5 screening naïve women had CIN2+. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (57.4%) women, Swede score was <4 and no biopsy taken.

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When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, Gynocular by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4%) for CIN2+ and stationary colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 66.1.6% (95% CI 58.9 - 72.8% for CIN2+ (table 2). For doctors, using the Gynocular and a cut-off value of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) and for the stationary colposcope the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) for detecting CIN2+ (table 3). The sensitivity decreased while specificity increased with increased Swede score for CIN2+, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3). A Swede scores of eight and above had high specificity for CIN2+ lesions (table 2 and table3)

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that VIA nurses trained in colposcopy in a low resource setting, detect high grade cervical lesions as similarly good as specialized doctors using the Swede score systematic colposcopy

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system. Also, there were no significant differences for the nurses or the doctors using the Gynocular and the standard colposcope in detecting cervical lesions, confirmed by a high agreement of Swedes scores and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[22] Other strengths are that all the biopsies were analyzed in a single-site laboratory, and the large number of included women were all examined in a single center.

The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. However, the Swede score has already been validated in Sweden and in the United Kingdom [12 13] and a cervical biopsy was recommended when a Swede score of 6 and above. The Swede score has also been used previous Gynocular studies in other low resource settings.[14 15] In our study, we lowered the Swede score biopsy threshold to 4, as we worked in a low resource setting with limited resources for follow-up and call back service of the included women. Interestingly, even when lowering the threshold for biopsy, we found few VIA women positive women with a CIN2+ lesion, results similar to our previous studies.[14 15] In screening naïve women, it was even more uncommon with CIN2+. It was reassuring to note that these women were detected by both nurses and doctors.

The cross-over design was chosen to lessen possible observer variability, but may also have influenced the scoring of the second instrument. Other study designs were evaluated, but would have been difficult to implement in a low-resource setting, where many poor women may never come back again to the colposcopy clinic. Also, blinding of which instrument used was not possible due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we reduced the risk of the second examination's possible influence of cervical

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impression to affect the statistical calculations. Further, the inclusion of postmenopausal women and possible breastfeeding women, could have affected the results, as Swede score has not been validated on postmenopausal women and breast feeding women.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year. [28 29 30] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [27 28] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap. [27 28]

The task-shifting could also be applied to colposcopy since 266 000 women die from cervical cancer each year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse colposcopists are an well-established resource within colposcopy, [16 17 18] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

Bowring et al.[13] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse colposcopist Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[11 12] and low-resource settings.[13 14]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested[13 14 15] that the Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. Thus, it is interesting to note that Swede score directed punch biopsies in women with a score of 4 and above, were more accurate than

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cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and Bangladesh.[14 15] Moreover, in a multi-center randomized controlled trial,[30] direct colposcopy identified more cervical lesions than repeat cytology and a studies from Bangladesh and Nigeria[20 31] concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[20 31]

A recent trial from Bangladesh summarised that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[21] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[32] VIA camps had a synergistic effect on the community, as women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[33] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment and further research on nurse led Swede score colposcopy in low resource settings and learning curve is needed. Improvement of patients' knowledge and proper counselling should be important component of this protocol. Women would then not have to accept treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings, and to promote and evaluate such programs in adequately powered research studies. Sankaranarayanan et al showed previously that adequately trained nurses can be used to deliver

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colposcopy and cryotherapy services and are important, reliable, and efficient alternate human resources.[32] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should further evaluate VIA screening and direct colposcopy in low-resource settings.

Conclusion

In summary, a Swede score colposcopy examination by a nurse or doctor colposcopist, using the Gynocular or stationary colposcope, is similary good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams a tool for early detection of cervical high-grade lesions. Nurse-colposcopy in low resource setting with the Gynocular and the Swede score should be further explored and evaluated

Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

Ethical approval

This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

Contributorship statement

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All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project. EWS and NA designed the study. NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing interests

EWS is the inventor of the Gynococular. EWS and IS are shareholders in Gynius.

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Data sharing

The dataset is available on request from the corresponding author:

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Figure Legends

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Figure 1

The Gynocular with tripod mounting clip that screws into any standard tripod

Figure 2

Cross tabulation of Swede score's by Gynocular of nurses and doctors with Kappa.

Figure 3

Cross tabulation of Swede score's by stationary colposcope of nurses and doctors.

Figure 4

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by Gynocuar and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 5

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by stationary colposcope and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 6

ROC curves for predicting a positive biopsy result CIN2+(CIN 2, CIN 3 and invasive cervical cancer) using Gynocular (Nurses first 50 vs rest).

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.7)	13 (2.5)
Chronic cervicitis		23 (5.7)	82 (15.7)
CIN1		19 (4.7)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
ICC		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		343 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) (*nurses, n = 228*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
≥9 vs <9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
≥6 vs <6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
≥5 vs <5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
≥4 vs <4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
≥3 vs <3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
≥9 vs <9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
≥6 vs <6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
≥5 vs <5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
≥4 vs <4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
≥3 vs <3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer *(doctors, n = 228)*.

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
≥6 vs <6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
≥6 vs <6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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The Gynocular with tripod mounting clip that screws into any standard camera tripod
90x134mm (300 x 300 DPI)

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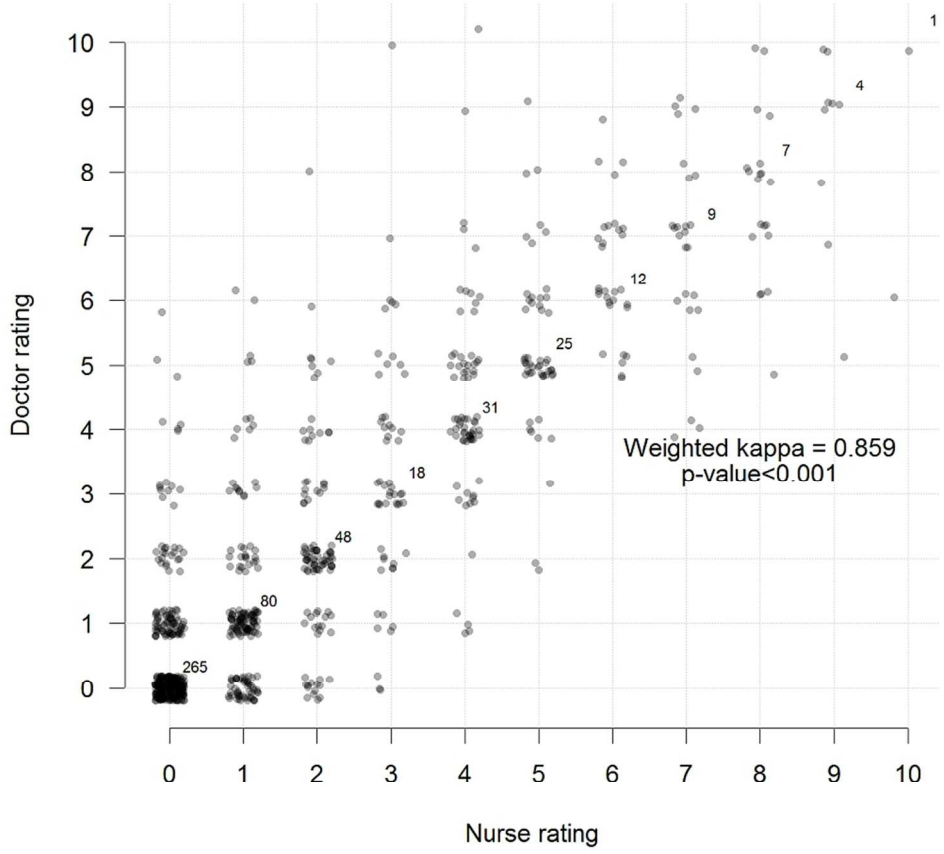

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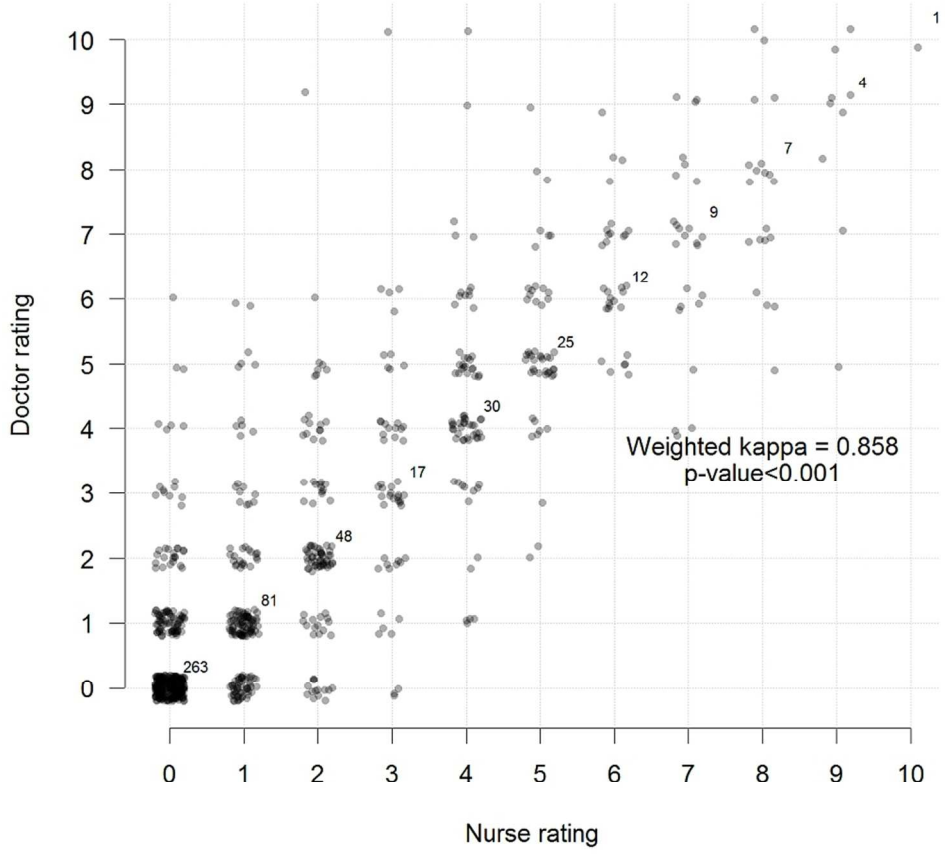

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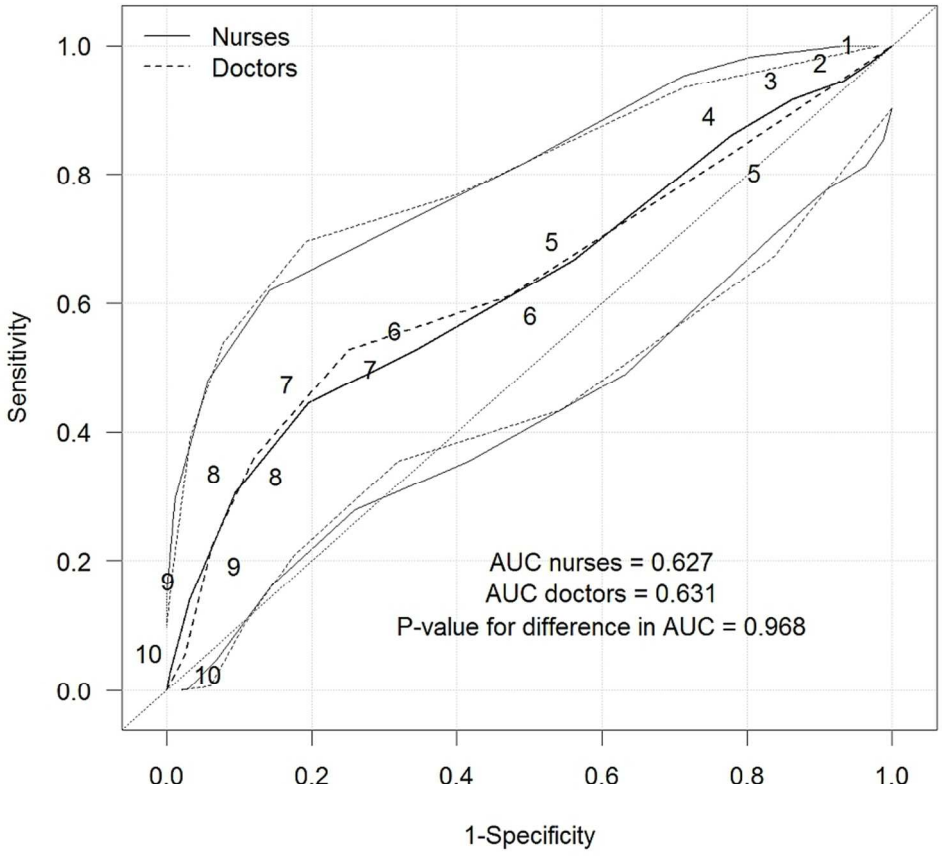

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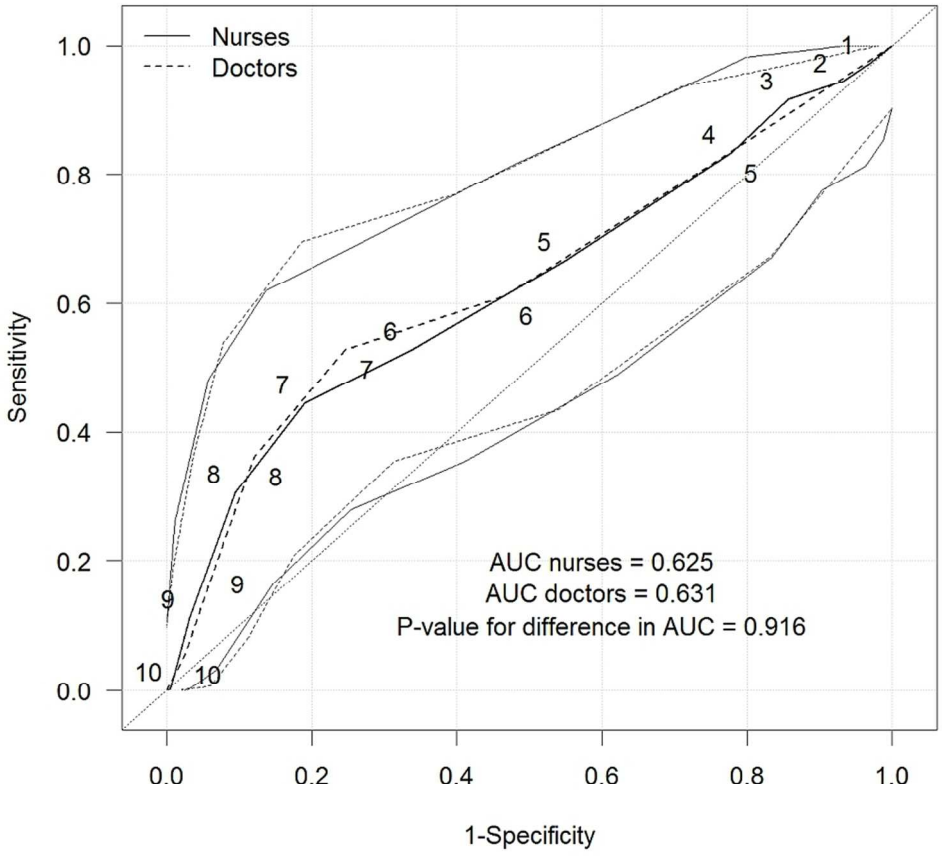

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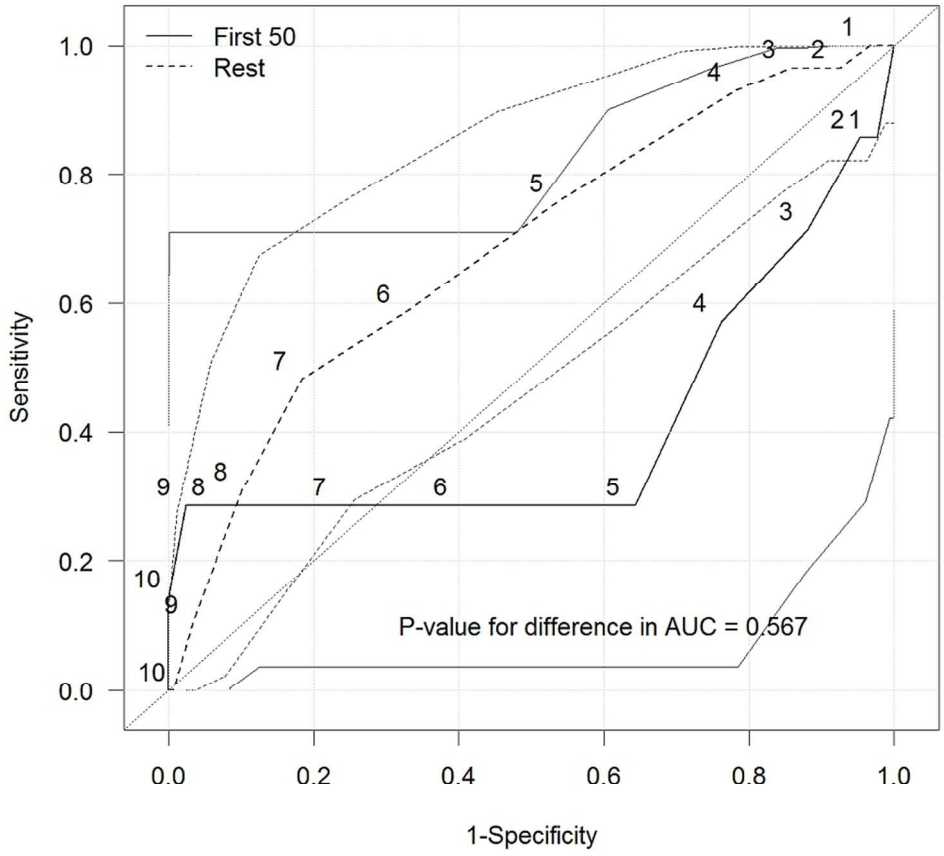

90x90mm (300 x 300 DPI)

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Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	167-169
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	182-187
Interventions	Interventions intended for each group	197-223
Objective	Specific objective or hypothesis	158-161
Outcome	Clearly defined primary outcome for this report	167-169
Randomization	How participants were allocated to interventions	201-202
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Not applicable
Results		
Numbers randomized	Number of participants randomized to each group	206
Recruitment	Trial status	Completed
Numbers analysed	Number of participants analysed in each group	All
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	268-297
Harms	Important adverse events or side effects	None
Conclusions	General interpretation of the results	376-281
Trial registration	Registration number and name of trial register	228-230
Funding	Source of funding	108-110

**this item is specific to conference abstracts*

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BMJ Open

Evaluation of the accuracy in detecting cervical lesions by nurses versus doctors using a stationary colposcope and Gynocular in a low-resource setting

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Manuscript ID:	bmjopen-2014-005313.R3
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Global health, Medical education and training, Diagnostics
Keywords:	Colposcopy < GYNAECOLOGY, GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Evaluation of the accuracy in detecting cervical lesions by nurses versus doctors using a stationary colposcope and Gynocular in a low-resource setting

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Abstract

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Objectives Evaluation of the performance of VIA (Visual inspection with acetic acid) trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular, as compared to doctors.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. Swede score grade cervical acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurses and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy. There was no significant differences compared to doctors in detecting cervical lesions by stationary colposcope or the Gynocular using the Swede score system. Swede score by the Gynocular performed by nurses could offer an accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. Other study designs were considered, but would have been difficult to implement in a low-resource setting, where many poor women might never come back again to the colposcopy clinic. Also, blinding of which instrument that was used was not possible, due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we consider the risk of bias reduced.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no evidence of statistically significant differences for nurses or doctors in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a high specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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Competing interests and funding statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Conscious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Contributions

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

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Data sharing statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer.

Transparancy Declaration

I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year, 528 000 women are diagnosed with cervical cancer worldwide and 266 000 die from the disease.[1] A majority (87%) of women diagnosed with cervical cancer live in less developed regions of the world.[1] Mortality varies highly, ranging from less than 2 per 100 000 in developed regions to more than 20 per 100 000 areas such as Melanesia, Middle and Eastern Africa.[1]

In Bangladesh, 11 956 new cases of cervical cancer are discovered yearly and each year 6 582 women die from the disease.[1] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability. [2 3] According to the IARC's projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[4] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[5] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most

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common approach.[6 7 8] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[6 7 8 9]

The role of colposcopy, is to visually assess size and extent of cervical lesions with strong illumination and magnification, and to select the most abnormal lesions for biopsy.[10] In low-resource settings, colposcopy is often used to assess the severity of the lesion in VIA positive women as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[11]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[11 12 13 14 15] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure.[11 12 14 15]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors,[16 17 18] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[13 14 15] By using the Swede score systematic colposcopy method, the findings of the colposcopic findings of the cervix[12 13] can be organized and scored in a structured manner.[12 13] The Swede score differ from other cervical scoring systems by adding the lesion size as a variable.[12 13]

The main aim of this study was to evaluate if nurse led Swede score colposcopy in a low resource setting, had a similar performance to a doctor Swede score colposcopy in detecting cervical lesions. The second aim of the study was to evaluate if a nurse or doctor Gynocular colposcopy had similar performances as compared to a stationary colposcopy in detecting cervical lesions. The third aim of the study was to evaluate if nurse led Swede score colposcopy could be a future option for detection of cervical lesions in low resource settings.

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METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst those who have been screened, approximately 4.8% were VIA positive. [6] The opportunistic VIA screening programme in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh. [18 19 20] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[18 19 20] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[6 8]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

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In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. The colposcopy specialists were accredited physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7] All women in the study were examined by one of the two nurses and one of the six colposcopy specialists and both by the stationary colposcope and the Gynocular.

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH & Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[22] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points. [12 13 14 15]

A self-holding non-lubricated speculum was applied into the vagina and the cervix was visualized. The nurse started the examination with inspection of cervical vessels of mosaic pattern, punctuation, atypical vessels or absence of vessels as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel patterns with both instruments as randomized. This procedure slightly differs from the original Swede score[12], where vessels are inspected after acetic acid application of the cervix. However, after application of acetic acid, the whitening effect on the cervix slowly fades. Therefore

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we chose to first inspect the vessel pattern, and then applicate the acetic acid to ensure both nurses and doctors would have enough time to accurately estimate the acetowhitening effect before fading. Thus, the cervix was wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution, and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. The results from the examinations were reported from the nurses and the doctors to the study nurse in a separate location. The other examiners could not overhear the reports and they could not see the results of the previous examiner. The nurses and the doctors were also not allowed to communicate the patient's examination results. The examination was completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4, [12 13 15] as doctors using the Swede score has been validated and biopsy recommended when Swede score of 6 and above, [12 13] and this study aimed to validate nurse colposcopist's Swede scoring in a low resource setting (which has not been validated before). The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[23]

Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cervical cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular.

The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

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The Gynocular (Gynius AB, Stockholm, Sweden) is a high resolution monocular colposcope with similar specifications to stationary colposcopes, [14 15] The Gynocular is small, handheld, battery-driven, measuring 50 x 33 x 166 mm with 300 mm focal distance, and three magnifications: 5x, 8x and 12x.[14 15] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non-invasive medical diagnostic class I tool, CE marked and FDA approved.

Statistical Analysis

All statistical analyses have been performed using R version 2.14.[24] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope. [12 13 14 15] Detection rates of CIN 1, CIN 2, CIN 3, ICC (invasive cervical cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of Swede scores between 4 and 10 for doctors and 0 and 10 for nurses. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. In Bangladesh, there are no published data on CIN2+ in previously unscreened population in Bangladesh verified by cytology, colposcopy and biopsy, only of

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CIN2+ in VIA positive women. However, data from India show a rate of 2.7% CIN2+ in unscreened women.[27] Thus, we assumed a similar rate in Bangladesh with an expected rate of CIN2+ of 2.5 % in naïve women and 7.5% in VIA positive women as a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the nurses colposcopists accuracy and Swede scoring compared to doctors[12 13]. Thus the aim was to include a total of approximately 1000 women.

In a retrospective power analysis based on the results from the present study, we estimated that approximately 1500 biopsies would have been needed (as compared to the 228 biopsies with in women with Swede score above 4 in this study) for 80 % power to detect a difference of 0.05 in AUC of the ROC curves at 5 % significance level.

RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. 256 women had a Swede score of at least 4 by a doctor and of them 228 had a biopsy, and 28 refused biopsy (excluded from ROC analyses). 59 biopsies were taken outside research protocol (excluded from ROC analyses). 27 VIA positive women had CIN2+ and 5 screening naïve women had CIN2+. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (57.4%) women, Swede score was <4 and no biopsy taken.

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When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, Gynocular by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4%) for CIN2+ and stationary colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 66.1.6% (95% CI 58.9 - 72.8% for CIN2+ (table 2). For doctors, using the Gynocular and a cut-off value of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) and for the stationary colposcope the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) for detecting CIN2+ (table 3). The sensitivity decreased while specificity increased with increased Swede score for CIN2+, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3). A Swede scores of eight and above had high specificity for CIN2+ lesions (table 2 and table3)

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that VIA nurses trained in colposcopy in a low resource setting, detect high grade cervical lesions as similarly good as specialized doctors using the Swede score systematic colposcopy

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system. Also, there were no significant differences for the nurses or the doctors using the Gynocular and the standard colposcope in detecting cervical lesions, confirmed by a high agreement of Swedes scores and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[22] Other strengths are that all the biopsies were analyzed in a single-site laboratory, and the large number of included women were all examined in a single center.

The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. However, the Swede score has already been validated in Sweden and in the United Kingdom [12 13] and a cervical biopsy was recommended when a Swede score of 6 and above. The Swede score has also been used previous Gynocular studies in other low resource settings.[14 15] In our study, we lowered the Swede score biopsy threshold to 4, as we worked in a low resource setting with limited resources for follow-up and call back service of the included women. Interestingly, even when lowering the threshold for biopsy, we found few VIA women positive women with a CIN2+ lesion, results similar to our previous studies.[14 15] In screening naïve women, it was even more uncommon with CIN2+. It was reassuring to note that these women were detected by both nurses and doctors.

The cross-over design was chosen to lessen possible observer variability, but may also have influenced the scoring of the second instrument. Other study designs were evaluated, but would have been difficult to implement in a low-resource setting, where many poor women may never come back again to the colposcopy clinic. Also, blinding of which instrument used was not possible due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we reduced the risk of the second examination's possible influence of cervical impression to

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affect the statistical calculations. Further, the inclusion of postmenopausal women and possible breastfeeding women, could have affected the results, as Swede score has not been validated on postmenopausal women and breast feeding women.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year. [28 29 30] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [27 28] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap. [27 28]

The task-shifting could also be applied to colposcopy since 266 000 women die from cervical cancer each year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse colposcopists are an well-established resource within colposcopy, [16 17 18] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

Bowring et al.[13] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse colposcopist Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[11 12] and low-resource settings.[13 14]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested[13 14 15] that the Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. Thus, it is interesting to note that Swede score directed punch biopsies in women with a score of 4 and above, were more accurate than

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cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and Bangladesh.[14 15] However, our study show that it is needed to further validate the Swede score's sensitivity and specificity to detect CIN2+ in low resource populations, possible with biopsies from Swede score 0 in both screening naïve, VIA positive women as well as HPV status. This important as the Swede score was previously validated in women with an abnormal referral cytology in high resource settings.[12,13]

Moreover, in a multi-center randomized controlled trial,[30] direct colposcopy identified more cervical lesions than repeat cytology and a studies from Bangladesh and Nigeria[20 31] concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[20 31]

A recent trial from Bangladesh summarised that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[21] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[32] VIA camps had a synergistic effect on the community, as women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[33] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment and further research on nurse led Swede score colposcopy in low resource settings and learning curve is needed. Improvement of patients' knowledge and proper counselling should be important component of this protocol. Women would then not have to accept

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treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings, and to promote and evaluate such programs in adequately powered research studies. Sankaranarayanan et al showed previously that adequately trained nurses can be used to deliver colposcopy and cryotherapy services and are important, reliable, and efficient alternate human resources.[32] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should further evaluate VIA screening and direct colposcopy in low-resource settings.

Conclusion

In summary, a Swede score colposcopy examination by a nurse or doctor colposcopist, using the Gynocular or stationary colposcope, is similary good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams a tool for early detection of cervical high-grade lesions. Nurse-colposcopy in low resource setting with the Gynocular and the Swede score should be further explored and evaluated

Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

Ethical approval

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This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

Contributorship statement

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project. EWS and NA designed the study. NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing interests

EWS is the inventor of the Gynococular. EWS and IS are shareholders in Gynius.

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Data sharing

The dataset is available on request from the corresponding author:

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Figure Legends

Figure 1

The Gynocular with tripod mounting clip that screws into any standard tripod

Figure 2

Cross tabulation of Swede score's by Gynocular of nurses and doctors with Kappa.

Figure 3

Cross tabulation of Swede score's by stationary colposcope of nurses and doctors.

Figure 4

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by Gynocuar and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 5

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by stationary colposcope and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 6

ROC curves for predicting a positive biopsy result CIN2+(CIN 2, CIN 3 and invasive cervical cancer) using Gynocular (Nurses first 50 vs rest).

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.7)	13 (2.5)
Chronic cervicitis		23 (5.7)	82 (15.7)
CIN1		19 (4.7)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
ICC		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		343 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) (*nurses, n = 228*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
≥9 vs <9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
≥6 vs <6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
≥5 vs <5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
≥4 vs <4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
≥3 vs <3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
≥9 vs <9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
≥6 vs <6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
≥5 vs <5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
≥4 vs <4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
≥3 vs <3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer *(doctors, n = 228).*

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
≥6 vs <6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
≥6 vs <6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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Accuracy of colposcopy by nurses versus doctors by stationary colposcope and Gynocular in a low-resource setting; A cross-over randomized trial

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Abstract

Objectives Evaluation of the performance of VIA (Visual inspection with acetic acid) trained nurses to learn colposcopy and the Swede score method to detect cervical lesions by using stationary colposcope or a portable, hand-held colposcope; the Gynocular, as compared to doctors.

Design Cross-over randomized clinical trial.

Setting The Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants 932 women attending the clinic as screening naïve for VIA screening (404) or women referred as VIA positive (528) from other VIA screening centers in the Dhaka region.

Intervention VIA trained nurses were trained at site in colposcopy and the Swede score systematic colposcopy method. Swede score grade cervical acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining. The women were randomized to start the examination by either stationary colposcope or the Gynocular. Swede scores were first obtained by a nurse and the same patient was equally evaluated by a doctor.

Primary and secondary outcome measures Agreement between nurses and doctors in Swede scores were evaluated using the weighted Kappa statistic for the Gynocular and standard colposcope. The ability to predict CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) using Swede scores was evaluated using ROC curves.

Results The Swede scores obtained by nurses and doctors using the Gynocular and stationary colposcope showed high agreement with a Kappa statistic of 0.858 and 0.859, respectively, and no difference in detecting cervical lesions in biopsy. Biopsy detected CIN 2+ in 39 (4.2%) of the women.

Conclusion Our study showed that VIA nurses can perform colposcopy. There was no significant differences compared to doctors in detecting cervical lesions by stationary colposcope or the Gynocular using the Swede score system. Swede score by the Gynocular performed by nurses could offer an accurate cervical diagnostic approach in low resource settings.

Trial registration ISRCTN53264564.

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ARTICLE SUMMARY

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability. Another strength is that all the biopsies were analyzed in single-site laboratory.

The main limitation of our study is that not all the women examined had a biopsy, which may have biased our results. The cross-over design may also have influenced the scoring of the second instrument. Other study designs were considered, but would have been difficult to implement in a low-resource setting, where many poor women might never come back again to the colposcopy clinic. Also, blinding of which instrument that was used was not possible, due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we consider the risk of bias reduced.

Our study show:

- VIA nurses trained in colposcopy detects high grade cervical lesions as accurate as specialized doctors using the Swede score systematic colposcopy system.
- There was no evidence of statistically significant differences for nurses or doctors in detecting cervical lesions by stationary colposcope or the Gynocular.
- The Swede score by both nurses and doctors have a high specificity for high grade lesions
- A Swede score of 8 and above would be appropriate for direct “see and treat” in remote areas.
- This study shows that the human resource gap within colposcopy could be filled by trained nurses, increasing the access to colposcopy and detection of cervical cancer in low resource settings.

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Competing interests and funding statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pd f and declare the following: NA, JSR, MAC, QK, RA and MT had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received economical support for study support in Bangladesh. EWS and IS are shareholders in Gynius. H&M Conscious Foundation and Gynius AB funded the research project. EWS is the inventor of the Gynococular.

Contributions

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project, NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

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Data sharing statement

Extra data is available by emailing Dr Elisabeth A Wikström Shemer.

Transparancy Declaration

I, Elisabeth Wikström Shemer, the lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained All the authors state of independence from the funders. All data will be shared at request. All patients gave their written consent to participate in the study.

INTRODUCTION

Cervical cancer is a common cause of death in women from low-resource settings. Recent data indicate that each year, 528 000 women are diagnosed with cervical cancer worldwide and 266 000 die from the disease.[1] A majority (87%) of women diagnosed with cervical cancer live in less developed regions of the world.[1] Mortality varies highly, ranging from less than 2 per 100 000 in developed regions to more than 20 per 100 000 areas such as Melanesia, Middle and Eastern Africa.[1]

In Bangladesh, 11 956 new cases of cervical cancer are discovered yearly and each year 6 582 women die from the disease.[1] Moreover, as the incidence rise sharply among women over 35 years of age, cervical cancer has vast impact on communities at a time when the woman's presence is vital to social and economical stability. [2 3] According to the IARC's projections for the coming decades, deaths from cervical cancer will continue to rise.[1]

In high-resource settings, cervical cytology screening programs have successfully reduced the rates of cervical cancer.[4] In many low-resource settings, few women have access to cytology screening programs due to the absence of national screening programs, lack of equipment and skilled technicians.[5] As a result, other low-cost methods have been implemented for screening, where opportunistic visual inspection with acetic acid (VIA) by trained nurses and doctors, is the most

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common approach.[6 7 8] Often, VIA positive women are referred for colposcopy in order to reduce the risk of overtreatment.[6 7 8 9]

The role of colposcopy, is to visually assess size and extent of cervical lesions with strong illumination and magnification, and to select the most abnormal lesions for biopsy.[10] In low-resource settings, colposcopy is often used to assess the severity of the lesion in VIA positive women as part of a 'see and treat' policy, as it may be more practical to treat the women immediately if a severe lesion is diagnosed, as she might not be able to return to the clinic.[11]

Colpscopy may also be used for primary screening in low-resource settings, especially when using the Swede score systematic colposcopy system, where the total score gives an indication of the severity of the visual impression of the cervix.[11 12 13 14 15] However, the limited access of doctors and the limitations of stationary colposcopes (heavy, requires an electrical grid and technical support), are reasons to why screening colposcopy have not reached widespread use in rural areas with poor infrastructure.[11 12 14 15]

In high-resource settings, nurse colposcopists have been trained to increase accessibility of colposcopy and achieve similar diagnostic accuracy as doctors,[16 17 18] and a similar approach in low-resource settings, with diagnosis and screening by the portable battery-driven colposcope, the Gynocular, could offer an accurate, cost-effective and pragmatic approach to combat cervical cancer.[13 14 15] By using the Swede score systematic colposcopy method, the findings of the colposcopic findings of the cervix[12 13] can be organized and scored in a structured manner.[12 13] The Swede score differ from other cervical scoring systems by adding the lesion size as a variable.[12 13]

The main aim of this study was to evaluate if nurse led Swede score colposcopy in a low resource setting, had a similar performance to a doctor Swede score colposcopy in detecting cervical lesions. The second aim of the study was to evaluate if a nurse or doctor Gynocular colposcopy had similar performances as compared to a stationary colposcopy in detecting cervical lesions. The third aim of the study was to evaluate if nurse led Swede score colposcopy could be a future option for detection of cervical lesions in low resource settings.

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METHODS

Design, participants, and procedures

This study was a randomized cross-over clinical trial for evaluating the accuracy of Swede scores of VIA nurses trained in the Swede score colposcopy method in detecting cervical lesions using biopsy as a criterion standard. All the participating women were randomized to be examined by both stationary colposcope and the Gynocular in a cross-over design. The nurses and the doctors examined the same women, but were blinded form each other's Swede scores.

In Bangladesh, 2.3% of the women have been screened with VIA so far, and amongst those who have been screened, approximately 4.8% were VIA positive. [6] The opportunistic VIA screening programme in Bangladesh was initiated in year 2004 by the government of Bangladesh. Trained paramedics, Senior Staff Nurses and doctors offer VIA to married women 30 years and above to detect the pre-cancer and early cervical cancer among women visiting VIA centres of different districts in Bangladesh. [18 19 20] VIA positive women are referred to BSMMU and government Medical College Hospitals for colposcopic evaluation and management.[18 19 20] The cervical cancer screening programme is an ongoing programme and colposcopy becomes an important part of this prevention programme. A woman is considered to be VIA positive when sharp, distinct, well-defined, dense acetowhite areas on the cervix are noticed during examination with or without raised margins, close to the squamocolumnar junction in the transformation zone.[6 8]

The inclusion criteria were (1) women positive for VIA at opportunistic screening by trained family welfare visitors, senior staff nurses, and doctors in the Dhaka region, Bangladesh, referred for colposcopy or women coming for VIA cervical screening at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) during June 1st to September 31st 2012**.** Other inclusion criteria were (2) ability to understand written and oral information (3) women signing an informed consent to participate in the study after receiving oral and written information from a social worker. Exclusion criteria were: (1) on-going vaginal bleeding, (2) any previous gynaecologic examinations less than one week (3) pregnancy. Women who chose not to take part in the study had a standard colposcopy examination.

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In total, 932 women were included in the study, of them 404 attending the clinic as screening naïve and 528 women referred as VIA positive. Two VIA nurses were trained at site in colposcopy and the Swede score systematic colposcopy method for 2 weeks before starting the study. The colposcopy specialists were accredited physicians or gynaecologists who were trained in colposcopy, cold coagulation, and loop electrical excision procedure at the colposcopy clinic of BSMMU.[7] All women in the study were examined by one of the two nurses and one of the six colposcopy specialists and both by the stationary colposcope and the Gynocular.

During the colposcopy examination, one of the two standard colposcopes (Leisegang 1DF, Leisegang, Feinmechanik-Optik GmbH, Berling, Germany or Karl Kaps Som 52, Karl Kaps GmbH & Co.KG,Asslar/Wetzlar, Germany) and the Gynocular (Gynius AB, Stockholm, Sweden) were used. Women were randomly allocated in blocks of 50 to start the examination by one of the nurses, followed by examination by one of the doctors with either the stationary colposcope or the Gynocular. Then, the same examiners examined the woman with the second instrument in order to assess the performance of agreement between the Swede scores of the nurse and the doctor and, of the two instruments. The cross-over design was chosen in order to lessen possible observer variability.[22] A total of 524 women started the examination with stationary colposcope and 408 women with the Gynocular. During the Swede score examination, each of the five colposcopic variables (acetowhiteness, margins plus surface, vessel pattern, lesion size, and iodine staining) was given a score of 0,1, or 2 points. [12 13 14 15]

A self-holding non-lubricated speculum was applied into the vagina and the cervix was visualized. The nurse started the examination with inspection of cervical vessels of mosaic pattern, punctuation, atypical vessels or absence of vessels as randomized with colposcope or the Gynocular using the red-free (green filter) mode and switched instruments. Then the doctor evaluated the vessel patterns with both instruments as randomized. This procedure slightly differs from the original Swede score[12], where vessels are inspected after acetic acid application of the cervix. However, after application of acetic acid, the whitening effect on the cervix slowly fades. Therefore

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we chose to first inspect the vessel pattern, and then applicate the acetic acid to ensure both nurses and doctors would have enough time to accurately estimate the acetowhitening effect before fading. Thus, the cervix was wiped with 5% acetic acid for 1 minute, followed by evaluation by the nurse of three Swede score variables (acetowhiteness, margins plus surface, and lesion size) and scored by the nurse by both instruments and then again by the doctor. Next, the cervix was swabbed with 5% Lugol iodine solution, and the nurse scored the Swede score's fifth variable (iodine staining) with both instruments as randomized and then again by the doctor. The results from the examinations were reported from the nurses and the doctors to the study nurse in a separate location. The other examiners could not overhear the reports and they could not see the results of the previous examiner. The nurses and the doctors were also not allowed to communicate the patient's examination results. The examination was completed with 1 or more biopsies taken from areas of suspected cervical lesions. Punch biopsies of the cervix were done in all women in which the doctor had scored a Swede score ≥4, [12 13 15] as doctors using the Swede score has been validated and biopsy recommended when Swede score of 6 and above, [12 13] and this study aimed to validate nurse colposcopist's Swede scoring in a low resource setting (which has not been validated before). The cervical biopsies were analysed at the histopathology laboratory of BSMMU. The histopathology diagnoses were graded according to the CIN classification system and was considered as gold-standard.[23]

Women with CIN1 lesions were given the choice of direct treatment or a follow-up examination after 6 months. Women with CIN2+ were offered a loop electrical excision procedure. Women with invasive cervical cancers were referred to the Gynecological Oncology Unit of the Department of Obstetrics and Gynaecology at BSMMU for management. This study was approved by the local ethics committees in Bangladesh and in Sweden: the Institutional Review Board of BSMMU; Dnr BSMMU/2012/3176 and the Stockholm Regional Ethical Review Board; Dnr 2012/545-31/1. The study was registered as ISRCTN53264564 at www.controlled-trials.com after enrolment of participants started, due to the publishing restraints of the parallel patenting process of the Gynocular.

The study protocol can be accessed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden.

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The Gynocular (Gynius AB, Stockholm, Sweden) is a high resolution monocular colposcope with similar specifications to stationary colposcopes, [14 15] The Gynocular is small, handheld, battery-driven, measuring 50 x 33 x 166 mm with 300 mm focal distance, and three magnifications: 5x, 8x and 12x.[14 15] The Gynocular has a tripod mounting clip that screws into any standard tripod, allowing the medical professional to perform colposcopy hands free mode for ease of biopsy (Fig. 1). The Gynocular has high-intensity LEDs for warm white illumination, a green filter light, and is powered by a rechargeable lithium-ion battery. The Gynocular is an approved product by the Swedish National Drug Authority as a non-invasive medical diagnostic class I tool, CE marked and FDA approved.

Statistical Analysis

All statistical analyses have been performed using R version 2.14.[24] The baseline patient characteristics of the women were summarized using means and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To test the level of agreement between colposcope and the Gynocular, the percentage agreement and the weighted kappa statistic was calculated.[26] Cervical lesions were classified by the Swede scores system using the Gynocular and a stationary colposcope. [12 13 14 15] Detection rates of CIN 1, CIN 2, CIN 3, ICC (invasive cervical cancer), AIS (adenocarcinoma in situ), benign, cervicitis and cervical tuberculosis in cervical punch biopsies were calculated. A positive biopsy results was defined as CIN2+ (CIN 2, CIN 3, CIN 3+) and we calculated the Swede score's sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using biopsy as a gold-standard for all cut-off levels of Swede scores between 4 and 10 for doctors and 0 and 10 for nurses. The results are presented in tables and as receiver operating characteristic (ROC) curves as well as the area under the curve (AUC). The comparison of AUC of the ROC curves was performed using the roc.test function in the pROC package.

Sample size

The sample size was estimated based on the expected number of positive biopsy results (defined as CIN2+) and not in terms of statistical power. In Bangladesh, there are no published data on CIN2+ in previously unscreened population in Bangladesh verified by cytology, colposcopy and biopsy, only of

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CIN2+ in VIA positive women. However, data from India show a rate of 2.7% CIN2+ in unscreened women.[27] Thus, we assumed a similar rate in Bangladesh with an expected rate of CIN2+ of 2.5 % in naïve women and 7.5% in VIA positive women as a sample size of 500 naïve and 500 VIA positive women would generate 50 positive biopsy results which were considered to give sufficient precision of the nurses colposcopists accuracy and Swede scoring compared to doctors[12 13]. Thus the aim was to include a total of approximately 1000 women.

In a retrospective power analysis based on the results from the present study, we estimated that approximately 1500 biopsies would have been needed (as compared to the 228 biopsies with in women with Swede score above 4 in this study) for 80 % power to detect a difference of 0.05 in AUC of the ROC curves at 5 % significance level.

RESULTS

A total of 932 women were included into the study, of which 404 (43 %) were screening naïve. The women's baseline characteristics are presented in Table 1. 256 women had a Swede score of at least 4 by a doctor and of them 228 had a biopsy, and 28 refused biopsy (excluded from ROC analyses). 59 biopsies were taken outside research protocol (excluded from ROC analyses). 27 VIA positive women had CIN2+ and 5 screening naïve women had CIN2+. Punch biopsy was benign in 7 (1.8%), chronic cervicitis in 23 (5.8%), CIN1 in 19 (4.8%) and CIN2 in 4 (1.0%). No women had CIN3 and 4 (1.0%) had invasive cervical cancer (CIN3+). In 1 (0.2%) woman biopsy showed tuberculosis. Swede score was <4 in 342 (85.5%) women and in those women, no biopsy was taken.

Among the referred VIA positive women, punch biopsy was benign in 13 (2.5%), chronic cervicitis 82 (15.7%), CIN1 in 90 (17.3%) and CIN2 in 21 (4.0%). Four women (0.8%) had CIN3 and 6 (1.2%) had invasive cervical cancer (CIN3+). Two (0.4%) women had tuberculosis in biopsy. In 303 (57.4%) women, Swede score was <4 and no biopsy taken.

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When cross tabulating Swede score's by Gynocular of nurses and doctors, the Kappa coefficient was 0.859, p-value <0.001 (Fig 2) and Swede score's by colposcope by nurses and doctors had a Kappa coefficient of 0.858, p-value <0.001 (Fig 3).

Cross tabulation of Swede scores by colposcope versus the Gynocular by nurses showed a Kappa coefficient of 0.997 (p-value <0.001), and a cross tabulation of Swede scores by colposcope and the Gynocular for the doctors, showed a Kappa coefficient of 0.998 (p-value <0.001).

There were no significant differences between the Swede scores of the nurses and the doctors in predicting a positive biopsy result (CIN2+), for both Gynocular (Fig 4) and colposcope (Fig 5).

A cut-off value of six and above for Swede score and biopsy, Gynocular by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 65.6% (95% CI 58.4 - 72.4%) for CIN2+ and stationary colposcope by nurses had a sensitivity of 52.8% (95% CI 35.5 - 69.6%) and a specificity of 66.1.6% (95% CI 58.9 - 72.8% for CIN2+ (table 2). For doctors, using the Gynocular and a cut-off value of six, the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 52.9% (95% CI 45.5 - 60.1%) and for the stationary colposcope the sensitivity was 61.1% (95% CI 43.5 -76.9%) and specificity 53.4% (95% CI 46.1 -60.6%) for detecting CIN2+ (table 3). The sensitivity decreased while specificity increased with increased Swede score for CIN2+, both for nurses and doctors, and with increasing Swede scores, nurses had a higher sensitivity in the upper Swedes scores in detecting CIN2+ (table 2 and table 3). A Swede scores of eight and above had high specificity for CIN2+ lesions (table 2 and table3)

We further sub analyzed the nurses 50 first Swede scores for predicting CIN2+ (Fig 6), where the specificity for high Swede scores was high, but sensitivity was lower than when the nurses have had further practice.

DISCUSSION

This study found that VIA nurses trained in colposcopy in a low resource setting, detect high grade cervical lesions as similarly good as specialized doctors using the Swede score systematic colposcopy

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system. Also, there were no significant differences for the nurses or the doctors using the Gynocular and the standard colposcope in detecting cervical lesions, confirmed by a high agreement of Swedes scores and the histopathological diagnosis from punch biopsy. Moreover, Swede scores of eight and above had high specificity for CIN2+ lesions.

Strength and limitations

The main strength of our study is its randomized cross-over design including both screening naïve women and women referred as VIA positive, thus given the examiners a wide range of normal to pathological colposcopic impressions, and a reduction of the risk of selection bias. The cross-over randomized design was used to reduce the risk of intra-observer variability.[22] Other strengths are that all the biopsies were analyzed in a single-site laboratory, and the large number of included women were all examined in a single center.

The main weakness of our study is that not all the women examined had a biopsy, which may have biased our results. However, the Swede score has already been validated in Sweden and in the United Kingdom [12 13] and a cervical biopsy was recommended when a Swede score of 6 and above. The Swede score has also been used previous Gynocular studies in other low resource settings.[14 15] In our study, we lowered the Swede score biopsy threshold to 4, as we worked in a low resource setting with limited resources for follow-up and call back service of the included women. Interestingly, even when lowering the threshold for biopsy, we found few VIA women positive women with a CIN2+ lesion, results similar to our previous studies.[14 15] In screening naïve women, it was even more uncommon with CIN2+. It was reassuring to note that these women were detected by both nurses and doctors.

The cross-over design was chosen to lessen possible observer variability, but may also have influenced the scoring of the second instrument. Other study designs were evaluated, but would have been difficult to implement in a low-resource setting, where many poor women may never come back again to the colposcopy clinic. Also, blinding of which instrument used was not possible due to the nature of the instruments. However, by using cross-over study design, block randomization and the large sample size, we reduced the risk of the second examination's possible influence of cervical impression to

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affect the statistical calculations. Further, the inclusion of postmenopausal women and possible breastfeeding women, could have affected the results, as Swede score has not been validated on postmenopausal women and breast feeding women.

In low-resource settings 535 900 women die from obstetric and pregnancy related conditions each year. [28 29 30] This has led to that task-shifting within obstetrics has been widely embraced in Sub-Saharan Africa, to make best use of available human resources by redistributing specific tasks from highly qualified specialists to the least specialized professional skilled of performing the assignment safe and reliably, including general practitioners or non-physician clinicians (NPC) such as nurses, midwives and surgical technicians. [27 28] NPCs perform caesarean section and instrumental delivery in several African countries, thus bridging the human resource gap. [27 28]

The task-shifting could also be applied to colposcopy since 266 000 women die from cervical cancer each year, and a majority of them in low-resource settings.[1] In many high resource settings, nurse colposcopists are an well-established resource within colposcopy, [16 17 18] and with the results from our study, we showed that task-shifting within colposcopy and with the Gynocular, is a feasible and safe opportunity to lessen the human resource gap within colposcopy also in low-resource settings, This pragmatic but also highly accurate approach may have widespread implications to lower the epidemic high incidence or cervical cancer.

Bowring et al.[13] showed that trainee unaccredited colposcopists were as accurate as accredited colposcopists in detecting cervical lesions using Swede score, findings analogous to ours of VIA nurse colposcopists compared to accredited doctor colposcopists. Our study also showed that a VIA nurse colposcopist Swede score of eight or above, had parallel high specificities of CIN2+ as the Swede score of the doctors. These results are comparable to CIN2+ specificities in Swede score trials by doctors from both high[11 12] and low-resource settings.[13 14]

The Swede score colposcopy system works well with various health care professionals and economical settings.

It has been suggested[13 14 15] that the Swede score may be used as a primary cervical screening as well as a see and treat method of cervical lesions in low-resource settings. Thus, it is interesting to note that Swede score directed punch biopsies in women with a score of 4 and above, were more accurate than

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cytology in detecting CIN2+ lesions than cytology in VIA positive women in Uganda and Bangladesh.[14 15] However, our study show that it is needed to further validate the Swede score's sensitivity and specificity to detect CIN2+ in low resource populations, possible with biopsies from Swede score 0 in both screening naïve, VIA positive women as well as HPV status. This important as the Swede score was previously validated in women with an abnormal referral cytology in high resource settings.[12,13]

Moreover, in a multi-center randomized controlled trial,[30] direct colposcopy identified more cervical lesions than repeat cytology and a studies from Bangladesh and Nigeria[20 31] concluded that immediate 'see and treat' protocol after colposcopic examination of high grade CIN, was cheaper, less time consuming, more effective with less complication and good compliance. It reduced the number of visits to the clinic and failure to receive treatment associated with good compliance.[20 31]

A recent trial from Bangladesh summarised that VIA should be used as the primary screening tool although it's low sensitivity and specificity due to the limitations of a low-resource country, and that the high false positive results and overtreatment can be minimized by colposcopy evaluation of the VIA positive women.[21] Also, a notable response was observed from women at the Upazila (sub-district) level on the days of VIA Camps, indicating the positive attitude of women of having an examination for prevention of a disease.[32] VIA camps had a synergistic effect on the community, as women attending VIA camp on 1st and 2nd day, informed other women about the VIA test and availability of the service at Upazila Health Complex (UHC).[33] Thus, a combination VIA camp and 'treatment camp' may be useful in remote rural areas of low-resource settings, by administering a 'See and treat' protocol with Gynocular, it could offer an attractive option for successful screening outcome. A mobile van equipped with an examination chair, Gynocular and LEEP could offer a future approach in rural areas of remote districts. This will also reduce travel costs and loss of working days for the VIA positive women not requiring treatment. However, expertise on colposcopy needs to be emphasized to reduce over treatment and further research on nurse led Swede score colposcopy in low resource settings and learning curve is needed. Improvement of patients' knowledge and proper counselling should be important component of this protocol. Women would then not have to accept

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treatment only on the basis of VIA result and risk the associated draw backs of over treatment. The similar benefit is applicable to other developing countries like Bangladesh.

There is now an opportunity for policy makers to reduce the human resource gap by organizing training programs for educating nurse colposcopists and out-reach see and treat teams in low-resource settings, and to promote and evaluate such programs in adequately powered research studies. Sankaranarayanan et al showed previously that adequately trained nurses can be used to deliver colposcopy and cryotherapy services and are important, reliable, and efficient alternate human resources.[32] Training of nurses on colposcopy and use of Gynocular could have a widespread effect in reducing the number of women dying from cervical cancer, which in turn could have a major impact on community structure and wealth.

Future research should further evaluate VIA screening and direct colposcopy in low-resource settings.

Conclusion

In summary, a Swede score colposcopy examination by a nurse or doctor colposcopist, using the Gynocular or stationary colposcope, is similary good in detecting cervical lesions.

The Gynocular offers an opening for reducing the human resource gap in low resource settings by enabling nurse-colposcopist teams a tool for early detection of cervical high-grade lesions. Nurse-colposcopy in low resource setting with the Gynocular and the Swede score should be further explored and evaluated

Footnotes

We would like to thank all the women who participated in the study. We would also like to thank the doctors and nurses who examined the women at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. We would also like to thank the BSMMU in Bangladesh and Karolinska Institutet in Sweden for allowing us to perform the study at their premises.

Ethical approval

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This study was approved by the research ethics committee of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh and the Karolinska Institutet, Stockholm, Sweden. All participants provided informed consent.

Contributorship statement

All authors performed literature searches and wrote and edited the article. EWS and IS initiated the project. EWS and NA designed the study. NA, JSR, MAC, QK, RA, MT and EWS provided gynecologic expertise. NA, JSR, MAC, QK, RA, CW collected the data. MT, IS and MT provided statistical expertise. All authors contributed to analysis of the data.

Competing interests

EWS is the inventor of the Gynococular. EWS and IS are shareholders in Gynius.

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NA, JSR, MAC, QK, RA and MT had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MT received financial support for the submitted work from Gynius AB for statistical expertise. CW received financial support for study support in Bangladesh. H&M Conscious Foundation and Gynius AB funded the research project.

Data sharing

The dataset is available on request from the corresponding author:

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Figure Legends

Figure 1

The Gynocular with tripod mounting clip that screws into any standard tripod

Figure 2

Cross tabulation of Swede score's by Gynocular of nurses and doctors with Kappa.

Figure 3

Cross tabulation of Swede score's by stationary colposcope of nurses and doctors.

Figure 4

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by Gynocuar and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 5

ROC curves for predicting a positive biopsy result for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) by stationary colposcope and Swede score 1-10 for nurses and Swede score 4-10 by doctors (as the doctor's Swede score decided if to biopsy).

Figure 6

ROC curves for predicting a positive biopsy result CIN2+(CIN 2, CIN 3 and invasive cervical cancer) using Gynocular (Nurses first 50 vs rest).

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Table 1. Baseline characteristics

		Screening naive (N=404)	VIA positive (N=528)
Age	**Mean (SD)**	35.1 (8.1)	34.1 (7.8)
Age when married	**Mean (SD)**	17.9 (4.5)	17.1 (3.6)
Age at first delivery	**Mean (SD)**	20.0 (4.4)	19.2 (3.5)
Parity	**n (%)**		
0		14 (3.5)	12 (2.3)
1		82 (20.3)	96 (18.5)
2		163 (40.4)	216 (41.5)
3		83 (20.6)	102 (19.6)
4		40 (9.9)	57 (11.0)
5		17 (4.2)	22 (4.2)
6		1 (0.2)	9 (1.7)
7		1 (0.2)	5 (1.0)
Over 8		2 (0.5)	1 (0.2)
Biopsy results	**n (%)**		
Benign		7 (1.7)	13 (2.5)
Chronic cervicitis		23 (5.7)	82 (15.7)
CIN1		19 (4.7)	90 (17.3)
CIN2		4 (1.0)	21 (4.0)
CIN3		0 (0.0)	4 (0.8)
ICC		4 (1.0)	6 (1.2)
Tuberculosis		1 (0.2)	2 (0.4)
No biopsy		343 (85.5)	303 (58.2)

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Table 2. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer) (*nurses, n = 228*).

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	2.8% (0.1 - 14.5%)	99.5% (97.1 - 100.0%)	84.3% (78.9 - 88.8%)	50.0% (1.3 - 98.7%)
≥9 vs <9	13.9% (4.7 - 29.5%)	96.8% (93.2 - 98.8%)	85.5% (80.1 - 89.9%)	45.5% (16.7 - 76.6%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	80.4% (74.0 - 85.8%)	88.4% (82.6 - 92.8%)	30.2% (18.3 - 44.3%)
≥6 vs <6	52.8% (35.5 - 69.6%)	65.6% (58.4 - 72.4%)	87.9% (81.4 - 92.8%)	22.6% (14.2 - 33.0%)
≥5 vs <5	66.7% (49.0 - 81.4%)	43.9% (36.7 - 51.3%)	87.4% (79.0 - 93.3%)	18.5% (12.2 - 26.2%)
≥4 vs <4	86.1% (70.5 - 95.3%)	22.2% (16.5 - 28.8%)	89.4% (76.9 - 96.5%)	17.4% (12.2 - 23.8%)
≥3 vs <3	91.7% (77.5 - 98.2%)	13.8% (9.2 - 19.5%)	89.7% (72.6 - 97.8%)	16.8% (11.9 - 22.8%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	0.0% (0.0 - 9.7%)	99.5% (97.1 - 100.0%)	83.9% (78.5 - 88.5%)	0.0% (0.0 - 97.5%)
≥9 vs <9	11.1% (3.1 - 26.1%)	96.8% (93.2 - 98.8%)	85.1% (79.6 - 89.6%)	40.0% (12.2 - 73.8%)
≥8 vs <8	30.6% (16.3 - 48.1%)	90.5% (85.4 - 94.3%)	87.2% (81.7 - 91.6%)	37.9% (20.7 - 57.7%)
≥7 vs <7	44.4% (27.9 - 61.9%)	81.0% (74.6 - 86.3%)	88.4% (82.7 - 92.8%)	30.8% (18.7 - 45.1%)
≥6 vs <6	52.8% (35.5 - 69.6%)	66.1% (58.9 - 72.8%)	88.0% (81.5 - 92.9%)	22.9% (14.4 - 33.4%)
≥5 vs <5	66.7% (49.0 - 81.4%)	45.0% (37.7 - 52.4%)	87.6% (79.4 - 93.4%)	18.8% (12.4 - 26.6%)
≥4 vs <4	83.3% (67.2 - 93.6%)	22.2% (16.5 - 28.8%)	87.5% (74.8 - 95.3%)	16.9% (11.7 - 23.3%)
≥3 vs <3	91.7% (77.5 - 98.2%)	14.3% (9.6 - 20.1%)	90.0% (73.5 - 97.9%)	16.9% (11.9 - 22.9%)
≥2 vs <2	94.4% (81.3 - 99.3%)	6.9% (3.7 - 11.5%)	86.7% (59.5 - 98.3%)	16.2% (11.5 - 21.9%)
≥1 vs 0	97.2% (85.5 - 99.9%)	3.2% (1.2 - 6.8%)	85.7% (42.1 - 99.6%)	16.1% (11.4 - 21.6%)

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Table 3. Sensitivity and specificity for different cut-off levels for CIN 2+ (CIN 2, CIN 3 and invasive cervical cancer *(doctors, n = 228).*

Gynocular	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	22.2% (10.1 - 39.2%)	93.7% (89.3 - 96.7%)	86.5% (81.0 - 90.8%)	40.0% (19.1 - 63.9%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	74.9% (68.1 - 80.9%)	89.4% (83.5 - 93.7%)	28.4% (18.0 - 40.7%)
≥6 vs <6	61.1% (43.5 - 76.9%)	52.9% (45.5 - 60.1%)	87.8% (80.4 - 93.2%)	19.6% (12.7 - 28.2%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.0% (16.3 - 28.5%)	87.5% (74.8 - 95.3%)	16.8% (11.6 - 23.1%)

Colposcope	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10 vs <10	5.6% (0.7 - 18.7%)	97.4% (94.0 - 99.1%)	84.5% (79.1 - 89.1%)	28.6% (3.7 - 71.0%)
≥9 vs <9	19.4% (8.2 - 36.0%)	93.2% (88.6 - 96.3%)	86.0% (80.5 - 90.4%)	35.0% (15.4 - 59.2%)
≥8 vs <8	36.1% (20.8 - 53.8%)	88.0% (82.5 - 92.2%)	88.0% (82.5 - 92.2%)	36.1% (20.8 - 53.8%)
≥7 vs <7	52.8% (35.5 - 69.6%)	75.4% (68.7 - 81.3%)	89.4% (83.6 - 93.7%)	28.8% (18.3 - 41.3%)
≥6 vs <6	61.1% (43.5 - 76.9%)	53.4% (46.1 - 60.6%)	87.9% (80.6 - 93.2%)	19.8% (12.9 - 28.5%)
≥5 vs 4	83.3% (67.2 - 93.6%)	22.5% (16.8 - 29.1%)	87.8% (75.2 - 95.4%)	16.9% (11.7 - 23.2%)

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The Gynocular with tripod mounting clip that screws into any standard camera tripod
90x134mm (300 x 300 DPI)

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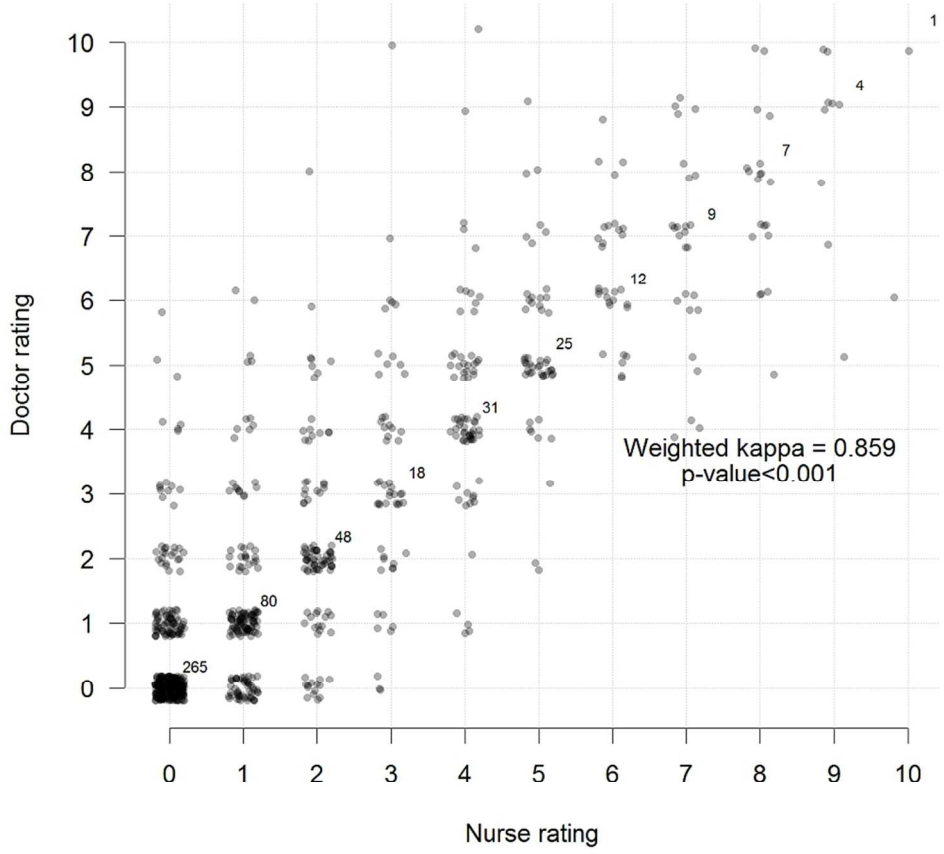

90x90mm (300 x 300 DPI)

nly

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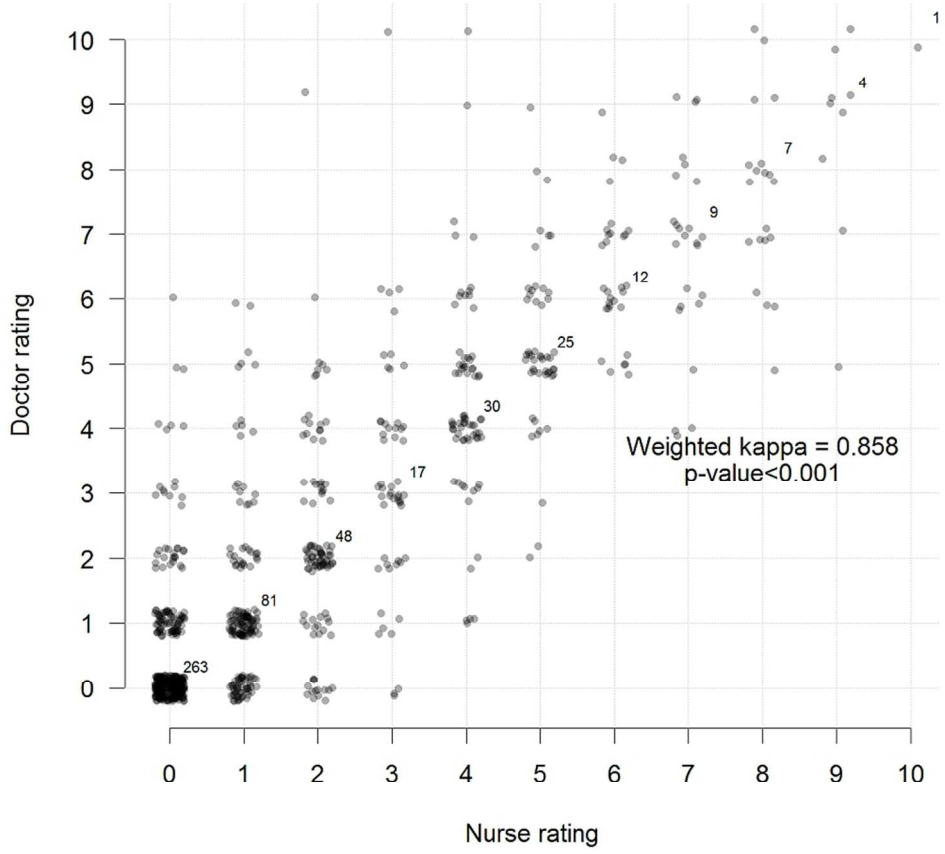

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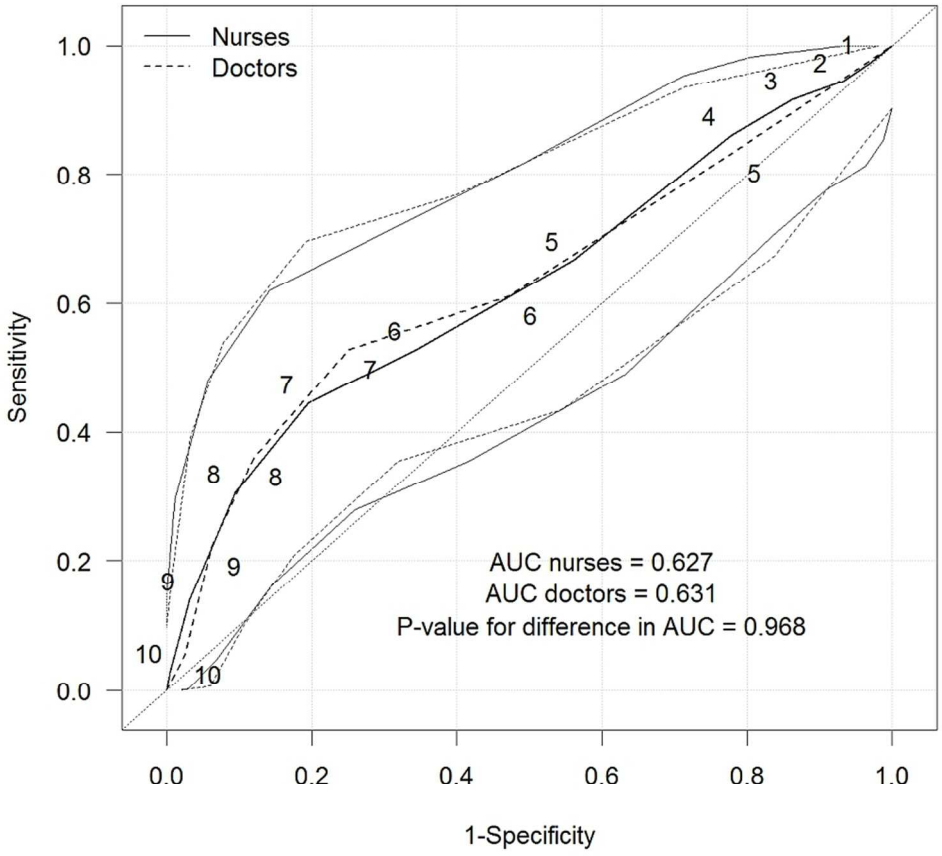

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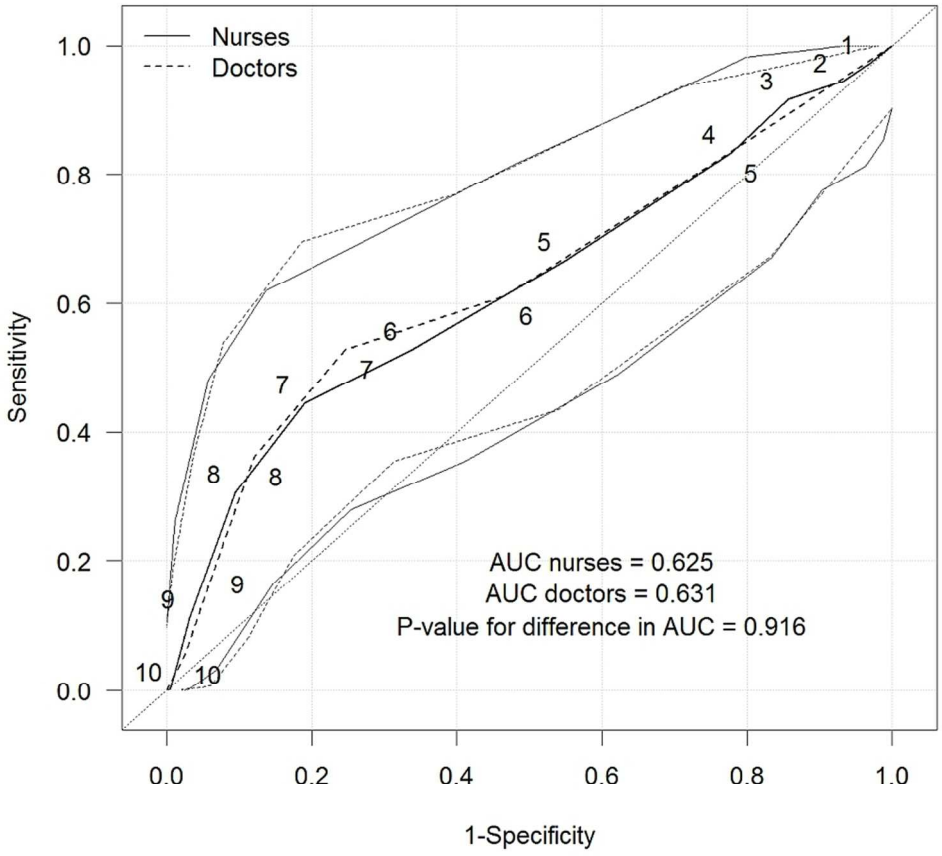

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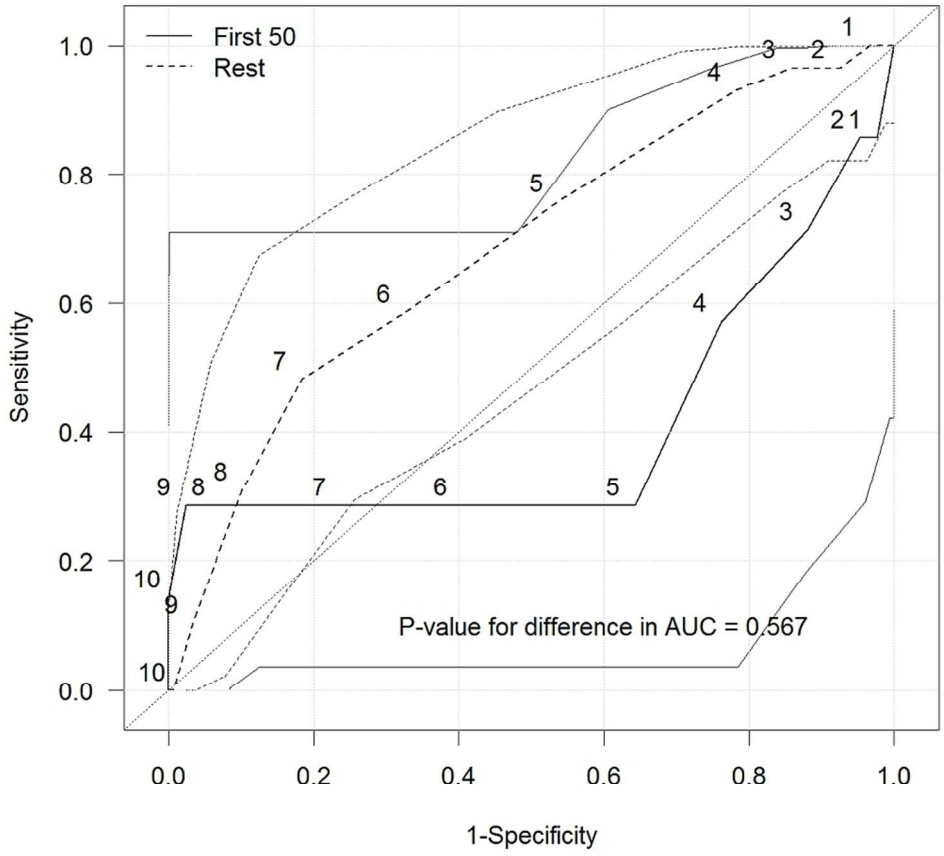

90x90mm (300 x 300 DPI)

nly

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Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	167-169
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	182-187
Interventions	Interventions intended for each group	197-223
Objective	Specific objective or hypothesis	158-161
Outcome	Clearly defined primary outcome for this report	167-169
Randomization	How participants were allocated to interventions	201-202
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Not applicable
Results		
Numbers randomized	Number of participants randomized to each group	206
Recruitment	Trial status	Completed
Numbers analysed	Number of participants analysed in each group	All
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	268-297
Harms	Important adverse events or side effects	None
Conclusions	General interpretation of the results	376-281
Trial registration	Registration number and name of trial register	228-230
Funding	Source of funding	108-110

**this item is specific to conference abstracts*

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