Liquid Based Cytology for the Detection of Cervical Intraepithelial Lesions among Women in Jimma Town, Ethiopia

Getnet Tesfaw (gettesfaw2@gmail.com)
Jimma University https://orcid.org/0000-0002-0344-784X
Yesuf Ahmed
Jimma University
Lealem Gedefaw
Jimma University
Lamessa Dube
Jimma University
Samson Godu
Jimma University
Kirubel Eshetu
International Clinical Laboratories
Mesfin Nigussie
International Clinical Laboratories
Haftamu Hailekiros
Mekelle University
Moses Joloba
Makerere University College of Health Sciences
Gelila Kidane Goba
University of Illinois at Chicago
Alemseged Abdissa
Jimma University

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Abstract

Background: Cervical cancer is the second leading type of female cancer in Ethiopia. Screening is primarily conducted using visual inspection with 5% acetic acid (VIA). Liquid-based cytology (LBC) has not yet been used in Ethiopia.

Method: Women aged 21-65 years were tested using LBC and VIA for the detection of cervical dysplasia. Logistic regression analysis was conducted to identify associated factors. Cohen's K test was conducted to test agreement between LBC and VIA.

Results: Forty-two percent (n=188) of 448 participants were 31 to 40 years of age and only two participants were above 60. Of the 448 participants, 419 (93.5%) were tested with LBC, 294 (65.6%) VIA and 272 (60.7%) with both LBC and VIA. Among women screened using LBC, 305(72.8%) were negative for intraepithelial lesion or malignancy (NILM), 97 (23.2%) had low grade squamous intraepithelial lesion (LSIL) and 17 (4.1%) high grade squamous intraepithelial lesion (HSIL). Presence of cervical lesions was generally lower in younger and older aged women. Majority, 39(40%) with LSIL and 10 (59%) of women with HSIL were 41-50 years old. Women aged 51-60 years were more likely to have abnormal intraepithelial lesions compared to women aged 21-30 (AOR= 20.9,95%CI=[7.2-60.9], p=0.00). Out of 47 (10.8%) HIV-patients,14(32.56%) had intraepithelial lesion of which 10(23.3%) and 4(9.3%) had LSIL and HSIL, respectively. Among women screened with VIA, 18 (6.1%) were positive. Among the 272 (60.7%) women screened using both LBC and VIA, 6 (2.2%) were positive on both LBC and VIA. The level of agreement between the two tests was weak and statistically significant (kappa value=0.155, p=0.006).

Conclusion: LBC detected high cervical squamous intra-epithelial lesions in our setting. VIA was a less reliable predictor of cervical squamous intra-epithelial lesions than LBC. Evaluating diagnostic accuracy of both LBC and VIA against histological endpoint should be completed before adopting either screening modalities.

Background

Human papilloma virus (HPV) is the most common sexually transmitted infection in the world [1]. Human papilloma virus (HPV) causes a variety of malignancies, with cervical cancer being the most important and prevalent [2]. Cervical cancer is a leading public health challenge globally. According to worldwide estimates of cancer, 569, 847 women were diagnosed for cervical cancer as new cases and 311,365 women died in 2018 [3]. Majority, (85%) of deaths occurred in low- and middle-income countries [4]. In Africa, 119, 284 new cases of cervical cancer were diagnosed and 81, 687 women died in 2018.The highest rate cervical cancer was found in eastern and western region [3].

In Ethiopia, 5.8% of national mortality is attributable to cancer. Incidence is increasing because of the aging population. Cervical cancer is the second leading cause of female cancer in women aged 15 to 44 years in Ethiopia [5]. According to Global Cancer Observatory estimate 6,294 new cases were diagnosed and 4,884 women died from the disease in 2018[6]. According to the Ethiopian Ministry of Health,

approximately 80% of reported cases of cancer are diagnosed at advanced stages when very little can be done to treat the disease[5].

In 2016, Ethiopia introduced a national cancer control plan that included a strategy of using visual inspection with acetic acid (VIA) and corresponding treatment of positives. Visual inspection with acetic acid (VIA) continues to be the only cervical cancer screening modality in the country [5]. There is no organized cytology-based cervical lesion screening program in Ethiopia.

As per the researchers' knowledge, no cervical cancer screening has ever been conducted in Ethiopia that combines liquid-based cytology (LBC) and visual inspection with acetic acid (VIA). This study documents the burden of cervical lesions and predictors of abnormal cervical cytology as well as comparing LBC and VIA screening modalities.

Methods

Study Design and Setting

A cross sectional study was conducted in Jimma Town from February 2017 to May 2018. Jimma is located 350 kilometers southwest of Addis Ababa. A total of 448 non-pregnant women ages 21-65 who visited Jimma University Hospital, Marie Stopes international and Family Guidance Association of Ethiopia (FGAE) Clinics for VIA screening as part of the national cervical cancer screening program were enrolled consecutively. Women with complete hysterectomy, gross tumor on the cervix, prior surgical procedures involving the cervix, menstruating, and those with no history of sexual activity were excluded. Written informed consent was obtained and the procedure of the test was explained to women.

Demographic and Risk Factors Data

Demographic information and risk factors for cervical cancer were collected using questionnaires prepared in *Afan Oromo* and *Amharic* languages. The collected data included occupation, educational status, age, parity, marital status, history of contraceptive use, age at first sexual intercourse, smoking, number of lifetime sexual partners, family history of cervical cancer, sexually transmitted infections (STIs) and alcohol consumption.

Liquid Based Cytology (LBC)

An automated liquid-based cytology, SurePath™ liquid-based Pap test (BD, USA), was employed for cytological sample preparation. After removing obscuring mucus from the cervix with a cotton swab, endocervical and ectocervical cells were collected with cytobrush. This cytobrush immediately rinsed in a vial containing SurePath Preservative Fluid. Samples were transported at room temperature for analysis at International Clinical Laboratories (ICL) in Addis Ababa using BD PrepMate^{TM} and PrepStain™ Slide Processor. Vials containing samples were labeled and placed into the BD PrepMate™ Slide Processor in

which a liquid-based filtration process removed mucus and debris, preserving cell morphology, and making a smear of even distribution. All slides were stained with the BD SurePath Kit Cytology Stain and examined by two pathologists [7] who enrolled in the College of American Pathologists (CAP) proficiency program and received stained LBC slides every three months and participating in the external quality assurance scheme. LBC test results were reported based on the Bethesda gynecologic cytology guideline [8].

Visual Inspection with Acetic Acid (VIA)

Women visited health facilities in Jimma Town involved in national cervical cancer screening program were enrolled for VIA. Women with invisible transformation zone were excluded from the study. After obtaining informed consent, sterile plastic spatula was inserted into the vagina to visualize the cervix. Then after, 5% acetic acid was applied to the cervix for one minute. Positive test was interpreted as a "sharp, distinct, well-defined, dense (opaque, dull or oyster white) aceto-white area with or without raised margins" according to the standard guideline [9,10]. VIA examination was done by experienced clinical nurses who participating in the national cervical cancer screening program using VIA.

Data Analysis

Data was checked for completeness, coded and entered into Epi data version 3.1 and exported to STATA[14] for analysis. Descriptive statistics, frequency and proportion were used to describe demographic variables. Sub-group analysis was conducted for HIV patients. Logistic regression analysis was used to identify risk factors for abnormal cervical cytology on LBC test. A Kappa test was used to assess the percent agreement between LBC and VIA. p-values < 0.05 at 95% confidence was considered statistically significant at 95% confidence.

Results

Characteristics of Study Participants

Mean age of participants was 38 years (SD=±9) and ranging from 21-65. Forty-two percent (n=188) of women fell between 31-40 years of age. Only two participants were above 60 years of age. Three hundred thirty-three (74.3%) were married. One hundred ninety-four (44.5%) had sexual debut at age 10-17 years old. Thirty-nine (8.8%) were primigravida, 339(74.1%) multigravida, and 163(38.3%) had two or / more lifetime partners. Seventy-eight (17.7%) had history of STIs and 47(10.8%) were HIV patients on ART follow -up at Jimma University's TB-HIV clinic (Table 1).

Table 1: Abnormal intraepithelial lesion by LBC, by demographic characteristic, Jimma, 2018.

Characteristics		N (%)	Liquid based cytology (LBC) Result		
			NILM	LSIL	HSIL
			n(%)	n(%)	n(%)
Age	21-30	105(25.06)	97 (92.38)	8 (7.62)	0(0.00)
	31-40	179(42.72)	144(80.45)	30(16.76)	5(2.79)
	41-50	102(24.34)	53(51.96)	39(38.24)	10(9.80)
	51-60	31(7.40)	11(35.48)	18(58.06)	2(6.45)
	>=61	2(0.48)	0(0.00)	2(100.00)	0(0.00)
Occupation	Government worker	159(38.8)	100(62.89)	46(28.93)	13(8.18)
	Merchant	30(7.3)	25(83.33)	4(13.33)	1(3.33)
	Student	11(2.7)	10(90.91)	1(9.09)	0(0.0)
	House wife	164(40.1)	127(77.44)	34(20.73)	3(1.83)
	Other	45(11)	36(80.00	9(20.00)	0(0.00)
Educational Status	Illiterate	84(20.14)	57(67.86)	26(30.95)	1(1.19)
	Primary	110(26.38)	91(82.73)	15(13.64)	4(3.64)
	Secondary	91(21.82)	66(72.53)	23(25.27)	2(2.20)
	University	132(31.65)	90(68.18)	32(24.24)	10(7.58)
Marital Status	Married	313(74.88)	240(76.68)	62(19.81)	11(3.51)
	Single	23(5.50)	20(86.96)	3(13.04)	0(0.00)
	Divorced	28(6.70)	22(78.57)	5(17.86)	1(3.57)
	Other	54(12.92	23(42.59)	26(48.15)	5(9.26)
Parity	Nulligravida	34 (8.17)	29(85.29)	3(8.82)	2(5.88)
	Primigravida	70 (16.83)	55 (78.57)	13 (18.57)	2 (2.86)
	Multigravida	312 (75.00)	219 (70.19)	80 (25.64)	13 (4.17)
Menstrual Bleeding Pattern	Irregular	151(37.1)	131(86.75)	18(11.92)	2(1.32)
	Regular	120(29.48)	111(92.50)	9(7.50)	0(0.00)
	Menopause	136(33.42)	53(38.97)	68(50.00)	15(11.03)
Postcoital bleeding	No	377(93.32)	268(71.09)	92(24.40)	17(4.51)
	Yes	27(6.68)	24(88.89)	3(11.11)	0(0.00)
Age of first sexual intercourse	10-17	183(44.74)	132(72.13)	45(24.59)	6(3.28)
	>=18	226 (55.26)	166(73.45)	49(21.68)	11(4.87)
Use of contraceptive	No	305(73.14)	203(66.56)	87(28.52)	15(4.92)
	Yes	112(26.86)	100(89.29)	10(8.93)	2(1.79)
Current sexual partner	No	138(33.17)	87(63.04)	43(31.16)	8(5.80)
	Yes	278(66.83)	216(77.700	53(19.06)	9(3.24)
Condom use during sexual intercourse	No	392(94.23)	282(71.94)	95(24.23)	15(3.83)
	Yes	24(5.77)	21(87.50)	1(4.17)	2(8.33)
Alcohol use	No	384(93.20)	276(71.88)	91(23.70)	17(4.43)
	Yes	28(6.80)	24(85.71)	4(14.29)	0(0)
Smoking	No	417(99.52)	303(72.66)	97(23.26)	17(4.08)
	Yes	2(0.48)	2(100)	0(0.00)	0(0.00)

Chronic corticosteroid use	No	396(96.82)	292(73.74)	87(21.97)	17 (4.29
	Yes	13(3.18)	6(46.15	7(53.85)	0(0.00)
Number of life time sexual partner	1	247(61.75)	174(70.45)	63(25.51)	10(4.05)
	>=2	153(38.25)	116(75.82)	30(19.610	7(4.58)
History of sexually transmitted diseases	No	339(82.48)	246(72.57)	80(23.60)	13(3.83)
	Yes	72(17.52)	53(73.61)	16(22.22)	3(4.17)
HIV status	Non-reactive	135(33.09)	104(77.04)	26(19.26)	5(3.70)
	Reactive	43(10.54)	29(67.44)	10(23.26)	4(9.30)
	Unknown	230(56.37)	163(70.87)	59(25.65)	8(3.48)
Family history of cancer	No	350(94.85)	254(72.57)	80(22.86)	16(4.57)
	Yes	19(5.15)	14(73.68)	5(26.32)	0(0.00)
Pelvic examination	Abnormal	7(1.78)	5(71.43)	1(14.29)	1(14.29)
	Normal	386(98.22)	284(73.58)	86(22.28)	16(4.15)
SCJ visible	No	120(33.06)	60(50.00)	47(39.17)	13(10.83)
	Yes	243(66.94)	207(85.19)	32(13.17)	4(1.65)

Intraepithelial Lesion Screening by LBC and VIA

Of 448 participating women, 28(6.3%) were missing LBC results, 1(0.22%) had inadequate sample. The remaining 419(93.5%) women had LBC results, 294(65.6%) had VIA results and 272(60.7%) had both LBC and VIA results.

Among women screened using LBC, 305(72.8%) were negative for intraepithelial lesion or malignancy (NILM), 97(23.2%) had LSIL and 17(4.1%) had HSIL. No ASC-US, ASC-H or squamous carcinoma was present. Cervical lesions, either LSIL or HSIL was present in 114 (27.2%) women. Presence of cervical lesions were generally lower in younger and older aged women compared to middle aged women. Among women with cervical lesions, 8 (7%) were below the age of 31 and 2(1.75%) were over 60. Of the remaining women, 70(30.7%) were 31-40, 49(43%) were 41-50, and 20(17.54%) were 51-60 years. Thirty-nine (40%) of the women with LSIL and 10(59%) with HSIL were between the 41-50 years of age. Among the 419 women tested using LBC, 120(33.1%) women had invisible SCJ during examination. Of these, 60(50%) had either LSIL or HSIL [Table 1].

Two hundred seventy-two (60.7%) women were screened using both LBC and VIA. Among women screened using VIA, 18(6.1%) tested positive. Eleven (4.7%) of the 18 that tested positive by VIA were among the 236 (86.8%) cases recorded as NILM by using LBC. Of the 36 (12.1%) women who had either LSIL or HSIL using LBC, 30 (83.3 %) tested negative using VIA. No women with HSIL tested positive using VIA. There was no agreement between the two screening tests using kappa measurement (kappa value=0.155, p=0.006) [Table 2].

Table 2: Cervical lesion abnormality among women screened by both LBC and VIA, Jimma, 2018

LBC Result	VIA Test Result		Total	Kappa value	P-value
	Negative	Positive		0.155	0.006
	n(%)	n(%)	N(%)		
NILM	225(95.34)	11(4.66)	236(100)		
LSIL or HSIL	30(83.33)	6(16.67)	36(100)		
Total	255(93.75)	17(6.25)	272(100)		

Characteristics of HIV Patients

A total of 47 HIV patients on ART who visited Jimma University Cervical Cancer Clinic were screened for cervical lesions. Of these, 21(45.7%) were married, 15(31.9%) were primigravida, 28(59.6%) multigravida, 23(48.9%) and had sexual debut between the ages of 11-17. Thirty-two (68.1%) had multiple sexual partners and 15(32%) had history of STIs.

Twenty-eight (59.6%) and 43(91.5%) HIV-positive women were tested with VIA and LBC, respectively. Only two HIV-patients were positive for VIA. Whereas, 14(32.6%) had either LSIL or HSIL on the LBC test. Of these women, 10(23.3%) and 4(9.3%) had LSIL and HSIL, respectively. Among HIV patients between the ages of 41-50, 7(77.78%) had intraepithelial lesions. Half of HIV-patients with interepithelial lesions were between the ages of 41-50.

Predictors of Abnormal Cytology by LBC

Bivariate logistic regression analysis revealed that parity, age and condom use during sexual intercourse were candidates for multivariate regression at p=<0.25. Multivariate regression revealed that age was an independent predictor of LSIL or HSIL. Odds of being positive for cervical squamous-extraepithelial lesions were higher in women older than 31 years of age.

Women aged 51-60 were more likely to have abnormal intraepithelial lesion compared to women aged 21-30 (AOR= 20.9,95%CI=[7.2-60.9], p=0.00) [Table 3].

Table 3: Predictors of abnormal cervical cytology using LBC, Jimma, 2018.

istics	N(%)	LBC Result		COR(95%:CI)	*P-Value*	AOR(95%: CI)	*P-Value*
		NILM	LSIL or HSIL				
		n (%)	n(%)				
Nulligravida	34(8.17)	29(85.29)	5(14.71)	1(ref.)		1	
primigravida	70(16.83)	55(78.57)	15 (21.43)	1.6(0.52-4.8)	0.42	1.4 (0.43-4.9)	0.56
Multigravida	312(75)	219(70.19)	93(29.81)	2.5(0.9-6.6)	0.07	1.1 (0.38-3.3)	0.85
21-30	105(25.06)	97(92.38)	8(7.62)	1(ref.)		1	
31-40	179(42.72)	144(80.45)	35(19.55)	2.9(1.3-6.6)	0.00	2.9(1.3-6.8)	0.00
41-50	102(24.34)	53(51.96)	49(48.04)	11.2(4.9-25.4)	0.00	11.4(4.8-26.9)	0.00
51-60	31(7.40)	11(35.48)	20(64.52)	22.0(7.8-61.5)	0.00	20.9(7.2-60.9)	0.00
>=61	2(0.48)	0(0.00)	2(100.00)	1			
No	392 (94.23)	282 (71.94)	110 (28.06)	2.7 (0.79-9.3)	0.12	1	
Yes	24 (5.77)	21 (87.50)	3(12.50)	1(ref)		1.9(0.52-6.9)	0.33

Discussion

In Ethiopia, 29 million women over 14 years of age are at risk of developing cervical cancer [5]. In 2018, 6,294 women were diagnosed as new cervical cancer cases and 4,884 women died from the disease [6].

Even though cervical cancer burden is high in Ethiopia, the national cancer screening program is based solely on VIA, which has high variability due to examiners' judgment [11]. Our study shares the results of the first cervical cancer screening in Ethiopia using LBC. In our study, prevalence of abnormal squamous intraepithelial lesion was 114(27%), which is higher than the 17% shown in a study in China [12]. Prevalence of LSIL and HSIL were 23.2% and 4.1 %, respectively, much higher than the 1.9% and 0.6% prevalence, respectively, observed in Sao Paulo. [13]. A study in India reported lower rate of LSIL (7.5%), but higher HSIL (10.5%) [14]. Significantly, lower prevalence of LSIL and HSIL (2%) and (2.4%) were shown the Netherlands and Germany, respectively, [15,16]. Low prevalence rate of cervical squamous intra-epithelial lesions in developed nations may be due to the availability of the HPV vaccines [17] and the presence of organized cervical cancer screening [18], which is new to Ethiopia.

In our study, higher proportion of women aged 41-50 tested positive on LBC screening test whereas we observed lower prevalence of cervical lesions in younger and older women. Visibility of SCJ is the prerequisite for VIA examination and women with invisible SCJ are exempt for VIA examination [19]. In our study, women with invisible SCJ, underwent LBC testing and 60 (50%) had either HSIL or LSIL by LBC.

Logistic regression showed women aged 51-60 years had higher odds of having cervical squamous intraepithelial lesion compared to younger ages. LBC screening was better at detecting HSIL and cervical lesions in older ages, which is not true for VIA screening [20].

HIV infection is a risk factor for persistent HPV-infection, a necessary condition for the development of squamous interepithelial lesions and HIV infected women are disproportionately affected by cervical lesions [21]. In our study, 14(32.56%) HIV-patients had cervical squamous intraepithelial lesions, higher than prevalence in the total study population (27%). While the rate of LSIL (23.3%) among HIV-positive patients was similar to the full study cohort and prevalence of HSIL (9.3%) was nearly double. A study in South Africa recorded higher prevalence of LSIL (32.5%) and HSIL (23.3%) [22] than our study whereas a study in Nigeria showed LSIL and HSIL rates to be 14.3% and 4.3%, respectively, among HIV-positive women [23].

VIA detected 18(6.1%) cases of cervical lesions, which is similar to the 5% reported in West Shewa, Ethiopia [24], but much lower than the 12.9% reported in another study in Jimma Town, [25] as well as studies in Rwanda and China, where 14.7% [26] and 11.4% [12] of women had cervical lesions, respectively. Among women who were tested using both LBC and VIA in our study, a high proportion (83.3%) that tested positive with LBC, tested negative on VIA, meaning VIA screening missed a considerable proportion of women with abnormal cervical lesions. This finding is similar to a study in China that showed VIA missed the majority of CIN2+ in older women and was less sensitive than LBC [12]. As our study showed, there was no agreement between LBC and VIA screening tests and variability was statistically significant (kappa =0.155, P=0.006).

Organized cytology-based screening is the most efficient screening method for the detection of cervical lesions and has resulted in significant reduction in cervical cancer in developed countries [27]. Financial constraints and technical challenges hinder implementing cytology-based screening in low- and middle-income countries like Ethiopia.

Conclusions

Given that VIA screening missed most cervical lesions detected by LBC in our study, and that a high number of cervical epithelial lesions were detected by LBC, a larger study should be undertaken to determine the diagnostic accuracy of both LBC and VIA against a histological endpoint before adopting either or both as screening modalities.

Abbreviations

VIA: visual inspection with 5% acetic acid; LBC: Liquid-based cytology; HPV: Human papilloma virus; FGAE: Family Guidance Association of Ethiopia; NILM: negative for intraepithelial lesion or malignancy; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion; SCJ:

squamouscolumnar junction; ICL: International Clinical Laboratories; STIs: sexually transmitted infections.

Declarations

Ethics Approval and Consent to Participate

Ethical clearance was obtained from Jimma University's Institutional Review Board (IRB). Written informed consent was obtained from study participants and voluntary participation was ensured. Confidentiality of study participants, including test results was

This study was funded by Jimma University Research and Postgraduate Coordinating Office. The funder has no role in designing the study, analysis of data and interpretation of the results.

Consent for Publication

"Not applicable."

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors have no competing interests to declare.

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Authors Contributions

GT, YA, LG, LD, SG, MN, KE, and AA conceptualized and designed the study. GT, YA, MN and KE led the data collection. GT, YA, LG, LD, SG, KE, MN, HH,MJ, GKG and AA ccontributed to the data analysis and interpretation of data. GT prepared the first draft of the paper and all authors contributed to the revisions, discussion of results and completion of the final manuscript. All authors have read and approved the manuscript.

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