RESEARCH ARTICLE

Benefits of Cervical Cancer Screening by Liquid-Based Cytology as Part of Routine Antenatal Assessment

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Abstract

Purpose: To determine the prevalence of abnormal cervical cytology, as diagnosed using a liquid-based cytology technique, in pregnant women attending the Antenatal Care (ANC) clinic at Siriraj Hospital. Materials and Methods: This cross-sectional study included 655 first-visit pregnant women who attended ANC clinic at Siriraj Hospital during June to November 2015 study period. After receiving routine antenatal care, cervical cytology screening was performed with the Siriraj liquid-based cytology technique. All specimens were reviewed by a certified cytopathologist using Bethesda System 2001 criteria. Patients with abnormal PAP results characterized as epithelial cell abnormalities were referred to a gynecologic oncologist for further management according to ASCCP Guidelines 2012. Results: Mean age of participants was 28.9±6.2 years. Prevalence of abnormal cervical cytology was 3.4% (95% CI: 2.0-4.7). Among this group, there were ASC-US, ASC-H, LSIL, HSIL for 12(1.8%), 2(0.3%), 7(1.1%) and 1(0.2%), respectively. In 633 specimens of the normal group, infection was identified in 158 specimens (24.1%) which were caused by *Candida* spp. and *Trichomonas vaginalis*. Regarding patient perception about the importance of cervical cancer screening, although most women perceived screening to be important, 54% of participants had never been screened for cervical cancer. Rate of loss to follow-up in the postpartum period was as high as 41.8%. Conclusions: Prevalence of abnormal cervical cytology in pregnant women attending the ANC clinic at Siriraj Hospital was 3.4%. Inclusion of cervical cancer screening as part of antenatal assessment can help to identify precancerous lesions or cervical cancers in patients who might otherwise not be screened, thereby facilitating early treatment and improved patient outcomes.

Keywords: Cervix - pap smear - liquid-based cytology - antenatal care

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Introduction

Over the past 30 years, the incidence of cervical cancer in the United States has decreased more than 50 percent due to widespread cervical cancer screening. A study conducted in the United States found that the incidence rate of cervical cancer was reduced from 14.8 per 100,000 women in 1975 to 6.6 per 100,000 women by 2006 (ACOG, 2012). Statistics from the National Cancer Institute of Thailand, however, reveal that the cervical cancer incidence rate increased from 17.7 per 100,000 women in 2005 to 24.5 per 100,000 women by 2008. After breast cancer, cervical cancer is the second most common cancer among Thai women, and therefore, a leading healthcare issue in Thailand.

Currently, cervical cancer screening strategies are ubiquitously implemented and Thai women conveniently participate in screening program across Thailand. As a result, gynaecologists can make early diagnosis and initiate appropriate treatment before malignant transformation or the development of distant metastasis. Moreover, the development of vaccinations against Human papillomavirus (HPV) 16 and 18, comprising 70 percent of all malignant transformation and probability of progression to invasive cervical cancer, accounts for a drastic diminution in cervical cancer incidence and mortality rate (McGraw et al., 2014; McNamara et al., 2016). The use of HPV vaccination, however, cannot prevent HPV infection in already HPV-infected women or protect against other high-risk non-vaccine HPV types. Accordingly, vaccinated women require cervical cancer screening as non-vaccinated women do.

Cervical cancer screening is performed by collecting sample cells from the uterine cervix and then examining for abnormal cervical cells under the microscope. This process is called "Papanicolaou smear", "Pap smear" or "Pap test". There are 2 methods to perform the Pap test, conventional cytology and liquid-based cytology. The liquid-based cytology technique resulted in a reduction in the number of unsatisfactory specimens and was

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more cost-effective than the conventional technique (Laiwejpithaya et al., 2008; Laiwejpithaya et al., 2009; Gupta et al., 2016). Current evidence indicates that there is no statistically significant difference in sensitivity or specificity for detection of cervical intraepithelial neoplasia of grade 2 or more (CIN II/III) when comparing liquid-based and conventional cytology (Arbyn et al., 2008; Siebers et al., 2009; Tanabodee et al., 2015). As such, both methods are generally accepted as standard cervical cancer screening tests.

The American Society for Colposcopy and Cervical Pathology (ASCCP) 2012 recommends that women aged 21-65 years should be screened with cervical cytology alone every 3 years by either conventional or liquid-based method. For women aged 30-65 years, HPV co-testing every 5 years is preferred (Massad et al., 2013). These guidelines also apply to all pregnant women. Williams Obstetrics (textbook), 24th edition, emphasizes that a Pap test is a typical component of routine prenatal care since there is a good opportunity to perform the test, particularly at the first prenatal visit. In this study, the authors collected the data from pregnant women who had their first visit at the ANC clinic, Faculty of Medicine, Siriraj Hospital, Mahidol University. Owing to the fact that pregnant women are at risk of HPV infection which contributes to abnormal Pap tests. From a study by Stillson et al. (1997), cervical cytologic screening during pregnancy using cytobrush and Ayre's spatula did not increase the risk of spot bleeding or spontaneous abortion. Nevertheless, Thai clinical practice regarding cervical cancer screening in pregnancy dictates that pregnant women will receive a Pap test during the postpartum period. However, many of these patients may be lost to follow-up due to non-compliance and, therefore, may not be screened for cervical cancer. Khaengkhor P. et al (Khaengkhor et al., 2011) reported a prevalence of abnormal cervical cytology in pregnant patients attending the ANC clinic at Thammasat University Hospital of 7%. By receiving antenatal cervical cancer screening, those patients received early detection and early treatment.

The aim of this study was to determine the prevalence of abnormal cervical cytology using liquid-based cytology technique in pregnant women who attended the Antenatal Care (ANC) clinic at Siriraj Hospital. The opportunity and convenience of screening pregnant women for cervical cancer during antenatal assessment may contribute to a significant decline in the incidence of cervical cancer and cervical cancer-related mortality. Moreover, a change in current screening protocol would help to ensure that we do not miss detection of identifiable cases in patients that are lost to follow-up during the postpartum period.

Materials and Methods

This cross-sectional study included 655 first-visit pregnant women who attended the ANC clinic at Siriraj Hospital during the June 2015 to November 2015 study period. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, and written informed consent was obtained from all participants prior to inclusion. The inclusion criteria were, as follows: pregnant patient of any gestational age; first-visit to the ANC clinic at Siriraj Hospital for antenatal evaluation and care; and, negative serology (Anti-HIV, VDRL and HBsAg). After receiving routine antenatal care, participating patients were asked to fill out a case record form. Cervical cytology screening was then performed using Siriraj liquid-based cytology technique (Laiwejpithaya et al., 2008). Specimens were gently collected from the posterior fornix and the endocervix by Siriraj liquid-based spatula. The tips of spatula were then placed in a bottle containing preserved cell solution (Siriraj liquid-based solution). All specimens were submitted to the Division of Cytology, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University. All specimens were processed and examined by a certified cytopathologist using Bethesda system 2001 criteria. Patients with abnormal PAP results characterized as epithelial cells abnormalities were referred to gynecologic oncologist for further management according to ASCCP Guidelines 2012.

The rate of loss to follow-up in postpartum period of pregnant women giving birth at Siriraj Hospital was retrospectively collected. Siriraj medical record consisting of pregnant women who delivered at Siriraj Hospital between April to June 2015 was retrospectively reviewed. Telephone was used to ask about postpartum follow up If the patient did not attend postpartum clinic at Siriraj Hospital. This data would provide us the problem of follow-up in postpartum period.

Data were analyzed using SPSS Statistics version 20.0 program. Descriptive statistics (frequency and percentage) were obtained for all continuous and categorical variables. Qualitative data were analyzed using chi-square test or Fisher's exact test. Quantitative data were analyzed using independent t-test or Mann-Whitney U test as appropriate. A p-value <0.05 was regarded as being statistically significant.

Results

Pap smear was performed in 655 pregnant women and none of the patients were excluded from the study. Demographic and clinical characteristics of participants are shown in Table 1. The vast majority of participants were in the reproductive age range (20-40 years old). Mean age was 28.9±6.2 years. Most of our patients were employed (75%) and educated in secondary school (37.4%). Most women (84.9%) earned a monthly income of 20,000 baht (600 USD) or less. Regarding health-related risk factors, 74.8% were non-smokers and 52.4% did not drink alcohol. Most participants (76.5%) reported not using a condom as a contraceptive method. No statistical significance was observed for any demographic data when compared between patients with normal cytology and patients with abnormal cytology.

Cervical cytology results by liquid-based cytology in 655 subjects are shown in Table 2. All specimens were satisfactory for cytologic evaluation. Prevalence of abnormal cytology was 3.4% (95% CI: 2.0-4.7). Abnormal cervical cancer screening test results were, as follows:

Table 1. Demographic and Clinical Characteristics of Pregnant Women Attending the ANC Clinic at Siriraj Hospital in 2015

Variables	Normal (%) n=633	Abnormal (%) n=22	Total(%) n=655	p-value
Age				
<21	72(11.4)	4(18.2)	76(11.6)	0.5501
21-30	278(43.9)	11(50)	289(44.1)	
31-40	268(42.3)	7(31.8)	275(42)	
>40	15(2.4)	0(0)	15(2.3)	
Occupation				
Unemployed	121(19.1)	6(27.3)	127(19.4)	0.4501
Employed	477(75.4)	14(63.6)	491(75)	
Student	35(5.5)	2(9.1)	37(5.6)	
Education				
Primary school or under	53(8.4)	1(4.5)	54(8.3)	0.1738
Secondary school	232(36.6)	13(59.1)	245(37.4)	
Vocational school	129(20.4)	4(18.2)	133(20.3)	
University	219(34.6)	4(18.2)	223(34)	
Salary (Thai baht/month)				
0-10000	289(45.6)	8(36.4)	297(45.3)	0.5265
>10000-20000	248(39.2)	11(50)	259(39.6)	
>20000-30000	67(10.6)	3(13.6)	70(10.7)	
>30000	29(4.6)	0(0)	29(4.4)	
Smoking				
None	476(75.2)	14(63.6)	490(74.8)	0.6292
Quit smoking	37(5.8)	2(9.1)	39(5.9)	
Current smoker	3(0.5)	0(0)	3(0.5)	
Family member is a smoker	117(18.5)	6(27.3)	123(18.8)	
Alcohol				
Never	332(52.4)	11(50)	343(52.4)	0.8038
Rarely	239(37.8)	10(45.5)	249(38)	
Often	3(0.5)	0(0)	3(0.4)	
Quit	59(9.3)	1(4.5)	60(9.2)	
Contraception				
Condom	149(23.5)	5(22.7)	154(23.5)	0.9297
No condom	484(76.5)	17(77.3)	501(76.5)	
History of delivery				
Nulliparous	321(50.7)	11(50)	332(50.7)	0.9478
Multiparous	312(49.3)	11(50)	323(49.3)	

Table 2. Prevalence of Abnormal Cervical Cytology by Liquid-Based Cytology in 655 Pregnant Women Attending the ANC Clinic at Siriraj Hospital in 2015

Pap results	Total = 655 n (%)
Normal	633 (96.6)
With infection	158 (24.1)
Without infection	475 (72.5)
Abnormal Pap smear	22 (3.4)
ASC-US	12 (1.8)
ASC-H	2 (0.3)
LSIL	7 (1.1)
HSIL	1 (0.2)

ASC-US: 12 patients (1.8%); ASC-H: 2 patients (0.3%); LSIL: 7 patients (1.1%) and HSIL: 1 patient (0.2%). In 4 cases of women aged below 21 who had abnormal cytology results according to Table 1., all of them had only low grade lesion as ASC-US (3 cases) and LSIL (1 case). Among the 633 normal group specimens, infection was identified in 158 specimens (24.1%). The causative pathogens were Candida spp. (22.9%) and Trichomonas vaginalis (1.2%).

Patient knowledge regarding the need or importance of cervical cancer screening was elicited in the case record form. Data regarding patient perceptions about cervical cancer screening are presented in Table 3. Eighty-four percent of participants perceived that cervical cancer screening is necessary for all women. Regarding specific conditions or settings, 9.8% of women said that cervical cancer screening is only necessary for sexually active women, postpartum women or women with abnormal vaginal bleeding. No participant reported believing that cervical cancer screening is not necessary.

Table 3. Knowledge of Cervical Cancer Screening among Women Attending the ANC Clinic at Siriraj Hospital in 2015

Knowledge	Total=655 n (%)
Necessary for all women	552 (84.3)
Necessary for all sexually active women	38 (5.8)
Necessary for women with abnormal vaginal bleeding	15 (2.3)
Necessary for postpartum women	11 (1.7)
Not necessary	0 (0)
No knowledge about cervical cancer screening	39 (5.9)

Reported sexual behavior of participants is given in Table 4. Most patients experienced coitarche when they were older than 19 years of age, followed by patients in the 16-19 age group. Mean age of coitarche in the normal and abnormal Pap result group was 20.5±4.8 years and

Table 4. Sexual Behavior of Patients Attending the ANC Clinic at Siriraj Hospital in 2015

Sexual behavior	Normal (%)	Abnormal (%)	Total (%)	p-value
	n=633	n=22	n=655	
Age of first coitus(yrs)				
<16	60(9.4)	3(13.6)	63(9.6)	0.1872
16-19	246(38.9)	12(54.6)	258(39.4)	
>19	327(51.7)	7(31.8)	334(51)	
Sexual partner				
Single partner	289(45.7)	4(18.2)	293(44.7)	0.0109
Multiple partner	344(54.3)	18(81.8)	362(55.3)	

Table 5. History of Cervical Cancer Screening Among Pregnant Women Attending the ANC Clinic at Siriraj Hospital in 2015

Screening history	Normal (%)	Abnormal (%)	Total (%)
	n=633	n=22	n=655
No history of prior screening	344(54.3)	12(54.5)	356(54.4)
History of prior screening	289(45.7)	10(45.5)	299(45.6)
Last screening ≤ 3 years	199(31.5)	7(31.9)	206(31.4)
Last screening > 3 years	90(14.2)	3(13.6)	93(14.2)

18.64±3.1 years, respectively. In a comparison between abnormal and normal Pap smear findings, patients with multiple sexual partners had a higher percentage of abnormal Pap results than single partner patients (81.8% *vs* 18.2%; p-value = 0.0109).

History of cervical cancer screening in participants is shown in Table5. Although most women perceived screening to be important, 54% of participants had never been screened for cervical cancer. Only 31% of women had their last cervical cancer screening within the last 3 years. This finding should be a major concern to policy makers in our health care system

Moreover, the authors also investigated the loss to follow-up rate among women who had given birth at Siriraj Hospital. This data was collected from Siriraj Hospital medical record system, consisting of pregnant women who delivered at Siriraj Hospital during April to June 2015 evaluation period. Of concern, 41.8% of those patients were lost to follow-up after giving birth. For normal patients that are authorized by current protocol to receive cervical cancer screening in the postpartum period only, 41.8% of the patients in this period could potentially have missed the opportunity for early detection and treatment.

Discussion

Human papillomavirus infection causing cervical cancer is common in women in their reproductive age. The natural course of progression in HPV infection is very slow. On average, high grade lesion may take 3-7 years to progress to invasive cervical cancer (ACOG, 2012). Most pregnant women who are in the reproductive age range would, therefore, have problems as precancerous lesion type. For many patients, the first antenatal visit is their first encounter with a gynecologist. As such, this is regarded as an opportune time to screen for and detect precancerous lesion by cervical cancer screening and initiate treatment in positive patients. Unfortunately, most healthcare centers in Thailand schedule cervical cancer screening during the postpartum period and some have no screening plan in their schedule.

Previous studies of abnormal cervical cytology in pregnancy in Thailand reported varying rates of prevalence. Sueblinvong et al. (2005) and Ngaojaruwong N et al in 2008 (Ngaojaruwong et al., 2008) reported prevalence of abnormal cervical cytology in pregnancy of 0.8% and 0.52%, respectively. In 2011, Khaengkhor et al. (2011) reported 7% prevalence of abnormal cervical cytology in pregnancy which were very high percentage.

In this study, prevalence of abnormal cervical cytology in pregnant women was 3.4% and prevalence of high grade lesion was 0.5%. Differences in cytology screening technique from the studies in 2005 and 2008 may help to explain differences in results. Liquid-based cytology technique was used in this study. The advantages of this technique include thin layer preparation which eliminates cell overlapping and unsatisfactory results. A study by Khaengkhor et al. (2011) also used liquid-based technique, but with a much smaller sample size than the sample size in our study. Differences in demographic characteristics and reproductive data between studies may explain the difference in results. In this study, among women aged below 21 with abnormal Pap results, there were all low grade lesions which can be regressed without any treatment. As a result, cervical cancer screening in women younger than 21 years old is not necessary. This is agreed with ASCCP guideline 2012.

Regarding patient perceptions about the importance and necessity of cervical cancer screening, 84% of participants perceived that cervical cancer screening is necessary for all women. Importantly, no women in this study reported believing that cervical cancer screening is not necessary. Interestingly, 54% of women had never undergone cervical cancer screening in their lifetime (Table 5). Moreover, only 31.4% of our patients reported having their last screening in 3 years or less. Some attractive data reported that 50% of women with cervical cancer had never received cervical cytology screening, and 10% had not been screened within 5 years (Spence et al., 2007). It can be therefore postulated that a significant percentage of cervical cancer diagnoses are the result of inadequate cervical cancer screening. Healthcare providers should, therefore, emphasize the importance of promoting cervical cancer screening and prevention within their patient populations.

More than half of the pregnant women (55.3%) in this study reported having had multiple sexual partners. This sexual behavior theoretically increases the risk of cervical cancer. In addition, this study reported that women who have had multiple sexual partners had a higher percentage of abnormal Pap results than women with a single sexual partner (81.8% *vs*. 18.2%, respectively; p=0.0109) (Table 4).

In conclusion, prevalence of abnormal cervical cytology in pregnant women attending the ANC clinic at Siriraj Hospital was 3.4%. Inclusion of cervical cancer screening as a component of antenatal assessment can

help to identify precancerous lesion or cervical cancer in patients who might otherwise not be screened for cervical cancer, thereby facilitating early treatment and improved patient outcomes.

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