A 1-Year Experience with Liquid-Based and Conventional Papanicolaou Smear in Thammasat University Hospital

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Objective: *The aim of the present study was to evaluate the prevalence of abnormal Pap smears as detected by liquid-based (LBP) and conventional (CPP) techniques in women who were patients in the gynecologic clinic, Thammasat University Hospital.*
Material and Method: *Retrospective analysis of cervical cancer screening, histopathological findings and operative procedures was done between January 2009 and December 2009. Of the 6,332 participants who underwent gynecological examination and cervical screening and had a Pap smear result as atypical squamous cells of undetermined significance or worse would be performed a further colposcopic examination.*
Results: *A total of 6,332 women were screened for cervical cancer in the one year period. A total of 169 abnormal Pap smears were found. Of 497 (8%) and 5,835 (92%) women were screened by LBP and CPP, respectively. The mean age of patients was 39.45 years old (14-90) and 1,550 (24.5%) women were post menopausal. The Prevalence of abnormal Pap smears was 4.0 and 2.6% in the LBP and CPP groups, respectively. Among LBP group, patients with atypical smear and LSIL (low grade squamous intraepithelial lesion) were 11 (2.29%) and 9 (1.8%), respectively. While CPP group, patient with atypical smear, LSIL, HSIL (high grade squamous intraepithelial lesion) and cancer were 73 (1.25%), 49 (0.84%), 25 (0.43%) and 2 (0.03%), respectively.*
Conclusion: *The prevalence of abnormal Pap smear in women who attended gynecologic clinic of Thammasat University Hospital was 4.0% and 2.6 % per LBP and CPP group, respectively. There was no significant difference in the incidence of atypical smear and false positive result between LBP and CPP.*

Keywords: *Abnormal Pap smears, Liquid-based, Conventional*

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Cervical cancer is the second most common cancer worldwide. Its Incidence is also the second ranked cancer among Thai women[1]. The natural progression of cervical cancer is slow. The use of Pap smear for cytology-based screening has been an effective tool for the prevention of cervical cancer in developing countries. The classic steps of conventional Papanicolaou smear (CPP) are the collection of exfoliated cells from the cervix, spreading the cells on to a slide, fixing the cells and staining, which is then followed by the visual cytologic examination. The problem of CPP is the poor condition of the slide. Often this results from a combination of poor sampling and only a partial transfer of the collected sample onto the slide. The sampling is also the major cause of false negative results which can be as high as to 62%[2]. An improvement of the sensitivity of CPP was the development of the liquid-based Pap smear (LBP), introduced in the mid-1990s. The steps of LBP are collecting exfoliated cells from the cervix, immersion and manually stirring vigorously the sample in the

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collection vial containing the cell preservative solution. In the slide preparation process, the fluid from containers are filtered to removed the artifacts then the total exfoliative cells are preserved and spread on the glass slide in a uniform monolayer, fixing, staining and then visual microscopic examination. This results in an increased rate of detection of abnormal cells for the liquid based sample.

High-risk human papillomavirus (HPV) is now known to be the cause of cervical cancer. HPV DNA testing is additionally used as an adjunctive test with Pap smear so as to improve the efficacy of Pap smear. In clinical use, the remaining fluid after the filtering step can be sent for HPV DNA testing and study.

Although the cost of LBP is higher than CPP, it has the advantage of a higher rate of detection of abnormal cells. In the year of 2009, LBP was introduced for optional cervical cancer screening in Thammasat University Hospital.

The aim of this retrospective study is to determine the prevalence of abnormal Pap smear by CPP and LBP in normal and hospital based population.

Material and Method

This research proposal received the approval of the Ethical Committee Clinical Research of Thammasat University Hospital in 2010. Mostly participants consisted of sexually active women who attended the gynaecologic clinic at Thammasat University Hospital during the period of January to December 2009. Known cases of immunocompromised, precancerous and cancerous women were excluded from the present study.

The ectocervix and endocervix were scraped with an Ayre's spatula and cotton bud, respectively. The collected exfoliative samples were spreading and processing as per the standard technique in the CPP pattern. While in LBP pattern, the specimens were collected from the ectocervix and endocervix with a cytobrush with 5 rounds made in a scraping pattern. The brush was immersed and manually stirred vigorously in a collecting vial containing preservative cell solution (Cytyc, Boxborough, MA). All specimens were submitted to the Department of Pathology, Thammasat University Hospital, where they were read by a certified cytopathologist to obtain accurate diagnoses using the Bethesda System 2001 criteria.

Patients who had abnormal results as "abnormal squamous/glandular cells of undetermined significant" (ASC-US/AGUS) or more over were referred to gynecologic oncologist for further investigation by colposcopic examination and biopsy.

Statistical analyses were performed with SPSS version 11.0 (SPSS, Chicago, IL) using descriptive statistical methods. The Chi-square or Fisher exact test and contingency table analysis were used for categorical data. Continuous variables were tested for significance using the t-test. The significant was considered at $p < 0.05$.

Results

In year 2009, 6,742 women have cervical cancer screening. During the present study period 6,332 women were included in the present study consisting of 5,835 and 497 women in CPP and LBP groups, respectively. The mean age of the women in CPP and LBP groups were 39.1 ± 13.1 and 43.1 ± 10.7 years old, respectively. Forty-nine women were lost from the present study for reasons of follow-up procedures to assess the final diagnosis. The cytological characters are shown in Table 1. Of 169 women, colposcopic directed biopsy (CDB) and endocervical curettage (ECC) were performed in 120 women (71%). Loop electrosurgical excision procedure (LEEP) was subsequently performed in 31 women who had CIN 2/3 on cervical biopsy or ECC while only 2 women were performed cryotherapy. After obtaining data from Pap smears, colposcopic examination and histopathological results for final diagnosis making, various types of treatment were performed: simple hysterectomy (5 cases), radical hysterectomy (3 cases) and radiotherapy (2 cases).

The final histopathology from the present study population varied from negative for precancerous lesion or malignancy (NILM) to invasive cancer. The details of histopathology are shown in Table 2. In brief, 37 cases (30.8%) of CPP had NILM, while 34 cases had

Table 1. Cytological results

	CPP	LBP
N	5,835	497
Mean	39.14 ± 13.1	43.09 ± 10.7
Range	14-90	19-89
ASC-US/AGUS	73	11
LSIL	49	9
HSIL	25	0
Carcinoma	2	0

ASC-US = Atypical squamous cells of undetermined significance, AGUS = Atypical glandular cells of undetermined significance, LSIL = Low grade squamous intraepithelial lesion, HSIL = High grade squamous intraepithelial lesion

CIN 2/3 or invasive cancers (28.3%). While in LBP group, 7 cases (35%) had NILM and 13 cases (37.1%) had only CIN 1. Of the five cases of invasive cancers, which came from the CPP group, all of them were squamous cell carcinomas. Three cases were good candidate for surgery, while the other two cases were treated by radiotherapy.

The present study was conducted to evaluate the prevalence of abnormal Pap smear in a normal hospital-based population as shown in Table 3. The overall prevalence of abnormal Pap smear in the present study was 2.7%. Comparing CPP and LBP, the prevalence of abnormal Pap smears were 2.6% and 4.0%, respectively. The percentage of atypical smear (ASC-US/AGUS) were 49% and 55% in CPP and LBP, respectively (p = 0.79). The false positive screening results in the present study were 37% and 35% in CPP and LBP, respectively (p = 1.0).

Discussion

The current strategies to control cervical cancer are the reduction of carcinogen exposure (HPV vaccination), early detection by precancerous condition screening, early detection of the early stages of cancers and early treatment.

Pap smear is categorized in early detection category by cytological method. It has been widely used for cervical cancer screening in developed and developing countries for over half a century.

Table 2. Histopathology results

	CPP	LBP	Total
Negative for CIN	37	7	44
CIN 1, HPV	29	13	42
CIN 2	9	0	9
CIN 3	20	0	20
Cancer	5	0	5
Loss F/U	49	0	49
Total	149	20	169

CIN = Cervical intraepithelial neoplasia

Table 3. Abnormal percentage of Pap smear

	CPP	LBP	p-value
Atypical/Abnormal cytology	73/149 (49%)	11/20 (55%)	0.79[a]
Normal/Abnormal histopathology	37/63 (37%)	7/13 (35%)	1.00[a]

p-value by Chi-square test[a]

In 2005 Thai Ministry of Public Health proposed screening coverage goal. The target was set at 80% of the reproductive age women for a 5-year time period. This was equivalent to 11.5 million women. It was the first target based gynecological campaign of this scale in the country. This concept lead to the implementation of Thailand's dual-track strategy for a cervical screening program using Pap smear for women age of 35-60 years and VIA-cryotherapy for women age of 30-45 years[3].

With the introduction of LBP as a routine service in some government hospitals, namely Thammasat University Hospital and Siriraj Hospital in Thailand by 2009, this offered an alternative method for cervical cancer screening. The former utilizes commercial kit (ThinPrep) while the latter developed its own in-house kit (Siriraj LBP). Commercial LBP is now a routine investigation in private hospitals. In the metropolitan area, the combination of HPV DNA testing and LBP constituted a highly rigorous screening method.

From the previous literature, the advantage of LBP is to reduce the false negative rate of conventional Pap smear (CPP) and also increase sensitivity. Some studies have shown that the LBP produced a higher yield of CIN2/3 lesions detected compared with CPP[4-6]. However, some literature reports argued that the accuracy of LBP was almost equal to that of CPP[7-9].

There are many commercial kits of LBP available. All claimed as their advantage an improved detection of squamous intraepithelial lesions and their higher-quality slides for interpretation than the CPP procedure[10,11]. In a recent study in Thailand, the Siriraj-LBP procedure was found to have had a signicantly higher rate of detection of Atypical smears, LSIL, HSIL and carcinoma results when compared with CPP. The prevalence of abnormal Pap smear in the Siriraj-LBP procedure and CPP were 3.70 and 1.76%, respectively[12]. In the present study, the use of Thin Prep LBP showed a slightly higher detection rate compared to CPP. A report from the recent cervical screening data in pregnant women yielded a similar result[13].

The number of targeted women for coverage in the campaign was 11.5 million women. If CPP which requires a screening interval for a 1 year period (annual) is used this would mean that the pathologists workload is to read 11.5 million slides of Pap smears per year. If

Thailand were to use LBP for screening on the other hand, the pathologists must read only half the number of slides corresponding to 5.75 million slides of Pap per year as the recommended screening interval for LBP is two years[14]. If more government institutions utilized LBP and purchased it as a combined wholesale order, the cost per each patient would be greatly lowered so that it would be made more affordable for such a large population. This is considered an alternative cancer screening method and would be the method of choice in the years to come.

Conclusion

The present study was the first year experience of LBP using for alternative cervical cancer screening tool in Thammasat University Hospital. The prevalence of abnormal Pap smear in normal healthy women was 4.0 and 2.6 % per LBP and CPP group. There was no significant difference in the incidence of atypical smear and false positive result between LBP and CPP.

Potential conflicts of interest

None.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-917.
2. Gay JD, Donaldson LD, Goellner JR. False-negative results in cervical cytologic studies. Acta Cytol 1985; 29: 1043-6.
3. Wilailak S. Epidemiologic report of gynecologic cancer in Thailand. J Gynecol Oncol 2009; 20: 81-3.
4. Castle PE, Bulten J, Confortini M, Klinkhamer P, Pellegrini A, Siebers AG, et al. Age-specific patterns of unsatisfactory results for conventional Pap smears and liquid-based cytology: data from two randomised clinical trials. BJOG 2010; 117: 1067-73.
5. Strander B, Andersson-Ellstrom A, Milsom I, Radberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program: a prospective randomized study. Cancer 2007; 111: 285-91.
6. Cheung AN, Szeto EF, Leung BS, Khoo US, Ng AW. Liquid-based cytology and conventional cervical smears: a comparison study in an Asian screening population. Cancer 2003; 99: 331-5.
7. Chacho MS, Mattie ME, Schwartz PE. Cytohistologic correlation rates between conventional Papanicolaou smears and ThinPrep cervical cytology: a comparison. Cancer 2003; 99: 135-40.
8. Hamashima C, Aoki D, Miyagi E, Saito E, Nakayama T, Sagawa M, et al. The Japanese guideline for cervical cancer screening. Jpn J Clin Oncol 2010; 40: 485-502.
9. Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. Obstet Gynecol 2008; 111: 167-77.
10. Fremont-Smith M, Marino J, Griffin B, Spencer L, Bolick D. Comparison of the SurePath liquid-based Papanicolaou smear with the conventional Papanicolaou smear in a multisite direct-to-vial study. Cancer 2004; 102: 269-79.
11. Park J, Jung EH, Kim C, Choi YH. Direct-to-vial comparison of a new liquid-based cytology system, liqui-PREP versus the conventional Pap smear. Diagn Cytopathol 2007; 35: 488-92.
12. Laiwejpithaya S, Benjapibal M, Laiwejpithaya S, Wongtiraporn W, Sangkarat S, Rattanachaiyanont M. Performance and cost analysis of Siriraj liquid-based cytology: a direct-to-vial study. Eur J Obstet Gynecol Reprod Biol 2009; 147: 201-5.
13. Khaengkhor P, Mairaing K, Suwannarurk K, Thaweekul Y, Poomtavorn Y, Pattaraarchachai J, et al. Prevalence of abnormal cervical cytology by liquid based cytology in the antenatal care clinic, Thammasat University Hospital. J Med Assoc Thai 2011; 94: 152-8.
14. Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer. J Low Genit Tract Dis 2003; 7: 67-86.

ประสบการณ์ 1 ปีของการตรวจคัดกรองมะเร็งปากมดลูกแบบแผ่นบางและดั้งเดิม ในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ มหาวิทยาลัยธรรมศาสตร์

คมสันติ์ สุวรรณฤกษ์, กรการณ์ ภมรประวัติธนะ, ยุทธเดช ทวีกุล, กริชา ไม้เรียง, เย็นฤดี ภูมิถาวร, จรรยา ภัทรอาชาชัย

วัตถุประสงค์: *เพื่อศึกษาความชุกของความผิดปกติของการตรวจคัดกรองมะเร็งปากมดลูกระหว่างแบบแผ่นบางและดั้งเดิม ในสตรีที่มารับการตรวจคัดกรองมะเร็งปากมดลูก ณ หน่วยตรวจผู้ป่วยนรีเวช โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ*

วัสดุและวิธีการ: *การศึกษาย้อนหลังของการตรวจคัดกรองมะเร็งปากมดลูกในสตรีที่มารับการตรวจคัดกรองมะเร็งปากมดลูกในปี พ.ศ. 2552 จำนวน 6,332 ราย โดยสตรีที่มีผลการตรวจคัดกรองตั้งแต่ระดับ ASC-US ขึ้นไปจะได้รับการตรวจด้วยกล้องส่องขยายปากมดลูกและตัดชิ้นเนื้อ*

ผลการศึกษา: *จำนวนสตรีที่เข้ารับการตรวจจำนวน 6,332 ราย พบความผิดปกติจากการตรวจคัดกรองจำนวน 169 ราย สัดส่วนของชนิดการตรวจคัดกรองมะเร็งปากมดลูกเป็นแบบแผ่นบางและดั้งเดิมคิดเป็นจำนวน ร้อยละ 8 (497 ราย) และร้อยละ 92 (5,835 ราย) ตามลำดับ อายุเฉลี่ยของสตรีที่รับการตรวจคือ 39.45 ปี (14-90) และร้อยละ 24.5 ของสตรีที่มารับการตรวจคัดกรอง (1,550 ราย) อยู่ในวัยหมดประจำเดือน ความชุกของความผิดปกติจากการตรวจคัดกรองมะเร็งปากมดลูก คิดเป็นร้อยละ 4 และ 2.6 ในกลุ่มแบบแผ่นบางและดั้งเดิมตามลำดับ ในสตรีที่รับการตรวจคัดกรองมะเร็งปากมดลูกแบบแผ่นบางพบความผิดปกติชนิดไม่จำเพาะและระดับ LSIL จำนวน 11 (2.29%) และ (1.8%) 9 ราย ตามลำดับ ขณะที่สตรีที่รับการตรวจคัดกรองมะเร็งปากมดลูกแบบดั้งเดิม พบความผิดปกติชนิดไม่จำเพาะ, LSIL, HSIL และมะเร็งจำนวน 73 (1.25%), 49 (0.84%), 25 (0.43%) และ 2 (0.03%) รายตามลำดับ*

สรุป: *อุบัติการณ์ของความผิดปกติของการตรวจคัดกรองมะเร็งปากมดลูกในสตรีปกติที่มารับตรวจแบบแผ่นบางและดั้งเดิมคิดเป็นร้อยละ 4 และ 2.6 ตามลำดับ ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างของการพบความผิดปกติแบบชนิดไม่จำเพาะและผลบวกลวงระหว่างวิธีทั้งสองแบบ*