Pattern of cervical smear abnormalities using the revised Bethesda system in a tertiary care hospital in Western Saudi Arabia

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ABSTRACT

الأهداف: تقييم تشخيص مسحات عنق الرحم التي أُخذت في مستشفى من الدرجة الثالثة، باستخدام نظام بيثيسدا التشخيصي فيها، بالإضافة إلى مقارنة النتيجة بدراسات أخرى مماثلة.

الطريقة: صممنا دراسة استرجاعية لإعادة فحص جميع مسحات عنق الرحم التي وردت إلى قسم علم الأمراض التشريحي، جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من يناير 2005م إلى ديسمبر 2009م.

النتائج: مجموع مسحات عنق الرحم التي فُحصت في قسم علم الأمراض التشريحي 7297 منها 1254 حالة كانت تمثل شذوذ الخلايا الظهارية (17.3%). وشملت أنواع الشذوذ الفئات التالية: شاذة الخلايا الحرشفية بنسبة 9.3%، وشاذة الخلايا الحرشفية بحيث لا يمكن استبعاد الآفات الحرشفية الظهارية المرتفعة بنسبة 0.8%، والآفات الحرشفية الظهارية الصنف المخفض بنسبة 2.7%، والآفات الحرشفية الظهارية الصنف العالي بنسبة 0.9%. وكان متوسط عمر الإصابة 40، 42، 47، 45 عاماً على التوالي. ومثل تشخيص سرطان الخلايا الحرشفية 0.06% مع حدوث متوسط العمر 46 عاماً. أما التغيرات التي تصيب فئة الخلايا الغدية فكان هناك 3.2% من الخلايا الغدية الشاذة ذات أهمية سريرية غير محددة، و0.1% من الخلايا الغدية الغير نمطية لصالح الأورام عموماً، و0.08% خلايا غير نمطية لصالح أورام بطانة الرحم.

خاتمة: أثبتت هذه الدراسة أن هناك زيادة حقيقية في معدل الإصابة الغير طبيعية لمسحات عنق الرحم من 4.7% سُجلت في دراسة سابقة من نفس هذا المستشفى إلى 17.3% في الدراسة الحالية. وتمثلت أكثر زيادة في تشخيص شاذة الخلايا الحرشفية وذلك بالمقارنة مع مسحات عنق الرحم الأخرى. وأثبتت هذه الدراسة أيضا زيادة ملحوظة في جميع التغيرات الخلوية التي تصيب عنق الرحم، والسؤال الذي يطرح نفسه هل هذه الزيادة حقيقية أم ظاهرة اصطناعية من جراء استخدام نظام بيثيسدا التشخيصي في ظل غياب برنامج فحص سرطان عنق الرحم.

Objectives: To evaluate Pap smear (PS) diagnoses at a tertiary care hospital using the revised Bethesda system, and to compare the results with other similar studies.

Methods: We designed a retrospective study to review all PS from the Cytopathology Department of King Abdulaziz University Hospital, Jeddah, Saudi Arabia from January 2005 to December 2009.

Results: Of the 7297 cases reviewed, 1254 cases (17.3%) had epithelial cell abnormalities. The categories included: atypical squamous cell of undetermined significance (ASC-US) found in 9.3%, atypical squamous cell, cannot exclude high squamous intraepithelial lesion (ASC-H) in 0.8%, low grade squamous intraepithelial lesion (LSIL) in 2.7%, and high grade squamous cell lesion (HSIL) in 0.9%. The mean age incidence (MAI) was 40 years for ASC-US, 42 years for ASC-H, 47 years for LSIL, and 45 years for MAI. Squamous cell carcinoma (SCC) was found in 0.06% with mean age incidence of 46 years. In the atypical glandular cell category, there was 3.2% atypical glandular cell of undetermined clinical significance not otherwise specified, 0.1% atypical glandular cells favoring neoplasm, and 0.08% atypical endometrial cells favoring neoplasm.

Conclusion: The incidence of abnormal PS has increased from previously 4.7%, to 17.3% in the present study. The ASC-US among total PS examined has also significantly increased. The increase in the number of positive PS raises concerns of whether the new BS results are an artificial increase in the prevalence and the predictive value of cytology to some extent.

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The World Health Organization (WHO) currently estimates that the Kingdom of Saudi Arabia (KSA), which has a population of 6.5 million women of age 15 years and older is at risk of developing cervical cancer (CC). Cervical cancer ranks as the eleventh most frequent cancer among women in KSA, and the eighth most frequent cancer among women between 15 and 44 years of age.[1] In KSA, invasive cervical carcinoma is less common and has variable distribution in different regions of the Kingdom. The highest reported incidence of 5.6% is noted in the Jouf region, followed by Hail 3.5%, Najran 3.2%, Baha 2.9%, Makkah 2.5%, and Jazan 2.2%.[2] Regions with rare frequency of CC are Riyadh, Qassim, Jazan, Najran, Asir, and Tabuk.[2] Cervical intraepithelial neoplasia, which is known as precursor lesions for CC is not registered because there is no well developed CC screening program nationwide. However, hospital based studies from different regions of the Kingdom show a slight increase in the prevalence of epithelial cell changes in pap smears (PS).[3-7] No data are available on the burden of human papilloma virus (HPV) among the general population of KSA, but HPV prevalence among females in the general population of Western Asia, to which KSA belongs, is 2.2% (low in comparison with other world regions).[1] A small scale study conducted on cervical specimens at King Abdulaziz University Hospital (KAUH) in Jeddah, KSA reported that HPV DNA was detected in 6% of the cases.[8] Worldwide, CC is the second most common cancer in women with an estimated 493,000 new cases and 274,000 deaths. Eighty-three percent of the cases occur in developing countries. The highest incidence rate reported in developing countries is Central and South America Age Standardized Rate (ASR 33.5), the Sub-Saharan Africa (ASR 31.0), and South-Central and Southeast Asia (ASR 26.5). The lowest incidence is reported in China (ASR 6.8) and in developed countries as North America, Japan, and Europe with an ASR of 4.5/100,000. A low incidence is also observed in developing countries such as the Middle East, Iran, and Turkey. Muslim and Jews tend to have the lowest rate compared with other religious groups predominantly Christian and Hindu.[9-12] The mortality rates of CC are lower than the incidence rate, the ratio of mortality to incidence is 55% (ranging between 63% in Europe to 73% in USA registries).[9] This marked variation in the frequency of CC in the developed and developing countries is due to the differences in cervical cancer screening programs (CCSP), and the prevalence of risk factors.[10] The incidence and mortality of CC has declined dramatically ever since the introduction and widespread utilization of the PS screening test, especially in developed countries with well established CCSP such as North America and Japan where the incidence was ASR 7.7 and 8.0, while mortality was ASR 2.0 and 2.8 respectively.[9,10]

The Papanicolaou smear was introduced in 1941 by Dr. Papanicolaou as a mass screening for sexually active women for early detection of CC and early pre-cancerous lesions.[10,11] Over the years, the original PS classification system has gone through many modifications in response to our growing knowledge of CC precursors, and our understanding of the role of HPV cervical carcinogenesis.[12-14] However, standardization of PS reporting using the revised Bethesda system (BS) has unified various overlapping and confusing terminologies, and hence has overcome the lags of inter observer variability in the interpretation and application of these terminologies to some extent.[12-14]

Reports describing the frequency and pattern of abnormal PS in KSA[3-7] and the Arab world,[15-18] using the revised BS are very few. For this reason, we conducted the current study to explore the pattern of PS abnormalities among females of the Western region of Saudi Arabia using the revised BS, and to compare the findings with other similar studies carried out within the same institutions,[5] and the same region.[4,6,7] In addition, we correlate our findings with other recent studies from the Arab world,[15-18] and other Muslim countries who have similar incidence rates and risk factors,[19-21] with an effort to highlight this preventable cancer by encouraging development of CCSPs in KSA, and to improve the utilization of the PS as a screening test for the early detection. The role of HPV infection and its pathogenesis is elaborated.

Methods. *Study setting and population.* We performed a retrospective evaluation of 7,297 PS of female patients performed at King Abdulaziz University Hospital (KAAUH) and Al-Khadra Laboratory, Jeddah, KSA from January 2005 to December 2009. The inclusion criteria were all PS of females attending KAAUH for routine, or for a medical indication, of all ages and nationalities. The exclusion criteria were unsatisfactory PS; repeat smears after short intervals with the same diagnosis were also excluded. The Faculty Ethics Committee approved the study, which we carried out in accordance with the Principles of Helsinki Declaration of 1975, as revised in 2000.

Data collection. We used a computerized search to collect the data from the archives of cyto-pathology at the Department of Anatomic Pathology, KAAUH, and Al-Khadra Laboratory, Jeddah, KSA. In KAUH, we use both conventional PS and liquid based cytology. We considered a smear sufficient when it was appropriately labeled with adequate sampling of the endocervical transformation zone with optimal preservation of the cells. We reviewed and reclassified all sufficient cervical cytology smears according to the revised 2001 BS of PS reporting.[14] The collected data included date of PS, personal identity (medical record number and age), and relevant clinical information (routine or for specific gynecological symptoms). We exported the computerized search to Microsoft Excel format and used it for analysis. We manually rechecked the data to delete duplications.

We analyzed the data using the Statistical Package for Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA). We obtained descriptive and frequency statistics for the variables studied. The total number of pap smears examined (TSE) after excluding unsatisfactory ones, and the total number and percentages of abnormal pap smears (TAPS) after exclusion of unsatisfactory smears were tabulated.

Results. A computerized search identified 7297 cervical PS. Screening of these PS identified 7235 (99.15%) sufficient smears, and 62 (0.85%) unsatisfactory smears. Of the 7235 sufficient smears 5369 (74.2%) smears were reported as negative for squamous epithelial abnormalities, while 1254 (17.3%) were diagnosed as positive for cervical epithelial abnormalities (**Table 1**). The smears positive for epithelial and glandular abnormalities were further

Table 1 - Distribution of Pap smear diagnoses using the revised Bethesda system among the study population (N=7235).[14]

Diagnoses	Spontaneous preterm births (n = 631)	
Negative for intraepithelial lesion	5369	(74.2)
Positive for epithelial abnormalities	1254	(17.3)
Quality indicators		
Inflammation	244	(3.4)
Hemorrhage	160	(2.2)
Unsatisfactory	62	(0.9)
Reactive cellular changes		
Associated with repair	29	(0.4)
Associated with squamous metaplasia	54	(0.75)
Associated with follicular cervicitis	1	(0.01)
Associated with organisms	37	(0.51)
Atrophy	87	(1.2)

Table 2 - Distribution of squamous and glandular epithelial cells using the revised Bethesda system among the study population (N=7235).[14]

Epithelial cell abnormalities	No. of cases	TAPS (1254)	TSE (7235)	Mean age incidence
Squamous cells	1009	80.5	13.95	44.48
ASC-US	674	53.75	9.3	39.73
ASC-H	60	4.8	0.8	41.75
LGSIL	198	15.8	2.7	46.93
HGSIL	63	5.0	0.9	44.87
HGSIL with suspicious invasion	10	0.8	0.1	47.50
SCC	4	0.3	0.06	45.50
Glandular cells	245	19.5	3.4	50.22
AG NOS	232	18.5	3.2	47.61
AG favoring neoplastic	7	0.6	0.1	50.69
Atypical endometrial favoring neoplastic	6	0.5	0.08	52.37

ASC-US - abnormal squamous cells of undetermined significance, ASC-H - abnormal squamous cells-high grade cannot be excluded LGSIL - low grade squamous intraepithelial lesion, HGSIL - high grade squamous intraepithelial lesion, AG NOS - atypical glandular cells not otherwise specific, AG - atypical glandular, SCC - squamous cell carcinoma, TAPS - Percentage of total abnormal pap smears, TSE - Percentage of total pap smears examined

classified according to the revised 2001 BS[14] as shown in **Table 2**. The categories included, atypical squamous cell of undetermined significance (ASC-US) found in 9.3%, atypical squamous cell, cannot exclude high squamous intraepithelial lesion (ASC-H) in 0.8%, low grade squamous intraepithelial lesion (LSIL) in 2.7%, and high grade squamous intraepithelial lesion (HSIL) in 0.9%. The mean age incidence (MAI) was 40 for ASC-US, 42 for ASC-H, 47 for LSIL, and 45 years for HSIL. Squamous cell carcinoma (SCC) was seen in 0.06% with an MAI of 46 years. In the atypical glandular cell category, there were 3.2% of atypical glandular cell of undetermined clinical significance not otherwise specified (AG NOS) with an MAI of 48, 0.1% of atypical glandular cells favoring neoplasm with an MAI of 51, and 0.08% atypical endometrial cells favoring neoplasm with an MAI of 52. We compared our study to other recent similar studies from the same institution published in 2006,[5] as shown in **Table 3**. We also correlated our findings with other studies from Saudi Arabia,[3-7] the Arab world,[15-18] and Islamic countries[19-21] as shown in **Tables 4, 5, and 6**.

Discussion. Since the development of cytology-based cervical cancer screening using the PS in the mid-20th century, the PS, and new cytology-based technologies such as liquid-based cytology have been implemented for secondary prevention of cervical cancer.[10] This has been most clearly demonstrated in

developed countries as Nordic countries, and in the United Kingdom.[10] In the USA, approximately 50 million women undergo Pap screening; 3.5-5 million of these require follow-up.[22] There are 2-3 million cases of ASC-US, 1.25 million LGSIL, and 300,000 HSIL in the USA.[22] Approximately three-quarters of all cervical cancers in USA are squamous cell and the remaining is adenocarcinoma.[23] The HPV 16 and 18 account for approximately 68% of SCC and 83% of adenocarcinomas.[23]

No authentic data are available to indicate the prevalence of HPV related cervical infections or their age specific incidence in Saudi Arabia because there are no screening programs for cervical cancer. Also, no studies are available to indicate the prevalence of HPV in the population. Our results and other studies from different parts of Saudi Arabia[3-7] herald the need for nationwide cervical screening programs to estimate the actual magnitude of cervical carcinoma and its precursor

lesions.[3-7] Although recently, more patients with earlier stages of cervical cancer have been treated, probably due to the marked improvement in health care delivery all over the Kingdom.[24]

If we compare the results of this study to the previous study from our institution (**Table 3**),[5] we find a significant increase in the number of smears examined, as well as the number of cases with ECA. It is obvious that there is a marked increase in the number of abnormal PS from 4.7% in the study published in 2006 to 17.3% in the current study. Squamous cell abnormalities have also increased from 3.5% in the previous study to 13.95%. Although all the preinvasive lesions were increased, however, SCC is less detected in the current study compared with the previous ones, and this could be explained by early detection of precursor lesions. All glandular cell abnormalities increased from 1.1% to 3.35%. These findings are definitely suggestive of an overall increase in the number of positive PS with a relative and significant increase in squamous cell abnormalities, especially the ASC-US category.

This study has certain limitations, and the results should be interpreted keeping these in mind. One of the limitations is that the diagnosis of ASC-US in our laboratory is over the accepted range. As a quality control measure, ASC-US should be approximately 1-2% of the total number of gynecologic samples, not exceeding 5%, or 2 to 3 times the total cases of squamous intraepithelial lesion.[4,6,7] However, we checked these cases, and compared them with the original diagnosis of the pathologist and cytotechnologist, and detected no major discrepancy. In our cytopathology laboratory, both cytotechnologists and pathologists are adherent to Bethesda's more stringent criteria when considering a diagnosis of ASC-US.[14] The increase in ASC-US diagnosis can be explained by a number of reasons, such as in the BS, ASC-US criteria and LSIL are similar, but

Table 3 - Summarized comparison of epithelial cell abnormalities in Pap smears using the revised Bethesda system[14] from the current study and a previous study also carried out at King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Categories	Current Study (2011)	Previous study (2006)[5]
Total no. of cases examined	7235	5132
Total abnormal pap smears	1254 (17.3%)	243 (4.7%)
ASC-US %	9.3	2.4
LGSIL %	2.7	0.6
HGSIL %	0.9	0.4
SCC %	0.06	0.1
AGC %	3.2	1.1
AGC favoring neoclassic %	0.2	0.06

ASC-US - abnormal squamous cells of undetermined significance, LGSIL - low grade squamous intraepithelial lesion, HGSIL - high grade squamous intraepithelial lesion, SCC - squamous cell carcinoma, AGC - atypical glandular cells

Table 4 - Summarized distribution of epithelial cell abnormalities in Pap smears using the revised Bethesda system[14] in recent studies from Saudi Arabia.

Studies	Year	No.	ECA %	Percentage of revised Bethesda categories					
				ASC-US	ASC-H	LGSIL (+ HPV)	HGSIL	SCC	AGUS
Altaf[3]	2001	3088	3.1	0.45	*	0.93	0.55	0.13	0.13
Elhakeem et al[4]	2005	2100	7.9	2.76	0.19	1.3	0.66	0.33	*
Altaf[5]	2006	5132	4.7	2.40	*	0.6	0.40	0.1	1.10
Abdullah[6]	2007	5746	5.0	1.84	0.10	1.0	0.55	0.37	0.53
Al-Jaroudi & Hussain[7]	2010	241	2.9	1.20	0.42	0.84	*	*	0.42
Present study	-	7297	17.3	9.23	0.82	2.71	0.86	0.05	3.17

ECA - epithelial cell abnormalities, ASC-US - abnormal squamous cells of undetermined significance, ASC-H - abnormal squamous cells-high grade cannot be excluded, LGSIL - low grade squamous intraepithelial lesion, HGSIL - high grade squamous intraepithelial lesion, AGUS - atypical glandular cells of undetermined significance, SCC - squamous cell carcinoma, *figures not stated in the studies

Table 5 - Summarized distribution of epithelial cell abnormalities in Pap smears using the revised Bethesda system[14] in recent studies from the Arab world.

Studies	Year	No.	ECA %	Percentage of revised Bethesda categories					
				ASC-US	ASC-H	LGSIL (+ HPV)	HGSIL	SCC	AGUS
Musmar[15]	2004	201	11.9	8	*	1	*	1	2
Ghazal Aswad et al[16]	2006	4055	3.6	2	*	0.77	0.54	0.07	*
Kapila et al[17]	2006	86434	4.2	2.2	*	1	0.20	0.05	0.8
Abd El All et al[18]	2007	5453	7.8 (N=424)	2.7 (N=146)	*	3.2 (N=174)	0.40 (N=22)	0.04 (N=2)	1.2 (N=66)

ECA - epithelial cell abnormalities, ASC-US - abnormal squamous cells of undetermined significance, ASC-H - abnormal squamous cells-high grade cannot be excluded, LGSIL - low grade squamous intraepithelial lesion, HGSIL - high grade squamous intraepithelial lesion, AGUS - atypical glandular cells of undetermined significance, SCC - squamous cell carcinoma, *figures not stated in the studies

Table 6 - Summarized distribution of epithelial cell abnormalities in Pap smears using the revised Bethesda system[14] in recent studies from other countries.

Studies	Year	No.	% of ECA	Percentage of revised Bethesda categories					
				ASC-US	ASC-H	LGSIL (+ HPV)	HGSIL	SCC	AGUS
Afrakhteh et al[19]	2007	13315	1.2 (N=184)	53.2 (N=8)	*	17.7 (N=28)	10.75 (N=17)	17.1 (N=27)	1.3 (N=2)
Yalti et al[20]	2005	28469	*	2.45 (N=699)	*	0.23 (N=67)	0.15 (N=43)	0.003 (N=1)	0.1 (N=31)
Mehmetoglu et al[21]	2010	332	1.2 (N=4)	*	*	0.6 (N=2)	0.6 (N=2)	*	*

ECA - epithelial cell abnormalities, ASC-US - abnormal squamous cells of undetermined significance, ASC-H - abnormal squamous cells-high grade cannot be excluded, LGSIL - low grade squamous intraepithelial lesion, HGSIL - high grade squamous intraepithelial lesion, AGUS - atypical glandular cells of undetermined significance, SCC - squamous cell carcinoma, *figures not stated in the studies,

quantitative rather than qualitative, which accounts for this rise in the ASC-US diagnosis. Another reason is that our hospital is a governmental tertiary care referral center in the region, and its set up could account for this high rise of ASC-US prevalence. It is the only center that treats cervical cytology abnormalities in all ladies (Saudi and expatriates) in the region in the absence of cervical cancer screening programs. Therefore, we recommend HPV DNA testing in all cases with ASC-US diagnosis, and the ones that have hrHPV then treated accordingly.[10] The cases of ASC-US that have no HPV DNA detected in their specimens should be followed up by another PS in 2-3 years time, or even longer.[10]

The diagnosis of atypical glandular cells should not exceed 1% of all gynecological cases. Most laboratories report between 0.3-0.5%,[23] but in our laboratory it was 3.35%. These findings further alert us to the magnitude of the problems we may have with the glandular component, especially endometrial, which requires further correlation and follow-up.

Several studies from Saudi Arabia,[3-6] and a study of subfertile Saudi females[7] showed a low prevalence of ECA, but still with a wide range of distribution between 2.9-17.3% (**Table 4**). This range is correlated very well with the actual difference in the distribution of invasive carcinoma of the cervix in the Kingdom.[2] Other studies from the Arab world have also reported a significant variation in the rate of ASC-US and atypical glandular cells of undetermined significance over the years. In a study from Egypt, Abd El All et al[18] reported an ECA of 7.8%. They found that the presence of HPV16/18 and other infections were associated with SIL and SCC.[18] In situ hybridization by polyclonal HPV was performed on 217 cases, 66% of their cases showed positive results, while 29% were negative, and 5% had no significant finding. One of the risk factors evaluated in Abd El All's study was infection with HPV. It was found that HPV 6/11, 16/18, 31/33 was present in cervical intraepithelial neoplasia (CIN) I, while HPV 16/18 was a common threat for cases with CIN II-III and invasive cancer.[18] Based on their findings they recommended cervical cancer screening programs, and follow-up for negative cases every 10 years. Regarding cases with inflammatory changes, they recommended follow-up once every year for 3 successive years.[18] Furthermore, and in agreement with another study from Jordan,[25] they recommended increasing female awareness of this health problem.

The Republic of Turkey has a low incidence rate of cervical carcinoma 8/100,000.[21] In 2002, cervical carcinoma comprised 4.9% of all cancers, and 4.1% of

all cancer deaths. It was the eighth most frequent cause of cancer morbidity and mortality. Different hospital based studies from Turkey showed an ECA ranging from 0.4-4.2%, and HPV prevalence of 2.1%.[21] Cervical screening programs are planned for future control of this preventable cancer.[21] This observation is in agreement with another study from Iran,[19] which again has a low rate of ECA ranging between 0.2-1.2%. Both Turkey and Iran are Islamic countries, and they share similar control of the sexual relationship within the context of marriage, which plays a major role for HPV transmission and subsequent cancer development.

In conclusion, the current study showed a significant increase in the number of abnormal PS, and this finding encourages us to call for cross-sectional studies in the Western Region of SA to evaluate the magnitude of this abnormality. Meanwhile, we recommend an organized approach to opportunistic screening with appropriate treatment and follow-up before the launching of cervical mass screening programs in the Kingdom of Saudi Arabia. We recommend HPV-DNA testing should be added routinely to all cases with ECA, and the positive cases should be treated and followed up properly. Cases with ECA and with negative HPV result may require re-screening for longer intervals, such as 10 years or less. More research is needed on the magnitude of this health problem, with a study of the epidemiological distribution of HPV in the Kingdom regions before an HPV vaccine is considered or introduced in this society.

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