

Prevalence and characteristics of abnormal Papanicolaou smear in Central Saudi Arabia

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ABSTRACT

Objectives: To assess the prevalence and characteristics of abnormal pap smear in the central region of Saudi Arabia.

Methods: In this retrospective case control study conducted in the Departments of Obstetrics and Gynecology, and Histopathology at King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia, all pap smears screened for Saudi women between 2008 and 2011 were reviewed. Approximately 5000 pap smears are screened annually at King Abdulaziz Medical City utilizing the Bethesda III System (2001). All abnormal smears patients' data were collected and compared to the data of randomly selected 200 normal smears' patients.

Results: Abnormal pap smear prevalence was found to be 4.3% (841/19,650 Saudi patients were found with atypical epithelial cells abnormalities). Its prevalence in the years 2008 was 5.7%, 2009 was 4.9%, 2010 was 4.2%, and 2011 was 2.5%. Abnormal smear patients have lower parity ($p=0.001$), and were less likely to use intra-uterine devices ($p=0.03$) compared with normal smear patients. Presence of abnormal cervical appearance was associated with increased epithelial cell abnormalities ($p=0.045$). The only positive history that has characterized patients with epithelial cell abnormalities was their previous history of abnormal pap smear ($p=0.001$). Squamous cell abnormalities were identified in 91% of the patients (767/841), and glandular cell abnormalities were identified in 9% of the patients (74/841).

Conclusion: Prevalence of abnormal pap smears in central Saudi Arabia is relatively low, while advanced glandular abnormalities prevalence was observed to be high.

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Cervical intraepithelial neoplasia (CIN) and invasive cervical carcinoma (CC) are documented to be less common in Saudi Arabian women community, as compared with some western communities.¹⁻⁴ This observation was based on studies carried out in Al Baha in the southern region, and Jeddah in the western region of the Kingdom of Saudi Arabia (KSA). No similar recent study was performed in the central region of KSA that allows a clear view on the prevalence of the disease and its characteristics. It is important to mention here that up-to-date, CC screening program has not been implemented in KSA, and pap smear screening is still performed on an opportunistic basis. Moreover, CIN is known to be related to high risk human papilloma virus (HPV) infections, in particular HPV types 16 and 18.^{5,6} These particular infections are proven to be preventable by available tested vaccines.⁶ However, there is not enough published data on the prevalence of HPV and its genotypes in KSA that justify cervical cancer preventive vaccination program. Over the last few decades, the financial status of the Saudi population has improved,⁷ resulting in change in lifestyle, higher mean female age, and more expatriates are mixing with the Saudi population.⁸ We believe that the prevalence of abnormal pap smear in KSA might be increasing. National alertness and governmental work for preventive program implementation might be an urgent requirement. Such preventive program may assist in early detection and mortality/morbidity reduction of CC.^{9,10} In this research, we aimed to report an assessment of the prevalence of abnormal pap smears in the central region of KSA, smears cytology findings, and the clinical and personal characteristics of patients who were diagnosed with abnormal pap smears.

Methods. This retrospective case-control study was conducted in the Departments of Obstetrics and Gynecology, and Histopathology at King Abdulaziz Medical City (KAMC), Riyadh, KSA. This hospital

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(KAMC) is a referral health care medical city with a capacity of more than 1,500 beds and multiple linked primary and secondary care centers that cover the whole central region of KSA. All pap smears carried out at KAMC's primary, secondary, and tertiary healthcare centers are sent to KAMC's cytology laboratory for evaluation. In addition, all patients who are identified to have abnormal pap smears are referred to KAMC's Departments of Obstetrics and Gynecology and/or Oncology for management. At KAMC, pap smears are collected by trained family medicine doctors or gynecologists utilizing cyto-brush to collect the samples from the uterine cervix transformation zone. The cyto-brush is then placed in a liquid-based cytology transport preservative, that is either PreservCyt® or SurePath.™ All performed smears are transferred to the cytology lab at KAMC where the cytology screening is performed by a cytologists. In the presence of any cellular abnormality, the smear is usually referred to a histopathologist for his/her second opinion. The smear screening reports are released on the medical computer system that is accessible to all KAMC medical staff. All smear reports are based on the Bethesda III system 2001 classification.^{11,12} On an annual basis, approximately 5,000 pap smears are screened in the Department of Histopathology, cytology lab at KAMC. All women who had their pap smears performed between January 2008 and December 2011 at KAMC were eligible to be included in this research. Throughout the study period, 19,650 pap smears were performed to Saudi women, of which 841 women were found with abnormal epithelial cells and were considered as the study's cases (group I). Two hundred normal pap smears were used as a control group (group II). The control group smears were selected

randomly out of the normal pap smears performed during the study period. Fifty normal smears from each study year were selected based on the patients' medical record numbers to formulate a total of 200 control smears. The paper and electronic medical records of all included patients in both groups were reviewed to collect information on their pap smear results and their clinical and demographic characteristics. Unsatisfactory smears were excluded from the research unless abnormal squamous or glandular cells have been identified. In the Bethesda III System (2001), smears cytology abnormalities were classified under 3 categories: atypical squamous cells (ASC); low-grade squamous intraepithelial lesions (LSIL); and high-grade squamous intraepithelial lesions (HSIL). The ASC category was subdivided into 2 categories: the unknown significance category (ASC-US); and the one, which high-grade lesions cannot be excluded (ASC-H). Glandular cell abnormalities included atypical glandular cells (AGC), atypical glandular cells favors cell growth or (neoplastic changes), endocervical adenocarcinoma in situ (AIS), and adenocarcinoma.^{13,14} The research and ethics committee approvals were obtained through the King Abdullah International Medical Research Center (KAIMRC). Patients' data was secured and was accessible only to the principle investigator and the co-investigators.

The research data was entered into the Statistical Package for the Social Sciences program version 16 (SPSS Inc., Chicago, IL, USA). The prevalence of abnormal pap smears was calculated collectively for the whole duration of the study and for every study year individually. Descriptive analyses for the cases of abnormal smears were carried by determining the

Table 1 - Characteristics of patients included in a study on normal versus abnormal smears in Riyadh, Kingdom of Saudi Arabia.

Patients characteristics	Group I (n=841)	Group II (n=200)	OR (95% CI)	P-value
Age, mean ± SD	45.4 ± 11.6	46.5 ± 10.6	-	0.19
Gravida, mean ± SD	6.3 ± 3.8	8.0 ± 4.0	-	0.001
Parity, mean ± SD	5.5 ± 3.4	6.9 ± 3.5	-	0.001
IUCD, yes, n (%)	102 (13.0)	35 (20.0)	0.63 (0.41-0.96)	0.03
Hormonal use, yes, n (%)	145 (19.0)	34 (19.0)	1.04 (0.68-1.58)	0.85
<i>Types of hormone used, n (%)</i>				
COCP, yes	79 (10.3)	13 (7.2)	1.49 (0.83-2.85)	0.19
Progesterone, yes	28 (3.6)	8 (4.4)	0.83 (0.38-1.96)	0.63
HRT, yes	27 (3.5)	10 (5.5)	0.63 (0.31-1.39)	0.24
Tamoxifen, yes	11 (1.4)	3 (1.6)	0.87 (0.26-3.92)	0.80

OR - odds ratio, CI - confidence interval, IUCD - intra-uterine device,
COCP - combined oral contraception pills, HRT - hormonal replacement therapy

Table 2 - Patient's history and clinical presentation included in a study on normal versus abnormal smears in Riyadh, Kingdom of Saudi Arabia.

Patients history	Group I n=769 (%)	Group II n=180 (%)	Odds ratio (95% confidence interval)	P=-value
Asymptomatic, yes	232 (30.0)	52 (29.0)	1.07 (0.75-1.52)	0.73
Post coital bleeding, yes	40 (5.0)	10 (6.0)	0.93 (0.46-1.90)	0.85
Irregular uterine bleeding, yes	176 (23.0)	45 (25.0)	0.89 (0.61-1.30)	0.55
Menorrhagia, yes	95 (12.0)	25 (14.0)	0.87 (0.54-1.40)	0.58
Lower abdominal pain, yes	86 (11.0)	16 (9.0)	1.29 (0.74-2.26)	0.37
Postmenopausal bleeding, yes	38 (5.0)	12 (7.0)	1.14 (0.60-2.17)	0.69
Abnormal vaginal discharge, yes	162 (21.0)	46 (26.0)	0.78 (0.53-1.13)	0.19
Previous abnormal smear, yes	188 (22.0)	4 (2.0)	14.1 (5.2-38.5)	0.001
Previous treatment of abnormal smear, yes	187 (22.0)	4 (2.0)	14.0 (5.2-38.3)	0.001
<i>Cervical clinical findings</i>				
Abnormal cervix, yes	234 (30.0)	41 (23.0)	1.48 (1.01-2.16)	0.045
Ectropion, yes	60 (8.0)	9 (5.0)	1.61 (0.78-3.30)	0.19
Bleeding on touch, yes	52 (7.0)	4 (2.0)	3.19 (1.14-8.94)	0.02
Ulcer, yes	32 (4.0)	1 (1.0)	0.47 (0.08-3.69)	0.32
Fungating mass, yes	14 (2.0)	0	NA	0.07
Polyp, yes	40 (5.0)	15 (8.0)	0.60 (0.33-1.12)	0.11
Bulky cervix, yes	44 (6.0)	11 (6.0)	0.93 (0.47-1.84)	0.84
Abnormal vascularity, yes	34 (4.0)	3 (2.0)	2.73 (0.83-8.99)	0.09

Table 3 - Pap smear screening results based on the Bethesda III 2001 criteria in a study in Riyadh, Kingdom of Saudi Arabia.

Pap smear screening results	Group I (n=841)	Group II (n=200)	OR (95% CI)	P-value
<i>Infection by organism</i>				
All organisms, yes	148 (18.0)	32 (16.0)	1.12 (0.74-1.71)	0.59
Bacterial vaginosis, yes	83 (56.0)	17 (53.0)	1.13 (0.53-2.43)	0.76
Trichomoniasis, yes	1 (1.0)	0	NA	1.0*
Actinomyces, yes	1 (1.0)	0	NA	1.0*
Candida (yeast), yes	55 (37.0)	14 (44.0)	0.76 (0.35-1.65)	0.49
Others, yes	8 (5.0)	1 (3.0)	1.77 (0.21-14.68)	1.0*
<i>Type of epithelial cell abnormality, n=841 (%)</i>				
<i>Squamous cell, yes</i>	767 (91.0)			
ASC-US	497 (65.0)			
ASC-H	49 (6.0)			
LSIL	170 (22.0)			
HSIL	43 (6.0)			
Squamous cell carcinoma	8 (1.0)			
<i>Glandular cell, yes</i>	74 (9.0)			
Atypical glandular cells	0			
AGUS	53 (72.0)			
AIS	0			
Adenocarcinoma	21 (28.0)			

*Fisher exact test. OR- odds ratio, CI - confidence interval, ASC-US - atypical squamous cells-unknown significance category, ASC-H - atypical squamous cells-high-grade lesions, LSIL - low-grade squamous intraepithelial lesions, HSIL - high-grade squamous intraepithelial lesions, AGC - atypical glandular cells, AGUS - atypical glandular cells of undetermined significance, AIS - endocervical adenocarcinoma in situ

frequency and percentage of the categorical variables, and mean with standard deviation for the continuous variables. The various differences between females with normal and abnormal pap smears was determined. Odds ratios (OR) with their 95% confidence intervals (95% CI) were calculated and presented. $P < 0.05$ was considered statistically significant.

Results. A total of 22,668 pap smears were performed between January 2008 and December 2011. Out of all smears, 19,650 were carried out to Saudi women. A total of 841/19,650 smears were with abnormal epithelial cells. Over the study period (2008-2011), the prevalence of abnormal epithelial cell smears was 4.3%. The prevalence of abnormal epithelial cell smears per study year was as the following: 2008 ($n=262/4594$) there was a prevalence of 5.7%; 2009 ($n=240/4942$) the prevalence was 4.8%; 2010 ($n=209/4996$) the prevalence was 4.2%; and finally during the year 2011 ($n=130/5118$) there was a prevalence of 2.5%. Table 1 presents the included women's characteristics. Mean ages were similar in both study groups; 45.4 ± 11.6 years for group I, and 46.5 ± 10.6 years for group II. Group I patients had lower parity ($p=0.001$), and gravidity ($p=0.001$), and were 37% less likely to use intra-uterine contraception device (IUCD) (OR= 0.63; 95% CI= 0.41-0.96; $p=0.03$). Table 2 presents the included patients clinical characteristics. Group I patients had 14 times increased chance to have previous abnormal smear (OR=14.1; 95% CI=5.2-38.5; $p=0.001$), they had also 14 times increased risk to have previous treatment for an abnormal smear (OR=14.0; 95% CI=5.2-38.3; $p=0.001$). Group I patients were more likely to have abnormally looking cervix (OR=1.48; 95% CI=1.01-2.16; $p=0.045$), and their cervixes tend more to bleed easily upon touching (bleeding on touch) (OR=3.19, 95% CI=1.14-8.94; $p=0.02$). Table 3 presents the different identified infections and the cervical epithelial abnormalities in the studied groups. There was no significant difference between the 2 groups with regard to the identified infections. In group I, the most common diagnosed cytological abnormality was squamous cell abnormalities ($n=767/841$ [91%]) where ASC-US represented 65% of these abnormalities. There were 74/841 (9%) glandular cells abnormalities, 53/74 (72%) of the glandular cells abnormalities were AGC favoring cell growth, and 21/74 (28%) were with adenocarcinoma. Upon stratifying the squamous cell abnormalities by age groups, there was significantly a higher proportion of abnormalities presented in the age

groups younger than 40 years compared with the older age groups (older than 60 years [$p=0.001$]). The most common abnormality presented in all the age groups was ASC-US (65%), followed by LSIL (20%). For patients aged above 60 years, ASC-H was the second highest abnormality (11%). Squamous cell carcinoma was found in a total of 8 patients (1%) in the study group who aged more than 50 years. Several modalities of treatment were offered to 632 (75%) of the 841 patients with abnormal smears. We have no document on any type of management given to the rest (25%) of patients who had abnormal smears.

Discussion. This study was performed to provide an insight on the magnitude and characteristics of abnormal pap smears in the central region of KSA. The pap smear results in this study revealed a relatively low prevalence of abnormal smears as compared with other studies carried out in the western (17.3%), south-western (7.9%),^{3,15} and eastern region (5%)¹⁶ of KSA. Our findings are similar to earlier studies carried out in Kuwaiti and United Arab Emirates who reported prevalence of abnormal smears as 4.3% (Kuwait), and 3.6% (United Arab Emirates).^{17,18}

The most common age to develop CC is between 40 and 50 years, and its precursor lesions usually occur 5-10 years prior.¹⁹ The mean age of Saudi patients with epithelial cells abnormalities was corresponding to their reproductive age.^{1-4,20} Although, the present study showed no significant difference in the mean ages of both cases and controls; presence of abnormal epithelial cells was higher for patients in their reproductive age (younger than 40 years). Our findings concerning patients' parity and their use of contraception methods are unique. High parity has been associated with increased CIN in many reports.^{21,22} However, in our data patients with abnormal smears were characterized with lower parity. Moreover, there was no significant difference between cases and controls use of oral contraception pills (OCP), contradicting other studies that has linked oral contraceptive use with more tendency to develop cervical intraepithelial abnormalities.^{23,24} It appears that our studied patients who developed cervical intraepithelial abnormalities, may carry different characteristics compared with others assessed populations; an area that requires an in-depth exploration. Furthermore, some studies²⁵ have linked the use of IUCD with higher risk of developing abnormal smear, while others have found an inverse association between the use of IUCD and CC.²⁶ Cellular immunity enhanced by the IUCD

might explain their findings. The use of IUCD was not associated with increased epithelial cells abnormalities in our study, our population's lower tendency to develop sexually transmitted diseases (STD),²⁷ and the declining prevalence of abnormal epithelial smear within the studied population may stand behind this finding. Patients with abnormal intraepithelial smears were 14 times more likely to have a previous abnormal smear. Although this finding might indicate the presence of associated risk factors, such as presence of HPV infection,^{5,6} it may result in these patients attendance for management in the gynecological clinics after referral for disease detection.

The current study showed that patients with an abnormal smear were more likely to have abnormal cervical appearance. A Bangladeshi study,¹⁹ has indicated that one-third of patients with abnormal smears had healthy looking cervix. On the other hand, it is well documented that negative smear can be found in the presence of epithelial cell abnormalities.²⁸ As cytologists usually base their recommendations on their cytology assessment only, the absence of cervical clinical appearance description, and abnormality consideration in the pap smear recommendations may contribute to possible late diagnosis.²⁸ Therefore, cervical abnormalities documentation and these abnormalities consideration by the cytologist are recommended. A total of 9% of all abnormal smears were found to have AGC. Cervical intraepithelial abnormalities for both glandular and squamous epithelium were reported to be linked to various genotypes of HPV infections.^{4,5} The presence of patients with AGC and even with concurrent ASC/SIL who test positive for HPV should alert to their higher risk for advanced intraepithelial abnormalities.²⁹ Moreover, HPV assessment is useful in identifying women at risk for AGC, as well as ASC.³⁰ This information, can be utilized to justify the implementation of HPV population screening and its genotypes identification. Such screening may highlight the need for national HPV vaccination program and help in assessing the suitability of the already available vaccines to our Saudi population.

This research has some weaknesses particularly those weaknesses related to its retrospective nature. Further, the included smears were performed in one institution in the central region of KSA. Although this population is likely to represent the central region, some element of bias cannot be ruled out. As no screening program has been implemented, it is likely that more symptomatic patients were assessed and therefore have

elevated the true prevalence of the disease. The findings of the research implicate the need for further works that assess in-depth Saudi population risk factors to develop cervical intraepithelial lesions, and to evaluate its association with various HPV genotypes. Finally, it highlights the need to implement national screening program for cervical cancer prevention.

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