RESEARCH ARTICLE

CERVICAL CYTOLOGY SCREENING IN SUB-SAHARAN AFRICA

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ABSTRACT

Purpose: The purpose of our study is to determine the ratio of abnormal cervical cytology among the results of the first cervical screening of women in the Darfur area of Central Africa.

Material and Method: The cytology results of women who had Pap smear tests done in a Saharan hospital between 2014-2015 were screened retrospectively. Women with abnormal cervical cytology results in the conventional evaluation were examined further. Women with cervical cytology results of ASC-US, ASC-H, LGSIL, HGSIL, and AGC were included in the study.

Findings: Abnormal smear results were detected in 178 (2.83%) of the 6279 women whose cervical cytology was examined. ASC-US was detected in 100 (56.1%), ASC-H in 5 (2.8%), LGSIL in 31 (17.5%), HGSIL in 14 (7.9%), AGC in 27 (15.3%) and cervical cancer in 1 (0.56%) of the cases. Sixty-three of the cases underwent colposcopy-guided biopsy. The biopsy results were reported as chronic cervicitis in 29 (46.3%), CIN1 in 13 (18.7%), CIN2 in 6 (9%) and CIN3 in 13 (20.3%) of the cases. The correlation between the cervical cytology and colposcopy-guided biopsy results was statistically significant (Kappa: 0.541 and $p<0.001$).

Result: Cervical cancer can be diagnosed early by cervical cytology evaluations and can even be prevented. Although the cervical cytology test is a readily available, easy and effective method, histopathological correlation gains importance in the evaluation of abnormal cervical cytology. Performing colposcopy-guided biopsy for histopathological evaluation is considered an appropriate approach for the management of abnormal cervical cytology.

INTRODUCTION

Cervical cancer is still one of the cancers with the highest morbidity and mortality rates worldwide and its annual incidence is 470000 (World Health Organization, 2006). The American Cancer Society estimated that 12200 new cervical cancer cases would be diagnosed in the year 2010 (Jemal *et al.,* 2010). However, in Africa, contrary to expectations, cervical cancer is the ninth most common cancer among women's cancers and its incidence has been reported as 4.6 in 100.000 (World Health Organization, 2006). There are major differences between the incidence of cervical cancer in developed and developing countries. The extensive implementation of cervical screening programs in developed countries is shown as most important factor behind the low

cancer incidence in developed countries. Early detection of premalignant lesions by cervical cytology and treatment has an important role in preventing progression to cancer. The highest risk factor for cervical cancer is never getting screened for cervical cancer. 500000 new cases of cervical cancer are diagnosed every year (Jemal *et al.,* 2011; Arbyn *et al.,* ?; World Health Organization, 2006). Eighty percent of all cervical cancer cases develop in developing and underdeveloped countries. While 80% of the cervical cancer cases diagnosed in developed countries are stage I and II, in underdeveloped countries 80% of the cases are diagnosed at stage III or IV (World Health Organization, 2006; Jemal *et al.,* 2010). According to the GLOBOCAN project conducted by the International Agency for Cancer Research in 2008, every year 530000 new cervical cancer cases are diagnosed and 275000 people lose their lives to cervical cancer (Arbyn *et al.,* 2004).

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The development, etiopathogenesis, screening strategies and treatment of cervical cancer have been established better than the other female genital cancers. Cervical cancer has many risk factors: (Robbins *et al.,* 2003; Fang, 1998; Rosai *et al.,* 2004)

- Multiple sexual partners,
- High-risk male partner (i.e. partner whose previous sexual partners have precancerous or cancerous cervical lesions),
- Human Papilloma Virus (HPV) (especially type 16, 18, 31, 33, 45).
- Marriage at young age,
- Youth pregnancy and birth,
- Becoming sexually active in adolescence,
- Smoking
- Immunosuppression (for example HIV).
- Herpes Simplex Virus 2 (HSV type 2)
- Moderate dysplasia in a pap smear screening test done within the last 5 years,
- Sexual intercourse within the first year after menarche.
- Never having been screened before.
- Low socioeconomic class.
- Race (risk is higher in the white race than it is in the black race).
- The use of oral contraceptive pills.

When we examined our region, Darfur, Sudan in sub-Saharan tropical Africa we saw that many risk factors such as poor socioeconomic conditions, multiple sexual partners, black race, sexual intercourse at young age, young pregnancy and birth, the prevalence of chronic diseases that lead to immunosuppressant and never having been screened before were prevalent in the region. This makes cervical cytology screening methods extremely important in this region. The first studies that investigated the detection of cervical cell abnormalities were performed in 1927 (Virtej and Vasiliu, 2003). In 1943, Papanicolaou and Trout developed the pap smear test to detect underlying cancer or precancerous lesions. They demonstrated the test on cells scaling off of the cervix uteri. After the development and utilization of this test the rate of death from cervical cancer in the United States has decreased by 75% (Ball and Madden, 2003). Studies have shown that more than 50% of the cervical cancers are detected in women who have never been screened for cervical cancer before and that 60% is detected in women that did not get a pap-smear screening in the last 5 years (Intitute Clinical Systems Improvement, 2003).

Therefore, the scope of the pap smear screening program for women under risk must be expanded and the test must be made available in primary care. In accordance with state policies the pap smear screening test has become the primary screening test in many countries. Precancerous diseases are most common between the ages of 25-35. Unfortunately, despite the presence of this effective method, most of our women in the Sudan Darfur area are not aware of it and it can be seen that health policies targeting this issue are not implemented effectively. The pap smear test has unique qualities as a screening method. It is cheap and easy to perform, it is easily accepted by patients and its use in public screening can reduce the death rate from cervical cancer by 90% (Intitute Clinical Systems Improvement, 2003). Colposcopy-guided biopsy is considered as the gold standard for evaluating cervical lesions. Performing colposcopic examination and guided biopsy in cases with abnormal conventional smear results is the primary diagnostic approach to detect cervical intraepithelial lesions and to select the appropriate treatment modality. This method makes the early diagnosis and treatment of precancerous lesions possible. This study aims to determine the prevalence of abnormal cervical cytology in women living in the district of Nyala in sub-Saharan central Africa. The correlation between abnormal cytologic findings and the histopathological examination of the biopsy samples obtained during colposcopic examination has also been investigated.

MATERIALS AND METHODS

Cases that had pap smear tests done for cervical screening in our gynecology clinic between April 2014-November 2015 were evaluated in our study.

Pap smear

After the cervical cytology was spread on the slide it was fixated in 95% alcohol and stained according to the Papanicolaou method. The cytopathological examination was performed according to the Bethesda system. Cases with pap smear results of Atypical Squamous Cells of Undetermined Significance (ASC-US), Atypical Squamous Cell cannot exclude HGSIL (ASC-H), Low Grade Squamous Intraepithelial Lesions (LGSIL), High Grade Squamous Cell Intraepithelial Lesions (HGSIL), Atypical Glandular Cells (AGC) were included in the study.

Colposcopy

Cases with abnormal cervical cytology underwent colposcopic examination for further evaluation and biopsy samples were obtained if necessary. In the colposcopic examination, the cervix was washed with normal saline solution and examined under large and small magnification and then 3% acetic acid was applied and it was waited for 60 seconds. The aceto-white areas were examined under small and large magnification and abnormal vascularization was evaluated through a green filter. The presence of areas not staining with iodine was determined using Lugol's solution. Biopsy samples were obtained from areas defined as abnormal in the colposcopic examination with cervical biopsy forcepses. Cases diagnosed with AGC or cases that demonstrate endocervical extension underwent endocervical curettage and endometrial sampling was performed in cases where it was deemed necessary. The biopsy material was fixated in formaldehyde and sent to the pathology laboratory for histopathological examination.

Statistical Analyses

The data was analyzed using the SPSS 17.0 software. Descriptive statistics were expressed as mean ± standard deviation, and nominal variables were expressed as case number and (%).

Findings

6279 cases that underwent cervical screening were evaluated in our study. Abnormal cytology was detected in 178 (2.83%)

cases. The abnormal Pap smear results are given in Table 1. Eighty-seven cases with abnormalities detected in the pap smear test were lost in follow-up, and 18 (9.9%) cases did not give consent for the colposcopic examination. In 11 of the cases that underwent colposcopic examination, no lesions were detected and no biopsy samples were taken. The biopsy results of the lesions detected in the colposcopic examination of 63 cases are given in Table 2.

Table 1. Abnormal cervical cytology results

Abnormal pap smear results	N (number)	%
Asc-us	100	56.1
Asc-h	5	2.8
Lgsil	31	17.5
Hgsil	14	7.9
Agc	27	15.3
Cervical cancer	1	0.56
Total	178	100

Table 2 .Colposcopy-guided cervical biopsy results

Colposcopy results	N (number)	%
Chronic cervicitis	29	46
Cin 1	14	22.2
Cin 2	6	9.5
Cin 3	13	20.6
Cervical cancer	1	1.58
Total	63	100

The correlation between cervical cytology results and the histopathological evaluation of the colposcopy-guided biopsies is shown in Table 3. According to this table, 23 (83.3%) of the cases reported as ASC-US were reported as chronic cervicitis, 3 (9.2%) as CIN1, 2 (5.5%) as CIN2 and 1 (1.9%) as CIN3. One (25%) of the cases reported as ASC-H was reported as chronic cervicitis, 1 as CIN1, and 2 (50%) as CIN3.

The Kappa value for the correlation between pap smear results and histopathological results was calculated as 0.541. A moderate degree of correlation was shown between the results of the cervical cytology and colposcopy-guided biopsy and the correlation was considered statistically significant (p<0.001).

DISCUSSION

Poor socioeconomic status, early onset of sexual activity (< 16 years of age), polygamy, polygamous spouse, smoking, history of HPV infection, and not having been screened with a pap smear test before may be listed among the risk factors for cervical cancer (World Health Organization, 2006; Jemal et al., 2010; Tuncer et al., 2009). Our hospital is located in the middle of sub-Saharan Africa in a vast, arid, and poor area with a population of 7 million connected to the state Darfur. Immigration from the suburbs to the safer central areas for safety during the civil war in 2006-2007 significantly raised the population in the area. Consequently, the already insufficient social and economic conditions worsened, and fundamental health care services were especially hindered. The polygamic increase in population has led to a poor socio-economical lifestyle, marriages at an early age, and an increase in sexually transmitted diseases, the HPV infection and pre-invasive lesions have especially become more common. However, there is no definitive documented data about this topic. The cervical smear samples of 6279 women living in the Darfur area of sub-Saharan Africa were examined in our study and the ratio of abnormal cervical cytology was calculated as 2.83%. According to the results of the study conducted by Branca et al, the most common abnormalities detected in in repeat smear tests are ASCUS (37%), LGSIL (26%) and HGSIL (4.9%) respectively (Branca et al., 2004).

Table 3. The comparison of abnormal cervical cytology with histopathology (%)

Abnormal cervical cytology	Chronic cervicitis N (%)	Cin 1 N (%)	Cin 2 N (%)	Cin 3 N (%)	Cervical cancer N (%)	Total N (%)
Asc-us	23(35.9)	3(4.6)	2(3.1)	1 (1.5)	-	29 (45.3)
Asc-h	1 (1.5)	1 (1.5)	-	2 (3.1)	-	4 (6.2)
Lgsil	2 (3.1)	8 (12.5)	3 (4.6)	4 (6.2)	-	17 (26.5)
Hgsil	-	1 (1.5)	2 (3.1)	5 (7.8)	-	8 (12.5)
Agc	5 (7.8)	-	-	-	-	5 (7.8)
Cervical cancer	-	-	-	-	1 (1.5)	1 (1.5)
Total	31(48.4)	13 (20.3)	7 (10.9)	12 (18.7)	1 (1.5)	64 (100)

Two (12.5%) of the cases reported as LGSIL were reported as chronic cervicitis, 8 (46.8%) as CIN1, 3 (15.6%) as CIN2, and 4 (25.6%) as CIN3. One (12.5%) of the cases reported as HGSIL was reported as CIN1, 2 (18.7%) as CIN2, and 5 (%62.5%) as CIN3. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ASC-US, LGSIL and HGSIL cervical cytology are given in Table-4. This table demonstrates that the specificity and positive predictive value of cytology is very high.

Table 4. Calculating the diagnostic value of cervical cytology

	Asc-us	Lgsil	Hgsil
Sensitivity	75	33.3	21.6
Specificity	85.7	89.7	100
Ppv (%)	83.3	85.7	100
Npv (%)	21.7	61.5	55.3

According to the punch biopsies, 49% of the patients were CIN I, 5.6% were CIN II and 17% were CIN III. High-grade colposcopy results were highly correlated with HGSIL detection and HPV positivity in the smear test. The most important diagnoses for predicting CIN III were defined as HGSIL, HPV positivity and high-grade colposcopy findings (Branca et al., 2004). According to the results of our study, in the cases with abnormal cervical cytology, the ratio of pathologic colposcopic finding detection is statistically higher than the ratio of pathologic findings in patients with lower grade lesions. Studies conducted in similar regions with low income rates have revealed similar results (Kurdoğlu et al., 2009). Seventy percent of the smear test results were reported as ASC-US, 13% as LGSIL, 13% as HGSIL and 4% as ASC-H. (Kurdoğlu et al., 2009). In the study by Findik et al. (2012), the abnormal cytology ratio was reported as 1.2%, 55% of

these were reported as ASC-US, 2% as ASC-H, 32% as LGSIL, 4% as HGSIL and 2% as cervical cancer. Keskin *et al.,* (2011), examined 18303 pap smears and detected abnormal cytology in 1.35% of the cases. In the current study, 57% of the cases were reported as ASC-US, 2.8% as ASC-H, 17.5% as LGSIL, 7.9% as HGSIL and 15.3% as AGUS. Our study contains the largest number of cases in the Central Africa Region. It can be seen that the incidence of abnormal cytology is higher in the Darfur region when compared to the results of studies in other areas of Africa. The fact that 49.1% of our patients were lost to follow up shows that the level of cervical cancer awareness is low and that the public is not aware of the importance of the cervical screening program. Senol *et al.,* (2012) reported that the awareness and knowledge levels on cervical cancer were low in Turkish women. It was identified that awareness increased as the level of education and income increased.

A common approach to high-grade lesions detected after cervical cancer screening was determined. The evaluation of the 411 HGSIL patients from one of the most extensive studies investigating abnormal cytology results, the ALTS study (ASCUS and LGSIL Triage Study) by Castle *et al* in a separate study, after a 2-year follow-up CIN III was detected at a ratio of 8-9% in the treatment arms, colposcopy, the HPV test and conservative treatment (Castle *et al.,* 2008). However, in our study we were unable to test for HPV and we were only able to follow-up abnormal cytology with colposcopic management. Although a standardization for the treatment of high-grade lesions like HGSIL and cancer has been achieved, there are various options presented for the management of low-risk lesions such as ASCUS and LGSIL. There is a small number of studies that compare these methods directly in literature. According to the ALTS study, colposcopy is the most appropriate approach to patients with LGSIL smear results (ALTS Group, 2003). According to the results of the ALTS study, the CIN and cancer detection ratio for cytology alone is 84.5% and this ratio rises to 96.4% with the addition of colposcopy (ALTS Group, 2003). In the ALTS study it was determined that it was appropriate to follow-up ASCUS patients with smear tests and that the detection of CIN III and higher grade lesions will be equivalently successful (ALTS Group, 2003).

Flannelly *et al.,* 1994 randomized patients with low-grade abnormal cytology to smear follow-up and colposcopy arms (Flannelly *et al.,* 1994). According to the results of this study, the detection ratio of CIN II and higher-grade lesions was higher in patients who underwent colposcopy than it was in patients that were followed up with smear tests. In the randomized controlled study performed by Shafi *et al.,* 1997 patients with low-grade cervical cytology abnormalities were evaluated (Shafi *et al.,* 1997). However, according to the results of this study, there was no difference between performing colposcopy immediately and performing repeat smear tests for 24 months in detecting CIN II and lesions with higher grades. According to the largest cost-effectiveness analysis of the management of low-grade cervical intraepithelial lesions the TOMBOLA (The Trial Of Management of Borderline and Other Low grade Abnormal smears) trial, patient follow-up and immediate colposcopy have no superiority over each other (TOMBOLA Group,

2009). Although we did not evaluate the sensitivity of the combinations of cytology and colposcopy or colposcopy and HPV-DNA we observed that positive results were more likely in the ASCUS and L-SIL cases. In these conditions, pap smear tests are more appropriate for the follow-up of low-grade lesions like ASCUS and LGSIL that are likely to regress after pathological diagnosis instead of high-cost and/or invasive tests that are not likely to yield positive results. However, also according to the results of this study one third of the ASCUS patients actually have higher grade diagnoses. Thus, it is important to ensure that the patient complies with the follow-up, and if patient compliance is doubted a HPV-DNA test or a colposcopic examination should be performed. However, it must not be forgotten that inadequate follow-up will be inevitable in very poor countries like Africa due to costs and this issue should be evaluated beforehand.

Preinvasive cervical lesions at various degrees were detected in 41.2% of the 63 cases that underwent colposcopic examination in our study. It was observed that the specificity and positive predictive value of cervical cytology for ASC-US, ASC-H and HSIL are high. Chronic cervicitis was detected in 83.3% of the ASC-US cases, CIN 1 was detected in 3 (5.5%), and CIN 3 in 1 (1.9%). On the other hand, Bayramov *et al*. detected higher grade cervical lesions in 34.5% of the ASC-US cases (Bayramov *et al.,* 2011). And, Boztosun *et al* detected cervical intraepithelial neoplasia in 28.4% of the ASC-US cases (Boztosun *et al.,* 2012). Although the number of ASC-H cases are low, the ratio of cervical intraepithelial neoplasia was detected higher (75%). Keskin *et al.* (1998) determined the ratio of cervical neoplasia in ASC-H cases as 50%. As the ASC-H cases are at higher risk for advanced cervical intraepithelial lesions and malignity than ASC-US cases it is strictly advised to perform further colposcopic examination in these cases (Barreth *et al.,* 2006).

Cervical intraepithelial lesions at various grades were detected in 87.5% of the LGSIL cases. Keskin *et al.* (1998) detected cervical intraepithelial lesions in 37.5% of 48 LGSIL cases. The ASC-US-LGSIL (ALTS) study showed that 20% of the LGSIL cases advanced to CIN II-III. It has been reported that the colposcopic examination of LGSIL cases revealed a 12-16% ratio of CIN II and higher grade lesions (Wright *et al.,* 2006). The ratio of cervical intraepithelial lesions in the LGSIL cases of our study was higher than the previous data. Wright *et al*. performed colposcopy on HGSIL cases and reported the ratio of CIN II and higher lesions as 52% (Wright *et al.,* 2006). In the ALTS study CIN II-III was detected in 70-75% of the HSIL cases (Cox *et al.,* 2003). We detected cervical intraepithelial lesions at various degrees in all of the HSIL cases in our study, and we detected a higher ratio of high-grade lesions than the literature data suggests. Cervical cytology is a screening test and biopsies must be obtained for histopathological examination to make the definitive diagnosis. The sensitivity and specificity of cervical cytology have been reported as 30-87% and 86-100% respectively (Nanda *et al.,* 2001). Our study results show that the specificity and PPV of cervical cytology for ASC-US, LGSIL and HGSIL are high. Additionally, as the grade of the cervical intraepithelial lesion advances its diagnostic value increases and its correlation with colposcopy gains significance.

RESULTS

In final words, cervical cancer is a cancer type with a long preinvasive process, it can be diagnosed early through cervical screening and its morbidity and mortality can be decreased. Expanding the scope of cervical screening and raising cancer awareness among women are the most important steps in preventing cancer.

Performing colposcopic examination in patients with abnormal cytology and initiating appropriate treatment and follow-up programs for patients that are diagnosed will decrease the incidence of cancer further. As a part of preventive medicine, we must continue to expand the scope of screening services, especially because the spread of sexually transmitted diseases is increasing.

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