

The effect of human immunodeficiency virus prevalence on the epidemiology of conventional cervical cytological abnormalities: an institutional experience

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Abstract

Objectives: Despite a shift towards other screening modalities, cervical cytology still has an important screening function in many settings. The worldwide human immunodeficiency virus (HIV) epidemic has impacted severely on cervical cancer, resulting in women presenting at a younger age with more advanced disease and poorer prognosis. The objective of this study was to compare different datasets from different time periods to assess the possible impact of HIV infection on the epidemiological characteristics of conventional cervical cytology screening results.

Design: The design was a comparative overview of two different cervical cytology datasets collected at different times.

Settings and subjects: Conventional cervical cytology screening data from non-pregnant patients at the gynaecological outpatient service of the Pretoria Academic Complex from 1991-2000, and data from pregnant patients attending the Kalafong Hospital antenatal clinic in 1993-1994 and 2008, were analysed.

Outcome measures: Abnormal smear rates, the distribution of different abnormal smears and HIV prevalence in pregnant women taking part in the annual, National Antenatal Sentinel HIV and Syphilis Prevalence Survey.

Results: The high prevalence of HIV in South Africa is associated with a higher prevalence of abnormal smears. It is also associated with a change in the distribution of detected abnormalities. High-grade squamous intraepithelial lesions (HSIL) are now much more common than low-grade squamous intraepithelial lesions (LSIL). The most pronounced change has been a shift in the ratio of LSIL to HSIL, where the value has changed from > 1 to < 1 .

Conclusion: The rate of abnormal smears as well as the distribution of abnormalities of conventional cervical cytology in South Africa has changed. It is possible that this change is associated with the high prevalence of HIV infection.

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Introduction

Cytological screening for cervical cancer has been in existence for over five decades, and has been extremely successful in lowering the incidence of cervical cancer in settings where population-based screening was adequately implemented.¹ Cervical cytology still remains an important screening option in 2013, despite the availability of human papillomavirus (HPV) screening and primary prevention by vaccination against the high-risk HPV 16 and 18 genotypes.

Cervical cytology findings correlate with the epidemiology of HPV infection. Low-grade lesions are mostly associated with transient HPV infection, and

high-grade lesions represent persistent HPV infection with high-risk HPV.²

According to published data, the incidence of abnormal smears varies in different populations, and is affected by ethnicity and the type of population studied.³ The incidence of abnormalities is lower in unscreened populations where cervical cytological screening is part of the healthcare system. Randomly selected data from different regions in the world are summarised in Table I.⁴⁻⁷ There is a clear trend in this data indicating that the prevalence of low-grade squamous intraepithelial lesions (LSIL) is significantly higher than that of high-grade squamous intraepithelial lesions (HSIL), while the prevalence of atypical squamous cells of

Table I: A selection of published data on general population cervical cytology abnormalities

Published data	USA ⁴	Nigeria ⁵	India ⁶	Turkey ⁷
Abnormal smears (%)	5.5	7.6	5	1.8
ASCUS (%)	3.3	1.99	0.3	1.07
LSIL (%)	1.2	3.89	2.7	0.3
HSIL (%)	0.3	1.54	0.7	0.17
LSIL:HSIL	4	2.5	3.8	1.76

ASCUS: atypical squamous cells of unknown significance, HSIL: high-grade squamous intraepithelial lesions, LSIL: low-grade squamous intraepithelial lesions

unknown significance (ASCUS) varies considerably. This correlates with the natural course of infection, confirming the fact that most women will be able to clear the initial infection, and only a small percentage will develop persistent infection.

The world has experienced a severe human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) epidemic in the last three decades, which has been particularly severe in Africa south of the Sahara. There are more than 5-million people living with HIV and AIDS⁸ in South Africa. It has been well documented that the combination of HIV and HPV infection is an extremely deleterious one, with HIV-infected patients presenting earlier and with a more advanced stage of cervical cancer. HIV-infected women also present more challenges with regard to the treatment of cervical cancer and generally have a poorer prognosis.⁹

Therefore, it is likely that the HIV epidemic can alter the epidemiology of conventional cervical cytological abnormalities in populations with a high prevalence of HIV infection. Several descriptive studies have reported on the epidemiology of HPV-related disease in HIV-positive subgroups, but thus far, little data are available that demonstrate an effect of this immune deficiency disorder on HPV disease in the general population.

Aiming to study the effect of a rapid increase in HIV prevalence on the incidence of HPV-related cervical disease, the investigators explored different datasets

from periods before and after the onset of the HIV epidemic. Two retrospective datasets collected over the years in the Department of Obstetrics and Gynaecology, University of Pretoria, were found to be appropriate with regard to investigating the effect of HIV on the epidemiology of conventional cervical cytology abnormalities.

Method and results

Cervical cytological abnormalities in gynaecology outpatient clinic patients

The first dataset consisted of patients with cervical cytology over a number of years in the department, prior to and during the early stages of the HIV epidemic. These patients were not pregnant, and were seen by the gynaecology outpatient service. No HIV data were available for this group of patients and the only available cervical cytology data were the number of abnormal smears, as well as the number of cancers detected on cervical cytology. In 1992, just over 5.3% of smears were reported to be abnormal. Table II clearly illustrates a gradual year-on-year increase in the percentage of abnormal smears. By 1998, the percentage of abnormal smears had doubled to 10.5%.

Table III illustrates the onset and course of the HIV epidemic, as measured in pregnant patients attending antenatal clinics in South Africa. In 1992, 2.2% of women attending antenatal clinics were HIV-infected. The prevalence of HIV infection increased to 22.8%

Table II: Data on abnormal smears in non-pregnant patients from 1991-2000

Data	1991-1992	1992-1993	1993-1994	1994-1995	1995-1996	1997-1998	1999-2000
Total number of smears	17 409	17 902	12 888	13 671	11 812	12 658	6 440
Number of normal smears	16 488	16 858	12 038	12 523	10 720	11 327	5 286
Number of abnormal smears	921	1 044	850	1 148	1 092	1 331	1 154
Percentage of abnormal smears	5.3	5.8	6.6	8.4	9.2	10.5	17.9
Number of cancers	132	124	96	121	105	117	112
Percentage of cancer	0.75	0.69	0.74	0.88	0.88	0.92	1.74

Table III: Human immunodeficiency virus prevalence data on pregnant women attending antenatal clinics from 1990-2003

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
% HIV prevalence	0.7	1.7	2.2	4	7.6	10.4	14.2	17	22.8	22.4	24.5	24.8	26.5	27.9

HIV: human immunodeficiency virus

Table VI: Cytology results of HIV positive and HIV negative women attending the antenatal clinic (2008)

	Total tested n (%)	HIV-positive n (%)	HIV-negative n (%)
Subjects	355	133 (37.46)	222 (62.54)
Abnormal smears	45 (12.67)	35 (26.3)	10 (4.5)
ASC	8 (2.3)	4 (3)	4 (1.8)
LSIL	17 (4.7)	13 (9.7)	4 (1.8)
HSIL	20 (5.6)	17 (13)	3 (1.4)
LSIL:HSIL	0.83	0.74	1.28

ASC: atypical squamous cells, HSIL: high-grade squamous intraepithelial lesions, LSIL: low-grade squamous intraepithelial lesions

in 1998. By the year 2000, 24.5% of pregnant women attending antenatal clinics were reported to be HIV-positive, and 17.9% of cervical smears were abnormal.

Cervical cytological abnormalities in antenatal clinic patients

The second dataset consisted of cytology surveillance on pregnant women in 1993-1994, and was repeated in 2008. An audit performed at the antenatal clinic at Kalafong Hospital in 1993-1994 suggests that routine cervical cytology screening had a very low yield for cervical abnormalities in this population. The incidence of abnormal cytology was 17/1 000 (1.7%) for women aged 27 years and older, and 4/1 000 (0.4%) for women younger than 27 years of age. Abnormal cervical cytology in this audit was found in 10.4/1 000 screened patients (1.04%). Routine screening of pregnant patients during the initial visit was subsequently abandoned, and only patients older than 27 years of age who had not been screened prior to their first antenatal visit were eligible for screening.

In 2008, when 29% of pregnant women attending antenatal clinics in South Africa were found to be HIV-infected,⁸ a study was undertaken to evaluate the validity of the adopted policy following the audit that was conducted in 1994. Conventional cervical cytology of 355 pregnant women who attended the antenatal clinic was evaluated. The mean age for this group was 30 years.

A total of 45 (12.67%) abnormal smears [atypical squamous cells (ASC), atypical glandular cells of unknown significance (AGUS), LSIL or HSIL] were reported for the whole group. Seventeen patients

(4.7%) had LSIL, 20 (5.6%) HSIL, and 8 (2.3%) ASCUS or AGUS lesions.

One hundred and thirty-three patients (37.46%) were HIV-positive, and 222 (62.54%) HIV-negative. Thirty-five patients who were HIV-positive (26.3%), and only 10 patients who were HIV-negative (7.5%), had abnormal smears. Seventy-five patients (21.1%) had cytological evidence of HPV infection. Fifty-two (39%) patients who were HIV-infected also had cytological evidence of HPV infection, while 23 (10%) patients who were HIV-negative had this report [p-value 0.000, odds ratio (OR) 5.55, 95% confidence interval (CI): 3.1-9.6]. The incidence of abnormal cytological findings in HIV-positive and HIV-negative women are compared in Table IV.

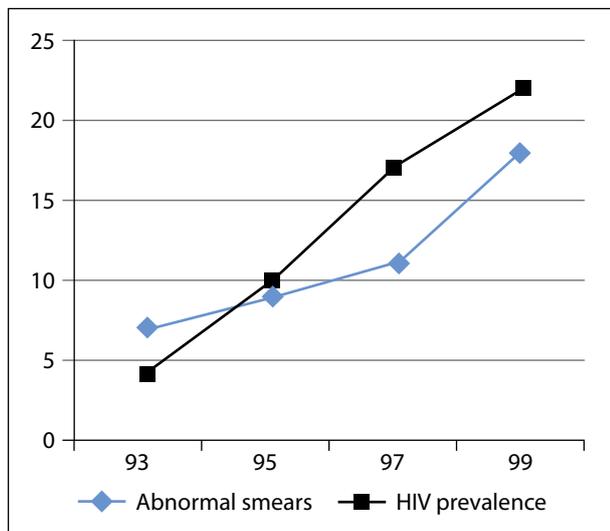
Of 167 women younger than 30 years of age, 26 had abnormal Papanicolaou smears (15.5% abnormal smear rate), compared to 19 abnormal smears in 188 women who were 30 years and older (10.1% abnormal smear rate). The rate of abnormal smears in patients younger than 30 years was not statistically significant compared to that in patients aged 30 years and older (p-value 0.1226, OR 1.64, 95% CI: 0.07-3.08).

Discussion

The published literature cites an abnormal cervical smear rate ranging between 4% and 10% for the general population. A breakdown of abnormal smears shows that ASCUS comprises the highest percentage of abnormal smears (up to almost 10%), followed by LSIL (up to 4%). Generally, HSIL contributes the smallest proportion (0.5- 1%). The rate of abnormal smears between 1992 and 1995 was similar to published data

from the rest of the world, including Africa, in the first dataset comprising non-pregnant patients tested in the gynaecology service of the department.

In addition, this dataset seems to show a correlation between the rising prevalence of HIV infection and the subsequent increase in the percentage of abnormal smears in non-pregnant patients over the decade under study. The prevalence of HIV infection in pregnant women increased from 2.2% to 10.4% from 1992-1995, and then rose quite sharply to 24.5% in 2000. The prevalence of abnormal smears in this population more than doubled from 8.4% to 17.9% from 1995-2000. These findings are illustrated in Figure 1.



HIV: human immunodeficiency virus

Figure 1: The rising human immunodeficiency virus prevalence and subsequent increase in abnormal smear rate

The effect of widespread HIV infection on cervical cytology is well illustrated in the second dataset. The epidemiology of the cervical cytological abnormalities in women who were HIV-negative attending the antenatal clinic resembles that of the pre-HIV era population, as well as that of published data. Only 4.5% of smears were abnormal in this group, 1.8% were ASCUS, 1.8% LSIL and 1.4% HSIL. The reason for the low incidence of ASCUS possibly relates to the high incidence of smear abnormalities in the general population. It has been suggested that a high incidence of abnormal smears influences cytology error rates in screening for cervical cancer. Thus, it is possible that this could also influence the rate of ASC diagnosis.¹⁰

There is a higher percentage of abnormal smears in the HIV-infected population. In addition, there has also been a clear shift in the pattern of abnormal smears, with the percentage of HSIL (13%) surpassing that of

LSIL (9.7%). The ratio of LSIL to HSIL of > 1 documented in the published literature in patients who are HIV-negative changes to < 1 in the HIV-positive population. Furthermore, the impact of the smear abnormalities in patients who are HIV-positive, affects the epidemiology of the whole population, resulting in a higher total incidence of HSIL (5.6%) compared to that of LSIL (4.7%), and a LSIL to HSIL ratio of < 1 . This ratio can possibly be interpreted to suggest that conventional cervical cytology also performs better in populations with a high HIV prevalence.

Recently published data by Richter et al confirm this trend.¹¹ In this study, cervical cytology was performed on 1 472 mainly unscreened women from an urbanised general population. The rate of abnormal smears in this population was 17.3%. ASCUS accounted for 4.7%, LSIL 3%, and HSIL 9.1%. The LSIL to HSIL ratio was very low at 0.32.

The datasets in this study, as well as the data published by Richter et al, describe the highest reported rate of cervical cytological abnormalities in unselected screening populations in the published literature. Our data further demonstrate the changing epidemiology of conventional cervical cytological abnormalities in the era of HIV.

While insightful, our study had several limitations. The Gynaecology Outpatient Clinic dataset did not specify the abnormal smear diagnoses. The latter, as well as the nature of the collected data, precludes reliable detailed statistical analysis. Although the antenatal clinic dataset was small, the data for women who were HIV-negative correlated well with the published data on non-pregnant women. In addition, the results of the whole pregnant population were similar to the findings of the population-based study that was published by Richter et al.

Conclusion

The data from this institution confirms a considerable shift in the pattern of abnormal smears in the era of HIV. This effect was probably a result of a combination of factors, including the fact that the population was largely unscreened and had a high prevalence of HIV infection. This immunocompromised, unscreened and untreated population with HPV disease contributed to higher exposure to HPV infection, and a resultant, higher incidence of high-grade lesions.

The shift in the LSIL to HSIL ratio translates into a better performance of conventional cervical cytology as a screening test in a population with a high prevalence of pre-invasive disease, as the test in this population detects more clinically significant abnormalities than lesions not requiring immediate treatment.

Thus, conventional cervical cytology remains a useful cervical cancer screening option that can also be utilised to screen pregnant patients. The HIV epidemic, as well as the mean age of the patients visiting these clinics, makes the antenatal clinic a unique screening opportunity for populations who do not have the benefit of a population-based cervical cancer screening programme, as more than 90% of patients visit these clinics during their pregnancy. The high prevalence of HSIL highlights the importance of increased implementation of cervical screening combined with an effective treatment programme utilising all existing healthcare facilities.

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