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Implications of inflammatory changes on cervical cytology

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Abstract

Objective—To assess premenopausal women with inflammatory changes on cervical cytology for genital infections and cervical abnormalities.

Design—Prospective study of women attending general practice and family planning clinics who had a recent cervical cytology result with inflammatory changes.

Setting—Department of genitourinary medicine.

Patients—102 Premenopausal women with recent cytology result showing inflammatory changes and with no history of antibiotic or antifungal treatment since their smear.

Investigations—Genital examination and microbiological screening for genital infections; colposcopic examination about six weeks later.

Main outcome measures—Detection of genital infections, particularly those sexually acquired, and abnormalities on colposcopy.

Results—Genital infections were isolated in 77 patients, and one or more sexually acquired infections were found in 22. Prevalence of sexually acquired infections was significantly correlated with younger age (particularly being under 25), being single, separated, or divorced; using non-barrier contraception; and recent change of sexual partner. An abnormality on colposcopy was found in 36 women. There was a strong correlation of a sexually acquired infection with an abnormality at colposcopy; hence younger women were more likely to have a colposcopic abnormality.

Conclusions—Inflammatory changes on cytology are often associated with the presence of a sexually acquired infection and premalignant disease of the cervix, particularly in younger, single women using non-barrier contraception.

patients who have inflammatory results of cervical cytology have been cited recently^{1,2} but these studies did not include comprehensive screening for genital infections or look at specific demographic details that might suggest high risk factors. The purpose of our study was to assess the significance of inflammatory changes on cervical smears taken as part of a routine community screening programme in regard to the presence of genital infections and the findings of colposcopy. Certain demographic details were documented to ascertain risk factors for the presence of sexually transmitted diseases or abnormalities on colposcopy.

Patients and methods

The study took place over a 12 month period. Patients were from three general practice areas (covered by 11 family practitioners) or from a community family planning clinic and had varying social and educational backgrounds.

All patients had had routine three or five yearly cervical smears taken at the practice or family planning clinic and the result had been reported as on cytology form HMR 101/5 (1982) showing inflammatory changes (box 24, 1). In some cases there was also a report of an inadequate specimen or negative results (box 23, 1 or 2), but in others no comment had been made on evidence of a neoplastic pattern.

Women were excluded from the study if they had received antibiotic or antifungal treatment since their smear had been taken or if they were post menopausal (to avoid inflammatory changes due to oestrogen depletion).

GENITOURINARY EVALUATION AND SPECIMEN COLLECTION

All patients were referred to the department of genitourinary medicine where a full genitourinary history and examination were performed. A bivalve vaginal speculum was inserted and vaginal specimens collected for microscopy and culture of *Gardnerella vaginalis*, *Candida albicans*, *Trichomonas vaginalis*, and mycoplasmas. Cervical and urethral specimens were collected for microscopy and culture for *Neisseria gonorrhoeae* and for *Chlamydia trachomatis* enzyme immunoassay. Serum was collected for serological tests for syphilis. If genital vesicles or ulcers were present swabs were taken from the skin lesions and from the cervix for culture for herpes simplex virus. Genital warts were diagnosed by clinical appearances.

LABORATORY METHODS

Neisseria gonorrhoeae—Gram stained urethral and

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Introduction

A previous study based in our department had shown that inflammatory changes on cervical cytology smears were linked with an increased risk of having a sexually acquired infection and often masked underlying premalignant disease of the cervix. (J D Wilson *et al*, Medical Society for the Study of Venereal Disease meeting, Antwerp, 1987).¹ This study has been based on patients attending the department, who could be considered a high risk population for both sexually transmitted diseases and cervical premalignancy. It was therefore not possible to extrapolate these findings to a community based group such as women attending general practice and family planning clinics, where most cytology screening occurs.

The risks of underlying premalignant disease in

cervical smears were examined microscopically for Gram negative intracellular diplococci. Culture was on modified New York City medium with confirmation by carbohydrate utilisation testing.

Chlamydia trachomatis—*C. trachomatis* was detected by the IDEIA chlamydia test (Novo Vio Laboratories, Cambridge).

Trichomonas vaginalis—Vaginal secretions were suspended in 0.85% sodium chloride solution and examined microscopically for characteristic motile forms. Culture was in trichomonas medium (Oxoid, Basingstoke).

Candida albicans—Gram stained vaginal smears were examined microscopically for yeasts and pseudohyphae. Culture was on Sabouraud's medium with confirmation by germ tube test.

Gardnerella vaginalis—Vaginal secretions were suspended in 0.85% sodium chloride solution and examined microscopically for clue cells. Culture was on blood agar media.

Mycoplasma hominis and *Ureaplasma urealyticum*—Culture was on mycoplasma-ureaplasma differential medium, reported as positive if growth was confluent.

Herpes simplex virus—Culture was on human fibroblasts with daily examination for cytopathic effect.

TREATMENT

Appropriate treatment was given, with tests of cure, for any infection that had been identified. Sexual contacts were seen if a sexually transmitted infection was found.

CYTOLOGY AND COLPOSCOPY

All patients were given an appointment for colposcopy about six weeks after their initial visit. Before colposcopic examination a cervical smear was taken with an Aylesbury spatula. Five per cent acetic acid was applied to the cervix and colposcopically directed biopsies taken of any acetowhite areas.

STATISTICAL METHODS

Statistical analysis of the data was by Wilcoxon rank test for unpaired data, and χ^2 with correction for continuity when testing contingency tables.

Results

One hundred and five patients were referred to the study, 96 from general practitioners and nine from family planning clinics. Three patients referred by general practitioners failed to attend for examination;

thus 102 were screened for infections. The mean age was 31.2 years (SD 9.85, range 17-52). At least one genital infection was isolated in 77 patients; table I shows the prevalence of these infections. One or more sexually acquired infections (that is, *C. trachomatis*, herpes simplex virus, genital warts, *T. vaginalis*) were present in 22.

The women with sexually acquired infections were significantly younger than those with no sexually acquired infection ($p=0.0002$). The median age of those with sexually transmitted infections was 20.5 years (17-52) compared with 31 years (19-49). Of 33 women under 25, 15 (46%) had a sexually acquired infection compared with 7 of 69 (10%) aged 25 and over.

There was a significant difference in the proportion of sexually acquired infections according to marital status: 15 of the 44 who were single, separated, or divorced (34%) had a sexually transmitted infection compared with seven of the 58 married women (12%; $p=0.02$).

At the time of initial visit 14 women used the sheath or a cap; 44 used the oral contraceptive pill; eight used an intrauterine contraceptive device; 19 had been sterilised; and 17 used no contraception. There was a significant difference in the prevalence of sexually transmitted infections between groups using barrier and non-barrier methods; a quarter of those using non-barrier contraception (22/88) had a sexually transmitted infection compared with none of the 14 using barrier contraception ($p=0.02$).

Patients' sexual histories were divided into those with a change of sexual partner within the past year and those with only one sexual partner for over one year. Those with a change of partner were significantly more likely to have a sexually transmitted infection (10/13 (77%) v 12/89 (14%); $p=0.001$).

Colposcopic examination was performed on 96 patients (the remaining six defaulted on appointments). The findings on colposcopy were normal in 60 women; wart virus infection was seen in 24; cervical intraepithelial neoplasia grade I was seen in three, grade II in two, grade III in six; and adenocarcinoma was seen in one. The colposcopy result was significantly related to the presence and number of sexually transmitted diseases (table II). Of the infections, only *C. trachomatis* correlated strongly with an abnormal result on colposcopy (table I).

Patients with abnormal results on colposcopy were significantly younger; the median age of those with normal colposcopy was 34 years (19-52) compared with 26 years (17-42) for those with abnormal colposcopy ($p=0.0002$). Single, separated, or divorced women were significantly more likely than married women to have abnormal results on colposcopy (23/41 (56%) v 13/55 (24%) respectively $p=0.001$). Women using barrier contraception were at somewhat lower risk of abnormal results on colposcopy (2/14 (14%) v 34/82 (42%) not using barrier contraception; $p=0.052$). Six of 12 women (50%) who had changed partners within the past year had abnormal results on colposcopy compared with 30/84 (36%) who had not changed partners.

Discussion

Inflammatory changes on cervical cytology among women tested in general practice or family planning clinics often indicate the presence of a sexually acquired infection. Risk factors include younger age; being single, separated, or divorced; using non-barrier contraception; or a change of sexual partner within the past year.

The most prevalent and potentially serious of the infections isolated was *Chlamydia trachomatis*, which was found in one in six of the patients. This was not

TABLE I—Prevalence of genital infections in women with inflammatory changes on cervical cytology

Organism isolated or infection	No (%) positive (n=102)	No (%) with colposcopy normal (n=60)	No (%) with colposcopy abnormal (n=36)
<i>Chlamydia trachomatis</i>	18 (18)	5 (8)	12 (33)*
Herpes simplex	3 (3)		3 (8)
Genital warts†	3 (3)	1 (2)	2 (6)
<i>Trichomonas vaginalis</i>	3 (3)	1 (2)	2 (6)
<i>Gardnerella vaginalis</i>	44 (43)	22 (37)	18 (50)
<i>Candida albicans</i>	19 (19)	12 (20)	4 (11)
<i>Mycoplasma hominis</i> or <i>Ureaplasma urealyticum</i>	33 (32)	18 (31)	12 (33)
None	25 (25)	20 (80)	5 (20)

* $p=0.002$, χ^2 test.

†Includes vulval or vaginal condylomata only; changes of wart virus infection found at colposcopy are not included.

TABLE II—Results on colposcopy related to number of sexually transmitted diseases (STDs) in women with inflammatory changes on cervical cytology

Colposcopy findings	No (%) of women with STDs		
	No STD	1 STD	2 STDs
Normal (n=60)	54 (90)	5 (8)	1 (2)
Abnormal (n=36)	21 (58)	11 (31)	4 (11)

$p=0.0003$, Wilcoxon rank test.

surprising as *C trachomatis* is now the most common sexually transmitted infection in Britain. Other community based studies on inflammatory results of cytology have not found such a high prevalence,^{1,2} but comments made at the time suggested that the infection rates were lower than would be expected.³ The prevalence of infections was higher than reported in studies of patients with symptoms attending general practice and family planning clinics, where *C trachomatis* was isolated in 8% and 9% respectively.^{4,5} Indeed, the prevalence of *C trachomatis* in our study group was similar to the 16% found in a study of screening before termination of pregnancy.⁶ Many doctors think that screening for sexually transmitted diseases should be performed before termination of pregnancy because of the high risk of the presence of a serious infection. We think that this would also be a sensible policy in patients who have had inflammatory changes on a smear as the recognition of asymptomatic infections such as *C trachomatis* is very important. A three to six months' delay in the diagnosis of cervical intraepithelial neoplasia is probably of no long term detriment to the patient, but such a delay in the diagnosis and treatment of *C trachomatis* cervicitis may result in long term complications of the upper genital tract and potential transmission of the infection to sexual partners.

There was a strong correlation between the presence of a sexually acquired infection and abnormalities on colposcopy. *C trachomatis* was the only individual infection to show strong correlation. The prevalence of the other infections was much lower so that many more patients would need to be studied before such correlations would become evident for these infections.

The abnormality rates of 13% for cervical intraepithelial neoplasia and 25% for wart virus infection are comparable with those found in other studies on inflammatory cytology.^{1,2} Interestingly, we found that patients with abnormal results on colposcopy were significantly younger than those with normal findings. This is contrary to the belief that inflammatory changes are more likely to be found in older women than in younger women, and thus to have more serious implications. It is not surprising, though, that contraceptive use at the time of examination or partner change over the past year showed no significant correlation with abnormality on colposcopy. Presumably any sexually transmitted agent implicated in the aetiology of cervical intraepithelial neoplasia infects the cervix some time before producing premalignant changes.

As from April 1989, and since this study was initiated, the cytology reporting form has changed to form HMR 101/5 (1989). The working party of the British Society for Clinical Cytology recommended that simple inflammatory changes need not be reported,⁷ but severe inflammatory changes may now

be reported to box 21 (cytology report) or as borderline changes; the management suggested is either to repeat the smear in so many months or to repeat after treatment when trichomonas, candida, or gardnerella have been identified. It is important to remember that *C trachomatis* has no specific cytological features other than inflammatory changes⁸ and may coexist with these infections.

It is obviously impractical to suggest that all premenopausal women with one smear showing inflammatory changes be referred to a department of genitourinary medicine or a colposcopy clinic. These already overstretched clinics would be unable to cope with the increase in patients. We suggest that women with one such smear who are under 25 or have recently changed sexual partner should be referred to a department of genitourinary medicine because of the risk of a sexually transmitted infection being present.

Most doctors now follow the recommendations of the British Society for Clinical Cytology working party and refer women with inflammatory changes on two consecutive smears to a colposcopy clinic.⁹ Most departments of genitourinary medicine now perform colposcopic examinations, and perhaps such patients should be referred there for both colposcopy and infection screening. Alternatively, when patients are seen at a colposcopy clinic we suggest taking, as a minimum, endocervical swabs for gonorrhoea and chlamydia in addition to colposcopy to exclude other readily treatable causes of inflammatory changes on a smear.

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Intravenous use of slow release morphine sulphate tablets

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Slow release morphine sulphate tablets are given to relieve severe pain and are prescribed for treatment at home. Misuse of this drug may have similar implications for prescribers to those reported for other drugs such as temazepam, buprenorphine, and cyclizine. Buprenorphine is reported to be the preferred drug of over half of intravenous drug users in contact with drug services in eastern Glasgow, and this figure rises to 69%

when use of buprenorphine in combination with other drugs such as temazepam is included.¹ We could not find any reports on intravenous misuse of slow release morphine sulphate tablets or on the amount of morphine that can be extracted from them. We report three cases of such misuse by people who obtained the drug on prescription or "on the street," and the results of our reproduction of the extraction procedure.

Case reports, method, and results

Case 1—A 26 year old man with a six year history of dependence on opiates presented after his use of opiates had increased over three months. He had progressed from oral to intravenous use and was using slow release morphine sulphate tablets, which he