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Management guidelines for women with normal colposcopy after low grade cervical abnormalities: population study

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Abstract

Objectives To develop an evidence based protocol for the follow up of women with low grade cervical abnormalities for whom treatment is not immediately indicated.
Design Population outcome study.
Setting Colposcopy clinic of an inner city teaching hospital.
Participants 566 women with low grade cytological abnormalities who were not treated at a first visit to the colposcopy clinic, followed up for a total of 881 years.
Main outcome measures Resolution of abnormalities, persistence of disease, and treated disease.
Results Abnormalities resolved in 306 (54.1%) women, whereas 138 (24.4%) had persistent disease and 122 (21.5%) were subsequently treated. Colposcopic opinion, smear test results, age, smoking history, and number of pregnancies were all significantly related to outcome. Logistic regression analysis produced a model that correctly identified 70% of women whose abnormalities resolved. Only 23 of 295 women (7.8%) with a normal cervix on colposcopy and a smear without dyskaryosis at a first visit were treated by the end of the observation period.
Conclusions Women referred with low grade cytological abnormalities who have a normal cervix on colposcopy and a negative or borderline repeat smear test result may be discharged from the colposcopy clinic. We propose a follow up protocol that could safely avoid unnecessary visits to a clinic.

Introduction

The national cervical screening programme detects over 250 000 women with mild or borderline abnormalities each year.[1] Present guidelines recommend referral for colposcopy after detection of three borderline and two mild abnormalities.[2] In over 50% of women these referrals are associated with a normal cervical transformation zone on colposcopy.[3] Women with a normal cervix may be suitable for discharge, but the safety of such a policy is uncertain. Those with a low grade lesion may be suitable for surveillance by repeated attendance at a clinic, aimed at monitoring the abnormalities in the hope that they resolve.[4–8] Attendance at a colposcopy clinic, however, is a likely cause of significant anxiety.[9] Owing to a paucity of data there are currently no nationally agreed guidelines on the management of women with low grade cytological abnormalities whose findings on colposcopy do not warrant immediate treatment. We aimed to identify factors that determine clinical outcome in such women to predict those who could be discharged to community follow up.

Participants and methods

Colposcopy clinic

The colposcopy clinic at City Hospital, Birmingham is permanently staffed by four consultants and two nurse colposcopists, along with trained research and academic staff. The clinic operates a selective treatment policy, which aims to treat all patients with high grade disease detected by cytology or colposcopy and to minimise intervention in those with low grade disease or no abnormalities; otherwise women undergo surveillance every six months until they have two consecutive negative smear results and colposcopic assessments, which result in discharge back to community care.

Dataset details

Data on patients attending the colposcopy clinic are collected and stored on a customised database (Microsoft Access). The data include both personal details and those related to visits. We identified patients eligible for inclusion in our study on the basis of several criteria: no smear test result worse than mild dyskaryosis before referral; date of the first recorded cytological abnormality available; not treated at the first visit to the colposcopy clinic (no suspicion of high grade disease or worse at the first colposcopic assessment); no history of treated or untreated cervical intraepithelial neoplasia; not pregnant at the time of the first assessment; not known to be unavailable for colposcopy at follow up; a minimum of two visits to the colposcopy clinic; and smoking history available.

Overall, 577 women referred between October 1986 and January 1997 fulfilled these criteria. These women were separated into four groups according to clinical

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Table 1 Patient characteristics. Values are numbers (percentages) or medians (interquartile ranges)

	Disease outcome			
	Resolved (n=306)	Persisted (n=138)	Treated (n=122)	Total
Smoker:				
No	211 (59)	81 (22)	68 (19)	360
Yes	95 (46)	57 (28)	54 (26)	206
Colposcopic opinion:				
Normal	253 (60)	103 (25)	63 (15)	419
Abnormal	53 (36)	35 (24)	59 (40)	147
Smear test result on first visit:				
No dyskaryosis	238 (66)	76 (21)	49 (13)	363
Dyskaryosis	68 (34)	62 (30)	73 (36)	203
Smear test result on referral:				
Borderline	144 (64)	50 (22)	30 (14)	224
Mild	162 (47)	88 (26)	92 (27)	342
Age (n=564)	35 (27-45)	30 (24-39)	30.5 (24-36)	32 (26-42)
No of pregnancies (n=562)	2 (1-3)	1 (0-3)	2 (1-4)	2 (1-3)
No of live births (n=562)	2 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
No of months followed up	14 (8-20)	19 (13-31)	19.5 (12-28)	17 (10-24)
No of visits	3 (2-3)	3.5 (3-5)	4 (3-5)	3 (2-4)

outcome. The persisted disease group comprised women (138 participants) who had persistent abnormalities on colposcopy or cytology that fell short of the criteria to treat (evidence of high grade disease). The resolved disease group comprised women (306) who had not been treated and who had had two consecutive negative results on colposcopy and cytology. The treated group comprised women (122) who had been treated. The non-confirmed group comprised women[11] who had only one negative result, but as they could not be confirmed as having disease that either resolved or persisted according to our own stringent definition, we excluded them from the analysis.

We examined and compared data for the 566 women in the persisted, resolved, and treated groups (table 1). Colposcopic opinion was graded as normal or abnormal ("warty atypia" or grades of cervical intraepithelial neoplasia). Age was calculated as that at the first visit. Initial analysis indicated that the outcome for women with borderline or negative smear test results at a first visit was similar. They were combined as showing "no dyskaryosis" to distinguish them from those smears on a first visit showing definite dyskaryosis.

A second set of data was collected from 87 women from the Birmingham Women's Hospital between January 1997 and January 1998. The information collected for each patient was identical except for the exclusion of the smear test result leading to referral, parity, and total number of visits (although total time being followed up was available).

Statistical analysis

To identify associations in the data, we used Pearson's χ^2 test for categorical variables. The non-parametric Wilcoxon two sample test was used to compare continuous measurements. We calculated odds ratios to determine the association between exposure to risk factors and outcome. Odds ratios, adjusted for all other predictive variables, were derived from logistic regression analyses. Patients in the persisted disease and treated groups were combined to devise a logistic regression model to "predict" those whose disease would resolve. All data from the first visit to the clinic were considered in the logistic regression analysis (year of first visit, smoking history, colposcopic opinion, smear test results of first visit and referral, age, number of pregnancies, parity). The year of the first visit to the clinic was included in an attempt to account for the influence of changes in practice over the 11 years of the study. Stepwise logistic regression analyses were carried out with a 5% significance level to determine independent factors for prediction of those women whose abnormalities would resolve. We calculated the accuracy of the model and its sensitivity, specificity, proportion of false positives and negatives, and overall percentage of correct predictions. The probability cut-off point was chosen to balance sensitivity and specificity and to minimise false positives. This model was then applied to the second dataset. The parameter estimates of all five variables were recalculated and the fit of the model to the new dataset assessed and presented. Data were analysed with SAS statistical software (SAS Institute, NC).

Results

Overall, 566 women were followed up for a median of 17 months. They attended a colposcopy clinic on average three times, representing 881 total years of follow up. Overall, 138 women (24.4%) had persistent disease, 122 (21.5%) were treated, and 306 (54.1%) had abnormalities that resolved. Univariate analysis of personal details and those related to the first visit showed that older, non-smoking women with a normal colposcopic opinion, borderline smear test result on referral, and a non-dyskaryotic smear test result on a first visit had a significantly better chance of being in the resolved disease group (table 2). The final logistic regression model was derived from 560 patients with complete data, 304 of whom were in the resolved disease group (table 3).

Table 2 Univariate analysis of disease outcome. Values are numbers or medians (interquartile ranges)

	Disease outcome		
	Persisted or treated (n=260)	Resolved (n=306)	Significance
Smoker:			
No	149	211	0.61 (0.43 to 0.85)**†
Yes	111	95	
Colposcopic opinion:			
Normal	166	253	0.37 (0.25 to 0.55)***†
Abnormal	94	53	
Smear test result on first visit:			
No dyskaryosis	125	238	0.27 (0.18 to 0.38)**†
Dyskaryosis	135	68	
Smear test result on referral:			
Borderline	80	144	0.50 (0.35 to 0.71)***†
Mild	180	162	
Age (n=564)	30 (24-37)	35 (27-45)	–4.26**†
No of pregnancies (n=562)	2 (0-3)	2 (1-3)	–1.34‡
No of live births (n=562)	1 (0-3)	2 (0-3)	–2.18‡
No of months followed up	19 (13-30)	14 (8-20)	7.05**‡
No of visits (n=565)	4 (3-5)	3 (2-3)	8.04**‡

**P<0.01; ***P<0.001.
†Odds ratio (95% CI); χ^2 test.
‡Wilcoxon test.

The analysis identified the grade of the smear test result on a first visit as the single most important predictor of resolved disease, women with dyskaryosis having a reduced odds of resolved disease. The other significant predictors of resolved disease were a normal colposcopic opinion, increased age, fewer pregnancies, and not smoking. Using a probability threshold of P = 0.56, our model correctly predicted 70% of those in the resolved disease group and 65% of patients in the treated and persisted disease groups. Overall, our model correctly identified 378 women (68%). Of the 91 patients with disease incorrectly predicted to resolve (30% false positive rate), 64 had persistent low grade disease and 27 were treated. Only five of the treated women had high grade disease; the earliest (cervical intraepithelial neoplasia grade 2) was detected at 15 months, which was preceded by a high grade smear test result.

Table 4 shows the influence of a smear test result on first visit and colposcopic opinion on outcome. Only 23 of the 295 women (7.8%) with a normal cervix on colposcopy and a negative or borderline smear test result on a first visit underwent treatment by the end of the observation period, but they attended 947 clinic visits. Only six of these women had high grade disease: two were detected at 17 months and the others at 27, 32, 41, and 45 months. Twelve of the 23 women were treated purely because they had persistent low grade abnormalities on smear tests for over three years.

Table 4 Influence of smear test result on first visit to clinic and colposcopic opinion on outcome. Values are numbers (percentages)

Smear result and colposcopic opinion	Disease outcome			Total
	Persisted	Resolved	Treated	
Dyskaryosis:				
Normal	41 (33)	43 (35)	40 (32)	124
Abnormal	21 (27)	25 (32)	33 (42)	79
No dyskaryosis:				
Normal	62 (21)	210 (71)	23 (8)	295
Abnormal	14 (21)	28 (41)	26 (38)	68

The logistic regression model (table 3) was then validated on the second set of data (table 5). As this dataset represents women referred more recently than that analysed for City Hospital, the validation set has a shorter duration of follow up (average nine months). Despite this, the overall proportion of patients correctly identified by our model increased to 82%, with high sensitivity (82%) and specificity (81%) and reduced rates for false positives (16%) and false negatives (21%). The three most important variables for prediction of resolved disease remained significant when applied to the validation data: smear test on first visit (P < 0.001), colposcopic opinion (P = 0.001), and age (P = 0.037). Number of pregnancies and smoking history become non-significant.

Discussion

Women with low grade cytological abnormalities on cervical smear tests who have a normal cervix on colposcopy may be safely discharged from the clinic and followed up in the community. As far as we are aware this is the first study to specifically analyse this group of women, whose management has yet to be included in the guidelines of the NHS cervical screening programme. By definition the dataset we analysed was highly selected but the entry criteria were rigid, resolution of disease only being accepted on the basis of two consecutive negative results on colposcopy and cytology. The number of low grade abnormalities before colposcopic assessment is unclear because the referral criteria in our area changed during the 11 years of the study. An undetermined number of women with normal results on colposcopy at a first visit represent false positive referral cytology. We made no attempt to identify those by reviewing the referral cytology, as exclusion from the analysis would make the dataset unrepresentative of patients attending other clinics and therefore would not be pragmatic. Inclusion of false positives in the referral population is unavoidable at present.

Resolution of abnormalities occurred in over 50% (306) of women but took up to 46 months, and in total the women had to attend over 900 appointments. From a logistic regression analysis we produced a model with a 70% chance of correctly predicting a woman at a first visit to a clinic whose disease would resolve. Of the 30% of women with abnormalities that were incorrectly predicted to resolve, only five had high grade disease, the earliest diagnosed at 15 months and preceded by a smear test result suggesting high grade disease. Therefore those women in whom abnormalities had been incorrectly predicted to resolve would have come to no harm if they had been followed up at a later stage rather than by colposcopy every six months. Our model had improved sensitivity and specificity when applied to the second dataset. This validation was, however, limited by utilising data with a

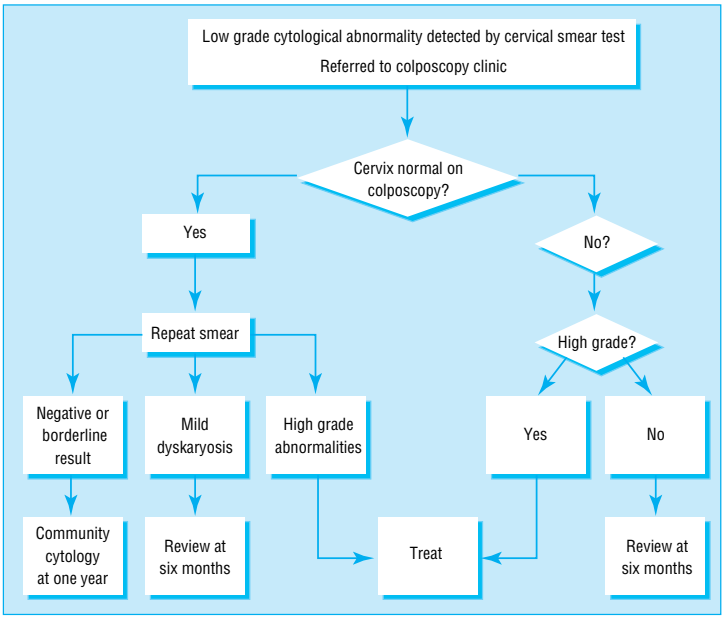
Table 3 Logistic regression model for prediction of resolved disease

Variable	Level	β	P value	Odds ratio (95% CI)
Intercept	—	0.68	0.128	—
Smear test result on first visit	No dyskaryosis *v* dyskaryosis	–1.22	<0.001	0.30 (0.20 to 0.43)
Colposcopic opinion	Normal *v* abnormal	–0.58	0.007	0.56 (0.36 to 0.85)
Age	Continuous	0.03	0.001	1.03 (1.01 to 1.05)
No of pregnancies	Continuous	–0.12	0.020	0.89 (0.80 to 0.98)
Smoking history	Never smoker *v* ever smoker	–0.41	0.035	0.67 (0.46 to 0.97)

Model accuracy: 68% correct; sensitivity 70%; specificity 65%; false positive rate 30%; false negative rate 36%.

Table 5 Patient characteristics of second (validation) dataset. Values are numbers (percentages) or medians (interquartile ranges)

	Disease outcome			Total
	Resolved (n=46)	Persisted (n=16)	Treated (n=25)	
Smoker:				
No	30 (57)	9 (17)	14 (26)	53
Yes	16 (53)	5 (17)	9 (30)	30
Colposcopic opinion:				
Normal	45 (67)	14 (21)	8 (12)	67
Abnormal	1 (5)	2 (10)	17 (85)	20
Smear test result on first visit:				
Negative	35 (83)	3 (7)	4 (10)	42
Mild or moderate	11 (24)	13 (29)	21 (47)	45
Age	33 (27-40)	31 (21-36)	26 (22-40)	32 (23-40)
No of pregnancies	2 (0-3)	0.5 (0-3.5)	1 (0-2)	1 (0-3)
No of months followed up	9.5 (5.5-12.5)	8 (8-12)	8 (3-10)	9 (4.5-12)



Follow up protocols after referral to colposcopy clinic with low grade cytological abnormalities

shorter duration of follow up and from a nearby hospital where clinical practice may reasonably be expected to be similar. Further validation on data from another region would be worthwhile.

Only 7.8% of the 295 women with normal colposcopy and a non-dyskaryotic repeat smear test result underwent treatment during the observation period, yet they attended the clinic a total of 947 times. Most of these visits were unnecessary. Discharging such women back to their doctor for follow up cytology would avoid the anxiety of attending a clinic and would have financial benefits. Attendance at a colposcopy clinic costs about £150. Assuming that all those women (134 participants) with negative cytology results within 12 months attended the clinic only once and the rest were seen at 12 months and their management remained otherwise the same, 459 appointments would have been avoided saving £68 850. This value underestimates the savings by exaggerating the number of women who would have required further attendance at a clinic. Of more importance is the anxiety that could be avoided. A visit to a colposcopy clinic can produce more anxiety than a major surgical procedure.[9] This does not imply that this group has no risk of developing cervical cancer. It is likely, however, that they would be at less risk than women treated for high grade cervical intraepithelial neoplasia who are routinely discharged to community care after a normal follow up smear test result. Such women, however, have a 3-5 times higher risk of cervical cancer than the general population.[10] Follow up protocols for women with negative colposcopy results based on the result of the repeat smear test are proposed in the figure. The safety of this protocol should ideally be tested with a randomised controlled trial, but the frequency of untoward events is likely to be so low as to make this impractical. Mitchell et al have previously shown the reliability of negative colposcopy results.[11] Our study further highlights the clinical potential of a normal result on colposcopy after detection of low grade cytological abnormalities.

What is already known on this topic

The optimal management of women with low grade cytological abnormalities whose findings on colposcopy do not warrant immediate treatment is unclear

Colposcopic surveillance is often undertaken, but the efficacy of this policy is unknown

What this study adds

Women who have a normal cervix on colposcopy and a negative or borderline smear test result on a first visit to a clinic may be safely discharged back to the community for cytological assessment rather than making repeated stressful and unnecessary visits to a colposcopy clinic

Such a policy would reduce the costs of the screening programme as a whole

Contributors: GT analysed and interpreted the data, participated in the statistical analysis, and wrote the manuscript; he will act as guarantor for the paper. DDM analysed the data, undertook the statistical analysis, and contributed to the writing and editing of the manuscript. CHM collected, stored, and interpreted the second dataset, discussed core ideas, and edited the manuscript. DML established the clinical database at City Hospital, initiated the study, retrieved the dataset, directed the analysis, discussed the analysis, and edited the manuscript.

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Endpiece

Amusing the patient

The art of medicine consists in amusing the patient while Nature cures the disease.

Voltaire