

The Management Dilemma of the Mildly Abnormal Smear: Fact or Fiction?

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Abstract

For at least 10 years, there has been much controversy regarding the management of women presenting with a first mildly dyskaryotic cervical smear. Argument has centred on many key issues, including the risk of progression to more serious disease, the anxiety caused to the patient, the risk of overtreating patients with minor disease and, more recently, the financial implications of prompt intervention and treatment. Essentially, it has been established for many years that only two main management options are appropriate. The first is a policy of referring all patients with mild dyskaryosis for prompt colposcopy and intervention. The second option is to keep such patients under cytological surveillance, with recourse to colposcopy only if the lesion persists or progresses on subsequent cytological screening. This review article aims at appraising the evidence that is currently available in an attempt to try and resolve the management dilemma posed by a mildly abnormal smear.

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Introduction

Carcinoma of the cervix is still a relatively common gynaecological malignancy. However, despite being potentially preventable it still claims the lives of many women even in those countries where organised screening programmes exist. Such programmes aim to detect the disease at the premalignant stage of cervical intraepithelial neoplasia (CIN). In the United Kingdom (UK) for example, the screening programme was introduced in 1964. Twenty-five years later 4.5 million smears are being taken annually, 200 000 of which are reported as abnormal. These abnormalities can range from borderline changes to evidence of invasive disease, and all these results require further action.

Where active screening programmes are in existence, mild dyskaryosis is a particular smear abnormality which attracts much attention. This is because of the controversy surrounding the management of women with this type of smear abnormality. In United Kingdom laboratories some 130 000 smears annually are reported as showing mild dyskaryosis and this represents a serious clinical dilemma as well as an important practical problem.

Why the Controversy?

The problem with mild dyskaryosis is that, in contrast to moderate or severe dyskaryosis, there is a feeling of uncertainty about its clinical significance. It is accepted

that women with moderate and severe dyskaryosis should be referred to colposcopy on the grounds of high risk of underlying severe disease, yet mild dyskaryosis appears to be prognostically vague. This has resulted in the employment of two possible management options; immediate referral for colposcopy or continued cytological surveillance. The fact that there is still no universally agreed management policy results mainly from uncertainty about the relationship between the cytological diagnosis and grade of co-existing CIN on the cervix. For example a woman with mild dyskaryosis may already have severe underlying disease or she may be at risk of developing severe disease later, or indeed she may have disease that is destined to regress spontaneously.

Adding to the difficulty of interpreting the significance of mild dyskaryosis is the fact that until recently there was no standardised cytological reporting system practised in the UK, and therefore diagnosing lesser degrees of cytological abnormality with confidence was difficult. Recent National Health Service guidelines¹ have tried to standardise the reporting of lesser smear abnormalities but the problem is far from resolved. There is also a similar difficulty in reporting mild histological abnormalities obtained from colposcopy biopsies, and this results in a low level of repeatability in the histological grading system for CIN (worse for low grade disease) whether by the same or different observ-

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ers.² To further complicate the situation there is confusion over the significance of human papillomavirus (HPV) in interpreting mild cytological or histological abnormalities in terms of the risk of disease progression.³ Finally this uncertainty over the natural history of mildly dyskaryotic smears in a background of balancing risks and benefits of the two management options completes the clinician's dilemma.

What are the Facts?

To help clarify the dilemma it is possible to review the advantages and disadvantages of both management options. The debate centres upon whether there should be immediate referral for colposcopy and treatment or whether there should be a programme of regular repeat smears with referral for colposcopy only if the smear abnormality persists. Essentially the arguments in favour of colposcopy and intervention are as follows. Firstly, colposcopy offers a prompt accurate diagnosis of CIN. Secondly it reduces the time scale over which CIN lesions may progress during repeat cytology. Thirdly, colposcopy can detect disease missed by cytology including those cases where there is poor patient compliance.

The arguments in favour of cytology follow up include the fact that a large proportion of women with mild dyskaryosis will have disease regression without treatment. Colposcopy is more expensive than cytology and requires special training and clinics. There is also the question of colposcopy causing much patient anxiety as well as exposing the women to the risk of over-treatment and cervical damage. Cervical stenosis may lead to difficult smear taking and there are implications with regard to infertility.

The debate regarding whether colposcopy or cytological surveillance is the management of choice still continues, yet with all the recently published reports it would seem reasonable that this issue could be resolved. The question of how mild dyskaryosis relates to the grade of underlying CIN appears to be the central issue followed closely by the problem of quantifying the risk of disease progression of CIN to cancer. A review of the literature reveals the following facts about the management of mild dyskaryosis which may help answer the problem.

The Malignant Potential of Mild Dyskaryosis is Low

The majority of women with mild cytological abnormalities are at low risk of progressing to higher grade disease.⁴ Furthermore the risk of developing cancer in women with mild dyskaryosis where subsequent smears have reverted to normal is very low. Robertson et al⁵ have reviewed smears from women with cervical cancer to find no evidence that mild dyskaryosis was a forerunner to invasive disease.

Large CIN Lesions are Detected by Cytological Surveillance

Lesion size appears important in correlating the smear result with histologically confirmed abnormality. The larger the size of the lesion the more likely it is to be detected by cytological surveillance.⁶ Furthermore persistent false negative results in cytological surveillance in the presence of large lesions are extremely rare. A larger lesion is more likely to show better correlation between smear cytology and biopsy histology and is also likely to have greater progressive potential.⁷⁻⁹

Mild Dyskaryosis Can Regress Spontaneously

Between a third and a half of all women with mild dyskaryosis will have a persistence of cytological abnormality resulting in referral for colposcopy while the remainder will have repeat smears that will return to normal without treatment.¹⁰ The important question is "What proportion of women with subsequent normal cytology are still harbouring clinically significant large high grade lesions?"

Cytological Surveillance Results in a Higher Yield of Disease at Colposcopy

Women with persistent smear abnormality on follow up of mild dyskaryosis are found on colposcopy to have a high chance of having CIN 3. This contrasts with the relatively low yield of high grade CIN found after referring for colposcopy immediately after the first mildly dyskaryotic smear.^{11,12}

Prompt Colposcopy Referral Results in Over-treatment

Referral for colposcopy and intervention following a first mildly dyskaryotic smear results in over-treatment.¹³ Given that a proportion of CIN lesions regress spontaneously without treatment, it is obvious that a blanket referral for colposcopy will result in women presenting with visible lesions that will get treated. As little as 20% of women referred will have CIN 3 and a similar proportion will have no visible lesion anyway.¹²

Colposcopy Causes More Patient Anxiety

The majority of women having colposcopy experience great anxiety¹⁴ and recent evidence concerning mild dyskaryosis has shown that colposcopy causes greater anxiety than cytological surveillance.¹⁵ The psychological problems associated with referral for colposcopy and the anxiety about further treatment may well outweigh the risk of the patient having significant disease. Some gynaecologists believe that a certain element of anxiety is necessary to encourage women to attend follow up whilst others will say that unnecessary anxiety is no substitute for better patient education (particularly as up to 40% of women with mild dyskaryosis think they have got cancer).

Another aspect of anxiety which is important concerns one major disadvantage of early colposcopy referral, namely the introduction of see-and-treat clinics. This policy has been encouraged partly as a result of the availability of large loop excision biopsy of the transformation zone. One large study reported that 27% of women had no abnormality or just koilocytotic atypia on biopsy obtained by loop excision.¹⁶ There is an argument that too many women are being exposed to high levels of anxiety in the absence of any disease being found. This situation is more significant given the well recognised complications of loop excision biopsy such as secondary haemorrhage, cervical stenosis and psychosexual morbidity.

Colposcopy is More Expensive than Cytology

A procedure associated with the use of special training and equipment is bound to be more expensive than the simple taking of a cervical smear. Colposcopy itself generates follow up smears and this can lead to more colposcopies. Published reports comparing the cost of colposcopy with that of cytological surveillance are scarce. An American paper quoted the cost of colposcopy including the evaluation and treatment of women with lesser smear abnormalities as ranging from 632 million to 1.5 billion dollars annually.¹⁷

A direct comparison of costs¹⁸ has shown that the extra cost of colposcopy was surprisingly small. The marginal cost of colposcopy in terms of detecting those CIN 3 lesions which would have been missed by cytology was approximately 300 pounds per case of CIN 3 detected.

Prospective Randomised Trials are Needed

The only objective way for deciding which management option to use is by prospective randomised controlled trials. For at least 10 years there have been calls for such studies and to date none has been universally successful. One such study has been reported by Flannelly et al¹⁹ and although this dealt with both mild and moderate dyskaryosis they concluded that cytological surveillance was safe. They also suggested that cytology was not efficient, but there was little evidence in their report to support this conclusion.²⁰

Poor Patient Compliance Undermines Cytological Surveillance

Loss of patient follow up is a serious flaw in cytological surveillance and this important point is often raised as an argument in favour of colposcopy. A proportion of women under follow up, whether it be cytology or colposcopy will eventually default. Even in Flannelly's study where intensive efforts were made to maintain follow up there was a high default rate. This increased with length of cytological surveillance from 10% at 6 months to 23% at 24 months. Going one step further

there is the fact that a large majority of invasive cancers are contracted by women who have never been screened or have been infrequently screened.²¹

Invasive Disease is Impossible to Predict

At present it is not possible to predict which women with an untreated mild smear abnormality will progress to invasive cancer. If the answer to this question was known the debate would be very close to resolution. Increasing evidence implicates certain subtypes of human papillomavirus as causing cervical cancer. The different strains of HPV identified also vary in their oncogenic potential. Research has been directed at finding the "higher risk viruses" on cervical cytology. HPV 16 and 18 are present in over 80% of invasive squamous cancers and CIN 3 lesions.^{22,23}

Other workers have attempted to look for other clinical variables which may help predict high risk patients with mild dyskaryosis. Luesley et al²⁴ reported that cigarette smoking was a powerful independent predictor of high grade CIN in women with mild dyskaryosis. This finding was challenged by workers²⁵ who found that no single clinical variable was of help in predicting high grade CIN in patients with mild dyskaryosis. Interestingly, a large recent study has shown that it is not possible to identify the majority of women with cervical abnormality by using a detailed risk factor profile.²⁶

What is the Solution?

Taking everything into consideration any solution which is put forward must have provisos. With the evidence that is currently available there would appear to be no place for a blanket referral policy advocating colposcopy for all women with a first mildly dyskaryotic smear. Such a policy incurs more expense and is emotionally traumatic for the patient. In addition colposcopy only provides a marginal reduction in invasive cancer with an increased number of often unnecessary colposcopies.²⁷

Cytological surveillance is generally safe (particularly with three smear follow up), but does require some provisos before it can be recommended as a better alternative to colposcopy. Patient compliance is a key issue and defaulting patients, once identified, should be offered colposcopy. Studies of populations where patient compliance is good as a result of vigorous clinical follow up have shown that cytological surveillance is safe. For example, in the North Buckinghamshire study¹² no patient with mild dyskaryosis developed invasive cancer after a follow up period ranging from approximately 24 to 36 months. The safety of cytological surveillance depends on the performance of the individual laboratories which should carefully audit their own performance to secure a good correlation between cytology report and grade of CIN found on biopsy.²⁸ They may also

choose to alter the level of surveillance. For example, in North Buckinghamshire it was shown that a policy of requiring 3 negative repeat smears before discharging the patient offered a level of safety better than that of only 2 repeat smears.

The current guidelines by the NHSCSP¹ in the UK suggest that cytological surveillance should be the management option for mild dyskaryosis with recourse to colposcopy if there is persistence or progression of the cytological abnormality. Interestingly the guidelines also show a certain lack of commitment by stating that immediate colposcopy referral may be indicated at the discretion of the individual clinician.

Conclusion

Due to the complexity of the argument only a guarded conclusion may be reached given the current state of knowledge. Until a randomised, multi-centre, prospective, controlled trial has shown colposcopy to have a significantly greater advantage over cytological surveillance in identifying high grade CIN in women with a first mildly dyskaryotic smear, it would appear that cytology is the management of choice. It seems that colposcopy cannot be justified in terms of clinical needs and cost, including cost to the patient. However, cytological surveillance is labour intensive and may need to be tailored to the needs of the local population. Some women will still require prompt colposcopy on the grounds of poor compliance. Compliance could be significantly improved with better patient education aimed at eradicating the fear of cancer in so many women. There is also the possibility that cytological screening may become more sensitive. For example, other means of predicting high grade CIN from smear material will help develop a better referral policy for colposcopy and it is quite likely that HPV typing will have a significant role.²⁹

Given the above, does managing mild dyskaryosis still pose a management dilemma? At the recent conference for the British Society of Colposcopy and Cervical Pathology the agenda once again included intense discussion aimed at attempting to resolve the problem. Despite a detailed current literature review no consensus was reached. However, one important consideration appears to have escaped attention and may offer a solution.³⁰ It is known that for a given population of women presenting with mild dyskaryosis cytological surveillance will result in a certain proportion of them needing colposcopy as a result of persistent smear abnormality. Current data suggests that approximately two thirds of women will eventually have colposcopy, particularly if surveillance is intense.¹² Assuming that the quality of cytological surveillance continues to improve as a result of the implementation of National guidelines and better screening tools then the proportion of women being referred

for colposcopy will increase still further. It is quite possible that the vast majority of women under cytological surveillance will eventually end up having a colposcopy anyway.

Individual hospitals can resolve the dilemma regarding their management option for mild dyskaryosis by carefully auditing the proportion of women eventually requiring colposcopy. Ideally a nationwide data collection should be undertaken and if this shows that most women eventually need colposcopy we shall suddenly find ourselves with nothing left to argue about.

REFERENCES

1. Cervical Screening. UK: NHSCSP Publication No. 7, 1997.
2. Robertson A J, Anderson J H, Swanson Beck J, Burnett R A, Howatson S R, Lee F D, et al. Observer variability in histopathological reporting of cervical biopsy specimens. *J Clin Pathol* 1989; 42:231-8.
3. Richart R M, Wright T C. Controversies in the management of low-grade cervical intraepithelial neoplasia. *Cancer* 1993; 71:1413-21.
4. Smith A, Elkind A, Eardley A. Making cervical screening work. *BMJ* 1989; 298:1662-4.
5. Robertson J H, Woodend B, Elliott H. Cytological changes preceding cervical cancer. *J Clin Pathol* 1994; 47:278-9.
6. Jarmulowicz M R, Jenkins D, Barton S E, Goodall A L, Hollingworth A, Singer A. Cytological status and lesion size: a farther dimension in cervical neoplasia. *Br J Obstet Gynecol* 1989; 96:1061-6.
7. Walker E M, Dodgson J, Duncan I D. Does mild atypia on a cervical smear warrant further investigation? *Lancet* 1986; 3:376-88.
8. McIndoe W A, Mclean M R, Jones R N, Mullins P R. The invasive potential of carcinoma in situ of the cervix. *Obstet Gynecol* 1984; 64:451-9.
9. Tilbury P, Singer A, Jenkins D. CIN 3: the role of lesion size in invasion. *Br J Obstet Gynecol* 1992; 99:583-6.
10. Robertson J H, Woodend B E, Grazier E H, Hutchinson J. Risk of cervical cancer associated with mild dyskaryosis. *BMJ* 1988; 297:18-21.
11. Austoker J. Screening for cervical cancer. *BMJ* 1994; 309:241-8.
12. Jones M H, Jenkins D, Cuzick J, Wolfendale M R, Jones J J, Balogun-Lynch C, et al. Mild cervical dyskaryosis: safety of cytological surveillance. *Lancet* 1992; 339:1440-3.
13. Shafi M I. Management of women with mild dyskaryosis. *BMJ* 1994; 309:590-1.
14. Posner T, Vessey M. Prevention of cervical cancer: the patient's view. London: Kings Fund, 1988.
15. Jones M H, Jenkins D, Singer A. The mildly dyskaryotic smear: is patient anxiety related to choice of management? *J R Soc Med* 1996; 89:257-60.
16. Luesley D M, Cullimore J, Redman C W, Lawton F G, Emens J M, Rollason T P, et al. Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. *BMJ* 1990; 300:1690-3.
17. Sedlacek T V. Clinical options in dealing with minor cytologic abnormalities. *The Colposcopist* 1992; 14:1-2.
18. Jones M H, Jenkins D, Singer A. The cost of detecting high grade precancer in women with mild dyskaryosis—a cost minimisation analysis. Paper presented at the British Society of Colposcopy and Cervical Pathology Annual Meeting; 1997 April; Glasgow.
19. Flannelly G, Anderson D, Kitchener H C, Mann E M, Campbell M, Fisher P, et al. Management of women with mild and moderate cervical dyskaryosis. *BMJ* 1994; 308:1399-403.
20. Jones M H, Jones J J. Colposcopy is not cost effective [letter]. *BMJ* 1994; 309:268.
21. Macgregor J E, Campbell M K, Mann E M F, Swanson K Y. Screening for

- cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. *BMJ* 1994; 308:1407-11.
22. Bavin P J, Giles J A, Deery A, Crow J, Griffiths P D, Emery V C, et al. Use of semi-quantitative PCR for human papillomavirus DNA type 16 to identify women with high grade cervical disease in a population presenting with a mildly dyskaryotic smear report. *Br J Cancer* 1993; 67:602-5.
 23. Cuzick J, Terry G, Ho L, Hollingworth T, Anderson M. Type-specific human papillomavirus DNA in abnormal smears as a predictor of high-grade cervical intraepithelial neoplasia. *Br J Cancer* 1995; 71:206-9.
 24. Luesley D, Blomfield P, Dunn J, Shafi M, Chenoy R, Buxton J. Cigarette smoking and histological outcome in women with mildly dyskaryotic cervical smears. *Br J Obstet Gynecol* 1994; 101:49-52.
 25. Jones M H, Jones J J, Jenkins D. Cigarette smoking and histological outcome in women with mildly dyskaryotic cervical smears. *Br J Obstet Gynecol* 1994; 101:927-8.
 26. Blomfield P I, Lancashire R J, Woodman C B J. Can women at risk of cervical abnormality be identified? *Br J Obstet Gynaecol* 1998; 105:486-92.
 27. Sherlaw-Johnson C, Gallivan S, Jenkins D, Jones M H. Cytological screening and management of abnormalities in prevention of cervical cancer; an overview with stochastic modelling. *J Clin Pathol* 1994; 47:430-5.
 28. Jones M H, Jenkins D, Singer A. Regular audit of colposcopic biopsies from women with a mildly dyskaryotic or borderline cervical smear results in fewer cases of CIN 3. *Cytopathology* 1996; 7:17-24.
 29. Herrington C S, Evans M F, Haliham F M, Gray W, McGee J. Human papillomavirus state in the prediction of high-grade cervical intraepithelial neoplasia in patients with persistent low-grade cervical cytological abnormalities. *Br J Cancer* 1995; 71:206-9.
 30. Jones M H. The management dilemma of mild dyskaryosis [letter]. *Cytopathology* October 1998 (In press).