Cervical cancers diagnosed after negative results on cervical cytology: perspective in the 1980s

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Abstract

Objectives—To assess the magnitude of the problem of interval cancers of the cervix (those that are diagnosed within a short time after negative screening test results) in the 1980s, to compare the nature of interval cancers in younger women with that in older women, and, by reviewing negative cervical smears, to determine the proportion of interval cancers that might represent the development of malignancy anew compared with the proportion that might be associated with difficulties in sampling or errors in reporting.

Design—An audit of the interval cases of cervical cancer that had been diagnosed within 36 months of a smear having been reported as negative by the Victorian Cytology Gynaecological Service among women registered with cervical cancer during 1982-6.

Setting—The Victorian Cytology Gynaecological Service, a free public sector cytology laboratory in Victoria, Australia.

Subjects—138 Women, all of whom had had cervical cancer diagnosed during the 36 months after having had a negative cervical smear. Subjects were divided into two age groups: younger women, aged <35; older women, aged 35-69.

Interventions—Negative slides were reviewed for evidence of optimal sampling and for the presence of cellular abnormalities that had been missed at the time of the original reporting.

Main outcome measures—The number of interval cases of cancer of the cervix registered during 1982-6. The proportion of interval cases occurring in younger women and the proportion occurring in older women. Division of women into three risk categories based on clinical history and screening history that broadly corresponded to the probability that a diagnosis of cervical cancer might be expected during the 36 months after the issuing of a negative smear report.

Results—138 Of 1044 (13·2%) women who had been registered with cervical cancer during 1982-6 had had one or more negative smears during the 36 months preceding the diagnosis of cancer. Interval cancers comprised a larger proportion of registrations of cervical cancer in women aged <35 years than in women aged 35-69 (21·1% *v* 11·0%, $p<0·001$). Women with interval cancer who had had at least three negative smears during the 10 years before the diagnosis of cancer were commoner in the younger age group than in the older age group (7·0% *v* 2·5%, $p<0·01$). When, however, the number of observed cases of squamous cell carcinoma was related to the number of expected cases in the absence of screening, no significant difference was found between the two age groups (6·8% *v* 4·8%, $p>0·10$). The rate of diagnosis of interval cancer per 100 000 negative tests was lower among younger women than among older women (10/100 000 *v* 16/100 000). Review of the negative slides showed that 11·9% were again considered to be negative with an optimal sample having been obtained as evidenced by the presence of endocervical cells or metaplastic cells, or both.

Conclusions—Interval cancers might comprise a larger proportion of all registered cases of cervical cancer among younger women owing to the larger proportion of such cancers being prevented in this age group. Among women with interval cancer review of the negative slides showed that most were accounted for by suboptimal sampling or by errors of reporting.

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Introduction

Cancers that are diagnosed within a short time after negative screening test results are a concern as they raise questions about the effectiveness of the screening test. There are three main reasons for the existence of these cancers—namely, suboptimal sampling, reporting error, and development of malignancy anew after a truly negative test result. Such cancers are referred to as either interval cancers or rapid onset cancers. The first is the preferred term as the second fails to acknowledge that the reasons for the existence of such cancers include suboptimal sampling and errors in reporting.

By definition, interval cancers may be diagnosed only among people who have been screened. Interval cancers of the cervix were numerically a small problem in the 1960s when only a minority of women were screened. In the 1980s, however, interval cancers became a larger problem because an increasing proportion of women at risk were being screened. Most reports of interval cancer of the cervix after negative Papanicolaou smear tests have been in younger women.[1-5] It is not clear whether this reflects the greater participation in screening by young women or because cervical cytology is less effective in preventing cervical cancer in younger women. A meta-analysis of the effectiveness of screening within centrally organised programmes found no age differences in the relative protection conferred against cervical cancer by negative cytological test results during the 1960s and 1970s.[6] Nevertheless, there is concern that the natural course of cervical cancer may have changed recently in cohorts of young women.

We report a study of interval cancers of the cervix diagnosed between 1982 and 1986 among women who had had negative screen results on smear testing by the Victorian Cytology Gynaecological Service, a free public sector laboratory. Since it started in 1965 the service has reported on more than five million Papanicolaou smears. Victoria has a population of 1·3 million women aged 18-69. It has been estimated from claims made to the Health Insurance Commission for smears reported by private sector laboratories that about 85% of all smears taken in Victoria during 1982-6 were reported by the service.

The aims of our study were: to assess the magnitude of the problem of interval cancers in the 1980s; to compare the nature of interval cancers in younger women with that in older women; and, by reviewing the negative slides, to determine the proportion of

interval cancers that might represent the development of malignancy anew compared with that associated with sampling difficulties or reporting errors.

Subjects and methods

The names of women with cancer of the cervix registered with the Victorian cancer registry between 1982 and 1986 were checked against the names of the women who had had cervical smear reports issued by the Victorian Cytology Gynaecological Service between 1979 and 1986. Matching of the women was based on surname, maiden name, first name, date of birth, and postcode of residence.

Cervical cancers that had been diagnosed within 36 months after a negative smear test result were regarded as interval cancers. This period is the longest recommended interval between screenings in Australia and is the interval during which the risk of developing cervical cancer has been shown to be fairly stable.[6] The year 1982 was chosen as the starting date for detecting interval cancers as this was the first year of compulsory registration of cancers in Victoria.

The proportion of registrations of cervical cancer accounted for by interval cancers was calculated for two age groups: younger women (aged <35 years at diagnosis) and older women (aged 35-69 at diagnosis). The cut off age of 35 was chosen to maintain consistency with the International Agency for Research on Cancer report.[6] Comparisons of age and the stage and histological type of the cancer were made between the cases of interval cervical cancer and all registrations of cervical cancer.

The proportion of all negative smear test results relating to the interval cancers was determined. To do this subanalysis we needed to restrict the interval cancers to those relating to negative cytology reports issued during 1982-3. This was the only period during which all interval cancers in Victoria associated with negative smear reports issued by the Victorian Cytology Gynaecological Service had been comprehensively registered. For example, some women who had received negative reports from the service during 1981 and who had had cervical cancer diagnosed in 1981 would not have been registered with the cancer registry. Also, some registrations of cervical cancer occurring in the third year after negative cytology reports issued during 1984 might not have been completed. The rate of diagnosis of interval cancer for the two age groups was determined as the number of cases for each 100 000 negative smear test results.

Women with interval cancer were grouped into three risk categories for cervical cancer from the perspective of a laboratory. Categorisation was based on the screening history and on clinical information provided at the time of the last negative cervical smear test. The three risk categories broadly corresponded to the probability of a diagnosis of cervical neoplasia that might be expected during the 36 months after the issuing of the negative cytology report. The low risk category comprised women without symptoms who had had a minimum of three negative cytology reports in the 10 years before the diagnosis of cancer had been made, and all of whose previous cytology reports had been negative. The high risk category included women with a previous smear predicting cervical intraepithelial neoplasia or worse (which might or might not have been treated) and women with symptoms or signs compatible with cervical neoplasia at the time of their last smear (abnormal bleeding or an abnormal cervix on clinical examination, or both). An intermediate risk category comprised all other women. The variables studied within each risk group were age, the stage and histological type of cancer, the time since the last negative smear test result, and the diagnosis on review of the negative cytology specimen.

Smears that had been reported as negative within 36 months of cervical cancer being diagnosed were reviewed by a senior scientist who was unaware of the specific details of the women or of the study, who did the review as part of the usual internal quality control procedures of the service. The scientist looked for evidence of optimal sampling, as indicated by the presence of endocervical columnar cells or metaplastic cells, or both,[7,8] and for cellular abnormalities that had been missed at the time of the original reporting. A cytopathologist graded these abnormalities into those showing stages of cervical intraepithelial neoplasia or worse and those showing only minor abnormalities.

The number of squamous cell carcinomas that would have been expected in the absence of screening for cervical cancer among women from Victoria during 1982-6 was determined by applying recent estimates of the incidence expected in a Western population in the absence of screening[6] to the 1984 intercensus estimate of the number of women resident in Victoria, after adjusting for the likely proportion of women in each age group who had had a hysterectomy.[6,9] The proportion of the expected total number of squamous cell carcinomas accounted for by the interval cancers was calculated.

Results

During 1982-6, 1044 incident cases of cervical cancer in women aged under 70 were notified to the Victorian cancer registry, and in 138 (13·2%) negative cervical smear reports had been issued by the Victorian Cytology Gynaecological Service during the 36 months before the diagnosis of cancer. More interval cancers were apparent among older than among younger women (90 *v* 48), but they comprised a larger proportion of registrations of cervical cancer among younger than among older women (48/227, 21·1% *v* 90/817, 11·0%). The odds ratio for an interval cancer in younger women compared with older women was 2·17 (95% confidence interval 1·47 to 3·19, p<0·001).

During 1982-3 the service issued 489 872 negative smear reports, comprising 92% of all reports issued during this period. Of the 138 cases of interval cancer, in 59 negative smear test results had been reported during 1982-3. Sixty two negative reports were issued to these 59 women, representing an average of 13 interval cancers per 100 000 negative smear reports issued during 1982-3. The rates of interval cancers were 10/100 000 in younger women and 16/100 000 in older women.

TABLE I—*Age distribution and type and stage of cancer for interval cancers and for all registrations of cervical cancer, 1982-6. Values are numbers (percentages)*

	Interval cancers		All registrations of cancer	
Stage and type of cancer	Age <35 (n=48)	Age 35-69 (n=90)	Age <35 (n=227)	Age 45-69 (n=817)
Microinvasive	13 (27)	16 (18)	54 (24)	75 (9)
Invasive:				
Squamous	17 (35)	49 (54)	96 (42)	517 (63)
Adeno or adenosquamous	16 (33)	19 (21)	41 (18)	125 (15)
Other	1 (2)	2 (2)	2 (1)	17 (2)
Carcinoma not otherwise specified	1 (2)	4 (4)	34 (15)	83 (10)

STAGE AND HISTOLOGICAL TYPE OF CANCER

Table I shows the stage of the cancers and their histological type for the interval cancers and for all registrations of incident cervical cancer. Just over half of the cases of interval cancer in older women were invasive squamous cell carcinomas. In the younger women with interval cancer the distribution was more equally divided among microinvasive cancers (27%), invasive squamous cell carcinomas (35%), and invasive adeno or adenosquamous cancers (33%).

Table II shows the distribution of time lapses since the last negative cervical smear test result for each stage and type of cancer. Microinvasive cancer developing within one year after a negative cervical smear report was a rare diagnosis among women of both age groups. Half of the invasive adeno and adenosquamous interval carcinomas in each age group were diagnosed within 12 months after a negative smear report. Among older women 45% of the interval cases of invasive squamous cell carcinoma were diagnosed within 12 months after a negative smear test report.

CLINICAL AND CYTOLOGICAL HISTORY IN CASES OF INTERVAL CANCER

Clinical notes were supplied on 99% (136/138) of the request forms for the negative smear taken before the diagnosis of cancer. Twenty nine (21%) women with cancer (five younger, 24 older) had had abnormal bleeding or a suspicious looking cervix noted at the time the smear was taken. Another 11 women (eight younger, three older) had had the smear taken during the puerperium, when the collection of cells might have been less than optimal.

Twenty one women with cancer (15%) had previously had appreciable abnormalities that were known to the service: 10 had had a preceding biopsy or diathermy, or both, for cervical intraepithelial neoplasia, and 11 had had a smear test result suggesting cervical intraepithelial neoplasia or invasive cancer that had not been treated.

In the 10 years before having cancer diagnosed 62 of the 138 women with cancer had had only one negative cytology report, 28 had had two, and 48 had had three or more. Eleven women had had five or six negative cytology reports issued during the preceding decade, five of whom had had a previous appreciable abnormality of the cervix.

Grouping the women with cancer into risk categories resulted in 44 women being classified at high risk of developing cervical cancer, 58 at intermediate risk, and 36 at low risk. The 36 women at low risk represented 3·5% of the total number of 1044 registrations of cervical cancer during 1982-6. The proportion of all registrations of cervical cancer accounted for by women at low risk was 7% among younger women and 2·5% among older women (odds ratio 3·02, 95% confidence interval 1·54 to 5·93, p<0·01).

Table III shows the numbers of women in each risk category by age, the stage and type of cancer, and the time interval since their last negative test result. In the high risk group most of the cancers were diagnosed within 12 months after the negative result whereas in the intermediate and low risk groups most were diagnosed during the second and third years.

TABLE II—*Distribution of time lapses since last negative cytology report by age group at time of diagnosis of cancer and by type and stage of cancer*

Stage and type of cancer	Time lapse since last negative smear (months) 0-11	12-23	24-35
Age <35			
Microinvasive	1	8	4
Invasive:			
Squamous	2	8	7
Adeno or adenosquamous	8	4	4
Other	0	1	1
Age 35-69			
Microinvasive	2	5	9
Invasive:			
Squamous	22	15	12
Adeno or adenosquamous	9	4	6
Other	5	1	0

TABLE III—*Distribution of women with interval cancer within risk groups by age group, type and stage of cancer, and time interval since last negative smear report. Values are numbers (percentages)*

	Risk category High (n=44)	Intermediate (n=58)	Low (n=36)
Age group:			
<35	8 (18)	24 (41)	16 (44)
35-69	36 (82)	34 (59)	20 (56)
Stage and type of cancer:			
Microinvasive	5 (11)	15 (26)	9 (25)
Squamous	26 (60)	24 (41)	16 (44)
Adeno or adenosquamous	10 (23)	14 (24)	11 (31)
Other	3 (7)	5 (9)	0
Time since last negative smear report (years):			
<1	25 (57)	15 (26)	9 (25)
1-1·9	14 (32)	20 (34)	12 (33)
2-2·9	5 (11)	23 (40)	15 (42)

TABLE IV—*Diagnoses on review of negatively reported smears from women with interval cancer during 36 months before diagnosis of cancer and most serious diagnosis. Values are numbers (percentages)*

	Risk group High	Intermediate	Low
Review diagnosis (n=136)*			
Cervical intraepithelial neoplasia or worse:			
With endocervical cells	2 (4)	7 (14)	2 (5)
Without endocervical cells	12 (26)	10 (20)	12 (31)
Total	14 (30)	17 (34)	14 (36)
Changes less than cervical intraepithelial neoplasia:			
With endocervical cells	3 (7)	7 (14)	2 (5)
Without endocervical cells	7 (15)	6 (12)	5 (13)
Total	10 (22)	13 (26)	7 (18)
Negative:			
With endocervical cells	4 (9)	1 (2)	6 (15)
Without endocervical cells	18 (39)	20 (39)	12 (31)
Total	22 (48)	21 (41)	18 (46)
Total No all diagnoses	46	51	39
Most serious diagnosis on review in each woman (n=122†)			
Cervical intraepithelial neoplasia:			
With endocervical cells	2 (5)	7 (14)	2 (6)
Without endocervical cells	12 (32)	10 (20)	11 (33)
Total	14 (37)	17 (34)	13 (39)
Changes less than cervical intraepithelial neoplasia:			
With endocervical cells	3 (8)	7 (14)	2 (6)
Without endocervical cells	6 (16)	6 (12)	4 (12)
Total	9 (24)	13 (26)	6 (18)
Negative:			
With endocervical cells	4 (11)	1 (2)	5 (15)
Without endocervical cells	11 (29)	20 (39)	9 (27)
Total	15 (40)	21 (41)	14 (42)
Total No all diagnoses	38	51	33

*Excludes seven slides considered unsatisfactory on review.
†Excludes five women whose only negative slide within 36 months of diagnosis of cancer was considered unsatisfactory on review.

CYTOLOGICAL REVIEW OF NEGATIVE CERVICAL SMEAR REPORTS

A total of 156 negative smear reports were issued for the 138 patients with interval cancer during the 36 months before their cancer was diagnosed. One hundred and forty three (92%) of these smears were located for review; seven were considered unsatisfactory owing to the presence of insufficient squamous cells or because of obscuring by blood cells. Table IV shows the diagnoses for the remaining 136 smears; 61 smears were again considered to be negative, 11 of which included endocervical cells and 17 of which included endocervical cells or metaplastic cells, or both. Based on the presence of endocervical cells as evidence of optimal sampling, only 11 (7·7%) of the 143 reviewed slides were considered to be negative specimens of high quality; based on the presence of endocervical cells or metaplastic cells 17 (11·9%) of the slides were considered to be of high quality.

Endocervical cells were less likely to be present in the slides from women at high risk (20%) than those from women at intermediate (29%) or low risk (26%). Twenty three (68%) of the 34 slides with endocervical cells present were reviewed as being abnormal compared with 52 (51%) of the 102 slides that lacked endocervical cells.

Table IV also shows the most serious diagnosis made on review for each woman during the 36 months before cervical cancer was diagnosed. The distribution of review diagnoses for the women in each risk category was similar, with about 40% of women in each category having negative cytological findings on review and 60% having some degree of abnormality detected.

The highest diagnosis made on review for 10 of the women was again negative cytology with endocervical cells being present. Sixteen women had negative cytology on review with endocervical cells or metaplastic cells being present, four from the younger age group and 12 from the older age group. The malignancies that were diagnosed in these 16 women were three microinvasive cancers (one younger woman, two older women), eight invasive squamous cell carcinomas (two younger, six older), and five invasive adeno or adenosquamous carcinomas (one younger, four older).

For 11 of the women with interval cancer no negatively reported slides could be located for review. If the review diagnoses for these women were comparable with those in the 127 women in whom review was possible then we estimated that 11 (equalling $10/127 \times 138$) of the women with interval cancer would have had a negative report on review if endocervical cells were present or 17 (equalling $16/127 \times 138$) if the requirement for an optimal sample was the presence of endocervical cells or metaplastic cells. Thus the proportion of all registrations of cervical cancer during 1982-6 for which there was possible evidence of a transition from negative cervical cytology to malignancy in less than 36 months was 1·1% (11/1044) if the presence of endocervical cells represented optimal sampling of the cervix or 1·6% (17/1044) if the presence of endocervical cells or metaplastic cells, or both, represented optimal sampling.

COMPARISON WITH NUMBER OF EXPECTED CANCERS IF NO SCREENING UNDERTAKEN

A total of 1760 cases of squamous cell carcinoma during 1982-6 might have been expected among women from Victoria aged under 70 if no screening for cervical cancer had been undertaken (399 among younger women, 1361 among older women). To estimate the number of observed squamous cell malignancies in women with interval cancer, proportional adjustments for registrations of microinvasive cancer and of carcinoma not otherwise specified were made according to the distribution of histological types among all the registrations of cervical cancer. This resulted in an estimate of 27 observed interval squamous cell malignancies among younger women and 65 among older women.

When the estimated number of observed interval cases of squamous cell carcinoma was expressed as a proportion of the number expected in the absence of screening there was no significant difference between the two age groups (6·8% in younger women *v* 4·8% in older women, odds ratio 1·45, 95% confidence interval 0·91 to 2·30, $p>0·10$).

Discussion

Interval cancers accounted for at least 13·2% of all registrations of cervical cancer in women from Victoria during 1982-6. This minimum estimate arose because some women who had been registered with cervical cancer might have had negative cytology reports issued by private sector laboratories. A maximum estimate of 15·5% would have applied if the quality of sampling and accuracy of reporting in the private sector laboratories were comparable with those of the Victorian Cytology Gynaecological Service (the Victorian Cytology Gynaecological Service workload accounted for 85% of all smears taken from women in Victoria).

AGE DIFFERENCES AND THEIR IMPACT ON SCREENING

In contrast to popular belief, more interval cancers were diagnosed among older women (90) than among younger women (48), and, furthermore, the rate of diagnosis of interval cancer per 100 000 negative reports was lower among younger women (10/100 000) than among older women (16/100 000).

Only 35% (18 younger women, 30 older women) of the interval cancers had developed in women who had had three or more negative smears during the preceding 10 years. A review of the Victorian Cytology Gynaecological Service screening history of the 906 cancers registered during 1982-6 that were not interval cancers in this study found another 21 women (four younger, 17 older) who had had three or more negative smears that had been reported by the service during the 10 years before the diagnosis of cancer. The mean time interval since the most recent negative test for these 21 women was 4·9 years (95% confidence interval 4·3 to 5·6). Thus 9·7% (22/227) of all registrations of cervical cancer among younger women and 5·8% (47/817) of all such registrations among older women were associated with a minimum of three negative smears during the 10 years before the diagnosis of cancer (odds ratio 1·76, 95% confidence interval 1·04 to 2·98, $p<0·05$).

Significant differences were therefore evident between younger women and older women on three variables: the proportion of registered cancers that were accounted for by interval cancers, the proportion of registered cancers that were accounted for by low risk interval cancers, and the proportion of registered cancers that were accounted for by women who had had three or more negative cytology reports during the preceding 10 years. On first impression these statistics appear to be incompatible with the lower probability of a diagnosis of cervical cancer during the 36 months after a negative report in younger women.

In interpreting these findings, however, it is necessary to remember that a proportion is the product of both its numerator and its denominator. Considering the proportion of registered cancers that were accounted for by interval cancers, the amount of participation in screening will have influenced both the numerator and the denominator of this proportion, but in opposite directions. Thus with increasing participation the numerator (number of interval cancers) would have increased as interval cancers may be diagnosed only in women who have been screened, and the denominator (number of registrations of cervical cancer) would have decreased as screening for cervical cancer results in fewer cancers being diagnosed. In an extreme situation in which participation by women of a defined age group is nearly complete interval cancers might comprise virtually all cancers detected within the age group. The age comparisons discussed might therefore be somewhat spurious if the age groups participate in screening to different extents.

Higher screening rates among younger women in Australia have been reported.[10,11] When comparing interval cancers among different age groups it is therefore more appropriate to relate the number of interval cancers to a denominator of number of cancers

expected in the absence of screening as this stabilises the denominator, allowing a more valid comparison to be made. When the number of squamous cell carcinomas expected in the absence of screening was used as the denominator in our study no significant difference in the proportion of cases accounted for by interval cancer was found between the two age groups (6·8% *v* 4·8%, p>0·10).

This problem would be overcome if the number of interval cancers was related to the number of negative screening tests issued for each age group. Under these circumstances if the test had equal sensitivity in all age groups the rate of diagnosis of interval cancer per 100 000 negative tests should be directly proportional to the underlying risk of cervical cancer for each age group. If the risk of cervical cancer does increase with age the rate of diagnosis of interval cancer per 100 000 negative tests should be higher in older women than in younger women. Our study confirmed this.

REVIEW OF THE CYTOLOGY

Our review of the negative smears disclosed that only 1·1% to 1·6% of all registrations of cervical cancer during 1982-6 were associated with a negative test of optimal quality as reported by the Victorian Cytology Gynaecological Service during the 36 months before the cancer was diagnosed. Our results are in accord with those of other studies, showing that most of the negative cytology reports that are issued in close proximity to a diagnosis of cancer being made are accounted for by difficulties in the sampling and reporting processes.[1 12 13] None of the smears that were considered to have been suboptimal at review because of a lack of endocervical cells or metaplastic cells, or both, had been reported as such at the time of the original reporting. The Victorian Cytology Gynaecological Service began routinely to comment on the absence of endocervical cells in 1987; women whose smears lack these cells are now recommended to have a repeat test after one year.

Our study also showed that among interval cancers a higher proportion of cases were adeno or adeno-squamous carcinomas, possibly confirming other evidence that cervical cytology has a lower sensitivity for the detection or prevention of these histological types.[14]

CONCLUSION

In conclusion, we consider three points to be of importance in relation to interval cancers. Firstly, it is necessary to determine the role of sampling difficulties and reporting errors before concluding that all interval cancers represent a rapid transition from a normal cervix to a malignant one. Though all interval cancers might be regarded as failures of the screening system, difficulties with sampling and reporting errors might be overcome by measures other than shortening the rescreening interval. When a hospital, laboratory, or clinician is concerned about a high incidence of diagnoses of cancer after negative cytology, rather than assuming that this provides evidence of the rapid onset of cancer, the negatively reported slides should be re-examined. It is likely that most of the cases will be accounted for by suboptimal sampling and by errors in reporting; evidence remains that the rapid biological development of cervical cancer is infrequent.

Secondly, the establishment of record systems that allow continuous monitoring of the rate of diagnosis of interval cancer in women who have been screened is preferable to relying on analyses that are based on crude numbers and proportions. This is particularly important when comparisons are made between age groups in which there are differential uptakes of screening.

Finally, this study has shown that the probability of a woman having cervical cancer diagnosed in the 36 months after a negative smear was substantially lower in women aged less than 35 than in women aged 35-69. These data agree with the traditional view that younger women are at lower risk of cervical cancer than are older women.

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Changes in determinants of blood rheology during treatment with haemodialysis and recombinant human erythropoietin

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The two main side effects of treatment with recombinant human erythropoietin in anaemic patients receiving regular haemodialysis are the aggravation of hypertension and thrombosis at the site of vascular access.[1] Changes in blood rheology during the treatment might contribute to these complications. Thus we studied the behaviour of various determinants of blood rheology in relation to the occurrence of side effects in patients receiving haemodialysis who were being treated with recombinant human erythropoietin.

Patients, methods, and results

We studied 21 clinically stable patients (seven men, 14 women; mean age 55 (range 23-74)) who had been receiving maintenance haemodialysis three times a week for a mean of 42 (6-120) months. Fifteen patients had hypertension that was well controlled with drugs. The starting dose of recombinant human erythropoietin (Boehringer Mannheim) was 80 units/kg administered as an intravenous bolus after each dialysis session; when the target packed cell volume (0·30-0·35) was