PAPERS AND SHORT REPORTS

Malignant hypertension in women of childbearing age and its relation to the contraceptive pill

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Abstract

Eleven of 34 women aged 15-44 with malignant phase hypertension were taking oral contraceptives at presentation. All had had normal blood pressure before starting to take the pill. In four the interval between the start of oral contraception and the diagnosis of malignant hypertension was less than four months, and in eight no other cause for the hypertension was found. Underlying renal disease and renal failure were less common among pill users than among non-users with malignant hypertension who were of similar age. No pill user became normotensive after withdrawal of the pill, but blood pressure was well controlled (diastolic <90 mm Hg) in three patients taking only one drug. By contrast, all 23 non-users needed two or more antihypertensive drugs to control blood pressure. Ten year survival was 90% among pill users and 50% among non-users.

These results suggest that oral contraceptives may be a common cause of malignant hypertension in women of childbearing age. If the pill is stopped and underlying renal disease excluded the long term prognosis for such patients is excellent.

Introduction

Malignant phase hypertension is a well recognised if uncommon complication of the contraceptive pill.¹⁻⁴ The pathogenesis, clinical features, and outcome of malignant hypertension in pill users,

however, have not been defined. We examined these issues using data from 69 women with malignant hypertension seen consecutively in Glasgow between 1967 and 1983.

Patients and methods

The case records of 69 women with malignant hypertension who were referred to the Blood Pressure Unit, Western Infirmary, Glasgow, between 1967 and 1983 or to the Renal Unit, Royal Infirmary, Glasgow, between 1979 and 1983 were reviewed to see whether they had been taking the contraceptive pill at the time of diagnosis. If this information had not been recorded in the notes the patients or their general practitioners were contacted; in this way a drug history was established for all but two patients. Every woman had severe hypertension with bilateral retinal haemorrhages and exudate, thus satisfying the criteria of the World Health Organisation for malignant hypertension.⁹ Forty four also had bilateral papilloedema. After initial assessment blood pressure, drug treatment, renal function, and other events were monitored to 1 April 1984. If death occurred in the United Kingdom record linkage with the Registrar General ensured that the date and certified cause of death were notified in each case.

Results

Relation of malignant hypertension to oral contraception and preparation taken—Thirty four of the 69 women were of childbearing age (arbitrarily defined as 15-44); of these, 11 were taking oral contraceptives at the time of presentation with malignant hypertension. None of the 35 patients aged 45 or over were taking oral contraceptives or other sex hormones. The mean age of the pill users was 31; that of women who were of childbearing age but not taking oral contraceptives was 30. Blood pressure was known to have been normal in six women immediately before they started taking the pill. In the remaining five women a normal blood pressure had been recorded two, two, three, 13 and 21 years before they started taking the pill but more recent measurements were not available. Four women developed malignant hypertension within four months after starting the pill; in the others it did not develop for 14 months to eight years. The commonest preparations were those containing 50 µg oestrogen or more (eight cases). Two patients developed malignant hypertension while taking 30 µg oestrogen, and one presented within eight weeks after starting a 20 µg oestrogen pill (blood pressure was 110/70 mm Hg immediately before treatment began). Apart from the oestrogen component, preparations taken included four different progestogens (norethisterone, levonorgestrel, lynoestrenol, and ethynodiol),

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two of which (norethisterone and levonorgestrel) were present in different doses.

Clinical features and prognosis—The table shows the clinical features of the 11 women who developed malignant hypertension while taking the contraceptive pill compared with those of the 23 women of similar age who were not taking the pill. Other details of four of the pill users have been reported elsewhere.⁷ Initial blood pressure and smoking habits were similar in the two groups. Eight (73%) pill users and 17 (74%) non-users smoked cigarettes; this proportion is higher than that in the Scottish population and in women attending the Glasgow blood pressure clinic with non-malignant hypertension.¹⁰ Pill users had less underlying renal disease and less renal

Comparison of women taking the pill with those not taking the pill

	Women taking the pill (n=11)	Women not taking the pill (n=23)
Age (years):		
Mean (SD)	31 (8)	30 (9)
Range	19-43	15-44
No (%) current smokers	8 (73)	17 (74)
Mean (SD) initial blood pressure (mm Hg)	233 (25)/149 (13)	230 (28)/151 (20)
No with underlying disease:		
Renovascular disease	2	2
Chronic pyelonephritis	1	6
Chronic glomerulonephritis		1
Chronic renal failure of undetermined cause		1
Phaeochromocytoma		1
Mean (SD) initial serum creatinine ($\mu\text{mol/l}$)	111 (26)	334 (386)
Mean (SD) blood pressure before 1 April 1984 or death (mm Hg)	156 (64)/88 (22)	154 (31)/94 (19)
Survival (%) to 1 April 1984:		
5 Years	89.5	62.3
10 Years	89.5	49.8

Differences in age, smoking habit, initial and final blood pressures, and initial serum creatinine concentration not significant by unpaired *t* test.

failure than non-users. The blood pressure achieved during treatment was similar in the two groups. None of the pill users became normotensive after withdrawal of the pill, but diastolic blood pressures consistently less than 90 mm Hg were recorded during follow up in three patients taking only one antihypertensive drug. By contrast, all 23 non-users required two or more drugs to control blood pressure. Ten year survival was 90% among the pill users but only 50% among the non-users. This was related at least in part to the higher incidence of renal failure in the non-users, eight of whom eventually developed end stage renal failure that required dialysis.

Discussion

Was use of oral contraceptives more common among our patients than among the general population? Regrettably, we cannot make such a comparison with any confidence. Data from Intercontinental Medical Statistics and the Registrar General for Scotland show that in 1981 (the only year for which such analyses are complete) 20.2% of 183 160 Scottish women aged 30-34 were taking the contraceptive pill. This compares with a prevalence of 32.3% for our patients, whose mean age was 31. Thus oral contraceptive use may have been more common than expected among our patients, but this is not certain from the available evidence. Better evidence that the association is sometimes causal is suggested by earlier reports¹⁻⁸ and by more detailed analysis of the 11 pill users in this study. Blood pressure was known to be normal in all 11 before they started the pill. In four the interval between the start of oral contraception and the onset of malignant hypertension was less than four months. In eight no other cause for the hypertension was found. Although blood pressure did not return to normal when the pill was withdrawn, this in itself is not evidence against a causal connection as hypertension is not always cured after removal of its underlying cause.¹¹

There are several mechanisms whereby the contraceptive pill could cause malignant hypertension. Malignant hypertension may develop as a consequence of the known pressor effects of oestrogens or progestogens. Thus the rapid rise in blood pressure that occurs in malignant hypertension may be an extreme example of the varied

increase in blood pressure that occurs when most women are given the pill.¹² Alternatively, malignant hypertension may develop as a consequence of some other property of oral contraceptives. Whereas the rise in pressure that occurs in most pill users is generally small, gradual in onset, and related to the duration of treatment,¹² malignant hypertension developed suddenly in four of our patients within four months of their starting the pill. This suggests a more abrupt mechanism such as thrombosis. Abnormalities of blood coagulation are well recognised in malignant hypertension that is not associated with oral contraceptives and may play a part in the development of the disease.^{13 14} Moreover, thrombosis is the likely explanation for the other cardiovascular complications of the pill.¹⁵⁻¹⁷ Thus thrombosis of either the main¹⁸ or intrarenal¹⁹ arteries might perhaps contribute to the development of malignant hypertension in pill users.

Although an association between malignant hypertension and the contraceptive pill is well recognised, the number of reported cases is small and the clinical course and outcome of the condition in pill users are uncertain. High oestrogen pills are most often incriminated, although our study shows that malignant hypertension may also develop in women taking lower doses of oestrogen. The role of progestogens is more difficult to assess as several progestogens have been used in varying doses. None of our patients was taking a "progestogen only" preparation. Previous work confirms that the time of onset of malignant hypertension in pill users varies widely.¹⁻⁶ Interestingly, six of the nine previously recorded patients had appreciable renal impairment.¹⁻⁶ By contrast, our experience suggests that if underlying renal disease can be excluded malignant hypertension associated with oral contraception occurs more commonly with normal or only mildly impaired renal function. This may reflect the fact that women who are known to be hypertensive or to be unwell for other reasons are less likely to be given oral contraceptives. Conversely, selection bias may have influenced the prevalence of renal impairment among the patients described in previous reports, many of whom were admitted to renal units.^{3 5 6}

As the degree of renal impairment at presentation is the single most important predictor of outcome in patients with malignant hypertension²⁰ it is perhaps not surprising that most of our patients did well. Although a return of blood pressure to normal after withdrawal of the pill is the exception rather than the rule (occurring in two of nine patients in previous reports and none of our 11 patients), blood pressure was well controlled in most of our cases and 10 year survival was 90%. This result compares favourably with the 10 year survival of only 50% among the women with malignant hypertension who did not take the pill. The higher prevalence of renal disease and renal impairment among the non-users seems the likely explanation.

In summary, a causal association between the contraceptive pill and malignant hypertension is suggested by a clear temporal relation in at least some women and a plausible mechanism for the rise in pressure. As one third of women aged 15-44 who develop malignant hypertension are likely to be taking oral contraceptives these drugs may be a common cause of the condition. The time of onset after a woman has started taking the pill varies from a few weeks to several years, and although most women will need to take antihypertensive drugs after the pill is withdrawn, the long term prognosis is excellent if underlying renal disease can be excluded.

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Childhood asthma in adult life: a further study at 28 years of age

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Abstract

A group of 323 subjects who had wheezed in childhood and 48 control subjects of the same age were studied prospectively from 7 to 28 years of age. A classification system based on wheezing frequency was found to correlate well with clinical and spirometric features of airway obstruction. The amount of wheezing in early adolescence seemed to be a guide for severity in later life with 73% of those with few symptoms at 14 continuing to have little or no asthma at 28 years. Similarly 68% of those with frequent wheezing at 14 still suffered from recurrent asthma at 28 years. Most subjects with frequent wheezing at 21 continued to have comparable asthma at 28 years. Of those with infrequent wheezing at 21, 44% had worsened at 28 years. Women fared better than men between 21 and 28 with 19% having worse symptoms compared with 28% of men. Treatment at all ages was generally inadequate. The number of smokers among those with asthma was of concern.

Introduction

This paper reports the progress of a group of asthmatics who have been studied for 21 years from the age of 7. The study of the clinical course of any chronic illness is best achieved by the long term follow up of a representative matched group of subjects sampled to cover the full range of the disease. The course of asthma can be documented only in this way, but few studies have been reported. These have either been hospital or clinic based,^{1,3} with the potential for biased selection, or community based, with the problems arising from movement in and out of the community and from the heterogeneity of ages studied.^{4,6} Unfortunately, studies on the epidemiology of asthma have generally used different definitions of the disease, making direct comparison between them difficult.^{1,2,4,5}

McNicol and Williams⁷⁻⁹ and Martin *et al.*¹⁰⁻¹⁴ described a com-

munity based group of children with asthma who had been randomly selected from one age cohort and studied to the ages of 14 and 21 respectively. This paper describes the state of their asthma at 28 years and the course of their illness from 21 to 28.

Subjects and methods

In 1964, 401 children were randomly selected from roughly 30 000 7 year olds living in Melbourne, Victoria. They comprised 106 children who had never wheezed and 295 who had been identified by questionnaire and interview as having wheezing of variable severity. These children were studied at 7 years of age and were recalled at the age of 10 for further investigation. At that stage a further 83 children from the same age cohort but with more severe asthma were added to the original study group. The subjects were not part of a clinic based population and the investigators were not responsible for their management: one of the conditions laid down by the local medical association for its cooperation was that no advice about management would be offered to the subjects or their families.

When the subjects had reached the age of 14 they were recalled and examined; 329 (82%) of the original group were seen (a slightly higher proportion of children with asthma attended than controls) together with 68 of the additional 83 children with asthma. Four grades of severity were defined at that time⁷: class A—children with no more than five episodes of wheezing up to 14 years of age; class B—children with more than five episodes of wheezing but none in the 12 months before examination; class C—children with a continuing history of asthma over several years who had continued to wheeze in the previous 12 months; class D—children with very frequent or unremitting asthma.

The group was restudied at the age of 21 in 1978-9, when 408 subjects were contacted. A full review was performed on 342, and questionnaire data only were obtained from a further 66. A new severity classification was defined as definitions used at 14 years could only be used at that age¹⁰: class W—subjects who had not wheezed for three or more years before the age of 21; class X—subjects who had wheezed in the previous three years but not in the previous three months; class Y—subjects who had wheezed in the previous three months but whose frequency of wheezing was less than once a week; class Z—subjects who had wheezed more frequently than once a week in the previous three months.

In the 12 months from March 1985, 371 of the original group were restudied (323 with wheezing in childhood and 48 controls). This comprised a full review in 286 (77%) and a postal questionnaire in 85 (23%). The full study consisted of a questionnaire, physical examination, skin testing with five common allergens, and respiratory function tests. Blood was taken for eosinophil counts and IgE concentration. The questionnaire and the definitions used in the physical examination at 21 were followed as closely as possible at the 28 year review. The class definitions developed at 21 were used again at 28 with the exception that the class names were changed: class W was renamed class S, X became T, Y became U, and Z became V. The same investigator performed all the interviews, examinations, and tests.

The dynamic lung volumes were measured using an 8 litre, dry rolling seal spirometer (Morgan TLCtest, P K Morgan, Chatham, Kent) and corrected

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