PAPERS AND ORIGINALS

Oral contraceptive use in older women and fatal myocardial infarction

J I MANN, W H W INMAN, MARGARET THOROGOOD

British Medical Journal, 1976, **2**, 445-447

Summary

A previous study of women who had died from myocardial infarction and of a control group of women matched with them for age suggested a fivefold increase in the risk of death from myocardial infarction among users of oral contraceptives aged 40-44 years compared with women not using such preparations. Only a small proportion of women in the infarction and control groups had used oral contraceptives, however, so the margin of error was wide. We therefore investigated a further 54 women in this age group who died from myocardial infarction and compared their oral contraceptive histories with those of age-matched, living controls. Combination of the findings from the present investigation with the previous results have enabled a revised estimate of a threefold increase in risk to be made. Although this risk estimate is similar to that previously shown for a younger age group, the total mortality attributable to complications associated with the use of oral contraceptives remained considerably greater among women over the age of 40.

Introduction

Previously[1] we showed an increased risk of developing fatal myocardial infarction among women using oral contraceptives. The data suggested an approximately fivefold increase in the risk of death among users of the preparations aged 40-44 years compared with a nearly threefold increase in the risk to younger women. The confidence limits of the risk estimates, based on a sample of deaths in the age group 40-44 years, were wide, however, since few women of this age were using oral contraceptives. We therefore studied those deaths in this age group not investigated previously to provide a more reliable estimate of risk among older women.

Department of Social and Community Medicine, University of Oxford, Oxford OX1 3QN
J I MANN, DM, PHD, lecturer
MARGARET THOROGOOD, BSC, research assistant

Committee on Safety of Medicines, London EC2A 1PP
W H W INMAN, MRCP, MFCM, principal medical officer

Patients and methods

A detailed account of the methods used for selecting women who had died from myocardial infarction and control patients, together with the investigation procedure, was given previously.[1] In brief, transcripts were obtained from the Registrar General of all death certificates of women under the age of 50 who had died in England and Wales during 1973, and which had been coded to rubric 410 in the eighth revision of the *International Classification of Diseases* (myocardial infarction and synonymous terms). All deaths among women aged under 40, every second death in the 40-44-year age group, and every third death in the 45-49-year age group were selected for the initial investigation. The 92 deaths in the age group 40-44 years not investigated in that study form the basis of this report. (Data are not given here for women aged 45-49 years, since too few infarction and control patients in this group had been using oral contraceptives to enable any definite conclusions to be made.)

Of the 92 deaths, 24 could not be investigated because the relevant medical records could not be found (7) or because general practitioners could not be traced (11) or were unable to help (6). The remaining 68 were investigated by medical field officers employed by the Committee on Safety of Medicines. Information on drug use was obtained chiefly from general practitioners, who were also asked to provide control information by selecting at random from their files a woman who matched each fatal case for age and marital state. Deaths were included in the final analysis only when the diagnosis of fatal myocardial infarction was substantiated by necropsy findings or by a history of chest pain together with electrocardiographic or enzymatic confirmation as defined by the World Health Organisation.[2] In 14 cases evidence for the diagnosis was considered to be inadequate. The findings for the remaining 54 deaths and controls are given below. In four cases the general practitioner did not provide control data. To give more reliable risk estimates the results were combined with information from the earlier study[1] on the 52 deaths in this age group (40-44 years).

The significance of differences in characteristics between the patients with infarction and the controls was assessed by a matched

TABLE I—*Oral contraceptive practice among women aged 40-44 years who died from myocardial infarction (MI) and controls*

Oral contraceptive practice	Present investigation		Combined series	
	No (%) of patients with MI	No (%) of controls	No (%) of patients with MI	No (%) of controls
Never used	36 (66·7)	40 (80·0)	78 (73·6)	86 (84·3)
Current users (used during month before death or during same calendar period for controls)	10 (18·5)	5 (10·0)	18 (17·0)	7 (6·9)
Ex-users (used only more than one month before death or during same calendar period for controls	8 (14·8)	5 (10·0)	10 (9·4)	9 (8·8)
	18 (33·3)	10 (20·0)	28 (26·4)	16 (15·7)
Total	54 (100·0)	50 (100·0)	106 (100·0)	102 (100·0)
Not known	0	4	2	8
Comparison between users and women not currently using oral contraceptives	Not significant		$\chi^2_1 = 4·35$; $P < 0·05$	

pairs method,[3] and confidence limits of the relative risk estimates were established by using the method of Miettinen.[4] Standardised relative-risk estimates and summary χ^2 values were calculated by an exact maximum-likelihood method.[5]

Results

Table I shows the oral contraceptive practices of the 54 patients with infarction and the controls. The difference in current use between the two groups was less than that reported previously and by itself is not statistically significant. For the combined series of 106 women aged 40-44 years who had died from myocardial infarction in England and Wales in 1973 the use of oral contraceptives in the month before death was significantly greater than in the control series ($P < 0·05$). The estimate of risk for contraceptive users compared with that for non-users was 2·8 to 1 (95% confidence limits: 1·2 to 7·2). Even with this larger number the confidence limits are still wide because the use of oral contraceptives in this age group is uncommon. When these data are considered in conjunction with the Registrar General's statistics the yearly death rate from myocardial infarction among women aged 40-44 years who were not using these preparations is estimated to be 12/100 000 compared with 32/100 000 among women who were using them. Since about 95 000 women aged 40-44 years in England and Wales were estimated to have used oral contraceptives during 1973, some 20 deaths from myocardial infarction in this age group could probably have been attributed to oral contraceptives.

Infarction and control patients were considered to be hypertensive or diabetic if they had received treatment for either of these conditions. In the combined series 23% of the infarction patients and 3% of the controls had been treated for hypertension, and 10% of the former and none of the latter for diabetes. The risk of myocardial infarction associated with the use of oral contraceptives was not appreciably altered after allowing for the effect of these two factors,[5] the risk estimate being reduced from 2·8 to 2·7.

Discussion

These findings again show that the risk of fatal myocardial infarction is increased among women using oral contraceptives and suggest that this cannot be explained by an association between the use of the preparations and the two risk factors for myocardial infarction (hypertension and diabetes) that we were able to include in this investigation.

By combining the results of this and our previous study we estimate the risk of fatal myocardial infarction among women aged 40-44 years using oral contraceptives to be about three times as great as among women in the same age group not using the preparations. A nearly fivefold increase in risk had been apparent in this age group when the estimates were based on a smaller sample of patients.[1] The wide margin of sampling error was stressed in our earlier report and the investigation of appreciably more deaths provided the opportunity to calculate more reliable risk estimates. The present risk estimate for this older group of oral contraceptive users is virtually identical with that calculated previously in the youngest age group (30-39 years). The attributable mortality, however, is much greater in the older group (20 deaths per 100 000 users yearly in the 40-44-year age group and 3·5 deaths per 100 000 users yearly in women aged 30-39 years). The results of a study of non-fatal myocardial infarction[6] suggest that the present revised estimate may be too low. In that investigation the risk of myocardial infarction was found to be 5·7 times greater in women aged 40-44 years who were using oral contraceptives than in women who had never used such preparations. This calculation was based on 40 women with myocardial infarction, of whom 11 were using oral contraceptives.

Attempts have been made to draw up a balance sheet of advantages and disadvantages of oral contraceptives. In one such study[7] it was concluded that the mortality associated with the use of oral contraceptives was of the same magnitude as the mortality from complications of unplanned pregnancies when less efficient contraceptive methods had been used. The calculations were made at a time when myocardial infarction was not recognised as a complication of oral contraceptive use. Several serious adverse reactions to oral contraceptives have been established, but thromboembolism[8] and myocardial infarction[1] probably account for most fatal adverse reactions. It therefore seems timely to attempt a comparison of deaths resulting from the use of oral contraceptives with deaths from the complications of unwanted pregnancies that might be expected among users of less effective methods of contraception—for example, the diaphragm.

The mortality estimates given in table II for the complications of oral contraceptive use are based on the results of this and an earlier study.[8] The age breakdown was chosen so that comparable statistics from the different studies could be shown. It should be remembered that the data for pulmonary and cerebral thromboembolism were collected at a time when oral contraceptives containing more than 50 μg of oestrogen were widely

TABLE II—*Yearly mortality from myocardial infarction, pulmonary and cerebral thromboembolism, and pregnancy, delivery, and the puerperium (unplanned pregnancies*) among women in the two age groups using oral contraceptives or diaphragm*†

	Yearly mortality (per 100 000 users)	
Age group of women (years):	20-34	35-44
Users of oral contraceptives		
Myocardial infarction	1·1	8·1
Pulmonary and cerebral thromboembolism	1·3	3·4
Pregnancy, delivery, and puerperium	0·1	0·5
Total	2·5	12·0
Users of diaphragm		
Pregnancy, delivery, and puerperium	1·1	2·5
Excess mortality attributable to oral contraceptives	1·4	9·5

**International Classification of Diseases*, 8th revision, rubrics 630-678.

†Results are calculated assuming a failure rate of 10% a year among women aged 20-34 and 5% a year among those aged 35-44 using the diaphragm, and 1% a year among users of oral contraceptives.

used. The figures for myocardial infarction refer to the period when oral contraceptives containing less than 50 μg of oestrogen were more often in use. The present mortality from pulmonary and cerebral thromboembolism attributable to oral contraceptives may therefore be slightly lower than that given in the table. We assumed that oral contraceptives are 99% effective as a method of contraception and that the failure rate among users of the diaphragm is 10% a year for women aged 20-34 years and 5% a year for women aged 35-44 years. There is an excess of 1·4 deaths per 100 000 in the younger age group of women using oral contraceptives and of 9·5 per 100 000 among women aged 35-44 years. The excess number of deaths attributable to complications of oral contraceptive use would have been greater if the 40-44-year age group had been considered, but relevant data for pulmonary and cerebral thromboembolism[8] were not available.

These simple calculations did not include several other aspects that may be relevant. Surgery for gall-bladder disease—more common among users of oral contraceptives[9 10]—may be associated with a significant mortality, as may cerebral haemorrhage[11] and other, less common adverse reactions.[12] Furthermore, widespread use of legal abortion of unwanted pregnancies among users of the diaphragm might reduce the number of deaths in this group. These observations, and the fact that a pessimistic failure rate for the diaphragm was assumed,[13] suggest that the estimate of the excess deaths among oral contraceptive users may have been a conservative one. In England and Wales the increased risk of death from thromboembolism to users of oral contraceptives aged 20-34 years may still be less than half that of death from road-traffic accidents, but for those in the 35-44-year age group the increased risk may be double that from road-traffic accidents.[14] Whether this is an acceptable risk for so effective a method of contraception remains to be decided.

The risk estimates for death from thromboembolism in table II were made before the introduction of oral contraceptives containing less than 50 μg of oestrogen. Since a dose-response relationship has been shown between higher oestrogen doses and deaths from thromboembolism,[15] probably oral contraceptives containing smaller amounts of oestrogen may be associated with an appreciably reduced risk. The prescribing of alternative methods of contraception for women at risk of myocardial infarction for other reasons—for example, hypercholesterolaemia, heavy cigarette smoking, hypertension, and diabetes—could further reduce the number of deaths associated with oral contraceptive use.[6]

We thank the medical officers on the committee's staff who carried out the interviews; the many doctors who gave their time to provide us with information; Sir Richard Doll and Professor M P Vessey for advice; Dr A M Adelstein and Mr J G Gerrard, of the Office of Population Censuses and Surveys, who arranged for us to receive transcripts of the death certificates; and Mrs A Renauld, Mrs M Spellman, and Mrs A Read for secretarial help.

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Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycaemia

RAYMOND J NEWMAN

British Medical Journal, 1976, **2**, 447-449

Summary

Metoprolol and acebutolol, two supposedly cardioselective beta-adrenergic receptor blocking agents, were tested in healthy volunteers against propranolol, a non-selective drug, for their effect on blood glucose levels during insulin-induced hypoglycaemia. There was no significant difference between propranolol and metoprolol, which both potentiated the initial hypoglycaemic action of the insulin and delayed the return to normoglycaemia. Acebutolol, even though potentiating the initial hypoglycaemia, did not possess a significant delaying effect. A similar trial should be undertaken in diabetics to determine with certainty the safety of such drugs in diabetes mellitus.

St James's Hospital, Leeds 9
RAYMOND J NEWMAN, BSC, MB, house physician (now demonstrator, Department of Anatomy, Leeds University School of Medicine)

Introduction

One of the body's most important responses to hypoglycaemia is the release of adrenaline from the adrenal medulla. This hormone stimulates glycogenolysis, and the subsequent release of glucose tends to restore the blood glucose level towards normal.[1]

The beta-adrenergic receptor blocking agents available are non-selective in their action and are thought to inhibit glycogenolysis. These drugs would therefore be expected to possess a hypoglycaemic effect, and indeed hypoglycaemia precipitated by propranolol has been reported.[2-4] After such reports it was suggested that drugs like propranolol should be used with extreme caution in insulin-treated diabetics and in patients prone to hypoglycaemia.[2 5-7]

The evidence published in the past decade on the effect of beta-adrenergic blockade on blood glucose levels has not, however, been unanimous in supporting this recommendation.