References

Ablett, J. J. L. (1967). *Symposium on Tetanus in Great Britain*, ed. M. Ellis, p. 1. Leeds, United Leeds Hospital.
Adams, E. B., Holloway, R., Thambiran, A. K., and Desai, S. D. (1966). *Lancet*, **2**, 1176.
Alam, M., Anrep, G. V., Barsoum, G. S., Talaat, M., and Weininger, E. (1939). *Journal of Physiology*, **95**, 148.
Alhady, S. M. A., Bowler, D. P., Reid, H. A., and Scott, L. T. (1960). *British Medical Journal*, **1**, 540.
Clark, M. M., and Taylor, J. F. N. (1966). *British Journal of Anaesthesia*, **38**, 840.
Clifton, B. (1964). *Lancet*, **1**, 785.
Corbett, J. L., Kerr, J. H., Prys-Roberts, C., Crampton Smith, A., and Spalding, J. M. K. (1969). *Anaesthesia*, **24**, 198.
Foldes, F. F. (1960). *Clinical Pharmacology and Therapeutics*, **1**, 345.
Freeman, N. E. (1933). *American Journal of Physiology*, **103**, 185.
Glossop, M. W. (1967). *Symposium on Tetanus in Great Britain*, ed. M. Ellis, p. 45. Leeds, United Leeds Hospital.
Kelman, G. R., and Prys-Roberts, C. (1967). *British Journal of Anaesthesia*, **39**, 523.
Kerr, J. H., Corbett, J. L., Prys-Roberts, C., Crampton Smith, A., and Spalding, J. M. K. (1968). *Lancet*, **2**, 236.
Kerr, J. H., Corbett, J. L., and Spalding, J. M. K. (1969). *Proceedings of the Royal Society of Medicine*, **62**, 659.
Lassen, H. C. A., Bjornboe, M., Ibsen, B., and Neukirch, F. (1954). *Lancet*, **2**, 1040.
Macmillan, A. L., and Stott, F. D. (1968). *Bio-medical Engineering*, **3**, 20.
Macrae, J. (1967). *Symposium on Tetanus in Great Britain*, ed. M. Ellis, p. 11. Leeds, United Leeds Hospital.
Melville, K. I. (1966). *Prevention of Ischaemic Heart Disease*, ed. W. Raab, p. 31. Springfield, Illinois, Thomas.
Mollaret, P., *et al.* (1958). *Revue Neurologie*, **99**, 501.
Northfield, T. C. (1967). *British Heart Journal*, **29**, 588.
Prys-Roberts, C., Corbett, J. L., Kerr, J. H., Crampton Smith, A., and Spalding, J. M. K. (1969). *Lancet*, **1**, 542.
Raab, W. (1966). *American Heart Journal*, **72**, 538.
Richards, D. W. (1965). *Handbook of Physiology, Circulation*, III, p. 1887. Washington, American Physiological Society.
Shild, H. O., and Gregory, R. A. (1947). *Proceedings of the XVII International Physiological Congress*, Oxford, p. 288.
Stirnemann, H. (1966). *Tetanus*, Bern, Huber.
Szakacs, J. E., and Mehlman, B. (1960). *American Journal of Cardiology*, **5**, 619.
Waser, P. G., and Harbeck, P. (1962). *Anaesthesist*, **11**, 33.

Oral Contraceptives and Myocardial Infarction

DOROTHY J. RADFORD, M. F. OLIVER

British Medical Journal, 1973, **3**, 428–430

Summary

Between January 1970 and December 1972 22 women aged between 31 and 45 years were admitted to the coronary care unit with acute myocardial infarction and six of these (27%) had been taking oral contraceptives. There were nine women aged 40 or less and five of them (55%) had been on oral contraceptives while three of the other four had been sterilized by tubal interruption.

Both these figures of prevalence of oral contraceptive use are significantly greater than estimates for the general population of women of similar age. For those aged 30-44 years, current estimates suggest that it is between 8 and 11%.

All the women in this study had risk factors recognized as being associated with the premature development of ischaemic heart disease, and the prevalence of these risk factors was similar in those taking oral contraceptives as in those not doing so. Oral contraceptives probably enhance the chance of developing myocardial infarction in women whose risk is increased for other reasons.

Introduction

A direct relation between acute myocardial infarction in young women and the use of oral contraceptives has not been statistically proved, but continued reporting of the association (Boyce *et al.*, 1963; Hartveit, 1965; Naysmith, 1965; Scharf *et al.*, 1968; Oliver, 1970; Dear and Jones, 1971; Waxler *et al.*, 1971; Weiss, 1972) suggests the need for caution in prescribing contraceptives to individual patients.

This paper reports the experience of the coronary care unit of the Royal Infirmary of Edinburgh over a three-year period, 1970-2, and is a sequel to a previous report (Oliver, 1970).

Royal Infirmary, Edinburgh EH3 9YW
DOROTHY J. RADFORD, M.B., M.R.C.P., Registrar in Cardiology and General Medicine
M. F. OLIVER, M.D., F.R.C.P., Consultant Physician, Department of Cardiology, and Reader in Medicine, University of Edinburgh

Method

From January 1970 to December 1972 22 women aged between 31 and 45 years were admitted to the coronary care unit in the Royal Infirmary of Edinburgh with clinical features of acute myocardial infarction. The diagnosis was substantiated by classical electrocardiographic changes classifiable according to the Minnesota code (Rose and Blackburn, 1968) or by raised serum creatine phosphokinase levels or by both methods.

All of the women were asked specifically about the use of oral contraceptive pills, and details of the type and duration of such therapy were confirmed with their general practitioners. All were assessed for risk factors known to be associated with the early development of ischaemic heart disease and a scoring system was used with one point being given for the presence of each of the following features: (1) hypertension—a diastolic blood pressure >100 mm Hg recorded before the acute event or six weeks or more after the acute myocardial infarction; (2) hypercholesterolaemia—a fasting serum cholesterol value >270 mg/100 ml found at an interval of at least six weeks after the acute event; (3) smoking—20 or more cigarettes daily at the time of infarction; (4) an abnormal glucose tolerance test of the diabetic type using a 50 g oral glucose load more than six weeks after the acute event; (5) family history—a myocardial infarct or known ischaemic heart disease under the age of 55 years in one or more near relatives; (6) obesity—weight greater than 10% above the standard for height and age; and (7) a premature menopause or bilateral oophorectomy.

The number of risk factors for each patient was totalled and is quoted as the risk score.

Results

Of the 22 women aged between 31 and 45 years admitted with acute myocardial infarction six were found to have been using oral contraceptives at or just before the time of their infarct. There were nine women aged between 31 and 40 years, and five of these had been using the pill. The sixth oral contraceptive user was aged 45 and she died of an extensive anterior acute myocardial infarction. Attention has been focused primarily on the group of younger women, aged 40 years or less, documented in the table. Their risk scores averaged 2·6.

Women Aged Between 31 and 40 Years with Acute Myocardial Infarction(A.M.I.)

Case	Age	Parity	Site of Infarct	Minnesota Code	Maximum C.K. (I.U.)	Oral Contra-ceptive	Duration of O.C. Therapy in Years	B.P. (mm Hg)	Serum Chol-esterol (mg/100 ml)	Cigarette Smoking (per Day)	Family History	Weight in Relation to Standard	Risk Score	Comments
1	40	1	Anteroseptal	1-1-1	180	Ovulen 50, Anovlar	8	170/110	226	30-40	+	+5%	4	O.C. ceased 5 weeks before A.M.I.
2	34	3	Anterior	1-1-1	1,640	Gynovlar	6	—	—	20	+	Standard	2	Died in cardiogenic shock three days after extensive anterior A.M.I.
3	38	3	Inferolateral	5-1-1	36	Anovlar	9	230/140	258	30	—	+28%	3	"Flat" curve after G.T.T. Serial enzymes not done
4	35	0	Anteroseptal	1-3-4 5-2-1	550	Lyndiol	3	160/100	180	Non-smoker	—	+15%	2	
5	39	3	Anterior	1-1-1	432	Sequens, Volidan, Ovulen 50	2	110/70	208	10-20	—	+32%	2	
6	35	2	Inferior	1-1-1	720	None	—	160/100	238	30-40	+	+13%	4	On O.C. for 2½ years then sterilized 2½ years before A.M.I. "Flat" curve after G.T.T.
7	39	4	Anterolateral	1-1-1	240	None	—	170/105	250	20	+	—15%	3	Sterilized six months before A.M.I.
8	39	2	Inferior	1-1-4	SGOT 99, HBD 586	None	—	100/70	185	20	—	+30%	2	Sterilized seven years. "Flat" curve after G.T.T.
9	31	2	Inferior	5-3	384	None	—	120/80	304	5-10	—	+18%	2	

C.K. = Serum creatine kinase level. O.C. = Oral contraceptive. SGOT = Serum aspartate aminotransferase. HBD = Serum hydroxybutyric dehydrogenase. G.T.T. = Glucose tolerance test.

Glucose tolerance tests were performed, except in case 2 where death occurred in cardiogenic shock and in case 4 where the patient left the country. The latter had a normal fasting blood sugar. No patient in this group had a diabetic glucose tolerance curve and no patient was prematurely menopausal.

Serum triglycerides were measured in all women except in cases 2 and 4 (see above) and ranged between 70-115 mg/100 ml—this is within the normal range for the autoanalyser method used.

Risk scores were similarly obtained for the other 13 patients, aged between 41 and 45 years. These also averaged 2·6.

Discussion

In this series of 22 women with acute myocardial infarction aged 45 years or less, six (27%) were using oral contraceptives at or just before the time of the onset of symptoms. In the group of nine younger women aged 31-40 years five (55%) were using contraceptives.

The use of oral contraceptives by women aged 15-44 years at any one time in England and Wales in the years 1970 and 1971 was estimated at 13-17% (M. P. Vessey, personal communication, 1973). As it is known that oral contraceptives are still predominantly used by younger women, Vessey (1973) expects the use in the age group 30-44 years to be appreciably lower than these figures. This view concurs with the estimates made for 1968 in the Royal College of General Practitioners' oral contraceptive study (C. R. Kay, personal communication, 1973) which showed an estimated prevalence of pill use of 13·5% in married women aged 30-34 years, of 8·2% in the age group 35-39 years, and of 3·5% in the 40-44 age group. From that study the expected pill use is 10·8% in women aged 30-39 years and 8·3% in women aged 30-44 years. The incidence of oral contraceptive use in the women in our study is significantly greater than that expected in the general population.

In the previously reported series from Edinburgh (Oliver, 1970) a high incidence of oral contraceptive use (50%) was also noted in the younger women (aged 31-41 years) with myocardial infarction.

Inman and Vessey (1968) pointed to a significant association between the use of oral contraceptives and death from coronary thrombosis in a subgroup of younger women aged 20 to 34 years, but this correlation was not present in the total series of women. In Denmark, 15% of 54 women aged 30-44 years who died of a coronary occlusion in 1967-8 were found to have been using oral contraceptives (Fischer and Mosbech, 1970). While the conclusion of this Danish study was that there was no support for any association between the use of oral contraceptives and the incidence of ischaemic heart disease, a further subdivision of that study into age groups shows that 25% of women aged 30-39 years were using the pill. There is thus some evidence that the use of oral contraceptives may be an added risk factor in younger women (under 40) who develop acute myocardial infarction.

In the group of women aged 31-40 years in the present study, the average duration of oral contraceptive use was 5·6 years and ranged from two to nine years of continuous therapy. Inman and Vessey (1968), when analysing deaths from coronary thrombosis in young women, made the suggestion that those who died from coronary thrombosis had been using oral contraceptives for rather longer than those who died of other thrombotic episodes while on the pill. In young women already at risk for developing ischaemic heart disease because of the presence of other factors it is possible that prolonged use of oral contraceptives becomes a progressively more important adverse influence.

Three of the four women aged 31-40 years who were not taking the pill when they had acute myocardial infarction had previously been sterilized: two had had bilateral salpingectomy and one had had tubal ligation. In each case the ovaries had been left intact and they had continued to menstruate. Whereas bilateral oophorectomy is followed by a rise in serum lipids (Oliver and Boyd, 1959), by increased coronary atheroma (Wuest *et al.*, 1953), and an increased incidence of clinical ischaemic heart disease (Robinson *et al.*, 1959), no such correlation has been documented with sterilization performed by tubal interruption. The apparent association between sterilization and acute myocardial infarction in the present small series

may well be fortuitous or related to the increasing use of this procedure, or may be related to the initial reason for advising sterilization. All three of our patients had psychological reasons for seeking sterilization and, in addition, one had already established hypertension on the basis of chronic pyelonephritis. The possibility exists that the relation between the use of oral contraceptives and the disease could be due to the contraception itself rather than to its methods of achievement. This might be worth looking into before concluding that oral contraceptives are a risk factor in acute myocardial infarction and before recommending sterilization as a preferable method of contraception.

It is now well established that the risks of developing ischaemic heart disease prematurely are increased in association with excess cigarette smoking (Doll and Hill, 1964), hypercholesterolaemia and hypertension (Truett *et al.*, 1967), abnormal carbohydrate tolerance (Epstein, 1967), a family history of the disease (Thomas and Cohen, 1955), a premature menopause (Sznajderman and Oliver, 1963), and perhaps also obesity (Truett *et al.*, 1967). Every patient in the present series had at least one of these predisposing risk factors for coronary artery disease and the average score for risk factors was 2·6.

Few women in the present series were non-smokers. Some of those not allocated a point score for smoking were, in fact, smokers, though of fewer than 20 cigarettes a day. Kay *et al.* (1969) observed that women using oral contraceptives were heavier smokers than non-users. Oliver (1973) found that 47% of women with documented ischaemic heart disease under the age of 45 years were smokers. This compares with 26% of women in the same age group in the general population of the United Kingdom (Todd, 1972). It is established that oral contraceptives can raise the concentration of serum cholesterol and triglycerides (Wynn *et al.*, 1969). Also there is an association between oral contraceptive therapy and the onset and aggravation of hypertension (Laragh *et al.*, 1967; Woods, 1967; Weir *et al.*, 1971). Obviously all these factors are interrelated and must be taken into account in interpreting the role of oral contraceptives in myocardial infarction.

The available evidence suggests that it would be wise to identify those risk factors commonly associated with ischaemic heart disease in young women about to start oral contraceptive therapy. It is easy to screen for hypertension and to monitor blood pressure subsequently. In those with a family history of precocious ischaemic heart disease a case can be made for screening for abnormalities in blood lipid concentrations and also for giving advice against cigarette smoking. In those with identifiable risk factors alternative contraceptive measures should be advised or, if personal circumstances demand, the duration of oral contraceptive use should be limited.

References

Boyce, J., Fawcett, J. W., and Noall, E. W. P. (1963). *Lancet*, **1**, 111.
Dear, H. D., and Jones, W. B. (1971). *Annals of Internal Medicine*, **74**, 236.
Doll, R., and Hill, A. B. (1964). *British Medical Journal*, **1**, 1399.
Epstein, F. H. (1967). *Circulation*, **36**, 309.
Fischer, A., and Mosbech, J. (1970). *Ugeskrift for Læger*, **132**, 2480.
Harveit, F. (1965). *British Medical Journal*, **1**, 60.
Inman, W. H. W., and Vessey, M. P. (1968). *British Medical Journal*, **2**, 193.
Kay, C. R., Smith, A., and Richards, B. (1969). *Lancet*, **2**, 1228.
Laragh, J. H., Sealey, J. E., Ledingham, J. G. G., and Newton, M. A. (1967). *Journal of the American Medical Association*, **201**, 918.
Naysmith, J. H. (1965). *British Medical Journal*, **1**, 250.
Oliver, M. F. (1970). *British Medical Journal*, **2**, 210.
Oliver, M. F. (1973). *American Journal of Cardiology*. In press.
Oliver, M. F., and Boyd, G. S. (1959). *Lancet*, **2**, 690.
Robinson, R. W., Higano, N., and Cohen, W. D. (1959). *Archives of Internal Medicine*, **104**, 908.
Rose, G. A., and Blackburn, H. (1968). *World Health Organization. Monograph Series*. No. 56.
Scharf, J., Nahir, A. M., Peled, B., and Asad, A. (1968). *Lancet*, **2**, 411.
Sznajderman, M., and Oliver, M. F. (1963). *Lancet*, **1**, 962.
Thomas, C. B., and Cohen, B. H. (1955). *Annals of Internal Medicine*, **42**, 90.
Todd, G. F. (1972). *Statistics of Smoking in the United Kingdom*. London, Tobacco Research Council.
Truett, J., Cornfield, J., and Kannel, W. (1967). *Journal of Chronic Diseases*, **20**, 511.
Waxler, E. B., Kimbiris, D., Van Den Brock, H., Segal, B. L., and Likoff, W. (1971). *American Journal of Cardiology*, **28**, 96.
Weir, R. J., *et al.* (1971). *Lancet*, **1**, 467.
Weiss, S. (1972). *New England Journal of Medicine*, **286**, 436.
Woods, J. W. (1967). *Lancet*, **2**, 653.
Wuest, J. H., Dry, T. J., and Edwards, J. E. (1953). *Circulation*, **7**, 801.
Wynn, V., Doar, J. W. H., Mills, G. L., and Stokes, T. (1969). *Lancet*, **2**, 756.

Preliminary Evaluation of "Duodenitis" by Endoscopy and Biopsy

P. B. COTTON, A. B. PRICE, J. R. TIGHE, J. S. M. BEALES

British Medical Journal, 1973, 3, 430–433

Summary

Difficulty in excluding duodenal ulceration by standard radiology has hampered investigation of duodenitis; endoscopy and biopsy add a new dimension. We have studied 51 patients with dyspeptic symptoms or bleeding in whom endoscopy revealed congested and irregular areas of duodenal bulb mucosa in the absence of ulcer or scar. Biopsy revealed unequivocal active inflammation—epithelial cell atypia and neutrophil infiltration—in 22 of these patients, but in none of 29 "control" patients with an endoscopically normal bulb. There were no reliable radiological markers of active duodenitis. These patients, and a group of 25 with known duodenal ulcers, shared similar clinical characteristics and a high incidence of gastric metaplasia in the bulb. In the short follow-up period most patients with active duodenitis remained symptomatic; two developed ulcers, and two others have undergone vagotomy and pyloroplasty, with poor short-term results. The clinical significance of visual and histological mucosal changes, and their relationship with ulcer disease, merit long-term study.

St. Thomas's Hospital, London SE1 7EH
P. B. COTTON, M.D., M.R.C.P., Senior Medical Registrar
A. B. PRICE, B.M., M.R.C.PATH., Senior Registrar in Pathology
J. R. TIGHE, M.D., F.R.C.P., Consultant in Surgical Pathology
J. S. M. BEALES, M.R.C.P., F.F.R., Consultant in Radiology

Introduction

The existence of a clinically significant duodenal inflammatory condition in the absence of ulceration—"duodenitis"—remains controversial despite an extensive literature dating back as far as 1837 (Baudin). Some early studies were firmly based on examination of the resected duodenal bulb (MacCarty, 1924; Judd and Nagel, 1927; Kirklin, 1929; Rivers 1931), but more