Myocardial infarction and oral contraceptives

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During 1968-1972, 4 women of 41 years or less were admitted with a myocardial infarction. Three of them had been taking oral contraceptives, all were moderate to heavy smokers, and the fathers of all of them had had a myocardial infarct after the age of 50 years. One had slight hypertension while using oral contraceptives and her serum cholesterol and lipids were increased. Details of all 3 cases are given and the current evidence of the relation between oral contraceptives and myocardial infarction reviewed.

The association between thromboembolism and oral contraceptives is gaining in importance as the number of women using them increases. The size of the risk was calculated to be nine times greater for a woman taking oral contraceptives than for one who does not (Vessey and Doll, 1969). The positive correlation between the dose of oestrogen and the risk of thromboembolic disease was reported by Inman *et al.* (1970). The relation of the 'pill' to myocardial infarction in young women seems to be less obvious, and study of well-documented cases is, therefore, important. This report concerns three premenopausal women who sustained acute myocardial infarction while on an oral contraceptive. They all had a family history and one was a rather heavy and two were moderate smokers.

Case report

Case 1

A 38-year-old white woman without any significant past illness was admitted to this hospital on 7 October 1968 with a sharp pain in the praecordium with no radiation. The pain lasted several hours. It was not pleuritic in nature and there were no respiratory symptoms. Her father and mother had died of heart attacks at the ages of 65 and 70 years, respectively. She had been smoking 10 to 20 cigarettes a day. She had been on Ovulen (ethynodiol diacetate 1 mg, mestranol 0.1 mg) for the past 4 years.

Physical examination did not reveal any gross abnormality. Her blood pressure was 140/90 mmHg. Electrocardiogram showed recent anteroseptal myocardial infarction. Chest x-ray showed a normal cardiac outline. SGOT was raised. The blood count, urine analysis, blood urea, and electrolytes were within normal limits. Serum cholesterol was 243 mg/100 ml and serum lipoproteins were within normal limits. Glucose tolerance test did not reveal any latent diabetic state.

She was treated with anticoagulants and oral contraceptives were discontinued. She made an uneventful recovery but about a week after her discharge had an episode of constricting chest pain and was readmitted. This time neither the electrocardiogram nor the serum enzymes showed evidence of any further myocardial infarction. Anticoagulants were continued for two years. She remained very well and is leading a normal life. Her present serum cholesterol is 235 mg/100 ml, triglycerides 132 mg/100 ml, with normal serum lipoproteins (cellulose acetate electrophoresis).

Case 2

A 27-year-old white woman was referred initially in March 1971 because her general practitioner found her blood pressure raised to 150/110 mmHg. At this time she had been on the contraceptive pill Lyndiol (lynestrenol 2.5 mg, mestranol 0.075 mg) for 3 years. The blood pressure came down to normal over a few months of follow-up without any antihypertensive treatment, though she continued with the 'pill' contrary to our advice. The patient was admitted to hospital on 28 October 1971 with a 4-week history of typical anginal pain. She smoked 10 cigarettes a day and there was a family history of ischaemic heart disease, her father having died from myocardial infarction at the age of 58 years.

Physical examination revealed a woman of normal body build with a blood pressure of 125/90 mmHg. There was an audible apical third heart sound but no other abnormality was demonstrated apart from a patch of *Lichen atrophicus*.

Electrocardiogram on admission showed evidence of recent septal infarction. Haemoglobin was 13.0 g/100 ml, ESR 51 mm in first hour (Westergren), and white cell count 15,000 per mm³. Serum cholesterol was 300 mg/100 ml. SGOT was 112 Frankel Units/ml. Blood urea, serum electrolytes, and liver function test were normal. Chest x-ray showed pulmonary oedema with normal heart outline. Triglycerides were 142 mg/100 ml but lipid nephelometry showed increase of prebetalipoprotein.

tein. Antinuclear factor and LE cells were not demonstrable.

She made an uneventful recovery and was discharged on phenindione therapy. Oral contraceptives had been discontinued. In the follow-up clinic her cholesterol came down to 233 mg/100 ml without any treatment. Coronary arteriography showed normal appearance of the right coronary artery, but there was evidence of generalized narrowing involving both circumflex and anterior descending branches of the left coronary artery. After being on phenindione for a few months the patient developed a malabsorption syndrome which gradually improved when phenindione tablets were stopped. The serum cholesterol level increased to 370 mg/100 ml during the follow-up and she was prescribed clofibrate capsules, 1 g b.d. At present her serum cholesterol is 180 mg/100 ml, triglycerides 132 mg/100 ml, and serum lipoproteins normal on cellulose acetate electrophoresis.

Case 3

A 37-year-old white woman without any significant past illness was admitted to this hospital on 7 January 1973 with severe retrosternal pain, radiating to the left arm, lasting for about 12 hours. Before this she had been experiencing effort angina for 5 or 6 weeks. Her father died of myocardial infarction at the age of 67 years. She has been smoking 30 to 40 cigarettes a day and had been on Gynovlar (norethistrone acetate 3 mg, ethinyl oestradiol 0.05 mg) for the past 5 years.

Physical examination did not reveal any gross abnormality except for the presence of an early diastolic murmur along the left sternal border. Electrocardiogram showed extensive antero-septal myocardial infarction. SGOT was raised. The blood count, urine analysis, blood urea, glucose tolerance test, and serum uric acid were within normal limits. The serum cholesterol was 252 mg/100 ml. Serological tests for syphilis were negative. The chest x-ray showed a normal cardiac outline. Triglycerides were 132 mg/100 ml. Lipoproteins, electrophoretic strip, and nephelometry were normal.

She made an uneventful recovery and remains well. Treatment consisted of anticoagulation. Oral contraceptives were discontinued.

Discussion

Precocious ischaemic heart disease is unusual in the reproductive period of women unless there is an associated hypertension, diabetes mellitus, or hyperlipidaemia.

In a study of the records of 95,000 women under the age of 40 seen in a 10-year period at the Mayo Clinic, the authors concluded that coronary heart disease practically did not exist in this age group in the absence of the above-mentioned predisposing causes (Underdahl and Smith, 1947).

Clinical and necropsy studies suggest such a protection to be due to oestrogen (Stamler, Best, and Turner, 1963), though this concept has been challenged by others (Tracy, 1966; Ritterband *et al.*,

1963). Potocki (1971) found that women receiving oestrogen during at least 10 years after the menopause had a smaller incidence of ischaemic heart disease and myocardial infarction than those of corresponding age but not treated.

In the Coronary Drug Project (1970, 1972), a collaborative study to evaluate long-term effects of several drugs influencing lipid metabolism, a regimen of conjugated oestrogens (5 mg daily) had to be discontinued because the patients in this group experienced an excess number of myocardial infarctions, pulmonary emboli, and thrombophlebitis compared with the placebo group. Such a risk, however, was not noticed with the dose of 2.5 mg a day. Similarly the Veterans Administration Co-operative Urological Research Group (1967) reported a substantial increase in cerebral and cardiovascular deaths in patients with prostatic carcinoma treated with oestrogens.

Considering the small population, a strikingly large number of published cases of coronary thrombosis in users of oral contraceptives have come from Denmark. Dalgaard and Gregersen (1969) presented the results of 4 necropsies on cases of coronary thrombosis in women between the ages of 31 and 38 years using oral contraceptives and compared them with 11 non-users who came to necropsy during the same period. They noticed that the former were much younger and only one of them had a predisposing cause as against 5 of the 11 non-users. Fischer and Morbeck (1970) collected 89 fatal cases of myocardial infarction in women in the age group 30 to 44 years in whom they could obtain definite information concerning the use of oral contraceptives. It appeared that 15 per cent of them used this form of contraception but as the figure corresponded to the general use of oral contraception in Denmark no evidence of causal connexion between oral contraception and the incidence of coronary thrombosis was postulated.

After the initial reports of isolated cases of myocardial infarction in young women on the 'pill' (Naysmith, 1965; Scharf *et al.*, 1968), Vessey and Doll (1969) collected from the hospitals of the North West Metropolitan Regional Board 17 cases of myocardial infarction in menstruating women, 2 (12%) of whom had been using oral contraceptives compared with the expected figure of 2.1, in keeping with their previous conclusion (1968) that the existence of a risk of a coronary thrombosis in this situation was not proved.

This, however, was not completely borne out by the extensive study of Oliver (1970), who saw 41 women, aged 41 years or less, with myocardial infarction, 11 of whom (30%) had been taking oral contraceptives. However, in all but 2 another pre-

disposing cause, e.g. hyperlipidaemia, hypertension, or excessive cigarette smoking, was also present.

During 1968–1972, 126 women with myocardial infarction were admitted into our Coronary Care Unit. Only 4 of these were in the under 41 age group, and 3 of them, subjects of this report, were on the 'pill' at that time. Two patients were moderate to heavy smokers and the fathers of all of them died of myocardial infarction after the age of 50 years. One patient had slight hypertension while on the oral contraceptive which returned to normal after this had been discontinued.

The modest rises in serum cholesterol and pre-beta lipoproteins in Case 2 can be explained on the basis of the contraceptive pill which has been shown to raise the levels of serum triglyceride, cholesterol, low density, and very low density lipoproteins (Wynn, Doar, and Mills, 1966; Aurell, Cramer, and Rybo, 1966; Stokes and Wynn, 1971). Such changes in the lipid pattern are said to resemble those in men and possibly predispose to the development of atherosclerosis (Swyer, 1968), and might have been responsible for the coronary arteriographic changes in Case 2. Waxler *et al.* (1971) documented in detail 3 cases of myocardial infarction associated with the use of the contraceptive pill. Two of the patients were smokers and the third one had a strong family history. All had normal serum lipids, but selective coronary arteriography showed a single, smooth, occluding lesion of the left coronary artery in each case, contrasting with the diffuse changes in our Case 2.

Stout (1969) described the necropsy of a patient who was on oral contraceptives and had a myocardial infarction where thromboses of the coronary arteries were present with atherosclerosis. Kimbiris *et al.* (1972), on the other hand, reported normal coronary angiographic findings in a female patient aged 36 years on oestrogen therapy, who had typical clinical and laboratory evidence of an acute myocardial infarction.

In rats oestrogen was found to have a direct effect on the vessels producing polyarteritis-like lesions (Cutts, 1966), though to our knowledge this has not been confirmed in any other animals and certainly not in human beings. Oral contraceptives, however, were shown to disturb the clotting mechanisms through an increase in activity of Factor 7 and to a lesser degree of Factor 10 (Poller and Thomson, 1966).

The duration of oral contraceptive therapy in the patients of Oliver (1970) varied from 6 months to 6 years and those of Waxler *et al.* (1971) from 8 months to 3 years. In our cases this period was from 3 to 5 years.

Considering these findings it seems possible that oral contraceptives may occasionally accelerate

thrombogenesis with or without associated serum lipid changes and result in myocardial infarction in menstruating women, especially those with family history or other predisposing causes. Our figures, though admittedly small, are consistent with this hypothesis. Only a larger collection of cases, however, can give more decisive information on this point.

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