Oral Contraceptives and Myocardial Infarction

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Summary: During 1965-9 22 women aged 41 years or less have been seen with myocardial infarction. Eleven had been taking oral contraceptives. This prevalence of oral contraception (50%) is appreciably greater than that estimated for women of the same age in the general population.

Nine of these 11 women had an independent increased risk of developing ischaemic heart disease because of hyperlipidaemia, hypertension, or excessive cigarette smoking. Ten of the 11 not taking an oral contraceptive also had a readily identifiable predisposing factor. None of the 22 showed carbohydrate intolerance. The similarity of the two groups is the striking finding. Details of 15 women of comparable age seen during 1960-4 before oral contraceptives were widely used are also presented, and they had similar characteristics.

Oral contraceptives do not appear on their own to increase the risk of developing myocardial infarction, but they may do so in women otherwise prone to ischaemic heart disease. Suggestions are made for the identification of these women.

Introduction

The relationship between the taking of oral contraceptives and the occurrence of myocardial infarction is uncertain. It will remain so until information is collected prospectively concerning the incidence of myocardial infarction in two comparable populations, one receiving oral contraceptives and the other acting as a control. Meanwhile, it is the responsibility of cardiologists who see many patients with ischaemic heart disease to describe their experience. The accumulation of individual series may indicate whether or not a relationship exists and may show if the risk is confined to any particular group of women.

It is the purpose of this paper to report details of 11 women who developed myocardial infarction while receiving an oral contraceptive. In an attempt to clarify the connexion between oral contraceptives and myocardial infarction, the characteristics of these women are compared with those of women who were not users of oral contraceptives but who developed myocardial infarction at a comparable age.

Methods

Serum cholesterol was estimated by the method of Jurand and Albert-Recht (1962) or by the Technicon AutoAnalyzer method N24A. Serum triglycerides were estimated in the fasting state as glyceride glycerol by the method of Carlson (1963). Glucose tolerance was carried out by estimating blood glucose at half-hourly intervals over two and a half hours following an oral load of 50 g. of glucose; blood glucose was estimated by an automated glucose-oxidase method.

The following scoring system has been used to record a history in patients or siblings of angina or myocardial infarction, of death from coronary thrombosis, or of a sudden death:

One parent aged 50-70 years	1 point
Two parents aged 50-70 years	2 points
One sibling aged 50-70 years	2 points
Two or more siblings aged 50-70 years	3 points
One parent aged less than 50 years	3 points
Two parents aged less than 50 years	4 points
One sibling aged less than 50 years	3 points
Two or more siblings aged less than 50 years	4 points

The points have been aggregated when more than one generation was affected.

Case Reports

The detailed characteristics of 11 women in whom myocardial infarction occurred while taking an oral contraceptive are given in Table I. For contrast, the same details are shown in Table II for 11 women who had never taken an oral contraceptive but who also developed myocardial infarction when aged 41 years or less. These 22 women were all seen during 1965-9 and represent the total number of women aged 41 or less seen during these years. Additional information is presented (Table III) from 15 women who developed myocardial infarction at 41 years or less during the quinquennium before oral contraceptives were widely used (1960-4).

The most striking finding is the similarity between the users and non-users of oral contraceptives, though the former were more parous, and in the latter there were more who smoked many cigarettes. Most of the users of oral contraceptives had characteristics which could operate independently to increase their risk of developing ischaemic heart disease prematurely. Six of the 10 who survived had hypercholesterolaemia or hypertriglyceridaemia; while a rebound rise after withdrawal of oestrogens is well documented (Oliver and Boyd, 1956), this lasts only about 10 to 12 weeks, and persistence of high levels at and beyond this time is probably independent of taking an oral contraceptive (Tables I and III). Those with the highest serum cholesterol levels were of blood group A (Oliver, Geizerova, Cumming and Heady, 1969). Two had hypertension (both also had hyperlipidaemia). None showed carbohydrate intolerance. If excessive cigarette smoking is taken into account as well, only two (Cases 6 and 9) did not have some measurable increase in risk; but Case 6 had a strong family history of ischaemic heart disease (Deutscher, Epstein, and Kjelsberg, 1966) and Case 9 had had an early menopause, which is associated with an increased incidence of ischaemic heart disease (Sznajderman and Oliver, 1963).

Discussion

The characteristics of these women are similar to those who developed myocardial infarction without taking oral contraceptives and also to a larger group of young women with myocardial infarction previously reported (Oliver, 1967). Accordingly, it cannot be concluded that oral contraceptives were the sole cause of myocardial infarction of these women. This finding contrasts with a Danish survey of 14 cases of coronary thrombosis in users of oral contraceptives (Dalgaard and Gregersen, 1969), which suggested that a predisposition to the disease was not a factor, though details of serum lipids, carbohydrate tolerance, blood pressure and smoking habits were not given since eight were not identified until after death. Nor can it be concluded that an oral contraceptive acts as a final trigger to the onset of infarction as 9 of the 11 patients reported here had been receiving oral contraception for long periods. Indeed, the long duration of treatment is in contrast with the experience of Keown (1969) for non-coronary arterial thrombi in users of oral contraceptives and with the short period of treatment in the Danish survey.

Nothing definitive can be said from such small numbers concerning any change in incidence during the past five years. The fact that 22 women aged 41 or less have been seen on account of acute myocardial infarction during 1965-9 compared with 15 during 1960-4 does not necessarily indicate a real increase, since a six-bedded coronary care unit

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TABLE I. — *Characteristics of Women Who Used Oral Contraceptives and Developed Myocardial Infarction During 1965-9. Glucose Tolerance Tests were Carried Out in All Women.*

Case No.	Age in Years	Para.	Site of M.I.	Mean Serum Cholesterol (mg./100 ml.)		Mean Fasting Serum Triglycerides (mmol/l.)		Mean B.P. (mm. Hg) 12-26 Weeks after M.I.	Weight at Time of M.I. in Relation to Standard	Family History of I.H.D.* (Score)	Blood Group	Pre-infarct Cigarette Smoking (per day)	Oral Contraceptive	Duration of Oral Contraception	Comments
				Within 12 Weeks of M.I.	12-26 Weeks after M.I.	Within 12 Weeks of M.I.	12-26 Weeks after M.I.								
1	35	3	Inferior	395	286	—	1.24	150/96	+20%	1	A +	15	Anovlar	3½ years	Nil
2	37	4	Anteroseptal	321	272	1.22	1.50	120/70	-20%	1	O +	20	Anovlar	6 years	Recurrent thrombophlebitis while receiving Anovlar
3	25	2	Anterior	187	136	1.63	1.02	110/70	-10%	0	B +	20+ for 10 years	Gynovlar	6 months—off for 1 year during pregnancy. On for 3 months before M.I.	Nil
4	41	4	Inferior	295	284	1.15	1.56	186/108	+10%	1	A	20	Ovulen	3 years	Recurrent thrombophlebitis while receiving Ovulen
5	37	4	Anteroseptal	—	286	—	1.21	180/110	+20%	0	O	5 for 15 years	Ovulen, Lyndiol	4 years	Pre-eclamptic toxæmia in all pregnancies. "Flat" curve after G.T.T.
6	34	2	Anterior	186	184	1.06	1.28	130/75	Standard	4	O +	0	Ovulen, Norinyl-1	1½ years	"Flat" curve after G.T.T.
7	41	2	Anteroseptal	272	420	1.80	2.10	112/70	+25%	0	A +	20	Anovlar	2 years	Bilateral xanthelasma. Type IV lipoproteinaemia
8	30	3	Inferior	653	596	2.16	2.32	122/78	Standard	2	A	15	Ovulen	3 months	Type II lipoproteinaemia. Xanthoma tendinosum. Calcification in circumflex coronary artery. "Flat" curve after G.T.T.
9	39	5	Inferior	—	195	—	0.91	112/72	-10%	0	O +	10	Anovlar, Gynovlar, Sequens	22 months	Infarct on day of hysterectomy
10	33	6	Anterior	202	245	1.89	1.40	100/60	Standard	0	AB	30	Anovlar (2 years) Ovulen (2 years)	4 years	Nil
11	33	2	Anteroseptal	177	—	1.2	—	108/60 (on admission)	Standard	2	A +	25 +	Norlestrin	3 years	Two definite M.I. with E.C.G. and enzyme changes. Second occurred 7 weeks after first and 12 days after recommencing Norlestrin. Died 2 months after second M.I. No necropsy

*For family history score see text.

TABLE II.—*Characteristics of Women Who Did Not Use Oral Contraceptives and Developed Myocardial Infarction During 1965-9.*

Case No.	Age in Years	Para.	Site of M.I.	Mean Serum Cholesterol (mg./100 ml.) 6-12 weeks after M.I.	Mean Fasting Serum Triglycerides (mM/l.) 6-12 weeks after M.I.	B.P. (mm. Hg) 6-12 weeks after M.I.	Weight at Time of M.I. in Relation to Standard	Family History of I.H.D.* (Score)	Blood Group	Pre-infarct Cigarette Smoking (per day)	Comments
12	34	0	Anterior	256	1.76	112/70	+50%	1	AB	25+	Lag curve during glucose tolerance test
13	37	2	Intramural, anterior	294	1.24	110/80	+10%	1	O+	20	Coronary angiogram = blocked right coronary artery. Angina for 1 year
14	32	4	Anterior	230	2.21	118/76	Standard	1	O	20+	Pre-eclamptic toxæmia in last pregnancy. Femoral embolectomy after myocardial infarction
15	34	1	Inferior	211	0.92	190/120	+10%	0	—	20	Known hypertensive on treatment
16	37	0	Anterior + inferior	302	1.60	160/100	+40%	0	A	40	Nil
17	35	0	Anteroseptal	317	0.51	115/90	Standard	0	O	25	Nil
18	39	7	Inferior	488	1.21	110/72	Standard	4	A	30	Nil
19	32	0	Inferior	318	2.27	115/75	+10%	0	B	20	Spontaneous menopause, aged 30
20	41	0	Anterior	327	3.60	108/76	-10%	6	A	20	Xanthoma tuberosum. Type IV hyperlipoproteinaemia
21	37	1	Inferior	393	1.04	160/110	-10%	0	A	10	Advanced renal disease and failure
22	38	3	Inferior	—	—	88/60 on admission	Standard	1	—	20	Ventricular fibrillation before and after admission to coronary care unit—died. No necropsy.

*For family history score see text.
Glucose tolerance tests were carried out in all women except case 11.

TABLE III.—*Some of the Characteristics of 37 Women with Myocardial Infarction Under 41 Years seen During 1960-9.*

Groups	Total No.	Mean Age in Years	Mean Parity	Mean Serum Cholesterol (≥ 270 mg./100 ml.)	Mean Serum Triglycerides (≥ 1.6 mM/l.)	S.B.P. ≥ 160 or D.B.P. ≥ 110	Family History Score ≥ 3	Cigarette Smoking ≥ 20 /Day	N.S.	10% or More Above Standard Weight
1965-9. Users of oral contraceptive (aged 25-41 years) (Table I)	11	34	3.4	60%*	20%*	20%	9%	55%	9%	36%
1965-9. Never had oral contraceptive (aged 32-41 years) (Table II)	11	36	1.6	64%	45%	27%	18%	91%	0	45%
1960-4. Never had oral contraceptive (aged 28-41 years)	15	37	2.1	53%	27%	40%	27%	40%	6%	46%

*Percentage with raised serum lipids is taken from figures obtained between 12 and 26 weeks after stopping the oral contraceptive.

opened in the Royal Infirmary in April 1966 and this enabled a more complete survey to be made of all patients with recent infarction. Further, the overall experience in this hospital has shown that more patients with acute myocardial infarction are now being referred by general practitioners. A personal interest in ischaemic heart disease in young women (Oliver, 1967) which is known locally, may also have contributed to the number of women referred.

On the other hand, the finding in this study that during 1965-9 50% of women with myocardial infarction aged 41 years or less were taking an oral contraceptive is of interest. The frequency of use of these preparations in the general population of similar ages rose from about 4% in 1965 to about 13% in 1969 and so, on this basis, only two women with myocardial infarction would have been expected to have been using oral contraceptives (M. P. Vessey, personal communication, 1970). It is difficult, however, to obtain accurate figures of the prevalence of oral contraception, and one as high as 22% in the higher income groups has recently been reported (Gorer, 1970).

The Committee on Safety of Drugs (Inman and Vessey, 1968) studied the relationship between oral contraception and myocardial infarction. In an analysis of 205 deaths from coronary thrombosis there was a slight excess of oral contraceptive users in women who had a coronary thrombosis when compared with the expected incidence. This was true, however, only for women without predisposing features, and the reverse applied in women with predisposing conditions, such as hypertension, a previous stroke or coronary thrombosis, diabetes, and hypercholesterolaemia. Vessey and Doll (1968) found no relationship between oral contraception and coronary thrombosis in married women under 40 discharged during 1964-6 from 16 large general hospitals; 13 of the 16 patients reported survived an attack of coronary thrombosis and only one had been using an oral contraceptive—details of

the three women who died are not available. Thus the evidence at present is such that if oral contraceptives play any part in the pathogenesis of coronary thrombosis their contribution is too modest to have been detected by the epidemiological techniques so far employed.

Nevertheless, oral contraceptives may have an aggravating effect in leading to coronary occlusion in highly prone women. This could operate in at least four ways—by raising certain serum lipids, by reducing carbohydrate tolerance, by leading to raised blood pressure, and by increasing platelet adhesiveness. Oral contraceptives have been shown to do all of these (Gershberg, Javier, and Hulse, 1964; Aurell, Cramér, and Rybo, 1966; Wynn, Doar, and Mills, 1966; Wynn and Doar, 1966; Woods, 1967; Laragh, Sealey, Ledingham, and Newton, 1967; Bolton, Hampton, and Mitchell, 1968; Wynn and Doar, 1969; Wynn, Doar, Mills, and Stokes, 1969; Doar and Wynn, 1970). It is also well documented that the risk of developing myocardial infarction at an early age is greater in the presence of hypercholesterolaemia and hypertension (Truett, Cornfield, and Kannel, 1967), abnormal carbohydrate tolerance (Ostrander, Francis, Hayner, Kjelsberg, and Epstein, 1965), and excess cigarette smoking (Doll and Hill, 1964).

In the present series an increased risk of developing myocardial infarction might have been recognized in 5 of the 11 cases. In two (Cases 4 and 5) hypertension should have been detected by regular clinical examinations; in one (Case 6) the family history of ischaemic heart disease might have mediated against recommending oral contraception, and xanthomatosis might have been recognized in Cases 7 and 8.

Two practical issues have to be faced. What advice should be given to those about to start oral contraception and what advice is necessary for those already using oral contraception?

With regard to the first question, a formal study is needed to find out whether women with initially raised serum lipids,

mild hypertension, and carbohydrate intolerance develop greater abnormality of these indices when on oral contraceptives compared with those in whom the initial levels were normal. If this turns out to be the case, then all women should be screened for these abnormalities before starting oral contraception.

With regard to the second question, identification in users of oral contraceptives of raised serum lipids or hypertension is desirable since these women should be advised to use other contraceptive measures, particularly if they also smoke cigarettes excessively or have had a rapid gain in weight.

All women on oral contraceptives should therefore be reviewed medically at regular intervals, certainly once a year. Their blood pressure and weight should be checked. Serum cholesterol should probably also be measured at least once during the first year after starting oral contraception, and figures above 270-300 mg./100 ml. indicate further investigation. Since there is doubt whether oral contraceptives have an adverse effect on carbohydrate tolerance (Clinch, Turnbull, and Khosla, 1969) and intolerance was not a feature of this series, it can probably be disregarded; at most, a postprandial check for glycosuria could be done annually.

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Urban and Social Origins of Childhood Bronchitis in England and Wales

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Summary: A survey of respiratory disease in over 10,000 children aged 6 to 10 years living in contrasting urban and rural areas of England and Wales showed pronounced social class gradient in the frequency of chronic cough, history of bronchitis, and also in disease of ears and nose. A consistent rise in the frequency of chest conditions with increasing local levels of air pollution was clearly seen only among the children of semi-skilled and unskilled workers. No such gradient was obvious for diseases of the ear and nose. These trends in chest disease in children paralleled similar trends in mortal and disabling bronchitis among adults in the same areas. The excess rate for bronchitis in children and adults found in South Wales could not be accounted for by local levels of air pollution.

Introduction

Evidence is accumulating that the level of bronchitis in early adult life depends in part on experience of respiratory disease in childhood and that environmental conditions, such as air pollution or other urban factors, may affect both chronic lung disease in adults and lower and perhaps upper respiratory tract disorders in children (Reid, 1969). In adults, however, smoking is of such importance that its effect obscures those of other environmental agents. Among children under the age of 11 years smoking has hardly begun (Todd, 1969). Surveys in children may thus show more clearly the influence of factors other than smoking on respiratory disease. Parental social class was important in the past (Grundy and Lewis-Fanning, 1957; Douglas and Bloomfield, 1958). Outside the home, urban conditions in general and air pollution in particular are

of prime interest. Of such factors outside the home, urban conditions in general and air pollution in particular are of prime interest.

We here describe an inquiry conducted in collaboration with the school medical officers of the areas concerned (see below) on the prevalence of both upper and lower respiratory tract diseases in boys and girls aged 6 to 10 in relation to their past history, their home and social circumstances, and the air pollution level and other environmental features of the area where they lived. Samples of children attending primary schools in areas representing a wide range of urban and rural environments were chosen in England and Wales. In England, Bolton and Newcastle were selected as large cities with high levels of air pollution, Bristol and Reading as large cities with much lower levels, while parts of the rural areas of Lancashire, Northumberland, Northampton, Essex, and West Sussex were taken as typical districts with relatively low levels. In South Wales, where anthracite and similar coals are burned and smoke pollution is relatively low, Merthyr Tydfil and rural Glamorgan were surveyed.

Sampling Within Areas

To give balanced samples of adequate size, 500 children of each sex in each year of life from 6 to 10 years were selected in each area. In the rural areas all the children attending the local primary schools were included in the survey. In Northamptonshire, Essex, West Sussex, and Glamorgan a single rural district yielded about 1,000 children aged 6 to 10 years, but in Lancashire and Northumberland more than one rural district had to be covered to give this total. Some primary schools, in rural areas but drawing large numbers of children from near-by towns, were excluded. In Bolton and Newcastle, where some areas housed largely working-class or upper- and middle-class families, a primary school within

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