Disturbances of insulin in British Asian and white men surviving myocardial infarction

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Abstract

Objective—To examine the role of insulin as a cardiovascular risk factor in British Asian and white men.

Design—Case-controlled study of survivors of first myocardial infarction.

Setting—District general hospital.

Patients—Consecutive series of 76 white and 74 Asian men who survived first myocardial infarction compared with 58 white and 61 Asian male controls without coronary artery disease who were randomly sampled from the community.

Results—More Asians than white subjects had impaired glucose tolerance or overt diabetes as measured by the two hour glucose tolerance test (23/74 (32%) *v* 11/76 (15%) ($p<0.001$) among patients; 17/61 (28%) *v* 3/58 (6%) ($p<0.001$) among controls). Insulin and C peptide concentrations were higher in both patient groups than in respective controls ($p<0.001$) and higher in Asian than in white subjects, irrespective of their glucose tolerance. Triglyceride concentrations were higher in patients than in controls (1·92 (SD 1·05) *v* 1·43 (0·82) mmol/l among Asian men; 1·65 (0·83) *v* 1·3 (0·61) mmol/l among white subjects; $p<0.001$).

Total cholesterol concentrations were lower in both groups of Asians than in respective white subjects (5·78 (0·99) *v* 6·22 (1·04) mmol/l ($p<0.01$) among patients; 5·54 (1·01) *v* 5·65 (1·11) mmol/l ($p<0.6$) among controls). High density lipoprotein cholesterol concentrations were lower in Asian than in white subjects. The ratio of total cholesterol to high density lipoprotein cholesterol was significantly higher ($p<0.001$) in both patient groups (6·69 (1·81) in Asian patients and 6·31 (1·91) in white patients) than in respective controls (5·24 (1·19) and 4·77 (1·43)).

Regression analysis identified C peptide concentration and the ratio of total to high density lipoprotein cholesterol as powerful independent predictors of myocardial infarction in Asian and white men. Total cholesterol concentration predicted infarction in white but not in Asian men.

Conclusions—Secretion and hepatic extraction of insulin are high in survivors of myocardial infarction and especially high in British Asians. Tissue resistance to the action of insulin, giving rise to increased pancreatic secretion, may be an important risk factor for coronary artery disease in both ethnic groups and may be partly responsible for the high incidence of diabetes and coronary artery disease in Asian populations.

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Introduction

The roles of insulin and hyperglycaemia in myocardial infarction have been debated for many years; several studies have reported an association between insulin and subsequent coronary events,[1,2] but the link has been questioned.[3] Migrant people who originate from the Indian subcontinent have an increased susceptibility to coronary heart disease.[4-9] The excess rates of coronary heart disease seem to occur in most subgroups originating from Gujarat, Punjab, Bangladesh, or southern India and living under diverse cultural, religious, socioeconomic, and dietary conditions. A parallel finding within these Asian communities has been the high prevalence of non-insulin dependent diabetes and impaired glucose tolerance, and some authors have attempted to explain the excess cardiovascular morbidity on this basis. McKeigue *et al* found higher concentrations of insulin and rates of overt diabetes in a Bangladeshi population in east London than in a white population in the same area.[10] Although rates of ischaemic heart disease were not assessed, an earlier study found an increased cardiovascular mortality in this Asian population.[4] Insulin resistance was proposed as a possible common pathophysiological basis for both conditions.[10]

Our study was designed to compare body morphology and lipid, insulin, and C peptide concentrations in Asian and white men who survived a first myocardial infarction with that in healthy controls matched for age and ethnic group.

Subjects and methods

PATIENTS

Consecutive patients who had been discharged from Northwick Park Hospital coronary care unit were recruited on the basis of the following entry criteria: a documented history of first myocardial infarction (using standard criteria[11]) between six months and two years previously; no family history or biochemical evidence of familial hyperlipidaemia; and no evidence of malignancy or other serious medical conditions. Blood samples were not drawn from diabetic patients receiving insulin, but these patients were included in the calculation of prevalence of diabetes. Three patients receiving β blockers and four receiving thiazide diuretics had this treatment withdrawn in view of the influence of these drugs on serum lipid concentrations[12,13] and were changed to a calcium antagonist.

Patients' ethnic origins were determined by birth place of their grandparents, and two broad ethnic groups were recruited in equal numbers. Asians included all patients originating from India, Pakistan, and Sri Lanka, including those who had migrated through east Africa, and white patients included those originating from the United Kingdom, Republic of Ireland, or northern Europe.

CONTROLS

After the patients had been recruited the control subjects were selected from the lists of four local general practitioners. Notes of 233 potential controls were selected by age stratified random sampling to match the mean ages of the respective patient groups. Those with a history of cardiac or peripheral vascular disease, stroke, mental handicap, familial hyperlipidaemia, or other serious disease were excluded (69 subjects). Diabetics treated with insulin were eligible, but blood samples were not taken from these subjects. The 164 potential control subjects were invited to participate by registered letter.

Non-respondents were personally contacted by their general practitioner and again invited to participate in the study. By these means 63/76 (81%) of the white and 64/88 (72%) of the Asian controls who were initially contacted attended for blood testing and examination.

Subjects were asked to fast from 10 pm on the day before attending the clinic. Each drank 75 g anhydrous glucose diluted in 500 ml water 90 minutes before attending the hospital. A single venous blood sample was drawn as near as possible to 120 minutes after the drink. Serum was separated immediately and concentrations of total cholesterol, high density lipoprotein cholesterol, triglyceride, and plasma glucose were measured within 24 hours by standard methods.[14-17] Serum concentrations of insulin and C peptide were then assayed in a single batch with a semiautomated radioimmunoassay. Glucose tolerance state was determined by World Health Organisation criteria.[18]

Blood pressure (sitting diastolic phase V measured with a random zero sphygmomanometer), weight, height, hip, and maximal abdominal girth were measured in all subjects by the same trained observer. Controls, including the known diabetics, were also screened at rest with a 12 lead electrocardiograph and excluded if the electrocardiogram showed evidence of previous infarction or ischaemia.[11]

STATISTICAL ANALYSIS

Values for triglyceride, glucose, insulin, and C peptide concentrations were logarithmically transformed to normalise their distributions. Group means were compared by analysis of variance and prevalence by χ^2 tests. Multivariate regression analysis was used to examine the influence of different variables on the relative risk of myocardial infarction in the two ethnic groups and to examine the relation between body mass, C peptide concentrations, and lipid concentrations.

Results

Of the 74 Asian patients recruited, 48 (63%) were of Gujarati origin and the others of Pakistani, Bengali, Punjabi, or Goan origin. After those controls with abnormal electrocardiograms had been excluded 45 (76%) Gujarati, 13 non-Gujarati Asian, and 57 white controls were included in the analyses.

Asian patients were younger than white patients (50·7 (range 25-69) *v* 55·9 (38-67) years; p<0·001), but controls were closely age matched (50·9 (28-66) *v* 51·5 (33-67) years). Asian men were shorter than white men and had lower body mass indices, but the waist to hip ratio was significantly higher in Asian patients than in white patients (0·95 (0·05) *v* 0·93 (0·06); p<0·02). Asian patients had lower blood pressures (table I).

Insulin and C peptide concentrations after glucose were significantly higher in both patient groups than in respective controls, and C peptide concentrations were significantly higher in all Asians than in all whites (p<0·001) (table II). Table III shows the logarithms of the insulin and C peptide concentrations. To highlight differences in insulin and C peptide concentration in comparable categories of blood glucose concentration each of the groups was subdivided according to glucose tolerance. More Asian patients 23/74 (32%) and controls 17/61 (28%) had impaired glucose tolerance or overt diabetes than the respective white groups (11/76 (15%) and 17/61 (6%)). Among Asian controls three of the seven diabetics were already known, as was the one diabetic white control. Glucose intolerance (overt diabetes and impaired glucose tolerance) was significantly more prevalent in white patients than controls (p<0·02). In both Asian groups and in white patients insulin and C peptide concentrations were significantly higher in subjects with impaired glucose tolerance than in those who were normoglycaemic (p<0·005). Among normoglycaemic subjects C peptide concentrations were significantly higher in both groups of patients than in respective controls (p<0·001) and higher in Asians than in whites (p<0·05). No difference in insulin concentrations was found between Asian patients and controls (table II), but in normoglycaemic controls the insulin concentrations were significantly higher in Asians than in whites (p<0·05) (table III).

Triglyceride concentrations were higher in patients than in controls: 1·92 (1·05) mmol/l *v* 1·43 (0·82) mmol/l in Asians and 1·65 (0·83) mmol/l *v* 1·30 (0·61) in whites (p<0·001) (table II). In all Asian subjects the mean triglyceride concentration (1·71 (0·91) mmol/l) was higher than in all white subjects (1·50 (0·72) mmol/l).

Total cholesterol concentration was higher in white patients than in white controls (6·22 (1·04) mmol/l *v* 5·65 (1·11) mmol/l), but no significant difference was found between Asian patients and controls. Concentrations in Asian patients (5·78 (0·99) mmol/l) were lower than in white patients. Concentrations of high density lipoprotein cholesterol were significantly lower in patients than in controls: 0·92 (0·24) mmol/l *v* 1·09 (0·23) mmol/l in Asian subjects and 1·04 (0·23) mmol/l *v* 1·25 (0·31) mmol/l in white subjects (p<0·001) and also in Asians than in respective groups of whites. Hence the ratio of total cholesterol to high density lipoprotein cholesterol was higher in patients

TABLE I—*Mean (SD) blood pressure, body mass index, and waist to hip ratio in Asian and white men*

	Patients		Controls		
	Asian (n=74)	White (n=76)	Asian (n=58)	White (n=57)	p Value*
Systolic blood pressure (mm Hg)	126·4 (17)	133·5 (16)	129·4 (18)	130·1 (15)	0·08
Diastolic blood pressure (mm Hg)	79·7 (10·7)	84·6 (10·1)	80·3 (11)	81·7 (11·4)	<0·04
Body mass index (kg/m^2)	24·5 (3·0)	25·5 (3·6)	23·7 (3·4)	25·4 (3·4)	<0·01
Height (cm)	170 (6·0)	174 (6·3)	169 (7·0)	175 (7·6)	<0·001
Weight (kg)	70·9 (8·4)	77·8 (12)	67·7 (11·1)	77·6 (10·8)	<0·001
Waist to hip ratio (units)	0·95 (0·05)	0·93 (0·06)	0·94 (0·05)	0·94 (0·05)	0·09
Waist (cm)	91·9 (6·8)	93·0 (10·1)	87·9 (10·6)	92·1 (8·9)	<0·06
Hip (cm)	96·5 (5·9)	99·8 (7·2)	93·4 (9·1)	98·2 (7·7)	<0·01

*Group differences compared by analysis of variance.

TABLE II—*Mean (SD) cholesterol and triglyceride concentrations and mean (SE) insulin and C peptide concentrations in Asian and white men who survived a first myocardial infarction and Asian and white controls*

	Patients		Controls		
	Asian (n=74)	White (n=76)	Asian (n=58)	White (n=57)	p Value*
Total cholesterol (mmol/l)	5·78 (0·99)	6·22 (1·04)	5·54 (1·01)	5·65 (1·11)	<0·001
High density lipoprotein cholesterol (mmol/l)	0·92 (0·24)	1·04 (0·23)	1·09 (0·23)	1·25 (0·31)	<0·001
Ratio of total cholesterol to high density lipoprotein cholesterol	6·69 (1·81)	6·31 (1·91)	5·24 (1·19)	4·77 (1·43)	<0·0001
Low density lipoprotein cholesterol (mmol/l)	4·86 (0·90)	5·18 (0·94)	4·45 (0·92)	4·40 (1·01)	<0·001
Triglyceride (mmol/l)†	1·92 (1·05)	1·65 (0·83)	1·43 (0·85)	1·30 (0·61)	<0·001
Insulin (pmol/l)	486 (53)	398 (50)	431 (48)	209 (20)	<0·001
C peptide (pmol/l)	1673 (90)	1362 (94)	872 (71)	685 (60)	<0·001

*Analysis of variance.
†All Asians 1·71 (0·91); all whites 1·50 (0·72).

than in controls: 6·69 (1·81) *v* 5·24 (1·19) in Asians and 6·31 (1·91) *v* 4·77 (1·43) in whites ($p<0·0001$).

Table IV shows the univariate effects of C peptide, insulin, glucose, triglyceride, total cholesterol, and high density lipoprotein cholesterol concentrations and the ratio of total cholesterol to high density lipoprotein cholesterol on the relative risk of infarction for Asian and white patients. In both ethnic groups C peptide concentration was the strongest predictor of infarction, even allowing for all other terms in a multiregression analysis. Triglyceride concentration was associated with an increased relative risk of infarction in both ethnic groups but dropped out when cholesterol was included in the regression model. In white but not in Asian patients total cholesterol concentration was a strong predictor of infarction. The ratio of total cholesterol to high density lipoprotein cholesterol was a strong predictor in both ethnic groups and remained so after other terms had been allowed for.

Table V shows the relation between body morphology, cholesterol, triglycerides, and C peptide. In both Asian and white subjects the body mass index was a significant predictor of C peptide concentration but only in Asians was the waist to hip ratio predictive of C peptide concentration. In white subjects triglyceride concentrations were predicted by C peptide concentration, body mass index, and waist to hip ratio, with all of these independent variables contributing significantly to the model. In Asians C peptide concentration was not related to triglyceride concentration, but triglyceride concentration was predicted by both body mass index and waist to hip ratio with a multiregression model.

TABLE III—*Mean (SD) two hour insulin and C peptide concentrations in Asian and white subjects by glucose tolerance category. Concentrations are logarithmically transformed*

Category	Patients		Controls	
	Asian (n=74)	White (n=76)	Asian (n=61)	White (n=58)
Normoglycaemic:				
No	50 (68%)	65 (85%)	44 (72%)	55 (94%)
Insulin (pmol/l)	2·39 (0·33)	2·30 (0·47)	2·40 (0·26)‖	2·18 (0·36)
C peptide (pmol/l)	3·11 (0·24)§	3·03 (0·16)§	2·75 (0·29)	2·73 (0·23)
Impaired glucose tolerance*:				
No	9 (12%)	8 (11%)	10 (16%)	2 (4%)
Insulin (pmol/l)	3·01 (0·22)‡	2·78 (0·24)‡	2·91 (0·15)‡	2·59 (0·04)
C peptide (pmol/l)	3·36 (0·19)‡	3·24 (0·16)‡	3·14 (0·14)‡	
Diabetic†:				
No	14 (20%)	3 (4%)	7 (12%)	1 (2%)
Insulin (pmol/l)	2·60 (0·38)	2·16 (0·56)	2·79 (0·46)	
C peptide (pmol/l)	3·22 (0·18)	2·99 (0·42)	3·10 (0·22)	

*Two hour glucose >7·8 mmol/l and <11·0 mmol/l.
†Two hour glucose >11·1 mmol/l.
‡Insulin and C peptide concentrations higher in those with impaired glucose tolerance than in those with normoglycaemia ($p<0·005$).
§C peptide concentrations higher than in respective controls ($p<0·001$) and higher in Asian than in white patients ($p<0·05$).
‖Insulin concentrations higher in Asian than in white controls ($p<0·05$).

Discussion

The patients studied here were survivors of a first myocardial infarction. As consecutive discharges from the only local coronary care unit and with less than 10% lost to follow up they were representative of this type of patient with coronary heart disease living in north west London, as discussed previously.[19] Sampling was carried out a minimum of six months after infarction to allow resolution of the metabolic changes associated with infarction. No specific dietary advice had been given to patients, and the biochemical values that we obtained probably reflected those before infarction. The controls were representative of the local population, having been randomly drawn from local general practice registers. Excluding those with a history or electrocardiographic evidence of cardiac or other serious diseases resulted in an apparently healthy group for comparison.

The Asian patients in this study arise from a local population with a high prevalence of glucose intolerance,[20,21] which several studies have shown increases subsequent cardiovascular risk.[22-24] The results of the two hour glucose tolerance test did not, however, differentiate Asian patients from apparently healthy Asian controls, nor was a high glucose concentration associated with an increased relative risk of myocardial infarction in Asians. Conversely, in white subjects glucose had a significant effect on the relative risk of infarction, and there were also significantly more white patients than controls with

TABLE IV—*Effects of C peptide, insulin, glucose, cholesterol, body mass index, and waist to hip ratio on relative risk of myocardial infarction for Asian and white men*

	Asians			Whites		
	p Value (patients *v* controls)	Relative risk (SE)	Relative risk for increase of 1 unit (95% confidence interval)	p Value (patients *v* controls)	Relative risk (SE)	Relative risk for increase of 1 unit (95% confidence interval)
Univariate analysis						
C peptide (log value)	<0·0001	4·23 (0·88)	68·7 (12·25 to 385)	<0·0001	3·31 (0·74)	27·4 (6·42 to 116·8)
Insulin (log value)	0·75	0·16 (0·51)	1·17 (0·43 to 3·19)	0·08	0·77 (0·44)	2·15 (0·91 to 20·3)
Glucose (log value)	0·23	1·03 (0·86)	1·11 (0·94 to 1·31)*	0·0006	4·58 (1·47)	1·58 (1·19 to 2·11)
Triglyceride (log value)	0·0005	3·16 (0·97)	23·5 (3·52 to 157)	0·004	2·81 (1·04)	16·6 (2·2 to 128)
Total cholesterol	0·12	0·29 (0·19)	1·34 (0·92 to 1·97)	0·0007	0·624 (0·198)	1·86 (1·27 to 2·75)
High density lipoprotein cholesterol	0·0001	−3·036 (0·86)	0·05 (0·01 to 0·26)	0·0001	−3·12 (0·87)	0·04 (0·008 to 0·24)
Ratio of total cholesterol to high density lipoprotein cholesterol	<0·0001	0·69 (0·16)	1·99 (1·44 to 2·74)	<0·0001	0·57 (0·14)	1·76 (1·34 to 2·33)
Body mass index	0·113	0·09 (0·06)	1·09 (0·97 to 1·23)*	0·512	0·04 (0·05)	1·03 (0·93 to 1·15)*
Waist to hip ratio	0·162	−5·80 (3·70)	0·56 (0·27 to 1·15)*	0·43	−2·8 (3·587)	0·75 (0·37 to 1·53)*
Multivariate analysis						
C peptide (log value)	<0·0001	4·64 (1·04)	103·5 (13·5 to 795) 1·6 (1·3 to 2·0)*	<0·001	3·20 (0·88)	24·6 (4·17 to 144) 1·4 (1·2 to 1·7)*
Triglyceride (log value)	0·41	−1·2 (1·47)	0·3 (0·02 to 5·34)	0·92	−0·16 (1·79)	0·85 (0·3 to 28·7)
Ratio of total cholesterol to high density lipoprotein cholesterol	<0·0001	0·84 (0·24)	2·32 (1·45 to 3·72)	0·002	0·58 (0·20)	1·79 (1·20 to 2·67)

*Relative risk for increase of 0·1 unit.

TABLE V—*Relation between cholesterol, triglyceride, C peptide, body mass index, and waist to hip ratio in Asian and white men, allowing for effect of specified variables*

	Asians			Whites		
	F	df	p Value	F	df	p Value
Cholesterol related to:						
Body mass index	0·03	1,128	0·86	6·44	1,130	0·012
C peptide	0·28	1,124	0·6	0·52	1,127	0·47
Waist to hip ratio	2·51	1,128	0·12	12·58	1,129	0·001
Triglyceride (log value)	19·56	1,126	<0·0001	38·79	1,130	<0·0001
Ratio of total cholesterol to high density lipoprotein cholesterol related to:						
Body mass index	3·79	1,126	0·05	2·13	1,125	<0·0001
C peptide	3·96	1,122	0·05	0·39	1,127	0·53
Waist to hip ratio	2·57	1,126	0·11	13·91	1,124	0·0003
Triglyceride (log value)	51·8	1,124	<0·0001	55·47	1,125	<0·0001
Triglyceride related to:						
Body mass index	9·27	1,126	0·003	15·00	1,130	0·0002
C peptide	0·01	1,122	0·92	7·17	1,127	0·008
Waist to hip ratio	8·13	1,126	0·005	14·40	1,129	0·0002
C peptide related to:						
Body mass index	6·28	1,126	0·014	6·91	1,127	0·01
Waist to hip ratio	5·03	1,125	0·027	2·03	1,127	0·16

glucose intolerance (11/76 (15%)) *v* (3/58 (6%); $p<0{\cdot}01$). Anthropometric differences between ethnic groups included lower weights and heights and narrower hips in the Asians, but the waist to hip ratio was higher in Asian than white patients.

Insulin and C peptide are secreted by the pancreas in equal amounts. Insulin is partially extracted on first pass through the liver but C peptide is unaffected. The hypothesis tested here, that secretion of excess insulin and its metabolic consequences are associated with established coronary heart disease, has been supported in both Asians and white subjects. The lack of difference in insulin concentrations between normoglycaemic patients and controls in both ethnic groups, coupled with the raised C peptide concentration in patients, suggests that both greater pancreatic secretion and greater hepatic extraction of insulin in response to glucose are found in patients with ischaemic heart disease. Together with epidemiological evidence that a raised insulin concentration is a predictor of new coronary events,[1,2] these data add further weight to the possibility of a pathogenic role of excess insulin secretion in the development of coronary heart disease or atheroma, or both. Among migrants from the Indian subcontinent Bangladeshi Asians living in Britain have been shown to have an increased mortality from coronary heart disease,[25] and raised insulin concentrations after two hour glucose tolerance tests have been reported in this group.[10] In our study the higher concentrations of C peptide and insulin in Asian than in white controls suggest a greater risk of cardiac disease in apparently healthy Asians than in age matched white people.

Higher C peptide concentrations were found in patients of either ethnic group compared with controls, irrespective of glucose tolerance state. Both insulin and C peptide concentrations were significantly higher in subjects with impaired glucose tolerance than in normoglycaemic subjects and were lower in those with overt diabetes than in those with impaired glucose tolerance, which is compatible with the "relative pancreatic exhaustion" hypothesis for developing non-insulin dependent diabetes, in which the insulin response to an increasing glucose concentration is inadequate.[26-28] The only data not fully supporting the "excess insulin secretion" hypothesis in the pathogenesis of coronary heart disease is that black Afro-Caribbeans, who have a much lower mortality from coronary heart disease than white people in the United Kingdom,[7,8] also show some features similar to the Asians studied here, including raised ratios of insulin to glucose two hours after challenge,[21] but this ratio was lower in the Afro-Caribbeans than in Gujaratis.[21] Nevertheless, the higher mortality from diabetes in Afro-Caribbean than in white populations, coupled with possibly increasing rates of coronary heart disease in black people living in Britain may indicate that these abnormalities of insulin action and metabolism may be present for many years before the clinical presentation of coronary heart disease and diabetes; they may serve as markers for later clinical disease.

Insulin has been shown to stimulate hepatic secretion of very low density lipoprotein or triglyceride particles, or both, and to increase hepatic synthesis of cholesterol.[29-31] Under normal conditions insulin promotes the disposal of triglyceride by stimulating lipoprotein lipase activity.[31] If this response to insulin is impaired higher concentrations of circulating triglyceride will result, as seen in this study. Additionally, high density lipoprotein cholesterol production may be reduced by impaired lipoprotein lipase activity. Low concentrations of high density lipoprotein cholesterol have been associated with increased cardiovascular risk in several studies.[32-34] Indeed, a cohort of obese subjects in the Framingham study who had low high density lipoprotein and high triglyceride concentrations had not only a threefold increase in the risk of developing diabetes, but also a greatly increased incidence of cardiovascular events. Asian patients in our study were in many ways similar to this Framingham study cohort, although only the waist to hip ratio, not the body mass index, was greater in Asian than in white patients. The significant relation between the two indices of obesity and the C peptide, cholesterol, and triglyceride concentrations suggests biochemical mechanisms by which the known cardiovascular risks associated with obesity might be mediated.

The higher values for total cholesterol concentration found in white patients compared with those in controls conform to the generaliy accepted predictive value of cholesterol concentration.[34] In contrast, total cholesterol concentration was not significantly higher in Asian patients than in controls and was lower than in respective groups of white subjects, confirming previous reports.[8,10] Because of differences in the high density lipoprotein cholesterol concentration between the ethnic groups the ratios of total cholesterol to high density lipoprotein cholesterol were similar in the groups of patients and significantly higher in patients than in controls. Thus the ratio may be the more valuable means of comparing cardiovascular risk between ethnic groups.

This study has supported a role for insulin in the pathogenesis of coronary heart disease, and tissue resistance to the action of insulin may be a primary factor in the excess incidence of both coronary heart disease and diabetes in British Asians.[10,35] The more powerful independent effect of C peptide concentration as a predictor of infarction than the insulin concentration measured here also raises several questions. Firstly, is C peptide itself pathogenic? Secondly, with the recent development of a highly specific assay for insulin, pro-insulin, and its split products,[36] will these fragments emerge as more precise markers for coronary disease? Finally, could the high concentrations of secreted insulin presented to the liver determine the adverse lipid profiles that are widely known and that we have reported here in patients with myocardial infarction?

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Influence of past reproductive performance on risk of spontaneous abortion

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Abstract

***Objective*—To investigate the incidence of spontaneous abortion in a population of women in order to establish their risk of spontaneous abortion and the obstetric factors predisposing to it.**

***Design*—Prospective study of women recruited by radio and poster appeal and from hospital outpatient clinics.**

***Setting*—English provincial community.**

***Patients*—630 Women from the general population intending to become pregnant.**

***Interventions*—The viability of the pregnancy was assessed by abdominal ultrasonography before completion of the eighth week, and the assessment was repeated if vaginal bleeding occurred.**

***Main outcome measure*—Spontaneous abortion or live births in women with or without a previous history of spontaneous abortion.**

***Results*—The overall incidence of clinically recognisable spontaneous abortion before 20 weeks of gestation was 12% (50/407 pregnancies). The risk of spontaneous abortion in each category of patient was classified with respect to the patient's past reproductive performance and found to be influenced greatly by her previous obstetric history. In primigravidas and women with a history of consistently successful pregnancies the incidences of abortion were low (5% (4/87) and 4% (3/73) respectively), whereas women with only unsuccessful histories had a much greater risk of aborting the study pregnancy (24% (24/98)), even when their sole pregnancy had ended in abortion (20% (12/59)). The outcome of the last pregnancy also influenced the outcome of the study pregnancy; only 5% of women (5/95) whose previous pregnancy had been successful aborted, whereas the incidence of loss of pregnancy among women whose last pregnancy had aborted was 19% (40/214).**

***Conclusions*—A knowledge of the patient's reproductive history is essential for the clinical assessment of her risk of spontaneous abortion. As the most important predictive factor for spontaneous abortion is a previous abortion, the outcome of a woman's first pregnancy has profound consequences for all subsequent pregnancies.**

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Introduction

Spontaneous abortion is the commonest complication of pregnancy, affecting roughly one in four of all women who become pregnant.[1] When a patient has just lost a pregnancy, however, it is difficult to give informed advice about a likely recurrence, as in most cases the aetiology of the abortion is unknown. In practice it is usually assumed that the cause is non-recurrent and the patient reassured that the chance of her next pregnancy continuing successfully is much higher than the chance of her miscarrying again. Quantifying the risk to an individual patient of an early pregnancy loss after repeated abortions is even more difficult. Opinions differ widely about whether patients who have experienced consecutive losses suffer from a distinct clinical disorder or are simply unlucky.[2,3] The lack of data also makes it impossible to assess the efficacy of treatment.

One problem in establishing accurate figures is the bias introduced by the selection of patients. Most reports have been retrospective, hospital based studies of pregnant women because this sampling method provides a quick way of obtaining a large pool of data. This approach, however, yields no meaningful information about loss in first pregnancies.[1,4,5] In prospective studies in which a declared pregnancy forms the basis for recruitment early abortions that do not require medical intervention are underrepresented.[6,7]

The Cambridge early pregnancy loss study was undertaken with three aims: to determine the incidence of spontaneous abortion in a well documented population recruited before pregnancy; to identify factors predisposing to spontaneous abortion; and to assess the risk of recurrent abortion. The study population afforded an ideal opportunity for accurate collection of these data, as all patients in the catchment area received their antenatal care and were delivered at a single hospital.