VASECTOMY AND NON-FATAL MYOCARDIAL INFARCTION

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Summary The incidence of non-fatal myocardial infarction among 4830 vasectomised men was 0·9 cases per 1000 man-years during 24 420 man-years of observation. This was slightly lower than the rate in 24 150 non-vasectomised men, matched with a vasectomised man for calendar year of birth and duration of observation. Review of medical records for a matched sample of study subjects indicated no measurable confounding by important cardiac risk factors.

Introduction

VASECTOMY is an effective, convenient method of contraception which is popular in the U.S.A. and elsewhere. Although the surgical procedure seems to be safe, and serious short-term complications are uncommon, there is little detailed information on long-term medical consequences of vasectomy.

Vasectomisd macaques had accelerated rates of atherogenesis both when fed high-fat diets[1] and when fed regular monkey chow.[2] There is as yet no evidence of any increase in rates of atherosclerotic disease among vasectomised men[3] (Goldacre M. J., Clarke J. A., Heasman M. A., Vessey M. P. Unpublished) but experience is still very limited. There has been no attempt to control for confounding by individual characteristics which might be associated with both vasectomy and atherosclerotic disease. The present study, part of an examination of all hospital admissions in men with vasectomy, was undertaken to investigate the risk of non-fatal myocardial infarction among vasectomised men.

Subjects and Methods

The men whose medical histories were analysed for this study were members of Group Hospital Cooperative of Puget Sound (GHC) based in Seattle, Washington. GHC is a consumer-owned health maintenance organisation which has been in operation since 1947 and currently has approximately 280 000 members. Individuals in the Seattle area can join GHC through contracts provided by local employers and unions, through individual contracts, or through Medicare and Medicaid. The age and sex distribution of plan members reflects that of the U.S.A. population, but the proportion of younger and middle-aged adults is somewhat larger.

GHC provides comprehensive medical care to its members, who receive outpatient services in scattered clinics and hospital treatment in two hospitals owned by the cooperative. Since 1972 records of hospital discharges have been computerised through the Commission on Professional and Hospital Activities-Professional Activity Study in Ann Arbor, Michigan. All medical records for current GHC members are readily accessible; records of non-current members cannot be reliably obtained.

Segments of the vas deferens are routinely sent to the pathology department when a vasectomy is performed. This enabled us to identify a group of vasectomised men by undertaking a hand review of all pathology department records, noting members for whom a vas specimen was submitted after routine vasectomy between Jan. 1, 1963, and Dec. 31, 1978. The record numbers of men so identified were then checked in central membership files, and classed as "current" or "non-current" members. We identified 4830 current members and 1339 non-current members who had had a vasectomy. The vasectomised current members identified represented 7·6% of the total GHC male population aged 25-64 in 1979. Of these men, 514 had had vasectomy before 1971, 2009 in 1971-74, and the remaining 2307 in 1975-78.

For each of the 4830 identified current members with a vasectomy, we selected five current members matched to the vasectomised man on sex, year of birth, and membership in the plan at the time the vasectomy had been performed. We realised at the time of selection that there would be some vasectomised men in the "non-vasectomised" group. The national prevalence of vasectomy in 1976 was 10·5% among husbands of women in the age range 15-44 years,[4] and this was regarded as an acceptable level of misclassification in our non-vasectomised group.

Data analysis proceeded in two steps:

1. We calculated the number of man-years at risk after vasectomy in the vasectomised group from 1972 through 1979, the years covered by computerised data on hospital admission. Similar calculations were applied to data on non-vasectomised men, counting as the beginning of observation the date of vasectomy for the vasectomised man to whom each non-vasectomised man was matched. Because of the matching procedure, the distribution in the vasectomised and non-vasectomised groups of years of observation by age and by elapsed time since vasectomy (or corresponding matched date for the non-vasectomised) was identical. Discharge diagnoses of myocardial infarction (codes 410·0–410·9 in the International Classifications of Diseases, eighth revision) in the vasectomised and non-vasectomised cohorts were then noted and rates of acute myocardial infarction calculated on the basis of only the first such diagnosis recorded for each individual. Rates were cross-tabulated by age and years elapsed since vasectomy. "Exact" confidence intervals for rate ratios were calculated by a binomial model for the distribution of cases between exposure groups.[5]

2. We evaluated the extent of confounding in the myocardial infarction rates obtained in step 1. To do this we derived a measure of the effect of vasectomy, corrected for confounding characteristics. The matched nature of the study design permitted an efficient system of obtaining this correction,[6] by means of a Cox proportional hazards model[7] with stratification by matching group. Proportional hazards analysis is a flexible, multivariate life-table procedure which yields statistics which are estimates of the factors by which a baseline incidence rate is multiplied in the presence of various predictive characteristics. A consequence of the equations defining these estimates is that matched sets in which no event (in this study, myocardial infarction) occurs drop out of the analysis.[6] Thus, the presence or absence of various confounding characteristics needed to be determined only for those matched sets in which at least one man had a myocardial infarction. To reduce the numbers of records to be abstracted without introducing systematic bias into the data,

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TABLE I—FIRST-TIME MYOCARDIAL INFARCTION RATES IN VASECTOMISED AND NON-VASECTOMISED MEN

—	Vasectomised			Non-vasectomised			Rate ratio (95% confidence interval)
	Cases	Person-years at risk	Rate × 1000 person-years	Cases	Person-years at risk	Rate × 1000 person-years	
*Interval**							
0–1	3	8366	0·4	14	41 830	0·3	1·1 (0·2, 3·8)
2–3	5	6813	0·7	35	34 065	1·0	0·7 (0·2, 1·8)
4–5	6	4152	1·4	18	20 760	0·9	1·7 (0·5, 4·4)
6–7	3	2590	1·2	22	12 950	1·7	0·7 (0·1, 2·3)
8–16	6	2499†	2·4	31	12 495	2·5	1·0 (0·3, 2·4)
Age							
25–34	0	6685	0·0	4	33 425	0·1	0·0 (0·0, 7·6)
35–44	6	11 240	0·5	28	56 200	0·5	1·1 (0·4, 2·6)
45–54	12	5430	2·2	64	27 150	2·4	0·9 (0·5, 1·8)
55–64	5	1065	4·7	24	5325	4·5	1·0 (0·3, 2·8)
Total	23	24 420	0·9	120	122 100	1·0	1·0 (0·6, 1·5)

*Years since vasectomy or corresponding date for non-vasectomised man.
†Includes 1357 person-years at 8–9 years follow-up, 537 at 10–11 years, and 605 at 12 or more years. Follow-up in the non-vasectomised is distributed proportionately.

we reduced the original five-to-one matching to one-to-one matching. Among the resulting matched pairs, we examined medical records for both members of each pair in which at least one myocardial infarction occurred. Abstracted data included demographic information, history of vasectomy, and history of myocardial infarction. We compared these data with those on the computerised files used in the first phase of the analysis. Additionally, cardiac risk factors, including obesity, hypertension, diabetes, and smoking history, were noted, along with the date of first mention of each condition or habit in the record. All hospital admissions were recorded, as well as all outpatient visits and all drug prescriptions during the two years before myocardial infarction (or up to the corresponding date in members of the matched pairs who did not have infarction). Chart review resulted in the following changes in vasectomy and infarction status: 5/47 infarctions were recorded as "no infarction" (1 gallbladder disease, 2 occurring before follow-up was started, 1 "trivial coronary artery disease," 1 erroneous coding); 6/47 "non-vasectomised" men had in fact had vasectomies. No man in the sets reviewed had been incorrectly classed as "no infarction" or "vasectomised". All pairs in which chart review resulted in a change of vasectomy or infarction status were dropped from the analysis because either both pair members had been vasectomised or neither pair member had had an infarction. Hypertension, obesity, and diabetes were classed as (1) not present, (2) present before infarction (or the corresponding date in the non-infarction pair member) but first noted after vasectomy (or the corresponding date in the non-vasectomised pair member), or (3) present before vasectomy (or the corresponding date). Men were classed as not smoking if there was no mention in the GHC record of smoking, a mention of never smoking, or a definite mention, before vasectomy, of having stopped in the past, with no further mention of smoking. In all other circumstances men were classed as smokers.

Results

Among vasectomised men, there were 23 first-time myocardial infarctions in 24 420 man-years at risk, giving a rate of 0·9 infarctions per 1000 man-years at risk. There were 120 first-time infarctions in 122 100 man-years at risk in the non-vasectomised group, giving a rate of 1·0 infarctions per 1000 man-years at risk. The rate ratio was 1·0 (95% confidence limits 0·6 to 1·5).

Throughout the period of observation, vasectomy had no apparent effect on infarction (table I). Incidence rates rose with time in both the vasectomised and the non-vasectomised groups as men became older. In eight and subsequent years of observation, the incidence rate ratio was 1·0, with 95% confidence limits of 0·3 and 2·4. Because of the relative sparsity of experience in this group (2499 man-years at risk for the vasectomised), the observed rate ratio is consistent both with an important increase and with a complete lack of vasectomy-attributable risk. In both vasectomised and non-vasectomised men, incidence rates of myocardial infarction rose with age. Incidence rates ranged from 0 to 4·7 cases and from 0·1 to 4·5 cases per 1000 man-years at risk in the vasectomised and non-vasectomised cohorts, respectively. No age-specific rate ratio was greater than 1·1. Distribution of myocardial infarction in the matched sets of six is shown in table II. The rate ratio, calculated by means of the proportional hazards model, was 0·9 with 95% confidence limits of 0·6 and 1·5.

TABLE II—DISTRIBUTION OF MATCHED SETS ACCORDING TO OCCURRENCE OF MYOCARDIAL INFARCTION (MI) IN ONE VASECTOMISED AND FIVE NON-VASECTOMISED SET MEMBERS

—	No. of non-vasectomised men with MI					
	0	1	2	3	4	5
Vasectomised:						
MI	22	1*	0	0	0	0
No MI	4695	107	3	2	0	0

Rate ratio 0·9, 95% confidence limits 0·6, 1·5.
*Order of MIs in this group: non-vasectomised first, vasectomised second.

The rate ratio in the matched pairs unadjusted for confounding was 1·25, with 95% confidence bounds of 0·6 and 2·4. The difference between the rate ratios for the sets of six and the matched pairs is due to the effect of coding changes, as noted previously, and to the operation of chance in selecting a subset of matched controls for the matched pairs analysis. The two rate ratio estimates are entirely compatible with one another.

The distribution of cardiac risk factors in the matched pairs is shown in table III. Obesity (pre-dating vasectomy) and smoking were both associated with infarction in both vasectomised and non-vasectomised men. Vasectomised men were more often obese, and less likely to be smokers; both obesity and smoking were more common in the men who had infarcts. Neither hypertension nor diabetes appeared to be associated with vasectomy. Simultaneous estimation of the incidence rate ratio for infarction attributable to vasectomy, obesity, and smoking in the matched pairs yielded an adjusted

TABLE III—DISTRIBUTION OF CARDIAC RISK FACTORS BY VASECTOMY STATUS AND OCCURRENCE OF MYOCARDIAL INFARCTION (MI)

	MI		No MI	
—	Vasectomy	No vasectomy	Vasectomy	No vasectomy
Hypertension:				
Pre-vasectomy*	1	1	1	1
Post-vasectomy†	4	3	0	2
Obesity:				
Pre-vasectomy	7	3	4	1
Post-vasectomy	3	3	2	4
Diabetes:				
Pre-vasectomy	1	0	0	0
Post-vasectomy	1	1	0	1
Smoking:				
Any‡	11	11	5	8
Total	20	16	16	20

*First notation in chart appears after vasectomy and before MI (or corresponding dates).
†First notation in chart appears before vasectomy (or corresponding date).
‡See text for exposure definition.

estimate of the rate ratio associated with vasectomy of 1·22, with 95% confidence limits of 0·6 and 2·7. Because the adjusted rate ratio (1·22) was almost the same as the unadjusted rate ratio (1·25), it is unlikely that the incidence rate ratios observed in this population were seriously affected by bias caused by confounding. The incidence rate ratios attributable to obesity pre-dating vasectomy and to smoking (with 95% confidence intervals) were 3·2 (0·7–15·0) and 4·1 (1·2–14·5), respectively. Addition of two and three way interaction terms to the proportional hazards model resulted in negligible and statistically non-significant changes in the vasectomy rate ratio estimates.

Discussion

We found no meaningful increase in the rate of myocardial infarction in this study of 4830 vasectomised men who were compared with a fivefold larger group of non-vasectomised men. The lack of association between vasectomy and non-fatal myocardial infarction appears not to have been a result of bias due to confounding by hypertension, obesity, diabetes, or smoking. The lack of a vasectomy-attributable effect was present throughout an observation period which provided extensive experience for seven years after vasectomy. In the late post-vasectomy observation (8–16 years), there was no indication of excess risk, but the data available were scant.

Some animal and laboratory data suggest that there may be long-term risks, as yet not manifested in human populations. In one-half to two-thirds of men who have a vasectomy, agglutinating and sperm-immobilising antibodies develop,[8-12] presumably as a result of epididymal leaking of soluble sperm antigens.[13] The sperm-immobilising antibodies fix complement,[8] and hence may mediate inflammatory reactions. One important class of such reactions is immune damage to arterial walls, which in turn promotes arteriosclerotic plaque formation in laboratory animals fed cholesterol-rich, high-fat diets. Repeated injections of foreign protein into rabbits resulted in arterial proliferative lesions, which were fat-laden when the animals were fed high-fat diets.[14] The effect was also produced by a single antigenic challenge followed by brief exposure to a high-cholesterol diet.[15] In baboons, multiple antigenic challenges and a high-cholesterol diet are clearly synergistic in the production of extensive atheromas.[16] Within less than a year, diffuse and severe atherosclerosis had developed in vasectomised macaques on high-fat diets.[1] Such atherosclerosis did not develop in sham vasectomised animals eating the same diet. Similar effects have been reported in vasectomised macques fed monkey chow, and examined many years after vasectomy.[2]

In the present study, continuation as a member of GHC has been treated as a potential confounding factor which has been controlled by restricting the study to those men who actually remained in the plan from the beginning of follow-up to the last study year, 1979. The results might still have been distorted if both of the following held true: (1) men who left the plan had first-time myocardial infarction rates which were different from those of men who continued as members; (2) the degree of this difference in infarction rates was itself different in vasectomised and non-vasectomised men. While (1) is plausible, (2) is not likely to have operated to such an extent as to bias the current findings to any important extent. Restriction of the study to members active in GHC at the beginning of 1979 limited this analysis to non-fatal myocardial infarction. Although an increase in fatal myocardial infarction rates among vasectomised men is possible, the absence of any change in the non-fatal infarction rates makes this danger seem remote.

No human study has yet provided useful, direct information on fatal myocardial infarction and vasectomy. Searches of death records and the accumulation of more extensive late follow-up data are planned for the men identified for this investigation. Long-term studies should become easier as large cohorts of men with vasectomy reach advanced ages, and considerably more information on later follow-up should be available within the next few years.

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