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PARITY AND DIABETES MELLITUS

BY

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The suggestion that pregnancy may play a part in the development of diabetes and account for the predominance of women among older diabetics derived initially from the findings of Mosenthal and Bolduan (1933) and Joslin, Dublin, and Marks (1936) that death from diabetes was more commonly recorded among married and widowed women than among single women (see also Joslin, Root, White, and Marble, 1959). More direct evidence was provided by Munro, Eaton, and Glen (1949), Pyke (1956), and Fitzgerald, Malins, O'Sullivan, and Wall (1961) that the frequency of clinical diabetes in women increases steadily with increasing parity. Interpretation of all three studies is rendered difficult because none considers only patients drawn from a known population and because of uncertainty about the distribution of parity in the general population. Pyke (1956) relied on data for parity in women aged 45 to 49, and Fitzgerald and others (1961) on that for a hospital population. Another study of diabetics seen in hospital failed to show any effect of parity (Vinke, Nagelsmit, van Buchem, and Smid, 1959), and some diabetes surveys have shown no relation between parity and the prevalence of diabetes in the general population (Keen, 1964; Bennett, Miller, and Burch, 1967).

The present investigation was designed to study the problem again, using only patients with newly-discovered diabetes drawn from a defined population, and taking advantage of the publication of data on the distribution of parity among women of all ages in the population of England and Wales at the 1961 Census (General Register Office, 1966).

MATERIAL AND METHODS

A study was made of the records of the 956 patients (543 women and 413 men) aged 40 to 79 years who attended the Radcliffe Infirmary Diabetic Clinic with newly-discovered and definite diabetes in the years 1954 to 1965, and came from a defined population.

Diabetes was considered to be newly-discovered if the patient was first seen in the clinic within 6 months of the date on which action leading to a definitive diagnosis or treatment was taken. It was considered definite if (*i*) a random blood sugar was 180 mg./100 ml. or more, irrespective of the method of determination; or (*ii*) a fasting blood sugar was 130 mg./100 ml. or more; or (*iii*) a glucose tolerance test was that of "florid diabetes" (Working Party, 1962); or (*iv*) there were typical symptoms of diabetes relieved by carbohydrate restriction, together with a random blood sugar above the maximum normal value in the glucose tolerance test (Working Party, 1962) in relation to the time of the last meal.

The defined population is that of the City of Oxford and surrounding districts (Caird, Hutchinson, and Pirie, 1965). The Radcliffe Infirmary Diabetic Clinic is the only one in the area; about 90 per cent. of the adult diabetics in the district are thought to attend it (Pyke, 1959). A correction was made for the increase in population between the Census of 1951 and that of 1961; the same annual rate of change was assumed to have continued in the years 1961 to 1965 (Middleton, 1967).

The distribution of parity by age among women in the population was taken as that for the population of England and Wales at the time of the 1961 Census (General Register Office, 1966). The distribution of civil state by age among men in the population was that for the defined population at the 1961 Census. The number of children by age was determined for married men from the distribution of parity among married women of the same age at the 1961 Census (General Register Office, 1966). This ignores illegitimacy, second marriages, and the difference between the ages of married men and their wives.

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RESULTS

The distribution of parity by age among the 543 diabetic women is shown in Table I.

TABLE I

DISTRIBUTION BY AGE AND PARITY OF 543 DIABETIC WOMEN

Age Group (yrs)	Mean Population	Parity						Total
		0	1	2	3	4–5	6+	
40–49	18,014	11	14	12	12	11	6	66
50–59	16,887	29	22	29	20	31	11	153
60–69	12,672	34	27	31	32	27	20	181
70–79	8,654	32	21	22	20	24	24	143
Total		106	95	94	84	93	71	543

Table II compares the percentage distribution of parity among these women and among women in the general population. The excess of diabetic women with four or more children is obvious.

TABLE II

PERCENTAGE DISTRIBUTION OF PARITY BY AGE IN GENERAL POPULATION (P) AND AMONG 543 DIABETIC WOMEN (D)

Age Group (yrs)	Parity											
	0		1		2		3		4–5		6+	
	P	D	P	D	P	D	P	D	P	D	P	D
40–49	25	17	23	21	26	18	14	18	9	17	3	9
50–59	33	19	28	22	21	19	9	13	8	20	4	7
60–69	36	19	19	15	18	17	11	18	10	15	6	17
70–79	34	22	16	15	16	15	11	14	12	17	8	17

The calculated attendance rates with newly-discovered diabetes per 100,000 at risk per year are shown in relation to age and parity in Table III. The rates increase with age, and, within each age group, with fair regularity with increasing parity. The comparable rates for men approximate at all ages to those for women with two children.

TABLE III

ATTENDANCE RATES WITH NEWLY-DISCOVERED DIABETES PER 100,000 PER YEAR

Age Group (yrs)	Parity of Women						Men
	0	1	2	3	4–5	6+	
40–49	21	28	21	41	54	84	38
50–59	43	59	69	107	182	135	68
60–69	63	92	113	197	179	305	103
70–79	91	128	129	169	186	213	108

From these figures it is possible to calculate for a patient aged 40 the cumulative risk of attendance with diabetes at ages from 50 to 80, in relation to parity. This risk increases with age and parity, and again the risk for men is of the same order as that for a woman with two children (Table IV).

TABLE IV

CUMULATIVE RISK PER CENT. OF DIABETES FOR PATIENTS AGED 40 YEARS

Age (yrs)	Parity of Women						Men
	0	1	2	3	4–5	6+	
50	0·21	0·28	0·21	0·41	0·54	0·84	0·38
60	0·64	0·87	0·90	1·48	2·35	2·19	1·06
70	1·36	1·80	2·02	3·42	4·10	5·17	2·08
80	2·25	3·06	3·09	5·05	5·89	7·19	3·14

Since the cumulative risk relative to that for a nullipara does not vary systematically with age, risks relative to that for nulliparae can be determined for ages from 50 to 80 (Table V).

TABLE V

CUMULATIVE RISK OF DIABETES IN RELATION TO THAT FOR NULLIPARAE (=1)

Age (yrs)	Parity of Women					Men
	1	2	3	4–5	6+	
50	1·38	1·00	1·95	2·57	4·05	1·81
60	1·36	1·41	2·31	3·67	3·42	1·66
70	1·32	1·49	2·51	3·01	3·80	1·53
80	1·36	1·46	2·24	2·62	3·20	1·40
Mean	1·36	1·34	2·25	2·97	3·62	1·60

Table VI compares these mean risks with similar estimates derived from the data of Pyke (1956) and Fitzgerald and others (1961). There is good agreement between the three studies, except for women with six or more children; discrepancies here may result from small numbers. Averages from these studies give the excess risk over that for a nullipara as approximately 20 per cent. for a woman with one child, 45 per cent. for two, 100 per cent. for three,

TABLE VI

MEAN CUMULATIVE RISKS OF DIABETES AT AGES 50 TO 80 YEARS RELATIVE TO NULLIPARAE (=1)

Series	Age (yrs)	Parity of Women					Men
		1	2	3	4–5	6+	
Pyke (1959)*	45	1·14	1·55	1·88	2·90	6·32	—
Fitzgerald and others (1961)	45	1·08	1·46	1·81	3·09	5·56	1·31
Present Study	40	1·36	1·34	2·25	2·97	3·62	1·60
Average		1·19	1·45	1·98	2·99	5·17	1·46

* Recalculated.

200 per cent. for four or five, and over 400 per cent. for six or more. Men have a risk almost 50 per cent. in excess of that for nulliparae, a figure virtually the same as that for women with two children.

Comparisons of various findings in relation to parity are given in Table VII. The following show no relation to parity, history of a first or second degree relative with diabetes, height, or prevalence of diabetic retinopathy or neuropathy within a year of diagnosis. Proteinuria shows an increase in prevalence with parity. Body weight (measured clothed, but without shoes, at first attendance) is significantly greater in parous than nulliparous women, but shows no further increase with increasing parity.

TABLE VII

RELATION OF VARIOUS FACTORS TO PARITY
(Percentages of Women of Different Parities)

Factors Studied		Total No. of Women	Parity					
			0	1	2	3	4–5	6+
Family History*		540	22	28	28	29	29	17
Height (in.)	<60	527	21	9	20	16	14	22
	>63		41	51	41	37	38	36
Weight (lb.)	<130	538	39	29	17	24	26	23
	>170		9	28	33	24	25	31
Neuropathy†		536	7	2	4	6	3	1
Retinopathy†		498	12	8	20	9	12	14
Proteinuria†		528	10	13	12	12	15	26

* Of a first or second degree relative with diabetes.
† Within a year of diagnosis of diabetes.

Tables VIII to XI show the findings on civil state and number of children in the 413 diabetic men. The distribution of civil state by age in the diabetics corresponds closely with that in the general population (Table IX) as does the number of children among married men (Table X). There is no systematic relationship in men between civil state or number of children and attendance rates with newly-discovered diabetics (Table XI, opposite).

TABLE IX

PERCENTAGE DISTRIBUTION OF CIVIL STATE BY AGE AMONG GENERAL POPULATION (P) AND DIABETIC MEN (D)

Age Group (yrs)	Civil State					
	Single		Married		Widower/ Divorced	
	P	D	P	D	P	D
40–49	11	13	87	84	2	3
50–59	10	9	86	84	4	3
60–69	9	6	83	83	8	11
70–79	9	4	69	76	23	20

TABLE X

PERCENTAGE DISTRIBUTION OF NUMBER OF CHILDREN BY AGE AMONG MARRIED MEN IN GENERAL POPULATION (P) AND DIABETIC MEN (D)

Age Group (yrs)	Number of Children											
	0		1		2		3		4–5		6+	
	P	D	P	D	P	D	P	D	P	D	P	D
40–49	14	17	25	27	30	32	16	13	11	7	4	5
50–59	21	24	27	28	25	19	13	12	10	8	5	8
60–69	24	17	24	27	22	27	13	13	11	10	7	7
70–79	22	25	20	25	21	19	14	13	14	11	10	8

DISCUSSION

The patients in this study are drawn from a population of known size and age and sex structure but, although the Radcliffe Infirmary Diabetic Clinic is the only one in the area, not all patients with newly-discovered diabetes attend it. The deficit is likely to be largest in the oldest age group, but there is no reason to believe that non-attendance is related to parity or family size. The figures given in Tables III and XI are therefore minimum estimates of the incidence of clinical diabetes in the population in question. The inclusion of patients in whom the diagnosis of diabetes is less certainly based than on

TABLE VIII

DISTRIBUTION BY AGE, CIVIL STATE, AND NUMBER OF CHILDREN OF 413 DIABETIC MEN

Age Group (yrs)	Mean Population	No. of Total Patients	Civil State				Number of Children (Married Men)						
			Not known	Single	Widower/ Divorced	Married	0	1	2	3	4–5	6+	Not known
40–49	18,158	78	2	10	2	64	11	17	20	8	4	3	1
50–59	16,750	137	1	12	4	120	27	32	22	14	9	9	7
60–69	9,927	126	0	7	14	105	17	27	27	13	10	7	4
70–79	5,553	72	1	3	14	54	13	13	10	7	6	4	1
Total		413	4	32	34	343	68	89	79	42	29	23	13

TABLE XI

ATTENDANCE RATES PER 100,000 PER YEAR IN MEN, BY CIVIL STATE AND NUMBER OF CHILDREN

Age Group (yrs)	All Men	Civil State			No. of Children (Married Men)					
		Single	Widower/ Divorced	Married	0	1	2	3	4–5	6+
40–49	38	42	54	34	41	35	35	27	20	43
50–59	68	59	57	69	74	68	51	63	53	113
60–69	103	64	147	106	73	116	124	104	90	104
70–79	108	52	93	118	127	143	106	113	95	88

the comparatively strict criteria used in this study would also of course increase the incidence rates.

The most satisfactory comparison between this and previous studies can be made on the basis of the risk of diabetes relative to that in nulliparae. The close quantitative agreement shown in Table VI between this study and those of Pyke (1956) and Fitzgerald and others (1961) is very striking, particularly in view of the fact that the three studies derive from different diabetic populations and different estimates of the distribution of parity in the general population. This agreement provides powerful support for the hypothesis that there is a true association between parity and the risk of diabetes in women.

The meaning of the association is, however, uncertain. The suggestion (McConnell, 1956) that women destined to develop diabetes may be unusually fertile has been rendered highly improbable by the finding by Fitzgerald and others (1961) that the risk of diabetes is the same in nulliparae whether or not they are married; married nulliparae may be presumed to be less fertile than unmarried. The association between multiparity and obesity has been thought to be the reason for the association between diabetes and multiparity (Joslin and others, 1936). Munro and others (1949) and Fitzgerald and others (1961) found a steady if slight increase in mean weight with parity in their diabetic women. Our data set out in Table VII are in agreement with those of Pyke and Please (1957) that, although nulliparae are less often obese than parous women, there is no increase in obesity with increasing parity.

A further possibility not previously explored is that the association between diabetes and parity might reflect a relation to family size. Such a relation might be ethnic in origin or might perhaps result from the differences in food intake and carbohydrate consumption which are known to exist between families of different size (Ministry of Agriculture, Fisheries, and Food, 1966). Any relation to family size is rendered improbable by the fact that attendance rates in single, married, and widowed and divorced men are essentially similar (Table XI). The method of calculating the distribution of number of children by age among married men is imperfect, but the absence of differences between the distribution of number of children among married men in the general population and married diabetic men (Table X) and the lack of any systematic relation between number of children and attendance rates with diabetes (Table XI) make any simple relation between diabetes and family size highly unlikely.

If then the association between parity and the risk of clinical diabetes in women is accepted as genuinely due to multiple pregnancy, it remains to consider what possible mechanisms could account for the association. Discussion is greatly limited by the lack of any precise knowledge of the basic mechanisms underlying human diabetes. Since insulin secretion is increased in pregnancy (Freinkel, 1965), successive pregnancies might result in islet-cell exhaustion. If this was so, an earlier onset of diabetes would be expected the more the pregnancies. In fact, the relation between age at childbirth and age at diagnosis of diabetes does not vary with parity (Munro and others, 1949; Fitzgerald and others, 1961), and the increased risk of diabetes associated with increasing parity persists unchanged from age 50 to age 80 (Table VI).

The discrepancy between the findings in studies of diabetics attending hospital and those found in population surveys is difficult to explain. In one of the two population studies where parity is mentioned, little detail is given (Keen, 1964); in the other, the population studied (the Pima Indians of Arizona) has an extremely high prevalence of diabetes (Bennett and others, 1967), which may perhaps override any effect of parity. It would seem reasonable to suppose that parity is one of the main determinants of the occurrence of clinical diabetes in older women, and that pregnancy may contribute to the gradual decline in carbohydrate tolerance with age (Butterfield, 1964).

One further point is of interest. Both Munro and others (1949) and Fitzgerald and others (1961) found that the frequency of positive family histories of diabetes declined with increasing parity. This

would be compatible with the idea that as environmental factors become more important in the genesis of diabetes in later life, genetic factors become less important. We find (Table VII) that the frequency of family histories of a first or second degree relative with diabetes does not decline with increasing parity. Perhaps the environmental influence is added to the genetic to give the increased risk of diabetes.

SUMMARY

A study was made of the records of 543 diabetic women and 413 men, aged 40 to 79 years. They came from a defined population and attended a diabetic clinic with newly-discovered diabetes in the years 1954 to 1965.

Among the women, the risk of diabetes increased with increasing parity. Comparison with other studies shows that between the ages of 50 and 80 years the excess risk, above that of a nullipara, is 20 per cent. for one child, 45 per cent. for two, 100 per cent. for three, 200 per cent. for four or five, and 400 per cent. for six or more children.

Parous women were heavier than nulliparous, but there was no increase in weight with increasing parity. The frequency of family histories of diabetes was unrelated to parity.

Among the men, the risk of diabetes was unrelated to civil state or to the number of children.

The aetiological implications of these findings are discussed.

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Notes