Maternal diabetes mellitus and congenital malformation

Survey of 205 cases

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Day, R. E., and Insley, J. (1976). *Archives of Disease in Childhood*, 51, 935. **Maternal diabetes mellitus and congenital malformation: survey of 205 cases.** Twenty-five out of 205 (i.e. 12%) babies born to diabetic mothers in the Birmingham Maternity Hospital in the period 1969–1974 were malformed as against 6% in a control group. The incidence was highest in the group where mothers were on insulin at the time of conception (17 out of 117, i.e. 15%). No correlation was observed between major malformation in this group and age of onset or duration of the diabetes, progressive vascular complications, maternal age, or parity. Cardiovascular malformations were over-represented.

In spite of numerous studies and reports, the association between maternal diabetes mellitus and fetal malformation is not clear. Part of the problem has been in definition, both of the form of diabetes and on the position of the dividing line which separates normal variation from true malformation. The number of malformations recognized has also been influenced by the intensity of investigation and length of follow-up of the infants. A review by Rubin and Murphy in 1958 proved inconclusive while Farquhar's (1969) personal series from Edinburgh did not show an increased incidence of fetal malformation. This is contrary to the experience in Copenhagen (Pedersen, Tygstrup, and Pedersen, 1964) and Sweden (Karlsson and Kjellmer, 1972), where there is a significantly higher incidence of malformation in the fetus of the diabetic mother. Geographical and racial factors could be invoked to account for the difference.

The present controlled but retrospective series presents further evidence of clear association between maternal insulin-dependent diabetes and severe fetal malformation.

Patients

The series included 205 babies of diabetic mothers born at Birmingham Maternity Hospital between 1969 and 1974. This represents an unrelated group of mothers attending the main diabetic clinic in the city or found to have diabetes after booking for delivery at this

hospital. For the purpose of this study each diabetic pregnancy was controlled with a nondiabetic pregnancy of a mother of equal parity whose hospital registration number was closest to that of the diabetic pregnancy. Hospital registration numbers were allocated at the time of the first attendance at hospital. As 90% of all babies born in Birmingham in 1972 were delivered in hospital, the control group is considered to be a representative sample of the population. All babies were examined by a doctor on at least two occasions during the first 10 days of life.

Definitions

Major malformations. Those leading to death, needing surgical correction, or likely to lead to deformity or handicap.

Minor malformations. All others. Insignificant problems such as skin tags and small naevi were not included.

Maternal diabetes. Group 1—those on insulin at time of conception. Group 2—those first diagnosed during the pregnancy and those whose diabetic tendency was only apparent in pregnancy. Group 3—established diabetics on diet or oral hypoglycaemics (but not insulin) at time of conception.

Results

Of the 205 diabetics who had babies during the period of study, 117 were group 1, 57 group 2, and the remaining 31 were in group 3. 205 babies were delivered (including one pair of twins),

TABLE I

Incidence of major and minor malformations among babies of mothers with insulin-dependent diabetes (group I), diabetes diagnosed in pregnancy (group II), and diabetes normally controlled with diet or oral hypoglycaemics (group III)

	All malformations			Major malformations				Minor malformations	
	Total no. of pregnancies	With malformed baby	% affected	Total	(%)	Fatal	(%)	Total	(%)
Group I	117†	17*	15	11*	(9)	7*	(6)	6 NS	(5)
Control	117	5	4	3	(3)	0		2	(2)
Group II	57	6 NS	11	2 NS	(4)	0		4 NS	(7)
Control	57	5	9	1	(2)	0		4	(7)
Group III	31	2 NS	6	2 NS	(6)	1	(3)	0 NS	(0)
Control	31	2	6	0		0		2	(6)
Total diabetic pregnancies	205	25*	12	15*	(7)	8*	(4)	10 NS	(5)
Control	205	12	6	4	(2)	0		8	(4)

*P < 0.05. NS, not significant. †Includes one pair of twins.

TABLE II

Major congenital malformation in offspring of insulin-dependent diabetic mothers related to maternal parity

	Parity					
	1	2	3	4	5 +	Total
Group I (insulin-dependent diabetes) (n = 117)	2/36 6% NS	2/40 5% NS	3/26 12% NS	3/10 30% NS	1/5 20% NS	11/117 9%*
Controls (n = 117)	1/36 3	1/40 3	1/26 4	0/10 —	0/5 —	3/117 3
Birmingham survey† 1950–1954	3	2	3	3	3	3

*P < 0.05. NS, not significant. †Personal communication, R. G. Record.

and of those not malformed 8 were stillborn and 2 died in the neonatal period. 25 out of 205 had recognizable congenital (major or minor) abnormalities but a breakdown by type of maternal diabetes (Table I) shows that a disproportionate number (17 out of 117, i.e. 15%) were born to mothers in group I, and that the incidence of malformation in the remaining diabetic groups was similar to that of the control groups (5%). The diabetic state of the mothers in group I whose babies had major malformation was analysed by age of onset, duration of disease, progressive diabetic vascular complications, maternal age and parity. None of these was statistically significant, though increasing parity did produce an apparent effect (Table II). However, the groups were small and none showed a sufficiently large difference to be significant. Most of the malformed babies in group I were born to mothers aged between 21 and

25 years, which further suggests that the effect is not related to maternal age.

The distribution of malformations by system is given in Table III and compared with that of the

TABLE III

Types of major congenital malformation

System	Group I (insulin-dependent diabetes)		Perinatal mortality survey
	No.	per 1000 births	per 1000 births
Cardiovascular	4	34	2.8
Central nervous	3	25	6.2
Gastrointestinal	2	17	2.3
Skeletal	1	8.5	4.6
Genitourinary	—	—	3.1
Other	1	8.5	6.4
Total	11	93.0	25.4

British Perinatal Mortality Survey of 1958 (Butler and Alberman, 1969). These figures suggest a predilection for the cardiovascular system, but numbers are small. The specific malformations are listed in Table VI. The stillbirth rate for babies without malformations is apparently raised for all types of diabetes, being significant only in group I ($P < 0.001$, Table IV). The rate for recent pregnancies shows a fall which may reflect the change in the management of the diabetic pregnancy. The neonatal death rate from causes other than malformation is only increased in group I (Table V) and this too shows a recent drop.

Discussion

This series shows a very high stillbirth rate (13%) among babies who were not malformed and a four-fold increase in the incidence of major congenital malformations among the babies of mothers in group I (on insulin at conception). The infants of group 2 (those diagnosed as diabetic during pregnancy) or group 3 (those taking oral hypoglycaemics at the time of conception) did not run a significantly increased risk. Two large series reported over the past 12 years by Pedersen *et al.* (1964) and Karlsson and Kjellmer (1972) noted that diabetic mothers

ran a considerable risk (11% and 6% respectively) of having a malformed child as compared with a nondiabetic rate of 2%.

Further attempts to define the significant factors have not always led to the same conclusions. These include the presence of progressive diabetic vascular complications (Pedersen *et al.*, 1964), and lack strict diabetic control in pregnancy (Karlsson and Kjellmer, 1972). The present series failed to show any relation to length of the disease, age of onset, maternal age, or the presence of vascular disease (Table VI). An apparent effect of increasing parity may well be related to poorer diabetic control with succeeding pregnancies, though there is no concrete evidence for this and, as recent trends have been towards maintaining stricter control during pregnancy, this effect may disappear.

We have shown a particular increase in cardiovascular malformations. This was no surprise, for other authors, including Rowland, Hubbell, and Nadas (1973), have already pointed out that heart malformations are over-represented. The defects were various and too few for comment, though previous series have suggested that ventricular septal defects, coarctations of the aorta, and transpositions of the great vessels are perhaps more common than might be expected.

TABLE IV
Stillbirths excluding those due to congenital malformations

	Total pregnancies	Diabetics, stillbirths	(%)	Controls, stillbirths	(%)
Group I					
Present pregnancies	117	4	3 NS	0	
All pregnancies†	207	28	14*	2	1
Group II					
Present pregnancy	57	3	5 NS	1	2
Group III					
Present pregnancy	31	1	2 NS	0	
All pregnancies†	54	5	9 NS	0	
Birmingham Maternity Hospital, 1973					1

* $P < 0.001$. NS, not significant. †All pregnancies includes previous and present pregnancies of patients concerned.

TABLE V
Neonatal deaths excluding those due to congenital malformations

	Total pregnancies	Diabetics, neonatal deaths	(%)	Controls, neonatal deaths‡
Group I				
Present pregnancies	117	3	3 NS	0
All pregnancies†	207	10	5*	0
Groups II & III				
Present pregnancies	88	0		0
All pregnancies‡	111	0		0

* $P < 0.001$. NS, not significant. †All pregnancies includes previous and present pregnancies of patients concerned. ‡Neonatal death rate for Birmingham Maternity Hospital was 1% of deliveries.

TABLE VI

Individual malformations by maternal age and progress of diabetes

Malformation	Maternal age	Age of onset of diabetes (yrs)	Duration of diabetes (yrs)	Retinopathy	Proteinuria	White classification (1949)
A. Congenital heart disease						
Single atrium, common atrioventricular canal, anomalous systemic venous drainage }	23	15	8	—	—	C
Cor triloculare	29	9	20	—	—	C
Persistent ductus arteriosus	26	16	10	—	—	C
Persistent ductus arteriosus	21	19	2	—	—	C
B. Central nervous system						
Microcephaly	35	27	8	+	—	D
Meningomyelocele	25	15	10	—	—	C
Anencephaly	22	7	15	—	—	C
C. Gastrointestinal						
Imperforate anus	23	17	6	—	—	C
Diaphragmatic hernia	24	5	19	—	—	C
D. Skeletal						
Abnormal lumbar spine }	31	26	5	—	—	B
Phocomelia }						
E. Other						
Microcephaly }	26	16	10	—	—	C
Hypoplastic lungs }						
Hypoplastic mandible }						
Limb deformities }						

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REFERENCES

- Butler, N. R., and Alberman, E. R. (1969). (Editors). *Perinatal Problems. Second Report of the Perinatal Mortality Survey*. Livingstone, Edinburgh.
- Farquhar, J. W. (1969). Prognosis for babies born to diabetic mothers in Edinburgh. *Archives of Disease in Childhood*, **44**, 36.
- Karlsson, K., and Kjellmer, I. (1972). The outcome of diabetic pregnancies in relation to the mothers' blood sugar level. *American Journal of Obstetrics and Gynecology*, **112**, 213.
- Pedersen, L. M., Tygstrup, I., and Pedersen, J. (1964). Congenital malformations in newborn infants of diabetic women. *Lancet*, **1**, 1124.
- Rowland, T. W., Hubbell, J. P., and Nadas, A. S. (1973). Congenital heart disease in infants of diabetic mothers. *Journal of Pediatrics*, **83**, 815.
- Rubin, A., and Murphy, D. P. (1958). The frequency of congenital malformations in the offspring of non-diabetic and diabetic individuals. *Journal of Pediatrics*, **53**, 579.
- White, P. (1949). Pregnancy complicating diabetes. *American Journal of Medicine*, **7**, 609.

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