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CONGENITAL MALFORMATIONS IN INFANTS OF DIABETIC MOTHERS

by

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INTRODUCTION

DURING the last two decades the outcome of pregnancy in the diabetic has improved greatly. In the Royal Maternity Hospital, Belfast, for example, the total fetal loss and perinatal mortality during the years 1972-78 have been 4.3 and 3.2 per cent respectively, whereas in earlier years figures well in excess of 10 per cent were common everywhere. In view of this the contribution of congenital malformations is assuming increasing importance as a factor in the survival of infants of diabetic mothers. Over the years the occurrence of congenital malformation in diabetic pregnancies has been the subject of some controversy but it is now generally accepted that the incidence is about two to four times greater than in the general population.

The purpose of this paper is to record the incidence of congenital malformations in infants of diabetic mothers born in the Royal Maternity Hospital, Belfast, during the years 1963 to 1978 inclusive, to assess their contribution to perinatal mortality and to consider ways in which this risk could be reduced.

PATIENTS AND METHODS

The series includes all diabetic women and their offspring treated in the Royal Maternity Hospital during the years 1963-78. Diabetic mothers attend the Antenatal Diabetes Clinic in the Royal Maternity Hospital, where they are seen by a Consultant Obstetrician and Physician who assume joint responsibility for their care during pregnancy, labour and the puerperium. Patients are referred from the Diabetes Clinic at the Royal Victoria Hospital, from the Greater Belfast area and other parts of the Province at the discretion of physicians, obstetricians or general practitioners.

Early referral is essential to establish good control as soon as possible and assess the gestational age of the fetus. Patients attend at fortnightly intervals, or more frequently if necessary. Before each visit mid-morning and mid-evening (2½ to 3-hour post-prandial) plasma glucose levels and urine tests for glucose and acetone (four tests in 24 hours) are available. An effort is made to keep plasma glucose values below 7.2 mmol/1 when ambulant and below 6.0 mmol/1 when resting in hospital. The nature and severity of the diabetes is classified according to the method proposed by White (1971). There are nine grades, A to I, of increasing severity. Women with abnormal glucose tolerance tests detected in pregnancy (Grade A) were excluded from the present series unless the abnormality was confirmed postpartum.

Careful control of the diabetes is attempted with twice daily soluble insulin or a combination of Soluble and Isophane (NPH) insulin, although since 1976 the highly purified pork preparations (Montgomery, 1979) have been used almost exclusively. Patients are maintained on diets with a total daily energy value of 7,500 to 8,500 kilojoules. Women of average weight are allowed to gain 6 to 10 kg during pregnancy. In the absence of complications the well controlled patient is admitted to hospital between 32 and 34 weeks of gestation to ensure even stricter control of the diabetes and to diagnose and treat any obstetric complications promptly.

In hospital a plasma glucose series (fasting, 1200, 1730 and 2200 hours) is obtained at least twice weekly. In special circumstances plasma glucose values are measured in the early hours of the morning (0200 to 0300 hours) to detect nocturnal hyper- or hypoglycaemia. Fetal wellbeing is monitored by serial urinary oestriols, human placental lactogen and biparietal diameter measurements by ultrasonic scan. At 37 or 38 weeks the lecithin-sphingomyelin ration is measured on a specimen of liquor obtained at amniocentesis. If this value is 2.0 or greater, delivery is effected within 48 hours. The timing of delivery, however, depends on the degree of diabetic control, the presence and severity of pre-eclampsia, the previous obstetric history and any other factors conferring special risks that might necessitate early delivery.

Provided the cervix is favourable and there are no obstetrical complications, labour is induced surgically followed by a syntocinon infusion. If labour has not begun within 12 hours or is not progressing satisfactorily, caesarean section is performed. During labour, patients receive an infusion of 10 per cent dextrose and diabetic control is maintained with injections of small doses of short-acting insulin, 4 to 6-hourly, or by continuous intravenous infusion of insulin and frequent measurement of plasma glucose levels. Expert paediatric care is provided from the moment of delivery for resuscitation and neonatal management.

For the purpose of this investigation a *congenital malformation* is defined as a structural abnormality present at birth and recognizable with the naked eye, by radiological investigation or alternatively at necropsy. A *major congenital malformation* is defined as one which caused death or affected a major organ system causing serious incapacity.

RESULTS

During the 16 years (1963-78) there were 195 consecutive diabetic pregnancies of which 184 lasted 28 weeks or more. There were 11 recorded abortions. Of the 184

viable pregnancies, 19 babies had congenital malformations (10.3 per cent). During the same period the fetal malformation rate in the Belfast area (control group) was 4.0 per cent. There were, however, a total of 24 malformations (a total malformed rate of 13.0 per cent) in the affected infants; 15 had one malformation each, three had two, and one infant had three lesions. Seven, or just over one-third, of the congenital malformations proved fatal in the perinatal period (36.8 per cent). They accounted for four of the 13 stillbirths and three of the ten neonatal deaths and were thus responsible for just under one-third of the perinatal deaths (30.4 per cent). Eleven abortions were recorded, one of which was excluded because it was performed for therapeutic purposes. Of the remaining ten, eight were spontaneous, one was missed and one was inevitable due to a complete procidentia. The recorded incidence of abortion in the diabetic pregnancies was 5.1 per cent, while that for the general pregnant population in the Belfast area was 8.7 per cent during the year 1976. The average maternal age of the patients in this series was 26.1 years, parity was 1.1, booking date was at 12 to 13 weeks and the incidence of previous miscarriage was 26.3 per cent. Table 1 shows the nature of the congenital malformation in the babies of the diabetic mothers compared with the findings in the general population.

TABLE I

Nature of congenital malformations in babies of diabetic mothers, compared with the general population

Type of congenital malformation per 1,000 births	*Diabetic mothers*	*General population*
Central nervous system	*16.2*	*3.5*
Cardiovascular system	*38.0*	*6.5*
Genitourinary system	*10.8*	*0.7*
Skeletal system	*27.1*	*1.1*
Major malformations	*59.7*	*25.3*

A more detailed breakdown of the lesions into severe and less severe malformations is given in Table II. Two women twice delivered a child with a congenital malformation. The first gave birth to a baby with a ventricular septal defect and an overriding aorta. A second child had an accessory auricle and asymmetry of teeth. The second woman gave birth successively to a malformed fetus with anencephaly, a healthy child, one with transposition of the great vessels and ventricular septal defect and finally a healthy child.

CONTROL OF MATERNAL DIABETES

The vast majority of the patients (93.4 per cent) were treated with insulin. Table III shows the method of diabetic management related to the outcome of the pregnancy. Most of the mothers of the malformed babies were on insulin, as would be expected in view of the high predominance of insulin treated mothers, but two women, one on a hypoglycaemic agent and one treated by diet alone, had malformed babies.

TABLE II

*Analysis of malformations by systems (*major malformation)*

System	*Non-fatal*		*Fatal*	
Central nervous			*Microcephaly	1
			*Anencephaly	2 (c, d)
Cardiovascular	*VSD and patent ductus ...	2	*VSD and overriding aorta	1
	*VSD	1 (e)	*ASD and absent tricuspid valve	1
			*Single atrium and transposition of great vessels	1
			*Transposition of great vessels and VSD ...	1
Genitourinary	Bilateral inguinal hernia ...	1		
	Unilateral inguinal hernia ...	1		
	Hypospadias	2		
	Unilateral undescended testis ...	2 (b)		
	Gonad (ovotestis) palpable in the groin	1		
Skeletal	*Sacral agenesis	1		
	Deformed great toe	1		
	Webbing of toes	1		
	Camptodactyly	1 (a)		
Others	Asymmetry of auricle	1		
	Haemangioma of scalp ...	1 (a)		
	Asymmetry of auricle	1		

(a) Intrauterine contraceptive device expelled at birth.
(b) Maternal thyrotoxicosis, on carbimazole treatment, in one case of undescended testis.
(c) Laparotomy at 13 weeks gestation for suspected ovarian cyst, in one case of anencephaly with polyhydramnios from 26 weeks gestation.
(d) Polyhydramnios from 34 weeks in other case of anencephaly.
(e) Polyhydramnios from 31 weeks.

TABLE III

Method of diabetic management related to fetal outcome

Diabetic management	*Result of pregnancy*	
	Normal baby	*Malformed baby*
Insulin	155	17
Hypoglycaemic agents	3	1
Diet only	3	1
Total	161	19

Although great efforts are expended to maintain good control of the maternal diabetes (the aims have been stated already), success is not always achieved. Control of the diabetes was judged to be good in the third trimester if the average plasma glucose 3 hours after breakfast and the evening meal was less than 7.2 mmol/1. Plasma glucose values between 7.2 and 8.4 mmol/1 were regarded as fair, while values greater than 8.4 mmol/1 were unsatisfactory and designated poor. When these criteria were adopted for the 172 patients on insulin, 59 had good control (34.3 per cent), 46 had fair control (26.7 per cent), and 71 (41.2 per cent) had poor control. Unfortunately, data on the degree of diabetic control at conception and during the first trimester are not available since most women booked for their confinement at the end of this period. In general, however, we suspect that the patient's degree of control in the third trimester mirrors fairly faithfully the control in the earlier months.

Table IV shows the fetal results related to the degree of control of the maternal diabetes during the last trimester. It can be seen that the incidence of congenital malformations increases as the degree of maternal diabetes control deteriorates. However, the numbers are too small for statistical analysis.

TABLE IV

Control of maternal diabetes in the third trimester related to the outcome of pregnancy

Diabetic control			*Outcome of pregnancy*	
	No.	*(percentage)*	*Normal baby*	*Malformed baby*
Good	59	(32.1)	55	4
Fair	46	(25.0)	40	6
Poor	71	(38.5)	63	8
No record	8	(4.3)	7	1
Total	184		165	19

TABLE V

Classification of maternal diabetes according to White's method, related to the outcome of pregnancy

Outcome of pregnancy	*White's classification*				*Not recorded*	*Total*
	B	*C*	*D*	*F*		
Normal birth	71	65	25	2	2	165
Congenital malformation	4	9	3	0	3	19
Abortion	4	3	1	0	3	11
Stillbirth	5	4	1	0	3	13
Neonatal death	5	4	1	0	0	10

Table V compares the outcome of the pregnancy in relationship to the classification of the maternal diabetes. Congenital malformations were commonest in Group C with nine infants affected, an incidence of 13.8 per cent, while four of Group B (5.6 per cent) and three of Group D (12.0 per cent) were affected.

DISCUSSION

In 1865, Lecorché reported the occurrence of hydrocephalus in diabetic mothers. However, the increased frequency of congenital malformations was not fully recognized until the second half of this century, when a number of authors (White, 1949; Koller, 1953; Reid, 1956; Driscoll, Benirschke and Curtis, 1960) drew attention to this finding in the offspring of diabetic mothers. On the other hand, some authors found no such increased frequency (Given, Douglas and Tolstoi, 1950; Reis, De Costa and Allweiss, 1950; Cardell, 1953; Farquhar, 1959). More recently, however, further reports have confirmed increased fetal malformations (Table VI).

TABLE VI

Incidence of malformation rates in infants of diabetic mothers from various centres

Author	*Date*	*City*	*Number*	*Malformation rate (percentage)*
Mölsted-Pedersen et al	1964	Copenhagen	853	6.4
Watson	1968	London	197	10.7
Farquhar	1969	Edinburgh	329	7.9
Yssing	1973	Copenhagen	749	11.0
Soler et al	1975	Birmingham	701	8.1
Komrower	1977	Oxford	213	9.8
Pedersen	1977	Copenhagen	1,452	8.0
Present study	1979	Belfast	184	10.3

In 1964, Pedersen and his colleagues from Denmark found a malformation rate of 6.4 per cent in 853 infants of over 1.0 kg birth weight, compared to 2.1 per cent in the control group. Major malformations occurred in 5.2 per cent as opposed to 1.2 per cent in the control group which is statistically significant. Watson (1968) found 10.7 per cent of 197 infants to have congenital malformations with a 5.6 per cent incidence in her control group, while Farquhar (1969), in a later study, found 7.9 per cent of 329 infants born after 24 weeks to be affected. He thought that this was higher than in the general population but found precise comparison impossible. Similarly, Yssing (1973), in a review of the work of the Danish group, confirmed that 11 per cent of 749 infants with a birth weight of over 1.0 kg surviving the neonatal period were affected, with congenital heart lesions and skeletal malformations predominant.

Rowland, Hubbell and Nadas (1973) specifically investigated congenital heart disease in these infants and found an incidence of 4.0 per cent in a series of 470 babies. Transposition of the great vessels, ventricular septal defects and coarctation of the aorta together formed over half of their 19 reported cases. Soler, Walsh and Malins (1976) in a study of 701 infants born between 1950 and 1974, found 8.1 per cent affected, a rate of three to four times greater than in the general population of Birmingham. In particular, cardiovascular system malformations were noted in 2.3 per cent (eight being fatal) compared to 0.21 per cent in the general population. Similar high rates in diabetic babies as opposed to control infants were reported by Komrower (1977) and Pedersen (1977) with the major emphasis on cardiac and skeletal malformations.

The present study confirms these findings. The incidence of fetal malformations in the Royal Maternity Hospital, Belfast, is about two-and-a-half times more frequent in babies of diabetic mothers (10.3 per cent) than in the general population (4.0 per cent). They were responsible for, or contributed largely to, a third (30.4 per cent) of the perinatal deaths in these babies during the period of the survey. Cardiovascular anomalies were the most frequent finding and occurred in over a third of infants affected (36.8 per cent). They accounted for six of the eleven major malformations and for four of the seven deaths. Our findings show that infants of diabetic mothers have a six-fold increased risk of a cardiovascular malformation than the general population. Three other babies died, one with microcephaly and two with anencephaly, but it is improbable that these are related to diabetes. More likely they reflect the high incidence of these lesions in the offspring of mothers in Northern Ireland as a whole.

Mölsted-Pedersen, Tygstrup and Pedersen (1964) suggested that the increased incidence of congenital malformation in infants of diabetic mothers was due to a "divergent gene pattern" and an "abnormal intrauterine environment" due to maternal vascular complications, a view supported by Rowland, Hubbell and Nadas (1973) who felt that hereditary and environmental factors interacted to various degrees. More recently, Pedersen (1977) has underlined the importance of an "incomplete metabolic compensation in the metabolic state during the first trimester". Our own findings show that in the third trimester the worst controlled mothers had the greatest number of malformed infants, a fact not brought out in previous studies. No figures are available for the early weeks of pregnancy when organogenesis is occurring, but we suspect that a mother who is poorly controlled

in the latter months of pregnancy is unlikely to be better controlled at the time of conception and in the first critical weeks following implantation. If this is so, and we have no reason to believe otherwise, it is possible, indeed probable, that indifferent or poor diabetic control with high plasma glucose levels may be a factor in the causation of fetal malformations. Since the achievement of good control of the metabolic state is regarded by all workers as the ideal to be aimed at during pregnancy it seems logical to recommend the same degree of control at conception and during the early weeks of fetal development. To do so, however, means that pregnancy in the diabetic woman must be a planned event with diabetic control carefully monitored for some weeks prior to conception. The recognition then of ovulation in a cycle, followed by a sustained rise in the progesterone level confirming conception, should be the signal to maintain as complete normalization of the plasma glucose as possible until pregnancy is ended.

In order to attain this ideal situation, considerable changes will need to take place in our attitudes to pregnancy in the young diabetic woman. Education about the risks of pregnancy to their offspring and the importance of good diabetic control at the time of conception will be needed as well as advice on family planning. At marriage, the diabetic woman should be referred for contraceptive advice, if needed, and when pregnancy is desired attention to the control of the diabetes can be stepped up. If contraception is not requested then careful control of the metabolic state will be necessary before the marriage takes place. Such a coordinated campaign might be a factor in helping to reduce fetal wastage and morbidity in this particularly vulnerable group of women.

SUMMARY

A retrospective survey of 195 consecutive diabetic pregnancies in the Royal Maternity Hospital, Belfast, between 1963 to 1978 revealed 184 pregnancies which exceeded 28 weeks. Of these, 19 congenitally malformed babies were born (10.3 per cent). The total malformation rate was 13.0 per cent (24 malformations in the 19 babies). Seven, or just over one-third of the congenital malformations proved fatal in the perinatal period. In all, congenital malformations contributed to just under one-third of the perinatal deaths.

Cardiovascular lesions were most frequent and were found in over one-third of infants affected. They accounted for six of the major malformations and for four of the seven deaths. Infants of diabetic mothers have a six-fold greater risk of a cardiovascular malformation than the general population.

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