

## Follow-up of children of diabetic mothers

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**SUMMARY** The results of a follow-up study of infants of diabetic mothers are presented. The antenatal care of all such mothers was supervised in a combined clinic by obstetricians and physicians, and good diabetic control was achieved in most of them. 51 mothers delivered 73 infants, all liveborn, between the years 1964 and 1972 inclusive at Hammersmith Hospital. There were no fetal deaths. 66 infants survived the neonatal period, and 63 the first 2 years of life. 51 children, including all those seriously ill in the neonatal period, could be traced. Detailed neurological and general examinations including skinfold measurements were made, and the IQ measured. Four children were found to have major handicaps. These were severe deafness, epilepsy, low IQ, and myopia. No other neurological abnormalities were detected, and the distribution of full-scale IQs was normal. The distribution of height and head circumference centiles was near normal, but an increased number of children had weights above the 90th centile. No significant congenital malformations were found in these 51 survivors, and none has so far developed diabetes.

In recent years the perinatal mortality of infants of diabetic mothers (IDM) has fallen from about 25% to single figures. This has been attributed to a combined approach to antenatal care by obstetricians and physicians. However, the perinatal mortality of these infants is still 2 to 3 times the national average.<sup>1-2</sup>

In several studies the incidence of handicap among IDM has also been found to be high. Major congenital malformations,<sup>3</sup> neurological abnormality,<sup>4</sup> and low intelligence<sup>5</sup> have been reported. Such children have also been found to have an abnormal growth pattern and an increased frequency of diabetes.<sup>6</sup> These problems have been related to maternal vascular complications,<sup>2</sup> low oestriol levels,<sup>7</sup> and acetonuria<sup>3 32</sup> during pregnancy. However, the findings are not consistent between series.

In this hospital between the years 1952 and 1963 the perinatal mortality of IDM was 25%. In an attempt to improve this situation a combined antenatal diabetic clinic was set up, and this coincided with a lower rate of perinatal mortality.<sup>8</sup> We have attempted to follow children born to the mothers who attended this clinic in the first 9 years of its existence to ascertain the extent of handicap among the survivors.

### Patients

Between the years 1964 and 1972 inclusive 51 diabetic mothers who attended the combined antenatal and diabetic clinic at Hammersmith Hospital delivered 73 infants of more than 24 weeks' gestation (including one set of twins). There were no intrauterine deaths. The details of management of pregnancy have been published elsewhere.<sup>8</sup> In 58 of the pregnancies the mothers required treatment with insulin, one mother was treated with chlorpropamide, and the remaining 13 received diet alone. Eight pregnancies were complicated by retinopathy, and one by renal involvement and severe neuropathy. The collective obstetric histories of these women included 9 stillbirths and 5 neonatal deaths.

The infant birthweight/gestation standards used were those of the National Birthday Trust's 1958 Perinatal Mortality Survey,<sup>31</sup> supplemented by Baltimore data at the lowest gestation weeks. The infants' case notes were abstracted for details of neonatal illness. Birth asphyxia was considered present in any infant in whom spontaneous respiration was not established by 2 minutes after birth. Respiratory distress, presumed to be hyaline membrane disease, was diagnosed in infants who had a respiratory rate greater than 60 per minute, costal recession, and grunting persisting after 4 hours of age. Hypoglycaemia was defined as blood glucose <20 mg/100 ml (1.1 mmol/l) on two consecutive readings. Jaundice was considered significant if total bilirubin reached 12 mg/100 ml (204 µmol/l).

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### Follow-up methods

During 1977 attempts were made to trace the surviving children of this group of diabetic mothers. A letter explaining the study was sent to each mother at her last known address. If no reply was obtained, the general practitioner and Family Practitioner Committee were contacted. As the latter only keep records of transfer dating to 1974, this was not always helpful. Other hospitals which had given maternal care were also asked for up-to-date addresses. It was not possible to have a matched control group.

A medical and developmental history was obtained from the parents. Psychological assessment was carried out together with general examination, neurological examination, urine analysis, and growth measurements.

**Psychological assessment.** IQ was measured by one of us (M N). The Wechsler Intelligence Scale for Children (WISC) was used for those aged at least 6 years, and the Wechsler Preschool and Primary School Scale of Intelligence (WPPSI) for those under 6 years.

**General examination.** This included measurement of blood pressure, and a search for significant congenital malformation. Urine analysis was carried out using Labstix.

**Neurological examination.** Detailed neurological examination was adapted from data on normal children at different ages collected by Touwen and Prechtl.<sup>9</sup> Particular attention was paid to tests of co-ordination which included finger tip touching, dysidiadochokinesis, rotation of forearm, and finger/nose testing. Each item was scored and the scoring system was adapted for use in the present study. Vision and hearing tests were also performed. Visual acuity was assessed with Snellen letters. The Stycar adaptation was used for the youngest children.<sup>10</sup>

**Growth measurements and anthropometry.** The children were measured using a stadiometer, and weighed in light underwear. Measurements were plotted on standard centile charts.<sup>11</sup> Occipito-frontal circumference was measured and compared with the standards of Paine and Oppé.<sup>12</sup> Skinfold thickness was measured with Harpenden calipers using the method described by Tanner and Whitehouse.<sup>13</sup> The 8 sites measured were bilateral biceps, triceps, subscapular and suprailiac folds. Triceps and subscapular measurements were plotted on centile charts (revised 1970).<sup>13</sup>

### Results

**Perinatal and infant details.** Birthweight in relation to gestational age is shown in Fig. 1; the distribution is relatively normal. There were 7 first-week deaths, giving a perinatal mortality of 9.6%. Five deaths were from hyaline membrane disease and its complications, and 2 were caused by lethal congenital malformations (anencephaly 1, multiple anomalies 1). The relationship of the deaths to maternal treatment is shown in Table 1.

Neonatal illness is shown in Table 2. Of the 19 hypoglycaemic infants, one was symptomatic, and the remaining 18 asymptomatic.

66 children survived the neonatal period, and there were 3 later deaths. One of the twins died suddenly at home at age 6 weeks, necropsy showing pneumonia. A second infant died at 5 weeks from congenital heart disease, and a third drowned at 18 months.

**Follow-up.** Of the 63 surviving children, 51 were traced. Strenuous efforts to find the remaining 12

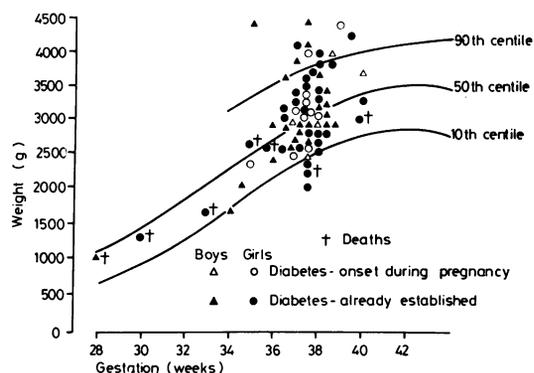


Fig. 1 Birthweights in relation to gestational ages.

Table 1 First-week deaths related to treatment of maternal diabetes

Mother's treatment	First week	
	Deaths	Survivors
Insulin	7	52
Oral agents	0	1
Diet	0	13

Table 2 Neonatal problems

Neonatal illness*	No.
Birth asphyxia	9
Respiratory distress syndrome	9
Hypoglycaemia	19
Jaundice	11

\*See text for definitions.

children failed. They included 3 pairs of siblings. There was nothing in our records to suppose they were abnormal. Three children had left the country and one was traced to Australia where he was examined for us by his paediatrician. The other 2 could not be found. Of the other 50 children examined, 4 were seen in their homes to save travelling long distances. The mean age at examination was  $7\frac{3}{4}$  years (range  $4\frac{1}{4}$  years to  $13\frac{1}{2}$  years).

#### Psychological assessment

48 of the 51 children were assessed with the Wechsler tests. Full-scale IQ scores were normally distributed (Fig. 2) with a mean of 97.5 and  $SD \pm 16$ . This seems consistent with the distribution of parental social class in this group which was similar to that in the general population, except that social class III (nonmanual) was not represented.<sup>14</sup> Three children could not be tested: one because he lived in Australia, one because she was severely deaf and could only communicate in sign language, and one because she had recently been diagnosed as myopic and failed to

bring her spectacles each time she was assessed. These children were rated by their schools as 'above average', 'of normal intelligence', or 'below average for her age'. The below-average rating of the third child (now aged 8) may partly be due to her previously undiagnosed myopia.

All but 2 of the children attend schools for normal children. One attends a school for the deaf, and the other (IQ 73) a secondary school for the educationally subnormal although he had attended a primary school for normal children. The only child with an IQ <70 was aged  $4\frac{1}{2}$  years and had already been treated for delayed speech. He also showed poor concentration and was hyperactive.

There was a discrepancy of 15 points or more between verbal and performance scale IQs in 9 (18%) children. This finding is reliable but is not statistically abnormal as verbal-performance discrepancies of 15.4 points or more can be expected in 25% of  $7\frac{1}{2}$ -year-old children and in 20% of  $10\frac{1}{2}$ -year-old children tested with the WISC.<sup>15</sup> There are similar findings in younger children tested with the WPPSI. 21% of a group of 150 children aged  $5\frac{1}{2}$  years had verbal-performance discrepancies of at least 16 points.<sup>16</sup>

The relationship of IQ to neonatal hypoglycaemia, to birthweight <10th centile, and to maternal retinopathy is shown in Table 3. There was no significant difference between the IQ of hypoglycaemic and nonhypoglycaemic groups (Student's *t* test). Four hypoglycaemic children had a mean IQ 8 points lower than their normoglycaemic siblings. However, the mean IQ of the other 4 sibling pairs, all of whom had normal blood glucose levels, also showed 7 points difference. The infant whose mother was treated with chlorpropamide had prolonged neonatal hypoglycaemia and had had several exchange transfusions.<sup>17</sup> He required speech therapy before schooling, but when seen at age 10 years was doing well with an IQ 109 and no abnormal neurological signs.

#### General and neurological examination

The major problems found from history and neurological examination are shown in Table 4.

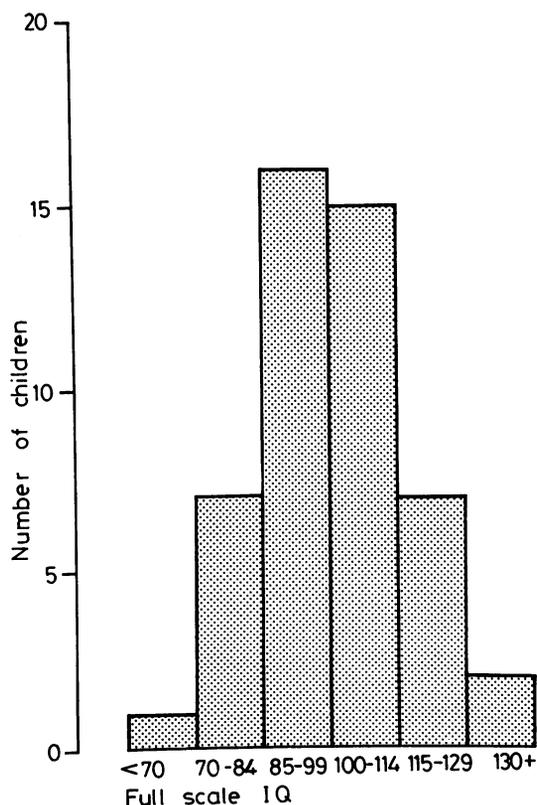


Fig. 2 Distribution of full-scale IQ.

Table 3 Full-scale IQ in relation to neonatal and maternal complications

IDM	Full-scale IQ	
	Mean	Range
Whole group (n = 48)	97.5	(65-131)
Hypoglycaemia (n = 11)	95.2	(73-116)
Normoglycaemia (n = 37)	101	(66-131)
Small-for-dates (n = 4)	98	(83-111)
Maternal retinopathy (n = 7)	110	(92-126)

Table 4 Major abnormalities at follow-up

Case	Problem	IQ	Maternal treatment in pregnancy
1	Severe deafness, OFC <3rd centile	Normal	Insulin
2	Myopia	Normal	Diet
3	Low IQ, hyperactive	65	Diet
4	Epilepsy, urinary infection	84	Insulin

These 4 children had normal neonatal periods without hypoglycaemia or other complications and were of reasonable birthweights. All these problems had been previously diagnosed and treated. The detailed examination and scoring system showed no other major abnormalities. One child was hypotonic, the others were within the expected normal range for their ages. General examination was also unremarkable. No significant congenital malformations were detected, and in particular, there was no evidence of congenital heart disease. Urine analysis was negative. All parents had tested their children's urine for glucose on at least one occasion. None asked us to carry out blood tests. In the past, 3 children had required speech therapy, 3 had had febrile convulsions, and 3 required surgical correction of squint.

#### Growth measurements

The relationship of height, weight, and head circumference centiles to one another is summarised in Fig. 3. Similar numbers of children had heights and weights >50th centile, but an increased number

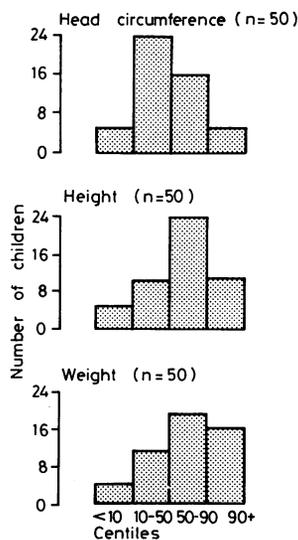


Fig. 3 Distribution of growth measurement centiles.

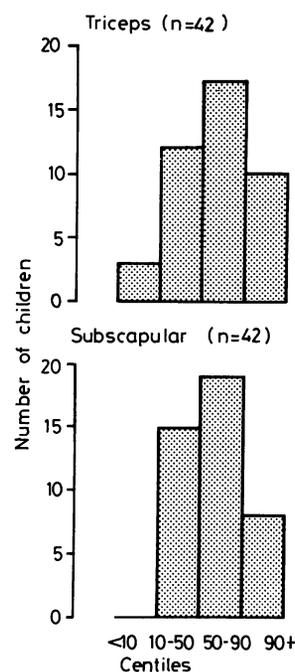


Fig. 4 Distribution of skinfold thickness centiles.

were disproportionately heavy with weights >90th centile. Head circumference tended to be less than expected for height, greater numbers being below the 50th centile. Two children had head circumferences <3rd centile with heights and weights >50th. One of these was the deaf child who was suspected, but not proved, to have had congenital cytomegalovirus infection. The other was a normal child with an IQ 114.

Skinfold measurement centiles are summarised in Fig. 4. One-fifth of the children had skinfolds >90th centile with very few <10th centile. Obesity correlated well with maternal obesity, but the large children were not those who had had large birthweights. The 6 most obese children were all <50th centile for birthweight.

#### Discussion

Our results show a good outcome for surviving children of diabetic mothers receiving intensive antenatal treatment. The 12 children lost to follow-up had not been seriously sick in the neonatal period and we have no reason to suppose they have any handicaps. The major problems encountered could not be related to severity of maternal diabetes. Two of the 4 mothers with handicapped children were

considered to have diabetes to a slight extent and were treated with diet alone during pregnancy. Several authors have shown an increased frequency of low IQ in IDM. This has been correlated with maternal hypoglycaemia, maternal acetonuria,<sup>3 5</sup> and neonatal hypoglycaemia.<sup>18</sup> We did not find an increased frequency of low IQ in our group. Hypoglycaemia during pregnancy was an accepted complication of management at this hospital and was expected to occur. Acetonuria was recorded rarely and most mothers achieved their best control of diabetes during pregnancy. Hospital admission occurred only rarely, so frequent urine analyses were unavailable.

There was no relationship between neonatal hypoglycaemia and low IQ in our series, and Haworth *et al.*<sup>19</sup> agreed that this was so. Tunçer<sup>20</sup> reported that 3 of 7 infants with hypoglycaemia were abnormal later. François *et al.*<sup>18</sup> found 4 children with psychomotor retardation in his series; 2 of these had suffered prolonged symptomatic hypoglycaemia. However a further 87 infants in his series had blood glucose levels <30 mg/100 ml (<1.6 mmol/l). Our one patient with prolonged hypoglycaemia is now apparently normal.

Neurological deficit among IDM has also been found increased. In a large series from Scandinavia, Yssing<sup>4</sup> found an unusually large number of children with cerebral palsy and epilepsy. This finding correlated with low maternal oestriol excretion.<sup>7</sup> Many of our patients did not have oestriol measurements and therefore a comparison with Yssing's work cannot be made. However, all small-for-dates children were followed up and no abnormalities found. Watson,<sup>21</sup> at King's College Hospital, in a study of children born between 1956 and 1962 found a 2.5% incidence of cerebral palsy or mental retardation, compared with 0.5% in a control group. Haworth *et al.*<sup>19</sup> recorded 11 of 37 children as having neurological or intellectual deficit at a mean age of 4½ years. Findings in both these studies were not directly related to maternal problems.

Later growth of these children has been a source of interest. Farquhar<sup>6</sup> found an excess of short boys and heavy girls; and in a subsequent study was able to relate heaviness to birthweight.<sup>22</sup> Hagbard *et al.*<sup>23</sup> and Haworth *et al.*<sup>19</sup> found an increased number of short children. In contrast others have found them taller,<sup>24</sup> or taller and heavier,<sup>25-26</sup> than expected. In the series by Amendt *et al.*<sup>27</sup> infants of birthweights >4 kg were taller and heavier at school age. Verdy *et al.*<sup>28</sup> demonstrated a correlation between adult obesity and birthweight in IDM. However, Whitelaw<sup>29</sup> showed that increased skinfold measurements are present at birth and return to normal levels during infancy. Our series showed an increase in

number of obese children which related to maternal obesity, but not to birthweight.

Lethal congenital malformations remain a serious problem for the IDM. They now represent at least half the perinatal mortality in these infants.<sup>30</sup> These major congenital malformations are largely responsible for the increased postneonatal mortality found by many authors including Hagbard *et al.*<sup>23</sup> Congenital malformations were responsible for 20% of our neonatal deaths and one of 3 postneonatal deaths. Nonlethal, but significant congenital malformations form a widely varying number in different series. Congenital heart disease has a particularly pronounced variation in frequency. Stebbens *et al.*<sup>3</sup> found 11% in their series. None was found in this series which was slightly larger. The wide variation in incidence of congenital heart disease reported from different centres has not been explained. Severe deafness of unknown aetiology was the only major congenital abnormality in our survivors.

The development of diabetes in these children is more likely than in the general population.<sup>6 18 23 26</sup> None of those in our series, or a sibling, has yet become overtly diabetic. Amendt *et al.*<sup>27</sup> carried out glucose tolerance tests on children of diabetic mothers. They found 18.4% were pathological and 15.9% borderline.

In conclusion 51 of 63 surviving children of diabetic mothers attending a combined antenatal diabetic clinic have been followed. The handicaps found did not apparently relate to maternal diabetes and IQ scores were not abnormally low. None has yet become diabetic.

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