

Neurodevelopmental outcome at early school age of children born to mothers with gestational diabetes

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Abstract

Aims—To study the metabolic derangements in the second half of pregnancy caused by gestational diabetes, on the long term development of children.

Methods—The neuropsychological function of 32 school age children born to 32 mothers with well controlled gestational diabetes and 57 control children matched by age, birth order, and parental socioeconomic status was studied.

Results—There were no differences in head circumference and height, but the children born to diabetic mothers were heavier. The verbal IQ scores of index children below the age of 9 years were lower than those of control children. No differences were found between the groups in various sensory and motor functions and in the Touwen and Prechtl neurological test. The young index group children performed less well than controls in fine and gross motor functions, as observed on the Bruininks–Oseretzký test of motor proficiency. The scores of young children born to mothers with gestational diabetes were also lower than controls on the Pollack tapper test, and there were more index group children who scored abnormally on the parents' Connors questionnaire. No correlation was found between the performance of the index group children on various neurodevelopmental tests and the severity of perinatal complications. The differences tended to disappear with age.

Conclusions—Gestational diabetes, as a result of the metabolic abnormalities in the second half of pregnancy, induces long term minor neurological deficits which are more pronounced in younger children. There does not seem to be any direct relation between the appearance of congenital anomalies and neurodevelopmental outcome.

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Diabetes during pregnancy is associated with an increased rate of spontaneous abortions, intrauterine death, and subsequent congenital anomalies.¹⁻⁸ These increases are directly related to the severity of the disease, and may be related to the blood concentrations of glycosylated haemoglobin (HbA1c).⁹⁻¹¹ In the past

10–15 years, the prevalence of congenital anomalies among offspring of diabetic mothers has decreased. This reduction is directly related to the improvement of glycaemic control in early pregnancy.^{3 6 7}

Various studies have addressed the question of possible brain damage induced by diabetes during the second half of pregnancy, which may result in developmental disorders. Some neurological dysfunction is to be expected as the major developmental events of the cerebral cortex such as migration, differentiation, and layering of the cortical neurons, myelination, and synapse formation occur during the second half of pregnancy.^{12 13}

In a recent study we found¹⁴ that when 10.5 day old rat embryos were cultured in serum obtained from diabetic patients, there was a high proportion of major congenital anomalies; serum from type 1 diabetic patients induced major congenital anomalies in 71% of the embryos. When serum from women with gestational diabetes was used as the culture medium, 53.3% of the embryos were malformed. This supports the view that diabetic metabolic abnormalities in gestational diabetes may affect the developing embryo. The observation that there is no increase in the prevalence of major congenital anomalies in children born to women with gestational diabetes can be explained by the fact that these metabolic changes occur when major organogenesis—with the exception of the brain—has already occurred.¹⁴

Stehbens *et al*¹⁵ examined children born to diabetic mothers when aged 1, 3, and 5 years. Small for gestational age children born to diabetic mothers had lower cognitive scores than controls. Similarly, Petersen *et al*¹⁶ found that the children of diabetic mothers who were small for gestational age had low verbal performance at 5 years, but that the children who did not sustain in utero growth retardation were normal. Cummins and Norrish¹⁷ did not find any differences in the cognitive scores of children born to diabetic mothers at 4.25–13.5 years compared with controls. Pearson and Gentz¹⁸ found no differences on these measures in children at 5 years of age born to diabetic mothers or to mothers with gestational diabetes. Rizzo *et al*¹⁹ did not find developmental delay in children born to diabetic mothers or to mothers with gestational diabetes, but found an inverse correlation between maternal blood β -hydroxy butyrate concentrations and scores on IQ tests for these children. In a later study Rizzo *et al*²⁰ found a significant negative correlation between maternal second and third trimester β -hydroxy

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Table 1 Comparison of parental SES between index group and controls

	Maternal education (years) Mean (SD)	Paternal education (years) Mean (SD)	Family size Mean (SD)	No of rooms Mean (SD)
Control	13.3 (2.3)	13.8 (2.9)	5.04 (0.93)	4.65 (1.41)
Mothers with gestational diabetes	12.7 (2.8)	12.6 (2.5)	5.39 (0.95)	4.87 (1.67)

No differences between groups were found.

butyrate concentrations and IQ test scores in these children at 6 to 9 years of age. Their performance on the Bruininks–Oseretzky test, which measures fine and gross motor abilities, was also significantly impaired. Sells *et al*²¹ found a higher incidence of developmental language delay among children born to diabetic mothers who started follow up late in pregnancy, and hence had poor glycaemic control.

Most of these studies, while providing important information on the sequelae of maternal diabetes, are limited by the fact that the children were examined at preschool age, while several important dysfunctions, such as attention deficit hyperactivity (ADHD) and learning difficulties can be diagnosed only at school age. Indeed, in a recent study²² we found that school age children born to diabetic mothers have normal cognitive scores, perform less well in fine and gross motor function, and have more inattention and hyperactivity when compared with matched controls.²²

This study aimed to assess the development of early school age children born to mothers with gestational diabetes compared with matched controls, using several cognitive, sensory, motor and neurological tests. We also intended to correlate the neurological function of these children to the degree of perinatal complications.

Methods

The sample consisted of 32 children (41% girls), born to 32 mothers with gestational diabetes during 1982–87 and 57 control children (46% girls) born to 57 non-diabetic healthy mothers matched for age, socioeconomic status based on parental education, occupation, family size and accommodation.²³ (table 1). None of the control mothers had gestational diabetes. All children were born at the Sheba Medical Center, Tel Hashomer, near Tel-Aviv, Israel. All mothers of children from the index group were treated in the high risk pregnancy clinic at Sheba Medical Center. At that time only women with a history of diabetes in the family, or with previous gestational diabetes, or women with a previous birth of a child over 4.0 kg, were tested for glucose tolerance during their pregnancy. Women with large fetuses in the current pregnancy or with glycosuria (all women were routinely screened for glycosuria) were similarly treated. Of these women, all those with an abnormal test (190 mg % glucose or more at 90 minutes, 165 mg % or more at 120 minutes, 145 or more at 180 minutes, or with 105 mg % or more fasting glucose blood concentrations) were considered to have gestational diabetes. Most women were diagnosed in the second trimester of pregnancy and some in the third trimester. Once diag-

nosed, a follow up fasting glucose was done once a week. Clinical follow up was carried out once every 2 weeks. Women with gestational diabetes were given low sugar diets. If fasting blood glucose was 110 mg % or more, or post-prandial glucose was 140 mg % or more, they were treated with insulin.

Forty four women with gestational diabetes, all treated with insulin, were therefore recruited. Eleven women could not, or refused to, participate in the study. One additional child was born with multiple anomalies and died at 2 years of age, so was excluded from the study. The remaining pregnancies resulted in the birth of 32 children over 32 weeks of pregnancy weighing over 1500 g at birth and without major anomalies. The results of laboratory tests relating to the degree of glycaemic control—glucose blood concentrations, glycosuria, and ketonuria—are incomplete and are therefore not presented here. When studied, the average age of the children in the index group was 8.5 (SD 2.1) years, ranging from 5.2–12.1 years (47% young children, 5–8 years of age; 53% older children, 9–12 years of age). The corresponding figure for the control children was 8.3 (1.7), ranging between 5.5–12.2 years, (5–8 years, 55%; 9–12 years, 45%). All were in normal schools.

We constructed our control sample by searching the birth records at the Sheba Medical Center for 1982–87, and by contacting parents by telephone. We found 67 children who lived up to 100 km from the hospital, and who were suitable to serve as matched controls. Of these, 32 parents (47%), mostly from areas far from the hospital, found it too difficult to participate and we examined the remaining 35 children from areas close to the hospital. All had been delivered in Sheba Medical Center. To complete the control group, we also included 22 children from a nearby school of the same ages and socioeconomic status. These children were also born in Sheba Medical Center during the same years. The 22 children from the school and the other 35 children had background characteristics and outcome variables similar to those described below. This group of 57 control children also served us in a previous study on the outcome of children born to diabetic mothers.²² The control and index children were matched by age and school placement—all studying in normal schools—as well as by gestational age. They were also similar in terms of parental education, family size, and number of rooms at home (table 1).

The following tests were administered to each participating child:

- A complete medical and neurological examination
- The Touwen–Prechtl neurological examination for children with minor nervous dysfunction.²⁴ Abnormal neurological findings on this test were scored, and a total score of 10 or more was considered abnormal—that is, pointing to some neurological impairment.²⁵
- Evaluation of the cognitive score using the Wechsler Intelligence Scales for Children Revised (WISC-R, 1974)

- Bender Visual Gestalt test²⁶ for the evaluation of eye–hand coordination
- Goodenough Draw a Man test²⁷
- Bruininks–Oseretsky Motor Development test²⁸ which examines the fine and gross motor development of children aged 4.5–14.5 years
- Southern California Integration Test²⁹ for the evaluation of children’s sensory functioning. This test includes three subtests: manual form perception (MFP), finger identification (FI), and localisation of tactile stimuli (LTS). The test was carried out by an occupational therapist.
- Conners Abbreviated Parents–Teachers’ Questionnaire for the diagnosis of inattention and hyperactivity³⁰
- The Pollack tapper test³¹ to assess attention deficits. The child is asked to repeat a specific sequence of light blinks and auditory taps presented by the tester. The number, sequence, and duration of these stimuli is adapted according to the child’s age. Children with attention deficit tend to obtain lower scores than those with a normal attention span.
- Achenbach’s questionnaire for the measurement of behaviour³²
- Home observation for measurement of environment questionnaire³³

For each control or index child we filled out a detailed questionnaire related to pregnancy complications—gestational bleeding, hypertension, urinary tract infections, toxemia, premature uterine contractions and pregnancy related hospital stays—and to perinatal complications—mode of delivery, birthweight in relation to gestational age, respiratory distress, hypoglycaemia and convulsions.

The first two assessments were carried out by a developmental paediatrician; the WISC-R, Bender, and Goodenough tests by a developmental psychologist, and the other assessments by an occupational therapist. In all cases the tester was blinded to the mother’s diabetic status.

We compared index and control groups using two tailed group *t* tests for each dependent variable. For comparison of the groups on various neurological tests, we used the Wilcoxon rank sum test (Mann Whitney test). Pearson correlation were calculated between the scores on the neurodevelopmental tests of the children and the perinatal complications.³⁴

Results

Table 2 shows the results of the physical examination at birth and subsequently. There were no significant differences between the groups in birthweight; the gestational age of the control children was higher than that of the index children but the differences were not significant (table 2). Although there were more perinatal and neonatal complications among the index group children than in the controls—for example, hypoglycaemia, respiratory distress, developmental delay—the differences were not significant. There was a significant difference in the rate of Caesarean sections: 31% in the index group vs 7.1% in the controls.

Table 2 Comparison of physical evaluations between control children and children of mothers with gestational diabetes

	Controls Mean (SD)	Mothers with gestational diabetes (index) Mean (SD)
Gestational age	39.7 (1.8)	38.7 (2.4)
Birthweight (g)	3254 (582)	3348 (676)
Head circumference percentile	48 (24)	47 (22)
Height percentile	44 (30)	49 (25)
Weight percentile	44* (30)	68 (27)
Weight/height (kg/mm ²)	21.4* (4.0)	24.5 (4.7)

Mean (SD).

*Significantly lower than mothers with gestational diabetes; *p*<0.05.

Table 3 Comparison of cognitive scores on WISC-R, Draw a Man, and on Bender Gestalt test of control children and those born to mothers with gestational diabetes

Test	Controls		Mothers with gestational diabetes (index)	
	Young Mean (SD)	Old Mean (SD)	Young Mean (SD)	Old Mean (SD)
IQ	*121 (8)	116 (12)	111 (14)	115 (13)
Verbal	*115 (11)	113 (13)	107 (11)	109 (12)
Performance	123 (11)	117 (12)	114 (17)	119 (15)
Bender (%)	*48 (25)	*49 (29)	32 (25)	32 (31)
Draw a man	99 (17)	98 (17)	97 (16)	94 (13)

*Significantly higher than young and/or old index group children; *p*<0.05.

Table 4 Comparison of motor development (Bruininks–Oseretsky) in control children and those born to mothers with gestational diabetes

Bruininks test	Controls Mean(SD)	Mothers with gestational diabetes (index) Mean (SD)
Total, young	*128 (23)	113 (28)
Total, old	127 (18)	131 (26)
Gross motor, young	*59.2 (130)	52.1 (15.5)
Gross motor, old	66.8 (10.3)	61.8 (14.7)
Fine motor, young	*53.4 (9.7)	45.9 (11.6)
Fine motor, old	46.9 (7.9)	52.1 (9.1)

*Significantly higher than index group children; *p*<0.05.

Furthermore, 12.5% of the index group children stayed an additional year in the kindergarten compared with only 5.4% of controls. On examination, the body weight of the children born to mothers with gestational diabetes was greater than that of controls (table 2). A similar finding was observed in the weight to height ratio (table 2). There were no differences in head circumference and height. A non-significant positive (*r*=0.16) correlation was found in the index group children between birthweight and the weight at examination.

COGNITIVE AND NEUROLOGICAL DEVELOPMENT

Table 3 shows the WISC-R, Goodenough Draw a Man, and Bender tests for the index and control children. The general IQ scores of the WISC-R test, and the verbal scores, were higher in the young controls than in the young index group children. The scores on the Bender test (in percentiles) were significantly lower in the young and older index groups. No differences were observed between the groups in the Goodenough Draw a Man test (table 3).

Results of the motor assessments of the children are given in table 4. Young index group children had significantly lower scores on the

Table 5 Comparison of Conners questionnaire with Pollack tapper test between control children and those born to mothers with gestational diabetes before and after 8 years of age

	Young		Old	
	Controls Mean (SD)	Index Mean (SD)	Controls Mean (SD)	Index Mean (SD)
Conners parents' questionnaire	7.9 (4.3)	8.0 (6.5)	7.0 (4.3)	6.8 (6.3)
Pollack — general	28.0 (3.2)	19.0 (12.4)	30.3 (6.9)	29.6 (10.5)
Pollack — sound	*14.8 (6.5)	10.6 (6.6)	15.6 (3.6)	14.9 (5.0)
Pollack — visual	**13.2 (2.0)	7.7 (5.9)	14.7 (3.4)	14.1 (5.4)

*Significantly higher than index group; $p < 0.05$.

**Significantly higher than index group; $p < 0.01$.

Bruininks–Oseretsky fine and gross motor scores compared with the controls. This was not so in children aged 9 years or older, and the average scores for both age group children were therefore similar in the controls and index children (table 4). A direct correlation was found between the weight of the young index children and their failure in gross motor functions. No significant correlation was found between weight and fine motor functions.

No significant differences between the index and control groups were observed in any of the three subtests of the Southern California sensory integration test (MFP, FI, and LTS) that were designed to reflect sensory–motor functioning (results not shown).

Children born to mothers with gestational diabetes were no different from controls in the number of soft neurological signs in the Touwen and Precht examination (results not shown).

The results of Conners Questionnaire and of the Pollack tapper test are shown in table 5. There were no differences between the groups in the average scores for inattention and hyperactivity on the parents' Conners Questionnaire, but five index group children (16%) had abnormal scores (above 14) compared with only two controls (3.5%). This difference was not significant (Wilcoxon test, $p = 0.06$). Children of the index group below the age of 9 years had significantly lower scores on the Pollack tapper test compared with controls on both sound and visual tests. The differences disappeared in the older age group (table 5).

There were no significant differences between the groups in the Achenbach questionnaire, but there were several measures where the difference between groups was close to significant, such as internalising events (results not shown).

The home observation for measurement of the environment was no different between the groups, implying that the children were raised in similar conditions.

No correlation was found between the medical status—for example, hypoglycaemia, convulsions—of the newborn infants and outcome of any of the associated variables in the index or control groups.

Due to incomplete data on maternal blood glucose concentrations, glycosuria, and acetonuria in the index group mothers, we did not study the possible correlation between developmental outcome and degree of maternal glycaemic control.

Discussion

School age children younger than 9 years, born to mothers with gestational diabetes, had a higher rate of attention deficit, lower cognitive scores, and lower gross and fine motor achievements than matched control children. These differences were highest in the young children and tended to diminish with age. No correlation was found between several measures related to perinatal and neonatal complications and neurodevelopmental outcome.

Studies describing the development of children born to diabetic mothers, or to mothers with gestational diabetes, usually report normal on physical and neurological development.^{16–21, 35} We found that many neurological functions were poorer in children born to mothers with gestational diabetes compared with controls.

More young index group children had subnormal scores on the Pollack tapper test and more had abnormal scores on Conners questionnaire than controls. These tests are good predictors for ADHD,²⁵ implying that ADHD and perhaps learning disabilities may be more common among children born to mothers with gestational diabetes. However, the differences in the results of these tests tended to disappear in the older index group children, a tendency that is rare in children with ADHD or with learning disabilities. Lambert and Sandoval³⁵ found a high prevalence of pre- and perinatal complications in children with ADHD, including more health problems in their mothers, when compared with control (normal) children. We already have described a high prevalence of minor neurological dysfunction among children born to diabetic mothers compared with control children,²² but in that study the differences among the groups did not lessen with age.

Soft neurological signs may be a sign of mild, non-specific brain damage.³⁷ Variability in muscle tone (hypertonicity or hypotonicity) may cause delayed or abnormal motor development,^{37, 38} and we saw this in the young index group children. Older index children may be able to compensate for slight motor impairment, and their achievement in the tests may be normal, as is their daily function. The gap in the maturation of the central nervous system in the index group children compared with that of the controls may have decreased with age, so that older index children functioned closer to controls. If this is the case, even higher gaps in preschool children born to diabetic mothers might have been expected, but we did not test this.

Young and older index group children weighed more than control children. We have already observed a similar finding among school age children born to mothers with type I or type II diabetes.²² Similar results were reported by Rizzo *et al*²⁰ and by Metzger *et al*³⁴ in children born to diabetic mothers. The increased weight of infants born to diabetic mothers or to mothers with gestational diabetes observed in many studies is probably due to fetal hyperinsulinism, which abnormally

increases the number of fat cells.³⁸ This may also be the trigger for overweight in childhood.

A direct correlation between birthweight and weight at examination would be expected, but we found no such correlation in our study as the birthweight of our index children did not differ from that of controls.

We conclude that gestational diabetes, as a result of the metabolic abnormalities in the second half of pregnancy, induces long term minor neurological deficits which are more pronounced in the younger children. This implies that, as these neurodevelopmental changes are related to diabetic metabolic factors in the second half of pregnancy, there is no direct relation between the appearance of congenital anomalies and the neurodevelopmental outcome. However, our group is relatively small, and our results need further corroboration.

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