

**LONG-TERM EFFECTS OF
MATERNAL DIABETES
ON THEIR OFFSPRINGS DEVELOPMENT AND BEHAVIOURS**

(MSc Project)

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ABSTRACT:

AIMS OF THE STUDY:

Our purpose was to assess whether the type and control of maternal diabetes, and its perinatal complications have any long-term influences on children's development, behaviours, and sensorineural hearing.

STUDY METHODS & DESIGN:

We looked into the notes of 89 pregnant diabetic women, delivered at Medway Maritime Hospital (Kent/ UK) between 1998 – 2003, which were selected randomly. A Questionnaire was sent to all of them, (75%) were filled and consented to participate in the study. Out of 105 children born to these 89 women (65%) were born to mothers with gestational diabetes, (28.5%) had T1DM, and (6.6%) had T2DM. We used Griffith Developmental Scale, and generic assessment for behavioural problems. A control group of 65 children was selected randomly from acute admissions to the assessment unit

at Medway Maritime Hospital with similar criteria.

RESULTS:

We found a significant correlation emerged between children born to diabetic's mothers and developmental/ behavioural problems compared to non-diabetic mothers. After assessment 14 children out of the 67 participated in the study were found to have behavioural/ developmental problems ($p < 0.0017$) with (CI of 0.209 +/- 0.097) and none was found to have sensorineural hearing problems. Out of these 14 children, 3 were already under follow up by the Child Development Centre for developmental delay and behavioural problems. In the control group only 2 children showed developmental/ behavioural problems.

CONCLUSIONS:

Diabetes during pregnancy (GDM, T1DM & T2DM) as a result of the metabolic abnormalities and the perinatal complications, particularly neonatal hypoglycaemia adversely affects development and behaviours of children aged 1- 6 years.

Few studies were done in this important area; further large-scale studies need to be done to explore the long-term consequences of maternal diabetes on children's development and behaviours. No association was found in this small-scale study between maternal diabetes and sensorineural hearing impairment in their offspring.

BACKGROUND:

Developmental abnormalities of the foetal pancreas may result in functional or anatomic anomalies. Under the influence of maternal hyperglycaemia and abnormal metabolic fuels, there is an acceleration maturation of the pancreatic B cells and the clinical manifestations are quite different.

The actual prevalence of gestational diabetes is difficult to assess because of a variety of factors that influence the disease

prevalence. It has been estimated that diabetes before pregnancy complicates 0.2 – 0.3 % of all gestations and that gestational diabetes accounts for additional 2 – 3 % of pregnant women.

Optimal metabolic control throughout and even preceding pregnancy can reduce the foetal morbidity and mortality by several folds.

During normal pregnancy, metabolic changes result in maternal B cells hypertrophy with increase insulin secretion; gestational diabetes occurs in those women with borderline B cell function. Accordingly, women with overt diabetes require substantial increase in insulin dosage during latter part of pregnancy.

In spite of the reduction of the rates of perinatal mortality and congenital malformations in offspring of diabetic mothers ⁽¹⁾, recent research indicates that these children remain at increased risk for a variety of developmental disturbances including neurobehavioral capacities.

Two mechanisms for these effects have been proposed:

The first links maternal metabolism and child development and the effects of altered antepartum fuels on developing foetal tissues.

The second links perinatal complications e.g., neonatal hypoglycaemia, foetal distress and neonatal respiratory distress syndrome, which in turn affects subsequent development and neurodevelopmental arrest ⁽²⁾.

Although very few studies have been done that look at behavioural and cognitive development in animal offspring of diabetic mothers, several studies support the notion that a diabetic intrauterine environment results in abnormal brain development. Similar to findings with human stillborn autopsies ⁽³⁾, decreased brain weight was reported in rat pups and adult rats

born to diabetic dams ⁽⁴⁾.

A study of genetically diabetic mice found that their offspring have lower brain weight as well as impaired development of myelin and neuronal membranes ⁽⁵⁾. In addition, the distance between synaptic terminals and the area of dendritic spines was increased in the Purkinje cells of the cerebellum in rat offspring of diabetics ⁽³⁾. In vitro studies found that an increase in extracellular glucose concentration results in an inhibitory effect on developing cranial neural crest cells in the rat ⁽⁶⁾. When taken from embryos of diabetic mothers, these cells showed decreased cell migration at all glucose levels, as well as decreased migratory expansion after culture in basal glucose concentrations. From these evidence it has been suggested that maternal diabetes may permanently influence the future development of premigratory cranial neural cells

METHODS & DESIGN:

We studied 89 pregnant diabetic mothers delivered at Medway Maritime Hospital 1998- 2003, randomly selected. A simple Questionnaire, patient information sheet and a consent form were sent together with a stamped self-address envelope to all the 89 women. And 2 weeks later a reminder was sent to those who did not respond. Only 67 Questionnaires and consent forms were completed to participate in the study. The rest presumed as not willing to participate in the study.

We checked all names of the participating children against the Child Development Centre database, 3 children are already known to the CDC and followed up for different development and behaviour problems. Also we looked into the West Kent Children Hearing Services Database, as all the names of children with hearing impairment are kept in the database. None of our participant names were found in the database.

Gestational diabetes was defined as blood glucose concentration of > 8 mmol/l two hours after a 75 gram oral glucose load. All women with strong family history of diabetes, previous macrosomic babies, unexplained miscarriage or a positive dipstick for glucosuria; are routinely offered glucose tolerance test during pregnancy.

Neonatal hypoglycaemia was defined as blood glucose concentration of < 2.6 mmol/l during the neonatal period.

For those who did not respond or couldn't attend for assessment, we accessed their files from the Child Health Surveillance Computer System; which contain information from health visitor checks and developmental routine checks by GP or community paediatrician.

We excluded extreme premature babies born less than 28 weeks of gestation, children with congenital malformations and severe neurological problems e.g., cerebral palsy, and those with chromosomal defects.

A control group of 65 children was chosen randomly by the same investigators (paediatric registrar who saw them while covering the Assessment Unit in the on-call duties, which are usually 1 in 6) from the children admitted the Assessment Unit at Medway Maritime Hospital.

The Assessment Unit accepts referral from local GPs, A&E department and review of children discharged recently from the children wards with acute conditions.

The entire control group aged 1 – 6 years with the same exclusion criteria. History including family, social, and past medical history including neonatal problems was taken. Complete physical and neurological examinations were done for all of them including fine and growth motor, speech and

language and behavioural problems.

ASSESSMENT OF THE INDEX CASES:

There were concerns about development and or behaviours of 14 children out of the 67 consented to participate in the study. Three of them are already known the CDC. One has Aspergers syndrome (Autistic Spectrum Disorder) and the other two are followed up for developmental delay.

Griffiths Mental Developmental Scales (for testing babies and young children from birth to eight years of age) used by a senior consultant community Paediatrician. We interviewed the child accompanied by his/ her parent(s) for an hour and we used generic assessment for behavioural problems. For those concerned about hyperactivity we used Short Connor's Parents questionnaire and contacted Nursery/ School for feedback about the child's behaviours, after parent consented, to have a complete picture.

RESULTS:

The sample consisted of 105 (children 60 boys and 45 girls) born to the 89 pregnant diabetic women. There may be a bias that those who did not respond to participate in the study may have healthy children and that is why they are not bothered to respond. Even though if we calculate the p value considering the total number of children (105) rather than the consented ones (67); ($p < 0.026$) with CI of 0.1333 +/- 0.0650

30 women had T1DM (28.6%), 7 had T2DM (6%) and 68 had GDM (64%).

77 women treated with insulin during pregnancy (73.3%). All those with T1DM and T2DM were treated with insulin. More than half of the GDM mothers were controlled by insulin and the rest were controlled only on diet.

We used HbA1c level of $< 7.5\%$ as a measure of good control. Only 27 women had antenatal records of HbA1c, those are mothers with pre-gestational diabetes, ranging 5.4 – 13.7 % (mean of 7.8%).

44 women had records of HbA1c during pregnancy ranging 4.2 – 13.0% (mean of 6.8%).

The mean HbA1c for women with GDM was 5.4%.

The incidence of hypoglycaemia in women with T1DM was 25 (83%) while it was 57% in T2DM and 51% in GDM.

The incidence of hypoglycaemia was the same in babies delivered by SVD and CS (72%).

All the macrosomic babies (birth wt. > 4.5 kg) had reported episodes of hypoglycaemias, while around 2/3 of babies weighted 3 – 4 & 4 – 4.5 kg had episodes of hypoglycaemias and ½ of babies weighted < 3 kg had reported episodes of hypoglycaemias. This indicates the positive relation between poor diabetic control, increased birth weight and neonatal hypoglycaemia.

Mothers with T1DM and T2DM both had poor diabetic control before and during pregnancy.

9 children out of the 12 born to GDM mothers had reported neonatal hypoglycaemias ranging 1.1 – 2.4 mmol/l and none of them were admitted to the SCBU.

DISCUSSION:

Although our study is relatively small, it indicates elevated incidence of developmental delay and behavioural problems in children born to diabetic mothers, compared to non-diabetic mothers delivered at Medway Maritime Hospital, 1998 - 2003.

Overactivity, short attention span and attention seeking were the main behavioural problems we could link to children born to diabetic mothers.

Ornoy et al found that attention span and activity level were worse among children at age 5 – 8 than at older ages, and ADHD does seem to be more severe at early school age and tend to decrease in severity around puberty.

Other investigators have shown that, children born to diabetic mothers; have many indicators of sensory-motor development been lower than in non-diabetic mothers ⁽⁷⁾.

A similar finding was described by Rizzo et al, who evaluated psychomotor development; fine and growth motor function in children at ages 6 to 9 years, and found a significant negative correlation between maternal second and third trimester hydroxybutyrate concentration and performance on the Bruiniks-Oseretzky test ⁽⁸⁾.

Growth motor skills and speech and language delay were the main development areas of concern we could link between maternal diabetes and development in children aged 1 – 6 years.

Psychomotor development in children with Type1 Diabetes (T1DM) or Gestational Diabetes (GDM), using Brunet-Lezine Psychomotor Development Scale, was found to be abnormal. Mainly speech, eye-movement coordination and social aspect were affected (*Kowalczyk et al 2002*).

The fact that in our study, 12 out of the 14 children with development/ behaviour problems, were born to mothers who had gestational diabetes mellitus **support the second part of our theory**; which is perinatal problems e.g. neonatal hypoglycaemia and foetal distress. Rather than the first part of the theory, which is glycaemic control in early pregnancy and whether high glucose

has teratogenic-like effects on the growing foetal brain?

On the other hand, other investigators found that children born to diabetic mothers develop normally, based on physical and neurological indices^(9, 8, 10).

Rizzo et al,⁽¹⁰⁾ found that many indicators of sensory-motor development were lower in children born to diabetic mothers.

We found that there is no clear correlation between marital status, ethnic group, smoking and alcohol during pregnancy and development/ behavioural problems in children born to diabetic mothers.

All the macrosomic babies, (wt. more than 4.5 kg) had reported hypoglycaemia

We couldn't establish a direct correlation between macrosomia and behavioural/ developmental problems in our study.

Only one of the index babies was born small for gestational age weight of 2.1 kg, had neonatal hypoglycaemia

In a recent study by Steninger⁽¹¹⁾ 13 children with, and 15 without, neonatal hypoglycaemia < 1.5 mmol/l found to have significantly more difficulties in a validated screening test for minimal brain dysfunction than the control and were also more often reported to be hyperactive, impulsive, and easily distracted. On psychological assessment they had lower total development score than normoglycaemic children born to diabetic mothers, and control children.

Some authors believe that asymptomatic neonatal hypoglycaemia has no effect on neurodevelopment⁽¹²⁾. On the other hand, Lucas has shown that moderate asymptomatic hypoglycaemia < 2.6 mmol/l may be associated with reduced mental and motor

development scores at 18 month of age⁽¹³⁾.

Our study showed no link between APGAR scores and behaviour or development as none of the 14 index cases had low APGAR scores at 5 minutes. The study also showed no association between smoking and alcohol during pregnancy and behaviour/developmental problems in children born to diabetic mother.

It is difficult to study the correlation between behaviour/development and HbA1c (before and during pregnancy) as only 2 out of 14 women had HbA1c done before pregnancy; and 4 out of 14 women, including the previous 2, had the test done during pregnancy.

Rizzo et al concluded that maternal diabetes during pregnancy might affect behavioural and intellectual development in the offspring⁽¹⁴⁾.

However, other studies by Peterson et al⁽¹⁵⁾ suggest that early (first trimester) foetal growth delay in diabetic pregnancies is associated with worse psychomotor deficit in children at ages 4 to 5 years. Presumably such delays are derived from mothers with worse diabetic control as judged by earlier evidence that such mothers had higher glycosylated haemoglobin levels. Previous studies have shown that the intelligence quotient of mother, her highest grade achieved, the father's highest grade achieved, and the family income are highly inter-correlated⁽¹⁶⁾.

One Swedish study found that intrauterine factors including maternal diabetes and neonatal factors are important in the pathogenesis of autism⁽¹⁷⁾. An increase number of autoimmune disorders suggest that in some families with autism, immune dysfunction could interact with various environmental factors to play a role in autism pathogenesis⁽¹¹⁾.

Another study done at Hebrew University, Jerusalem showed that

pregestational or gestational diabetes adversely affect attention span and motor function of offspring at school age, but not their cognitive ability. These effects were negatively correlated with the degree of maternal glycaemic control, and were more pronounced in younger children⁽¹⁸⁾.

Marital status and ethnic group in diabetic mothers is not linked to developmental delay or behavioural problems.

Out of the 14 index children 12 were born to mothers who had Gestational Diabetes Mellitus and the other 2 were born to mothers with T1DM and non-was born to mothers with T2DM, this fact stresses the importance of glycaemic control in the second half of pregnancy.

Our study showed that all the 5 children with varying degrees of developmental delay were born to mothers who had Gestational Diabetes Mellitus and all of them had neonatal hypoglycaemia (1.1 – 2.4 mml/l).

11 out of the 14 children with behavioural problems were born to mothers who had GDM; and 9 of them had neonatal hypoglycaemias. This stresses the link of maternal hypoglycaemia as a perinatal complication and long-term influences on development and/or behaviours; and the importance of addressing the significance of treating gestational diabetes and anticipating neonatal hypoglycaemia.

Other investigators came to same conclusion that the effects of maternal diabetes may result from the adverse effects of metabolic factors mainly during the second half of pregnancy that correlate with the degree of glycaemic control, these results emphasise the importance of good control throughout pregnancy^(18,19).

Studies reporting the presence of neurological delay in the

offspring of diabetic mothers vary from 3.9% to 37% of the offspring tested ⁽²⁰⁾.

One review reported a number of central nervous system abnormalities thought to be caused by intrauterine exposure to maternal diabetes, including impaired motor function, low intelligence, and Erb's palsy, seizure disorders, cerebral palsy, mental retardation, speech disturbances, reading difficulty, behavioural disturbances, psychosis, and deafness ⁽²¹⁾.

Such complications were reportedly minimized with good control of glucose levels; such intelligence and behaviour were not noticeably different in controls ^(22, 23).

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