

High incidence of Down's syndrome in infants of diabetic mothers

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Abstract

The incidence of Down's syndrome was studied in 1870 infants of diabetic mothers out of 22 300 neonates born between January 1987 and April 1994 in our institution. All pregnancies were screened for diabetes and all cases of Down's syndrome were confirmed by chromosome analysis. Down's syndrome (all trisomy 21) was diagnosed in 35 infants: seven were born to mothers with gestational diabetes and 28 to non-diabetic mothers. The incidence of Down's syndrome was higher in infants of diabetic mothers (3.75 per 1000 *v* 1.36 per 1000) ($p=0.02$) with a relative risk of 2.75. No significant difference was found in maternal age between both groups ($p=0.67$) and the rate of Down's syndrome was higher in infants of diabetic mothers when compared with infants of non-diabetic mothers of similar age.

Down's syndrome should be added to the congenital malformations already known to occur more frequently in infants of diabetic mothers.

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Congenital malformations are more frequent in infants of diabetic mothers than in the normal population. It is not generally known nor mentioned in standard obstetric and paediatric textbooks that Down's syndrome could also have a higher incidence in this group. During a study of infants of diabetic mothers in our hospital over the past few years, we found a higher incidence of Down's syndrome in these infants when compared with the rest of the population. We therefore undertook a review of all children born with Down's syndrome in our hospital over a period of seven years, assessed any relation with maternal diabetes, and reviewed the available data in the literature.

Subjects and methods

All infants diagnosed with Down's syndrome and born in our hospital from January 1987 until April 1994 were studied. Their charts were reviewed as well as their parents' for the presence of diabetes, other endocrine or autoimmune disease, and for maternal age at the infant's birth.

All pregnancies are screened for diabetes at 24 weeks of gestation: one hour after ingestion of 50 g of oral glucose, the presence of a venous plasma glucose greater than 7.8 mmol/l is con-

sidered abnormal and a full oral glucose tolerance test is carried out. It is considered diagnostic of gestational diabetes if at least two values of venous plasma concentrations were equal to, or greater than, 5.8 mmol/l when fasting, 10 mmol/l at one hour, 9.1 mmol/l at two hours, and 8.0 mmol/l at three hours after the ingestion of 100 g of oral glucose.¹ Screening was carried out earlier in pregnancy if risk factors existed, that is, family history of diabetes, previous history of stillbirth, neonatal death or macrosomia, or maternal obesity. Maternal diabetes was defined as pregestational if it was present before, and gestational when first recognised during that particular pregnancy. Carbohydrate metabolism was not systematically studied in the fathers of infants with Down's syndrome unless diabetes was clinically suspected. All cases of Down's syndrome were confirmed by chromosomal analysis.

The comparison with the incidence of Down's syndrome in infants of diabetic mothers versus the rest of the population was studied by the Fisher's exact test and calculation of relative risk with 95% confidence intervals (CI). The comparison of maternal age between both groups was analysed with the Mann-Whitney U test. The rate of Down's syndrome was compared in similar age groups in diabetic and non-diabetic mothers and relative risk was calculated with 95% CI.

Results

A total of 22 300 infants was born in our institution during the study period. This included 1870 infants born to diabetic mothers (1748 with gestational diabetes and 122 with pregestational diabetes) who did not have any evidence of other autoimmune or endocrine problems.

Thirty five children with Down's syndrome were born during this same period (table 1). All had trisomy 21 on chromosomal studies and no translocations were identified.

Seven babies with Down's syndrome were born to diabetic mothers (two boys and five girls). Their mothers all had gestational diabetes, six were treated by diet alone and only one received insulin. None had other children with Down's syndrome, developed subsequent diabetes, nor had other autoimmune or endocrine problems. The maternal age ranged from 27 to 48 years (mean 36.8). The fathers were not diabetic, nor did they have any endocrine or autoimmune disease.

Twenty eight babies with Down's syndrome were born to non-diabetic mothers (16 boys and 12 girls). The maternal age ranged from 15

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Table 1 Infants with Down's syndrome

	Infants of non-diabetic mothers	Infants of diabetic mothers	p Value
No of infants	28	7	0.02*
Boys	16	2	0.17*
Mean maternal age (years)	31.7	36.8	0.67†

*Fisher's exact test; †Mann-Whitney U test.

to 50 years (mean 31.7). One father had diabetes; all other fathers and mothers had no endocrine or autoimmune disease.

The incidence of Down's syndrome was 3.75 per 1000 infants of diabetic mothers and 1.36 per 1000 in other infants (table 2), with a statistically significant difference ($p=0.02$; Fisher's exact test). The relative risk was 2.75 (the 95% CI being 1.20 to 6.29).

There was no significant difference in maternal age ($p=0.67$) nor in the sex distribution ($p=0.17$) in both groups of infants. When the rate of Down's syndrome was calculated in similar age groups in diabetic and non-diabetic mothers (table 2), it was up to three times higher in infants of diabetic mothers than in infants of non-diabetic mothers in all age groups; this did not, however, reach statistical significance in view of the small numbers within each age group, although a statistically significant difference was found ($p=0.02$) when all age groups were consolidated.

Discussion

Although the incidence of Down's syndrome in this study was similar to other reports from Saudi Arabia, it was found to be 2.75 times higher in infants of diabetic mothers than in offspring of non-diabetic mothers, in agreement with previous reports.² As all the infants had trisomy 21 and none had translocation, maternal age was studied as a possible confounding factor. However, we found that the groups were not significantly different in respect to maternal age, and that at any maternal age, the incidence of Down's syndrome was more frequent in infants of diabetic mothers when compared with other infants, thus making maternal diabetes an independent risk factor for Down's syndrome, irrespective of maternal age.

Diabetes mellitus in patients with aneuploid chromosome aberrations and their parents were reviewed by Nielsen.³ Chemical and clinical diabetes were found in 29 and 8% of patients with Klinefelter's syndrome and in 10 and 9% of their mothers and fathers respectively,^{4,5} and in 26 and 5% of patients with Turner's syndrome and in 2 and 5% of

their mothers and fathers respectively.⁶⁻⁹ Milunski and Neurath showed a definite association of diabetes mellitus and Down's syndrome.¹⁰ It is not clear whether the occurrence of diabetes in Down's syndrome simply reflects an increased frequency of diabetes in these families, or whether chromosomal aberration predisposes to the development of diabetes.² The same author found an incidence of diabetes of 19.1% in 42 parents (24 mothers and 18 fathers) of 24 children with Down's syndrome compared with 6.8% of parents in the general population. Another 38.1% of the studied parents also showed some abnormality in their glucose tolerance test. Since abnormalities in glucose tolerance occur more often in people with a family history of diabetes, these results may simply reflect a high frequency of diabetes in these families of children with Down's syndrome. The question arises whether parental or familial diabetes or prediabetes could predispose to development of chromosomal aberration. Another study noted that 75% of mothers of infants with Down's syndrome had an altered carbohydrate metabolism.¹¹

The increased tendency to autoantibody formation in type 1 insulin dependent diabetics could implicate autoimmunity in chromosomal abnormalities.¹² However, as most previous studies which showed an association of aneuploidy with parental diabetes comprised many cases of chemical and non-insulin dependent diabetes (type 2),²⁻¹⁰ and all diabetic mothers of children with Down's syndrome in our study had gestational diabetes, where autoimmunity is not thought to be involved, factors other than autoantibodies have to be implicated. Other proved mechanisms for non-disjunction include advanced biological aging,¹³⁻¹⁵ or have a molecular basis such as the apolipoprotein E allele in young mothers of infants with Down's syndrome,¹⁶ although these have yet to be studied in diabetic pregnancies.

Further studies of carbohydrate metabolism, advanced biological aging, biochemical factors like apolipoprotein E, and the role of autoimmunity in parents of children with Down's syndrome or other aneuploid chromosome abnormalities are needed to elucidate whether there is an increased risk of non-disjunction. As mothers with gestational diabetes were euglycaemic at the time of conception, hyperglycaemia cannot be responsible for the chromosomal events; the degree of diabetic control is therefore unlikely to have any effect on the incidence of aneuploidy in the fetus. The unstudied question of antenatal genetic diag-

Table 2 Distribution of Down's syndrome by maternal age

Age (years)	Non-diabetic mothers			Diabetic mothers					
	No of mothers	No of infants with Down's syndrome	Down's syndrome rate per 1000	No of mothers	No of infants with Down's syndrome	Down's syndrome rate per 1000	Relative risk	95% CI	p Value
Below 30	9228	11	1.18	453	1	2.20	1.85	0.24 to 14.33	0.43
30-34	7551	8	1.06	810	2	2.47	2.33	0.5 to 10.9	0.25
35-39	3014	4	1.33	501	2	3.99	3.01	0.55 to 16.38	0.20
40-44	684	3	4.39	77	1	12.99	2.96	0.31 to 28.1	0.34
45-50	93	2	21.46	29	1	34.48	1.60	0.15 to 17.05	0.5
Total	20 570	28	1.36	1870	7	3.75	2.75	1.2 to 6.29	0.02

nosis of the offspring of diabetic mothers should be addressed with this new evidence.

Our study confirms that Down's syndrome occurs more frequently in infants of diabetic mothers. This should be added to the list of congenital anomalies known to occur more frequently in these infants. Parents should also be made aware of this risk, but our data neither substantiate a need for antenatal diagnosis of Down's syndrome in maternal diabetes nor that its incidence is likely to be reduced by better management of the abnormal carbohydrate metabolism.

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