Childhood cognitive ability: relationship to gestational diabetes mellitus in India

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Abstract

Aims/hypothesis Our aim was to test the hypothesis that gestational diabetes mellitus (GDM) in mothers is associated with poorer cognitive ability in their offspring in India. **Methods** During 1997 to 1998 maternal GDM status was assessed by OGTT at 30±2 weeks of gestation. Between 2007 and 2008, at a mean age of 9.7 years, 515 children (32 offspring of GDM mothers [ODM]; 483 offspring of non-GDM mothers [controls]) from the Mysore Parthenon birth cohort underwent cognitive function assessment using tests from the Kaufman Assessment Battery for Children—Second Edition and additional tests measuring learning, long-term storage/retrieval, short-term memory, reasoning, attention and concentration, and visuo-spatial and verbal abilities.

Results Compared with controls, ODM scored higher in tests for learning, long-term retrieval/storage ($p=0.008$), reasoning ($p=0.02$), verbal ability ($p=0.01$), and attention and concentration ($p=0.003$). In multiple regression, adjust-

ed for the child's age, sex, gestation, neonatal weight and head circumference, maternal age, parity and BMI, and the parent's socioeconomic status, education and rural/urban residence, this difference remained significant only for learning, long-term retrieval/storage ($\beta=0.4$ SD (95% CI 0.01–0.75); $p=0.04$) and verbal ability ($\beta=0.5$ SD (95% CI 0.09–0.83); $p=0.02$), and not with other test scores.

Conclusions/interpretation In this population of healthy Indian children, there was no evidence of lower cognitive ability in ODM. In fact some cognitive scores were higher in ODM.

Keywords Children · Cognitive function · Gestational diabetes mellitus · India

Abbreviations

GDM Gestational diabetes mellitus
ODM Offspring of mothers with gestational diabetes mellitus
SES Socioeconomic status

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Introduction

The prevalence of gestational diabetes mellitus (GDM) is increasing in India and is estimated to be as high as 10–20% in urban populations [1]. Some studies have reported language impairment, inattention, motor delays and lower intelligence score among offspring of GDM mothers (ODM) [2, 3]. The Mysore Parthenon cohort was established to study the effects of GDM on offspring body composition and glucose/insulin metabolism [4], and enabled us to examine cognitive ability in children (aged 9–10 years) in relation to maternal GDM status.

Methods

The cohort methodology has been reported in detail elsewhere [4]. Of 785 pregnant women recruited in 1997–1998 who completed an OGTT at 30 ± 2 weeks' gestation, 630 delivered live, normal babies at the Holdsworth Memorial Hospital, Mysore, India. GDM (defined by Carpenter–Coustan criteria [5]) was diagnosed in 49 (6.9%) women. Following the OGTT, women diagnosed as having GDM were managed by their consultant obstetricians and therefore no information is available about the treatment and metabolic control of these women. The children had detailed anthropometric measurements at birth, and then each year until the age of 5 years and every 6 months thereafter. We extracted data from labour ward records concerning complications in pregnancy (pre-term delivery, pregnancy-induced hypertension, maternal infection), mode of delivery and neonatal Apgar score.

During 2007–2008, cognitive function was assessed among 515 available children (82% of the original cohort, aged 9–10 years: 32 ODM and 483 offspring of non-GDM mothers [controls]) using three core tests from Kaufman's Assessment Battery for Children—Second Edition [6] and additional tests [7, 8] measuring learning, long-term retrieval/storage (Atlantis), short-term memory (word order), reasoning (pattern reasoning), attention and concentration (Coding-Wechsler Intelligence Scale for Children—Third Edition), visuo-spatial (Kohs block-design test) and verbal abilities. Detailed descriptions of these tests are described in the Electronic supplementary material (ESM) Table 1 and also reported in our earlier publication [9].

We also collected data on: maternal age, parity, BMI, height and urban/rural residence in pregnancy; the child's sex, gestation, neonatal weight and head circumference, and current age, BMI and height; and the parent's educational level and socioeconomic status (SES) measured using the Standard of Living Index [10].

The hospital research ethics committee approved the study and informed consent was obtained from parents and children.

Statistical methods Variables with skewed distributions were either log-transformed (maternal BMI and visuo-spatial ability) or square-root transformed (pattern reasoning). Cognitive test scores (transformed and non-transformed) were z-standardised. Differences between ODM and controls were analysed using unpaired *t* tests and chi-square tests. Multiple regression analysis, adjusting for potential covariates/confounders, was performed to examine offspring cognitive ability in relation to GDM status. Stata version 10 (Stata Corporation, College Station, TX, USA) was used for all analyses.

Results

As previously described [4] GDM women were older, shorter, had higher BMI in pregnancy, and better educational attainment than non-GDM women (Table 1). SES and the proportion living in an urban rather than rural setting were higher among the GDM group, although these differences were not statistically significant. ODM had higher birthweight, larger neonatal head circumference and higher current BMI than controls.

All the cognitive scores increased with increasing SES and parental educational level ($p<0.001$ for all; data not shown). Children of primiparous mothers performed better than children of multiparous mothers in tests of learning, long-term retrieval/storage ($p=0.004$), short-term memory ($p=0.03$), reasoning ($p=0.001$) and verbal fluency ($p=0.001$). The cognitive performance of urban children was better than rural children in tests of learning, long-term retrieval/storage ($p<0.001$), short-term memory ($p=0.004$), reasoning ($p=0.001$) and visuo-spatial ability ($p=0.001$). Reasoning and visuo-spatial ability scores increased with increasing maternal age ($p<0.001$ for both).

Mean cognitive scores were higher in ODM than controls, statistically significantly for long-term retrieval/storage, reasoning, verbal ability and attention and concentration (Table 2). In multiple regression analysis the differences remained significant for learning, long-term retrieval/storage and verbal ability adjusted for the child's current age, sex, gestation, neonatal weight and head circumference, maternal age, parity and BMI, and the parents' SES, education and rural/urban residence. Although cognitive performance was better in girls than boys, there were no interactions between sex and GDM in relation to cognitive ability. Among controls, maternal 120 min glucose concentrations during OGTT, but not fasting glucose, were positively associated with the children's verbal ability ($p=0.02$) and Atlantis score ($p=0.07$).

Discussion

In this study of healthy Indian school-age children born in one maternity unit, cognitive scores were higher among ODM than controls. Both maternal GDM and higher cognitive performance in the children were associated with higher parental education and/or SES. However, the associations of GDM with better offspring learning, long-term storage/retrieval and verbal ability remained statistically significant after adjusting for these and all other potential confounding factors measured.

Strengths of the study were that we measured a battery of cognitive function tests specifically adapted for, and validated in, a South Indian population and also collected

Table 1 Covariates/confounders according to maternal GDM status

Covariates	ODM (<i>n</i> =32)	Controls (<i>n</i> =483)	<i>p</i> value ^b
Maternal factors in pregnancy			
Age (years)	28.7 (4.9)	23.6 (4.0)	<0.0001
Parity 2+, <i>n</i> (%)	6 (18.8)	82 (17.0)	0.8
Height (cm)	152.2 (5.8)	154.4 (5.3)	0.02
Body mass index (kg/m ²) ^a	27.1 (25.0, 29.1)	23.1 (20.9, 25.9)	<0.0001
Fasting glucose concentration (mmol/l)	5.8 (1.7)	4.5 (0.4)	<0.0001
120 min glucose concentration (mmol/l)	9.8 (4.0)	5.8 (1.1)	<0.0001
Infant factors at birth			
Gestational age (weeks)	39.3 (1.2)	39.3 (1.6)	0.9
Birthweight (kg)	3.270 (0.459)	2.854 (0.441)	<0.0001
Birthweight (SD score)			
Boys	0.6 (0.9)	−0.002 (1.01)	0.08
Girls	1.2 (1.1)	−0.07 (1.0)	<0.0001
Head circumference (cm)	34.3 (1.2)	33.8 (1.4)	0.04
Head circumference (SD score)			
Boys	0.4 (0.8)	−0.01 (1.0)	0.2
Girls	1.04 (0.5)	−0.04 (1.0)	0.03
Children's factors at the time of cognitive testing			
Age (years)	9.7 (0.3)	9.7 (0.3)	0.3
Height (cm)	131.3 (6.2)	130.7 (5.7)	0.6
Height (SD score)			
Boys	−0.70 (1.07)	−0.63 (0.88)	0.8
Girls	−0.65 (0.97)	−0.85 (0.95)	0.3
Body mass index (kg/m ²)	15.9 (1.8)	14.5 (1.8)	<0.0001
Body mass index (SD score)			
Boys	−0.75 (1.13)	−1.36 (1.24)	0.1
Girls	−0.18 (1.04)	−1.26 (1.22)	0.0001
Parents' SES			
Standard of living index (score)	37.4 (7.8)	36.2 (8.3)	0.4
Maternal education, <i>n</i> (%)			
<10 completed years	3 (9.4)	186 (38.6)	0.001
10 completed years	10 (31.2)	149 (30.9)	
>10 completed years	19 (59.4)	147 (30.5)	
Paternal education, <i>n</i> (%)			
<10 completed years	7 (21.9)	186 (38.6)	0.02
10 completed years	20 (62.5)	183 (38.0)	
>10 completed years	5 (15.6)	113 (23.4)	
Residence			
Rural, <i>n</i> (%)	5 (15.6)	134 (27.7)	0.1
Urban, <i>n</i> (%)	27 (84.4)	349 (72.3)	

Values are mean (SD) unless otherwise stated

^a Transformed variable; values are median (interquartile range)

^b *p* values are for the difference between ODM and controls derived using *t* tests or chi-squared tests

data on a range of potential covariates/confounders. Limitations in our study were a relatively small number of ODM, lack of data on the severity of GDM, treatment and maternal diet, and no information on parental intelligence and/or the home environment.

A recent case–control study reported a higher risk of language impairment in ODM compared with controls [2]. A recent review has reported no difference in cognitive ability among children born to mothers with or without

GDM, although compared with controls, ODM performed less well in fine and gross motor functions. Further, this review reported inverse associations of offspring intelligence scores, attention, language development, learning, memory span, and mental and psychomotor development with the severity of GDM assessed by glycosylated haemoglobin level and ketonuria, suggesting that the cognitive performance of offspring could be within normal limits in well-controlled GDM [3]. The reasons for our

Table 2 Association between maternal GDM status and children's cognitive test scores

Cognitive tests	ODM (<i>n</i> =32)	Controls (<i>n</i> =483)	<i>p</i> value ^b	β (95% CI)	<i>p</i> value ^c	β (95% CI)	<i>p</i> value ^d	β (95% CI)	<i>p</i> value ^e
Learning, long-term retrieval/storage (Atlantis)	75.9 (16.2)	67.5 (17.1)	0.008	0.48 (0.12, 0.84)	0.009	0.37 (0.02, 0.71)	0.04	0.38 (0.01, 0.75)	0.04
Short-term memory (word order)	17.0 (2.7)	16.4 (2.6)	0.2	0.18 (−0.19, 0.54)	0.3	0.02 (−0.33, 0.37)	0.9	0.03 (−0.35, 0.40)	0.8
Reasoning ability ^a (pattern reasoning)	12.5 (9.0, 16.0)	10.0 (4.0, 14.0)	0.02	0.37 (0.01, 0.73)	0.04	0.24 (−0.10, 0.58)	0.2	0.14 (−0.23, 0.51)	0.4
Verbal ability—animals (verbal fluency)	13.1 (3.0)	12.0 (3.3)	0.07	0.31 (−0.05, 0.67)	0.09	0.23 (−0.12, 0.59)	0.2	0.22 (−0.16, 0.61)	0.2
Verbal ability—names (verbal fluency)	18.2 (5.2)	16.0 (4.9)	0.01	0.36 (0.01, 0.71)	0.04	0.29 (−0.05, 0.64)	0.09	0.46 (0.09, 0.83)	0.02
Visuo-spatial ability ^a (Kohs block-design)	85.3 (68.1, 97.3)	76.2 (62.6, 87.8)	0.1	0.30 (−0.06, 0.66)	0.1	0.17 (−0.18, 0.52)	0.4	0.01 (−0.36, 0.39)	0.9
Attention and concentration (Coding-WISC-III)	36.8 (8.0)	32.4 (8.1)	0.003	0.42 (0.09, 0.75)	0.01	0.34 (0.01, 0.67)	0.04	0.32 (−0.04, 0.67)	0.08

Values are mean $\pm$ SD unless otherwise stated

β is the change in the SD of the outcome (transformed and non-transformed) comparing children of GDM mothers with children of non-GDM mothers, derived using multiple linear regression

^aTransformed variable; values are median (interquartile range)

^b*p* values are for the difference between ODMs and controls derived using *t* tests

^c*p* value derived using multiple linear regression adjusted for child's sex, gestation and age

^d*p* value derived using multiple linear regression adjusted for child's sex, gestation, age, SES, parents' education and rural/urban residence

^e*p* value derived using multiple linear regression adjusted for child's sex, gestation, age, SES, parents' education, rural/urban residence, maternal age, BMI and parity in pregnancy and child's weight and head circumference at birth

WISC-III, Wechsler Intelligence Scale for Children—third edition

finding of higher cognitive function in ODM may be that there were no cases of severe or uncontrolled GDM in our study and/or that we were unable to completely adjust for the fact that in our population GDM was associated with higher maternal education, urban residence (and thus better schooling) and better childhood nutritional status (ODM had higher BMI). This effect may not be evident in studies in industrialised populations, where GDM tends to be associated with lower SES and lower maternal education [2]. Alternatively, the fetus of a mother with GDM is exposed to higher concentrations of glucose and fatty acids transferred across the placenta from the maternal circulation [11]. Theoretically these could enhance brain development. This is perhaps supported by our finding of positive associations of maternal 120 min glucose concentrations during OGTT with verbal ability and long-term retrieval/storage among controls; unfortunately we do not have data on maternal circulating fatty acids.

In conclusion, in this population of healthy Indian children, there was no evidence of lower cognitive ability in ODM. In fact, some cognitive scores (two of the six cognitive parameters tested) were higher in ODM. This may be due to residual confounding. Although we adjusted for a number of confounding factors, no SES score can perfectly capture all the effects of SES, especially in India where there is a wide range of SES. Even in the SES-matched analysis there were significant differences in other important factors, such as maternal education, age and BMI, and child's birthweight and current BMI, between cases and controls. Alternatively the difference may be due to biological effect. The study suggests a need for further research to examine the relationship between GDM and cognitive ability in offspring in larger studies.

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References

1. Seshiah V, Balaji V, Balaji MS, Paneerselvam A, Kapur A (2009) Pregnancy and diabetes scenario around the world. India. *Int J Gynaecol Obstet* 104:S35–S38
2. Dionne G, Boivin M, Séguin JR, Périus D, Tremblay RE (2008) Gestational diabetes hinders language development in offspring. *Pediatrics* 122:e1073–e1079
3. Ornoy A (2005) Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatr Endocrinol Rev* 3:104–113
4. Hill JC, Krishnaveni GV, Annamma I, Leary SD, Fall CH (2005) Glucose tolerance in pregnancy in South India: relationships to neonatal anthropometry. *Acta Obstet Gynecol Scand* 84:159–165
5. Carpenter MW, Coustan DR (1982) Criteria for screening for gestational diabetes. *Am J Obstet Gynecol* 159:768–773
6. Kaufman AS, Kaufman LN (2004) Kaufman assessment battery for children. Manual, 2nd edn. AGS Publishing, Circle Pines
7. Kohs SC (1923) Intelligence measurement: a psychological and statistical study based upon the block-design test. Macmillan, New York
8. Wechsler D (1991) Manual for the Wechsler Intelligence scale for children, 3rd edn. Psychological Corporation, San Antonio
9. Veena SR, Krishnaveni GV, Wills AK et al (2010) Association of birthweight and head circumference at birth to cognitive performance in 9–10 year old children in South India: prospective birth cohort study. *Pediatr Res* 67:424–429
10. International Institute for Population Sciences (IIPS) and Operations Research Centre (ORC) Macro (2001) National Family Health Survey (NFHS-2), India 1998–1999. IIPS, Maharashtra
11. Ortega-Senovilla H, Alvino G, Taricco E, Cetin I, Herrera E (2009) Gestational diabetes mellitus upsets the proportion of fatty acids in umbilical arterial but not venous plasma. *Diabetes Care* 32:120–122