Cognitive Function and Army Rejection Rate in Young Adult Male Offspring of Women With Diabetes

A Danish population-based cohort study

GUNNAR LAUGE NIELSEN, MD[1]
CLAUS DETHLEFSEN, MSC, PHD[2]
HENRIK TOFT SØRENSEN, DMSC[1]
JAN FOG PEDERSEN, DMSC[3]
LARS MOLSTED-PEDERSEN, DMSC[4]

OBJECTIVE — While maternal diabetes is a known risk factor for perinatal complications, there is little data on long-term intellectual outcome in offspring. We compare the rejection rate and cognitive functioning of military conscripts according to maternal diabetes status during pregnancy.

RESEARCH DESIGN AND METHODS — We identified a cohort of Danish male offspring of diabetic mothers born between 1976 and 1984 and followed this cohort together with population-based control subjects to military conscription. The main outcome was army rejection rate and cognitive function measured with a validated intelligence test.

RESULTS — The army rejection rate was 52.5% among 282 men whose mothers had diabetes during pregnancy and 45.4% among 870 control subjects (risk difference 7.3 [95% CI 0.6–14.0]). Mean cognitive scores were 41.4 units (95% CI 40.2–42.6) in diabetes-exposed conscripts and 42.7 units (42.0–43.4) in control subjects. Stratification by gestational age, Apgar score, and White's class (A–F) did not change the associations. In a subgroup analysis using available data on A1C levels during pregnancy, this variable was inversely associated with cognitive functioning. In men with maternal A1C <7%, cognitive scores were identical to those in control subjects.

CONCLUSIONS — The slightly higher army rejection rate in men with maternal diabetes indicates higher morbidity. The identical cognitive functioning in cases of well-controlled maternal diabetes compared with that in control subjects is reassuring, but the negative association between A1C and cognitive score highlights the importance of striving for optimal metabolic control in diabetic women who are or plan to become pregnant.

Diabetes Care 30:2827–2831, 2007

Maternal diabetes is a risk factor for some perinatal complications that increase the risk of neurological morbidity (1,2). An altered intrauterine environment, deliveries complicated by a higher prevalence of both preterm and overweight babies, and prolonged stay in intensive care units raise concerns about adequate intellectual development in later life (3).

Previous studies have reported normal development in the first 5–7 years of life of full-term children born to diabetic mothers, but data on outcomes among older children are scarce (3–5). Rizzo et al. (6) conducted a series of intellectual and psychomotor tests in children aged 7–11 years in a Chicago cohort originally comprising 196 children born to mothers with type 1 and type 2 diabetes. They found that average scores on a full-scale intelligence test were inversely correlated with maternal A1C levels in the second trimester and with B-hydroxybuturate levels in the third trimester (7). However, only 94 and 119 children contributed data for the two variables at follow-up, making the study vulnerable to selection bias.

Accurate data on cognitive performance in children of diabetic women is important to both mothers and their physicians. If offspring of diabetic mothers show worse cognitive performance than control subjects, one could attempt to identify modifiable risk factors. Alternatively, documentation of normal intellectual development would be reassuring.

To address this question, we analyzed cognitive function in young men at the time of army conscription according to their mothers' diabetes status during pregnancy. In a subgroup with data on A1C level, we analyzed the association between this variable and cognitive function. Because a fraction of the conscripts is rejected without actual draft examination, we also assessed the differences in rejection rate according to maternal diabetes status during pregnancy.

RESEARCH DESIGN AND METHODS

From the medical records of obstetrics departments in two Danish hospitals (Rigshospitalet, Copenhagen, and Aalborg Hospital, North Jutland County), we formed a consecutive cohort of all boys born between 1976 and 1984 to women with pregestational and gestational diabetes (diabetes-exposed pregnancies). In Denmark, all pregnant women are routinely offered regular and free outpatient care and hospitalization if necessary. Care of pregnant diabetic women in eastern Denmark (1.5 million inhabitants) and North Jutland County (0.5 million inhabitants) is confined to these two departments. Studies on

From the [1]Department of Clinical Epidemiology, Aalborg University Hospital, Aalborg, Denmark; the [2]Center for Cardiovascular Research, Aalborg Hospital, Aalborg, Denmark; the [3] Department of Radiology, Glostrup University Hospital, Glostrup, Denmark; and the [4]Diabetes Centre, Department of Obstetrics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
Address correspondence and reprint requests to Gunnar Lauge Nielsen, Aalborg Hospital, Department of Clinical Epidemiology, Forskningens Hus, Aalborg Hospital, 9000 Aalborg, Denmark. E-mail: guln@rn.dk.
Received for publication 28 June 2007 and accepted in revised form 2 August 2007.
Published ahead of print at http://care.diabetesjournals.org on 13 August 2007. DOI: 10.2337/dc07-1225.
Abbreviations: IQ, intelligence quotient; RD, risk difference.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

perinatal and neonatal outcomes of diabetic pregnancies in the 1976–1984 period have been published previously (8,9).

For each diabetes-exposed pregnancy, we identified three control pregnancies from the nationwide Central Office of Civil Registration (CPR Registry) and matched the exposed and unexposed offspring by birth year and maternal residence at time of birth.

Rejection rate and cognitive score at Draft Board

It is mandatory that all Danish men register with the military Draft Board sometime between the ages of 18 and 20 years, whereas actual military service may be postponed according to individual preferences, such as education plans. At the time of conscription, all young men complete a health questionnaire in which they report chronic health problems that could preclude military service. The Draft Board verifies such reports with health care providers, and men deemed ineligible for military service are exempt from further examination. If the diagnosis is uncertain, draftees are referred to medical specialists for further evaluation. When appropriate, those with severe chronic diseases are excused from the draft at this point. Reasons for exemption are recorded in the Conscript Registry according to the ICD-10 (10). Men exempted following input from primary health care providers or medical specialists are not required to present for a medical examination or cognitive testing under the auspices of the Draft Board. Conscription test results are thus unavailable for these men (hereafter referred to as "nonpresenters"). To assess the extent of selection bias due to neurological and mental/behavioral conditions among the nonpresenters, we constructed a variable comprising ICD-10 codes F (psychiatric and behavioral disorders) and G (diseases of the nervous system) for this group.

The draft suitability of the remaining men (hereafter referred to as "presenters") is determined by a routine Draft Board evaluation, consisting of a medical examination (with special emphasis on conditions that may interfere with the ability to serve in the military forces) and an intelligence test. All disease conditions detected in presenters are categorized according to the ICD-10 and filed in the Conscript Registry.

All presenters take the Boerge-Prien test, a 45-min validated group intelligence test developed for the Danish draft board in 1957 and used since then in an unmodified form (11). This 78-item test has four subscales (letter matrices, verbal analogies, number series, and geometric figures). The score equals the total number of correct answers for all 78 questions and is highly correlated with the verbal intelligence quotient (IQ) (0.78), performance IQ (0.71), and full-scale IQ (0.82) on the Wechsler adult intelligence scale (WAIS). In a validation study, the mean full-scale IQ was 105.8 and the mean Boerge-Prien test score was 44.2 (11).

Following the Draft Board examination, all draftees are categorized as accepted, conditionally accepted, or rejected for military service based on a global assessment of the medical examination and cognitive test results. Evaluation at the Draft Board concerns all branches of the Danish armed services. We retrieved data on all outcomes for both the diabetes-exposed and control groups from the Conscript Registry.

Data on pregnancy-related covariates

Data on gestational age and Apgar score at 5 min were collected from hospital records and the Danish Medical Birth Registry. The Medical Birth Registry contains information on all births in Denmark since 1 January 1973. Data are obtained from the official reports filed by the midwives who attend all deliveries in Denmark.

For the diabetes-exposed mothers, we extracted maternal White's classification data from hospital records (12). White's class A women are treated with diet only, whereas classes B, C, D, and F all represent women with pregestational insulin dependency. In addition, we had access to data on maternal A1C levels for 50 pregnancies in the North Jutland subcohort.

Linkage of data sources

Since 1968, all Danes have received a 10-digit personal registration number at birth or upon immigration. This unique identifier is used in virtually all Danish registries and thus permits unambiguous data linkage.

Statistical analyses

Median and mean values for each outcome category and associations between exposure and cognitive scores were computed with 95% CIs. The Mann-Whitney test was used to compare *P* values for medians. We used a significance level of 95%. The distribution of cognitive scores in the diabetes-exposed and control groups was displayed graphically with an Epanechinikov kernel density estimation (13). All analyses using the cognitive score outcome were stratified by week of completed gestation (31st to 38th), two levels of Apgar score (7–10 or <7), and two levels of White's class (A–C and D–F) in order to test for interaction from these variables. We then fitted an ordinary regression model for cognitive test score as a function of diabetes exposure and these variables. Because the distribution of cognitive scores was slightly skewed to the left, we repeated the regression analyses using a Box-Cox transformation with estimated $\lambda = 1.5$ (14). We also analyzed outcomes for the subgroups of men with scores in the lowest 25th and 10th percentiles of the entire Boerge-Prien distribution. In the subgroup from North Jutland with available A1C measurements, this variable was analyzed as a continuous variable and displayed in a scatter plot. To assess the potential impact of missing Boerge-Prien scores in nonpresenters, we conducted sensitivity analyses in which missing values were imputed with scores ranging from 36 to 48 Boerge-Prien units. We used version 9.0 SE of Stata software for all analyses (13).

The study was approved by the regional ethics committee (file no. 2-16-4-5-95.

RESULTS

Descriptive data

Of the 295 young men exposed to maternal diabetes, 4 (1.4%) died between 1 month and 17 years of age, 6 emigrated, 1 was granted draft deferment, 1 was rejected from military service due to a criminal sentence, and 1 was lost to follow-up, leaving 282 (96%) men born to 259 mothers with information on acceptance or rejection for military service. The control group consisted of 870 young men with this information.

Rejection for military service

In the diabetes-exposed group, 54 (19.2%) were rejected as nonpresenters compared with 134 (15.4%) in the control group (risk difference [RD] 3.8% [95% CI −1.4 to 8.9]). The prevalence of rejection due to diagnoses from ICD-10 categories F and G was 6.0 and 5.2%, respectively (0.8% [−13.8 to 13.0]).

When presenters and nonpresenters were combined, the rejection rate was 52.5% (148 of 282) among the diabetes-exposed group compared with 45.4% (395 of 870) among the control group (RD 7.3% [95% CI 0.6–14.0]). The medical reasons for rejection among both nonpresenters and presenters were evenly distributed among the other ICD-10 categories without predominance of diagnoses that could be related to cognitive performance (data not shown).

Cognitive scores

Boerge-Prien scores were available for 227 diabetes-exposed conscripts and 736 control subjects. Median scores were 43 units (interquartile range 36–48 units in diabetes-exposed and 37–49 units in control subjects) in both groups (P = 0.12). Mean values were 41.4 units (95% CI 40.2–42.6) in diabetes-exposed and 42.7 units (42.0–43.4) in control subjects.

This difference of 1.27 units (95% CI −2.70 to 0.14) equals 3.0 points on the commonly used IQ scale. Estimates from analyses stratified for gestational week, categories of 5-min Apgar scores, and maternal White's class were virtually identical to the crude estimates. Because inclusion of these three variables in the regression model did not change the estimates, we report results from the crude analysis only.

The results after the Box-Cox transformation of cognitive scores were consistent with the findings from the regression analysis with the untransformed Boerge-Prien scores (data not shown). Figure 1 shows the densities of cognitive scores in the two groups estimated with an Epanechinikov kernel density. In the subgroups with cognitive scores in the lowest 25th (n = 241) and 10th (n = 97) percentiles, the estimates were also identical with the crude analysis (data not shown). The associations remained virtually unchanged when the analyses were repeated in a subcohort of women in which only the first recorded pregnancy for each woman was included.

In the sensitivity analyses with imputed Boerge-Prien scores in the 189 cases without available data, we recalculated the estimated difference in scores in the two groups by each imputation level. With an imputation level of 39 units, the difference was −1.18 (95% CI −2.36 to 0.01), and the association became gradually more negative for all lower imputed values.

In the subgroup of 39 pregnancies with available data on both A1C and cognitive score, we found that a 1% point increase in A1C value was associated with a 2.6% point decrease in cognitive score (95% CI 1.8–4.8). In 19 pregnancies with A1C values ≤7.0%, the mean cognitive score was 42.6 units, whereas the score was 39.1 units in 20 pregnancies with A1C >7.0%, equivalent to a difference of 3.5 units (0.6–7.9) compared with control subjects. Figure 2 depicts the association between A1C and cognitive score together with a Box-and-whisker plot of the scores among control and diabetes-exposed subjects without A1C values.

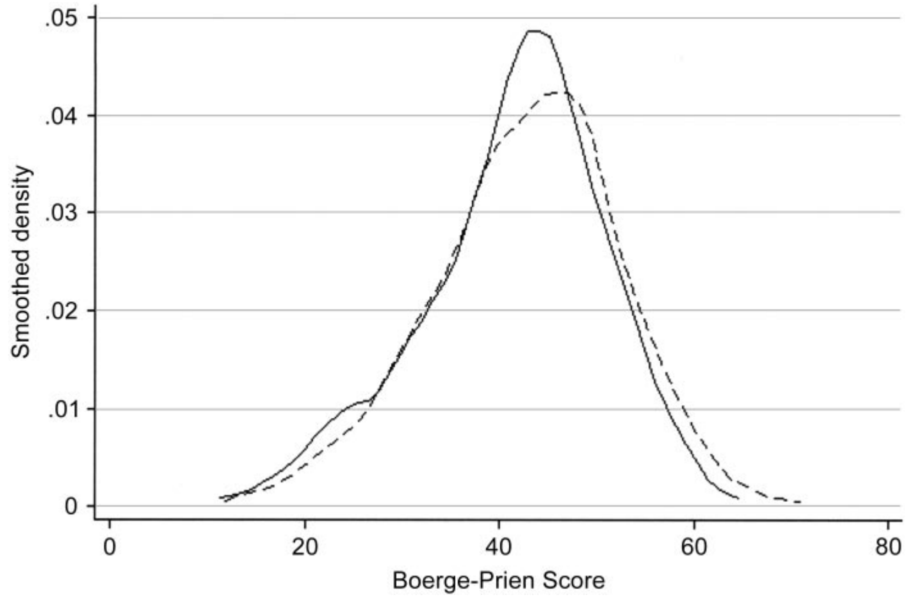

Figure 1—*Distribution of Boerge-Prien scores for diabetes-exposed and control groups using Epanechinikov kernel density estimation. Full line, diabetes exposed group; dashed line, control group.*

CONCLUSIONS— To our knowledge, this is the largest cohort study to date of the cognitive consequences of exposure to maternal diabetes, with the longest and most complete follow-up. The diabetes-exposed cohort constitutes a population-based consecutive sample with almost complete follow-up into young adulthood. We also procured a concurrent, population-based control group, as evaluation by the Draft Board is mandatory for all Danish men.

When presenters and nonpresenters were considered together, the rate of rejection for military service was higher in the diabetes-exposed group. Among presenters there was only a small decrease in cognitive score associated with diabetes exposure. In the subgroup with available data on A1C, we found a significant negative association between maternal A1C level and cognitive score adjusted for other perinatal risk factors. However, the cognitive scores in men exposed to A1C <7% were identical with those observed among control subjects.

Several potential study weaknesses deserve discussion. Differences in reasons for rejection in nonpresenters could introduce selection bias. However, our observation of identical proportions of rejection due to neurological and mental/behavioral conditions in both presenters and nonpresenters decreases this concern. In the sensitivity analyses, the association remained stable throughout a wide range of imputed cognitive scores, indicating that the observed association is fairly robust. Data entry errors are another possible source of bias, but all data were collected prospectively without knowledge of maternal exposure status. Such errors are likely to be nondifferential and would lead to underestimation of the true associations. Another concern is that some draftees may have intentionally performed worse on the test than would be expected according to their actual IQ level in order to avoid military service. However, we find it unlikely that such behavior would depend on maternal diabetes status during pregnancy. Likewise, we find it unlikely that deterioration of maternal disease status with subsequent need for additional care at time of conscription would seriously affect the performance of a son at conscription. In

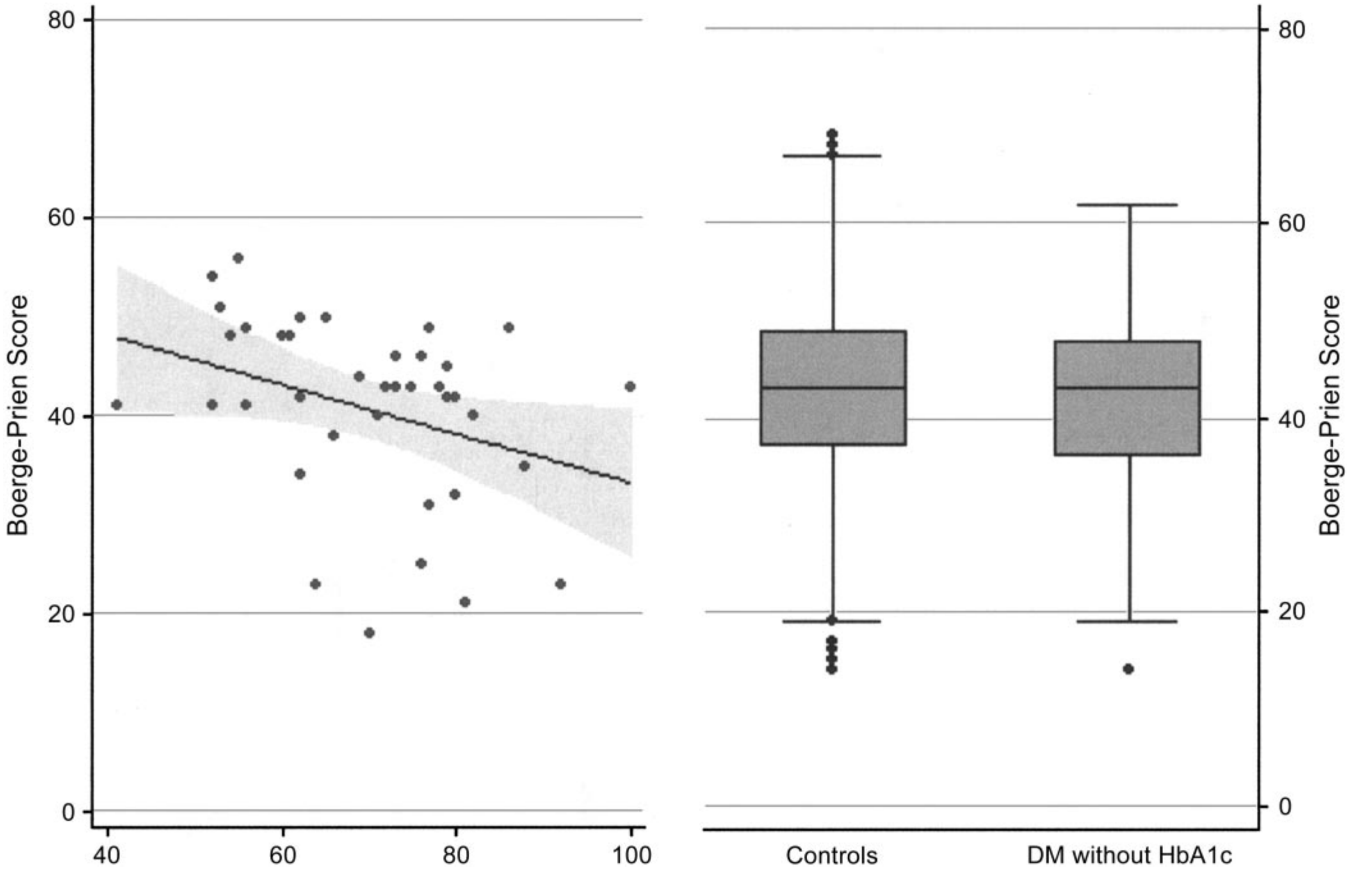

Figure 2—*Box-and-whisker plot of Boerge-Prien scores for control and diabetes-exposed subjects without A1C values and the association between A1C and Boerge-Prien score in 39 diabetes-exposed subjects with A1C values.* Left panel: *Scatter plot with regression line of A1C versus cognitive score in 39 diabetes-exposed subjects with A1C values. Shaded area represents 95% confidence band.* X-*axis label represents A1C values from 4.0 to 10.0%.* Right panel: *Control* (n = *736) and diabetes-exposed* (n = *189) subjects without A1C values. The middle lines mark the median, the top and bottom of the boxes mark 75th and 25th quartiles, and the whiskers extend from the quartiles to observations no farther than 1.5 times the interquartile range. More extreme observations are plotted individually*.

Denmark, patients with chronic conditions, like blindness, receive supplementary benefits, and arrangements for private care of diseased or disabled family members are therefore rare.

Registry data lack information about several factors that could confound the observed association if they were unevenly distributed by maternal diabetes status. Examples include maternal smoking and duration of breastfeeding, which have been previously shown to be associated with cognitive performance (15,16). However, available research findings indicate that parental socioeconomic factors only partially mediate the association between restricted fetal growth and low intellectual performance at conscription (17). Additional data on socioeconomic indicators are thus not likely to dissolve the observed associations. In the majority of the diabetic pregnancies, we unfortunately lack clinical details regarding both metabolic control and comorbidity. Diabetic women could have a higher degree of comorbidity than women without diabetes. However, in the case of vascular complications, these conditions would be reflected in White's classes D and F, and adjusting for White's class did not affect our findings.

Data on A1C were not routinely collected during the study period. Because the subgroup with available A1C data may represent a selected group of pregnancies, our observation of a negative association between A1C and cognitive score should be interpreted with caution. At the same time, however, our findings are in accordance with those of Silverman et al. (7), who observed a negative association between maternal A1C and B-hydroxybuturate and intellectual performance at school age. It is also noteworthy that in men exposed to an A1C level in the lower half of the observed A1C range, cognitive scores were identical with those found in control subjects, whereas the score was 3.5 units lower in men exposed to a high intrauterine A1C level. Due to a low number of pregnancies with recorded A1C values, our associations did not reach statistical significance at the 95% CI level, but a difference corresponding to 8.4 points on the commonly used IQ scale seems clinically important. Our results therefore support the notion that the beneficial impact of optimal metabolic control during pregnancy extends well beyond the neonatal period.

The observation of identical cognitive scores in young adulthood in offspring of diabetic women with A1C $<7\%$ and control subjects is reassuring for diabetic women who plan to become pregnant, but the observed negative association between metabolic control and adult cognitive functioning adds further evidence of the importance of striving for optimal metabolic control during pregnancy (18–20). The higher morbidity among sons of diabetic mothers accords with a nationwide Swedish registry–based study reporting a slight increase in the number of hospitalizations in children born to mothers with diabetes compared with population-based control subjects (21). The reasons for these observations and the pattern of excess morbidity deserve more detailed analyses.

In a cohort of 282 Danish men aged 18–20 years and born to diabetic mothers, we found a slightly higher army rejection rate compared with that of population control subjects. A minor difference in intellectual performance was found between the two groups, but subgroup analyses indicate that the difference may be confined solely to women with suboptimal metabolic control during pregnancy.

Acknowledgments— This study was funded by grants from Det Obelske Familiefond, Handelsgartner Ove William Buhl Olesens og ægtefælle Edith Buhl Olesens Mindelegat, the Western Danish Research Forum for Health Sciences (Vestdansk Forskningsforum), and the Aalborg Hospital Department of Clinical Epidemiology's Research Foundation.

The researchers conducted their research independently from their funding sources in all respects.

References

1. Gabbe SG, Graves CR: Management of diabetes mellitus complicating pregnancy. *Obstet Gynecol* 102:857–868, 2003
2. Greene MF: Spontaneous abortions and major malformations in women with diabetes mellitus. *Semin Reprod Endocrinol* 17:127–136, 1999
3. Ornoy A: Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatr Endocrinol Rev* 3:104–113, 2005
4. Ornoy A, Ratzon N, Greenbaum C, Peretz E, Soriano D, Dulitzky M: Neurobehaviour of school age children born to diabetic mothers. *Arch Dis Child Fetal Neonatal Ed* 79:F94–F99, 1998
5. Weiss PA, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH: Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care* 23:905–911, 2000
6. Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL: Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. *Am J Obstet Gynecol* 173: 1753–1758, 1995
7. Silverman BL, Rizzo TA, Cho NH, Metzger BE: Long-term effects of the intrauterine environment: the Northwestern University Diabetes in Pregnancy Center. *Diabetes Care* 21 (Suppl. 2): B142–B149, 1998
8. Mølsted-Pedersen L, Kühl C: Obstetrical management in diabetic pregnancy: the Copenhagen experience. *Diabetologia* 29: 13–16, 1986
9. Nielsen GL, Nielsen PH: Outcome of 328 pregnancies in 205 women with insulin-dependent diabetes mellitus in the county of Northern Jutland from 1976 to 1990. *Eur J Obstet Gynecol Reprod Biol* 50:33–38, 1993
10. Schiøler G, Mosbech J: *Klassifikation af Sygdomme*. 10th rev. Copenhagen, Munksgaard, 1996 [book in Danish]
11. Mortensen EL, Reinisch JM, Teasdale TW: Intelligence as measured by the WAIS and military draft board group test. *Scand J Psychol* 31:315–318, 1990
12. Pedersen J, Pedersen LM, Andersen B: Assessors of fetal perinatal mortality in diabetic pregnancy: analysis of 1,332 pregnancies in the Copenhagen series, 1946–1972. *Diabetes* 23:302–305, 1974
13. *Stata Statistical Software.* College Station, TX, StataCorp LP, 2006
14. Box GEP, Cox PR: An analysis of transformations. *Journal of Royal Statistical Society Series B* 26:211–246, 1964
15. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM: The association between duration of breastfeeding and adult intelligence. *East Afr Med J* 287:2365–2371, 2002
16. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM: A dose-response relationship between maternal smoking during late pregnancy and adult intelligence in male offspring. *Paediatr Perinat Epidemiol* 19:4–11, 2005
17. Bergvall N, Iliadou A, Tuvemo T, Cnattingius S: Birth characteristics and risk of low intellectual performance in early adulthood: are the associations confounded by socioeconomic factors in adolescence or familial effects? *Pediatrics* 117:714–721, 2006
18. Evers IM, de Valk HW, Visser GH: Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 328: 915, 2004
19. Jovanovic L, Druzin M, Peterson CM: Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med* 71:921–927, 1981
20. Suhonen L, Hiilesmaa V, Teramo K: Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia* 43: 79–82, 2000
21. Åberg A, Westbom L: Association between maternal preexisting or gestational diabetes and health problems of their children. *Acta Paediatr* 90:746–750, 2001