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Glucose Tolerance, Insulin Sensitivity, and Insulin Secretion in Children Born Small for Gestational Age

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Intrauterine growth retardation is associated with an increased risk of developing adult diseases, such as noninsulin-dependent diabetes mellitus (NIDDM). NIDDM could result from a decreased insulin sensitivity or a reduced insulin secretion or a combination of both. Glucose tolerance, insulin sensitivity, and insulin secretion were studied in prepubertal children born small for gestational age (SGA). Twenty-nine SGA children with a mean age of 9.1 ± 1.1 yr and 24 children born appropriate for gestational age (AGA), with a mean age of 9.0 ± 1.1 yr, were studied. All children were born at term and were prepubertal. Children were studied on two separate days after 12 h of overnight fasting. Day 1: Glucose tolerance was studied with an oral glucose tolerance test. $AUC_{ins0-120min}$/$AUC_{gluc0-120min}$ was used to estimate β-cell function in the two groups. Day 2: A hyperinsulinemic euglycemic clamp study was performed to determine insulin sensitivity (M-value). Glucose tolerance and β-cell function were not different between the two groups. M-value in SGA children was significantly lower than M-value in AGA children: 12.9 ± 4.0 mg/kg·min *vs.* 15.6 ± 2.3 mg/kg·min [$P = 0.009$; after adjustment for appropriate gestational age body mass index (BMI), $P = 0.001$]. The M-value tended to be higher in SGA children without catch-up growth compared with SGA children with catch-up growth (15.8 ± 4.3 *vs.* 12.3 ± 3.8 mg/kg·min; $P = 0.079$) and was comparable to AGA controls (15.6 ± 2.3 mg/kg·min). The M-value in SGA children who had shown catch-up growth was comparable to AGA children (13.4 ± 3.4 *vs.* 15.6 ± 2.3 mg/kg·min; $P = 0.06$), provided they had a BMI of 17 kg/m^2 or less. However, the SGA children with catch-up growth and a BMI greater than 17 kg/m^2 were those having the lowest M-values (9.3 ± 3.4 mg/kg·min). In conclusion, during oral glucose tolerance tests, no differences were found in glucose tolerance and β-cell function between the SGA and AGA groups. However, the hyperinsulinemic clamp showed a reduced insulin sensitivity in SGA children, which may contribute to the enhanced risk of developing NIDDM in adult life, especially in SGA children with catch-up growth and a high BMI. The implications of our findings in relation to height are unclear, but might be of potential importance when considering GH treatment. In addition, interventions to improve fetal growth and to control obesity in childhood seem to be important factors in the prevention of NIDDM. (*J Clin Endocrinol Metab* 87: 4657–4661, 2002)

INTRAUTERINE GROWTH RETARDATION (IUGR) is associated with an increased risk of developing chronic diseases in adulthood, such as noninsulin-dependent diabetes mellitus (NIDDM). Inverse associations of NIDDM in adult life with size at birth were first identified in two cohorts of adults born in England (1, 2) and have since been confirmed in three other populations (3–5). Few studies, however, specifically investigated subjects born small for gestational age (SGA) because length of gestation was not precisely known.

NIDDM is often undiagnosed for many years in a lot of patients and is in time attended by cardiovascular, renal, and neurological complications. Most studies concerning NIDDM are done in adults when environmental effects could have been of influence in the development of NIDDM. To avoid these effects, it seems to be important to study young adults and children as well, who are at an increased risk of developing NIDDM in later life. Leger *et al.* (6) showed that young adults born after IUGR had normal glucose tolerance, but higher plasma insulin and proinsulin levels during an oral glucose tolerance test (OGTT) than controls. This hyperinsulinemia suggests the development of insulin resistance in early adulthood, which was recently confirmed (7). Studies in young prepubertal children have shown that plasma glucose levels after an oral glucose load are inversely related to birth weight (BW; Ref. 8) or to ponderal index (9) and that low BW is associated with increased insulin resistance estimated according to the homeostatic model (homeostasis model assessment–insulin resistance; Refs. 10, 11). Until now, there has been general agreement that the euglycemic insulin clamp technique is the best available standard for the measurement of insulin action. Mechanisms underlying the relation between low BW and NIDDM are still unclear. The relationship could be mediated by alterations in insulin sensitivity (12, 13), insulin secretion (14), or a combination of both. The aim of the present study was to investigate glucose tolerance, β-cell function during OGTT, and insulin sensitivity using the hyperinsulinemic euglycemic clamp technique in prepubertal Caucasian children born SGA, compared with that in children born appropriate for gestational age (AGA). All children were born at term. The influence of catch-up growth in height and body mass index (BMI) was taken into account.

Abbreviations: AGA, Appropriate for gestational age; AUC, area under the curve; BW, birth weight; IUGR, intrauterine growth retardation; NIDDM, noninsulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; SGA, small for gestational age.

Subjects and Methods

Study population

The study was a case-control study in which all subjects were selected according to their birth data. Since 1980, information of all pregnancies,

deliveries, and perinatal events of children born in this hospital have been registered. This database was used to trace individuals. The study protocol was approved by the ethics committee of the VU University Medical Center of Amsterdam.

The study was performed in 29 Caucasian prepubertal SGA children with a mean age of 9.1 ± 1.1 yr (range, 7.1–11.0 yr). Twenty-four Caucasian children, born AGA, with a mean age of 9.0 ± 1.1 yr (range, 7.1–11.8) served as controls because there are no standards of insulin sensitivity in literature in children born AGA. AGA controls were selected from the same database according to their birth data. One AGA control was a girl friend of a SGA subject, and two AGA controls were relatives of children who were treated at the outpatient clinic. All parents and children received a letter with information of the study and an invitation for an information meeting at which they were more extensively informed and at which they could ask questions. SGA was defined as a BW less than the 10th percentile corrected for gestational age, gender, and parity; AGA was defined as a BW of the 10th percentile or above, using Dutch references (15). All children were born at term. At the time of the study, all subjects were in good health as assessed by medical history and physical examination. They were at a prepubertal stage according to the criteria of Tanner (16), confirmed by measurements of plasma testosterone in males and estradiol in females. Questionnaires of family history in terms of type 2 diabetes, cardiovascular disease, and hypertension were recorded. None received any medication that could interfere with the tests. After full explanation of the study, all subjects and parents gave written informed consent.

Methods

Children were studied on two separate days after 12 h of overnight fasting.

Day 1. Measurements of the subject's weight, using an electronic scale (SECA, Hanover, MD), and height, with a stadiometer (Holtain Ltd., Crymych, Dyfed, UK), were used to calculate the BMI, defined as weight divided by the height squared. A tape measure was used to measure waist and hip circumferences, and skin-fold thickness were measured by a single observer with Harpenden skin-fold calipers at the biceps, triceps, subscapular, and suprailiacal sites. Total body fat mass was calculated by the sum of the four sites in millimeters.

After physical examination, an OGTT (1.75 g/kg glucose, with a maximum of 75 g) was performed. Blood samples were taken every 15 min during 2 h for the measurement of glucose and insulin concentrations. To assess β-cell capacity, $AUC_{ins0-120min}/AUC_{gluc0-120min}$ was determined (17). Bone age was determined in all subjects by making an x-ray of the left hand.

Day 2. A 2-h hyperinsulinemic euglycemic clamp was performed to determine insulin sensitivity by peripheral glucose uptake as described by De Fronzo *et al.* (18). Two children of the AGA group dropped out and decided not to participate in the clamp study because of the invasive character of the study. Insulin (Velosulin, Novo Nordisk A/S, Bagsvaerd, Denmark) was infused at a rate of 60 mU/kg·h after a priming dose of 6 mU/kg. Hepatic glucose production is known to be suppressed in nondiabetic subjects by this insulin infusion rate (19). The blood glucose level was measured every 5 min. Every 15 min, blood was drawn to determine plasma insulin concentrations. Euglycemia (5 mmol/liter) was maintained with 20% D-glucose infusion. Under steady state conditions of euglycemia, the rate of exogenous glucose infusion is equal to the rate of insulin-stimulated glucose disposal. Insulin sensitivity was calculated from the glucose infusion rate (milligrams per minute) between 60 and 120 min of the euglycemic clamp, divided by body weight (kilograms; M-value).

Analytical methods

Blood glucose was measured immediately by the glucose oxidase method using a Yellow Springs Instrument Co. glucose analyzer (YSI, Inc., Yellow Springs, OH). Plasma insulin concentrations were measured by RIA techniques (Immunoradiometric Assay, Medgenics Diagnostics, Fleurus, Belgium).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 9.0 software (SPSS, Inc., Chicago, IL). Results are expressed as means ± SD. Differences between the SGA and AGA group were tested by χ^2 test for qualitative variables and *t* test for quantitative variables. Glucose concentrations were normally distributed. Insulin concentrations were normalized by log transformation. The effect of group (SGA *vs.* AGA) on peripheral glucose uptake, adjusting for BMI, total of skin-fold thickness, or waist circumference was studied using regression models (general linear models procedure). The independent effect of SGA on insulin secretion relative to insulin sensitivity was tested using the log-transformed variables in a general linear models procedure. A *P* value of 0.05 or less was considered to be significant.

Results

Clinical characteristics

Family history in terms of type 2 diabetes, cardiovascular disease, and hypertension was not statistically different in the two groups (Table 1).

Table 2 shows the clinical characteristics of the two groups at birth and at the time of the study. As defined, BW was significantly lower in SGA children ($P < 0.001$). Length at birth as well as ponderal index were significantly lower in SGA children. Gestational age and gender distributions were similar in both groups. At the time of the study, mean age, actual length, and BMI did not significantly differ between the two groups (Table 2). When an arbitrarily chosen cut-off of BMI greater than 17 kg/m^2 was used, 7 children in the SGA group were considered having a high BMI, whereas in the AGA group 11 children had a BMI greater than 17 kg/m^2 (data not shown). In the SGA group, five children did not show catch-up growth, defined as an actual height 1.3 SD or more below the target height SD score (height SD score − target height SD score). Characteristics are shown in Table 2. All AGA children did grow within their target height SD score. Bone ages, expressed as bone age minus chronological age, were not different in SGA and AGA children (−0.1 ± 14.1 months *vs.* −1.6 ± 11.1 months respectively; $P = 0.7$; Table 2). Bone ages of the five SGA children with attenuated linear growth were not different from those of the SGA children with normal growth (−10.0 ± 19.1 months *vs.* 0.2 ± 9.1 months; $P = 0.09$).

OGTT

Blood glucose levels in the IUGR group were slightly higher at all time points studied, but not statistically significant. Table 3 shows the results of oral glucose tolerance testing at 0, 30, and 120 min in the two groups. Plasma insulin levels were not different between SGA children and AGA children during the first and second hours of the test.

β-Cell function

The ratio of areas under the curves ($AUC_{ins0-120min}/AUC_{gluc0-120min}$) was not significantly different between

TABLE 1. Family history in SGA and AGA children

	SGA (n = 29)	AGA (n = 24)	*P* value
Type 2 diabetes (n = 15)	10	5	0.27
Hypertension (n = 30)	16	14	0.82
Cardiovascular disease (n = 26)	13	13	0.50

TABLE 2. Clinical characteristics at birth and at time of the study in SGA and AGA children

	AGA (n = 24)	SGA (n = 29)	SGA no catch-up (n = 5)	SGA catch-up BMI ≤ 17 kg/m^2 (n = 18)	SGA catch-up BMI > 17 kg/m^2 (n = 6)
At birth					
Gender (male/female)	12/12	12/17	3/2	7/11	2/4
Gestational age (d)	278 ± 10	276 ± 10	274 ± 9	278 ± 10	272 ± 9
Birth weight (g)	3471 ± 475	2442 ± 279	2355 ± 144	2468 ± 335	2436 ± 166
Birth length (cm)	51 ± 2.3	47 ± 2.3	45 ± 2.3	47 ± 2.3	48 ± 1.5
Ponderal index (g/cm^3 × 100)	26.6 ± 3.2	24.0 ± 2.5	25.9 ± 4.5	23.8 ± 1.9	22.9 ± 1.1
At time of study					
Age (yr)	9.0 ± 1.1	9.1 ± 1.1	8.5 ± 1.0	9.0 ± 1.1	9.3 ± 1.2
Body weight (kg)	30.9 ± 5.5	29.5 ± 7.5	23.9 ± 5.9	27.4 ± 4.7	40.2 ± 5.2
Height (cm)	138.0 ± 6.2	135.2 ± 9.1	126.1 ± 7.7	134.6 ± 7.8	144.5 ± 5.0
HtSDS − THSDS	−0.46 ± 0.77	−0.56 ± 0.84	−1.91 ± 0.37	−0.40 ± 0.51	0.20 ± 0.63
BMI (kg/m^2)	17.3 ± 3.5	15.8 ± 2.4	14.5 ± 2.3	15.0 ± 1.4	19.1 ± 1.7
Waist circumference (cm)	58.3 ± 4.7	57.2 ± 6.6	53.1 ± 4.6	55.1 ± 4.4	65.9 ± 5.2
Total skin-fold thickness (mm)	30.7 ± 14.4	32.2 ± 14.2	27.1 ± 17.7	28.4 ± 9.8	47.3 ± 13.6
Bone age (months)	−1.6 ± 11.1	−0.1 ± 14.1	−10.0 ± 19.1	0.33 ± 9.7	−0.2 ± 8.1
M-value	15.6 ± 2.3	12.9 ± 4.0	15.8 ± 4.3	13.4 ± 3.4	9.3 ± 3.4

Data represent mean ± SD. HtSDS − THSDS, Height SD score − target height SD score.

TABLE 3. Blood glucose and plasma insulin concentrations in SGA and AGA children

	SGA	AGA	*P* value
Glucose (mmol/liter)			
0 min (n = 53)	4.7 ± 0.5 (n = 29)	4.5 ± 0.4 (n = 24)	0.18
30 min (n = 53)	7.7 ± 1.6 (n = 29)	7.3 ± 1.2 (n = 24)	0.45
120 min (n = 53)	6.1 ± 1.4 (n = 29)	5.6 ± 1.3 (n = 24)	0.21
Insulin (pmol/liter)			
0 min (n = 53)	47.5 ± 18.2 (n = 29)	56.0 ± 25.4 (n = 24)	0.24
30 min (n = 53)	357.6 ± 253.6 (n = 29)	363.0 ± 163.8 (n = 24)	0.46
120 min (n = 52)	280.5 ± 262.6 (n = 28)	293.2 ± 221.3 (n = 24)	0.71

Data represent mean ± SD.

AGA children (n = 22) and SGA children (n = 28) (151.3 ± 78.1 *vs.* 140.6 ± 82.7 pmol/mmol; $P = 0.44$); means adjusted for M-value for the two groups were 154.9 ± 18.9 *vs.* 129.9 ± 16.2 pmol/mmol ($P = 0.34$).

Hyperinsulinemic euglycemic clamp

Plasma insulin and blood glucose measured at steady state (60–120 min) did not differ significantly between SGA subjects and AGA children (plasma insulin, 383 ± 89 *vs.* 407 ± 85 pmol/liter; plasma glucose, 5.0 ± 0.2 *vs.* 5.0 ± 0.2 mmol/liter). In the 51 children studied, BW correlated significantly to insulin sensitivity ($r = 0.30$; $P = 0.032$). In the SGA and AGA groups separately, a positive correlation was also found but was not statistically significant (both $r = 0.20$; not significant). The M-value was significantly lower in the SGA group than in the AGA group (12.9 ± 4.0 *vs.* 15.6 ± 2.3 mg/kg·min; $P = 0.009$) after adjustment for BMI ($P = 0.001$; Table 2). BMI had a strong independent effect ($P < 0.001$) on the insulin-stimulated glucose uptake. A similar result was shown after adjustment for the percentage of body fat (expressed as the total of the skin-fold thickness, $P = 0.005$; or for the waist circumference, $P = 0.001$). The M-value tended to be higher in SGA children without catch-up growth compared with SGA children with catch-up growth (15.8 ± 4.3 *vs.* 12.3 ± 3.8 mg/kg·min; $P = 0.079$) and was comparable to AGA controls (15.6 ± 2.3 mg/kg·min; Table 2). The M-value in SGA children who had shown catch-up growth was comparable to AGA children (13.4 ± 3.4 *vs.* 15.6 ± 2.3 mg/kg·min; $P = 0.06$), provided they had a BMI of 17 kg/m^2 or less. SGA children with catch-up growth and a BMI greater than 17 kg/m^2 were those having the lowest M-values (9.3 ± 3.4 mg/kg·min; Table 2). This was significantly lower than the M-value in AGA children (15.6 ± 2.3; $P < 0.001$) and significantly lower than the M-value in SGA children with catch-up growth and a BMI of 17 kg/m^2 or less (13.4 ± 3.4; $P = 0.02$).

Discussion

There is no general agreement on whether the association between IUGR with type 2 diabetes in adult life is mediated through insulin resistance or through impairment of β-cell function as originally suggested by Hales and Barker (14). In the thrifty phenotype hypothesis, it is suggested not only that during intrauterine malnutrition the fetus makes metabolic adaptations that benefit in the short time by increasing fuel availability, but also that these changes become permanent, lasting through life, and are responsible for the development of insulin resistance.

On the other hand, malnutrition may also affect structure and function of the β-cells causing restricted insulin secretory capacity in further life (20). In rats, a reduced β-cell mass in the offspring at birth is seen after maternal food restriction during late pregnancy. Subsequent renutrition is followed by increased β-cell proliferation but insufficiently to fully restore β-cell mass (21).

In the present study, insulin sensitivity was measured using the hyperinsulinemic-euglycemic clamp technique in young prepubertal children born SGA. Insulin sensitivity,

expressed as the M-value, was significantly lower in children who were born SGA, compared with controls. This difference between the two groups became even more significant after adjustment for BMI, which is known to have a strong independent effect on insulin resistance. Some studies have suggested that low BW is a risk factor for the later development of abdominal or truncal obesity, which enhances insulin resistance (22, 23). In our study population, however, BMI and abdominal circumference were higher in AGA than in SGA children, which explains that the reached significance became higher after adjustment for BMI. Consistent with findings of others, we found that SGA children with the highest current BMI are the most insulin resistant (10, 12, 24).

Hofman *et al.* (25) showed that short prepubertal IUGR children have an impaired insulin sensitivity compared with their normal BW peers. However, they did not include IUGR children who had shown catch-up growth. Interestingly, in the present study, the M-value tended to be higher in SGA children without catch-up growth compared with SGA children with catch-up growth and was comparable to AGA controls. However, in our study, these children without catch-up growth in height in our study group had lower BMI values than the children who did catch-up. Here arises, however, the question whether children who do show catch-up growth in height become fatter as well and so more insulin resistant. This was also recently observed by Forsén *et al.* (26), who concluded that the increased risk for NIDDM associated with small size at birth is further increased by high growth rates after 7 yr of age. They demonstrated that men and women who developed type 2 diabetes caught up in both height and weight, possibly resulting from high energy intake in childhood and development of above-average BMI values in the women.

Cianfarani *et al.* (27) did not find a relation between insulin sensitivity and postnatal growth. In the present study, however, the M-value in SGA children who had shown catch-up growth was comparable to AGA children, provided they had a BMI of 17 kg/m^2 or less. However, the SGA children with catch-up growth and a BMI greater than 17 kg/m^2 were those having the lowest M-values, thus at high risk of developing diabetes type 2 in later life. The implications of our findings in relation to height are unclear, but might be of potential importance when considering GH treatment. In addition, interventions to improve fetal growth and control obesity in childhood seem to be important factors in the prevention of NIDDM.

To ensure normal glucose tolerance in persons with a reduced insulin sensitivity, a higher insulin secretion is needed to compensate for the insulin resistance.

In our study of young prepubertal children, SGA children appeared to be more insulin resistant compared with AGA children. Although not statistically different, during the OGTT, blood glucose levels were higher at all time points in the IUGR group compared with controls. The $AUC_{ins0-120}/AUC_{gluc0-120}$ during the OGTT, which correlates well with β-cell function, were not different between SGA children and AGA children showing no decreased β-cell capacity in SGA children.

For now, we can only ascertain insulin resistance as a fixed condition in SGA newborns. Close follow-up of these patients is needed to allow early intervention to prevent or postpone long-term complications of NIDDM. Special attention should be paid to additional factors such as obesity and physical inactivity that further increase insulin resistance, and it may even be questioned whether high energy intake should be encouraged in infancy and early childhood in children who were born SGA.

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References

1. **Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD** 1991 Fetal and infant growth and impaired glucose tolerance at age 64. Br Med J 303:1019–1022
2. **Phipps K, Barker DJP, Hales CN, Fall CHD, Osmond C, Clark PMS** 1993 Fetal growth and impaired glucose tolerance in men and women. Diabetologia 41:1133–1138
3. **Curhan GC, Willett WC, Rimm EB, Spiegelmann D, Ascherio AL, Stampfer MJ** 1996 Birth weight and adult hypertension and diabetes mellitus in US men. Circulation 94:3246–3250
4. **McCance DR, Pettitt DJ, Hanson RL, Jacobson LTH, Knowler WC, Bennett PH** 1994 Birthweight and noninsulin-dependent diabetes: thrifty genotype, thrifty phenotype or surviving small baby genotype? BMJ 308:942–945
5. **Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell U, Leon DA** 1996 Relationship of size at birth to noninsulin-dependent diabetes and insulin levels in men aged 50–60 years. BMJ 312:406–410
6. **Leger J, Levy-Marchal C, Bloch J, Pinet A, Chevenne D, Porquet D, Collin D, Czernichow P** 1997 Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study. BMJ 315:341–347
7. **Jaquet D, Gaboriau A, Czernichow P, Levy-Marchal C** 2000 Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. J Clin Endocrinol Metab 85:1401–1406
8. **Yajnik CS, Fall CH, Vaidya U, Pandit AN, Bavdekar A, Bhat DS, Osmond C, Hales CN, Barker DJ** 1995 Fetal growth and glucose and insulin metabolism in four-year-old Indian children. Diabetic Med 12:330–336
9. **Law CM, Gordon CM, Shiell AW, Barker DJP, Hales CN** 1995 Thinness at birth and glucose tolerance in seven-year-old children. Diabetic Med 12:24–29
10. **Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C** 1999 Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 48: 2422–2429
11. **Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC** 1999 Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 22:944–950
12. **Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C** 1994 Thinness at birth and insulin resistance in adult life. Diabetologia 37:150–154
13. **Barker DJP, Hales CN, Fall CHD, Osmond C, Phipps K, Clark PMS** 1993 Type 2 (noninsulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 36: 62–67
14. **Hales CN, Barker DJP** 1992 Type 2 (noninsulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35:595–601
15. **Kloosterman GJ** 1970 On intrauterine growth. The significance of prenatal care. J Clin Endocrinol Metab 83:1243–1246
16. **Tanner JM** 1981 Growth and maturation during adolescence. Nutr Rev 39: 43–55

17. **Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van Haeften T, Renn W, Gerich J** 2000 Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 23:295–301
18. **De Fronzo RA, Tobin JD, Andres J** 1979 Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237:E214–E223
19. **Ferrannini E, Mari A** 1998 How to measure insulin sensitivity. J Hypertens 16:895–906
20. **Phillips DIW** 1998 Birth weight and the future development of diabetes. Diabetes Care 21(Suppl 2):B150–B155
21. **Garafano A, Czernichow P, Bréant B** 1998 β-Cell mass and proliferation following late fetal and early postnatal malnutrition in the rat. Diabetologia 41:1114–1120
22. **Ravelli, G, Stein ZA, Susser MW** 1995 Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 295:349–354
23. **Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP** 1994 Birthweight and adult health outcomes in a biethnic population in the USA. Diabetologia 37:624–631
24. **Crowther NJ, Cameron N, Trusler J, Gray IP** 1998 Association between poor glucose tolerance and rapid postnatal weight gain in seven-year-old children. Diabetologia 41:1163–1167
25. **Hofman PL, Cutfield WS, Robinson EM, Bergman RN, Menon RK, Sperling MA, Gluckman PD** 1997 Insulin resistance in short children with intrauterine growth retardation. J Clin Endocrinol Metab 82:402–406
26. **Forsén T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D** 2000 The fetal and childhood growth of persons who develop type 2 diabetes. Ann Intern Med 133:176–182
27. **Cianfarani S, Geremia C, Germani D, Scire G, Maiorana A, Boemi S** 2001 Insulin resistance and insulin-like growth factors in children with intrauterine growth retardation. Is catch-up growth a risk factor? Horm Res 55(Suppl 1):7–10

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