The Influence of Maternal BMI and Age in Twin Pregnancies on Insulin Resistance in the Offspring

RUTH J.F. LOOS, PHD[1,2]
DAVID I.W. PHILLIPS, MA, PHD, FRCP[3]
ROBERT FAGARD, MD, PHD[4]
GASTON BEUNEN, PHD[2]
CATHERINE DEROM, PHD[1]
CHANTAL MATHIEU, MD, PHD[5]
JOHAN VERHAEGHE, MD, PHD[6]
ROBERT VLIETINCK, MD, PHD[1]

OBJECTIVE — There is strong evidence that low birth weight is associated with glucose intolerance and diabetes in adults. We have carried out a twin study to distinguish among maternal influences, which affect both twins; fetoplacental influences, which are unique to each twin; and the genetic factors that may underlie this association.

RESEARCH DESIGN AND METHODS — We identified a sample of 423 twin pairs (250 monozygotic and 173 dizygotic) from the East Flanders Prospective Twin Survey who were born between 1964 and 1982. Data collected in this study included the mother's body composition and weight gain during pregnancy, the twins' birth weights, and gestational age. The twins (aged 18–34 years) attended a research center for measurement of height, weight, and waist-to-hip ratio as well as fasting glucose, proinsulin, and insulin concentrations.

RESULTS — Among twin pairs discordant for birth weight, we found little evidence that the lighter twin had abnormal glucose-insulin metabolism in adult life. However, both a low prepregnancy maternal BMI and older maternal age at delivery were associated with hyperinsulinemia and evidence of insulin resistance in the offspring. Fasting insulin increased by 1.3% (95% CI 0.1–2.6%) per unit fall in maternal BMI and by 1.1% (0.02–2.0%) per year increase in maternal age. These associations were independent of the twins' BMI and waist-to-hip ratio and their zygosity.

CONCLUSIONS — These novel findings suggest that in twin pregnancies, maternal factors are more important than fetoplacental factors in determining glucose-insulin metabolism in the offspring.

Diabetes Care 25:2191–2196, 2002

There is strong evidence that low birth weight is associated with insulin resistance, impaired glucose tolerance, and type 2 diabetes in adult life (1). Because the nutrients and oxygen that a fetus receives are major determinants of its growth rate and eventual size at term, these observations have led to the hypothesis that diabetes may result from fetal undernutrition arising from an imbalance between the supply of nutrients to the fetus and its nutrient requirements (2). It is suggested that this imbalance results in metabolic and endocrine adaptations that benefit the fetus in the short term but are detrimental in the longer term. Relatively little, however, is known about the processes that lead to fetal nutrient imbalance. The availability of nutrients to the fetus is determined by both maternal factors such as the mother's nutritional status, which include her nutritional reserves and dietary intake, and the fetoplacental factors that govern the nutrient transfer to the fetus. Recently, a number of studies have suggested that a low maternal weight or BMI is linked with insulin resistance and hyperglycemia in the offspring (3–5). However, factors originating in the fetus, such as a genetic predisposition to both low birth weight and glucose intolerance (6), or local intrauterine influences, such as uteroplacental blood flow and the size of the placenta and its transfer capabilities, could also explain the associations (7).

Studies of twins may shed light on the relative contribution of these processes. Twins share the same maternal environment; therefore, the influence of maternal factors such as nutrition will be shared by both fetuses. However, each fetus has its own fetoplacental environment, which may differ substantially from that of its cotwin. This occurs because of unequal partitioning of nutrients or placental blood supply between twins and may lead to large differences in birth weight between the twins. Moreover, because of the genetic identity of monozygotic (MZ) twins, associations between within-pair differences in birth size in MZ pairs and adult outcomes must be due to environmental differences, including fetoplacental influences, and specifically exclude the influence of genetic factors. Few studies, however, have examined the long-term effects of discordant twin growth on glucose tolerance in adult life. An analysis based on the Danish Twin Register identified 14 MZ twin pairs who were discordant for type 2 diabetes and showed that the diabetic twins had lower birth weight than the nondiabetic cotwins (8). This

From the [1]Center for Human Genetics, Faculty of Medicine, Katholieke Universiteit Leuven, Leuven, Belgium; the [2]Department of Sport and Movement Sciences, Faculty of Physical Education and Physiotherapy, Katholieke Universiteit Leuven, Leuven, Belgium; the [3]Medical Research Council Environmental Epidemiology, University of Southampton, Southampton, U.K.; the [4]Hypertension and Cardiovascular Rehabilitation Unit, Faculty of Medicine, Katholieke Universiteit Leuven, Leuven, Belgium; the [5]Department of Experimental Medicine and Endocrinology, Faculty of Medicine, Katholieke Universiteit Leuven, Leuven, Belgium; and the [6]Department of Obstetrics and Gynaecology, Faculty of Medicine, Katholieke Universiteit Leuven, Leuven, Belgium.

Address correspondence and reprint requests to Ruth Loos, Faculteit voor Lichamelijke Opvoeding en Kinesitherapie, Tervuursevest 101, B-3001 Leuven, Belgium. E-mail: ruth.loos@med.kuleuven.ac.be.

Received for publication 23 April 2002 and accepted in revised form 15 September 2002.

Abbreviations: DZ, dizygotic; MZ, monozygotic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

suggests that the inverse association between birth weight and diabetes cannot be entirely accounted for by genetic factors. Moreover, this together with two other studies using the same approach applied to blood pressure suggests that causes of variation in fetal growth between twin pairs are sufficient to exert programming effects and draws attention to the importance of the fetal supply line (9,10). However, more recent studies have not confirmed these initial findings (11–13).

We have studied a sample of twins from East Flanders Prospective Twin Survey, a population-based twin register in which obstetric and perinatal data on all twins was collected. Because of the unique data available, we have been able to examine the relative contribution of maternal factors and the influence of the fetoplacental unit, as indicated by twin differences in size at birth to plasma glucose and insulin concentrations.

RESEARCH DESIGN AND METHODS

Subjects

The East Flanders Prospective Twin Survey includes details of all twins born in the Belgian Province of East Flanders since 1964. Birth weight and duration of gestation (calculated from the date of the last menstrual period) were abstracted from the obstetrical records, and placental examination was carried out within 24 h after delivery. Zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase, and DNA fingerprints (14). Between July 1964 and May 1982, the East Flanders Prospective Twin Survey had registered 1,685 twin pairs with birth weight ≥500 g or gestational age ≥22 weeks, where both twins were alive and residents of the East Flanders area. We randomly contacted 803 pairs. Of these, 423 pairs (52.7%) agreed to participate, of which 179 pairs were both men (119 MZ and 60 dizygotic [DZ]), 187 were both women (131 MZ and 56 DZ), and 57 were of opposite sex. Of 46 pairs (11 MZ and 32 DZ), only one member participated. Perinatal characteristics of the participants are representative for the East Flanders twin population. The twins gave informed consent, and the project was approved by the Committee of Medical Ethics.

Methods

Between February 1997 and April 2000, the twins attended a 2-h examination, which took place in the morning after an overnight fast. Standing height (cm) was measured to the nearest 0.1 cm with a Harpenden fixed stadiometer and body weight (kg) on a SECA balance scale to the nearest 0.1 kg. BMI, as a measure of overall body composition, was calculated as body weight divided by the square of height (kg/m^2). Blood samples were taken to measure glucose, insulin, and proinsulin concentrations. Plasma glucose was analyzed by using the hexokinase method (Olympus AU600), plasma insulin by using microparticle enzyme immunoassay (Abbott Axsym), and intact proinsulin by an ELISA (Mercodia, Uppsala, Sweden). Homeostasis model assessment was used to assess insulin resistance and β-cell function, based on fasting insulin and glucose levels as described by Matthews et al. (15). None of the subjects reported abnormal kidney or liver function. The mothers of the twins were contacted and given a questionnaire at the time the twins were invited to our research center, inquiring about weight before pregnancy, weight gain during pregnancy, and current height. Maternal BMI (kg/m^2) was calculated as weight (before and at the end of pregnancy) divided by the square of current height. Of the 423 mothers, 13 were deceased and 78 did not recall their weights.

Statistical analyses

Linear regression was used to estimate the association between within-pair differences in birth size and within-pair differences in adult glucose or insulin concentrations. These analyses were performed using SAS version 6.12. In the analysis of maternal effects, twins were analyzed as individuals using multilevel regression analysis to model the paired structure of the data (MlwiN 1.10.0006). Because the fasting concentrations of glucose, proinsulin, and insulin and the indexes of insulin resistance and β-cell function had skewed distributions, they were log transformed to normality before analysis. We adjusted for the twins' sex, adult BMI, and age. All tests were two sided, and P values <0.05 were considered significant.

RESULTS — The characteristics of the twins according to sex and zygosity are shown in Table 1. Although there were no differences in the mothers' age, height, or weight between MZ and DZ twins, MZ twins weighed significantly less at birth than DZ twins among both men (P = 0.003) and women (P = 0.025) and had a shorter gestation (P = 0.02). The twins' adult age, height, weight, BMI, fasting concentrations of insulin and proinsulin, and insulin resistance were similar. Fasting glucose concentration was higher and β-cell function lower in MZ men. Four twins (two MZ and two DZ) had impaired fasting glycemia (fasting glucose concentration ≥6.1 and <7.0 mmol/l).

Within-pair analysis: influence of the fetoplacental unit

The mean within-pair birth weight difference was 259 g (SD 214) in MZ twins and 314 g (SD 260) in DZ twins. Means as well as variances were significantly different between MZ and DZ twins (P = 0.02 and P = 0.005, respectively).

Table 2 shows the results of an analysis relating within-pair differences in adult glucose and insulin levels for every 100-g difference in birth weight. Among MZ twins, the within-pair birth weight difference was unrelated to within-pair differences in fasting glucose, proinsulin, and insulin concentrations as well as insulin resistance and β-cell function. Similar results were obtained in DZ twins, although there was evidence that fasting insulin concentrations (P = 0.04) were somewhat higher in the smaller twin at birth and β-cell function was increased in the smaller twin at birth when all pairs were combined. These results were similar for men and women and were not affected by adjustment for any maternal characteristic (weight or BMI before pregnancy, weight gain during pregnancy, and maternal age).

Between-individual analysis: influences of maternal environment

In a combined analysis of all 800 individual subjects, there were no statistically significant associations between birth weight and fasting glucose, proinsulin, insulin, concentrations, and insulin resistance, even after adjustment for gestational age, sex, adult BMI, and age (Table 3), with the exception of β-cell function, which fell with increasing birth weight

Table 1—*Maternal characteristics, birth size, and adult characteristics of the twins according to sex and zygosity*

	MZ (n = 250)	DZ (n = 173)
Mother's age at delivery (years)	27.2 ± 5.1	28.1 ± 4.6
Mother's height (cm)	162.7 ± 6.2	163.2 ± 6.1
Mother's prepregancy weight (kg)	58.8 ± 9.7	59.0 ± 9.6
Mother's prepregancy BMI (kg/m^2)	22.2 ± 3.4	22.1 ± 3.3
Gestational age (weeks)	36.9 ± 2.5	37.5 ± 2.4

	Men		Women	
	MZ (n = 232)	DZ (n = 156)	MZ (n = 257)	DZ (n = 155)
Birth weight (g)	2,537 ± 467	2,684 ± 481	2,449 ± 488	2,560 ± 474
Adult				
Age (years)	25.3 ± 4.6	26.2 ± 4.8	25.1 ± 4.6	26.0 ± 4.7
Weight (kg)	70.4 ± 9.7	72.0 ± 11.8	60.7 ± 10.6	61.2 ± 10.3
Height (cm)	178.1 ± 6.3	178.6 ± 6.5	165.3 ± 6.2	166.2 ± 6.2
BMI (kg/m^2)	22.2 ± 2.9	22.6 ± 3.3	22.2 ± 3.8	22.1 ± 3.5
Fasting glucose (mmol/l)*	4.95 ± 1.09	4.80 ± 1.09	4.54 ± 1.09	4.57 ± 1.08
Fasting proinsulin (pmol/l)*	5.49 ± 1.90	5.28 ± 1.88	5.28 ± 1.89	4.87 ± 2.33
Fasting insulin (pmol/l)*	33.1 ± 1.56	33.1 ± 1.57	37.2 ± 1.57	40.0 ± 1.50
Insulin resistance (HOMA)*	1.45 ± 1.59	1.39 ± 1.56	1.47 ± 1.58	1.55 ± 1.51
β-Cell function (%) (HOMA)*	92.3 ± 1.56	103.3 ± 1.63	146.3 ± 1.65	146.8 ± 1.61

Data are means ± SD. HOMA, homeostasis model assessment. *Geometric means ± SD.

(P = 0.04). Similar results were obtained in separate analyses of MZ and DZ twins.

However, low maternal BMI before pregnancy was significantly associated with raised fasting insulin and proinsulin concentrations and increased insulin resistance and β-cell function. In analyses stratified by sex, the associations between maternal BMI and the offspring's fasting insulin and insulin resistance were significant in women (P = 0.003 and P = 0.005, respectively) but not in men (P = 0.8 and P = 1.0, respectively). The interaction between sex and maternal BMI was tested in a regression model with insulin as the dependent variable and maternal BMI, sex, adult BMI, and the interaction term (sex × maternal BMI). The interaction term was significant at P = 0.02. Similar results were obtained with insulin resistance (P = 0.03).

Older maternal age was also related to higher fasting insulin concentrations, insulin resistance, and increased β-cell function in the offspring. Fasting insulin increased by 1.3% (95% CI 0.1–2.6%) per unit (kg/m^2) fall in maternal BMI and by 1.1% (0.02–2.0%) per year increase in maternal age. The effect of maternal age was similar in both sexes.

The effects of maternal BMI and age were independent from each other. Table 4 shows that at any level of maternal BMI, older maternal age was associated with increased fasting insulin concentrations, while among both younger and older mothers, the twins' insulin concentrations fell as their mothers' BMI increased. Mothers who were older and thinner had twin offspring with the highest insulin levels. Similar effects were observed with the indexes of insulin resistance and hyperinsulinemia (β-cell function). These effects were independent of other maternal characteristics (weight gain during pregnancy, gestational age, and birth order) (results not shown).

A multiple regression analyses was carried out with fasting insulin as the dependent variable and maternal BMI and age, current offspring's BMI and age, birth weight, and zygosity as independent variables. This showed that in addition to maternal BMI before pregnancy (P = 0.04) and maternal age at delivery (P = 0.01), current BMI (β = 0.6% per kg/m^2, P < 0.001) and age (0.2% per year, P < 0.001), but not birth weight (−0.08% per 100 g, P = 0.09), gestational age (0.1% per week, P = 0.31), or zygosity (P = 0.63), were associated with fasting insulin concentrations in the twin offspring. Similar results were obtained for insulin resistance.

CONCLUSIONS — In this study, we found little evidence that low birth weight in twin pairs is associated with abnormal glucose-insulin metabolism in adult life. However, we report for the first time that maternal effects, specifically low maternal BMI and older age at delivery, are dominant in predicting insulin resistance in the twin offspring. These maternal effects were independent of the birth weights of the twins and were additive: the oldest

Table 2—*Difference in fasting glucose, proinsulin, and insulin concentrations and insulin resistance and β-cell function for every 100-g within-pair difference in birth weight in MZ and DZ twins, and in all twins combined*

	MZ (n = 239)			DZ (n = 138)			All (n = 377)		
	Slope	95% CI	P	Slope	95% CI	P	Slope	95% CI	P
Fasting glucose (mol/l)	0.01	(−0.004 to 0.02)	0.17	−0.01	(−0.03 to 0.01)	0.20	0.00	(−0.01 to 0.01)	0.93
Fasting proinsulin (pmol/l)	−0.02	(−0.14 to 0.10)	0.77	−0.004	(−0.23 to 0.22)	0.97	−0.01	(−0.13 to 0.10)	0.82
Fasting insulin (pmol/l)	−0.12	(−0.70 to 0.47)	0.70	−1.03	(−2.01 to −0.05)	0.04	−0.51	(−1.0 to 0.02)	0.06
Insulin resistance	−0.004	(−0.03 to 0.02)	0.79	−0.02	(−0.08 to 0.01)	0.12	−0.02	(−0.04 to 0.01)	0.16
β-Cell function (%)	−2.55	(−5.31 to 0.21)	0.07	−2.75	(−6.39 to 0.90)	0.14	−2.63	(−4.8 to −0.44)	0.02

Data were adjusted for sex and BMI.

Table 3—*Relationship between fasting glucose, proinsulin, and insulin concentrations and insulin resistance and β-cell function and birth weight and maternal characteristics in all 800 twins*

	Birthweight			Maternal BMI before pregnancy			Maternal age at delivery		
	% Change per 100 g	95% CI	*P*	% Change per 1 kg/m^2	95% CI	*P*	% Change per 1 year	95% CI	*P*
Fasting glucose	0.0%	(−0.1 to 0.2%)	0.74	0.2%	(−0.1 to 0.4%)	0.17	−0.1%	(−0.3 to 0.1%)	0.22
Fasting pro-insulin	−0.3%	(−1.5 to 1.2%)	0.71	−3.1%	(−5.1 to −1.1%)	0.003	0.7%	(−0.7 to 2.1%)	0.32
Fasting insulin	−0.8%	(−1.6 to 0.1%)	0.09	−1.3%	(−2.6 to −0.1%)	0.04*	1.1%	(0.2 to 2.0%)	0.012
Insulin resistance (HOMA)	−0.6%	(−1.5 to 0.3%)	0.20	−1.3%	(−2.6 to 0.0%)	0.05†	0.9%	(0.0 to 1.8%)	0.04
β-Cell function (HOMA)	−1.0%	(−1.9 to −0.1%)	0.04	−2.1%	(−3.6 to −0.7%)	0.005	1.4%	(0.4 to 2.4%)	0.008

Data were adjusted for sex, gestational age, adult BMI, and age. *Interaction with sex: $P = 0.02$; men: 0.1% change per 1 kg/m^2, $P = 0.82$; women: −2.7% change per 1 kg/m^2, $P = 0.003$. †Interaction with sex: $P = 0.03$; men: 0.0% change per 1 kg/m^2, $P = 0.99$; women: −2.5% change per 1 kg/m^2, $P = 0.005$.

mothers with the lowest BMI had the most insulin-resistant offspring.

Our study is based on a substantial number of twin pairs who were identified through the East Flanders Prospective Twin Survey, which included accurate obstetric and perinatal data as well as zygosity determination. Although the mothers' weight and height were self-reported, other studies have shown that these recalled anthropometric measurements correlate closely with actual measurements (16,17). In this study, insulin resistance was based on a single fasting measurement of insulin and glucose. These correlate well with measurements of insulin resistance by the euglycemic clamp, but they are less precise. As a result, the data may underestimate the strength of relationships between maternal age or BMI and the offspring's insulin resistance (18). Our twins were young, with a narrow range of fasting insulin and glucose concentrations, but as there is good evidence that hyperinsulinemia in young adults is predictive of glucose intolerance and diabetes in later life, it is likely that these maternal influences will be associated with these adverse health outcomes in later life (19).

The adverse effect of low maternal BMI on insulin resistance in the offspring has never been described in twins, but it is consistent with findings in studies of singletons. Among middle-aged men and women in Scotland (3) and China (5), low maternal BMI in early pregnancy has been associated with raised fasting insulin concentrations in the offspring. In addition, the Dutch famine study showed that exposure to the famine in utero results in insulin resistance in adulthood, especially if the mothers had a low BMI in pregnancy (4). We found that the mother's prepregnancy BMI, but not her pregnancy weight gain, predicted insulin resistance in the offspring. We speculate that a low BMI indicates either a low lean body mass or low fat mass that would reduce the supply of amino acids or fatty acids to the fetus, resulting in fetal undernutrition (20).

Our data suggest that the association between maternal BMI and insulin resistance in the offspring was observed in women but not men. While the explanation for this is not clear, there are known to be marked sex influences in the early programming of insulin resistance and related conditions in both animal studies and human populations. These may arise because of sex differences in fetal growth patterns and permeability of the fetoplacental unit to programming mediators such as steroid hormones (21). They may also arise because of sex differences in the way that sex steroids and insulin interact in their actions on tissues in adult life (22).

Also, older maternal age was associated with indices of insulin resistance in the twins. While little is known about the influence of maternal age on pregnancy outcome in twins, older maternal age is known to be associated with a modest increase in fetal growth retardation and an increased incidence of both antenatal and intrapartum complications in singletons (23). We speculate that twinning challenges the maternal capacity to supply nutrients, especially during the last trimester of pregnancy when intrauterine twin growth rates fall markedly below those of singletons (24), and this effect is amplified by advancing age (25).

We hypothesized that within-pair differences in birth weight would correlate with within-pair differences in adult outcomes. In the case of MZ twins, this

Table 4—*Means of fasting glucose, proinsulin, and insulin concentrations and insulin resistance and β-cell function according to maternal BMI before pregnancy and maternal age at delivery*

	Maternal age at delivery (years)	Maternal BMI before pregnancy (kg/m^2)				
		<20	−22.5	−25	≥25	All
n		152	222	139	89	602
Fasting glucose (mmol/l)	<30	4.69	4.73	4.74	4.71	4.72 (1.04)
	≥30	4.70	4.68	4.71	4.70	4.71 (1.05)
Fasting proinsulin (pmol/l)	<30	5.34	5.38	5.27	5.04	5.28 (1.41)
	≥30	5.57	5.27	5.14	4.91	5.22 (1.48)
Fasting insulin (pmol/l)	<30	36.0	35.6	34.9	35.0	35.5 (1.34)
	≥30	39.1	36.7	35.6	35.4	36.1 (1.29)
Insulin resistance (HOMA)	<30	1.46	1.46	1.44	1.43	1.45 (1.34)
	≥30	1.60	1.47	1.46	1.45	1.48 (1.3)
β-Cell function (%) (HOMA)	<30	120.6	118.0	114.8	118.0	118.2 (1.28)
	≥30	127.0	122.4	121.0	122.1	121.2 (1.3)

Data are geometric means ± SD. Data were adjusted for sex, adult BMI, and age.

would provide a test of the importance of environmental versus genetic factors in explaining the link between birth size and glucose tolerance. Although there were substantial within-pair differences in birth weight in MZ twins, these differences did not correlate with within-pair differences in adult glucose-insulin metabolism. Similar findings have been reported in a study based in Birmingham (U.K.) (12).

Our data contrast with the substantial evidence from singleton studies that low birth weight is associated with insulin resistance and glucose intolerance later in life (26–28). There are a number of possible explanations. First, it is unlikely that the factors that limit fetal growth in singletons are the same as those operating in twins; for example, there is evidence that maternal factors constraining the size of the fetus act disproportionately in twins compared with singletons (29). Second, our assessment of insulin resistance was based on fasting insulin and glucose measurements rather than on the response to a glucose tolerance test. Although these measurements are interrelated and have shown association with low birth weight (26,30), assessing post–glucose tolerance test insulin and glucose concentrations may have been a more sensitive test of disordered carbohydrate metabolism (18). Furthermore, our twins were younger than subjects of previous studies. It may be that the effect of prenatal programming amplifies throughout life.

Our findings suggest that within the limitations of the available data on fetal growth in this study and its interpretation, fetoplacental factors appear to be less important than maternal factors in predicting glucose-insulin metabolism in the offspring.

Acknowledgments— R.J.F.L. is supported by a grant from the Fund for Scientific Research, Flanders (Belgium). R.F. is holder of the Prof. A. Amery Chair in Hypertension Research, founded by Merck Sharp and Dohme B.V.-Belgium. The Prenatal Programming Twin Study was funded by a grant (3.0269.97) from the National Fund for Scientific Research (Belgium). The East Flanders Prospective Twin Survey is partly supported by the Association for Scientific Research in Multiple Births.

We are grateful to all the twins who took part in the study and to Kathleen Gysen, Hilde Van Gucht, and Nathalie Muermans who carried out the fieldwork.

References

1. Barker DJP: *Mothers, Babies and Health in Later Life*. Edinburgh, Churchill Livingstone, 1998
2. Phillips DIW: Insulin resistance as a programmed response to fetal undernutrition. *Diabetologia* 39:1119–1122, 1996
3. Shiell AW, Campbell DM, Hall MH, Barker DJP: Diet in late pregnancy and glucose-insulin metabolism of the offspring 40 years later. *Br J Obstet Gynaecol* 107:890–895, 2000
4. Ravelli ACJ, van der Meulen JHP, Michels RPJ, Osmond C, Barker DJP, Hales CN, Bleker OP: Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 351:173–177, 1998
5. Mi J, Law C, Zhang K-L, Osmond C, Stein C, Barker DJP: Effects of infant birthweight and maternal body mass index in pregnancy on components of insulin resistance syndrome in China. *Ann Intern Med* 132:253–260, 2000
6. Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S: Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet* 19:268–270, 1998
7. Robinson J, Chidzanja S, Kind K, Lok F, Owens P, Owens J: Placental control of fetal growth. *Reprod Fertil Dev* 7:333–344, 1995
8. Poulsen P, Vaag AA, Kyvik KO, Moller Jensen D, Beck-Nielsen H: Low birth weight is associated with NIDDM in discordant monozygotic and dizygotic twin pairs. *Diabetologia* 40:439–446, 1997
9. Poulter NR, Chang CL, MacGregor AJ, Snieder H, Spector TD: Association between birth weight and adult blood pressure in twins: historical cohort study. *BMJ* 319:1330–1333, 1999
10. Dwyer T, Blizzard L, Morley R, Ponsonby A-L: Within pair association between birth weight and blood pressure at age 8 in twins from a cohort study. *BMJ* 319: 1325–1329, 1999
11. Ijzerman RG, Stehouwer CDA, Boomsma DI: Evidence for genetic factors explaining the birth weight-blood pressure relation: analysis in twins. *Hypertension* 36: 1008–1012, 2000
12. Baird J, Osmond C, MacGregor A, Snieder H, Hales CN, Phillips DIW: Testing the fetal origins hypothesis in twins: the Birmingham twin study. *Diabetologia* 44:33–39, 2001
13. Hübinette A, Cnattingius A, Ekbom A, De Faire U, Kramer M, Lichtenstein P: Birthweight, early environment, and genetics: a study of twins discordant for acute myocarial infarction. *Lancet* 357:1997–2001, 2001
14. Loos R, Derom C, Vlietinck R, Derom R: The East Flanders Prospective Twin Survey (Belgium): a population-based register. *Twin Res* 1:167–175, 1998
15. Matthews DR, Hosker AS, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
16. Casey VA, Dwyer JT, Berkey CS, Coleman KA, Gardner J, Valadian I: Long-term memory of body weight and past weight satisfaction: a longitudinal follow-up study. *Am J Clin Nutr* 53:1493–1498, 1991
17. Klipstein-Grobusch K, Kroke A, Boeing H: Reproducibility of self-reported past body weight. *Eur J Clin Nutr* 52:525–528, 1998
18. Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH: Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *Am J Epidemiol* 151:190–198, 2000
19. Haffner SM: Epidemiology of type 2 diabetes: risk factors. *Diabetes Care* 21:C3–C6, 1998
20. James WP: Long-term programming of body composition and longevity. *Nutr Rev* 55:S31–S41, 1997
21. Montano MM, Wang MH, vom Saal FS: Sex differences in plasma corticosterone in mouse fetuses are mediated by differential placental transport from the mother and eliminated by maternal adrenalectomy or stress. *J Reprod Fertil* 99:283–290, 1993
22. Livingstone C, Collison M: Sex steroids and insulin resistance. *Clin Sci* 102:151–166, 2002
23. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL: Delayed childbearing and the outcome of pregnancy. *N Engl J Med* 322:659–664, 1990
24. Bleker OP, Breur W, Huidekoper BL: A study of birth weight, placental weight and mortality of twins as compared to singletons. *Br J Obstet Gynaecol* 86:111–118, 1979
25. Aldous MB, Edmonson MB: Maternal age at first childbirth and risk of low birth weight and preterm delivery in Washington state. *JAMA* 270:2574–2577, 1993
26. McKeigue PM, Lithell H, Leon DA: Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth. *Diabetologia* 41:1133–1138, 1998
27. Flanagan DE, Moore VM, Godsland IF, Cockington RA, Robinson JS, Phillips

DIW: Fetal growth and the physiological control of glucose tolerance in adults: a minimal model analysis. *Am J Physiol* 278: E700–E706, 2000
28. Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 37: 150–154, 1994
29. Phillips DIW, Davies MJ, Robinson JS: Fetal growth and the fetal origins hypothesis in twins: problems and perspectives. *Twin Res* 4:327–331, 2001
30. Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC: Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. *Diabetes Care* 22:944–950, 1999