Impaired Insulin Secretion After Prenatal Exposure to the Dutch Famine

Susanne R. de Rooij, msc[1]
Rebecca C. Painter, md, msc[1]
David I.W. Phillips, md, frcp[2]
Clive Osmond, phd[2]
Robert P.J. Michels, md, phd[3]
Ian F. Godsland, phd[4]
Patrick M.M. Bossuyt, phd[1]
Otto P. Bleker, md, phd, frcog[5]
Tessa J. Roseboom, phd[1]

OBJECTIVE — We previously reported that people prenatally exposed to famine during the Dutch Hunger Winter of 1944–1945 have higher 2-h glucose concentrations after an oral glucose tolerance test in later life. We aimed to determine whether this association is mediated through alterations in insulin secretion, insulin sensitivity, or a combination of both.

RESEARCH DESIGN AND METHODS — We performed a 15-sample intravenous glucose tolerance test in a subsample of 94 normoglycemic men and women from the Dutch Famine Birth Cohort. We used the disposition index, derived as the product of insulin sensitivity and the first-phase insulin response to glucose as a measure of the activity of the β-cells adjusted for insulin resistance. In all analyses, we adjusted for sex and BMI.

RESULTS — Glucose tolerance was impaired in people who had been prenatally exposed to famine compared with people unexposed to famine (difference in intravenous glucose tolerance test K_g value −21% [95% CI −41 to −4]). People exposed to famine during midgestation had a significantly lower disposition index (−53% [−126 to −3]) compared with people unexposed to famine. Prenatal exposure to famine during early gestation was also associated with a lower disposition index, but this difference did not reach statistical significance.

CONCLUSIONS — Impaired glucose tolerance after exposure to famine during midgestation and early gestation seems to be mediated through an insulin secretion defect.

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There is increasing interest in the effects of early nutrition on the predisposition to glucose intolerance and type 2 diabetes. In several animal models, a restricted diet during gestation has been shown to impair glucose tolerance in later life (1–4). A number of animal studies suggest that impairment of glucose tolerance is caused by an insulin secretion defect due to permanent alterations in the structure and function of the pancreatic β-cell made by the fetus when nutrient supplies failed to meet demand (5–9). However, other animal studies suggest that insulin resistance and hyperinsulinemia cause the impaired glucose tolerance after prenatal undernutrition (1,10,11).

Evidence for a direct link between prenatal nutrition and glucose and insulin metabolism in humans is scarce. Research in recent years has focused on the long-term consequences of variations in birth weight and of gestational diabetes. Small babies have been found to develop more impaired glucose tolerance and type 2 diabetes in later life (12–16). Above-average birth weight babies and babies exposed to maternal gestational diabetes are also at increased risk for type 2 diabetes (17,18).

The results of most low–birth weight studies imply that the impaired glucose tolerance and type 2 diabetes are caused by hyperinsulinemia and insulin resistance (15,16,19–22). In contrast, a study that introduced the disposition index as a measure of insulin secretion in low–birth weight people found impaired insulin secretion in subjects who were small at birth (23). However, birth weight is a summary variable of fetal growth that only indirectly relates to maternal nutrition.

The Dutch Famine Birth Cohort Study provides a unique opportunity to evaluate the effects of maternal undernutrition on the predisposition to glucose intolerance and diabetes and its mediating mechanisms. In 1944–1945, severe famine affected the western part of the Netherlands. This famine lasted 5 months and was clearly delineated in time, which enables us to study effects of exposure to famine during specific periods of gestation. Previously, we reported an association between prenatal exposure to famine and impaired glucose tolerance at age 50 years as well as at age 58 years (24,25). In this study, we aim to determine whether prenatal exposure to famine resulted in defective insulin secretion, an increase in insulin resistance, or a combination of both factors.

RESEARCH DESIGN AND METHODS

The Dutch Famine Birth Cohort

All singletons born alive between 1 November 1943 and 28 February 1947 in Wilhelmina Gasthuis, Amsterdam, were eligible for the Dutch Famine Birth Cohort. The selection procedures for this cohort have been described elsewhere (24). A total of 2,414 babies were included, of whom 1,423 (58%) were living in the Netherlands and whose current address was known to the investigators.

Exposure to famine

We defined the famine period according to the daily official food rations for the general population aged >21 years. The official rations accurately reflect the vari-

From the [1]Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; the [2]MRC Epidemiology Resource Centre, University of Southampton, Southampton, U.K.; the [3]Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; the [4]Department of Endocrinology and Metabolic Medicine, Imperial College London, London, U.K.; and the [5]Department of Obstetrics and Gynaecology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands.

Address correspondence and reprint requests to Susanne de Rooij, AMC-KEB, J1B-210, Meibergdreef 9, P.O. Box 22660, 1100DD, Amsterdam, Netherlands. E-mail: s.r.derooij@amc.uva.nl.

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Abbreviations: AIR_G, acute insulin response to glucose.

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

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ation over time in the total amount of food available in the west of the Netherlands (26). We considered fetuses to have been exposed to famine if the average daily rations during any 13-week period of gestation were <1,000 calories. Therefore, babies born between 7 January and 8 December 1945 were considered exposed. We used periods of 16 weeks each to differentiate between people who had been exposed in late gestation (born between 7 January and 28 April 1945), in midgestation (born between 29 April and 18 August 1945), and in early gestation (born between 19 August and 8 December 1945). People born before 7 January 1945 and conceived after 8 December 1945 were considered unexposed.

Participants

In the Dutch Famine Birth Cohort, 810 people (57%) agreed to participate at age 58 years. We were able to perform a standard 75-g oral glucose tolerance test on 699 subjects (86%). Results of the oral glucose tolerance test are described elsewhere (25). Based on the results, we randomly selected 100 normoglycemic individuals (10 men and 10 women from each of the five study groups) for participation in the intravenous glucose tolerance test. We excluded men and women with glucose intolerance or overt diabetes because these conditions are known to affect insulin secretion and insulin action. We defined normoglycemia as 120-min glucose concentrations <7.8 mmol/l in accordance with the definition in our previous study and the 1999 World Health Organization recommendations (24,27).

Study parameters

The medical birth records provided information about the mother, the course of the pregnancy, and the size of the baby at birth (24). After an overnight fast, participants underwent a 15-sample intravenous glucose tolerance test performed by trained nurses (20). Each participant received a glucose dose of 0.5 g/kg body wt as 50% wt/vol dextrose. Insulin sensitivity measured by this protocol has been validated against the reference euglycemic clamp technique ($r = 0.92$) (28). Blood was sampled from the opposite arm at the following time points: −30, −5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, and 180 min. Plasma glucose concentrations were measured by standardized enzymatic photometric assay on a Modular P analyzer (Roche, Basel, Switzerland), and plasma insulin concentrations were measured by immunoluminometric assay on an Immulite 2000 analyzer (Diagnostic Products, Los Angeles, CA). We measured height with a portable stadiometer and weight with a portable Tefal scale. We asked participants about their use of medication. Information on socioeconomic status, medical history, and lifestyle was retrieved from a standardized interview. Current socioeconomic status was coded according to International Socio-Economic Index 92, which is a numeric scale based on the person's or his or her partner's occupation, whichever status is highest (29).

Statistical analysis

We calculated basal glucose and insulin as the mean of the two fasting samples. We used the intravenous glucose tolerance test glucose elimination index (K_g) as a measure of overall glucose tolerance and calculated it as the least square slope of the log of the glucose concentrations between 20 and 60 min after the glucose load (i.e., the regression slope of the decay line). A low value of K_g indicates poor glucose tolerance. We used the trapezoidal rule (base × average height under insulin curve) to determine the first-phase or acute insulin response to glucose (AIR_G) as area under the curve for insulin from 0 to 10 min and the second-phase insulin response to glucose as area under the curve for insulin from 10 to 180 min. Insulin sensitivity (S_i) and glucose effectiveness (S_g) were determined using the minimal model of glucose disappearance (30), with model identification by nonlinear regression using the MLAB mathematical modeling package (Civilized Software, Bethesda, MD). S_i quantifies insulin sensitivity as the fractional rate of clearance of the glucose distribution space per unit plasma insulin concentration. S_g represents the fraction of the glucose distribution space cleared per minute solely as a result of the ability of elevated glucose levels to stimulate their own normalization. We derived the disposition index as the product of S_i and AIR_G. Disposition index is a measure of the activity of the β-cells, adjusted for the level of insulin resistance. A low disposition index indicates impaired insulin secretion. The variables basal glucose, insulin, K_g, AIR_G, second-phase insulin response, S_i, S_g, disposition index, BMI, and current socioeconomic status had skewed distributions and were logarithmically transformed to normality. We used linear regression analysis to compare the metabolic variables among people exposed in early gestation, midgestation, and late gestation and people unexposed to famine. We adjusted for sex and BMI in all analyses. Additional adjustment was done for maternal and birth characteristics, smoking, levels of physical exercise, and socioeconomic status.

RESULTS

— Of the 100 selected subjects, three individuals were unable to participate. The test was terminated in a further three individuals due to a vasovagal reaction or difficulties with venepuncture. The group of 94 participants thus consisted of 47 women and 47 men. They were aged 58 years (SD 1 year). A total of 54 people (57%) had been prenatally exposed to famine. Table 1 shows that mothers of people exposed to famine in early gestation gained more weight during the last trimester than unexposed mothers. Mothers exposed in late gestation gained almost no weight in the last trimester. Mothers exposed in midgestation weighed less at the last antenatal visit. Babies exposed to famine during midgestation were lighter than unexposed babies. At adult age, socioeconomic status was lower in participants exposed to famine in early gestation compared with unexposed participants.

Famine exposure

Figure 1 shows the plasma glucose and insulin concentrations during the intravenous glucose tolerance test for participants who had been exposed to famine in utero compared with unexposed participants. There were no differences in basal glucose and insulin concentrations between the exposed and unexposed groups (Table 2). After the glucose load, participants prenatally exposed to famine had lower glucose tolerance compared with unexposed participants, as indicated by a lower glucose tolerance index (K_g) (−21% [95% CI −41 to −4]). The reduction in K_g was most marked in participants exposed in midgestation and early gestation (late gestation: −4% [−29 to 19], midgestation: −24% [−52 to −1], and early gestation: −37% [−68 to −12]). There was a small nonsignificant decrease in first-phase insulin response (AIR_G) in participants exposed to famine in midgestation and early gestation. The second-phase insulin response did not differ between exposed and unexposed groups. S_i and S_g were both lower in participants who had been exposed during midgestation and early gestation, but

Table 1—*Maternal, birth, and adult characteristics according to timing of prenatal exposure to the Dutch famine*

	Born before famine	Exposed to famine in late gestation	Exposed to famine in mid-gestation	Exposed to famine in early gestation	Conceived after famine	All	*n*
General							
n	19	18	18	18	21	94	
Proportion of men	0.47	0.56	0.50	0.44	0.52	0.50	94
Age (years)	59	58	58	58	57	58 ± 1	94
Maternal characteristics							
Proportion of primiparous women	0.32	0.22	0.39	0.50	0.22	0.34	94
Weight gain third trimester (kg)	1.9	−0.1*	4.5	5.8*	3.1	2.8 ± 3.2	63
Weight at last antenatal visit (kg)	68.8	65.4	64.0*	70.0	69.5	67.7 ± 7.6	84
Birth outcomes							
Gestational age (days)	284	285	285	291	289	286 ± 10	82
Birth weight (g)	3,311	3,361	3,155*	3,497	3,698	3,413 ± 458	94
Ponderal index (kg/m^3)	26.2	27.9	25.8	25.6	27.2	26.6 ± 2.5	92
Adult characteristics							
BMI (kg/m^2)	27.4	27.1	29.0	28.2	27.9	28.1 ± 1.1†	94
Current smoking	0	22	22	28	15	17	93
Current socioeconomic status (ISEI)	48	53	47	40*	49	47 ± 1†	92

Data are means ± SD unless otherwise indicated. *Statistically significant difference ($P < 0.05$) compared with people unexposed to famine in utero. †Geometric means ± SD. ISEI, International Socio-Economic Index.

these differences did not reach statistical significance. The disposition index was significantly lower in participants exposed in midgestation (−53% [−126 to −3]) and tended to be lower in participants exposed in early gestation (−30% [−90 to 12]). Additional adjustment for smoking, levels of physical exercise, and socioeconomic status did not alter the results.

Maternal and birth characteristics

Basal glucose and insulin concentrations, second-phase insulin response, and S_g were not associated with maternal characteristics or with any birth outcome. Primiparity was associated with K_g, AIR_G, and disposition index. Compared with people with a multiparous mother, K_g of people with a primiparous mother decreased by 22% (95% CI −42 to −4), AIR_G decreased by 38% (−78 to 7), and disposition index decreased by 65% (−119 to −24). S_i was associated with maternal weight gain during the third trimester. S_i decreased by 5% (−11 to 0) with each gained kilogram. Birth weight was associated with AIR_G. Per kilogram decrease in birth weight, AIR_G decreased by 35% (−80 to −2).

Additional adjustment for parity did not greatly attenuate the effect of famine exposure on K_g (exposure in midgestation: −21% [95% CI −47 to 1], exposure in early gestation: −32% [−61 to −8]) and disposition index (exposure in midgestation: −36% [−99 to 7]). There was a trend toward a significant interaction between exposure to famine in early gestation and weight of the mother at the last antenatal visit. Additional adjustment for other maternal and birth characteristics did not change results on prenatal famine exposure.

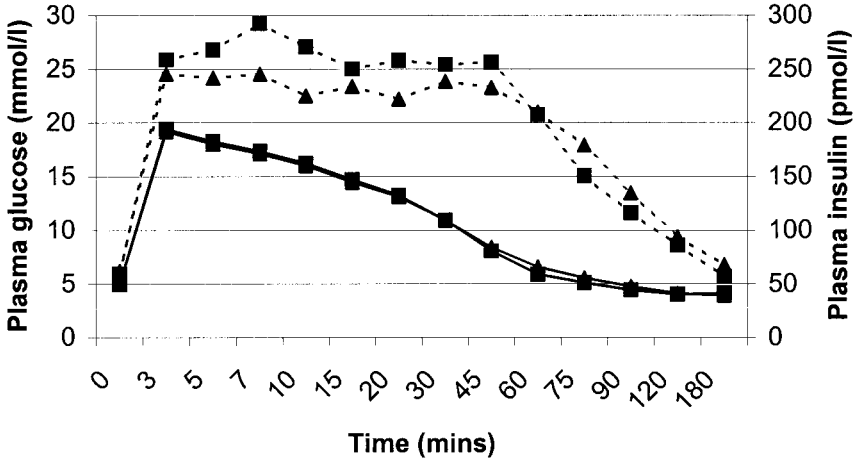

Figure 1—*Geometric means of plasma glucose (solid line) and insulin (dotted lines) concentrations during the intravenous glucose test for people who were exposed (▲) or unexposed (■) to famine in utero.*

CONCLUSIONS— We found that prenatal exposure to famine, especially during midgestation or early gestation, was related to impaired glucose tolerance as measured by an intravenous glucose tolerance test and that this is likely to be caused by an insulin secretion defect.

Table 2—*Glucose and insulin variables derived from the intravenous glucose tolerance test, according to timing of prenatal exposure to the Dutch famine*

	Born before famine	Exposed to famine in late gestation	Exposed to famine in mid-gestation	Exposed to famine in early gestation	Conceived after famine	All	*n*
Basal glucose (mmol/l)	5.1	4.8	5.0	5.0	5.0	5.0 ± 1.1	93
Basal insulin (pmol/l)	55	60	56	71	63	61 ± 1.6	93
Glucose tolerance index (K_g) ($10^{-2} \cdot min^{-1}$)	1.96	1.82	1.55*	1.41*	1.87	1.72 ± 1.4	90
First-phase insulin response (AIR_G) ($min \cdot pmol \cdot l^{-1}$)	2,343	2,354	2,095	2,118	2,648	2,311 ± 1.8	88
Second-phase insulin response ($min \cdot pmol \cdot l^{-1}$)	20,308	21,299	26,515	24,680	24,212	23,211 ± 1.9	85
S_i ($10^{-4} \cdot min^{-1}$ per pmol/l)	0.67	0.64	0.54	0.59	0.61	0.61 ± 1.8	94
S_g ($10^{-2} \cdot min^{-1}$)	1.81	1.91	1.69	1.65	2.00	1.81 ± 1.5	94
Disposition index ($S_i \times AIR_G$)	1,576	1,539	1,059*	1,252	1,576	1,392 ± 2	88

Data are geometric means ± SD unless otherwise indicated. *Statistically significant difference ($P < 0.05$, adjusted for sex and BMI) compared with people unexposed to famine in utero.

The results of the intravenous glucose tolerance test indicated that people who were exposed to famine in utero had decreased glucose tolerance compared with people unexposed to famine in utero. These results match the results of the oral glucose tolerance tests we performed in this cohort at age 50 and 58 years (24,25). People who were exposed in mid-gestation had a lower disposition index than unexposed people. People exposed in early gestation also had a lower disposition index, but the difference from unexposed people did not reach statistical significance. In contrast to the evidence of many animal studies (1,10,11), we found no association between prenatal undernutrition and insulin resistance. This may be related to the type of exposure in utero. Animals, in which insulin resistance was found, were protein restricted during gestation, while the participants in our study were prenatally exposed to a hypocaloric diet and were deprived of protein, carbohydrate, and fat (1,10,11).

The disposition index evaluates insulin secretion, while at the same time taking insulin sensitivity in account, and can therefore provide an index of how effective insulin secretion is in compensating for insulin resistance (31). A low disposition index indicates that β-cell functioning is inadequate for the degree of insulin resistance. Defective β-cell functioning may thus mediate the association between prenatal famine exposure in mid-gestation and early gestation and impaired glucose tolerance in later life. Our results confirm the results of many experimental animal studies in which the offspring of mothers exposed to a low-protein diet during gestation showed reduced β-cell mass and impaired β-cell function (5–9). Our results also confirm the findings of Jensen et al. (23) who found that men who had low birth weight, which is a proxy for a poor fetal environment, had a lower disposition index.

We can only speculate about the mechanism underlying the link between fetal undernutrition and impaired functioning of the β-cell. Rats exposed to a low-protein diet during pregnancy and lactation had reduced β-cell mass caused by decreased rates of β-cell proliferation and increased rates of β-cell death (32). Bilateral uterine artery ligation in the rat, which mimics placental insufficiency, caused an insulin secretion defect that was specific for glucose stimulation. This suggests a possible impairment in glucose sensing or a defect in the signaling pathway that elicits insulin secretion by the β-cell (33).

We studied a cohort of people who were born immediately before, during, or after the 1944–1945 Dutch famine. A limitation of our study is that the famine had a profound effect on early mortality and fertility, which may have introduced selection bias in our study (34). Early mortality rates were highest among people born before the famine and lowest among people conceived after the famine. These two groups, however, were similar in terms of the parameters we investigated. Also, adjusting for maternal characteristics, which may be proxies for determinants of fertility, did not greatly attenuate the effects we found of prenatal famine exposure. We therefore think selective early mortality and fertility can have had only a limited influence.

Other limitations of our study were the small sample number and the possible bias introduced by the study design. We excluded all people with impaired glucose tolerance and type 2 diabetes as indicated by an oral glucose tolerance test. We chose this design because if we had included people with impaired glucose tolerance and type 2 diabetes, we probably would have found insulin deficiency as a consequence of the present pathology and not necessarily because of the prenatal exposure to famine. Excluding these people could, however, have affected our results.

Although based on a small study sample, this is the first direct evidence suggesting that an insulin secretion defect mediates the association between fetal undernutrition and the development of impaired glucose tolerance in humans.

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