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Chapter 6

GLUCOSE TOLERANCE IN ADULTS AFTER PRENATAL EXPOSURE TO FAMINE


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Chapter 6

Abstract

Background
Reduced growth in utero is associated with type 2 (non-insulin-dependent) diabetes and impaired glucose tolerance in adult life. There is no direct evidence in human beings that maternal nutrition during gestation affects insulin-glucose metabolism. We therefore investigated glucose tolerance in people born around the time of famine in the Netherlands during 1944-45.

Methods
We included 702 people born between Nov 1, 1943, and Feb 28, 1947, in Amsterdam, for whom we had detailed prenatal and birth records. We compared glucose and insulin responses to a standard oral glucose load in participants exposed to famine at any stage during gestation (exposed participants) with those who were born in the year before or conceived in the year after the famine (non-exposed participants).

Findings
Glucose concentrations were increased 2 h after a standard glucose load among exposed participants (p=0.006), and were highest in men and women exposed during mid and late gestation. Mean 2 h glucose concentration among non-exposed participants was 5.8 mmol/L; concentrations were 0.5 mmol/L (95% CI 0.1 to 0.9) higher among participants exposed during late gestation, 0.4 mmol/L (0.0 to 0.8) higher among those exposed during mid gestation, and 0.1 mmol/L (-0.4 to 0.6) among those exposed during early gestation. Participants born as thin babies to mothers with low body weights had the highest concentrations and concentrations were especially high among people exposed to famine who became obese as adults. Prenatal exposure to famine was related to increased fasting proinsulin (p=0.05) and 2 h insulin concentrations (p=0.04), which suggests an association with insulin resistance.

Interpretation
Prenatal exposure to famine, especially during late gestation, is linked to decreased glucose tolerance in adults. Poor nutrition in utero may lead to permanent changes in insulin-glucose metabolism, even if the effect on fetal growth is small. This effect of famine on glucose tolerance is especially important in people who become obese.

Introduction
Decreased fetal growth is related to the occurrence of type 2 (non-insulin-dependent) diabetes mellitus in later life. In various populations and in different countries, decreased glucose tolerance in adults has been associated with low birth weight and thinness at birth. Associations between decreased fetal growth and impaired insulin-glucose metabolism have also been found in children and adolescents.

Retarded growth in utero during sensitive periods of development leads to permanent long-term changes in the body’s structure, physiology, and metabolism. The "fetal origins hypothesis" proposes that impaired glucose tolerance and type 2 diabetes, together with the related disorders coronary heart disease and hypertension, are initiated by impaired fetal growth in mid to late gestation, which leads to disproportionate body size at birth. Nutrient supply to the fetus is thought to have strong influence on the fetus. Nutrient supply is determined by the mother’s own fetal and childhood growth, her nutrition before and during pregnancy, and transfer
capacity across the placenta. The fetal origins hypothesis is supported by studies on animals. If rats are undernourished during pregnancy, the offspring show persisting changes in insulin secretion and responsiveness to the hormone. \(^6,7,18,20\)

No studies directly link human maternal nutrition during specific periods of gestation with glucose tolerance later in life. The Dutch famine, which occurred in the Western part of the Netherlands at the end of World War II, provides a unique opportunity to study such an effect. \(^21,22\) The famine is clearly delineated in time (late November, 1944, to early May, 1945). The official rations varied from 400 to 800 calories per day in the first months of 1945. We investigated glucose and insulin responses in people who had been exposed to famine at any point during gestation (exposed participants) and in those who were born in the year before or conceived in the year after famine (non-exposed).

**Methods**

We traced 5425 people born between November, 1943, and February, 1947 in the Wilhelmina Gasthuis, one of the principal hospitals in Amsterdam at that time, for whom we obtained detailed records of the course of gestation and birth. Most patients were in the lower and middle social classes, but little is known about the referral pattern during that period. We retrieved from the Gemeentearchief (city archive) of Amsterdam the medical records of the 1380 liveborn singletons who were born between Nov 1, 1944, and Feb 28, 1946. We also retrieved details of a random sample of 650 liveborn singletons born between Nov 1, 1943, and Oct 31, 1944, and 650 liveborn singletons born between March 1, 1946, and Feb 28, 1947, making a total of 2680 children. Of these, 27 (1.0 %) were excluded because their main medical records were missing, and 239 (8.9 %) were excluded because the gestational age at birth was less than 259 days, calculated either from the date of the last menstrual period or by the obstetrician’s estimation at the first prenatal visit and at the physical examination of the child at birth. Therefore, we included 2414 liveborn singletons.

The Bevolkingsregister (population registry) of Amsterdam traced 2155 (89.3%) of these 2414 people, 265 had died, 199 had emigrated from the Netherlands, and 164 refused to allow their addresses to be given to us. The population registry provided us with the current address of the remaining 1527. We asked 912 subjects who lived in or close to Amsterdam to attend the Academic Medical Center (AMC) for an oral glucose tolerance test during the morning after an overnight fast. In the last stage of selection, we invited more men and all people born in the last three months of 1945 to enrol because these groups seemed to be under-represented. 32 (3.5%) of these 912 were excluded because they had diabetes. 718 (82.0%) of the remaining 880 participants attended the clinic and 702 successfully completed the glucose tolerance test. Birth weights, according to prenatal exposure among those people, were similar to those of the 2414 people who were originally eligible, therefore, bias originating from the selection procedure is unlikely.

We took birth measurements and maternal data from the medical records. We took placental length to be the longest placental diameter and width to be the longest perpendicular diameter. Placental area was estimated as \(\pi \times \text{length} \times \text{width} \times 0.25\). Head circumference was estimated as \(\pi \times (\text{biparietal diameter} + \text{occipito-frontal diameter}) \times 0.5\). We calculated the ponderal index, a measure of thinness, as birth weight divided by the cube of length. Mother’s weight was that at the last prenatal visit, always within 2 weeks of birth.

Trained research nurses took all measurements during the clinic visits between March, 1995, and August, 1996. Blood measurements included plasma glucose and
insulin concentrations at 0 min, 30 min, and 120 min after a 75 g oral glucose load, and concentrations of fasting proinsulin and 32-33 split proinsulin. We measured plasma glucose by the glucose dehydrogenase method (H747, Merck 12194, Netherlands); plasma insulin by immunoenzymometric assay (Medgenix SA, Fleurus, Belgium); proinsulin by a microtitre plate time-resolved fluorescence assay (Delfia); and 32-33 split proinsulin by a two-site immunometric assay. We used the fasting insulin and 32-33 split proinsulin concentrations as measures of insulin resistance because they are thought to reflect the degree of exposure of the pancreatic β cell to glucose and, therefore, to increased demands for insulin. We used the 30 min relative insulin increment log ([30 min insulin - fasting insulin]/30 min glucose) as a measure of insulin deficiency.

We measured height with a fixed stadiometer, weight with a SECA scale, and waist circumference with a flexible tape measure midway between the costal margin and the iliac crest, and the hip circumference at the widest part of the hips, generally at the level of the greater trochanter. We calculated adult body-mass index as weight divided by the square of height. Current socioeconomic status was determined from the person’s or their partner’s occupation, whichever was highest paid, according to the socioeconomic index (ISEI-92). This scale represents the education needed for an occupation and the income generated by it, with a scale ranging from 16 for the lowest to 87 for the highest status. We also recorded smoking history.

We defined the famine period according to official daily rations for the general population aged 21 years and older. Rations were set weekly by the authorities and varied according to class of labour. The calorific intake from protein, carbohydrate and fat decreased proportionately. Daily rations were about 1800 calories in December, 1943, decreasing gradually to about 1400 calories by October, 1944, and fell to below 1000 calories on Nov 26, 1944. The daily rations varied between 400 calories and 800 calories from December, 1944, to April, 1945, and rose to more than 1000 calories after May 12, 1945. In June, 1945, rations were more than 2000 calories. We took fetuses to have been exposed to famine if the average maternal daily ration during any 13-week period of gestation was less than 1000 calories. Therefore, children born between Jan 7, 1945, and Dec 8, 1945, were exposed. We used three 16-week periods to distinguish between children who were exposed during late gestation (Jan 7 to April 28), mid gestation (April 29 to Aug 18), and early gestation (Aug 19 to Dec 8).

We analysed exposure in two groups (exposed to famine in utero or not) and also calculated the differences in 120 min plasma glucose concentrations between non-exposed people and those exposed in late, mid or early gestation. We used multiple linear regression to analyse continuously distributed variables and multiple logistic regression to analyse proportions. We log transformed all glucose and insulin concentrations before analysis, results are given as geometric means and SD. We adjusted for sex and adult body-mass index in all analyses.
Results

202 (28.8%) of the 702 people were born before the famine, 279 (39.70%) were exposed to famine during gestation, and 221 (31.4%) were conceived after the famine. Characteristics of mothers and babies (table 1) have been described in a detailed analysis of all 2414 births in the hospital (unpublished). Mothers exposed to famine in mid or late pregnancy weighed less than those not exposed. Babies born after famine exposure during mid and late gestation had lower birthweights, lengths, head circumferences, and placental areas than those exposed during early gestation or not exposed before birth. Their increased head-to-birthweight ratio suggests "brain sparing". Of the 702 participants, fewer men than women had been exposed to famine. Those exposed to famine in early gestation had higher body-mass indices as adults. We also found that 120 min plasma glucose concentrations increased by 2.4% (95% CI 1.9 to 2.9) per kg/m² in body mass index. Adult height, waist-to-hip ratio, current socioeconomic status and the frequency of current smoking were similar across exposure groups.

Exposed participants had higher fasting proinsulin concentration, and higher 120 min plasma glucose and insulin concentrations than those who not exposed (Table 2). The highest 120 min glucose concentrations were among participants exposed during mid or late gestation. After adjustment for sex and adult body-mass index, the 120 min plasma glucose concentration was higher by 0.5 mmol/L (0.1 to 0.9) among participants exposed during late gestation, 0.4 mmol/L (0.0 to 0.8) among those exposed during mid gestation, and by 0.1 mmol/L (-0.4 to 0.6) among those exposed in early gestation than among those not exposed. After adjustment for adult body-mass index and sex, the fasting concentration of insulin and 32-33 split proinsulin, and the 30 min relative insulin increment were not significantly different, which suggests that the high unadjusted means of these variables (table 2) can be explained by the higher adult body-mass index. Adjustment for other confounding variables (maternal age, parity, current socioeconomic status and current smoking) made little difference to any of these results.

84 (12.0%) of participants had impaired glucose tolerance (120 min glucose concentration of 7.8-11.0 mmol/L) and 27 (3.8%) had newly diagnosed type 2 diabetes (120 min glucose concentration ≥ 11.1 mmol/L). Participants exposed during late gestation had the highest rates of impaired glucose tolerance or type 2 diabetes (21%).

Weight of the mother at the last prenatal visit was inversely related to the 120 min glucose concentration: an increase in mother’s weight of 1 kg was associated with a decrease in 120 min glucose concentration of 0.5% (0.2 to 0.8). Birth weight, body length, and head circumference were inversely associated and the head-to-birthweight ratio was positively associated with 120 min glucose concentration. These concentrations fell by 3.8% (1.6 to 5.9) for each SD increase in birth weight, by 4.2% (2.0 to 6.3) for each SD increase in body length, and by 3.1% (0.9 to 5.3) for each SD increase in head circumference, and rose by 3.5% (1.2 to 5.9) for each SD increase in head-to-birthweight ratio. Although ponderal index was not linearly associated with 120 min glucose concentrations, the participants with a ponderal index in the lower quarter of distribution (< 25.0 kg/m²) had significantly higher 120 min glucose concentration than the other participants (6.2 vs.5.9 mmol/L, p = 0.02). Placental area and 120 min glucose concentrations were not associated.

The effect of prenatal famine exposure on 120 min glucose concentrations was larger than could be explained by the famine-related variations in birth measurements. The difference in birthweight between exposed and non-exposed participants was 254 g (table 1). With this difference, a relative difference in 120 min glucose concentration
of about 2% (254 g x 3.8%/466 g) might be expected, whereas the observed difference was 9% (table 2).

The highest 120 min glucose concentrations were among participants who were exposed during gestation, and who had low birth weights or became obese as adults (table 3).

Discussion

We found an association between exposure to famine during gestation and decreased glucose tolerance in adults about 50 years. Glucose tolerance was decreased most among participants who were exposed to famine during mid or late gestation. Previous studies in human beings of the long-term effects of maternal malnutrition have used body size at birth as an indirect measure of fetal nutrition.26 We found links between decreased glucose tolerance and decreased fetal growth (low birthweight, short body length, small head circumference, high head-to-birthweight ratio low ponderal index in babies born at term) and low bodyweights of the mother close to delivery.

It has been suggested that people exposed to an adverse environment in utero may continue to experience a similar adverse environment after birth, and that this adverse prenatal environment permanently affects metabolism.22,23,24 In our study, exposed participants had worse glucose tolerance non-exposed participants. This finding strongly supports the role of poor maternal nutrition during pregnancy in permanent changes to fetal metabolic control systems. Our results were not affected by adjustment for other variables related to fetal growth, including maternal age and parity, or influences in adult life, including current socioeconomic and smoking status.

The Dutch famine affected body size at birth, especially in babies born after famine exposure during late gestation. Great changes in maternal nutrition are required to produce changes in size at birth.30 The effect of the Dutch famine on 120 min glucose concentrations was greater than can be explained by the reductions in birth size. The calorie intake that produced these effects is not well known, because other sources of food were available in addition to the official rations.31

We found that the 2 h plasma glucose concentrations were highest in exposed people who became obese as adults. This finding has important implications for the prevention of type 2 diabetes. People exposed to famine in utero should avoid obesity by exercise and an appropriate diet. For future generations, promotion of women’s health before and during pregnancy will also be important.

The underlying mechanisms that link prenatal exposure to famine with lower glucose tolerance remain unclear. We did not find any association of famine exposure during gestation and fasting insulin or 32-33 split proinsulin, measures of insulin resistance, or relative insulin increment, a measure of insulin deficiency. However, fasting proinsulin and 120 min insulin concentrations were raised in the exposed group, which suggests that insulin resistance might be the main determinant of the poor glucose tolerance associated with prenatal exposure to famine. More detailed studies are necessary to resolve this matter.

Exposure to the Dutch famine in the first half of pregnancy has been shown to result in higher rates of obesity in young men.32 We found an association between exposure to famine in early gestation and a raised adult body-mass index, but not between exposure and waist-to-hip ratio. Prenatal exposure was associated with adult glucose tolerance at all adult body-mass indices, which suggests that this effect is not mediated by a high body-mass index or abdominal obesity. Future analyses of blood pressure, cholesterol, triglycerides will show the extent to which prenatal exposure to
famine is the common origin of the components of the syndrome X or insulin-resistance-syndrome (ie, hyperinsulinemia, hypertension and hyperlipidemia). 13

The direct link between maternal malnutrition and reduced glucose intolerance in adults fits with ideas that poor nutrition during fetal life leads to permanent changes in the function of pancreatic β cells or in the sensitivity of tissues to insulin, which become apparent in later life—the so-called "thrifty phenotype hypothesis". 42 The acuteness and the short duration of the Dutch famine as well as the lack of information about the exact food intake make it impossible to use the size of the effects found in this study to estimate the importance of maternal nutrition for public health in prevention of diabetes. Undernourishment for longer periods is likely, however, to have had more profound effects because fetal growth is determined by the mother's nutrition during pregnancy and by her diet and body composition before pregnancy.
Table 1: Maternal characteristics, birth outcomes, and adult characteristics among men and women exposed to famine.

|                          | born before famine n=202 |Exposed to famine
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>in late gestation n=116</td>
</tr>
<tr>
<td>men/women</td>
<td>50%/50%</td>
<td>48%/52%</td>
</tr>
</tbody>
</table>

**Maternal characteristics**

- weight last prenatal visit (kg): 66.4
- age (years): 29
- primiparous: 35%

**Birth outcomes**

- gestational age at birth (d): 284
- birth weight (g): 3388
- body length (cm): 50.6
- head circumference (cm): 32.9
- placental area (cm²): 299
- ponderal index (kg/m²): 26.2
- head/weight ratio (cm/kg): 9.9

**Adult characteristics**

- height (m): 171.0
- body mass index (kg/m²): 26.8
- waist/hip ratio: 0.87
- current socio-econ. status: 47
- current smoker: 35%

*given as mean, except where given as %.

70
### Table 2: Geometric means of plasma glucose and insulin concentrations.

<table>
<thead>
<tr>
<th></th>
<th>born before</th>
<th>Exposed to famine in late</th>
<th>Exposed to famine in mid</th>
<th>Exposed to famine in early</th>
<th>Total (SD)</th>
<th>p</th>
<th>Missing observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>famine n=202</td>
<td>gestation n=116</td>
<td>gestation n=100</td>
<td>gestation n=63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fasting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose (mmol/l)</td>
<td>5.8</td>
<td>5.8</td>
<td>5.7</td>
<td>5.8</td>
<td>5.6</td>
<td>5.7 (1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>insulin (pmol/l)</td>
<td>46.7</td>
<td>48.9</td>
<td>45.4</td>
<td>52.6</td>
<td>47.0</td>
<td>47.5 (1.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>proinsulin (pmol/l)</td>
<td>5.8</td>
<td>6.3</td>
<td>5.9</td>
<td>6.6</td>
<td>5.9</td>
<td>6.0 (1.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>32-33 proinsulin (pmol/l)</td>
<td>6.2</td>
<td>6.9</td>
<td>6.1</td>
<td>7.5</td>
<td>6.6</td>
<td>6.5 (2.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>30-minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose (mmol/l)</td>
<td>9.0</td>
<td>8.8</td>
<td>8.7</td>
<td>9.2</td>
<td>8.8</td>
<td>8.9 (1.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>insulin (pmol/l)</td>
<td>314</td>
<td>285</td>
<td>303</td>
<td>327</td>
<td>319</td>
<td>310 (1.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>relative insulin increment*</td>
<td>3.4</td>
<td>3.3</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4 (0.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>120-minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose (mmol/l)</td>
<td>5.7</td>
<td>6.3</td>
<td>6.1</td>
<td>6.1</td>
<td>5.9</td>
<td>6.0 (1.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>insulin (pmol/l)</td>
<td>160</td>
<td>200</td>
<td>190</td>
<td>207</td>
<td>181</td>
<td>181 (2.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>prevalence of IGT or NIDDM</td>
<td>15%</td>
<td>21%</td>
<td>14%</td>
<td>16%</td>
<td>15%</td>
<td>16%</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* not geometric.
Table 3: Geometric mean 120 min plasma glucose concentrations by exposure, birth weight and body-mass index. Figures in parentheses are numbers of subjects.

<table>
<thead>
<tr>
<th></th>
<th>born before famine</th>
<th>Exposed to famine</th>
<th></th>
<th>in early gestation</th>
<th></th>
<th>conceived after famine</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>in late gestation</td>
<td></td>
<td>gestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>birth weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 2750</td>
<td>6.0 (15)</td>
<td>6.6 (21)</td>
<td>6.4 (9)</td>
<td>6.9 (6)</td>
<td>6.2 (14)</td>
<td>6.4 (65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2750 - 3250</td>
<td>5.9 (68)</td>
<td>6.4 (44)</td>
<td>6.3 (46)</td>
<td>6.3 (15)</td>
<td>6.2 (65)</td>
<td>6.2 (238)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3250 - 3750</td>
<td>5.3 (75)</td>
<td>6.2 (40)</td>
<td>5.8 (36)</td>
<td>5.8 (28)</td>
<td>6.0 (82)</td>
<td>5.8 (261)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3750</td>
<td>5.8 (44)</td>
<td>5.7 (11)</td>
<td>6.4 (9)</td>
<td>6.1 (14)</td>
<td>5.5 (60)</td>
<td>5.7 (138)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

body mass index (kg/m²)

|                  |                   |                  |     |                    |     |                        |     |       |
| <= 24.0          | 5.0 (56)          | 5.3 (22)         | 5.5 (34) | 5.6 (11)           | 5.2 (46) | 5.2 (169)              |     |       |
| 24.0 - 26.5      | 5.5 (39)          | 5.8 (44)         | 5.7 (19) | 6.1 (20)           | 5.7 (51) | 5.7 (173)              |     |       |
| 26.5 - 30.0      | 5.6 (66)          | 6.7 (27)         | 6.2 (28) | 5.4 (18)           | 6.0 (65) | 5.9 (204)              |     |       |
| >30.0            | 7.1 (41)          | 8.2 (23)         | 7.9 (19) | 7.4 (14)           | 6.7 (59) | 7.2 (156)              |     |       |

all | 5.7 (202) | 6.3 (116) | 6.1 (100) | 6.1 (63) | 5.9 (221) | 6.0 (702) |
References:


27. Ben-Shlomo Y, Smith GD. Deprivation in infancy or in adult life: which is more important for mortality risk? Lancet 1991;337:530-4.


