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Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes

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OBJECTIVES: To analyse the development of body weight and frequencies of overweight and obesity in infants of long-term insulin-dependent diabetic mothers as compared to those of gestational diabetic mothers.
DESIGN: Retrospective study.
SUBJECTS: Two hundred infants of mothers with pregestational insulin-dependent diabetes mellitus (IDM) and 117 infants of gestational diabetic mothers (IGDM) born between 1980 and 1990 at the Clinic of Obstetrics and Gynaecology, Berlin-Kaulsdorf, Germany.
MEASUREMENTS: Birth weight, birth length, plasma insulin, interscapular skinfold, symmetry index (SI) and body mass index (BMI) at birth; SI and BMI in childhood (1–9 y of age).
RESULTS: Neonatally, mean relative weight (SI) was found to be increased in both groups of infants. It was positively correlated to interscapular skinfold ($P < 0.001$) and insulin ($P < 0.005$). However, IDM had higher insulin levels ($P < 0.001$) and a higher frequency of obesity ($P < 0.05$) than IGDM at birth. Throughout childhood frequencies of overweight ($SI > 1.1$) were elevated in both IDM as well as IGDM. In IDM the percentage of obesity ($SI > 1.2$) displayed a significant increase from 11.2% in children 1–4 y old up to 25.8% at 5–9 y ($P < 0.05$). Similar frequencies and a highly significant increase of overweight during childhood of IDM ($P < 0.005$) were observed when BMI ≥ 95th percentile was used to determine overweight. Relative weight in childhood was positively correlated to relative weight at birth ($P < 0.05$). Large-for-gestational-age infants displayed a significantly higher percentage of overweight ($SI > 1.1$) in childhood than appropriate-for-gestational-age infants ($P < 0.05$).
CONCLUSIONS: Infants of mothers with diabetes during pregnancy are predisposed to develop overweight and obesity during childhood. These alterations seem to be related to insulin and relative body weight at birth. Pathophysiological mechanisms which might be involved into the development of these changes are discussed. Prophylactic measures are recommended to reduce morbidity in infants of diabetic mothers.

Keywords: children of diabetic mothers; insulin; birth weight; overweight; obesity

Introduction

Obesity in childhood represents a growing problem in public health since frequencies of affected children seem to increase continuously in Europe as well as in the United States.[1–3] Even in childhood, obesity predisposes to metabolic and cardiovascular diseases.[4] In a number of countries prevention programs were initialized to lower the percentage of obese children and adolescents.[5] An effective way to prevent development of obesity and related cardiovascular and metabolic disorders could be the identification and characterization of high risk groups. Insights obtained from animal models of diabetes during pregnancy indicate that the offspring of diabetic mothers is at increased risk of developing overweight and obesity in juvenile life.[6] These observations are supported by some clinical studies.[7–9] Nevertheless, most clinical studies were subjected to infants of pregestational long-term diabetic mothers while data on offspring of gestational diabetic mothers are rare. Furthermore, only a few data are available on the development of body weight throughout childhood in these groups of children.

The analysis presented here was performed to characterize the development of relative body weight in infants of long-term diabetic mothers, as compared to those born to mothers with gestational diabetes, and with regard to the situation at birth.

Methods

Subjects

A retrospective analysis was carried out involving data of 317 term infants (175 males, 142 females)

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born to women with diabetes during pregnancy. All children were delivered between 1980 and 1990 at the Department of Neonatology of the Clinic of Obstetrics and Gynaecology in Berlin-Kaulsdorf and were also clinically investigated there. As a center of local community health services, the Clinic at Kaulsdorf was attended by around 1800 white caucasian pregnant women per year for delivery. They represented a population from both urban and rural parts in the Southeast of Berlin. All children of the study were derived from a total of 741 children born to diabetic mothers during the whole observation period. In 317 out of these infants data on development during childhood were available. All of these children were involved into the study. Two hundred out of the 317 infants were born to mothers with pregestational insulin-dependent diabetes mellitus (IDDM) belonging to White classes B-R (infants of diabetic mothers, IDM). Mean duration of maternal diabetes before pregnancy was 9.2 ± 5.5 y. One hundred and seventeen out of the 317 children were delivered by women with gestational diabetes (infants of gestational diabetic mothers, IGDM). Gestational diabetes was diagnosed between the 26th and 28th week of gestation according to criteria established by Fuhrmann.[10] Seventy-eight gestational diabetic women were treated with insulin and diet, 39 with diet alone. Once a month 24 h glucose monitoring was performed in all pregnants to control glucose homeostasis. Retrospectively, data on anthropometrics before pregnancy were available of 70 mothers: Mean body weight: 66.7 ± 13.4 kg; mean height: 163.7 ± 5.8 cm; mean body mass index (BMI): 24.9 ± 4.6 kg/m^2. In 46 cases paternal data were available: Mean body weight: 74.6 ± 11.3 kg; mean height 176.1 ± 7.6 cm; mean paternal BMI: 24.0 ± 2.7 kg/m^2. Mean of maternal age was 26.1 ± 5.5 y, mean paternal age was 29.1 ± 6.1 y. Informed parental consent was given in all cases.

Neonatal parameters

After delivery, birth weight and birth length were measured in all infants. Percentages were calculated for newborns who were found to be small for gestational age (namely < 5th percentile of body weight; SGA), large for gestational age (namely > 95th percentile; LGA) and those who were appropriate for their gestational age (AGA). Data on thickness of the interscapular skinfold were available of 97 newborns. Skinfold was measured 2 cm below the 7th cervical vertebra, using a Lange Skinfold Caliper. Peripheral capillary blood was collected within 45 min after delivery for the determination of fasting insulin in 145 neonates. Immunoreactive plasma insulin was measured by a double antibody radioimmunoassay (Serono, Freiburg, FRG; standard: 1.IRP 66/304). Cross reactivity with proinsulin was 15%, those with C-peptide was < 0.01%. Interassay precision was 5.6–10.5%, intraassay variation coefficient was 4.5–8.2%.

Measurements in childhood

Examinations were performed in 178 nonselected, clinically healthy children aged 1–9 y. For detailed analysis of development of relative body weight children were divided into two age groups: A younger group aged 1–4 y consisting of 167 infants (mean age: 2.0 ± 1.0 y) and an older group of 46 children 5–9 y (mean age: 6.4 ± 1.4 y). During physical examination weight and height were measured and Farquhar's symmetry index (SI) was calculated.[11] The SI as a measure of weight/height-ratio in relation to weight/height-ratio of a standard population was determined as follows: relative weight (namely weight divided by median standard weight for age and sex) divided by relative height (namely height divided by median standard height for age and sex). Median standard weight and height for age and sex were obtained from Flügel *et al.*[12] Data of this reference population were collected by cross-sectional studies between 1979 and 1982 at the whole territory of the former GDR (East Germany), including measurements in 38 121 male and 35 869 female children, thereby representing the largest collection of anthropometric data of East Germany. Data match up with the values suggested as standards for European populations.[13] As suggested by Silverman *et al.*,[9] symmetry index >1.2 indicates obesity, while SI >1.1 shows overweight. These cutoff-values reflect relative weight >120% and relative weight >110%, respectively, which were used by a number of authors to define obesity and overweight in childhood.[2,14–17] However, to improve validity and comparability of our data, in all children body mass index (BMI) was calculated additionally. According to criteria of Himes *et al.*,[18] frequencies of overweight children (BMI ≥ 95th percentile for age and sex) were determined using percentile curves for white caucasian children.[19]

Statistics

Data are expressed as means ± standard error (s.e.m.). Unpaired Student's *t*-test or chi-square-test were performed for the determination of significant differences between two groups. Spearman's rank correlation test was performed to analyse relations between variables. Statistical comparisons are two-tailed with $P < 0.05$ considered significant. The SPSS PC+ package (Microsoft) was used for all statistical evaluations.

Results

Neonatal period

No significant differences in means of birth weight and birth length were found between the two groups of neonates (Table 1). Nevertheless, in both groups mean SI appeared to be increased to the same degree of 5%. Percentages of LGA-, AGA- and SGA-infants were found to be very similar in IDM and IGDM. About one third of IDM as well as IGDM displayed overweight determined by SI > 1.1 at birth and this well corresponded with the frequencies of LGA observed in the newborns (Table 1). Relative weight at birth (SI) was positively correlated to interscapular skinfold ($r = 0.5608$; $P < 0.001$) and plasma insulin ($r = 0.2326$; $P < 0.005$). However, IDM displayed significantly higher insulin values than IGDM ($P < 0.001$), accompanied by higher thickness of interscapular skinfold and a higher frequency of obesity at birth (both P-values < 0.05; Table 1).

Development in childhood

The mean SI remained increased throughout childhood (1–9 y of age) in both groups of infants (IGDM: 1.04 ± 0.02; $n = 45$; IDM: 1.04 ± 0.01; $n = 133$). No significant differences were observed between the groups. In Table 2, data for children aged 1–4 y are compared to those 5–9 y old. Frequency of overweight (SI > 1.1) rose in IDM, while it remained on a stable level with rising age in IGDM. Both groups of children displayed an increase of obesity (SI > 1.2) with rising age. This elevation was significant in IDM ($P < 0.05$).

Table 3 shows comparison of age groups 1–4 and 5–9 y, using the body mass index as criterion for overweight (BMI ≥ 95th percentile). Again, with rising age both groups of children displayed an increase of overweight which was highly significant in IDM ($P < 0.005$).

SI in childhood was found to be positively correlated to SI at birth ($r = 0.1449$; $P < 0.05$). In addition, BMI in childhood was positively correlated to SI as well as BMI at birth ($r = 0.1582$ and $r = 0.1625$, respectively; both values $P < 0.02$). Children who were large for gestational age at birth (LGA) displayed overweight in childhood in a significantly higher frequency than those who were appropriate for their gestational age ($P < 0.05$; Table 4).

Table 2 Frequencies of overweight (SI > 1.1) and obesity (SI > 1.2) using the symmetry index in infants of mothers with gestational diabetes (IGDM) and those born to mothers with long-term insulin-dependent diabetes (IDM) 1–4 y of age as compared to 5–9 y of age

		IGDM (n)	*IDM (n)*
Overweight:	1–4 y of age	30.9% (13/42)	23.2% (29/125)
	5–9 y of age	26.6% (4/15)	35.5% (11/31)
Obesity:	1–4 y of age	9.5% (4/42)	11.2% (14/125)
	5–9 y of age	13.3% (2/15)	25.8% (8/31)*

n = number of cases; * $p < 0.05$ *vs* 1–4 y of age; chi-square-test.

Table 3 Frequencies of overweight (BMI ≥ 95th percentile) using the body mass index in infants of mothers with gestational diabetes (IGDM) and those born to mothers with long-term insulin-dependent diabetes (IDM) 1–4 y of age as compared to 5–9 y of age

	IGDM (n)	*IDM (n)*
1–4 y of age	14.3% (6/42)	6.4% (8/125)
5–9 y of age	20.0% (3/15)	25.8% (8/31)*

n = number of cases; * $P < 0.005$ *vs* 1–4 y of age; chi-square-test.

Table 4 Frequencies of overweight and obesity in 1–9 y old children of diabetic mothers (IGDM and IDM) who were small for gestational age (SGA), appropriate for gestational age (AGA) or large for their gestational age (LGA)

	SGA (n)	*AGA (n)*	*LGA (n)*
Overweight (SI > 1.1)	26.7% (4/15)	25.8% (33/128)	45.7% (16/35)*
Obesity (SI > 1.2)	6.7% (1/15)	12.5% (16/128)	22.9% (8/35)

SI = symmetry index; n = number of cases; * $p < 0.05$ *vs* AGA: chi-square-test.

Discussion

The results of this study show that children of mothers with diabetes during pregnancy develop high frequencies of overweight and obesity throughout childhood. Interestingly, no significant differences were found between children of mothers with pregestational insulin-dependent diabetes (IDM) and those born to gestational diabetic mothers (IGDM). Furthermore, development of overweight seems to be related to the metabolic and anthropometric situation at birth.

Table 1 Neonatal parameters in infants of gestational diabetic mothers (IGDM) as compared to infants of long-term insulin-dependent diabetic mothers (IDM)

	IGDM (n)	*IDM (n)*
Birth weight (g)	3500.8 ± 50.8 (117)	3443.5 ± 45.5 (200)
Birth length (cm)	51.5 ± 0.22 (117)	50.9 ± 0.22 (200)
Symmetry index (SI)	1.05 ± 0.01 (117)	1.05 ± 0.01 (200)
Small-for-gestational-age (SGA)	5.1% (6/117)	8.5% (17/200)
Appropriate-for-gestational-age (AGA)	67.5% (79/117)	65.0% (130/200)
Large-for-gestational-age (LGA)	27.3% (32/117)	26.5% (53/200)
Plasma insulin (μIU/ml)**	40.3 ± 5.47 (60)	78.1 ± 5.95 (85)
Interscapular skinfold (mm)*	7.08 ± 0.31 (38)	8.10 ± 0.31 (59)
Overweight (SI > 1.1)	29.0% (34/117)	31.0% (62/200)
Obesity (SI > 1.2)*	7.7% (9/117)	16.0% (32/200)

Values are expressed as means ± s.e.m.; n = number of cases; IGDM *vs* IDM.
* $P < 0.05$; ** $P < 0.001$; unpaired t-test.

While both groups of newborns displayed mean birth weights within a normal range the relative birth weight was increased indicating a tendency towards overweight. Plasma insulin values were found to be elevated in both groups of neonates: In newborns of healthy, non-diabetic mothers plasma insulin ranges from 6.4[20] to maximum 27.2 μIU/ml.[21] Since Pedersen's fundamental work[22] it is known that an increase of insulin results from stimulation of the fetal pancreatic beta cells induced by maternal hyperglycaemia, thereby leading to increased body weight and body fat in the newborn. IDM had significantly higher insulin values than IGDM, possibly due to a more pronounced and/or prolonged maternal hyperglycaemia in pregnant long-term diabetic women. Consequently, obesity was found to appear significantly more frequent in newborn IDM. This was associated with a higher thickness of interscapular skinfold in IDM, underlining the greater accumulation of fat in this group. The relationship between neonatal plasma insulin and relative body weight is supported by a positive correlation between SI and insulin in our study. Neonatal insulin is known to be positively correlated to histological fat cell parameters in newborns of diabetic mothers.[23]

Although very specific methods for the determination of obesity were developed during the past years, for practical purposes Berenson *et al.*[4] suggested that obesity in children should be estimated by measuring weight, height and skinfold thicknesses. The symmetry index (SI) established by Farquhar[11] was supposed to have advantages in estimating overweight in childhood. Because it is linked to age- and sex-specific values of a standard population, data of children of different ages can be combined for analysis. A number of investigators used the SI or a variant of this measure to estimate overweight in children.[8,9,15] Weight/height-ratios are known to be good predictors of body fat.[24] In Europe, the use of weight/height-ratio is recommended for estimation of obesity in childhood.[25] In a variety of studies, cutoff values of 110% and 120% of relative weight were used to define childhood overweight and obesity, respectively.[2,14–17]

However, to improve validity and comparability of our data, frequencies of overweight were calculated by means of BMI too. BMI is significantly correlated to body fat in childhood.[26] According to official recommendations by Himes *et al.*[18] 95th percentile was used as cutoff value indicating overweight. Choice of appropriate reference percentiles was complicated by the fact that no BMI percentiles for German children are available while BMI data published for other European populations in childhood[27,28] do not provide 95th percentile values. Therefore, the percentiles for white caucasian children published by Hammer *et al.*[19] were chosen which provide 95th percentile values for infants of all ages, while 50th percentiles are very similar to those in the European studies[27,28] and 10th as well as 90th percentiles are also in very good accordance.[19,28]

Table 5 Prevalences of childhood overweight in European populations

Country (Ref.)	*Age (years)*	*Method*	*Prevalence*
Great Britain[2]	7	Relative weight > 120%	2.0–6.3%
Netherlands[29]	0–17	BMI > 95th percentile	0.5–10%
Finland[30]	6–9	BMI > 90th percentile	5–7%
Germany[17]	11–13	Relative weight > 120%	4–6%
Italy[14]	4–8	Relative weight > 110%	2–13%

BMI = body mass index; Ref. = reference.

Most actual prevalences of childhood overweight in European populations are presented in Table 5, indicating that overweight occurs in 0.5 to maximum 13% of children and adolescents in Europe. According to official data of the German Society of Nutrition 4–6% of children and adolescents in Germany are considered to be overweight.[17] With regard to these data, it seems obvious that in IDM as well as in IGDM frequencies of overweight and obesity were markedly elevated. About every 5th child of an insulin-dependent or gestational diabetic mother developed overweight until the age of 9 y. Frequencies of increased body weight remained high during the whole observation period with a significant increase of the prevalence of obesity found in IDM. Generally, frequencies of overweight assessed by BMI $\geq$ 95th percentile were lower than those calculated by means of SI > 1.1. On the other hand, they were similar to those estimated by SI > 1.2. This finding is in accordance with reports of other investigators.[14,30] It should be stressed that 95th percentile represents a cutoff value with high specificity but low sensitivity,[18] possibly leading to underestimation of minor degrees of obesity. Nevertheless, analysis of our data by means of BMI as a second independent method, using a different reference population, confirmed an increase of frequencies of overweight with rising age in infants of diabetic mothers. These observations are in good accordance with those reported by Silverman *et al.*[9] and Gerlini *et al.*[8]

Indicating a persistence of increased body weight from birth to later life we observed positive correlations between SI and BMI at birth and SI and BMI in childhood, respectively. Verdy *et al.*[31] reported that overweight newborns of diabetic mothers are at increased risk to be overweight in adulthood too. With regard to observations of Barker *et al.*[32] we were not able to find any evidence that small-for-gestational-age newborns are at increased risk to develop obesity already in childhood. Nevertheless, our findings might represent specific features of infants of diabetic mothers.

To estimate the influence of parental anthropometrics, we also looked for possible associations to maternal or paternal BMI. No significant correlations were found between relative weights of the parents and birth weight, birth length, SI at birth and SI in childhood. From the absence of positive parent-child-correlations it might be suggested that in this special population of infants of diabetic mothers epigenetic factors like the hyperglycaemic and, consequently, hyperinsulinaemic intrauterine environment may determine the child's weight to a higher degree than hereditary factors do. However, contrary results were found by Silverman *et al.*[9] who described a positive correlation between child's SI and body weight of its diabetic mother, indicating that this question needs further investigation. In this context, it should be mentioned that due to the retrospective design of our study, some parameters, particularly of the parents, were available in a proportion of the sample only and theoretically the possibility of bias resulting from this cannot be clearly excluded. Therefore, it is emphasized that no selection of children attending the study took place and incompleteness of some parameters was accidental.

Pathophysiological mechanisms responsible for the development of obesity in infants of diabetic mothers still remain unclear. Dörner[33] found that, in terms of a 'functional teratogenesis', unphysiological levels of hormones during critical periods of fetal and neonatal development could be responsible for later development of chronic diseases. Freinkel[34] suggested that by 'fuel mediated teratogenesis' abnormal concentrations of maternal fuels, like glucose and amino acids, may influence fetal development leading to increased morbidity in later life. In animal experiments hyperinsulinism during fetal and neonatal development was shown to play a key role in the pathogenesis of obesity.[6] On the other hand, recent research on the nature and possible sides of action of the ob/ob-coded protein leptin has focused further attention on hypothalamic structures well-known to be involved into the regulation of body weight and feeding.[35,36] Interestingly enough, studies of our group have shown that a temporary intrahypothalamic hyperinsulinism during brain development can induce increased weight gain and marked obesity in juvenile and adult age in rats.[37,38] Although it remains hard to draw conclusions from these animal models, it seems possible that alterations of the intrauterine environment and, consecutively, altered concentrations of fetal hormones and/or metabolic substrates may influence the differentiation and maturation of central nervous regulators and thereby could lead to a kind of 'malprogramming' of neuro-endocrine systems of metabolism and body weight control. This concept agrees with observations in the Pima Indian study which suggest that obesity is more likely to develop in offspring of gestational diabetic women than in offspring of nondiabetic or prediabetic women, namely women who developed diabetes only after the pregnancy.[7]

Obesity in childhood is known to be a health problem with enormous physical and psychological consequences in a large number of children and adolescents.[39] From this point of view it is necessary to try to prevent all conditions that are known to lead to overweight or obesity in childhood.

Conclusions

A general glucose intolerance screening during pregnancy and, consecutively, special health care for all pregnant diabetics, namely long-term as well as gestational diabetics, are recommended to avoid, or at least to reduce, the risk of increased morbidity in their newborns and children by primary prevention.[33,34,38] Moreover, it seems necessary to pay special attention on later development of children born to mothers with diabetes during pregnancy, for example by regular physical examinations, to reduce the risk of development of overweight and associated metabolic and cardiovascular disturbances.

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