

Intrauterine Adiposity and BMI in 4- to 5-Year-Old Offspring from Diabetic Pregnancies

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Key Words

Maternal diabetes · Fetal growth · Fetal head-to-abdominal circumference ratio · Postnatal growth

Abstract

Background: Pregnancies complicated by maternal diabetes are associated with disproportionate intrauterine growth that subsequently may lead to pediatric adiposity. **Objectives:** We investigated whether disproportionate intrauterine growth leads to differences in BMI in 4- to 5-year-old offspring from pregnancies complicated by type 1 (ODM1), type 2 (ODM2), or gestational diabetes (OGDM). **Methods:** Ultrasound data of fetal head-to-abdominal circumference (HC/AC) ratio obtained between 32 and 36 weeks of gestational age were related to offspring anthropometrics that were retrieved from infant welfare centers. **Results:** Data from 27 ODM1, 22 ODM2, and 24 OGDM were obtained. Ultrasound measurements for the HC/AC ratio were performed at a mean of 33–34 weeks, with a mean Z-score of the HC/AC ratio of –0.801, –0.879, and 0.017 in ODM1, ODM2, and OGDM. Mean BMI SDS was highest in ODM2 as compared to ODM1 and OGDM. In ODM1 there was a negative correlation between HC/AC ratio and BMI SDS at the ages of 4 and 5 years, but not in ODM2 or OGDM. The birth weight Z-score

was positively correlated to BMI SDS in ODM2 and OGDM. **Conclusion:** Disproportionate intrauterine growth, expressed as the HC/AC ratio, was inversely related with BMI SDS in ODM1 at the ages of 4–5 years, but not in ODM2 or OGDM. Weight and maybe obesity in ODM1 offspring are likely to be related to intrauterine adiposity, whereas overweight in ODM2 and OGDM offspring seems more related to other factors such as birth weight centile, maternal obesity, and altered lifestyle factors during childhood.

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Maternal diabetes is linked to short-term consequences for offspring with a birth weight distribution shifted to the right, a high mean birth weight Z-score, and increased incidence of macrosomia [1–3], as well as higher risks for assisted vaginal delivery and caesarean section [2]. As children, adolescents and adults, offspring from women with diabetes are at risk for obesity, type 2 diabetes, and the metabolic syndrome [4–10]. The fuel-mediated teratogenesis described by Pedersen and later extended by Freinkel [11] states that maternal hyperglycemia leads to increased transplacental transfer of glucose, lipids, and amino acids which in turn lead to fetal hyperinsulinism and increased growth. Maternal insulin itself does not cross the placenta.

The effect of maternal metabolic abnormalities is reflected in wide-ranging changes in fetal islets, fat stores, and muscles, and perhaps even changes in habitus [11]. This cascade, set off by an abnormal intrauterine environment, may lead to changes in offspring phenotype [12]. Intrauterine overnutrition programs adaptations of the fetal metabolism in order to cope with enriched intrauterine nutrients, which might echo into postnatal life and result in an increased risk for pediatric adiposity [12].

Not all tissues are sensitive to the effect of fetal hyperinsulinism. Insulin stimulates growth of subcutaneous fat depots, but has no effect on the growth of the brain and skull. Fetal hyperinsulinism and disproportionate growth may therefore be reflected in utero by a lower head-to-abdominal circumference (HC/AC) ratio, even in neonates with a normal birth weight [13–15]. To the best of our knowledge, there are no studies in which measures of intrauterine adiposity have been related to childhood BMI.

We explored whether disproportionate intrauterine growth, expressed as the HC/AC ratio, is associated with a higher childhood BMI in 4- to 5-year-old offspring from women with type 1 (ODM1), type 2 (ODM2), or gestational diabetes (OGDM). Additionally, we analyzed whether weight at birth is correlated to BMI in these infants.

Methods

Women with a pregnancy complicated by type 1, type 2, or gestational diabetes who delivered in the University Medical Center Utrecht, the Netherlands, between 2000 and 2006 were contacted to participate in a follow-up study regarding offspring growth. Maternal characteristics at pregnancy and pregnancy outcomes were retrieved from records of the University Medical Center Utrecht. None of the women with type 1 diabetes mellitus were diagnosed with microangiopathy. Two women in this group had hypertension. Gestational diabetes was diagnosed using a 75-gram oral glucose tolerance test in 22 cases (92%); the other patients were diagnosed through elevated fasting glucose levels or an abnormal glucose profile. The Medical Ethics Committee of the University Medical Center approved this study.

Ultrasound data on head circumference (HC) and abdominal circumference (AC) between 32 and 36 weeks of gestation were retrieved from the patient records. When 2 measurements were available, the mean was calculated. HC/AC ratio was calculated by dividing the absolute HC in mm by AC in mm, and the Z-score for HC/AC ratio was calculated as follows: (HC/AC ratio minus mean HC/AC ratio for gestational age) divided by Z-score HC/AC ratio for gestational age [16].

Offspring height and weight were retrieved from infant welfare records after parental informed consent was received. Overweight and obesity were calculated based on the International Obesity Task Force (IOTF) cutoff values [17]. BMI SDS was calculated based on national age- and gender-specific data [18].

For comparisons between data of ODM1, ODM2, or OGDM, the χ^2 test was used to compare categorical variables; for continuous variables, the Student t test was used with normally distributed parameters and the Mann-Whitney U test was used with skewed parameters. Data were analyzed using IBM® SPSS Statistics version 23.0 for Mac.

Results

Between 2000 and 2006, 27 ODM1, 22 ODM2, and 24 OGDM were analyzed. Maternal and offspring characteristics are shown in table 1. Preconceptional maternal BMI was highest in women with type 2 diabetes mellitus, followed by gestational diabetes and type 1 diabetes with a mean BMI of 31.9, 27.7, and 24.8, respectively ($p < 0.001$). All women with type 1 and type 2 diabetes were treated with insulin during pregnancy, as well as 50% of women with gestational diabetes. Mean HbA_{1c} levels during pregnancy were below 6.6%, which is slightly higher than the normal mean in pregnancy of 4.7–6.3%, and there were no statistically significant differences between the groups [19]. Third trimester fetal measurements were performed at a mean of 33–34 gestational weeks with the lowest Z-score for the HC/AC ratio in ODM2, followed by ODM1 and OGDM ($p < 0.001$). Mean birth weight was comparable between the three groups. One third to 50% of the infants were large for gestational age at birth, with the highest incidence in ODM1 (n.s.).

At the age of 4–5 years, the percentage of overweight (including obesity) was highest in ODM2, followed by OGDM and lowest in ODM1 (36, 17, and 7%, respectively; $p < 0.05$). None of the ODM1 was obese at these ages, whereas 18% of ODM2 and 4% of OGDM were obese ($p < 0.05$). Mean BMI SDS was also highest in ODM2 as compared to ODM1 and OGDM, although differences between groups were only significant at the age of 4 years (table 2). The difference was numerically similar at the age of 5 years, but small groups precluded statistical significance.

Offspring BMI in Relation to the Fetal HC/AC Ratio

The correlation between BMI SDS at 4–5 years and intrauterine HC/AC ratio is shown in figure 1a. In this figure, a single BMI SDS is presented for each child with BMI SDS at either 4 or 5 years of age. In ODM1 there was an inverse correlation between the HC/AC ratio and BMI SDS ($r = -0.46$; $p = 0.02$; table 2; fig. 1a); in other words, the higher the AC in relation to the HC, the higher the BMI SDS. No such association was found in ODM2 or in OGDM.

Table 1. Characteristics of study population

	ODM1 (n = 27)	ODM2 (n = 22)	OGDM (n = 24)	p
Maternal characteristics				
Pregestational BMI	24.8±4.2	31.9±7.3	27.7±5.2	<0.001
Age at delivery, years	34±3.7	34±4.8	34±5.7	n.s.
Primiparous	13 (48)	4 (18)	10 (42)	<0.05
Preconceptional A _{1C} , %	7.1±0.88	6.6±0.55	N/A	n.s.
Pregnancy A _{1C} , %	6.6±0.98	6.1±0.74	5.9±0.82	n.s.
Insulin use in pregnancy	27 (100)	22 (100)	12 (50)	<0.001
Preeclampsia	3 (11)	1 (4.5)	2 (8)	n.s.
Caesarean section	18 (67)	4 (18)	11 (46)	<0.05
Offspring characteristics				
Gestational age HC/AC ratio, weeks	34±1.0	33±1.7	34±1.6	n.s.
Mean HC/AC ratio	0.989±0.08	0.990±0.04	1.023±0.06	n.s.
Z-score HC/AC ratio	-0.801±1.21	-0.879±0.56	0.017±0.06	<0.001
Gestational age at delivery, weeks	37±1.3	38±1.7	39±2.0	<0.05
Female gender	13 (48)	11 (50)	13 (54)	n.s.
Birth weight, g	3,506±556	3,701±509	3,582±576	n.s.
Large for gestational age	13 (48)	9 (41)	8 (33)	n.s.
Overweight (including obesity) at 4–5 years	2 (7)	8 (36)	4 (17)	<0.05
Obese at 4–5 years	0	4 (18.2)	1 (4.2)	<0.05

Values represent means ± SD or n (%).

Table 2. BMI SDS and correlations with fetal HC/AC and birth weight Z-score

	ODM1 (n = 27)	n	p	ODM2 (n = 22)	n	p	OGDM (n = 24)	n	p
BMI SDS at age 4 years	0.15±0.8	27		1.12±1.6	22		0.37±0.2	21	0.03
BMI SDS at age 5 years	0.07±1.6	3		2.19±2.2	8		0.87±1.1	7	0.19
Correlations									
BMI SDS at ages 4–5 years × HC/AC ratio	-0.46		<i>0.02</i>	0.07		<i>0.74</i>	-0.25		<i>0.24</i>
BMI SDS at ages 4–5 years × BW Z-score	0.29		<i>0.15</i>	0.45		<i>0.04</i>	0.53		<i>0.00</i>

Significant p values are italicized.

The correlation between birth weight Z-score and BMI SDS is shown in figure 1b. The birth weight Z-score was positively correlated to BMI SDS in ODM2 ($r = 0.45$; $p = 0.04$) and OGDM ($r = 0.53$; $p < 0.01$; table 2; fig. 1b), but was not significant for ODM1 ($r = 0.29$, n.s.).

Discussion

We found that disproportionate intrauterine growth, expressed as the HC/AC ratio, was inversely related to BMI SDS in ODM1 at the ages of 4 and 5 years, but not

in ODM2 or OGDM. This suggests that offspring BMI in ODM1 partly has its origins in intrauterine programming, expressed as fetal abdominal adiposity [20]. In contrast, we found no evidence that disproportionate fetal growth in ODM2 and OGDM was related to overweight at early childhood. For the latter groups, the birth weight Z-score gave a better prediction of BMI SDS. In these groups, with the highest BMI in the mothers, intrauterine adiposity does not seem to be a risk factor for offspring adiposity, whereas birth weight (centile) is.

Many studies have shown that infants of women with diabetes have an increased rate of overweight/obesity.

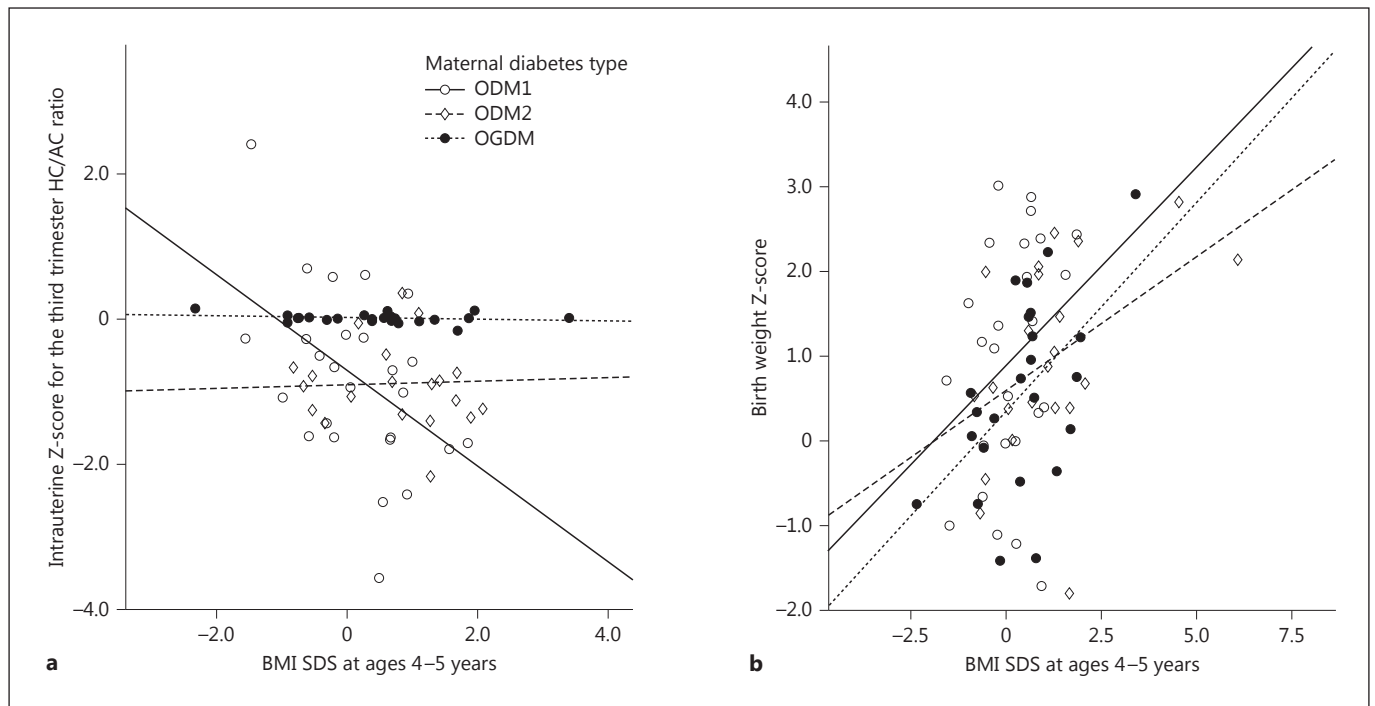


Fig. 1. **a** Scatter plot for intrauterine Z-score for the HC/AC ratio (y-axis) and standard deviation score for BMI for offspring aged 4–5 years in ODM1, ODM2, and OGDM. **b** Scatter plot for birth weight Z-score and SDS for BMI in offspring aged 4–5 years in ODM1, ODM2, and OGDM. The plots show a single measurement per child.

However, when correcting for maternal BMI, most of these associations disappear, suggesting that maternal obesity is the most important factor related to childhood obesity and/or metabolic syndrome [6, 21–23]. In one study that followed infants to age 16 years, it was clearly shown that maternal BMI was the driving factor behind childhood obesity [21]. The presence of maternal gestational diabetes mellitus did not affect outcome, but in combination with maternal obesity it resulted in the highest incidence of overweight in offspring [21]. In other words, maternal obesity seems to be the most important factor, with diabetes being an additional risk factor.

In our study, the highest incidence of being large for gestational age occurred in infants of women with type 1 diabetes, but these infants had the lowest BMI and lowest incidence of overweight at the age of 4–5 years. The highest BMI was found in offspring of women with type 2 diabetes who themselves had by far the highest BMI. These data strengthen the concept that maternal BMI is probably the most important factor affecting overweight/obesity in offspring. The relation between HC/AC ratio

and childhood overweight in women with type 1 diabetes may well show the additional effect of abnormal fetal growth in women with a normal BMI, an effect that might have been overruled by other maternal factors in case of overweight in women with type 2 diabetes or gestational diabetes mellitus.

Childhood obesity may also be related by other factors during the first years of life such as lifestyle, but unfortunately there are no studies investigating lifestyle and eating habits in nurturing of offspring of women with diabetes.

In conclusion, we found that disproportional fetal growth as a consequence to fetal hyperinsulinism was related to the BMI in 4- to 5-year-old infants of women with type 1 diabetes, which suggests an effect of an abnormal intrauterine environment on later outcome. This relation was absent in offspring of women with type 2 diabetes or gestational diabetes mellitus, indicating that other factors such as maternal obesity may have played a more important role. Larger studies are necessary to validate our findings.

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Author's Contributions

N.M.H. wrote the manuscript and researched data, H.V. and G.V. reviewed/edited the manuscript and contributed to discussion, and D.B. contributed to discussion.

Statement of Ethics

The ethical approval was granted by the Medical Ethics Committee at the University Medical Center, Utrecht in the Netherlands (application No. 13/179, reference No. WAG/om/13/053639) on April 9, 2013.

Disclosure Statements

The authors have nothing to disclose.

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