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ORIGINAL ARTICLE

# Assessment of selected carbohydrate parameters in children exposed to gestational diabetes *in utero*

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**Abstract**

**OBJECTIVES:** The study was undertaken to assess the selected carbohydrate parameters in children exposed to gestational diabetes *in utero*.

**METHODS:** 50 children exposed to gestational diabetes were compared with 46 control subjects. Anthropometric parameters of a newborn were obtained from the medical records. In all participants height, body mass, waist and hip circumferences were measured; BMI, WHR and WHtR were calculated. Values of fasting glucose, insulin, C-peptide and HbA1c were measured and HOMA2-IR, HOMA2-S, HOMA2-B were calculated. In obese children (BMI ≥95th percentile) OGTT was performed.

**RESULTS:** The prevalence of overweight/obesity in the study group was 38%, in the control group 41% ($p$=0.19). Higher fasting glucose level ($p$=0.02) and HbA1c ($p$=0.00004) were found in the study group comparing to the control. In children exposed to GDM *in utero* a positive correlation of fasting insulin and WHR (Rs=0.31, $p$=0.028) as well as significantly lower HOMA2-B ($p$=0.03) were observed. In the study group higher HOMA2-IR ($p$=0.0002) and HOMA2-B ($p$=0.0000039) and also lower HOMA2-S ($p$=0.0002) were observed among participants with overweight/obesity comparing to children with normal body weight. In the study group a correlation of HOMA2-IR and SD of the birth weight was found (Rs=0.28, $p$=0.049).

**CONCLUSIONS:** Children exposed to gestational diabetes *in utero*, in spite of similar prevalence of overweight/obesity comparing to their non-exposed peers, could have higher risk of glucose intolerance and diabetes mellitus in future. Towards observed decreased insulin sensitivity and compensatory increase in insulin secretion, prevention of overweight and obesity in this group seems to be essential.

Abbreviations:
BMI - body mass index
DI - disposition index
GDM - gestational diabetes mellitus
HbA1c - glycosylated hemoglobin A1c
HOMA2-B - homeostasis model assessment – β-cell function
HOMA2-IR - homeostasis model assessment – insulin resistance
HOMA2-S - homeostasis model assessment – insulin sensitivity
IADPSG - International Association of Diabetes and Pregnancy Study Groups
IFG - impaired fasting glucose
IGT - impaired glucose tolerance
OGTT - oral glucose tolerance test
Rs - Spearman's rank correlation coefficient
SD - standard deviation
WHR - waist-to-hip ratio
WHtR - waist-to-height ratio

## INTRODUCTION

Many studies show the relationship of the intrauterine development and the risk of chronic diseases in the future. There is growing number of evidence that abnormal fetal growth is related with increased risk of cardiovascular disease (hypertension, coronary heart disease), metabolic complications (hyperlipidemia, hypercortisolemia, obesity, glucose intolerance, insulin resistance, type 2 diabetes mellitus), chronic obstructive pulmonary disease and fertility disturbances (Rinaudo & Wang, 2012; Warner & Ozanne, 2010).

The diabetic intrauterine milieu has a great impact on developing fetus. The fluctuations of glucose levels in the mother with gestational diabetes mellitus and fetal insulin secretion as a response, requires constant metabolic adaptation of the fetus to the current placental nutrient transport. This *fetal programming* caused by GDM may have long-lasting effect and predispose to obesity, glucose intolerance and diabetes in the offspring (Plagemann, 2005; Silverman *et al.* 1995).

The epidemiological studies of children exposed to maternal diabetes *in utero* showed the correlation of increased birth weight with the occurrence of overweight and obesity in the future, in contrast to children with increased birth weight but from non-diabetic pregnancies (Dabelea & Petit, 2001). Moreover, children exposed to GDM *in utero* have higher risk of glucose homeostasis disturbances. Glucose intolerance is more common in the offspring exposed to diabetes *in utero* comparing to their unexposed siblings, what proves the significant influence of intrauterine milieu on the risk of disorders of carbohydrate homeostasis, regardless of genetic factors (Silverman *et al.* 1995). The predisposition to glucose intolerance may be independent from the type of diabetes in pregnancy; however, strongly correlates with mother's hyperglycemia (Silverman *et al.* 1998).

The aim of this study was to assess the selected carbohydrate parameters in children exposed to gestational diabetes mellitus *in utero*.

## MATERIAL AND METHODS

The study was conducted in a cohort of 96 children. The study group consisted of 50 patients, 7–15 years of age (mean 10.8±2.13), 22 girls (44%) and 28 boys (56%), exposed to gestational diabetes mellitus *in utero*. The control group comprised 46 healthy children, 7–16 years of age (mean 10.8±3.03), 21 girls (45.65%) and 25 boys (54.35%) from non-diabetic pregnancies. The participants were admitted to the Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age of the Pomeranian Medical University of Szczecin, Poland.

Data including the course of pregnancy (also GDM treatment), anthropometric parameters and status of a newborn, dietary habits in the first year of life and family history for diabetes mellitus were obtained from the interview and medical records. Pediatric physical examination with Tanner assessment of pubertal development was conducted. In all children height, body weight, waist and hip circumferences were measured. Body mass index (BMI), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated. The overweight/obesity was diagnosed if child's BMI was at 85$^{th}$ percentile or higher. The anthropometric characteristic of the participants is presented in Tables 1–2. In all children values of fasting glucose, insulin, C-peptide and glycosylated hemoglobin (HbA1c) were measured. In obese participants (BMI ≥95th percentile) the oral glucose tolerance test (OGTT) was performed. The following parameters were calculated using the homeostasis model assessment (HOMA2) calculator, version 2.2.3.: insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2-S), which is the opposite of insulin resistance, and β-cell function (HOMA2-B).

### *Statistical methods*

The Mann-Whitney test was used to compare measurable variables between the groups. Correlations between measurable variables within each group were analyzed by Spearman's rank correlation coefficient (Rs). The threshold $p$-value for statistical significance was set at $p<0.05$. The analysis was performed using the Statistica 10.

## RESULTS

The prevalence of overweight/obesity in the study group was 38%, in the control group 41% ($p$=0.19). Fasting plasma glucose, fasting insulin level, C-peptide and HbA1c values were measured in all subjects. OGTT was conducted in 20 children (13 from the study group and 7 from the control). The values of HOMA2-IR, HOMA2-S and HOMA2-B were determined (1 person from the control group was excluded from the analysis because of fasting hypoglycemia). The results are presented in Tables 3–6.

Impaired fasting glucose was observed in 2 (4%) patients from the study group and 1 (2%) from the con-

**Tab. 1.** Anthropometric characteristic of study participants.

| Feature | Study group (n=50) | | Control group (n=46) | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| Height SD | 0.28±1.11 | 0.28 (–1.84±2.02) | 0.81±1.03 | 0.73 (–1.49±3.64) | 0.02 |
| Body mass SD | 1.36±2.28 | 1.03 (–2.35±6.88) | 1.67±1.94 | 1.66 (–2.35±6.05) | NS |
| BMI SD | 1.53±2.48 | 1.22 (–2.59±7.02) | 1.48±2.11 | 1.02 (–2±6) | NS |
| Waist circumference SD | 2.29±2.52 | 1.72 (–2±7.13) | 1.93±2.02 | 1.54 (–1.55±6.15) | NS |
| Hip circumference SD | 0.86±1.81 | 0.60 (–3.01±4.84) | 0.88±1.56 | 0.92 (–2.54±4.18) | NS |

**Tab. 2.** Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) of study participants.

| Feature | Study group (n=50) | | Control group (n=46) | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| WHR | 0.89±0.06 | 0.89 (0.77–1.04) | 0.86±0.06 | 0.86 (0.72–1.02) | NS |
| WHtR | 0.48±0.07 | 0.48 (0.36–0.64) | 0.47±0.06 | 0.45 (0.36–0.62) | NS |

**Tab. 3.** Mean glucose concentration of study participants.

| Glycemia | Study group | | Control group | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| Fasting [mg/dL] | n=50 | | n=46 | | |
| | 88±6.38 | 88 (72–101) | 82±10.77 | 84.5 (50–107) | 0.02 |
| 60th minute of OGTT [mg/dL] | n=13 | | n=7 | | |
| | 127±23.90 | 118 (99–185) | 132±29.50 | 130 (87–132) | NS |
| 120th minute of OGTT [mg/dL] | n=13 | | n=7 | | |
| | 112±18.26 | 108 (84–157) | 111±25.50 | 100 (94–165) | NS |

**Tab. 4.** Mean insulin concentration of study participants.

| Insulin | Study group | | Control group | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| Fasting [mg/dL] | n=50 | | n=46 | | |
| | 12.47±10.26 | 9.98 (1.48–65.23) | 11.66±7.20 | 8.71 (3.26–32.8) | NS |
| 60th minute of OGTT [mg/dL] | n=13 | | n=7 | | |
| | 145.29±92.69 | 97.38 (27.81–321.2) | 143.53±124.25 | 137.8 (28–398.7) | NS |
| 120th minute of OGTT [mg/dL] | n=13 | | n=7 | | |
| | 121.98±108.18 | 98.52 (31.84–439.4) | 108.04±81.27 | 64.3 (29.5–224.1) | NS |

**Tab. 5.** Mean C-peptide concentration and the percentage of HbA1c in the study participants.

| Feature | Study group (n=50) | | Control group (n=46) | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| C-peptide [ng/mL] | 1.98±0.99 | 1.76 (0.7–6.72) | 1.97±0.87 | 1.85 (0.6–4.83) | NS |
| HbA1c [%] | 5.37±0.22 | 5.37 (4.96–5.91) | 5.12±0.26 | 5.11 (4.59–5.62) | 0.000004 |

trol cohort. Impaired glucose tolerance was discovered in 1 (2%) child in the study group and 1 (2%) from the control. Fasting glucose level and percentage of HbA1c were significantly higher in the study group comparing to the control, whereas HOMA2-B was significantly lower. The values of fasting insulin, C-peptide,

HOMA2-IR and HOMA2-S did not significantly differ between the groups.

The relationship of chosen glucose homeostasis parameters and anthropometric parameters was analyzed. The results are presented in the Tables 7–8 and Figures 1–2. In the study group, the higher waist-to-hip ratio, the higher fasting insulin concentration was observed (Rs=0.31, $p$=0.028). In children exposed to GDM HOMA2-IR and HOMA2-B were significantly higher in overweight/obese children comparing to those with BMI below 85$^{th}$ percentile, whereas HOMA2-S was higher in slim participants. In the control group the significant differences in HOMA2-IR, HOMA2-B and HOMA2-S were not observed. In the study group a relationship of HOMA2-IR and birth weight SD was found. There was no significant correlation of birth weight SD and HOMA2-B (R=0.25, $p$=0.08).

**Tab. 6.** Insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2-S) and β-cell function (HOMA2-B) of study participants.

| Feature | Study group (n=50) | | Control group (n=45) | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| HOMA2-IR | 1.44±0.72 | 1.29 (0.5–5.03) | 1.44±0.63 | 1.33 (0.51–3.5) | NS |
| HOMA2-S | 82.01±31.76 | 78 (19.9–201) | 82.93±35.98 | 75.2 (28.6–196) | NS |
| HOMA2-B | 128.81±44.79 | 117.2 (72.9–276.7) | 143.66±42.22 | 138.6 (70.8–245.5) | 0.03 |

* In 1 participant from the control group HOMA2-IR, HOMA2-S, HOMA2-B were not measured because of fasting hypoglycemia (50mg/dL).

**Tab. 7.** Insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2-S) and β-cell function (HOMA2-B) of study participants regarding BMI.

| Feature | BMI <85th percentile | | BMI ≥85th percentile | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min. – max.) | Mean ± SD | Median (min. – max.) | |
| STUDY GROUP | | | | | |
| | n=31 | | n=19 | | |
| HOMA2-IR | 1.17±0.36 | 1.1 (0.5–2.15) | 1.88±0.94 | 1.59 (0.82–5.03) | 0.0002 |
| HOMA2-S | 93.8±30.26 | 91.1 (46.6–201) | 62.79±24.31 | 63 (19.9–122) | 0.0002 |
| HOMA2-B | 107.2±23.79 | 101.5 (72.9–178.4) | 164.03±49.06 | 169.9 (94.3–276.7) | 0.0000039 |
| CONTROL GROUP | | | | | |
| | n=27 | | n=19 | | |
| HOMA2-IR | 1.32±0.66 | 1.11 (0.51–3.5) | 1.58±0.56 | 1.53(0.79–2.82) | NS |
| HOMA2-S | 91.47±40.09 | 90.4 (28.6–196) | 71.2±26.14 | 65.4 (35.5–127.3) | NS |
| HOMA2-B | 136.13±42.44 | 135.2 (70.8–240.1) | 153.9±40.78 | 146.5 (94.5–245.5) | NS |

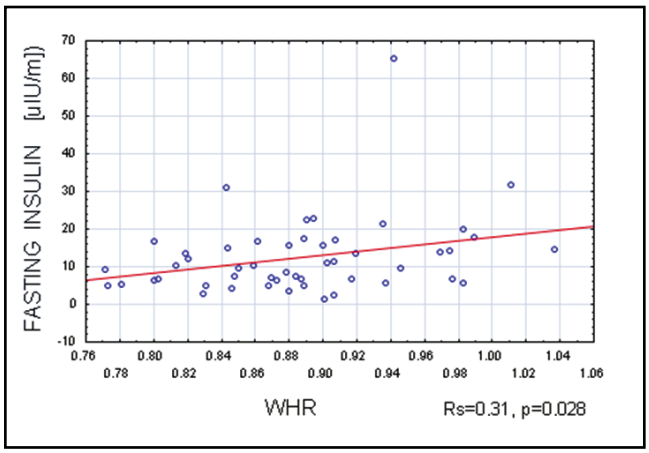


**Fig. 1.** Correlation of mean fasting insulin concentration with waist-to-hip ratio in the study group.

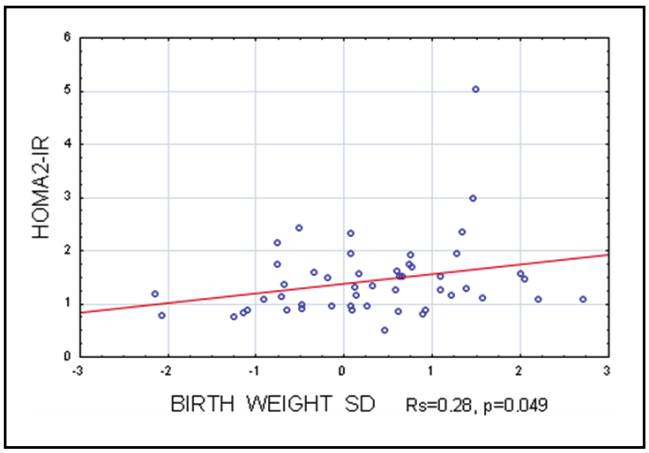


**Fig. 2.** Correlation of insulin resistance (HOMA2-IR) with birth weight SD in the study group.

## DISCUSSION

Gestational diabetes mellitus is one of the most common pregnancy complication. The increasing incidence of GDM, as a consequence of introduction of International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria, is currently widely discussed (Benhalima *et al.* 2012; Helseth *et al.* 2014). Benhalima *et al.* (2012) noted a significant increase of GDM prevalence, from 3.3% to 5.7%, after usage of new criteria. More cases of GDM will cause the growth in the number of children exposed to gestational diabetes *in utero*. Many studies highlight the increased risk of obesity in this group of children (Chandler-Laney *et al.* 2011; Krishnaveni *et al.* 2010; Vaarasmaki *et al.* 2009). Baptiste-Roberts *et al.* (2011) observed that offspring of GDM mothers at the age of 7 had higher body weight, BMI and BMI z-score comparing to their unexposed peers and this effect was independent of the birth weight. However, the direct relationship of gestational diabetes mellitus and future obesity in the offspring has not been confirmed. In our investigation the prevalence of overweight/obesity in the study group was 38%, in the control 41% and the difference was not significant. Similarly, Gillman *et al.* (2003) did not observed increased number of overweight/obese children, 9–14 years of age, born to GDM mothers. No differences in the percentage of overweight/obesity between study and control groups may be the result of effective screening of GDM and appropriate, intensive treatment thanks to approved diagnostic criteria. That improves the mother's metabolic compensation and intrauterine environment for growing fetus, decreasing the risk of i.e. macrosomia and its future consequences. Additionally, the increasing incidence of overweight/obesity in general pediatric population may be responsible for high percentage of children with excessive body weight in the control group and mask the effect of maternal diabetes.

Apart from the risk of obesity in the offspring exposed to gestational diabetes *in utero*, the disturbances of glucose homeostasis in this group are widely discussed. In many studies the higher prevalence of diabetes in children of mothers with carbohydrates intolerance during pregnancy is highlighted (Dabelea *et al.* 2008; Petit *et al.* 1993; Young *et al.* 2002). The increased risk of other than diabetes disturbances in glucose tolerance is also observed (Davis *et al.* 2013, Krishnaveni *et al.* 2005, Plageman *et al.* 1997). In the participants of our study the criteria of diabetes were no fulfilled, however impaired fasting glucose (IFG) was noted in 4% of the study group and 2% of the control. Impaired glucose tolerance (IGT) was diagnosed in the same percentage (2%) in both groups. Hummel *et al.* (2013) observed similar prevalence of IFG and IGT in children of mothers with gestational diabetes (2.56% for both disorders). Comparably to the other authors, in our study the group exposed to GDM had significantly higher fasting glucose level (whereas the fasting insulin level did not differ) than their non-exposed peers (Patel *et al.* 2012).

**Tab. 8.** Correlation of β-cell function (HOMA2-B) and chosen anthropometric parameters of study participants.

| Anthropometric parameter | HOMA2-B | |
|---|---|---|
| | Rs | *p*-value |
| Body mass SD | 0.57 | 0.000016 |
| BMI SD | 0.63 | 0.0000009 |
| Waist circumference SD | 0.65 | 0.0000002 |
| Hip circumference SD | 0.57 | 0.000015 |
| WHtR | 0.59 | 0.000008 |

In presented study the indicators of insulin resistance (HOMA2) were assessed. In children exposed to GDM, comparing to the control group, decreased β-cell function (HOMA2-B) was observed, whereas the insulin resistance (HOMA2-IR) and insulin sensitivity (HOMA2-S) did not differ significantly. Holder *et al.* (2014) compared the insulin secretion in children exposed and unexposed to GDM using disposition index (DI), the product of measures of insulin sensitivity and first-phase insulin secretion. In his study not only worse β-cell function was observed in the offspring of the mothers with gestational diabetes, but the author noted also the progressive decrease of insulin sensitivity in this group. Furthermore, in their follow-up, in 31.1% of children exposed to GDM IGT or diabetes type 2 was diagnosed, in contrast to the control (8.6%) (Holder *et al.* 2014). Interesting outcomes come from the studies on animal models. In the offspring exposed to maternal hyperglycemia *in utero*, in early childhood the insulin secretion is increased (probably as an effect of fetal programming), but subsequently decreases in later developmental periods (Boloker *et al.* 2002; Holemans *et al.* 2003). This lowered insulin secretion may be the result of the autocrine signaling or endoplasmatic reticulum stress response of pancreatic β-cells (Bouche *et al.* 2010; Fonesca *et al.* 2010). In children from pregnancies with GDM, in a case of growth of insulin resistance (during puberty or in obesity) the progressive decline of insulin secretion may significantly increase the risk of glucose intolerance. Additionally, higher percentage of HbA1c in the study group comparing to the control observed by authors, proves the relatively constant increase of blood glucose levels in this children. This may be the result of the decreased pancreatic secretion as well as be the cause of further β-cells destruction.

The insulin sensitivity in the follow-up studies of children from GDM pregnancies is also investigated. Kelstrup *et al.* (2013) reported decreased insulin sensitivity in the offspring exposed to GDM comparing to non-exposed control. Bush *et al.* (2011) analyzed the group of children aged 5–10 and observed the

relationship of glucose level in the pregnant mother and future decreased insulin sensitivity and increased insulin secretion in their offspring, regardless of the fat mass in the child's body composition. The growth of insulin secretion was independent from the insulin sensitivity in that observation, what may suggest that it is not only the compensation of glucose homeostasis abnormalities, but also may be secondary to the programmed *in utero* higher threshold for insulin secretion as a response to intrauterine hyperglycemia.

Our observations confirm the relationship of the child's anthropometric parameters and glucose homeostasis indicators. Overweight/obesity in children exposed to gestational diabetes mellitus seems to intensify the insulin resistance and leads to compensatory increase of insulin secretion. In presented study, in the group of children exposed to GDM, HOMA2-IR and HOMA2-B were significantly higher in overweight/obese subjects comparing to slim participants. It was not observed in the control cohort. Another confirmation of this supposition is the positive correlation of the child's anthropometric parameters (such as expressed in SD: body weight, BMI, waist and hip circumference, but also WHtR) with β-cell function (HOMA2-B). It shows the growth in insulin secretion in conjunction of the increase of mentioned parameters, and the strongest relationship was observed for waist circumference SD and BMI SD. Wroblewska-Seniuk *et al.* (2009) also observed higher BMI and insulin resistance in children from pregnancies with GDM. The positive correlation of fasting insulin level and WHR noted by authors may be the result of the compensatory increase in insulin secretion in overweight/obese children from the study group.

Searching for the relationship between glucose homeostasis indicators and anthropometric parameters of the newborn of the mother with GDM we found the correlation of birth weight SD and HOMA2-IR. The higher the birth weight, the higher insulin resistance at the moment of the investigation was observed. This may also be a potential background for future disturbances in glucose homeostasis in children exposed to gestational diabetes mellitus *in utero* and indicates higher risk of abnormalities in this area in children with higher birth weight (especially with macrosomia) (Boney *et al.* 2005).

This study was conducted in the group of children aged 7 and more what suggests the important role of dietary habits and physical activity in the obesity development, apart from genetic and fetal metabolic factors. Not including mentioned data authors regard as a limitation of this study. Conversely, the strength of presented study is the usage of HbA1c as one of the parameters describing long-term glucose levels in investigated groups. HbA1c is rarely used as a tool for the assessment of blood glucose in children exposed to GDM, it is usually the indicator of the metabolic control in diabetic mother.

## CONCLUSIONS

On the basis of the presented data the following conclusions can be drawn.

Children exposed to gestational diabetes *in utero*, in spite of similar prevalence of overweight/obesity comparing to their non-exposed peers, could have higher risk of glucose intolerance and diabetes mellitus in future.

Towards observed decreased insulin sensitivity and compensatory increase in insulin secretion, prevention of overweight and obesity in this group seems to be essential.

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