

Maternal plasma adipokines and insulin concentrations in relation to fetal biometry in the gestational diabetes

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Abstract

OBJECTIVE: Maternal insulin sensitivity have strong correlation with fetal growth. The dysregulation of adiponectin and leptin is found in insulin resistance. The aim of this study was to determine whether there is an association between ultrasound fetal biometry and the maternal plasma cytokines and insulin concentrations at the beginning of gestational diabetes treatment.

METHODS: 121 women with gestational diabetes diagnosed between 26th and 30th weeks, were included to the study. Plasma levels of adiponectin, leptin, insulin and glucose were quantified with the measurements and percentiles of the biparietal diameter, head circumference and abdominal circumference, estimated fetal weight and the actual birthweight.

RESULTS: Associations between both of the adipokines and fetal biometry measurements were not evident. There were also no differences in their serum concentrations between groups of women with and without accelerated fetal growth. Adiponectin negatively correlated with pre-pregnancy BMI ($r=-0.366$, $p=0.01$). Leptin positively correlated with pre-pregnancy BMI ($r=0.42$, $p=0.002$), fasting insulin ($r=0.51$, $p=0.0006$) and HOMA-IR ($r=0.43$, $p=0.005$). No association was found between adiponectin, leptin, fasting insulin, HOMA-IR and neonatal birth weight or birth percentile.

CONCLUSION: The results of this study imply that adiponectin, leptin and insulin maternal plasma concentrations in the third trimester do not have influence on fetal growth in gestational diabetes.

Abbreviations:

AC	- abdominal circumference	GCT	- glucose challenge test
AGA	- appropriate for gestational age	GDM	- gestational diabetes mellitus
BMI	- body mass index	HOMA-IR	- homeostasis model assessment - insulin resistance
BPD	- biparietal diameter	IUGR	- intrauterine growth restriction
ECLIA	- electrochemiluminescence immunoassay	OGTT	- oral glucose tolerance test
EFW	- estimated fetal weight	SGA	- small for gestational age
FL	- femur length	TNF α	- tumor necrosis factor alpha

INTRODUCTION

Gestational diabetes mellitus (GDM), affecting up to 10% of pregnancies has been a multidisciplinary point of interest for years (Gabbe 1986), and incidence of macrosomia among diabetes-affected pregnancies still remains an issue to address for many clinicians. It increases the incidence of adverse pregnancy outcomes and has significant influence on mother's and child's wellbeing. Even in developed countries, avoiding GDM and macrosomia – related perinatal complications have proved to be difficult (Kapoor *et al.* 2007). It's been also postulated that women with GDM are more likely to develop diabetes in the future, and fetal endocrine disturbances may result in increased risk of metabolic disorders in childhood, like hiperlipidaemia and obesity (Catalano 2003). Gestational diabetes is an effect of impaired insulin sensitivity and hyperinsulinaemia, and understanding pathophysiologic changes of insulin target tissues, is ever so important. Among the pregnancy – related metabolic changes set to facilitate dynamically changing energy needs of the growing fetus and placenta, adipogenesis and adipolysis are regarded the most relevant ones. Major influence on the adipogenesis has the carbohydrates utilization, mostly regulated by insulin and adipocyte-derived cytokines (adipokines), which interfere with insulin effects (Greenberg & McDaniel 2002). Recent studies suggest that some of the adipokines may promote insulin's actions (adiponectin) while the others antagonise it (TNF α , IL-6, leptin). The aim of this study was to investigate associations between maternal plasma insulin and adipocytokines (adiponectin and leptin) concentrations and fetal biometry in early third trimester of GDM – affected pregnancies, what may indicate their influence on fetal growth during this time.

MATERIAL AND METHODS

121 women with singleton pregnancy, who were referred to Gestational Diabetes Outpatient's Clinic following GDM diagnosis were enrolled in the study. The study was approved by Ethical Committee of Warsaw Medical University and all the patients consented prior to enrollment.

GDM diagnosis was established in keeping with current Polish Gynaecology Association guidelines and based on: 1) screening fasting glucose measurements in first trimester (two results of 126 mg/dl or above indicating diabetes), 2) 50 g glucose challenge test (GCT) and 75 g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. 200 mg/dl in GCT or at least one of the following results in OGTT were consistent with diabetes diagnosis: fasting glucose greater than or equal 100 mg/dl, 1-hour glucose of 180 mg/dl or above and 2-hour glucose of 140 mg/dl or above. For cases with first trimester glucose measurements between 100–125 mg/dl and GCT 1-hour glycaemia of

140–199 mg/dl OGTT was performed to establish or exclude GDM diagnosis. Venous blood samples were used for glucose levels evaluation.

Fasting blood samples were obtained and fetal ultrasound performed between 26 and 30 weeks of gestation either while hospitalized for further tests or as a part of routine outpatient's visit. Blood was centrifuged and partially used for immediate glucose and insulin measurements. The rest of the serum was frozen at -70°C for further measurements (adipokines). ALOKA ultrasound system was used for obstetric ultrasound that included fetal biometry (bi-parietal diameter (BPD), femur length (FL), abdominal circumference (AC), estimated fetal weight (EFW)). Adiponectin and leptin concentrations were measured by ELISA kits: Human Adiponectin/Acrp30 and Human Leptin Quantikine Kit (RnD Systems, Minneapolis, USA). For insulin assessment electrochemiluminescence immunoassay (ECLIA) kit and Elecsys Systems analyzer (Roche) was used. Insulin resistance was expressed by HOMA –IR score: $\text{HOMA-IR} = \text{fasting glucose [mmol/l]} \times \text{fasting insulin } [\mu\text{U/ml}] / 22.5$.

Statistical analysis was performed using Statgraphics Centurion XV software. For finding associations between fetal biometry and adipocytokines, as well as mother's anthropometry we used Pearson's correlations. Because adiponectin, leptin and insulin concentration results were significantly skewed, as well as HOMA-IR score, normal logarithmic transformation of the data was used for uni-variable and multiple-variable analysis, to achieve it's normal distribution, with results back-transformed for presentation. For finding differences between groups of women with and without altered fetal growth t-test was performed. We used AC results for identifying pregnancies with accelerated fetal growth (AC percentile cut-off value of 90), as it's been proved to reflect well asymmetrical subcutaneous fat distribution, predictive of macrosomia at birth (Landon *et al.* 1989).

RESULTS

Maternal and neonatal anthropometric data are shown in Table 1. Table 2 summarizes data on adipokines, insulin and insulin resistance. On Pearson's correlation analysis we found no associations between both of the adipokines and biometry measurements. There were also no differences in their serum concentrations between groups of women with and without accelerated fetal growth (Table 3). Adiponectin negatively correlated with pre-pregnancy BMI ($r=-0.366$, $p=0.01$), with no relation to age or weight gain during pregnancy. There was also no correlation between adiponectin and fasting insulin, leptin, fasting glucose and HOMA-IR. Leptin, on the other hand, positively correlated with pre – pregnancy BMI ($r=0.42$, $p=0.002$), fasting insulin ($r=0.51$, $p=0.0006$) and HOMA-IR ($r=0.43$, $p=0.005$) – data partially shown in Figure 1, with no correlation

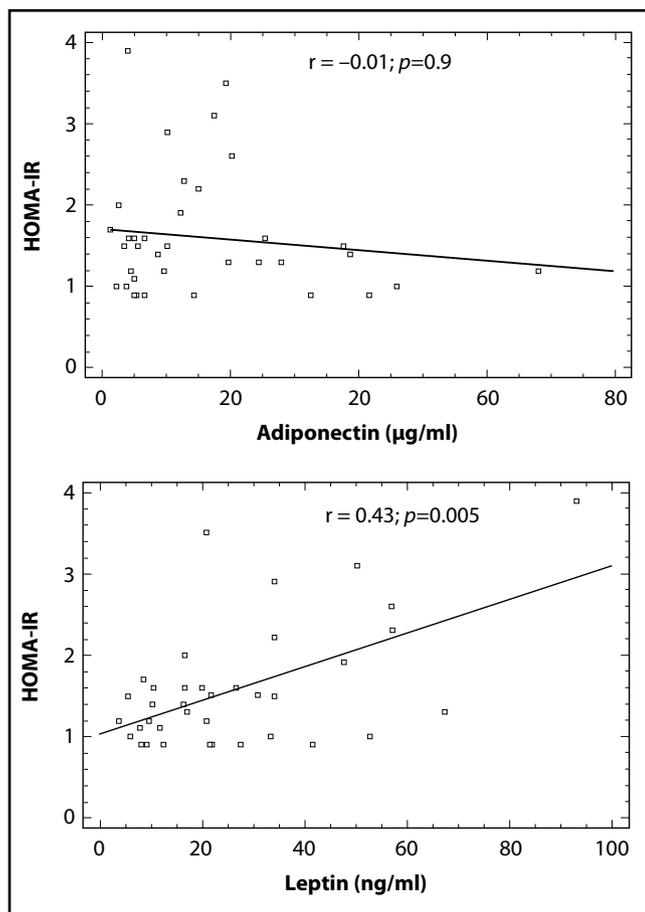


Fig. 1. Adiponectin and leptin correlation to HOMA-IR.

with adiponectin and fasting glucose. No association was found between adiponectin, leptin, fasting insulin, HOMA-IR and neonatal birth weight or birth weight percentile either while considering all women with gestational diabetes or diabetic pregnancies with and without accelerated fetal growth separately. In our study population we found no differences in age, prepregnancy weight, prepregnancy BMI and parity between the above groups as well. There was however significant difference in weight gain between the groups (Table 3).

DISCUSSION

Adipose tissue is currently considered an active endocrine organ, producing a number of cytokines (adipocytokines), like adiponectin, leptin and TNF- α . Adiponectin was found to be strongly, inversely related to fat mass in humans, with its plasma concentration significantly reduced in obesity (Arita *et al.* 1999) and also obesity – related disorders, like type 2 diabetes (Hotta *et al.* 2000). It's also reduced in GDM pregnancies, in lean as well as in obese women, in early and late pregnancy (Lain *et al.* 2000; Vitoratos *et al.* 2008; Ranheim *et al.* 2004), and this reduction extends into early postpartum (Vitoratos *et al.* 2008). These findings

Tab. 1. Maternal and neonatal characteristics of study population. Data are means \pm SD, when applicable.

Maternal data:	
Age	31.1 \pm 4.58
Pre-pregnancy weight (kg)	65.1 \pm 12.3
Pre-pregnancy BMI	24.03 \pm 4.63
Pre-pregnancy BMI \geq 30 (%)	9.61
Insulin therapy (%)	19
Weight gain until assessment (kg)	9.61 \pm 4.08
Neonatal data:	
Gestational age at delivery (wks)	38.52 \pm 1.04
Birth weight (g)	3501.48 \pm 461.1
CC percentage (%)	28

Tab. 2. Plasma concentration of adipokines, insulin and HOMA-IR in women with gestational diabetes mellitus at the beginning of treatment. Adiponectin, leptin, insulin and HOMA-IR values are shown as medians followed by interquartile range in parentheses. Fasting glucose value as mean \pm SD.

Adiponectin (μ g/ml)	8.46 (4.49-12.09)
Leptin (ng/ml)	22.89 (12.52-40.6)
Insulin (μ U/ml)	8.55 (7.56-9.5)
Fasting glucose (mg/dl)	75.15 \pm 16.2
HOMA-IR	1.45 (1.28-1.62)

have triggered the discussion as to possible adiponectin influence on fetal growth and its abnormalities in GDM. As adiponectin is abundant in human plasma (Diez & Iglesias 2003), its nature and contribution in creating sub-optimal conditions in GDM – affected pregnancies is likely to be vital.

Unlike adiponectin, leptin is positively related to fat mass in general, acting as satiety communicator for hypothalamus. Its influence on favouring negative energy balance is caused by decreased appetite and increased energy release. Leptin concentration is normally higher in pregnant women, with even greater, significant increase in GDM pregnancies (Kautzky-Willer *et al.* 2001). Although it's produced mainly by adipose tissue of mother and fetus, relevant placental contribution to overall leptin quantity has also been noted (Mostyn *et al.* 2001). It is postulated that leptin play an important role in pathogenesis of obesity in babies born from GDM – affected pregnancies, as increased body fat accumulation may lead to leptin, as well as insulin resistance (Muhlhausler & Smith 2009).

Although multiple data is available on variation of adiponectin and leptin concentrations in diabetic pregnancies, there is very little information regarding relation between adiponectin and leptin and fetal growth in

Tab. 3. Maternal parameters and neonatal birth weight in pregnancies with fetal AC < 90 and ≥ 90 percentile. The results are means ± SD or medians followed by interquartile range in parentheses (adiponectin, leptin, insulin and HOMA-IR).

	AC < 90 percentile	AC ≥ 90 percentile	p-value
Prepregnancy weight (kg)	64.46 ± 13.43	64.56 ± 11.06	ns
Prepregnancy BMI	23.84 ± 4.52	23.13 ± 3.24	ns
Weight gain (till study entry)(kg)	8.34 ± 3.67	11.08 ± 5.18	0.013
Adiponectin (µg/ml)	10.19 (4.9–15.5)	11.05 (5.0–17.5)	ns
Leptin (ng/ml)	21.94 (15.5–28.0)	30.97 (11.8–50.3)	ns
Insulin (µU/ml)	7.81 (6.7–8.4)	8.71 (6.7–10.6)	ns
Fasting glucose (mg%)	74.16 ± 9.91	76.09 ± 15.63	ns
HOMA-IR	1.35 (1.14–1.55)	1.4 (1.0–1.7)	ns
Neonates:			
Gestational age at delivery (wks)	38.69 ± 1.67	37.94 ± 1.95	ns
Birth weight (g)	3333.91 ± 500.3	3621.25 ± 472.37	0.02
Birth weight percentile	49.35 ± 28.36	70.7 ± 22.54	0.002

GDM pregnancies. It has been reported however, that adiponectin levels are lower and leptin levels higher in women with intrauterine growth restriction (IUGR) fetuses when compared to women with appropriate for gestational age (AGA) fetuses, with no differences in neonatal adiponectin and leptin between the two groups (Kyriakakou *et al.* 2008). Decrease in leptin concentration in small for gestational age (SGA) when compared to AGA neonates have been shown in other studies (Pighetti *et al.* 2003; Catov *et al.* 2007). Leptin importance as factor influencing fetal growth has been investigated in clinical and experimental animal studies of normal pregnancies, showing no influence of possible clinical significance (Forhead & Fowden 2009).

Present study shows no correlation between plasma concentrations of specific adipocytokines and fetal biometry in third trimester of gestation, nor we found any maternal adiponectin or leptin relation to actual birthweight. Also when assessing groups of GDM patients with and without accelerated fetal growth we did not identify significant differences in adiponectin or leptin levels between them.

There were also no differences in maternal anthropometry and insulin and insulin resistance between the groups. While discussing this fact, it needs to be stated, that appropriate GDM management was employed for all the subjects in order to maintain proper glycemia until successful delivery.

Adiponectin levels in our GDM women have proven to be inversely related to prepregnancy BMI which presumably cannot be explained only by reflection of adipose tissue content, as no similar relation is found in non – diabetic pregnancies (Kinalski *et al.* 2005; Soheilykhah *et al.* 2009), especially in third trimester (Mazaki-Tovi *et al.* 2007). Majority of studies investigating BMI influence on adiponectin levels in gestational

diabetes have shown similar association (Ranheim *et al.* 2004; Retnakaran *et al.* 2004; Kinalski *et al.* 2005), while others found no relation whatsoever (Tsai *et al.* 2005; Thyfault *et al.* 2005; Altinova *et al.* 2007). These discrepancies may probably be linked to differences in BMI between the studies reported.

In contrast to other studies (Retnakaran *et al.* 2004; 2005; Altinova *et al.* 2007) no association between serum adiponectin and insulin and insulin resistance described by HOMA-IR was shown in this study. And although in the study by Altinova *et al.* mean HOMA-IR value was much higher and GDM group much smaller than our study population, we have no explanation as to differences between our results and results of the studies by Retnakaran *et al.*, except for larger study group.

Leptin levels in present study were positively correlated with prepregnancy BMI, insulin and insulin resistance, which is in keeping with other studies (Kautzky-Willer *et al.* 2001; Atègbo *et al.* 2006; Maghbooli *et al.* 2007). This may reflect relevant adipose tissue contribution to overall, higher than in normal pregnancies leptin content in diabetic pregnancies. The reason for higher concentrations of leptin in diabetic pregnancies is still unclear, as well as whether it's positive relation to insulin resistance is a cause or an effect.

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