Maternal plasma cytokines concentrations and insulin resistance in first trimester in relation to fetal growth

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Abstract

OBJECTIVE: Fetal growth is determined by genetic factors and placental supply. There is evidence that insulin might contribute to the up-regulation of placental transporter activity. The dysregulation of adiponectin and leptin is found in insulin resistance. The objective of this study was to evaluate the relation of maternal plasma cytokine and insulin concentrations in the first trimester of pregnancy to fetal growth.

METHODS: 55 women with singleton pregnancy, between 12th and 14th weeks of gestation, were included to the study. Plasma concentrations of adiponectin, leptin, insulin and glucose were analyzed together with fetal ultrasound measurements and neonatal birth weight. The HOMA-IR were calculated (fasting insulin (μU/ml) × fasting glucose (mmol/l/22.5) to assess the insulin sensitivity.

RESULTS: Mean concentrations of adiponectin, leptin and insulin were 15.29 ± 13.83 μg/ml, 6.93±5.39 ng/ml and 43.59±26.28, respectively. The average insulin resistance defined by HOMA-IR was 1.35±0.8. The ratios of adiponectin to leptin, adiponectin to insulin and HOMA-IR were calculated. The percentiles of fetal crown-rump length (CRL) were negatively correlated with adiponectin plasma concentration (r=–0.32; $p<0.05$), with no relation to leptin and insulin plasma concentration. Correlations between fetus CRL percentile and the ratio of adiponectin to leptin concentration (r=–0.37; $p<0.02$) and adiponectin to HOMA-IR (r=0.35; $p<0.05$) were also observed. No association between adiponectin, leptin, fasting insulin, HOMA-IR and neonatal birth weight or birth weight percentile was found. The percentile of fetal CRL in the 1st trimester was positively correlated with neonatal birth weight percentile (r=0.3; $p<0.05$).

CONCLUSIONS: The results of this study imply that maternal adiponectin concentration may play a role in early determination of fetal growth.

ORIGINAL ARTICLE

Abbreviations :

AGA - appropriate for gestation age
BMI - body mass index
BPD - biparietal diameter
CRL - crown-rump length
GDM - gestational diabetes mellitus
ECLIA - electrochemiluminescence immunoassay
HOMA-IR - homeostasis model assessment – insulin resistance
IUGR - intrauterine growth retardation
SGA - small for gestation age

INTRODUCTION

Fetal growth is determined by genetic factors and placental supply. There is evidence that insulin might contribute to the up-regulation of placental transporter activity (Janssen, 2006). Recent studies suggest that adiponectin may promote the activity of insulin, while leptin antagonises it (Catalano, 2006). Different concentrations of both cytokines are found in fetal growth disturbance. It has been reported that adiponectin concentrations are lower and leptin concentrations higher in women with intrauterine growth restriction (IUGR) fetuses when compared to women with appropriate for gestational age (AGA) fetuses (Kyriakakou, 2008). In contrast, adiponectin concentration in early gestation was negatively correlated with gestation diabetes (GDM) development (Lain, 2008; Williams, 2004) . Unlike adiponectin, elevated leptin concentrations were found to be positively correlated with GDM risk (Qiu, 2004). Adiponectin stimulates fatty acid oxidation, reduces plasma triglycerides concentration and improves glucose metabolism by increasing insulin sensitivity (Williams, 2004). It is postulated that leptin plays 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, 2009).

The objective of this study was to evaluate the relation of maternal plasma cytokines and insulin concentrations in the first trimester of pregnancy to fetal growth.

MATERIAL AND METHODS

54 healthy women with singleton pregnancy were enrolled in the study. The study was approved by Ethical Committee of Medical University of Warsaw and all the patients signed an informed consent prior to enrollment. BK Medical ultrasound system was used for obstetric ultrasound that included fetal biometry (crown-rump length (CRL), biparietal diameter (BPD)) between 11 and 14 weeks of gestation. Fasting blood samples were obtained just before ultrasound examination. Blood was centrifuged and partially used for immediate glucose and insulin concentration measurements. The HOMA-IRs were calculated (fasting insulin (μU/ml) × fasting glucose (mmol/l/22.5) to assess the insulin sensitivity. The rest of the serum was frozen at –70°C for further measurements (adipokines). Adiponectin and leptin concentrations were measured by ELISA kits: Human Adiponectin/Acrp30 and Human Leptin Quantikine Kit (RnD Systems, Minneapolis, USA). Electrochemiluminescence immunoassay (ECLIA) kit and Elecsys Systems analyzer (Roche) was used for insulin concentration assessment. Statistical analysis was performed using Statgraphics Centurion XV software. Pearson's correlations were used in order to find relation between fetal biometry and adipocytokines, as well as mother's anthropometry. Because adiponectin, leptin and insulin concentrations results were significantly skewed, normal logarithmic transformation of data was used for uni-variable and multiple-variable analysis, to achieve it's normal distribution, with results back-transformed for presentation.

RESULTS

Maternal, fetal and neonatal anthropometric data are shown in Table 1. Table 2 summarizes data on adipokines, insulin and insulin resistance. The ratios of adiponectin to leptin, adiponectin to insulin and HOMA-IR were calculated. Plasma adipokines had no signifi-

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

Maternal data	
Age (years)	28.0 ± 3.8
Pre-pregnancy BMI	22.7 ± 4.73
Days of pregnancy	89.71 ± 4.57
Fetal data:	
CRL (mm)	65.82 ± 8.47
BPD (mm)	22.10 ± 2.71
Neonatal data:	
Gestational age at delivery (wks)	39.2 ± 1.7
Birth weight (g)	3441 ± 549

Tab. 2. Plasma concentration of adipokines, insulin and HOMA-R in women at first trimester of pregnancy. (mean values followed by range in parentheses)

Adiponectin [μg/ml]	15.29 (0.88–74.30)
Leptin [ng/ml]	5.39 (1.14–25.47)
Insulin [pmol/l]	43.59 (10.19–131.81)
HOMA-IR [fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5]	1.14 (0.26–3.84)

cant variability between 11 and 14 weeks of gestation according to the last menstrual period. Adiponectin had no relation to pre-pregnancy BMI or maternal age. There was also no correlation between adiponectin and fasting insulin, leptin, fasting glucose concentrations and HOMA-IR. Leptin concentrations, on the other hand, positively correlated with pre – pregnancy BMI (r=0.83, $p<0.001$), fasting insulin (r= 0.40, $p<0.01$) and HOMA-IR (r=0.39, $p<0.01$), with no correlation with adiponectin and fasting glucose concentrations. The percentiles of fetal crown-rump length (CRL) were negatively correlated with the adiponectin plasma concentration (r=–0.32; $p=<0.05$), with no relation to leptin and insulin plasma concentration. Correlations between fetus CRL percentile and the ratio of adiponectin to leptin concentration (r=–0.37; $p<0.02$) and adiponectin to HOMA-IR (r=0.35; $p<0.05$) (Figure 1) were observed. No correlations between both adipokines, fasting insulin concentration, HOMA-IR and neonatal birth weight or birth weight percentile were found on Pearson's correlation analysis. The percentile of fetal CRL in the 1st trimester was positively correlated with neonatal birth weight percentile (r=0.3; $p<0.05$).

There was one case of fetal demise at 16th week of gestation. Ultrasound pregnancy scan performed between 11th and 14th week did not reveal any abnormalities. Maternal cytokine analysis showed very high adiponectin and very low leptin plasma concentrations. Adiponectin to leptin concentration ratio reached the maximum in the study group.

DISCUSSION

Relations between the early pregnancy maternal plasma adiponectin, leptin, insulin concentrations and the fetal and neonatal biometry were analyzed. The adiponectin concentration was negatively correlated with the percentiles of fetal crown-rump length but not with actual birth weight or birth weight percentile. In the above study the lower level of adiponectin in early gestation was correlated with increased risk of gestational diabetes. It is postulated that adiponectin plays an important role in regulating insulin resistance and glucose homeostasis (Mazaki-Tovi, 2007). It was demonstrated that decreased maternal adiponectin concentration and insulin sensitivity may increase the risk of fetal overgrowth in women suffering from GDM (Tsai, 2005). In contrast to other studies (Catalano 2006, Retnakaran, 2005; Altinova, 2007) no correlations between serum adiponectin, insulin and insulin resistance described by HOMA-IR were shown in this study. Kajantie *et al.* (2005) reported that adiponectin concentrations were unrelated to insulin sensitivity both in preeclamptic and normotensive subjects. The majority of studies investigating pre-pregnancy BMI influence on adiponectin concentration have shown negative correlation (Mazaki-Tovi, 2007; Lain, 2008). There was no relation between maternal adiponectin and pre-pregnacy BMI in the above study. Williams *et al.* (2004) found the negative correlation between early pregnancy adiponectin concentration and pre-pregnancy BMI among GDM patients but not among control group. These discrepancies may probably be linked to differences in BMI between the reported studies.

Leptin concentrations in the above study were positively correlated with prepregnancy BMI, insulin and insulin resistance, which is cohesive to other studies (Kautzky-Willer, 2001; Atègbo, 2006; Maghbooli, 2007). The study results show no correlation between plasma concentration of maternal leptin or insulin and HOMA-IR relation to actual birthweight. Clausen *et al.* (2005) also demonstrated that early pregnancy maternal leptin concentration was not associated with macrosomia after adjusting for maternal BMI and that only slim women with macrosomic infants had higher insulin concentration than those with normal weight infants.

Some authors demonstrated that abnormal maternal leptin concentrations are correlated with a poor pregnancy outcome (Tommaselli, 2006). There was one case of late miscarriage in the study group with high adiponectin and low leptin concentrations. Tommaselli *et al.* (2006) demonstrated that serum leptin concentrations were significantly lower in the group of women with missed abortion than in patients with threatened

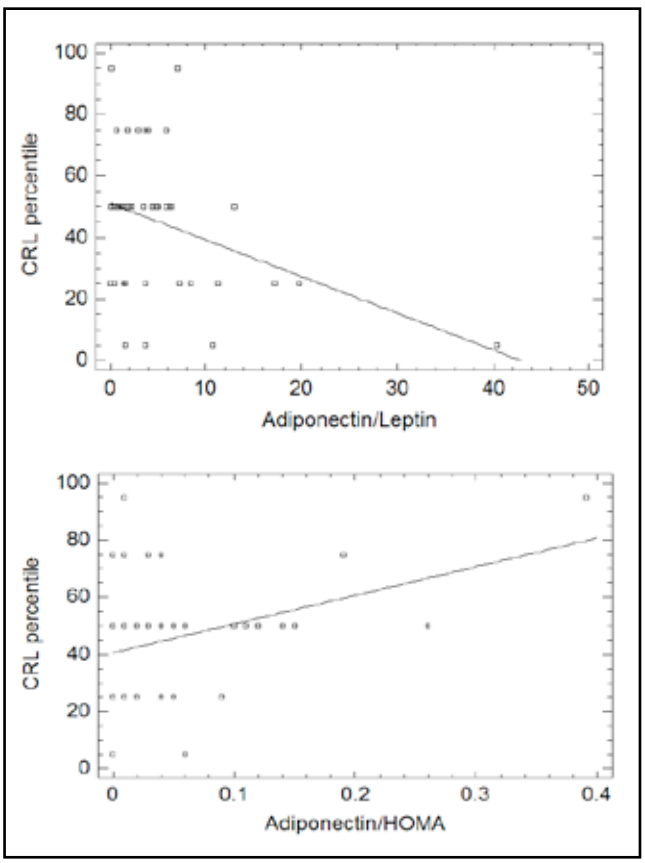

Fig. 1. The fetal CRL percentile correlation to adiponectin/ leptin and adiponectin/HOMA-IR ratio (r=-0.37; $p=0.01$ and r=0.35; $p=0.02$).

miscarriage who delivered at term and the women with subsequent miscarriage. Laird *et al*. (2001) also showed that women with previous recurrent miscarriage had significantly lower leptin concentrations at 5–6 and 7–8 weeks of gestation in comparison to women who delivered at term. The above study shows the negative correlation between fetus CRL percentile and the ratio of adiponectin to leptin concentrations. It is possible that the proportion in adiponectin and leptin concentrations can be important for fetal development.

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