

Placental first trimester's measurements in relation to maternal plasma adiponectin, leptin and insulin concentrations

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Abstract

OBJECTIVE: The dysregulation of adiponectin and leptin is found in insulin resistance. There is evidence that both cytokines and insulin might contribute to the placental development and the fetal growth. The objective of this study was to evaluate the relationship of maternal plasma cytokine and insulin concentrations with the placental dimension in the first trimester of pregnancy.

METHODS: 34 women with singleton pregnancy, between 11th and 14th weeks, were included to the study. Plasma levels of adiponectin, leptin, insulin and glucose were quantified with ultrasound measurements of the placenta. HOMA-IR were calculated to assess the insulin sensitivity.

RESULTS: Mean concentrations of adiponectin, leptin and insulin were $18,39 \pm 13.99$ $\mu\text{g/ml}$; 6.99 ± 5.67 ng/ml and 43.98 ± 23.89 pmol/l respectively. The placenta thickness was positively associated with the maternal adiponectin plasma concentration ($r=0.36$; $p=0.037$). There were no associations between placental measurements and leptin, fasting insulin, fasting glucose and HOMA-IR. There was not significant correlation between placental measurements and the fetal Crown Rump Length (CRL).

CONCLUSIONS: The results of this study imply that maternal adiponectin plasma concentration may have a role in placental growth.

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

Normal anatomy and function of placenta determines proper fetal development. Trophoblast invasion into blood vessels in the first trimester of pregnancy establish appropriate fetal growth during second and third trimester of pregnancy. According to available data there is a correlation between placental size assessed in 12 weeks of gestation or later and intrauterine fetal growth restric-

tion and preeclampsia (Hafner *et al.* 2003). On the other hand fetal overgrowth in pregnancies complicated by diabetes is considered to be related with increased placental transport (Jansson *et al.* 2006). Recent studies provide evidence that placental transport is mainly regulated by insulin concentrations (Jansson *et al.* 2003; Ericsson *et al.* 2005). There is also a correlation between insulin resistance and placental gene expression resulting in increased production and transport of lipids (Jansson *et al.* 2006).

Recent studies suggest that some of the adipokines may promote insulin's actions (adiponectin) while the others antagonise it (TNF α , IL-6, leptin) (Catalano *et al.* 2006). There is evidence that cytokines and insulin might contribute to the placental development (Lappas *et al.* 2005). The objective of this study was to evaluate the relationship of maternal plasma adiponectin, leptin and insulin concentrations with the placental dimension in the first trimester of pregnancy.

MATERIAL AND METHODS

34 healthy women with singleton pregnancy were enrolled in the study. The study was approved by Ethical Committee of Warsaw Medical University and all the patients consented prior to enrollment. BK Medical ultrasound system was used for obstetric ultrasound that included fetal biometry (crown-rump length (CRL),

biparietal diameter (BPD)) and placental measurements (thickness, longitudinal diameter and area) between 11 and 14 weeks of gestation. Fasting blood samples were obtained just before ultrasound exam. Blood was centrifuged and partially used for immediate glucose and insulin measurements. The HOMA-IR were calculated (fasting insulin (μ U/ml) \times 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). For insulin assessment electrochemiluminescence immunoassay (ECLIA) kit and Elecsys Systems analyzer (Roche) was used. Statistical analysis was performed using Statgraphics Centurion XV software. For finding associations between placental measurements and adipocytokines, fasting insulin and insulin resistance we used Pearson's correlations. Because adiponectin, leptin and insulin concentration results were significantly skewed, normal logarithmic transformation of the data was used for uni-variable and multiple-variable analysis, to achieve its normal distribution, with results back-transformed for presentation.

RESULTS

The plasma concentration of adipokines, insulin and HOMA-IR in women at the first trimester of pregnancy are shown in Table 1. The maternal adiponectin plasma concentration was positively associated with placenta thickness ($r=0.36$; $p=0.037$), with no relation to the longitudinal diameter and placental area (data partially shown in Figure 1). On Pearson's correlation analysis we found no associations between and placental measurements and leptin, fasting insulin, fasting glucose and HOMA-IR. Placental measurements and plasma adipokines had not significant variability between 11 and 14 weeks of pregnancy, described by the number of days from the last period. There was also not significant correlation between placental measurements and the fetal crown rump length (CRL). No association was found between placental measurements in the first trimester and neonatal birth weight or birth weight percentile.

DISCUSSION

Placenta has an endocrine and transporting functions and therefore determines physiological fetal growth. Abnormalities in placental anatomy and function may result in intrauterine growth restriction as well as fetal overgrowth. Hypotrophic and macrosomic fetuses are more likely to develop hypertension and diabetes in adolescence (Barker *et al.* 1993). This study shows correlation between adiponectin concentrations in physiological pregnancies and placental thickness assessed in late first trimester. Adiponectin concentration does not change during pregnancy and is considered to be

Tab. 1. Plasma concentration of adipokines, insulin and HOMA-R in women at first trimester of pregnancy. (mean values followed by range in parentheses).

Adiponectin [μ g/ml]	18.39 (1.84-74.30)
Leptin [ng/ml]	6.99 (1.14-25.47)
Insulin [pmol/l]	43.98 (10.19-131.81)
HOMA-IR *	1.16 (0.3-3.8)

* [fasting insulin (uU/ml) \times fasting glucose (mmol/l) /22.5]

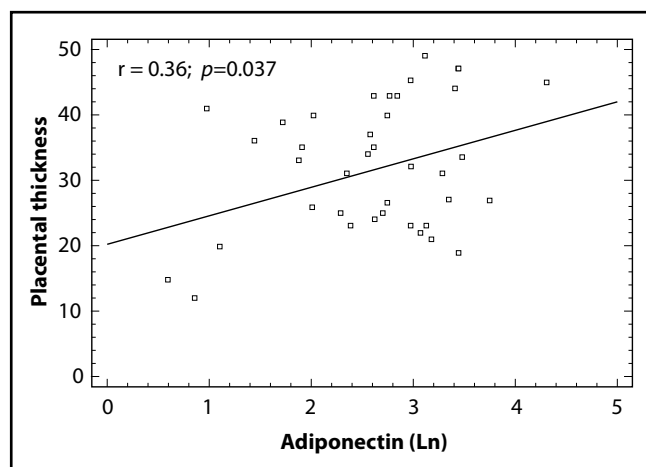


Fig. 1. Placental thickness correlation to adiponectin logarithm.

a protective factor in regulation of normal fetal growth (Mazaki-Tovi *et al.* 2007). It has been reported that adiponectin levels are lower in women with intrauterine growth restriction (IUGR) fetuses when compared to women with appropriate for gestational age (AGA) fetuses (Kyriakakou *et al.* 2008). Also D'Anna *et al.* (2005) demonstrated the lower adiponectin levels in pregnancy complicated by hypertension and IUGR. In contrast the preeclamptic women have higher adiponectin concentrations than normotensive pregnant women in Kajantie *et al.* study (2005). The early pregnancy hypoadiponectemia was also associated with gestational diabetes development (Cseh *et al.* 2004, Lain *et al.* 2005, Worda *et al.* 2004).

According to recent studies there is a correlation between increased placental dimensions in second and third trimester of pregnancy and fetal growth restriction as well as increased fetal growth (Elchalal *et al.* 2000). Placental volume assessment in subsequent trimesters showed decreased dynamics of placental development in SGA fetuses only before 12 weeks of pregnancy. In patients with preeclampsia decreased placental development was observed after 16 weeks of gestation (Metzenbauer *et al.* 2001). Increased placental volume is observed in pregnancies complicated by gestational diabetes as well as significantly increased ratio of placental volume to birth weight (Lao *et al.* 1997). Nelson *et al.* (2008) proved positive correlation between adiponectin concentrations and fetal-weight to placental-weight ratio in type-1 diabetes complicated pregnancy. It seems that abnormal relation between adiponectin concentration and placental development in the first trimester of pregnancy is related with increased risk of IUGR, preeclampsia and fetal macrosomy in the second and the third trimester of gestation. During the first trimester of gestation there is a physiological increase of tissue sensitivity to insulin resulting in increase in fat tissue accumulation in pregnant women. According to available data insulin is an important factor in regulation of placental transport (Jansson *et al.* 2003; Ericsson *et al.* 2005). The tissue sensitivity to insulin increase in subsequent trimesters of pregnancy. There is a relation between tissue sensitivity to insulin and placental genes expression resulting in increased placental production and transport of lipids (Jansson *et al.* 2006). Leptin is considered to be responsible for increase of tissue sensitivity to insulin in pregnancy. According to recent studies leptin concentration is related to fetal growth restriction.

Leptin concentration is significant increase in GDM pregnancies (Kautzky-Willer *et al.* 2001). 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). In our analysis we found no associations between and placental measurements in the first trimester of pregnancy and leptin, fasting insulin, fasting glucose and HOMA-IR. It seems that leptin dependant increase of

tissue sensitivity to insulin in second and third trimester of pregnancy (which may be observed in patients with preeclampsia and gestational diabetes) results in abnormal placental function. That was also observed as a decreased development of placental volume in women with preeclampsia after 16 weeks of gestation (Hafner *et al.* 2003). Metzenbauer *et al.* (2001) showed poor relation between volume of placenta and CRL in the first trimester of pregnancy. It is probable that because of relatively small study group such relation could not be confirmed with two-dimensional ultrasound measurement of the placenta in this research. There was no relation between placental dimensions and gestational weeks calculated from last menstrual period.

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