RESEARCH LETTER

Determinants of adiponectin levels during pregnancy in women with type 1 diabetes mellitus

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Introduction A pregnancy complicated by maternal type 1 diabetes is associated with an increased risk of severe perinatal complications. Poorly controlled blood glucose levels could lead to numerous congenital malformations as well as an elevated risk of early pregnancy loss.[1] The optimal control of glucose levels could additionally reduce the risk of other diabetes-associated conditions such as retinopathy, nephropathy, gestational hypertension, and neonatal acidosis.[1,2]

Adiponectin is a type of adipose-derived hormone, which plays a significant role in the maintenance of systemic metabolic homeostasis. It has been reported that changes in adiponectin levels during pregnancy are associated with decreased insulin sensitivity; however, their contribution to lipid metabolism is uncertain.[3] Although the function and regulation of adipose tissue hormone secretion were well described in the general population, there have been no studies focusing exclusively on pregnant women with type 1 diabetes. Therefore, the aim of this study was to assess the determinants of adiponectin levels throughout the pregnancy of patients with type 1 diabetes.

Patients and methods A cross-sectional study of 88 pregnant women with type 1 diabetes was conducted in the Department of Reproduction at Poznan University of Medical Sciences (Poznań, Poland). According to our management protocol for women with type 1 diabetes, patients were admitted to our department 3 times during their pregnancy: the first planned admission was scheduled before the end of 12 weeks of gestation; the second, between the 20th and 24th week; and the third, between the 34th and 39th week. Patients with multiple pregnancy, preterm delivery (before the 34th week), preterm prelabor rupture of membranes, ongoing infection, miscarriage, or stillbirth were excluded from the study.

Anthropometric data (weight, height, waist and hip circumference) were collected during the first hospitalization. Biological samples were obtained from patients during the 3 planned hospital stays. Blood samples were collected after overnight fasting. Adiponectin concentrations were determined in serum by an enzyme-linked immunosorbent assay kit (Mediagnost, Reutlingen, Germany). Furthermore, we determined the levels and assessed the effect of the following parameters on adiponectin secretion: C-reactive protein (CRP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glycated hemoglobin (HbA_{1c}), creatinine clearance, and estimated glucose disposal rate (eGDR), calculated using the following formula: $eGDR = 24.31 - (12.22 \times WHR) - (3.29 \times HTN) - (0.57 \times HbA_{1c})$, where WHR is waist-to-hip ratio, HTN is hypertensive status (0 = "no"; 1 = "yes"), and HbA_{1c} is expressed in %.[4]

The study protocol was approved by the Institutional Ethical Committee of the Poznan University of Medical Sciences (no. 673/12). Written informed consent was obtained from each patient before enrollment.

Statistical analysis Statistical analysis was performed using the Statistica software, version 13.3 (TIBCO Software, Palo Alto, California, United States). Testing for normality of data distribution was performed using the Shapiro–Wilk test. Differences in adiponectin levels were analyzed using the Friedman test. The analysis of associations between adiponectin concentrations and anthropometric measurements or laboratory results was performed using the Spearman rank correlation coefficient. The variables that were found to be significantly correlated with adiponectin values

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TABLE 1 Correlations between adiponectin levels and study parameters

Correlation		R	*P* value
First-trimester adiponectin	WHR	–0.31	0.01
	First-trimester TG	–0.29	0.02
	First-trimester hs-CRP	–0.35	0.005
	First-trimester daily protein urinary secretion	0.27	0.03
Second-trimester adiponectin	BMI	–0.38	0.02
	Second-trimester TG	–0.48	0.004
	Second-trimester creatinine clearance	–0.36	0.04
Third-trimester adiponectin	Third-trimester HbA_{1c}	0.44	0.007

Abbreviations: BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; hs-CRP, high-sensitivity C-reactive protein; TG, triglycerides; WHR, waist-to-hip ratio

were included in the multiple regression analysis. Nonnormally distributed variables prior to inclusion in multiple regression models were log transformed. The results were considered significant if the estimated *P* value was lower than 0.05.

Results The demographic and clinical characteristics of 88 patients enrolled in this study are presented in Supplementary material, *Table S1*, while the results of laboratory tests, in Supplementary material, *Table S2*.

Median (interquartile range [IQR]) first-trimester adiponectin levels were relatively high (14.7 μg/ml [9.1–20.2 μg/ml]); then, in the second trimester, a decrease in adiponectin concentrations was observed (10.2 μg/ml [8.2–14.4 μg/ml]). In the third trimester, median (IQR) adiponectin levels returned to those observed in the first trimester (13.9 μg/ml [10.5–20.8 μg/ml]). Our analysis revealed that the changes in serum adiponectin levels during gestation were significant ($P = 0.02$). There were no correlations between adiponectin levels and insulin requirements throughout pregnancy or differences in adiponectin concentrations among patients treated with insulin pumps and multiple injections (data not shown).

First trimester Adiponectin levels measured in the first trimester of pregnancy were negatively correlated with the WHR, but no correlation was observed with body mass index (BMI; $R = –0.24$, $P = 0.06$). Additionally, an inverse correlation was noted between adiponectin and triglyceride levels. Furthermore, there was a negative correlation between adiponectin and CRP levels as well as a positive correlation between adiponectin levels and daily protein urinary secretion. Statistically significant correlations are shown in TABLE 1. To assess the association between adiponectin levels and other metabolic and inflammatory parameters, multiple regression models were developed. The first multiple regression analysis model included first-trimester CRP ($P = 0.03$) and triglycerides ($P = 0.46$). The second regression model included: first-trimester CRP, triglycerides, and WHR. After the inclusion of WHR, the associations with CRP ($P = 0.1$) and other parameters were no longer significant. In both models, a close to normal distribution of residuals was noted.

Second trimester In the second trimester, there were negative correlations between adiponectin levels and BMI, triglyceride levels, and creatinine clearance. Data are presented in TABLE 1. There was no correlation between adiponectin levels and WHR ($R = –0.2$, $P = 0.23$).

Third trimester In the third trimester, adiponectin levels were markedly correlated only with HbA_{1c} levels (TABLE 1). Body mass index ($R = –0.07$, $P = 0.67$) and WHR ($R = –0.13$, $P = 0.44$) were not correlated with adiponectin levels.

Discussion The changes in adiponectin levels throughout pregnancy in women with type 1 diabetes described in our study were found to be significant. In contrast to our results, Mazaki-Tovi et al[5] did not report any differences in adiponectin levels during pregnancy. The discrepancies between studies might be related to different inclusion criteria, as their study group included women without diabetes. Randeva et al[6] compared adiponectin levels during pregnancy in women with type 1 diabetes and nondiabetic women, and significantly higher adiponectin levels were noted in diabetic patients.

It has been proved that adiponectin levels in the general population are negatively correlated with obesity and increased insulin resistance. The results of studies conducted in patients with gestational diabetes are consistent with this hypothesis.[7,8] In our study, first-trimester adiponectin concentrations were negatively correlated with WHR, and second-trimester adiponectin levels were negatively correlated with BMI. We did not observe any significant correlations between third-trimester adiponectin levels and obesity. Based on our results and the above studies, we can formulate a hypothesis that adiponectin values are more significantly associated with anthropometric parameters in patients diagnosed with gestational diabetes than in those with type 1 diabetes. This can be explained by much higher rates of overweight and obesity in women with gestational diabetes. To assess insulin resistance in early pregnancy, we used the eGDR. Surprisingly, we did not find any significant correlation between adiponectin values and eGDR.

Abnormal body fat distribution and insulin resistance were found to be the main determinants of CRP levels in pregnant patients with type 1 diabetes.[9] In our study, CRP concentrations were negatively correlated with first-trimester adiponectin levels. C-reactive protein was also included in the multiple regression analysis models. The association between CRP and first-trimester adiponectin values was no longer significant after adjustment for WHR. Nevertheless, the hypothesis that a low-grade inflammation during pregnancy

is responsible for decreasing serum adiponectin levels could be formulated.

Furthermore, third-trimester HbA_{1c} values were found to be positively correlated with third--trimester adiponectin concentrations. In the first part of pregnancy, adiponectin concentrations were mainly determined by both BMI and WHR, but the situation changed in the late third trimester. An increase in blood adiponectin levels could sensitize the liver to insulin secretion in response to higher mean blood glucose values.[10]

Significant changes in the serum lipid profile are physiological in the second and third trimester of pregnancy. Healthy pregnant women compared with nonpregnant controls have significantly higher serum concentrations of total cholesterol, triglycerides, LDL-C, HDL-C, and apolipoproteins.[11] Mantzoros et al[12] found a positive correlation between adiponectin and HDL-C levels, as well as negative correlations between adiponectin values, triglycerides, and non-HDL-C. The negative correlation between serum adiponectin and triglyceride levels found in our study is also consistent with the results reported by Mantzaros et al[12] in nonpregnant women.

Ethnic homogeneity (the Caucasian race), a relatively small study group, and the fact that anthropometric measurements were performed only during the first trimester (we cannot exclude that adiponectin values could correlate with BMI and WHR measured at later stages of pregnancy) could be regarded as possible limitations of our research.

To conclude, this study demonstrated alterations to adiponectin concentrations during the pregnancy of women with type 1 diabetes. Our findings demonstrate an association between first- and second-trimester adiponectin levels and anthropometric parameters, such as WHR and BMI. Based on the described correlation between CRP and adiponectin values, we speculate that chronic low-grade inflammation during pregnancy could be regarded as a potential causative agent in the development of hypoadiponectinemia. The association between adiponectin and HbA_{1c} levels should be investigated in further studies.

SUPPLEMENTARY MATERIAL

Supplementary material is available with the article at www.mp.pl/paim.

ARTICLE INFORMATION

NOTE PG is a member of Club 35, a Polish Society of Gynecologists and Obstetricians.

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CONFLICT OF INTEREST None declared.

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REFERENCES

1 McCance DR, Casey C. Type 1 diabetes in pregnancy. Endocrinol Metab Clin North Am. 2019; 48: 495-509.

2 Gutaj P, Mantaj U, Zawiejska A, et al. Maternal risk factors for neonatal acidosis in women with type 1 diabetes. Pol Arch Intern Med. 2019; 129: 316-320.

3 Catalano PM, Hoegh M, Minium J, et al. Adiponectin in human pregnancy: implications for regulation of glucose and lipid metabolism. Diabetologia. 2006; 49: 1677-1685.

4 Williams KV, Erbey JR, Becker D, et al. Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes. 2000; 49: 626-632.

5 Mazaki-Tovi S, Kanety H, Pariente C, et al. Maternal serum adiponectin levels during human pregnancy. J Perinatol. 2007; 27: 77-81.

6 Randeva HS, Vatish M, Tan BK, et al. Raised plasma adiponectin levels in type 1 diabetic pregnancies. Clin Endocrinol (Oxf). 2006; 65: 17-21.

7 Lacroix M, Battista MC, Doyon M, et al. Lower adiponectin levels at first trimester of pregnancy are associated with increased insulin resistance and higher risk of developing gestational diabetes mellitus. Diabetes Care. 2013; 36: 1577-1583.

8 Soheilykhah S, Mohammadi M, Mojibian M, et al. Maternal serum adiponectin concentration in gestational diabetes. Gynecol Endocrinol. 2009; 25: 593-596.

9 Gutaj P, Krzyżanowska P, Brązert J, Wender-Ożegowska E. Determinants of C-reactive protein concentrations in pregnant women with type 1 diabetes. Pol Arch Med Wewn. 2016; 126: 230-236.

10 Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab. 2002; 13: 84-89.

11 Mazurkiewicz JC, Watts GF, Warburton FG, et al. Serum lipids, lipoproteins and apolipoproteins in pregnant non-diabetic patients. J Clin Pathol. 1994; 47: 728-731.

12 Mantzoros CS, Li T, Manson JE, et al. Circulating adiponectin levels are associated with better glycemic control, more favorable lipidprofile, and reduced inflammation in women with type 2 diabetes. J Clin Endocrinol Metab. 2005; 90: 4542-4548.