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Adiponectin Levels in Gestational Diabetes Mellitus and in Pregnant Women Without Glucose Intolerance*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Objectives. The aim of the study was to determine serum adiponectin levels among patients with gestational diabetes mellitus (GDM) and normal pregnant women without glucose intolerance, and to investigate the relationship between these levels and clinical factors at the time of the diagnosis, at delivery and in the *post-partum* period.
Material and Methods. The subjects' serum adiponectin concentration was measured using the enzyme-linked immunosorbent assay (ELISA) method at 24th–28th week of gestation, at delivery (in maternal circulation and the umbilical cord) and 24 h after delivery. The relationship between these groups' measurements and other established clinical-laboratory factors were investigated.
Results. Serum adiponectin concentrations were significantly lower ($p = 0.02$) in GDM patients compared with patients with normal glucose tolerance at 24th–28th week of gestation. During delivery, maternal serum adiponectin concentrations were significantly lower ($p = 0.03$) in GDM patients compared with patients with normal glucose tolerance. In the *post-partum* period, serum adiponectin concentrations were significantly higher ($p = 0.009$) in GDM patients compared *wi*th patients with normal glucose tolerance. Umbilical cord adiponectin concentrations were significantly lower ($p = 0.005$) in GDM patients compared with patients with normal glucose tolerance.
Conclusions. Adiponectin concentrations in GDM patients' circulation were regulated by changes in glucose and insulin metabolism. A reduction in serum adiponectin levels seems to play a role in GDM patients' insulin resistance (**Adv Clin Exp Med 2015, 24, 1, 85–92**).

Key words: gestational diabetes mellitus, adiponectin, insulin resistance, glucose intolerance, adipokines.

Gestational diabetes mellitus (GDM) is glucose intolerance that is first diagnosed during pregnancy period and characterized by clinical hyperglycemia (1). Although there is a diabetogenic state in normal pregnancy, GDM does not develop in every pregnant woman. It has been determined that insulin resistance is not only related to the hormonal contra-insulin effect that occurs in the physiology of normal pregnancy. Lipolysis is increased in adipose tissue, and insulin sensitivity is decreased due to physiological changes in the metabolism during pregnancy [2].

The underlying physiopathological mechanism of GDM is believed to be the composition of

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decreased insulin sensitivity of the mother before pregnancy and insufficient insulin response during the pregnancy [1]. Women with GDM have decreased insulin sensitivity or increased insulin resistance compared with normal pregnant women. Insulin resistance starts in the middle of the second trimester and continues progressively in the third trimester [3]. The mechanism of the development of insulin resistance underlying the pathogenesis of GDM has not been completely defined.

Maternal adiposity and placental hormones are blamed for the insulin resistance that develops in GDM. Adipokines, which are newly defined and still under investigation, are physiologically active polypeptide hormones which originate from adipose tissue and cause insulin resistance in pregnancy and GDM [4]. Evidence for the roles of these molecules on insulin resistance has been gaining strength. Due to this possible role in the pathogenesis of GDM, adipose tissue resembles an autonomous endocrine organ. Adiponectin is one of the members of this hormone group [5].

Adiponectin reduces the use of insulin by the stimulator effect in the beta oxidation of fatty acids in the skeletal muscles. Adiponectin, synthesized by adipose tissue with 30 kDa weight, is a collagen-like protein. Adiponectin levels are inversely related to obesity and insulin resistance [6, 7]. Low adiponectin levels are related to type 2 DM and coronary artery disease, as well as to GDM. This is related to decreased insulin sensitivity and pancreatic β-cell functions. The risk of GDM is 5–6 times higher in women with low adiponectin levels when compared with women with high levels [8].

The aims of the present study were to investigate serum adiponectin levels at the time of diagnosis (at 24^{th}–28^{th} gestational weeks), at delivery and in the *post-partum* period in women with normal pregnancies, who had no glucose intolerance, and in GDM patients; to determine the relationship between serum adiponectin level and other prognostic and clinical factors and processes; to investigate possible roles of this hormone in fetal growth and development by measuring the levels in the umbilical cord blood at delivery; and to assess the extent of fetal influence.

Material and Methods

The study involved 55 patients with a single fetus diagnosed with GDM at 24^{th}–28^{th} week of gestation, and 50 women with normal pregnancies and without glucose intolerance, who were registered at the gynecology and obstetrics outpatient clinic of Dokuz Eylul University during one year. A two-stage screening method was preferred for the GDM diagnostic criteria. After a 50 g glucose challenge test (GCT), pregnant women with 140 mg/dL and over were given a 100 g oral glucose tolerance test (OGTT). GDM was diagnosed when 2 or more of the values of 4 maternal blood samples were high according to the Carpenter and Coustan criteria (normal glucose values: fasting ≥ 95, at hour 1 ≥ 180, at hour 2 ≥ 155, at hour 3 ≥ 140 mg/dL) [9]. Subjects for the control group were selected from healthy pregnant women who did not meet the following exclusion criteria:

– multiple pregnancies;

– kidney, liver, cardiac and chronic systemic inflammatory and infectious diseases;

Type 1 or Type 2 DM, chronic hypertension, polycystic ovary syndrome, hyperlipidemia before pregnancy, metabolic syndrome history;

– endocrine disorders;

– the use of drugs that might affect blood glucose and insulin levels;

– malignancies; and

– smoking habits.

During the follow-up, patients who experienced the following were also excluded (the number excluded from each study group is given in parentheses):

– pregnancy-induced hypertension, pre-eclampsia, eclampsia (3 GDM, 1 control);

– preterm delivery (2 GDM, 1 control);

– pre-term membrane rupture or received drugs for pre-term delivery risk (corticosteroids, ritodrine etc.) (2 GDM, 1 control);

– fetuses with malformations and/or metabolic disease (1 GDM);

– newborns delivered with intrauterine development retardation (1 control);

– fetal distress during delivery (3 GDM, 3 controls);

– women who did not continue the pregnancy follow-up at the outpatient clinic were also withdrawn from the study (4 GDM, 3 controls).

The study was conducted on a total of 80 patients (40 patients with GDM and 40 controls), and was designed as a single-center multidisciplinary controlled prospective clinical trial. The Clinical Trials Ethics Committee of Dokuz Eylul University approved the study. Informed consent forms were obtained from the study participants. Detailed anamneses including age, gravida, parity, previous and present pregnancy histories, personal history, family history, drug use, arterial blood pressure and weight gain during pregnancy were obtained. The patients' gestation dates were defined according to the first day of the last menstruation. In uncertain cases, the gestational week was estimated retrospectively by measuring the crown-rump length in the first trimester ultrasonography.

Weight and height measurements were performed for each patient included in the study. Body mass index (BMI) was calculated using the standard equation (weight [kg]/height^2 [m^2]). Pregestational weight and BMI were also recorded.

Patients diagnosed with GDM were hospitalized and a diabetic diet was started. Patients whose blood glucose was not regulated by diet alone were switched to insulin treatment. The blood glucose levels of discharged patients after blood glucose regulation were checked every two weeks under outpatient clinic conditions. All the pregnant women were followed up until delivery. Weight measurement was repeated at delivery, and weight gained during the pregnancy and the BMI at delivery were calculated. The weight and height of the fetus, gender, delivery route and Apgar scores in the 1st and 5th minutes were also recorded.

Laboratory Methods

At 24th–28th gestation weeks, maternal venous blood samples of 10 mL were collected from the antecubital area after fasting at least 8 h. Total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, hemoglobin A1c (HbA1c) and glucose levels were measured in the fasting maternal blood samples in an Abbott Architect C 16000 analyzer, using original Abbott kits (Abbott Laboratories, Abbott Park, IL, USA). Low density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula. Insulin and C-peptide levels were studied in an Immulite 2500 device (Siemens Healthcare Diagnostics, Deerfield, IL, USA) using the solid phase chemiluminescent immunometric method.

Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) index, using the formula [fasting glucose (mmol/mL) X fasting insulin (μIU/mL]/22.5. Adiponectin concentrations were measured using the enzyme-linked immunosorbent assay (ELISA) method (Assaypro, St. Charles, MO, USA). Detection limits were 0.5 ng/mL for adiponectin, and interassay co-efficient of variation (CV) values were calculated.

Maternal venous blood samples of 10 mL were again collected from the participants on the day of delivery and 24 h *post-partum*, after fasting for 8 h. In all participants, regardless of the route of delivery, 10 mL fetal blood samples were collected from the umbilical veins after clamping the umbilical cords during the delivery, after the fetus was out and before the placenta was detached. Adiponectin values were again measured separately for these serum samples.

Statistical Analyses

Statistical analyses were performed using SPSS software (Statistical Package for Social Sciences, version 15.0). Continuous variables were given as mean ± standard deviation (SD). The distribution of data was examined using the Kolmogorov-Smirnov test. For parametrically distributed data, Student's *t*-test was used in comparisons of the means of two groups. For non-parametrically distributed data, the Mann-Whitney *U* test was used. Correlations between data were investigated using Pearson's correlation test. In multiple variable examinations, the linear regression model was used for continuous variables, whereas the logistic regression model was used for categorical variables. The level of statistical significance for all tests was set at $p < 0.05$.

Results

A total of 80 pregnant participants were analyzed; 40 of the participants had GDM, and 40 were healthy. There was no significant difference between the GDM group and the control group in terms of age, gravidity, parity, weight, BMI and weight gain up to the 24th–28th week of gestation. Adiponectin levels in the GDM group were significantly lower than in the control group at 24th–28th week of gestation (the means were 2.45 ± 2.73 and 4.39 ± 4.33, respectively; $p = 0.02$).

A diabetic diet was started in all patients with GDM (n = 40). Insulin was added to the diabetic diet in 26 patients whose blood glucose levels were not regulated by diet alone. Insulin doses were increased until blood glucose levels were regulated. No diet or treatment was started in the control group.

At delivery, there was no significant difference between the GDM group and the control group in terms of delivery route, delivery week, newborn gender and weight, Apgar scores, maternal weight, weight gain and BMI during pregnancy.

During delivery, adiponectin levels were significantly lower in the GDM group (mean 3.92 ± 4.65) than in the control group (mean 6.7 ± 6.49; $p = 0.03$). In the umbilical cord, adiponectin levels were significantly lower in the GDM group (mean 20.77 ± 12.04) than in the controls (mean 27.78 ± 9.29; $p = 0.005$). In the fasting serum collected from the mother 24 h after delivery, adiponectin levels were significantly higher in the GDM group (mean 11.81 ± 5.81) when compared with the control group (mean 7.8 ± 5.97; $p = 0.009$). The results are presented in Table 1.

Table 1. Adiponectin levels in maternal serum and in the umbilical cord at delivery and *post-partum*

	GDM (n = 40)	Control (n = 40)	p
Adiponectin levels at delivery (ng/mL)	3.92 ± 4.65	6.7 ± 6.49	0.03*
Adiponectin levels in umbilical cord (ng/mL)	20.77 ± 12.04	27.78 ± 9.29	0.005*
Post-partum adiponectin levels (ng/mL)	11.81 ± 5.81	7.8 ± 5.97	0.009*

* – $p < 0.05$, significant.

Table 2. Correlations between adiponectin levels and the other variables at 24th–28th week of gestation

n = 80	Adiponectin levels at 24th–28th week	
	r	p
Age	0.03	0.79
BMI before pregnancy	0.094	0.4
BMI at 24th–28th week	0.061	0.59
Weight gain up to the 24th–28th week	0.085	0.45
Glucose challenge test	–0.095	0.4
HbA1C	–0.109	0.33
C-peptide	–0.093	0.41
Insulin	–0.094	0.4
C-peptide/insulin	–0.03	0.79
Fasting glucose	–0.087	0.44
HOMA-IR	–0.084	0.45
Triglyceride	–0.059	0.6
Total cholesterol	0.257	0.02*

* – $p < 0.05$, significant.

It was observed that in both groups the adiponectin levels in the umbilical cord were unaffected by fetal gender (p = 0.33), route of delivery (p = 0.11), fetal weight (p = 0.93), maternal BMI at delivery (p = 0.20), weight gain during pregnancy (p = 0.55) or maternal weight at delivery (p = 0.39). No differences in the adiponectin levels in the umbilical cord were detected in relation to insulin use by the GDM patients (in diet-only GDM patients the mean was 22.52 ± 13.06; in insulin users the mean was 19.60 ± 11.44; p = 0.43).

While maternal BMI at delivery was significantly higher in insulin receivers when compared with the diet-only GDM patients (p = 0.03), there was no significant difference between insulin receivers and diet-only GDM patients in terms of maternal serum adiponectin levels (p = 0.48), newborn weight (p = 0.36), maternal weight at delivery (p = 0.1) and maternal weight gain during pregnancy (p = 0.08).

For both the GDM group and the control group, there were no significant differences between serum adiponectin levels collected at delivery and those collected at 24th–28th week of gestation (in the GDM group, p = 0.73; in the controls, p = 0.07). While in patients with GDM adiponectin

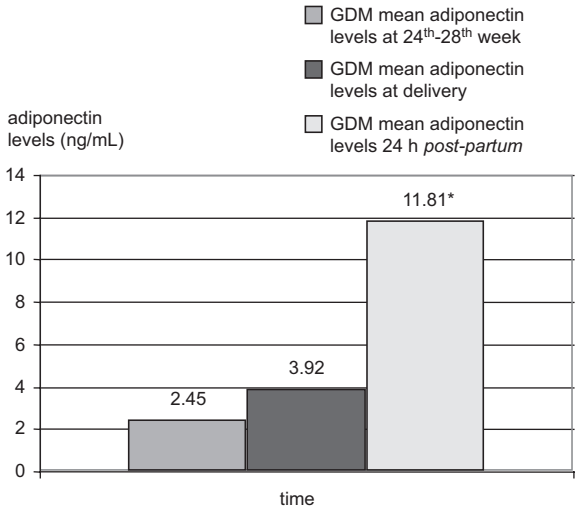

Fig. 1. Adiponectin levels in the GDM group
* GDM adiponectin levels at delivery and *post-partum*; $p < 0.001$

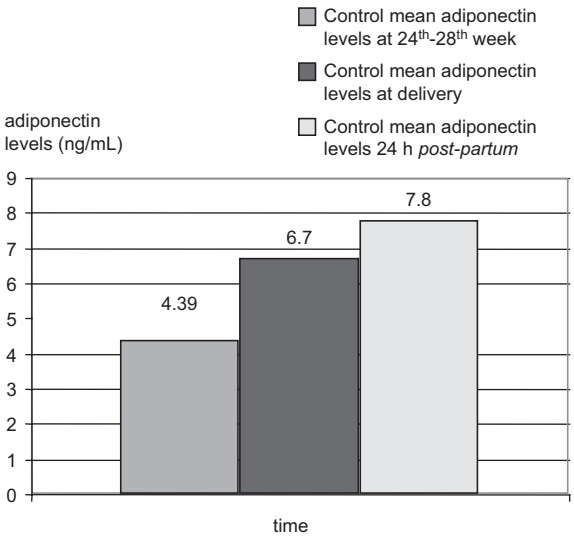

Fig. 2. Adiponectin levels in the control group

Table 3. Correlation between umbilical cord adiponectin levels and the other variables at delivery

n = 80	Umbilical cord adiponectin levels	
	r	p
BMI at delivery	–0.137	0.22
Maternal weight at delivery	–0.156	0.16
Maternal weight gain at delivery	0.208	0.64
Newborn weight	–0.026	0.81
Delivery week	0.258	0.02*
Adiponectin at diagnosis	0.026	0.81
Post-partum adiponectin	0.006	0.96

* – $p < 0.05$, significant.

Table 4. Multiple linear regression analysis model when adiponectin was defined as the dependent variable

Variable	β	Standard error	t	P
Age	0.106	0.079	0.914	0.36
Gestational week at diagnosis	0.264	0.233	2.333	0.02*
BMI before gestation (kg/m^2)	0.32	0.218	1.057	0.29
BMI at diagnosis (kg/m^2)	–0.2	0.223	–0.638	0.29

Dependent variable: adiponectin levels at 24th–28th gestational week; model $r^2 = 0.139$; * – $p < 0.05$, significant.

levels in maternal serum at delivery were significantly lower (mean 3.92 ± 4.65) than 24 h after delivery (mean 11.81 ± 5.81; $p < 0.001$), no significant difference was observed in the control group (maternal adiponectin mean at delivery 6.7 ± 6.49, and *post-partum* mean 7.8 ± 5.97; $p = 0.42$). Adiponectin levels during pregnancy in the GDM group and the control group are summarized in Fig. 1 and 2, respectively.

While there was significant favorable correlation between adiponectin levels at 24th–28th weeks and total cholesterol in Pearson's correlation ($p = 0.021$; $r = 0.257$), there was no correlation with the other parameters. Adiponectin levels at 24th–28th weeks of gestation and the other variables are shown in Table 2.

No correlation was observed between adiponectin levels in maternal serum at delivery and the other variables.

There was a significant correlation between adiponectin levels in the umbilical cord and the delivery week ($p = 0.02$, $r = 0.258$). There was no correlation with the other parameters. Pearson's correlation is shown in Table 3 for adiponectin levels in the umbilical cord and the other variables.

A multiple linear regression analysis was performed to determine the effects of the demographic characteristics of the subjects on adiponectin levels at 24th–28th weeks of gestation. When adiponectin was defined as the dependent variable, a correlation was found between adiponectin levels and the gestational week at which the subjects were included independently in the study ($\beta = 0.264$; $p = 0.02$). No independent correlation was found with the other variables. The multiple linear regression analysis model with adiponectin as the dependent variable is shown in Table 4.

In the model where adiponectin levels at delivery were defined as the dependent variable, none of the variables mentioned above was observed to affect adiponectin levels at delivery (model $r^2 = 0.096$).

In the model where adiponectin levels in the umbilical cord were defined as the dependent variable, GDM was observed to independently affect adiponectin levels in the umbilical cord ($\beta = 0.24$; $p = 0.04$; model $r^2 = 0.208$). Delivery week, fetal birth weight, gender of the fetus, maternal weight gain during pregnancy, route of delivery, maternal BMI and maternal adiponectin levels at delivery did not independently affect adiponectin levels in the umbilical cord.

Discussion

Adiponectin is a protein secreted from adipocytes, which are believed to play a role in the pathogenesis of GDM. There have been studies showing that adiponectin levels decrease in GDM patients when compared with normal pregnant women [10, 11], and also studies indicating that the levels in GDM patients do not differ from those of normal pregnant subjects [12]. In the present study, serum adiponectin levels were lower in GDM patients than in normal pregnant subjects at 24th–28th week of gestation. Contrary to expectations, a moderate positive correlation was found only between total cholesterol levels and adiponectin levels at 24th–28th week of gestation. It has been shown in many studies that adiponectin concentrations in the circulation are negatively correlated with triacylglycerol levels and positively correlated with HDL levels [12, 13]. Meanwhile, as the gestational age increased in both healthy and GDM patients, serum levels of hormone related cholesterol,

phospholipid and triglyceride were observed to physiologically increase [14, 15]. This finding was not consistent with the potential anti-atherogenic effect of adiponectin. Hotta et al. showed that low adiponectin levels were related to an increased risk of coronary artery disease [16]. It is known that adiponectin has anti-inflammatory effects on macrophage and endothelial cells. Therefore, it is believed that adiponectin can affect maternal immune tolerance against the fetus, directly or indirectly. New studies are required to evaluate how adiponectin changes blood lipid levels in different diseases and pregnancy.

In the regression analysis performed in this study, it was observed that only the gestational week and GDM independently affected adiponectin levels at 24th–28th week of gestation. This could be related to endocrine changes during pregnancy caused by ovarian and placental steroid hormones, which have previously been shown for leptin [17]. Thus, this finding also indicated that secretion or production of adiponectin could be induced by physiologically increasing insulin resistance during pregnancy. Altınova et al. performed a study on 34 GDM patients and 31 normal pregnant subjects, and they reported that adiponectin levels at 24th–28th week of gestation were lower in the GDM group. They found that there was an independent relationship only between this ratio and the HOMA-IR ratio [18]. Cseh et al. performed a study in non-diabetic pregnant subjects, and they reported lower adiponectin levels in the second and third trimesters when compared with the first trimester. They therefore suggested that low adiponectin levels in pregnancy, especially in GDM, played a role in insulin resistance [19]. The results of the current study also support this.

In rat studies, it has been shown that there was no change in adiponectin levels between pregestation and second trimester, and that the levels in the second trimester were decreased by increasing insulin resistance [20, 21]. Decreases in adiponectin levels became more prominent as glucose intolerance developed in the second trimester. Changes in adiponectin levels between the last trimester and delivery have not been clarified. As insulin sensitivity returned to normal limits in the *post-partum* period, increases in adiponectin levels were observed. It has not been confirmed whether there is adiponectin secretion from the placenta. Lappas et al. investigated adiponectin levels in maternal adipose and muscle tissues and in placenta and fetal membranes in 15 GDM and 15 normal pregnant subjects who underwent cesarean section. They showed that 70% of the adiponectin secretion was from maternal adipose tissue, and that part of the remaining adiponectin was secreted from the placenta, but they did not find a significant difference between the GDM and normal pregnant subjects [22]. When Corbetta et al. investigated adiponectin in fetal tissues, they observed that there was no adiponectin in the placenta [23]. In the current study, no difference was observed in adiponectin levels between the 24th–28th weeks of gestation and delivery. Adiponectin levels at delivery were lower in GDM patients than those in normal pregnant women. No significant difference was detected in the control group between adiponectin levels in the *post-partum* period when compared with the values at delivery; but it was observed that *post-partum* values were significantly increased in GDM patients. The results obtained showed that there was no change in adiponectin levels in the last trimester. Moreover, regardless of the treatment, the lower adiponectin levels in GDM patients compared to the controls were consistent with the study results of Corbetta et al., whose study was performed in weeks 37–41 of gestation [23]. In the current study *post-partum* adiponectin levels were found to be higher in GDM patients than in normal pregnant women.

Adiponectin can be found in fetal circulation at 24th week of gestation at the earliest. As gestational age increases, adiponectin levels in fetal circulation is observed to increase [24], and fetal adiponectin levels have been found to be markedly higher than those in the mother [25]. The current study yielded similar results. A moderate correlation was noted between the gestational age and adiponectin levels in the umbilical cord. No correlation between adiponectin levels in the maternal circulation and fetal circulation was detected in the present study, as it has been in previous studies [26, 27]. Adiponectin with 30 kDa molecular weight has most probably been secreted separately in the maternal and fetal circulation, because there is no transplacental crossing of molecules larger than 500 Da. This indicates that different mechanisms may play a role in adiponectin production and regulation in the fetus and the mother. In the regression analysis in this study, only the presence of GDM independently affected adiponectin levels in the umbilical cord. This suggests that adiponectin has an important role in fetal carbohydrate metabolism, especially in fetal circulation in the presence of GDM.

Comparing the results of this study with previous studies, contradictory results were found for other risk factors for GDM. In the present study, age, gestational age, BMI before gestation, BMI at diagnosis, BMI at delivery, maternal weight gain at diagnosis and during pregnancy were not independent risk factors for GDM. This indicates that adiponectin levels play a more important role in

glucose intolerance than the BMI. Abbasi et al. reported similar findings in their study [28].

Cseh et al. reported a negative correlation between maternal adiponectin levels and the birth weights of newborns in GDM patients when compared with pregnant subjects with normal glucose tolerance [19]. However, Chan et al. did not observe such a correlation in their study [26]. Low adiponectin levels and decreased insulin sensitivity may increase glucose support to the fetus, so they may increase the risk of fetal overgrowth in GDM patients [4]. In the present study, no correlation was found between adiponectin levels and fetal weight, nor were differences observed between the newborn weights in GDM patients and in pregnant subjects with normal glucose tolerance.

In conclusion, the current study is the first trial which compares adiponectin levels at 24th–28th week of gestation (the diagnostic weeks for GDM), at delivery (maternal circulation and umbilical circulation) and *post-partum* in GDM patients with those of pregnant women with normal glucose tolerance. The results suggest that a decrease in adiponectin levels may play a role in the development of insulin resistance in GDM patients. Circulating adiponectin levels in GDM patients may be regulated by changes in glucose and insulin metabolism. Further large scale and prospective studies are required to evaluate whether adiponectin decreases may be an early predictor for the development of type 2 diabetes in GDM patients.

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