ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

Adropin in pregnancy complicated by hyperglycemia and obesity — a preliminary study

Authors: Lukasz Adamczak, Pawel Gutaj, Ewa Wender-Ozegowska

DOI: 10.5603/GP.a2022.0031

Article type: Research paper

Submitted: 2022-01-12

Accepted: 2022-03-28

Published online: 2022-05-27

Adropin in pregnancy complicated by hyperglycemia and obesity — a preliminary study

Lukasz Adamczak, Pawel Gutaj, Ewa Wender-Ozegowska

Department of Reproduction, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan University of Medical Sciences, Poland

Corresponding author:
Lukasz Adamczak
Department of Reproduction, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan University of Medical Sciences, 33 Polna St, Poznan, Poland
e-mail: lukaszadamczak91@gmail.com

ABSTRACT

Objectives: According to the data, approximately 33–37% of women of reproductive age are obese. These numbers are reflected in the increasing number of complications in pregnancy, including gestational diabetes.

The study aims to assess the concentrations of adropin in the course of gestational diabetes and their possible relationship with the occurrence of obstetric complications characteristic for it.

Material and methods: The study included 65 obese and overweight pregnant patients (BMI > 27 kg/m^2) with glycemic disorders diagnosed during pregnancy. Blood samples we collected during visits: V0 — the first half of pregnancy V1 — 28–32 weeks of gestation, and V2 — 37–39 weeks of gestation. The concentrations of adropin were measured during V1 and V2 by ELISA tests. We analyzed the studied patients' anthropometric, metabolic parameters and obstetrical results.

Results: In the study group, at the visit V1, the mean level of adropin was 525.5 mmol/mL and 588.1 mmol/mL for the V2 visit. The comparison of adropin concentration between visits showed a statistically significant increase (p = 0.02). The concentration of adropin did not

differ between obese and morbidly obese patients at V1, but at V2, there was a significant lover adropin level in morbidly obese patients.

Conclusions: In overweight and obese pregnant patients with gestational diabetes, the levels of adropin in serum increased significantly in the last trimester of pregnancy. The increase in concentration was significantly lower in the morbidly obese patients than in the obese group. The study provides the basis for further analyses of the role of adropin in pregnancies complicated by obesity and gestational diabetes.

Key words: adropin; gestational diabetes mellitus; obesity; pregnancy

INTRODUCTION

Hyperglycemia in pregnancy, defined either as gestational diabetes mellitus (GDM) or overt diabetes/diabetes in pregnancy (DIP), is associated with adverse feto-maternal outcomes [1]. The Hyperglycemia and Pregnancy Outcomes (HAPO) study showed that the risk of adverse perinatal outcomes increased due to maternal glycemia, even within ranges considered normal for pregnancy [2]. Both GDM and even diabetes in pregnancy rarely present with symptoms. Diagnosis is made by screening and clinical risk factors used to identify it in early pregnancy or between 24 and 28 weeks. Gestational diabetes mellitus (GDM) has become more prevalent since the introduction of more stringent criteria for diagnosis (World Health Organization [WHO], 2013) and a constantly growing number of overweight and obese women of reproductive age. According to national guidelines every women in Poland should be screened for risk factors for hyperglycemia in pregnancy. In high-risk women, 75 g oral glucose tolerance test (OGTT) at first visit during gestation confirms or excludes the GDM (PSOG, PDS) [3].

Maternal hyperglycemia is a well-known risk factor for adverse neonatal outcomes. Nowadays, increasing evidence shows that non-glycemic risk factors for perinatal complications are still more frequent in diabetic pregnancies despite improved maternal metabolic control [4]. Among them, particularly maternal obesity has gained growing attention as an independent contributor to feto-maternal complications.

Body mass index (BMI) is a risk factor in pregnancy to identify women at risk of developing hyperglycemia and other perinatal complications. Several adipokines may also serve as factors confirming the role of adipose tissue in developing carbohydrate disturbances. Adropin is a peptide hormone involved in glucose and fatty acids metabolism [5]. It is

produced mainly in the liver, CNS tissues, kidneys and pancreas. In mice, adropin promotes muscle glucose oxidation more than fatty acid oxidation. It increases glucose tolerance by reducing insulin resistance. In a mouse model, it has also been shown that adropin reduces blood glucose levels by inhibiting its production in the liver [6]. The role of adropin in pregnancy complicated by diabetes and obesity has not been extensively studied in humans.

We wanted to confirm that hyperglycemia detected in early pregnancy is related to the degree of maternal obesity and that severity of obesity is associated with feto-maternal complications. We assumed also that hyperglycemia detected in early pregnancy and its consequences together with other metabolic aterations, might be associated with changes in concentration of adropin.

MATERIAL AND METHODS

We analyzed 389 pregnant women with hyperglycemia detected during pregnancy, admitted to the Department of Reproduction at Poznan University of Medical Sciences in 2018–2020. The study included 65 patients who met the inclusion criteria: single pregnancy, age ≥ 18 years, BMI before pregnancy ≥ 30.0 kg/m^2 and hyperglycemia diagnosed during pregnancy.

The study protocol encompassed three visits: the enrolment visit (V0) — the first patient's admission to the Department immediately after diagnosing glycemic disorders, the first study visit (V1) between 28 and 32 gestational weeks (GW), and the second study visit (V2) between 37 and 39 GW. Finally, we analyzed the feto-maternal results. On the V1 and V2, anthropometric measurements and blood sample collection we performed in all patients. In the study group, hyperglycemia during pregnancy was diagnosed according to the diagnostic criteria of the Polish Diabetes Association of 2017 (4). Diabetes in pregnancy (DIP) was diagnosed according to the 2013 IADPSG and WHO classification and adopted in our country [7]. Upon the first admission, all referred women participated in the dietary treatment and glucose self-control training. In women with DIP, insulin therapy in a basal-bolus mode was initiated immediately after the admission. Women with GDM had their follow-up visits scheduled every two to three weeks in the outpatients' clinic. If glycemic targets were not met at the first follow-up visit, we added insulin therapy in a basal-bolus mode to the diet.

The study group was divided according to the severity of obesity based on the WHO classification [8]. The obese patients were compared with morbidly obese to find possible differences between patients with the first grade of obesity and morbid obesity.

Blood samples were taken overnight in the fasting state and immediately transported for analysis. Serum concentrations of adropin we determined during the V1 and V2, using the enzyme-linked immunosorbent assay (ELISA) [Commercial kits Human AD (Adropin) ELISA Kit]. Fetal weight diagnosed as LGA — large for gestational age or as SGA — small for gestational age were defined according to Fetal Medicine Foundation criteria [9].

We used Statistica 13.1 program. Descriptive statistics characterized parameters — the D'Agostino-Pearson test we used for testing the normality of data distribution. Student's t-test we used to check t the difference between two continuous variables If data fitted normal distribution. Comparisons of non-normally distributed data we performed using the Mann-Whitney test. The Chi-Square test was used to examine differences between categorical variables.

RESULTS

The study group was characterized by anthropometric and metabolic parameters, obstetric results, and neonatal outcomes. They are presented in Table 1.

Comparing patients with the first degree of obesity with patients with the third degree of obesity has shown a significant difference in HbA1c values between both groups, only during the V0 visit. There were also no differences in daily insulin doses between groups. In patients with lower stage of obesity, a more significant increase in HbA1c we noted than in morbidly obese patients both between individual visits and during the entire period of pregnancy. We noticed a significant increase in adropin concentrations measured at V1 and V2 ($p = 0.02$) (Tab. 1).

We also analyzed the correlations between adropin concentration with BMI, weight gain, HbA1c, triglycerides, CRP, placental weight. There were no significant correlations. Adropin did not differ between obese and morbidly obese patients at visit V1. At the end of pregnancy at V2, adropin's concentration was significantly lower in morbidly obese patients than in obese. Adropin concentration in the third trimester was significantly higher in obese patients than in the second one. There were no differences in neonatal outcomes between these two analyzed groups.

DISCUSSION

In our preliminary study, a significant increase in the concentration of serum adropin was observed in the third trimester among hyperglycemic women with obesity and but not in women with morbid obesity. We know from previous studies that adropin levels in women with gestational diabetes are lower than those in healthy pregnant women [10]. However, our study showed increased adropin concentration in the last weeks of pregnancy, especially in the slimer subgroup, which has not been previously reported. It has been demonstrated in animal models that the exogenous administration of adropin promotes the reduction of insulin resistance and enhances glucose tolerance [11]. Our patients, in whom we observed an increase in adropin concentration, were well metabolically controlled and maintained low fat and low carbohydrate diet, as was evidenced by proper HbA1c values. Most of them were treated with insulin from the end of the first trimester. It might have affected the endogenous increased secretion of adropin, which regulates the glucose metabolism in the pregnant state. The available studies have reported that BMI significantly influences the concentration of adropin [12]. In the entire study group, during V1, the difference in adropin concentration was not significant; however, at the end of pregnancy concentration of adropin increased significantly in the slimer liner group of patients.

Adropin influences the expression of an inducible nitric oxide synthase, explaining its potential role in predicting endothelial dysfunction in patients with diabetes mellitus [13]. We would like to emphasize that both groups differed metabolically only in CRP concentrations aside from BMI and anthropometrics. We speculate that it might be the critical factor predisposing to lower adropin concentration in morbidly obese women, especially in late pregnancy when insulin resistance rises significantly. The literature described a reduction in adropin levels in obese people, as shown in our study [14]. We showed no correlation between the concentration of adropin and the newborns' birth weight.

Qiu et al. [15] assessed the correlation between adropin in the umbilical cord blood. They found no correlation with the birth weight of newborns, but a positive correlation occurred with the weight of the placenta what we also observed in our study. The available literature does not explain this phenomenon, but there are assumptions that adropin is also partly produced by the placenta.

Despite being morbidly obese, the patients were metabolically well-controlled, which probably resulted in the lack of significant differences in obstetric results in both groups. Interestingly, patients with the first degree of obesity in the third trimester experienced a significantly higher adropin concentration than patients with the third degree. We speculate that a lower BMI is conducive to endogenous adropin production and its protective effect on insulin resistance increase at the end of pregnancy.

To conclude, our study presents novel findings on the role of adropin in the pathomechanism of insulin resistance and carbohydrate disturbances in pregnancy complicated with obesity. In some cases, we have found that the ability to produce adropin in a higher amount reduces insulin resistance and might protect against hyperglycemia. However, it also has significant limitations such as relatively small sample size and lack of healthy controls. Addressing these issues in future studies could further explain the role of this adipokine in pregnancy-related complications.

Contribution statement

LA and EWO conceived the idea for the study. EWO contributed to the design of the research. LA was involved in data collection. LA and PG analyzed the data. All authors edited and approved the final version of the manuscript.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Cremona A, O'Gorman C, Cotter A, et al. Effect of exercise modality on markers of insulin sensitivity and blood glucose control in pregnancies complicated with gestational diabetes mellitus: a systematic review. Obes Sci Pract. 2018; 4(5): 455–467, doi: 10.1002/osp4.283, indexed in Pubmed: 30338116.

2. Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL): A Randomized Controlled Trial. Diabetes Care. 2016; 39(1): 24–30, doi: 10.2337/dc15-0511, indexed in Pubmed: 26223239.

3. Diabetology C. 2017 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clinical Diabetology. 2017; 6(1): 1–80, doi: 10.5603/DK.2017.0001.

4. Barrett HL, Dekker Nitert M, D'Emden M, et al. Validation of a triglyceride meter for use in pregnancy. BMC Res Notes. 2014; 7: 679, doi: 10.1186/1756-0500-7-679, indexed in Pubmed: 25264288.

5. Marczuk N, Cecerska-Heryć E, Jesionowska A, et al. Adropin - physiological and pathophysiological role. Postepy Hig Med Dosw (Online). 2016; 70(0): 981–988, doi: 10.5604/17322693.1220082, indexed in Pubmed: 27668650.

6. Thapa D, Xie B, Manning JR, et al. Adropin reduces blood glucose levels in mice by limiting hepatic glucose production. Physiol Rep. 2019; 7(8): e14043, doi: 10.14814/phy2.14043, indexed in Pubmed: 31004398.

7. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract. 2014; 103(3): 341–363, doi: 10.1016/j.diabres.2013.10.012, indexed in Pubmed: 24847517.

8. Kopelman PG. Obesity as a medical problem. Nature. 2000; 404(6778): 635–643, doi: 10.1038/35007508, indexed in Pubmed: 10766250.

9. Nicolaides KH, Wright D, Syngelaki A, et al. Fetal Medicine Foundation fetal and neonatal population weight charts. Ultrasound Obstet Gynecol. 2018; 52(1): 44–51, doi: 10.1002/uog.19073, indexed in Pubmed: 29696704.

10. Celik E, Yilmaz E, Celik O, et al. Maternal and fetal adropin levels in gestational diabetes mellitus. J Perinat Med. 2013; 41(4): 375–380, doi: 10.1515/jpm-2012-0227, indexed in Pubmed: 23314506.

11. Gao Su, McMillan RP, Zhu Q, et al. Therapeutic effects of adropin on glucose tolerance and substrate utilization in diet-induced obese mice with insulin resistance. Mol Metab. 2015; 4(4): 310–324, doi: 10.1016/j.molmet.2015.01.005, indexed in Pubmed: 25830094.

12. Butler AA, Tam CS, Stanhope KL, et al. Low circulating adropin concentrations with obesity and aging correlate with risk factors for metabolic disease and increase after gastric bypass surgery in humans. J Clin Endocrinol Metab. 2012; 97(10): 3783–3791, doi: 10.1210/jc.2012-2194, indexed in Pubmed: 22872690.

13. Topuz M, Celik A, Aslantas T, et al. Plasma adropin levels predict endothelial dysfunction like flow-mediated dilatation in patients with type 2 diabetes mellitus. J Investig Med. 2013; 61(8): 1161–1164, doi: 10.2310/JIM.0000000000000003, indexed in Pubmed: 24113736.

14. Zang H, Jiang F, Cheng X, et al. Serum adropin levels are decreased in Chinese type 2 diabetic patients and negatively correlated with body mass index. Endocr J. 2018; 65(7): 685–691, doi: 10.1507/endocrj.EJ18-0060, indexed in Pubmed: 29669965.

15. Qiu X, He JR, Zhao MG, et al. Relationship between human cord blood adropin levels and fetal growth. Peptides. 2014; 52: 19–22, doi: 10.1016/j.peptides.2013.11.013, indexed in Pubmed: 24284417.

Table 1. Characteristics of the study group

	Study group (n 65)	Obese (n 20)	Morbidly obese (n 21)	p*
Maternal parameters				
Maternal age [years]	32.4	32.2	32.2	0.9
Maternal BMI BP [kg/m^2]	36.9	32.6	43.7	0.02
Maternal BMI V1 [kg/m^2]	38	34.6	43.2	< 0.01
Maternal BMI V2 [kg/m^2]	38.8	35.5	44.2	< 0.01
Maternal weight change (BP to V1) [kg]	2.4	5.9	−1.4	< 0.01
Maternal weight change (V1 to V2) [kg]	2.5	2.5	2.5	0.9
Maternal weight change (BP to V2) [kg]	4.6	7.0	1.25	0.004
Metabolic parameters				
Gestational diabetes in previous pregnancy n [%]	15	3	6	0.3
Diabetes in I grade relatives n [%]	44	16	18	0.7
75g OGTT results				
0 min [mg/dL]	100	100.1	103.1	0.2
60 min [mg/dL]	179.5	188.7	181.8	0.3
120 min [mg/dL]	141	148.2	149.3	0.5
Beginning of dietary treatment [week of pregnancy]	12	11	11	0.5
Beginning of insulin therapy [week of pregnancy]	16	15	14	0.6
Insulin therapy n (%)	56	16 (80)	18 (86)	0.6
HbA1c V0 [%]	5.3	5.1	5.4	0.02
HbA1c V1 [%]	5.1	52	5.0	0.3
HbA1c V2 [%]	5.5	5.3	5.5	0.9
HbA1c change V0–V1	−0.1	0.19	−0.38	< 0.01
HbA1c change V1–V2	0.3	0.2	0.34	0.2
HbA1c change V0–V2	0.2	0.37	0.03	0.01
CRP V0 [mg/dL]	8.12	5.0	14.0	0.001
CRP V1 [mg/dL]	7.48	6.1	13.4	0.008
CRP V2 [mg/dL]	8.3	5.2	7.1	0.2
Chronic hypertension n (%)	12	4 (20)	8 (38)	0.2
Gestational hypertension n (%)	8	4 (20)	3 (14)	0.7
Preeclampsia n (%)	7	2 (10)	3 (14)	0.4
Adropin concentration V1 [pg/mL]	525.5	557.8	534.7	0.7
Adropin concentration V2 [pg/mL]	588.1	690.2	551.5	0.04
Adropin concentration change V1–V2 [pg/mL]	62.6	143.4	10.6	0.04
Perinatal outcome				
Week of delivery median [week] (IQR)	38 (0)	38 (0)	38 (0)	
Premature birth n (%)	4 (6)	1 (5)	1 (5)	0.7
Cesarean section n (%)	45 (68,5)	14 (70)	16 (76)	0.6
Elective	33 (73)	12 (86)	12 (75)	1
Urgent	12 (27)	2 (14)	4 (25)	0.4
Neonatal birthweight median [g] (IQR)	3610 (680)	3540 (590)	3640 (675)	0.5
Birthweight centile acc. to FMF [centile]	89	70	74	0.2

LGA > 90 n (%)	30 (45.5)	8 (40)	14 (67)	0.2
SGA < 10 n (%)	2 (3)	1 (5)	0	0.1
Neonatal birthweight > 4000 g n (%)	8 (12)	3 (15	2 (10)	0.6
Neonatal birthweight > 4250 g n (%)	3 (4.5)	2 (10)	0	0,1
Apgar score 1st minute — median (IQR)	10 (1)	10 (1)	10 (1)	0.6
Apgar score 5th minute — median (IQR)	10 (1)	10 (0)	10 (0)	0.6

p* — the difference between obese and morbidly obese group; BP — first visit in pregnancy; CRP — C-reactive protein; DBP — diastolic blood pressure; HbA1c — glycated hemoglobin; SBP — systolic blood pressure; TAG — triglyceride; $V_{0,}$ — inclusion visit; V_1 —28–32 GA visit; $V_{2,}$— 37–40 GA visit