

## CLINICAL STUDY

# Serum vaspin levels in normal pregnancy in comparison with non-pregnant women

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## Abstract

**Objective:** Pregnancy represents a state of insulin resistance (IR). Vaspin (SERPINA12) is a novel insulin-sensitizing adipokine that might be implicated in endogenous glucose regulation. However, its role in pregnancy and its circulating levels have not been adequately studied. We aimed to evaluate serum vaspin levels in pregnancy and their correlation with known markers of IR.

**Design:** A group of 106 women (age  $27.9 \pm 0.4$  years) at the 24–30th week of gestation (pregnancy group) and another 106 age-matched healthy non-pregnant controls (control group) were included in the study.

**Methods:** Serum glucose, insulin, vaspin, adiponectin, and lipid parameters were measured. The quantitative insulin sensitivity check index (QUICKI) was used as an insulin sensitivity index.

**Results:** Pregnant women had significantly higher body mass index (BMI), lipids, and serum insulin and lower serum glucose and vaspin levels than controls. Vaspin was positively correlated to adiponectin in both groups ( $P < 0.001$  and  $P < 0.004$  respectively) but was not correlated to BMI, serum insulin levels, or the QUICKI index in either group. Furthermore, vaspin was negatively correlated to lipid parameters (total cholesterol, triglycerides, and low-density lipoproteins) in the pregnant but not in the non-pregnant women.

**Conclusions:** Vaspin cannot serve as a marker of IR in either pregnant or non-pregnant women, although it is significantly correlated with adiponectin. On the other hand, vaspin might be useful as a surrogate marker of lipid metabolism in pregnancy if confirmed by subsequent studies.

*European Journal of Endocrinology* 164 579–583

## Introduction

Human pregnancy is characterized by insulin resistance (IR), traditionally attributed to the effects of placental hormones (1); as pregnancy advances, IR becomes more intense and could lead to the development of gestational diabetes, a majority of which manifests at the 24–28th week of gestation (2). A large amount of evidence has recently supported the role of adipose tissue in the regulation of IR in both non-pregnant and pregnant women. In this respect, adipocyte-derived hormones, the adipokines, have been implicated in the regulation of maternal metabolism and gestational IR.

Recently, visceral adipose tissue-derived serpin (vaspin or SERPINA12), a member of serine protease inhibitor family, has been identified as a novel adipokine with potential insulin-sensitizing effects that might be implicated in endogenous glucose regulation (3, 4). High vaspin mRNA expression in the adipose tissue of obese and type 2 diabetic subjects has been reported, and it has been proposed that it could represent a

compensatory mechanism associated with severe IR (5, 6). Indeed, vaspin mRNA expression decreased with body weight loss and worsening of diabetes in both animal models (3, 7) and humans (8).

Vaspin circulating levels are likely to reflect its expression in the adipose tissue (9). Higher vaspin and lower adiponectin levels have been reported in obese humans (9, 10); physical training (9, 11) and weight loss (12) are associated with a reduction of circulating vaspin, insulin, and IR, evaluated by homeostasis model of assessment-IR (HOMA-IR). In type 2 diabetic subjects, both higher (13, 14) and similar vaspin levels (8, 9, 15) compared with controls have been reported. Vaspin levels have been negatively correlated with adiponectin (10) and positively correlated with body mass index (BMI), triglycerides (TG), fasting insulin, and IR, evaluated by HOMA-IR or euglycemic-hyperinsulinemic clamp (EHC) in most (9, 10, 12) but not all the studies (8, 11, 15, 16).

During pregnancy, vaspin expression in the placenta has been reported to increase gradually, reaching the

highest levels at the end of gestation (17). However, in an animal model, vaspin levels did not change throughout pregnancy (18). The only study evaluating circulating vaspin levels in pregnant women reported no correlation between vaspin and parameters of insulin sensitivity or lipid metabolism (19). In the same study, vaspin levels were similar between women with gestational diabetes and normal pregnancy.

The aim of this cross-sectional study was to evaluate serum vaspin levels in normal pregnancy compared with healthy age-matched controls and their correlations with known markers of IR, in an attempt to investigate vaspin's role in a physiological model of IR, such as pregnancy.

## Patients and methods

### Patients

Pregnant women were recruited at the outpatient obstetrics clinics of the Fourth Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Thessaloniki, Greece. Non-pregnant controls were recruited from the female military staff referred to the 424 Military Hospital, Thessaloniki, Greece, for their annual check-up examination. A group of 106 consecutive Caucasian women (age  $27.9 \pm 0.4$  years) at the 24–30th week of gestation were included in the study (pregnancy group) and 106 consecutive age-matched healthy Caucasian women (age  $27.1 \pm 0.5$  years) served as controls (control group). Exclusion criteria were i) abnormal glucose homeostasis (impaired fasting glucose, impaired glucose tolerance, or overt type 1 or 2 or gestational diabetes); ii) diseases or conditions that could affect glucose homeostasis; and iii) any medication that could affect glucose homeostasis during the last month. The study was approved by the local Ethics Committees and was in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice.

### Methods

Gestational age was determined by first trimester ultrasound in all pregnant women. Baseline assessment included history, physical examination, and BMI calculation at the given time point of pregnancy. Morning (0800–0900 h) fasting blood samples were obtained from all the women. The samples were centrifuged immediately and serum was separated and stored at  $-30^\circ\text{C}$ ; all measurements were performed simultaneously at the end of the study. Parameters studied included serum levels of glucose (Glu – enzymatic-u.v. method, Roche Diagnostics – normal range 70–100 mg/dl), total cholesterol (TC – enzymatic chromatometry, Roche Diagnostics – normal range  $<200$  mg/dl), TG (enzymatic chromatometry, Roche

Diagnostics – normal range  $<150$  mg/dl), high-density lipoprotein (HDL – enzymatic chromatometry, Roche Diagnostics – normal range female  $<45$  mg/dl), low-density lipoprotein (LDL – enzymatic chromatometry, Roche Diagnostics – normal range 88–188 mg/dl), insulin (electrochemiluminescence immunoassay, Roche Diagnostics – sensitivity  $0.2 \mu\text{IU/ml}$ , intra-assay coefficient of variation (CV) 1.5–2.0%, inter-assay CV 2.1–2.8%), adiponectin (ELISA, Ray Biotech, Norcross, GA, USA – sensitivity 25 pg/ml, intra-assay CV  $<10\%$ , inter-assay CV  $<12\%$ ), and vaspin (ELISA – sensitivity 2.62 ng/ml, intra-assay CV  $<10\%$ , inter-assay CV  $<15\%$ ). The quantitative insulin sensitivity check index (QUICKI) calculated by the formula  $\text{QUICKI} = 1/\log \text{insulin } (\mu\text{IU/ml}) + \log \text{glucose } (\text{mg/dl})$  was used as an insulin sensitivity index.

### Statistical analysis

Assessment of normality was performed with the use of Kolmogorov–Smirnov test. Data were described as mean  $\pm$  s.e.m. or median (interquartile range) on the basis of distribution. Differences between two groups were assessed using the non-parametric Mann–Whitney *U* test. Associations between variables were assessed by Spearman's rank correlation. Multiple regression analysis was not undertaken since dependent variables significantly departed from normality, even after a series of data transformations. Two-tailed statistical significance was set at 5%. Statistical analyses were performed with SPSS software version 17.0 (SPSS, Chicago, IL, USA).

## Results

Anthropometric and metabolic characteristics of the women in the two groups are presented in Table 1.

Pregnant women had significantly higher BMI, serum insulin, TC, TG, HDL, and LDL levels and lower serum glucose and vaspin levels than controls. The two groups did not differ in serum adiponectin levels and the QUICKI index.

The vaspin and adiponectin levels in the pregnant women classified according to the gestational week are depicted in Fig. 1.

### Correlations

Correlations between serum vaspin and the other measured parameters in the two groups are presented in Table 2. Vaspin was positively correlated to adiponectin in both the pregnant and the non-pregnant women ( $P < 0.001$  and  $P < 0.004$  respectively) but was not correlated to BMI, serum insulin levels, or the QUICKI index in either group (Table 2). Adiponectin was positively correlated to the QUICKI index and negatively correlated to insulin in the non-pregnant

**Table 1** Anthropometric and metabolic characteristics of the pregnancy and control groups. Data are described as mean  $\pm$  S.E.M. for parametric and as median (interquartile range) for non-parametric variables.

	Pregnancy (n=106)	Controls (n=106)	P value
Age (years)	28 (6)	27 (8)	0.178
BMI (kg/m <sup>2</sup> )	25.95 (5.01)*	22.04 (4.19)	<0.001
Glu (mg/dl)	83.7 $\pm$ 0.8*	92.5 $\pm$ 0.8	<0.001
Insulin ( $\mu$ U/ml)	7.1 (5.1)*	5.6 (4.6)	0.040
QUICKI	0.361 $\pm$ 0.003	0.368 $\pm$ 0.003	0.143
TC (mg/dl)	253.9 $\pm$ 4.6*	186.9 $\pm$ 3.1	<0.001
TG (mg/dl)	187.0 (82.5)*	78.0 (39.3)	<0.001
HDL (mg/dl)	72.2 $\pm$ 1.3*	56.5 $\pm$ 1.2	<0.001
LDL (mg/dl)	138.0 (54.5)*	110.5 (38.8)	<0.001
Adiponectin (pg/ml)	1050.0 (2409.6) (79.4–11 500.0) <sup>a</sup>	400.0 (1767.5) (125.5–10 750.0) <sup>a</sup>	0.106
Vaspin (ng/ml)	26.0 (15.0)*	32.0 (18.5)	<0.001

\* $P$ <0.05 versus controls. BMI, body mass index; Glu, glucose; QUICKI, quantitative insulin sensitivity check index; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins.  
<sup>a</sup>Minimum and maximum value.

women ( $r=0.287$ ,  $P=0.003$  and  $r=-0.309$ ,  $P=0.001$  respectively) but not in the pregnant women ( $r=0.063$ ,  $P=0.524$  and  $r=-0.037$ ,  $P=0.707$  respectively).

Vaspin was negatively correlated to lipid parameters (TC, TG, and LDL) in the pregnant but not in the non-pregnant women (Table 2). Adiponectin was not correlated to lipid parameters in either group.

## Discussion

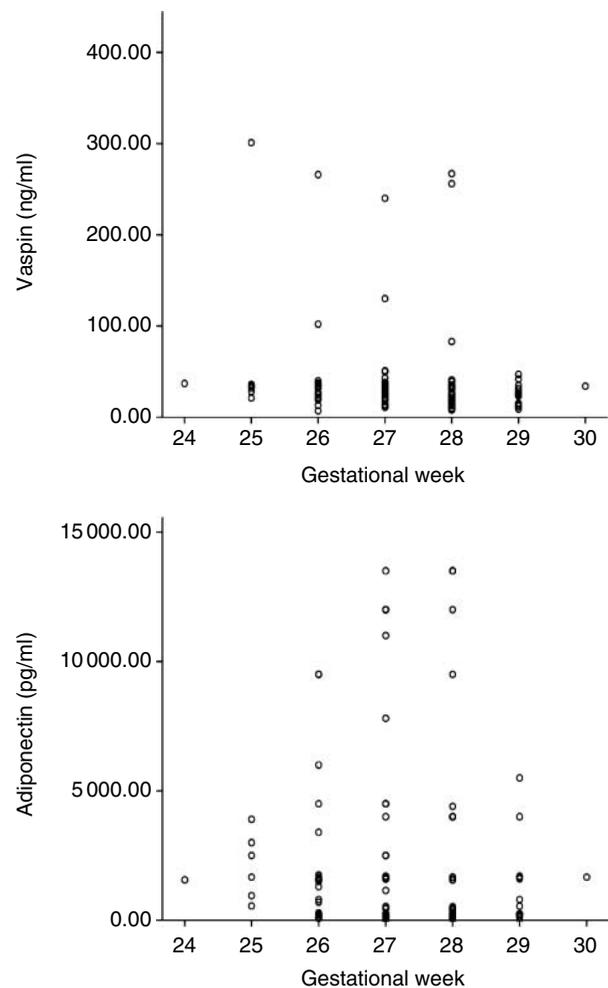
Vaspin is a novel insulin-sensitizing adipokine that might be implicated in endogenous glucose regulation. In this study, we evaluated serum vaspin levels in normal pregnancy compared with age-matched controls and their correlations with known markers of IR, in an attempt to investigate its potential role in gestation-induced IR.

Pregnant women in our study had significantly lower glucose and higher insulin levels, as expected (2). Vaspin levels were lower in pregnant women than in non-pregnant controls. To the best of our knowledge, we are the first to report this finding.

Obesity or poor control of diabetes and therefore increased glucose levels have been associated with increased vaspin (8, 9), while metformin treatment in women with diabetes (8) or polycystic ovary syndrome (20) resulted in significant decrease of vaspin levels. Furthermore, *ex vivo*, the production and secretion of vaspin was dose dependently increased when the adipose tissue was cultured with the addition of glucose, but not with the addition of insulin (20). It is of interest that in our study, the pregnant women had lower glucose and lower vaspin levels compared with the non-pregnant ones, in accordance with the above findings.

Vaspin was positively correlated to adiponectin in both the groups. This finding seems to be reasonable since both of them are insulin-sensitizing adipokines. In the only other study reporting circulating levels of vaspin in normal pregnant women, no correlation with adiponectin levels was found (19). In non-pregnant populations, conflicting data exist in the literature, with reports about both negative (10) and no correlation (11) between vaspin and adiponectin, in contrast to our findings. This discrepancy could be due to the younger age of the subjects in the above studies (10, 11), the use of mixed gender populations (10, 11), race differences (11), or finally BMI differences (10, 11), since these studies evaluated obese subjects, whose weight and adipose tissue distribution differs from the observed in a pregnancy state.

Despite the correlation with adiponectin in our study, vaspin levels were not correlated to BMI, serum insulin levels, or the QUICKI index in either group. In the literature, conflicted data have been published, as some studies in normal and obese subjects reported a positive



**Figure 1** Vaspin and adiponectin levels as a function of the gestational week.

**Table 2** Correlations between serum vaspin and the other measured parameters in the two groups (Spearman's rank correlation).

	Pregnancy (n=106)		Controls (n=106)	
	r	P	r	P
Age	-0.127	0.195	-0.008	0.937
BMI	-0.156	0.115	-0.025	0.800
Glu	-0.099	0.315	0.053	0.588
Insulin	-0.030	0.762	0.039	0.693
QUICKI	0.056	0.572	-0.047	0.635
TC	-0.287	0.003 <sup>†</sup>	0.095	0.334
TG	-0.223	0.022 <sup>*</sup>	0.045	0.647
HDL	0.100	0.312	0.235	0.015 <sup>*</sup>
LDL	-0.321	0.001 <sup>†</sup>	0.007	0.940
Adiponectin	0.636	<0.001 <sup>†</sup>	0.274	0.004 <sup>†</sup>

\* $P < 0.05$ , <sup>†</sup> $P < 0.01$ . BMI, body mass index; Glu, glucose; QUICKI, quantitative insulin sensitivity check index; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

correlation with BMI, fasting insulin, and IR, estimated by HOMA-IR (10, 12) or EHC (9), while others reported negative (8, 11) or even no correlation (13, 16). Differences in sample size, population characteristics (gender, race, and BMI), presence of concomitant diseases that could affect glucose metabolism, or the methodology used to estimate insulin sensitivity/resistance could be responsible for these discrepancies. The lack of correlation between vaspin and BMI in our cohort, in contrast to studies in obese subjects, could also be attributed to the fact that body weight augmentation in pregnancy is quite different than in obesity, as it does not represent just an increase of the adipose tissue. Additionally, no correlation between BMI, insulin, and insulin sensitivity was observed in diabetic patients in several studies, in accordance to our findings (8, 9, 15). Furthermore, Seeger *et al.* (15) found no association between vaspin and BMI or insulin sensitivity in patients on chronic hemodialysis. Finally, the lack of correlation between vaspin and parameters of insulin sensitivity in our data is in accordance with the only other study evaluating circulating vaspin levels in pregnant women (19).

Serum TC and TG concentrations are expected to increase markedly during pregnancy (21). Indeed, in our population, increased lipid levels were observed in pregnant compared with non-pregnant women. In our pregnant subjects, lower vaspin levels were associated with higher levels of TC, TG, and LDL. This correlation was not evident in the non-pregnant women. In patients with carotid stenosis, low serum vaspin was correlated with recent ischemic events, despite the lack of association between circulating vaspin and parameters of atherosclerosis severity (4). In the study by Stepan *et al.* (19) in pregnant women, no correlation between serum vaspin and parameters of lipid metabolism was also reported, in contrast to our findings.

In our control population, a positive correlation between vaspin and HDL was observed, in accordance

with other studies in subjects with normal renal function (glomerular filtration rate (GFR) > 50 ml/min) (15) and type 2 diabetes (13).

Although it has been reported that maternal adiponectin levels in the third trimester are lower than those in the pregravid condition (22), they were similar between pregnant and non-pregnant women in our study, in accordance to other studies (23).

In our non-pregnant women, serum adiponectin was positively correlated to insulin sensitivity (QUICKI) and negatively correlated to insulin levels, as expected (24). However, these correlations were lost in the pregnant subjects; in accordance to our study, McLachlan *et al.* (25) found no correlation between adiponectin and insulin sensitivity, as estimated by intravenous glucose tolerance test (IVGTT), in 19 older Australian pregnant women with higher BMI; on the other hand, in contrast to our study, in 219 Asian pregnant women of similar BMI, adiponectin was negatively correlated to insulin and indirect IR parameters during oral GTT (26). Differences in sample size, race, or methodology could be responsible for this discrepancy.

Our study has some limitations. First, this is a cross-sectional study, and thus it is difficult to evaluate a cause-effect relationship between the serum vaspin levels and the course of IR during pregnancy. Second, the time of blood drainage in the pregnant women (24–30th week of gestation) was chosen on the basis of screening for gestational diabetes; since highest placental vaspin expression is observed at the end of gestation, it might be more appropriate to test our hypothesis at a later gestational age.

In conclusion, our data suggest that vaspin, although lower in pregnancy and significantly correlated with adiponectin, may not be an important regulator of glucose metabolism and cannot serve as a biomarker of IR in either pregnant or non-pregnant women. On the other hand, vaspin might be used as a surrogate marker of lipid metabolism in pregnancy if confirmed by subsequent studies. Further investigations are needed to understand the regulation of vaspin and its role in the course of pregnancy.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 21 January 2011

Accepted 31 January 2011