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Originals

The Relation Between Adiponectin and four Hypercoagulable, Inflammatory Biomarkers During Normal Pregnancy

Katsumi Tomobe M.D.

Department of Obstetrics and Gynecology, Dokkyo Medical University Koshigaya Hospital, Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan

SUMMARY

Eendothelial dysfunction may not occur, even though the hemostatic balance is displaced toward hypercoagulability during pregnancy with enhanced inflammation. Also adiponectin, an adipose tissue-specific plasma protein, was recently revealed to have anti-inflammatory effects on the cellular components of the vascular wall. However, it is still unclear whether or not plasma adiponectin concentrations change during normal pregnancy. Despite a lot of research on the physiological adaptation to pregnancy, relatively little is known about the biological adaptation in the hemostatic, inflammatory changes and endothelial damage. To evaluate the relationship between various biomarkers for endothelial damage and the hypercoagulable, inflammatory state during pregnancy, five biomarkers, namely plasma adiponectin, soluble thrombomodulin (sTM), interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and thrombin-antithrombin complex (TAT) were measured in 15 nonpregnant healthy women, 60 pregnant women (namely 10th, 20th, 30th, and 38th week of gestation) and 15 postpartum women. The present study revealed that during pregnancy the plasma adiponectin concentrations were increased, while the concentrations of sTM and TNF-alpha did not change and those of TAT and IL-6 were elevated. Elevating the adiponectin concentrations, diminishing endothelial damage and leading to an antithrombotic and anti-inflammatory environment may be beneficial during pregnancy.

Key Words : Adiponectin, Hypercoagulable state, Inflammatory state, Endothelial damage, Pregnancy

INTRODUCTION

Although studies have shown that blood coagulation is activated and inflammatory cytokines increase with gestational age, endothelial damage may not increase significantly in normal pregnant women [1,2]. The important physiological adaptations may occur in pregnant women. The normal antithrombotic and anticoagulant balance of the endothelium can be disturbed by circulating mediators, damage or disease, leading to prothrombotic and procoagulant complications [3]. Recently, several markers for coagulation, inflammation and endothelial damage have been described [3,4].

Adipocytes are a rich source of molecules that modulate cardiovascular and metabolic risk [5]. The recently identified hydrophilic protein adiponectin is exclusively produced by adipocytes [6]. Plasma adiponectin concentrations are decreased in obesity [7], insulin resistance [8], and type 2 diabetes [9]. Also adiponectin decreased tu-

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Reprint requests to : Katsumi Tomobe, M.D.
Department of Obstetrics and Gynecology, Dokkyo Medical University Koshigaya Hospital, Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan

mor necrosis factor (TNF)-alpha induced macrophage attachment to endothelial cells by reducing the expression of adhesion molecules in endothelial cells through protein kinase A-mediated interference of nuclear factor κB signaling[10]. Furthermore, it has been shown that adiponectin suppresses TNF-alpha production and phagocytic activity in macrophages[11]. These indicate that adiponectin has anti-inflammatory properties. In addition, adiponectin is detectable in the catheter-injured vessel wall, rather than in intact vessels in animal models[12]. These observations indicate that adiponectin may be a protective adipocytokine against endothelial damage and dysfunction.

Thrombomodulin (TM) is an endothelial proteoglycan which acts as an endothelial thrombin receptor and represents a major determinant of the antithrombogenicity of the vessel wall[13]. TM is present in the endothelium of the maternal and fetal vasculature, which covers the entire trophoblastic surface[14]. A soluble form of TM (sTM) exists in plasma and urine[15]. It can often be used as a marker of endothelial damage in a variety of diseases[16]. TM activates the protein C pathway[17], and directly inhibits fibrin formation, platelet aggregation and factor V activation. These actions shift thrombin activity from procoagulant to anticoagulant.

Thrombin is an essential regulatory enzyme in hemostasis. The conversion of prothrombin to thrombin is accomplished via limited proteolysis catalyzed by a complex of an enzyme, factor Xa, in company with a cofactor, factor Va. After the conversion, thrombin and prothrombin fragment 1 + 2 (F1 + 2) are formed. Thrombin is immediately inactivated through 1 : 1 binding to antithrombin. This results in a stable stoichiometric complex, thrombin-antithrombin complex (TAT)[18]. TAT and F1 + 2 are sensitive markers of thrombin formation[19]. Measurement of some activated products formed by coagulation factors is impossible because they are labile. However, it is now possible to measure many activated products and their complexes with inhibitors. One of these complexes is TAT. Studies have shown that blood coagulation, which is reflected by TAT and other markers, is activated in normal pregnant and/or preeclamptic women[1,20,21].

The cytokines TNF and Interleukin (IL)-6, by inducing the production of prostaglandins, may be key intermediates in the mechanism of preterm labor associated with intrauterine infection. In contrast, a recent study showed that biologically active TNF and IL-6 are present in normal pregnancy[22]. Such an inflammatory response is already well developed in normal pregnancy.

Based on the studies mentioned above, we used adiponectin as a marker for a protective adipocytokine against inflammation, endothelial damage and dysfunction, and used sTM for endothelial damage, TNF-alpha, IL-6 for inflammatory cytokines, and TAT for thrombin formation. The purpose of the present investigation is to characterize the concentrations of these five laboratory variables as markers in normal pregnant women. It is of great importance using many blood markers in normal pregnant women to analyze the relationship between adiponectin concentrations , blood hypercoagulability, inflammation and endothelial damage. Because pregnancy is associated with various changes in both the hemostatic and immunological systems, and with vascular changes.

MATERIALS AND METHODS

Subjects

Information on subjects is summarized in Table. 1.

The subjects were three groups of 90 women, consisting of 15 healthy non-pregnant women with regular menstrual cycles, 60 pregnant women with single fetuses and 15 postpartum women. The pregnant women comprised 15 uncomplicated, normotensive women in the 10th week of gestation, 15 in the 20th week, 15 in the 30th week and 15 in the 38th week. The mean age did not differ among the three groups. Gestational age was estimated based on the crown-rump length of the fetuses measured by ultrasonography at least twice between the 7th and the 10th weeks of gestation with at least a two-week interval between measurements. Healthy non-pregnant women were randomly selected. No subject had symptoms of a urinary tract infection, and none had glycosuria when tested with Ames reagent strips for urinalysis (Uristix ; Bayer Medical Ltd., Tokyo, Japan). No subject had proteinuria when tested with Uristix. No hyperglycemia was detected in any subject in the fasting state. None of the subjects had been receiving any kind of known platelet function-altering drugs or anti-

Table 1 Information on the subjects

Variable	non-preg	preg 10w	preg 20w	preg 30w	preg 38w	postpartum
N	15	15	15	15	15	15
Age (Ys)	26 ± 3.4	24 ± 3.7	25 ± 3.0	26 ± 3.6	25 ± 3.8	26 ± 3.2
Gestational week (weeks)		10 ± 1.8	20 ± 1.9	30 ± 1.8	38 ± 2.0	
Body weight (Kg)	48 ± 4.9	51 ± 5.2	53 ± 5.4	57 ± 4.9	59 ± 4.6 †	53 ± 6.3
Blood pressure (systolic/diastolic)	108 ± 10.1/63 ± 8.9	109 ± 9.7/62 ± 7.8	109 ± 10.1/65 ± 7.4	113 ± 9.7/64 ± 8.2	117 ± 10.9/68 ± 10.2	109 ± 9.5/65 ± 7.1
Leukocyte counts ($/mm^3$)	6700 ± 1300	7300 ± 1700	6800 ± 1500	7600 ± 1800	8500 ± 1400*	7300 ± 1500*
Platelet counts ($104/\mu L$)	25 ± 7.6	27 ± 9.5	28 ± 8.9	27 ± 9.3	29 ± 8.3	27 ± 9.1

Data are mean ± SD. The age did not differ significantly among these six groups.
non-preg : non-pregnant women ; preg 10w : pregnant women (10w) ; preg 20w : pregnant women (20w) ; preg 30w : pregnant women (30w) ; preg 38w : pregnant women (38w) ; postpartum : postpartum women
*$p < 0.01$, † $p < 0.001$ vs. non-pregnant women

coagulants for at least 14 days before examination, and none were smokers. Samples of peripheral venous blood were taken at 10 : 00 − 12 : 00 a.m. No blood samples were taken within 3 hours after a meal. The separated plasma was collected and stored at − 80℃ until analysis. The subjects chosen for this investigation were fully informed about the nature and the aims of the study, an essential prerequisite to obtaining accurate information.

Data analysis of biomarkers

The concentrations of adiponectin in the plasma were measured by the sandwich enzyme-linked immunosorbent assay (ELISA) method using a commercial kit (Human Adiponectin ELISA kit, Otsuka pharmaceutical Co., Ltd, Tokyo, Japan) according to the manufacturer's instructions. The quantification limit of Human Adiponectin ELISA is 1.0 μmol/L with a CV < 10 %.

The concentrations of soluble TM in the plasma were measured by an enzyme immunoassay (EIA) sandwich method with mouse monoclonal antibodies against human placental TM (TM MGCC EIA, Mitsubishi Gas Chemical Co., Tokyo, Japan) as previously described. CV value is 3.9 %.

The concentrations of TNF-alpha in the plasma were measured by the sandwich ELISA method with human monoclonal antibodies (Human TNF-alpha kit, Japan immunoresearch laboratories Co., Ltd., Gunma, Japan). CV value is 2.0 %.

The concentrations of IL-6 in the plasma were measured by the sandwich chemiluminescent enzyme immunoassay (CLEIA) method with human monoclonal antibodies (Human IL-6 CLEIA Fujirebio, Fujirebio Co., Ltd., Tokyo, Japan). CV value is 2.0 %.

The concentrations of of TAT in the plasma were measured in these samples by the enzyme immunoassay method (Enzygnost TAT ; Dade Behring Ltd., Tokyo, Japan). CV value is less than 10 %.

Statistical analysis

StatFlex ver. 5 (Artec.,Osaka) was used for statistical analyses. Data were statistically analyzed using Kruskal-Wallis test and Dunn test. P values < 0.05 were considered to be statistically significant.

RESULTS

Results are presented as means ± 1 standard deviation .

Adiponectin :

Changes in the mean concentrations of adiponectin are depicted in Fig. 1.

The mean concentrations of adiponectin were significantly increased in normal pregnant women (10th week : 10.4 ± 2.9, 20th week : 10.8 ± 4.0, 30th week : 9.4 ± 1.8, and 38th week : 9.2 ± 2.2 μg/ml), as compared to those in age-matched control subjects (7.3 ±

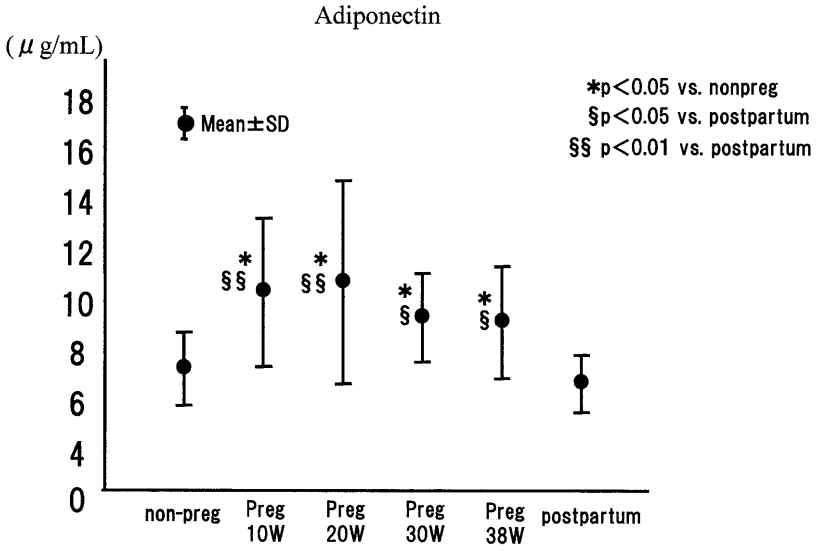

Fig. 1 Plasma adiponectin concentrations in healthy non-pregnant, normal pregnant and postpartum women.
*P < 0.05 vs. non-pregnant women ; §P < 0.05 vs. normal pregnant women in the postpartum ; §§P < 0.01 vs. normal pregnant women in the postpartum.

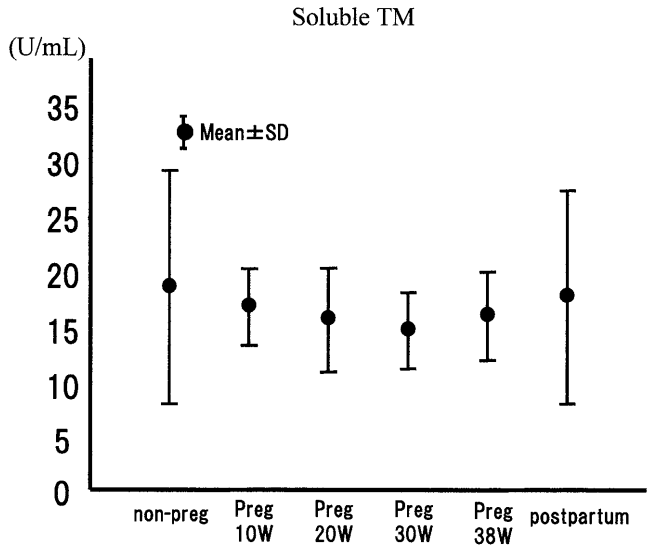

Fig. 2 Plasma soluble TM concentrations in healthy non-pregnant, normal pregnant and postpartum women. There were no significant differences among these groups.

1.5 μg/ml) ($p < 0.05$) and postpartum women (6.8 ± 1.1 μg/ml) ($p < 0.05$ or $p < 0.01$)

Soluble TM :

Changes in the mean concentrations of sTM are depicted in in Fig. 2.

The mean concentrations of sTM did not differ significantly among these six groups. (Non-pregnant women : 18.8 ± 10.5, normal pregnant women 10th, 20th, 30th, and 38th weeks : 17.0 ± 3.5, 15.9 ± 4.7, 14.9 ± 3.4, and 16.2 ± 4.0, respectively, postpartum women : 17.9 ± 9.6 U/mL).

TNF-alpha :

Changes in the mean concentrations of TNF-alpha are depicted in Fig. 3.

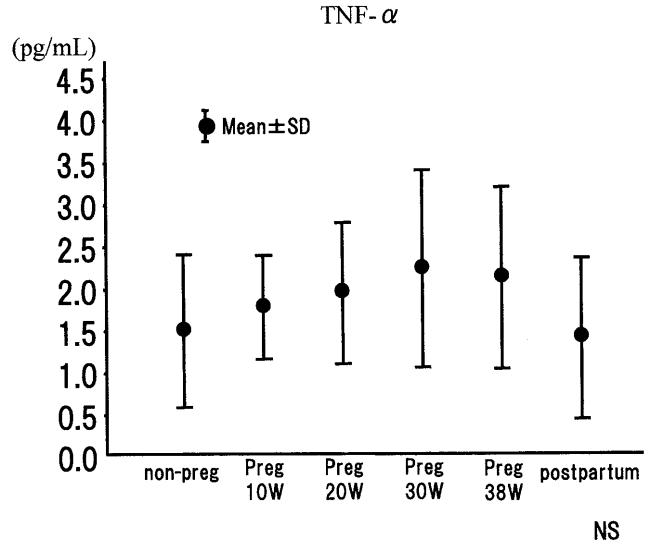

Fig. 3 TNF-alpha concentrations in healthy non-pregnant, normal pregnant and postpartum women. There were no significant differences among these groups.

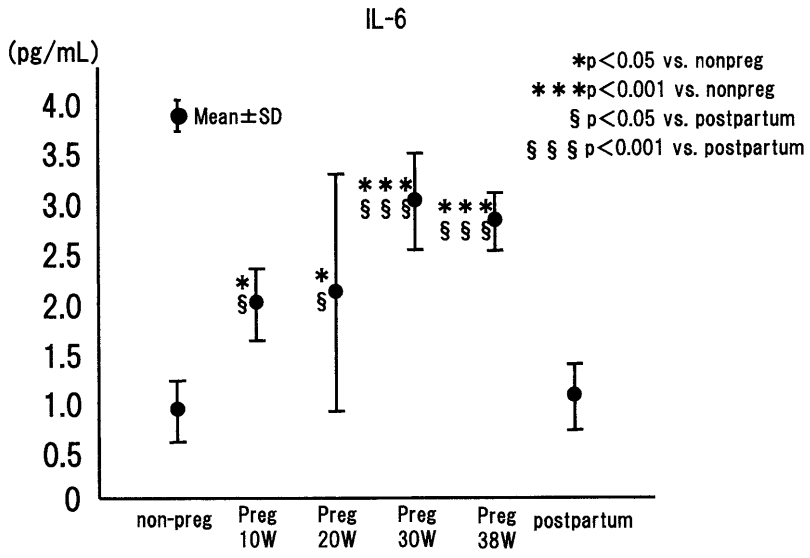

Fig. 4 IL-6 concentrations in healthy non-pregnant, normal pregnant and postpartum women.
*P < 0.05 vs. non-pregnant women ; ***P < 0.001 vs. non-pregnant women ; § P < 0.05 vs. normal pregnant women in the postpartum ; §§§P < 0.001 vs. normal pregnant women in the postpartum.

The mean concentrations of TNF-alpha did not differ significantly among these six groups. (Non-pregnant women : 1.55 ± 0.91, normal pregnant women 10th, 20th, 30th, and 38 th weeks 1.78 ± 0.62, 1.95 ± 0.84, 2.23 ± 1.18, and 2.12 ± 1.08, respectively, and postpartum women : 1.41 ± 0.96 pg/mL). But there was a tendency toward increase as pregnancy progressed.

IL-6 :

Changes in the mean concentrations of IL-6 are depicted in Fig. 4.

The mean concentrations of IL-6 were significantly increased in normal pregnant women (10th : week

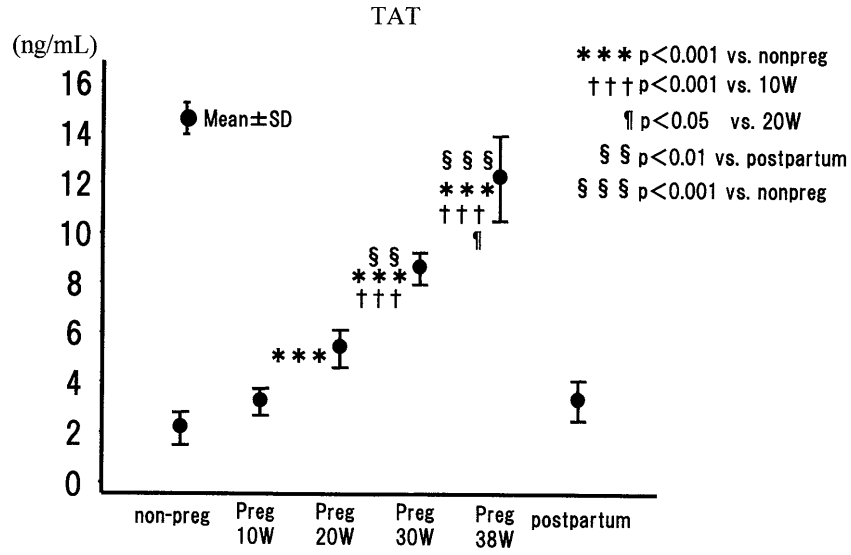

Fig. 5 TAT concentrations in healthy non-pregnant , normal pregnant and postpartum women.
$^{***}P<0.001$ vs. non-pregnant women ; $^{\dagger\dagger\dagger}P<0.001$ vs. normal pregnant women in the 10th gestational week ; ¶ $P<0.05$ vs. normal pregnant women in the 20th gestational week ; $^{\S\S}P<0.01$ vs. normal pregnant women in the postpartum ; $^{\S\S\S}P<0.001$ vs. normal pregnant women in the postpartum.

1.99 ± 0.36, 20th week : 2.10 ± 1.19 pg/ml, 30th week : 3.01 ± 0.48, and 38th weeks : 2.81 ± 0.29 pg/ml), as compared to those in age-matched control subjects (0.91 ± 0.31 pg/ml) ($p<0.05$ or $p<0.001$) and postpartum women (1.05 ± 0.33 pg/ml) ($p<0.05$).

TAT :

Changes in the mean concentrations of in TAT is depicted in Fig. 5.

The mean concentrations of TAT were 2.13 ± 0.65 in non-pregnant women, 3.21 ± 0.55 in 10th week of gestation (w.g.), 5.36 ± 0.76 in 20th w.g, 8.57 ± 0.64 in 30th w.g, 12.19 ± 1.70 in 38 th w.g, and 3.29 ± 0.79 ng/mL in postpartum women. They were increased significantly with gestational age,but were decreased significantly after delivery.

DISCUSSION

Normal pregnancy is accompanied by important changes in the hemostatic mechanism, that is, overall increased concentrations of coagulation factors [23]. Platelet factor-4 and β-thromboglobulin concentrations were significantly higher in the normal pregnant women than in the non-pregnant control subjects [24]. This study revealed that the TAT concentrations were significantly increased in pregnant women as compared to non-pregnant women as pregnancy progressed, providing the evidence that blood coagulation, which is reflected by the TAT concentrations, is activated in pregnancy. This study also revealed that the sTM concentrations did not change significantly during normal pregnancy, suggesting that endothelial damage did not occur with the progression of pregnancy. The physiological function of sTM in the plasma as a significant anticoagulant remains to be determined. However, since sTM in plasma is derived entirely from endothelial membrane TM [15,25], the amount of membrane TM may be reduced as plasma concentrations of soluble TM increase. These findings suggest that a hypercoagulable state during pregnancy may not result from endothelial damage.

Also, it has been reported that inflammatory cytokine mRNA is commonly expressed in human gestational tissues and maternal plasma IL-6 increased during pregnancy [26,27]. The normal antithrombotic and anticoagulant balance of endothelium can be disturbed by circulating mediators, damage or disease, leading to prothrombotic and procoagulant complications [3]. This

study showed that the concentrations of IL-6 were significantly increased as pregnancy progressed. However, the mean concentrations of TNF-alpha did not differ significantly among these six groups. In sum, these findings and the evidence previously described suggest that endothelial damage does not occur during pregnancy, although inflammatory cytokines and coagulation factors are increased.

In this study, it has also been demonstrated that adiponectin was elevated in pregnant women as compared with non-pregnant and postpartum women, suggesting an enhanced synthesis of this peptide occurs in pregnancy. The mechanisms responsible for maintaining these changes remain to be elucidated. However, since adiponectin concentrations in pregnancy increased in this study, augmentation of plasma adiponectin would be relevant to physiological adaptations in pregnant women, regulating endothelial activation. The physiological role of adiponectin in human pregnancy is not yet fully understood.

The central processes of inflammation is a dramatic increase in endothelial cell surface expression of molecules that support the adhesion of blood leukocytes, stimulated by thrombin or histamine within minutes or by endotoxin, IL-1, or TNF-alpha within hours [28]. Thus, endothelial activation is an intrinsic part of the inflammatory response and mediates its characteristic features of a locally increased blood supply to the inflamed area with increased capillary permeability, leukocyte adherence before extravasation, chemotaxis, and phagocytosis [29].

Normal pregnancy is already characterized by similar changes, in some aspects as intense as those observed in patients requiring intensive care for major sepsis. Normal pregnancy itself, for whatever reason, stimulates an inflammatory response. By the end of the first trimester there is a significant granulocytosis and monocytosis [30].

Also, it is of interest that adiponectin was accumulated only in the injured vascular walls but not in intact vessels. This suggests that circulating adiponectin can interact with or bind to some molecules in subendothelial space or medial wall when exposed to the vascular lumen by endothelial injury [12]. Adiponectin is likely to regulate inflammatory responses negatively through at least two mechanisms : suppression of mature macrophage functions and inhibition of growth of macrophage precursors. The former is considered to play an important role in the control of early responses of inflammation, and the latter may act in late events of inflammation to prevent immune responses from continuing chronically. Adiponectin is involved in the termination of inflammatory responses. The treatment with adiponectin strongly inhibits LPS-induced TNF-alpha gene transcription in macrophages, suggesting that adiponectin may have therapeutic applications in diseases caused by excessive inflammatory responses[11].

Several investigations have suggested that certain hypercoagulable and inflammatory states are causative of pregnancy complications [31]. Therefore, elevating adiponectin concentrations, diminishing endothelial damage, and leading to an antithrombotic and anti-inflammatory environment, may be beneficial during pregnancy. The physiology of adiponectin during pregnancy is still under investigation. It has been reported that adiponectin did not differ significantly in pregnancy [32]. Also, adiponectin were reportedly lower in the healthy pregnant group than in the nonpregnant group [33]. Furthermore, some studies indicated a strong association between hypoadiponectinamia and the risk of hypertensive disorders and diabetes in pregnancy [34,35], suggesting that increased adiponectin concentrations might be suitable and beneficial for normal pregnancy.Therefore it was of interest to identify whether adiponectin concentrations was increased or not by measuring simultaneously several biomarkers for endothelial damage, inflammatory cytokines and hypercoagulable states during pregnancy.

In conclusion, although the precise correlation among these biomarkers remains to be apparent, this study provides evidence that adiponectin is increased, raising the possibility that it may play some role in the regulation of the endothelial activation during pregnancy. However, further research is needed to elucidate clearly the role of adiponectin in human pregnancy.

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