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Serum level and placental expression of resistin in pregnancies complicated by preeclampsia: relationship with disease severity

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Summary

The authors aimed to compare the maternal serum level and placental expression of resistin in pregnancies complicated by preeclampsia and clarify their relationship with disease severity. This cross-sectional study included 50 healthy pregnant women, 50 women with mild preeclampsia, and 48 women with severe preeclampsia. Serum resistin levels were measured by enzyme immunoassay and placental resistin expression was determined by immunohistochemistry. Resistin levels were significantly higher in women with mild and severe preeclampsia than in the healthy controls ($p = 0.012$ and $p < 0.001$, respectively). Placental resistin expression was significantly higher in women with severe preeclampsia compared to women with mild preeclampsia ($p = 0.003$) and healthy controls ($p < 0.001$). Serum resistin levels were positively correlated with gestational age and umbilical and uterine artery Doppler indices, as well as systolic and diastolic blood pressure, but negatively correlated with birth weight ($p < 0.05$). On the other hand, placental resistin expression was positively correlated with systolic blood pressure and uterine artery indices, but negatively correlated with birth weight ($p < 0.05$). In conclusion, increased circulating levels and placental expression of resistin in pregnancies complicated by preeclampsia were correlated with disease severity.

Key words: Immunohistochemistry; Pregnancy; Preeclampsia; Resistin.

Introduction

Preeclampsia is a serious complication of pregnancy characterised clinically by maternal hypertension and proteinuria after 20 weeks of gestation, affecting 3–5% of all pregnancies, and results in substantial maternal and neonatal morbidity and mortality [1]. The mechanisms involved in the etiology of this disorder have not been clearly identified. Endothelial dysfunction, which is one of the early stages of atherosclerosis, plays an important role in the pathogenesis of preeclampsia. Insulin resistance and low-grade systemic inflammation may contribute to the pathogenesis of endothelial dysfunction. In addition, placental ischaemia secondary to an initial defective placentation and generalised endothelial cell damage have been proposed to be the pathogenic mechanisms underlying preeclampsia [2].

Adipose tissue is not only involved in energy storage but also functions as an endocrine organ that expresses and secretes a variety of hormones and cytokines, which are collectively named as adipokines. Some of the adipokines, such as leptin, adiponectin, resistin, and ghrelin play roles in the regulation of glucose metabolism and are involved in the development of obesity, diabetes mellitus, inflammation, auto-immunity, and metabolic syndrome [3]. In addition, adipokines have a role in regulating maternal energy metabolism and insulin sensitivity during gestation and have been implicated in pregnancy complications, including gestational diabetes mellitus, fetal growth restriction, and preeclampsia [4-6].

Resistin, also known as adipocyte secreted factor (ADSF), is a cysteine-rich adipokine that was originally described as a molecular link between obesity and insulin resistance in mice, as its serum levels are increased in both diet-induced and in genetic mouse models of obesity [7]. In animal models, resistin is expressed almost exclusively in adipocytes, whereas human resistin is expressed and secreted predominantly from mononuclear cells, and plays important roles in regulating energy homeostasis [8, 9]. Resistin impairs glucose tolerance and opposes the action of insulin in peripheral tissues [10]. Previous studies have suggested roles of resistin in obesity and insulin resistance, although these remain controversial. Some studies have shown positive correlations with body fat mass and insulin resistance [11, 12], whereas others have found no such cor-

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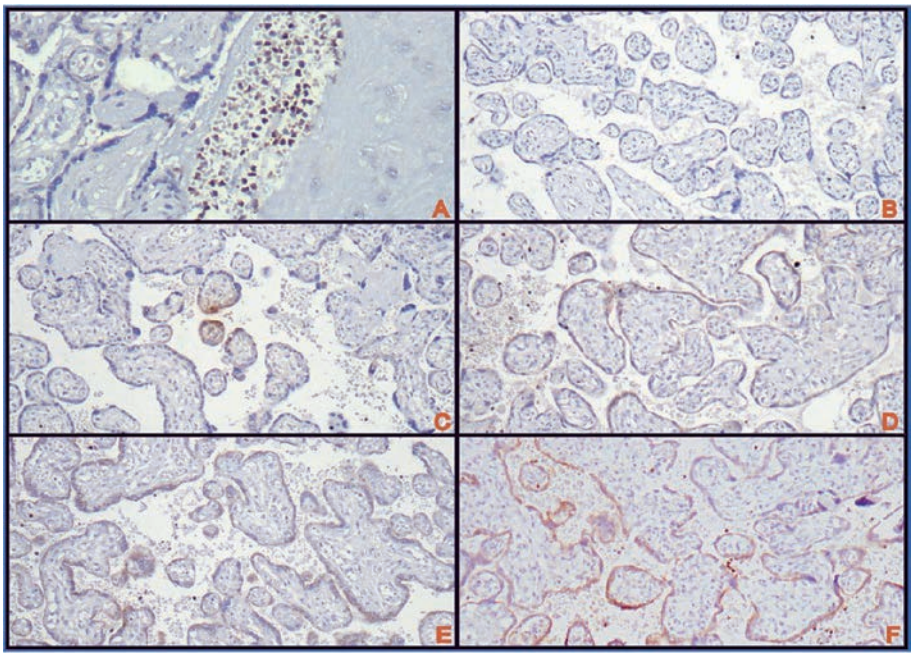

Figure 1. — Histopathologic photomicrographs demonstrating immunohistochemical staining for resistin. A) strong cytoplasmic resistin staining of mononuclear cell in vascular lumina (used as positive internal control). Magnification ×200. B) absence of resistin expression in trophoblast (score 0). Magnification ×100. C) ≤ 10% of the cells were stained (score 1). Magnification ×100. D) 11-50% of the cells were stained (score 2). Magnification ×100. E) 51-80% of the cells were stained (score 3) Magnification ×100. F) ≥ 81% of the cells were stained (score 4). Magnification ×100.

relations with body mass index (BMI) or insulin sensitivity [7, 13]. Although resistin was first postulated to contribute to insulin resistance, accumulating evidence suggested that it might also be involved in inflammatory processes. In human, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as lipopolysaccharides, strongly induce resistin mRNA expression [14]. Moreover, resistin can up-regulate the expression of IL-6, IL-1β, and TNF-α, and thereby enhance its own activity by positive feedback [15]. Resistin has also been linked to inflammation in that serum resistin levels were shown to be associated with many inflammatory markers in patients with severe inflammatory conditions [16].

Given the potential role of resistin as a mediator of insulin sensitivity and inflammation, the present authors evaluated the serum level and placental expression of resistin in normal pregnancies and in those complicated by preeclampsia. They hypothesised that circulating concentrations and placental expression of resistin may be altered in relation to disease severity.

Materials and Methods

This cross-sectional study was conducted at Antalya Training and Research Hospital, Antalya, Turkey, between January 2012 and March 2013. The Institutional Ethics Committee approved the study, and the patients who agreed to participate provided signed informed consent.

The study groups consisted of 50 women with mild preeclampsia and 48 women with severe preeclampsia. All subjects in these groups had late-onset preeclampsia diagnosed at gestational week 34 or later. The control group consisted of 50 normotensive healthy pregnant women. The study and control groups were matched for age and BMI. All the pregnant women enrolled in the study were non-smokers, had similar demographic backgrounds, and were admitted for delivery. Additionally, the authors selected only women who delivered via elective cesarean section, thus eliminating any possible influence of labor or premature membrane rupture. The indication for elective cesarean section in all patients was a prior cesarean section. Exclusion criteria included multiple gestation, chronic hypertension, diabetes mellitus, vascular or inflammatory diseases, premature rupture of membranes, known fetal structural anomalies, clinical choriamnionitis, previous exposure to magnesium sulfate, and active labor.

Preeclampsia was defined as the presence of hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least two occasions, six hours apart) and proteinuria (≥ 300 mg in 24-hour urine collection or at least one dipstick measurement ≥ 1+) after the 20th week of gestation as defined by the International Society of Hypertension in Pregnancy [17]. Blood pressure was taken with the woman in the sitting position after a ten-minute rest period. Preeclampsia was classified as severe if the woman had one or more of the following symptoms: blood pressure ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic, ≥ 3+ protein by dipstick test in two urine samples taken at four hour or more apart or five grams of protein in 24-hour urine sample, epigastric or right upper-quadrant pain, blurring of vision, cerebral disturbance, abnormal liver function, pulmonary edema or cyanosis, low platelet level, and oliguria < 500 ml in 24 hours. Gestational age was determined by the last menstrual period and confirmed by ultrasonographic examination performed during the first trimester. BMI values were calculated using the following formula: weight (kg)/height (m^2).

All patients underwent Doppler examination at admission prior to delivery. Doppler examinations were performed using a 2–7-MHz transabdominal transducer in the lateral decubitus position to avoid supine hypotension. Doppler measurements were performed in the absence of fetal movements and during voluntarily suspension of maternal breathing. Spectral Doppler parameters were determined automatically from three or more consecutive

Table 1. — *Comparison of obstetric characteristics, Doppler parameters, and neonatal outcome of study groups.*

Variables	Control (n=50)	Mild preeclampsia (n=50)	Severe preeclampsia (n=48)	*p*	p^1	p^2	p^3
Maternal age[a]	28.1 ± 5.7	25.6 ± 5.8	28.8 ± 5.8	0.148			
Gestational age (week)[a]	38.4 ± 0.7	37.9 ± 1.5	37.2 ± 1.2	0.001	0.115	< 0.001	0.038
Gravidity[b]	2 (1-7)	1 (1-5)	2 (1-10)	0.072			
Parity[b]	1 (0-4)	1 (0-3)	1 (0-3)	0.119			
Systolic blood pressure (mmHg)[a]	108.1 ± 10.4	145.9 ± 11.4	160.4 ± 13.9	< 0.001	< 0.001	< 0.001	< 0.001
Diastolic blood pressure (mmHg)[a]	68.9 ± 7.5	94.6 ± 7.5	104.2 ± 11.9	< 0.001	< 0.001	< 0.001	0.001
BMI (kg/m^2)[a]	29.5 ± 3.1	31.9 ± 5.2	30.1 ± 4.2	0.267			
Umbilical artery PI[a]	0.70 ± 0.17	0.75 ± 0.22	1.16 ± 0.71	< 0.001	0.345	< 0.001	0.002
Umbilical artery RI[a]	0.52 ± 0.14	0.55 ± 0.13	0.66 ± 0.22	0.005	0.355	0.002	0.026
Uterine artery PI[a]	0.69 ± 0.29	0.79 ± 0.28	1.07 ± 0.41	0.001	0.131	< 0.001	0.018
Uterine artery RI[a]	0.45 ± 0.14	0.47 ± 0.11	0.57 ± 0.12	0.001	0.399	0.001	0.004
Birth weight (g)[a]	3474 ± 332	3107 ± 710	2596 ± 622	< 0.001	0.038	< 0.001	< 0.001

Values are given as [a] mean ± SD (standard deviation) or [b] median (range). If the Kruskal–Wallis test was positive ($p < 0.05$), then post-hoc analysis was applied. *p*, between three groups; p^1, between mild preeclampsia and control; p^2, between severe preeclampsia and control; p^3, between severe preeclampsia and mild preeclampsia. BMI; body mass index, PI; pulsatility index, RI; resistance index.

waveforms, holding the angle of insonation as close to 0° as possible. Umbilical artery Doppler velocimetry was performed on a free loop of the umbilical cord located distant from the points of fetal and placental insertions. Both uterine arteries were assessed at the level at which they crossed the external iliac arteries. The mean values of parameters derived from both uterine arteries were calculated and used in statistical analyses.

None of the preeclamptic patients or controls received any medications before blood sampling. A fasting venous blood sample (five ml) was obtained from all participants prior to cesarean section. All samples were kept at room temperature for at least 30 minutes to allow the blood to clot and centrifuged at 2,500 rpms for 15 minutes at 4°C to separate serum. Serum specimens were aliquoted and stored at −80°C until batch assay. For measurement of resistin, a commercially available sandwich immunoassay kit was used according to the manufacturer's instructions. The sensitivity of the assay was 0.016 ng/ml and the inter- and intra-assay coefficients of variation were less than 15% and 10%, respectively. The assay results are expressed as ng/ml.

The placentas were obtained immediately after delivery in all subjects. Biopsies were taken from the central region of the placentas and stored immediately in 10% formaldehyde. After fixation, samples were embedded in paraffin after routine tissue work-up. Immunohistochemical staining of the placental tissues was performed by incubation with anti-resistin primary antibody (rabbit monoclonal, clone EPR3506, dilution 1:100. Sections were then washed with PBS and incubated with biotinylated secondary antibody for 20 minutes. The antigen-antibody complexes were visualised using DAB and counterstained with haematoxylin.

Expression rates for the positive cells in the specimens were evaluated by two observers (DS, RE) who were unaware of the patients' clinical features. Strong cytoplasmic staining was observed in mononuclear cells in the vascular lumina (Figure 1A). This cytoplasmic staining observed in lymphocytes was used as a positive internal control. Fibroblasts, smooth muscle cells, vessel endothelium, and vessel walls within the cross-sections showed no staining. Absence of expression in these structures was used as a negative internal control. Immunohistochemical staining for resistin was mainly observed in villous cytotrophoblasts, with staining occasionally in syncytiotrophoblasts. In cases positive for cytotrophoblastic resistin expression, staining was cytoplasmic and accompanied by weak membrane staining. This membrane staining was ignored and cytoplasmic staining was evaluated. Immunohistochemical staining score was calculated semiquantitatively as the percentage of positive cytotrophoblast as follows: 0, no staining; 1, ≤ 10% of the cells were stained; 2, 11−50% of the cells were stained; 3, 51−80% of the cells were stained, and 4, ≥ 81% of the cells were stained. Immunohistochemical score ≥ 1 was accepted as positive resistin expression. There was close agreement (> 95%) in the evaluation of resistin levels between both investigators. In cases of disagreement, a final grading was determined by consensus. Figures 1B-F shows various resistin staining scores.

Statistical analysis

Data distribution was assessed using the Kolmogorov–Smirnov test. The continuous variables are presented as mean ± standard deviation if normally distributed or median (minimum-maximum) if not normally distributed. Comparison of numerical variables between groups were performed using the Kruskal–Wallis test, and post hoc comparisons were performed using the Mann–Whitney U-test with Bonferroni's correction for non-normal data. Correlations between resistin levels and other variables were evaluated using Spearman's rank test. All tests were two-sided at a significance level of $p < 0.05$. Statistical analysis was performed using the SPSS statistical package, ver. 18.0.

Results

The demographic characteristics, Doppler parameters, and neonatal outcomes of the study groups are shown in Table 1. As participants were matched in terms of maternal age and BMI, these parameters were similar among all groups ($p > 0.05$). As expected, systolic and diastolic blood pressure, pulsatility and resistance indices (PI and RI) of the umbilical and uterine arteries were significantly higher, whereas gestational week and birth weight were significantly lower in the severe preeclampsia group than in the control and mild preeclampsia groups ($p < 0.05$ for all).

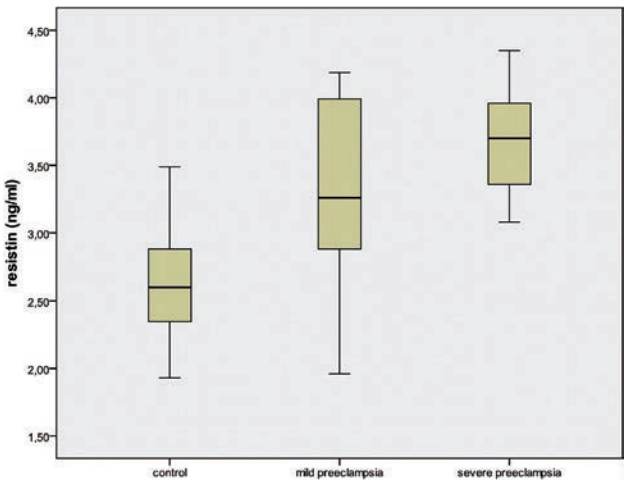

Figure 2. — Distribution of serum resistin levels in the control, mild and severe preeclampsia groups.

Table 2. — *Relationship between serum level and placental expression of resistin with other parameters assessed in all groups.*

	Serum resistin level		Placental resistin expression	
	r	*p*	*r*	*p*
Gestational age	0.433	< 0.001*	0.116	0.314
BMI	0.081	0.482	0.114	0.321
Systolic blood pressure	0.609	< 0.001*	0.275	0.015*
Diastolic blood pressure	0.598	< 0.001*	0.189	0.098
Umbilical artery PI	0.36	0.001*	0.103	0.368
Umbilical artery RI	0.28	0.013*	0.088	0.445
Uterine artery PI	0.322	0.004*	0.304	0.007*
Uterine artery RI	0.294	0.009*	0.295	0.009*
Birth weight	- 0.543	< 0.001*	- 0.321	0.004*

BMI; body mass index, PI; pulsatility index, RI; resistance index;
* Significant difference.

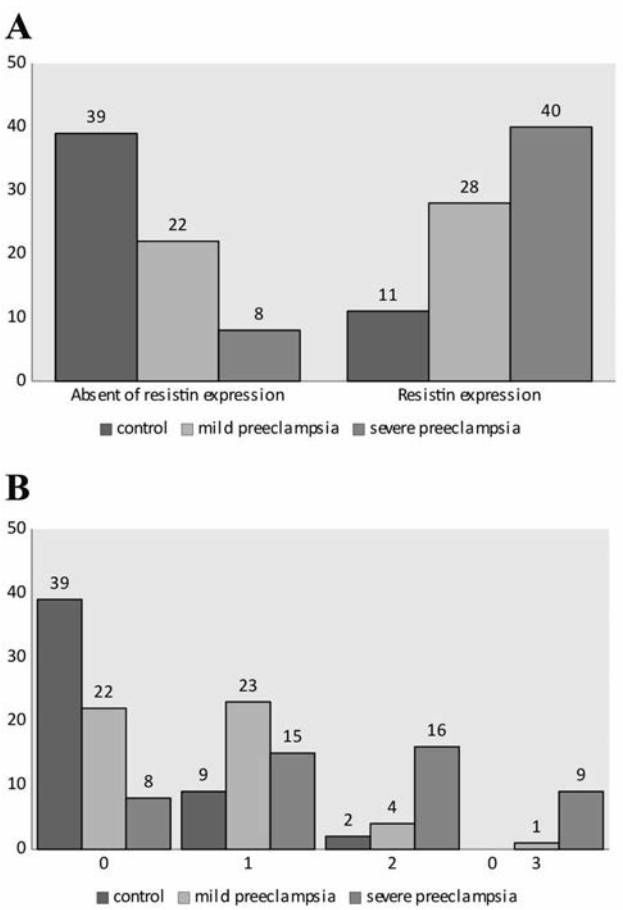

Figure 3. — Comparison of placental resistin expression (A) and immunohistochemical staining score (B) in control subjects and in study groups. Values are given as numbers.

In Figure 2, the box plots represent the distribution of serum resistin levels in all groups. There was a statistically significant between-group difference in serum resistin concentrations ($p < 0.001$). The mean serum resistin levels was 2.61 ± 0.37 ng/ml in the control group, 3.32 ± 0.61 ng/ml in the mild preeclampsia group, and 3.82 ± 0.35 ng/ml in the severe preeclampsia group. Pairwise comparisons between the groups revealed significantly higher resistin levels in the severe preeclampsia group compared to the mild preeclampsia and control groups ($p = 0.042$ and $p < 0.001$, respectively). Moreover, a significant difference was evident between the mild preeclampsia and control groups ($p = 0.012$).

Figure 3 shows the immunoreactivity scores and expression of resistin in the placentas of the three groups. There was a statistically significant between-group difference in placental resistin expression ($p < 0.001$). Pairwise comparisons between the groups revealed significantly increased resistin expression in the severe preeclampsia compared to mild preeclampsia ($p = 0.003$) and controls ($p < 0.001$).

The relationships between serum level and placental expression of resistin and other measured variables in all subjects are shown in Table 2. Serum resistin levels were negatively correlated with birth weight ($r = -0.534$, $p < 0.001$), but positively correlated with gestational age ($r = 0.433$, $p < 0.001$), systolic and diastolic blood pressure ($r = 0.609$, $r = 0.598$, respectively, $p < 0.001$ for both), umbilical artery PI ($r = 0.36$, $p = 0.001$) and RI ($r = 0.28$, $p = 0.013$), uterine artery PI ($r = 0.322$, $p = 0.004$) and RI ($r = 0.294$, $p = 0.009$). On the other hand, placental resistin expression was positively correlated with systolic blood pressure ($r = 0.275$, $p = 0.015$), uterine artery PI ($r = 0.304$, $p = 0.007$) and RI ($r = 0.295$, $p = 0.009$), but negatively correlated with birth weight ($r = - 0.321$, $p = 0.004$).

Discussion

In the present study, the authors investigated for the first time serum level and placental expression of resistin in relation to severity of preclampsia. The results indicated an increase in serum resistin concentrations and placental resistin expression in severe preeclampsia compared with mild preeclampsia and healthy controls.

In normal pregnancy, maternal serum resistin concentration is significantly elevated compared to the non-pregnant state, and resistin gene expression in term placental tissue is more prominent than in first trimester chorionic tissue [18]. Many investigators have shown that the placenta is the major source of resistin during pregnancy, and the main production site of placental resistin is the cytotrophoblast, but resistin can also secreted by extravillous cytotrophoblast and decidua [19]. Resistin plays a role in regulating energy metabolism during pregnancy. It contributes to decrease of insulin sensitivity in the second half of pregnancy, which may be related to the development of postprandial hyperglycemia and be beneficial for rapid fetal growth [20]. Although the mechanisms regulating resistin secretion during pregnancy have not been fully elucidated, insulin seems to be an important regulator of resistin gene expression and protein release; however, both inhibitory and stimulatory effects have been reported [21,22].

In addition to maternal biological functions, resistin plays critical roles in the developing fetus. Resistin is a physiological constituent of amniotic fluid, and its concentration increases with advancing gestation and plays a role in immune response against intra-amniotic infection [23]. In addition, resistin has been shown to be involved in fetal growth regulation, and markedly high resistin concentration in umbilical plasma may prevent neonatal hypoglycemia at birth by facilitating hepatic glucose production [24]. Its metabolic pathways may be impaired in fetuses with macrosomia and growth restriction [25]. Furthermore, resistin has been reported to induce the secretion of vascular endothelial growth factor (VEGF) and the proliferation of the fetoplacental unit, which may be another potential mechanism by which resistin contributes to normal fetal development [26].

Previous studies in women with established preeclampsia reported contradictory results in relation to resistin levels. Haugen *et al.* [27] reported elevated circulating resistin concentrations in patients with preeclampsia as compared to normal pregnant controls, although placental resistin gene expression was found to be unaltered. However, differences in resistin plasma levels between preeclampsia and normal pregnancies are lost after controlling for insulin resistance. Cortelazzi *et al.* [28] reported lower circulating resistin levels in preeclampsia as compared to normotensive healthy pregnant women, but gestational age at sampling varied widely (20 -37 weeks) compared to the present study. This finding was corroborated by Chen *et al.* [29], and the authors postulated that lower levels of resistin in preeclampsia may be related to a reduction in placental production of this peptid due to smaller size of the placenta; however, this was not confirmed by determination of placental resistin expression. Hendler *et al.* [30] found no differences in circulating resistin levels between pregnant women with and without preeclampsia. In addition, the authors observed no correlation between serum resistin level and BMI, in agreement with our observations. Seol *et al.* [31] reported marked elevation of serum resistin levels in women with preeclampsia compared to those with normal pregnancies, but no significant differences in placental expression between the two groups were observed. In contrast, the present authors found significantly increased placental resistin expression in patients with severe preeclampsia compared to mild preeclampsia and healthy pregnant controls. Some of these discrepancies can be attributed to the differences in study design and sample size, assessment of patients at different gestational ages, lack of adjustment for BMI, and to other confounding factors, such as smoking, maternal age, and parity. Differences in assay methods must also be taken into consideration. Although all studies used commercially available immunoassays, some evaluated resistin in plasma [27, 28, 30], while others investigated serum levels [29, 31].

The results presented here indicated that preeclampsia is associated with higher serum levels and placental expression of resistin. Moreover, this study indicated that deterioration of fetoplacental and uteroplacental blood flow, manifested as increased umbilical and uterine artery Doppler indices, is related to serum resistin level and placental expression. Elevated blood pressure is a major clinical manifestation of preeclampsia and the present authors found that both systolic and diastolic blood pressure were positively correlated with serum resistin concentration. This study also indicated a negative correlation between serum resistin level and neonatal birth weight, and therefore maternal resistin levels have important clinical implications for birth weight. The changes in circulating maternal resistin serum concentrations favour a state of insulin resistance, which enhances the availability of glucose to the fetus as well as to maternal vital organs. The present authors suggested that elevated placental resistin expression in preeclampsia might be a compensatory response to increase nutrient delivery to the underperfused placenta.

The present study had several limitations. Mean gestational age was inherently lower in the mild and severe preeclampsia groups compared with healthy controls, although all samples anaylsed were taken in the third trimester. Furthermore, the authors could not investigate fetal cord levels of resistin, thus this apparently unknown feature will require further investigation to clarify.

Conclusion

The present findings suggest that increased serum level and placental expression of resistin may play a role in the pathogenesis of preeclampsia, and seems to be correlated with disease severity. Further studies are required to confirm the present results.

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