Published in final edited form as:

J Perinat Med. 2007 ; 35(6): 513–521.

RESISTIN: A HORMONE WHICH INDUCES INSULIN RESISTANCE IS INCREASED IN NORMAL PREGNANCY

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Abstract

Aims—Resistin, a newly discovered adipokine, is thought to play a key role in the regulation of insulin resistance. The objectives of this study were to develop a nomogram of maternal plasma concentrations of resistin from 11 weeks of gestation to term and to determine whether resistin concentrations differ between normal and overweight pregnant women.

Methods—In this cross-sectional study, plasma concentrations of resistin were determined in normal pregnant women of normal body mass index (BMI 18.5–24.9; n=261), overweight pregnant women (BMI ≥25; n=140), and non-pregnant women of normal weight (n=40). Blood samples were collected once from each woman between the first trimester and term. Percentiles for resistin concentration were determined for five pre-specified windows of gestational age. Plasma resistin concentration was determined by immunoassay. Non-parametric statistics were used for analysis.

Results—The median maternal plasma concentration of resistin between 11 to 14 weeks of gestation in women of normal weight was significantly higher than non-pregnant women; The plasma concentration of resistin increased with gestational age.

Conclusions—Normal pregnant women have a higher median plasma concentration of resistin than non-pregnant women and the concentration of this adipokine increases with advancing gestation. Alterations in the maternal plasma concentration of resistin during pregnancy may contribute to metabolic changes of pregnancy.

Keywords

Adipokines; Resistin; Pregnancy; Obesity; Nomogram

INTRODUCTION

Pregnancy is a unique state characterized by physiological insulin resistance that resolves postpartum [11–13,15,16,28,54,57,60,74,85,92]. However, the mechanisms responsible for insulin resistance are not well understood. By increasing glucose availability, insulin resistance may facilitate delivery of energy to the fetus [55,74,84]. Insulin resistance during pregnancy is commonly attributed to the increased concentration of several placental hormones in maternal serum. Evidence in support of this hypothesis includes: 1) infusion of human placental lactogen (hPL), a hormone produced abundantly by the placenta, can induce metabolic changes in non-pregnant subjects [44,87]; 2) similar effects have been observed after treatment with progesterone [8,45], estrogen[76] or glucocorticosteroids [7,44]; 3) insulin action on adipocytes is impaired after *in vitro* exposure to progesterone, cortisol, prolactin, and human placental lactogen [86]; and 4) insulin resistance during pregnancy rises as a function of increasing plasma concentrations of placental hormone secretion.

The conventional view is that the placenta plays a key role in the mechanisms responsible for insulin resistance in pregnancy. However, recently the role of adipose tissue in the pathophysiology of insulin resistance has been a subject of interest [33,39,42,43,63,69,82,93,97]. Adipose tissue can exert its effects by several mechanisms, including the secretion of bioactive peptides. These bioactive substances, collectively termed adipokines, include leptin [26,29,30], adiponectin [2,9,41,64], tumor necrosis factor α [38,98], interleukin-6 [100,101], C-reactive protein [10,70], resistin [6,37,49,94] and others [56,82,83]. Recently, adipokines have been implicated in the regulation of insulin resistance during pregnancy. Serum concentrations of tumor necrosis factor- α [52,65], adiponectin [18,61,65,81], leptin and C-reactive protein [65] correlate with indices of insulin resistance during pregnancy.

Resistin is a novel adipokine with a molecular weight of 12.5 kDa [37,49,66,77,94,104]. In mice, the synthesis of resistin is restricted to adipocytes. However, in humans, adipocytes, muscle [56], pancreatic islets [68], mononuclear cells [47] and placenta [34,58,107] can synthesize this protein. Several lines of evidence support the association between resistin and insulin resistance: 1) in mice, obesity is associated with increased plasma resistin concentrations [77]; 2) resistin mRNA expression in adipocytes is low during fasting but increases significantly when fasting mice are refed with a high carbohydrate diet (25-fold) or treated with insulin (23-fold) [49]; 3) treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action; 4) administration of anti-resistin antibodies potentiates insulin-stimulated glucose uptake in mice with diet-induced obesity [94]; 5) *in vitro* neutralization of resistin results in enhanced insulin-stimulated glucose uptake by adipocytes [94]; and 6) in humans, plasma resistin concentration correlates with insulin resistance indices and obesity [89,95].

The objective of this study was to generate a nomogram of maternal plasma concentrations of resistin during pregnancy by determining concentrations of this hormone during first, second and third trimesters of pregnancy. In addition, we sought to determine whether BMI affects the maternal plasma concentrations of resistin.

MATERIALS AND METHODS

Study Design and population

This retrospective, cross-sectional study compared maternal plasma resistin concentrations among pregnant women of normal weight ($n=261$), overweight pregnant women ($n=140$) and non-pregnant women ($n=40$). Non-pregnant women were included in the study if they had no chronic disease, did not use oral contraception, and had a body mass index (BMI) <25 kg/m². The inclusion criteria for the pregnant group were: 1) singleton pregnancies; 2) no prior

diabetes mellitus or other chronic diseases; 3) no obstetrical, maternal, or fetal complications; 4) a normal plasma glucose concentration in the first trimester; 5) a normal oral glucose tolerance test in the third trimester; and 6) delivery at term of a neonate with birthweight appropriate for gestational age. The first trimester BMI was calculated with the following formula: $BMI = \text{weight (Kg)} / \text{height (m)}^2$. A normal BMI was defined when the values were between 18.5 and 24.9 kg/m². A patient was considered overweight if the BMI was equal to or greater than 25 kg/m² [24].

Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board. Many of the samples from these patients have been employed to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concentrations in non-pregnant women, normal pregnant women and those with pregnancy complications.

Blood collection and resistin immunoassay

Blood samples from non-pregnant women were obtained during the secretory phase of the menstrual cycle, and from pregnant women at 11–14 weeks, 15–18 weeks, 27–30 weeks, or >37 weeks of gestation. These samples were collected into vials containing ethylenediamine tetra-acetic acid and centrifuged for 10 minutes at 4°C. Plasma was stored at –70°C until analysis. Plasma resistin concentrations were determined with Human Resistin ELISA (LINCO Research Inc, St Charles, MO, USA), following the recommendations of the manufacturer. The sensitivity of the assay was 0.095 ng/ml and the inter- and intra-assay coefficients of variation were 5.9% and 5.8%, respectively.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk test. The plasma resistin concentrations were not normally distributed. Thus, non-parametric tests were used in the data analysis. The relationship between maternal plasma resistin concentration and gestational age was examined using a Spearman rank test. Comparisons of the median resistin concentration among groups were performed using the Kruskal-Wallis test. Post hoc analyses were done with Mann-Whitney *U*-test. Analysis of covariance (ANCOVA) was performed to control for confounding factors that could affect plasma resistin concentrations during pregnancy.

RESULTS

Table 1 displays the demographic characteristics and plasma resistin concentrations of the three study groups. No significant differences in age, weight, and BMI were observed between pregnant women of normal weight and non-pregnant women. There was a higher proportion of nulliparous women in the non-pregnant group ($P < 0.05$).

Resistin was detected in the plasma of all subjects. Pregnant women of normal weight had a significantly higher median plasma resistin concentration than did non-pregnant women (Table 1). These results did not change after adjusting for parity (Non pregnant nulliparous median: 10.2 ng/mL, range: 5–16 vs. pregnant nulliparous median: 12.5 ng/mL, range: 5–40; $P = 0.04$; and non pregnant multiparas median: 9.9 ng/mL, range: 6.3–24.2 vs. pregnant multiparas median: 13.3 ng/mL, range: 6–81.4; $P = 0.02$).

Pregnant women between 11 and 14 weeks of gestation had significantly higher plasma concentrations of resistin than did non-pregnant women ($P = 0.003$; Figure 1). A significant positive correlation was observed between plasma resistin concentrations and gestational age ($r = 0.22$; $P < 0.01$). Maternal plasma concentrations of resistin at term were significantly higher than those of patients in the first (11–14 weeks), second (15–18 weeks) or early third (27–30

weeks) trimester. In contrast, there were no significant differences in resistin concentrations of this hormone among the first, second, and early third trimester groups (Figure 2).

In order to examine the effects of confounding factors that may affect maternal plasma concentrations of resistin, analysis of covariance was applied, including maternal age, parity, BMI during first trimester, and gestational age (categorized into <37 and ≥ 37 weeks). This model showed that BMI did not contribute to the maternal plasma concentrations of resistin during pregnancy. Indeed, there were no significant differences in plasma resistin concentrations between normal weight and overweight women at different gestational ages (Figure 3).

Table 2 presents the reference plasma resistin concentrations in non-pregnant women and pregnant women of normal weight, including the 10th, 25th, 50th, 75th and 90th percentiles.

DISCUSSION

Principal findings of this study

1) Pregnant women of normal weight had a significantly higher median plasma resistin concentration compared to non-pregnant women; 2) plasma resistin concentrations change as a function of gestational age; 3) maternal plasma concentrations of resistin were significantly higher at term than in the first, second, or early third trimester; and 4) a nomogram for maternal plasma resistin concentration is presented.

Pregnancy as a *forme fruste* of the metabolic syndrome

A “physiological adaptation” of normal pregnancy includes insulin resistance [11–13,28,60,74,85,92], hyperlipidemia [17,22,73,91], increased weight and fat deposition [14,25,40,51,75]. These changes are considered components of the metabolic syndrome [1], although physiological alterations during pregnancy do not necessarily meet the threshold values for the definition of the metabolic syndrome. The profound metabolic changes are thought to be necessary for meeting the energy demands of the rapidly growing fetus and placenta. Insulin resistance is the best studied metabolic change during pregnancy. This is probably due to the fact that it stands out as a potential causative factor for other metabolic changes [1], or to the significant clinical consequences of gestational diabetes. While there is ample literature regarding the changes in glucose and insulin metabolism during gestation, data regarding the specific mechanisms underlying these changes are scant. Placental hormones such as hPL are thought to be the main factors in inducing gestational insulin resistance. This hypothesis was supported by the finding that placental hormones have diabetogenic effects both *in vitro* [86] and *in vivo* [7,8,44,45,76,87]. In addition, insulin resistance rises with the increased maternal serum concentrations of multiple placental hormones and resolves soon after delivery.

Adipose tissue, adipokines and insulin resistance in pregnancy

Pregnancy is characterized by insulin resistance, traditionally attributed to the effect of placental hormones [7,8,44,45,62,76,86,87]. A single mechanism is unlikely to explain the link between pregnancy and insulin resistance. A large body of evidence has supported the role of adipose tissue in the induction and regulation of insulin resistance in non-pregnant and pregnant subjects. Indeed, during the last decade, the notion of adipose tissue as an important endocrine organ has emerged [23,43,83], and the role of adipocytes and other cellular components of adipose tissue has been strengthened. Moreover, adipokines, which are adipocyte-derived hormones, have been implicated in the regulation of insulin resistance during pregnancy. Several findings support the role of adipokines in the physiology and pathophysiology of insulin resistance during pregnancy: 1) maternal serum concentrations of tumor necrosis factor- α [52,65], adiponectin [18,61,65,81], leptin and C-reactive protein [65] are correlated with

clinical indices of insulin resistance; 2) in the third trimester, insulin resistance in obese women increased by 40% [90], but only 25% in non-obese women [15]; and 3) patients with gestational diabetes have increased maternal serum concentrations of tumor necrosis factor- α [4,50,52,65,103], C-reactive protein [65], hyperleptinemia [4,48,52,65], and hypoadiponectinemia [4,50,79,96,102,104,105,107]. The insulin resistance during pregnancy is accompanied by a remarkable increase in adipose tissue deposits, suggesting that adipose tissue has a role in the induction and regulation of gestational insulin resistance. Our findings of elevated plasma resistin concentrations during pregnancy and further increases in the concentrations at term support the association between adipokines and insulin resistance during pregnancy.

Resistin and insulin resistance in non-pregnant subjects

Resistin is a newly-discovered adipokine [37,49,66,77,94,104]. *In vivo* studies in rodents confirmed the exclusive production of this hormone by adipose tissue. However, studies in humans have revealed that resistin is not tissue-specific and that it can be produced by muscle [56], pancreatic islets [68], mononuclear cells [47] and placenta [34,58,107]. Preliminary studies (*in vitro* and in animals) suggest that resistin has a role in insulin resistance and that this adipokine could be the link between obesity and insulin resistance [5,94]. Indeed, exposure of adipocytes to resistin impairs insulin-stimulated glucose uptake, while anti-resistin antibodies prevent this effect [94]. Hyper-resistinemia is a characteristic of obese mice, and treatment with resistin induces insulin resistance in mice with diet-induced insulin resistance, while immunoneutralization of resistin reduces hyperglycemia [94]. Finally, resistin induces hepatic insulin resistance in rats [78].

There is a controversy in the literature regarding the association between resistin, insulin resistance and obesity in humans. Hyper-resistinemia has been documented in subjects with HIV lipodystrophy and hyperinsulinemia [46], patients on chronic haemodialysis [27] and subjects with Prader-Willi Syndrome [71], all conditions closely linked to insulin resistance. Moreover, higher plasma concentrations of resistin have been reported in obese individuals compared to lean subjects [32] and in patients with diabetes (compared to normal subjects) [31,106]. However, other investigators have not found an association between resistin and insulin resistance or obesity [3,35,59,80,88].

Resistin and insulin resistance in human pregnancy

Only a handful of studies have investigated serum concentrations of resistin in human pregnancy [19–21,34,36,72,99,107]. Our finding of higher plasma resistin concentrations in pregnant women compared to non-pregnant subjects are consistent with reports by Yura et al. [107], Cortelazzi et al. [21], and Palik et al [72]. However, Chen et al. reported that differences between serum resistin concentrations of non-pregnant and pregnant women are significant only in the third trimester [19]. The finding that BMI does not contribute to the plasma concentrations of resistin during pregnancy is in agreement with a study by Hendler et al. [36] in which maternal serum resistin is not correlated with BMI. Herein, we report a positive correlation between maternal plasma resistin and gestational age, which contrasts with a previous report by Cortelazzi et al. [21] However, differences in study design and sample size may contribute to the differences among studies. In particular, this study was conducted using a relatively large number of patients at gestational ages ranging from the first trimester to term, and with different BMIs.

Why do maternal serum/plasma concentrations of resistin increase during pregnancy?

Our results indicate that pregnancy is associated with higher plasma concentrations of resistin than in the non-pregnant state and that a further elevation is observed during the third trimester. This elevated concentration in maternal blood correlates positively with gestational age. Several explanations can account for this finding:

1. Insulin resistance during pregnancy: Maternal serum resistin was associated with surrogate indices of insulin resistance in patients with gestational diabetes [72]. The data obtained in the present study do not allow us to discern cause-and-effect relationships; however, the possibility that alterations in maternal plasma concentrations of resistin during pregnancy have a role in the regulation of the metabolic changes during pregnancy should be considered.
2. Increased fat deposition during pregnancy: Pregnancy is characterized not only by insulin resistance but also by a remarkable increase in adipose tissue deposits. Given that resistin is produced by adipose tissue, it is plausible that plasma resistin is increased simply due to this increase in fat mass.
3. Increased visceral fat depot during pregnancy: Some data supports an increase in intra-abdominal fat during pregnancy [51]. Of note, the visceral fat was significantly increased during the third trimester, when maternal serum resistin concentrations are at their peak. These findings are in accordance with the report by McTernan et al., which demonstrated higher resistin mRNA expression [67] and protein [66] in visceral fat than in peripheral fat in thigh and breast. Taken together, the regional alteration in fat distribution during pregnancy may be related to the increase in maternal plasma resistin.
4. Secretion by the placenta: The human placenta has been reported to be a site of resistin production [34,58,107]. Resistin gene expression in term placentas more prominent than in first trimester [107]. The hypothesis that the placenta is a major contributor to maternal plasma resistin is in line with our findings of higher plasma concentrations of resistin in the pregnant state, the dramatic increase observed during the third trimester, as well as the lack of correlation with maternal BMI.

CONCLUSIONS

In summary, the results presented herein indicate that pregnancy is associated with higher plasma concentrations of resistin than in the non-pregnant state and a further increase occurs during the third trimester. This elevated concentration in maternal blood correlates positively with gestational age but not with maternal BMI. The possibility that alterations in the maternal plasma concentration of resistin during pregnancy have a role in the regulation of the metabolic changes during pregnancy should be considered. Finally, we have presented a nomogram for plasma resistin concentrations during pregnancy that may lay the groundwork for further studies.

Acknowledgements

Supported by the Intramural Research Program of the National Institute of Child Health and Human Development, NIH, DHHS.

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Figure 1. Comparison of median plasma resistin concentrations between non-pregnant women and pregnant women in the first trimester
Pregnant women had a higher median plasma resistin concentration than non-pregnant women.

Figure 2. Maternal plasma resistin concentrations during pregnancy in pregnant women of normal weight (BMI 18.5–24.9kg/mL)

Plasma resistin concentrations remained invariable before term (11–14 wks vs. 15–18 wks, $p=0.18$; 11–14 wks vs. 27–30 wks, $p=0.44$; 15–18 wks vs. 27–30 wks, $p=0.66$). In contrast, a significant increase of plasma resistin concentrations was observed at term (** $p<0.05$ for each comparison. All p -values were adjusted for multiple comparisons).

Figure 3. Plasma resistin concentrations of normal-weight (BMI 18.5 – 24.9kg/mL) and overweight (BMI ≥ 25 kg/mL) pregnant women

No significant differences were observed in the plasma resistin concentrations between both groups at different gestational ages.

Table 1

Clinical characteristics and plasma resistin concentrations of the study population. Values are expressed as median (range) or number (%)

	Non-pregnant (n=40)	Normal-weight (n=261)	Overweight (n=140)
Age (years)	25 (19 – 38)	25 (15 – 42)	28 (15 – 42)
Nulliparity	21 (53%)	101 (39%) [*]	35 (25%) [*]
Weight (kg)	54 (50 – 64)	54 (40 – 68)	66(52 – 108) ^{**}
BMI (kg/mL)	22 (19 – 24.9)	22 (19 – 24.9)	27 (25 – 40) ^{**}
Plasma resistin (ng/ml)	10.3 (6.5 –24.2)	14.1 (1.6 –159) ^{*†}	14.8 (5.1 – 107) ^{* †}

Values are expressed as median (range) or number (percentage).

BMI – Body Mass Index.

*
p<0.05 compared to non-pregnant women.

**
p<0.05 compared to pregnant women of normal weight.

†
Adjusted for parity: p<0.05 for each group.

Table 2
Percentile ranges for plasma resistin concentrations (ng/ml) in non-pregnant and pregnant women (BMI 18.5 – 24.9)

	5th	10th	25th	50th	75th	90th	95th
Non-pregnant (n=40)	6.3	6.5	7.8	10.2	12.7	16.1	17.3
Pregnant							
11–14 weeks (n=63)	6.3	7.3	9.6	12.8	16.9	25.8	49.8
15–18 weeks (n=68)	7.8	9.2	11.2	14.3	19.0	24.3	28.9
27–30 weeks (n=65)	5.8	8.1	11.1	12.8	17.9	30.3	34.5
> 37 weeks (n=65)	8.6	10.9	13.6	15.7	19.9	28.5	30.9

BMI – body mass index.