Serum adiponectin levels are significantly reduced during the second half of normal pregnancy

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Summary

Purpose: To demonstrate the physiologic changes in adiponectin levels during the first vs second half of pregnancy. *Methods:* Sixty-six females with uncomplicated pregnancies and normal pre-gestational BMI had serum adiponectin levels obtained at various gestational ages. Thirty-one samples were obtained during the first half of their pregnancy vs 35 in the second half. Thirty-three healthy non-pregnant females with comparable ages and BMI were controls. *Results:* Mean adiponectin levels were 9.55 μg/dl (95% CI 8.2-10.77) vs 9.48 μg/dl (95% CI 8.44-10.66) in the control group in the first half of pregnancy (p = NS). We noted a 21% reduction in mean adiponectin levels (7.51 μg/dl) during the second half of pregnancy ($p = 0.03$) compared to the first half of pregnancy. *Conclusion:* Early pregnancy does not affect adiponectin levels. However, there is a significant reduction in adiponectin levels during the second half of pregnancy.

Key words: Adiponectin; Insulin resistance; Pregnancy.

Introduction

Adipose tissue has been increasingly recognized as an important endocrine organ secreting a number of biologically active "adipokines" [1]. Of these adipokines, adiponectin has recently attracted much attention because of its anti-diabetic and anti-atherogenic effects [2-4]. Interest in the clinical significance of adiponectin has been rising constantly since its discovery by Scherer *et al*. in 1995 [5]. Adiponectin levels have been reported to be reduced in obese individuals, particularly those with visceral obesity, and to correlate inversely with insulin resistance [6, 7]. Prospective and longitudinal studies have shown that lower adiponectin levels are associated with a higher incidence of type 2 diabetes [8, 9] and is independently associated with the metabolic syndrome [10-12], hypertension [13], and ischemic heart disease [14]. In women, hypoadiponectinemia was associated with breast cancer [15], endometrial cancer [16], and polycystic ovarian syndrome [17].

A number of studies have been performed involving adiponectin and pregnancy. They showed that adiponectin concentrations were significantly lower in women with gestational diabetes mellitus (GDM) [18-20] and who subsequently developed GDM [21] or hypertensive disorders during pregnancy [22]. Nevertheless, most studies showed a paradoxical increase in adiponectin levels after the actual development of preeclampsia [23, 24]. The impact of normal pregnancy on adiponectin levels has not been clearly established. We conducted a prospective cross-sectional study to demonstrate the physiological changes in adiponectin levels during normal pregnancy and whether it is related to the increase in insulin resistance in late pregnancy.

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Materials and Methods

Women presenting for prenatal care or ultrasound evaluation at Cooper University Hospital between April 2006 and March 2007 were considered for inclusion in the study. After obtaining Institutional Review Board approval, 72 pregnant women between 15 and 44 years of age with pre-pregnancy or first trimester body mass index (BMI) ranging between 18.4 kg/m^2 and 24.9 kg/m^2 were included in the study. Participants were asked to provide a blood sample for serum adiponectin level. Thirty-three healthy non-pregnant women within the same age group and BMI range consented to act as controls. Exclusion criteria included the presence of diabetes, hypertension, ischemic heart disease, hyperlipidemia, anorexia, bulimia, polycystic ovarian disease, and chronic debilitating diseases such as systemic lupus erythematosis or cancer. Additional exclusion criteria for the pregnant group included the presence of multiple gestations, hyperemesis with dehydration, and a prior history of or the development of gestational diabetes, hypertension or preeclampsia during the index pregnancy.

All the subjects were enrolled from the outpatient clinics or the antepartum diagnostic center at Cooper University Hospital. Subjects were interviewed at the time of enrollment following strict selection criteria. All women had their weight and height measured at the initial visit and BMI calculated. The BMI of the pregnant women was based on their pre-pregnancy weight or first trimester weight. Pregnant women had their weight measured at every prenatal visit as part of the routine obstetrical care to assure normal weight gain during pregnancy. Each subject provided one random blood sample. Random blood samples were obtained rather than fasting samples as previous studies did not show a change in adiponectin level with fasting or food intake [25-27]. Serum adiponectin levels were analyzed using ELISA testing through Quest Diagnostics Laboratories. Of the pregnant group, 35 had their blood drawn during the first half of their pregnancy before 21 weeks of gestation while another 37 had their blood drawn during the second half of pregnancy. The mean gestational age at the time of blood draw for the two pregnant groups was 14 weeks and 30 weeks, respectively. All pregnant women were followed throughout their pregnancy and their charts were reviewed prior to data analysis to detect any

exclusion criteria. Ninety-nine subjects were included in the statistical analysis using SPSS database analysis software, SPSS incorporation, Chicago, IL.

Results

The three groups were comparable in regards to race, and parity as seen in Table 1. Forty percent (14/35) of the adiponectin samples were drawn in the first half of pregnancy in primipara women vs 57% (19/37) in the second half of pregnancy. The mean age was 28.4 years for the non-pregnant group, 29.3 years for the first half group, and 24 years old for the second half group. The age in the second half of pregnancy group was statistically significantly lower than the other two groups. Upon analysis of variants, age had no significant effect on the adiponectin level within each group. Six pregnant women were excluded from the study; four in the first half of pregnancy, and two in the second half. Of the excluded subjects, one had a hemolytic blood sample, one had termination of pregnancy, three developed gestational diabetes, and one developed hypertension later in pregnancy. Thus the serum adiponectin levels of 66 pregnant women were used for the final analysis.

The mean adiponectin level of each group and its standard deviation is shown in Table 2. The three groups were compared using the one-way Anova test which showed a significant difference ($p = 0.01$) in mean adiponectin levels between the groups. There was no significant difference in adiponectin levels between the group in the first half of pregnancy and the non-pregnant group.

Table 1. — *The three study groups comparing race*.

	Non-pregnant	First half	Second half	Total
Caucasian	19	21	15	55
Black	7	7	9	23
Hispanic	4	5	11	20
Asain	3	2	2	7
Total	33	35	37	105

Table 2. — *Mean adiponectin levels in non-pregnant women vs those obtained in the first or second half of pregnancy*.

	N	Mean	Std. Deviation	SEM	95% CI
Non-pregnant	33	9.48	3.62	0.63	8.20-10.77
First half	31	9.55	3.03	0.54	8.44-10.66
Second half	35	7.51	2.66	0.45	6.60-8.42

One-way ANOVA showed a significantly lower adiponectin level ($p = 0.01$) in adiponectin levels drawn during the second half of pregnancy compared to the first half in non-pregnant women.

Discussion

Pregnancy is a state of insulin resistance that becomes more profound with increasing gestational age [28, 29]. The increased insulin resistance seems to be caused by pregnancy-related changes in the secretion of progesterone, estradiol, human placental lactogen and prolactin [30]. Adiponectin plays a major role in glucose metabolism and is a major promoter of insulin sensitivity. Whether adiponectin plays a role in pregnancy-induced insulin resistance is still to be determined [31, 32].

One study on pregnant mice by Kondo *et al*. demonstrated a decrease in adiponectin during late pregnancy [33]. Recent studies on humans showed controversy whether adiponectin levels change with pregnancy. Cseh *et al*. demonstrated decreased adiponectin levels in the second (n = 12) and third trimester (n = 13) compared to the first trimester of pregnancy (n = 15) [34]. Two small longitudinal studies involving ten and 11 subjects each showed lower adiponectin levels during late pregnancy [35, 36]. On the other hand, two other studies failed to demonstrate a significant change in adiponectin levels with pregnancy [24, 37].

The largest study to date to demonstrate changes in adiponectin levels with pregnancy recently came from the Perinatology Research Branch of the National Institute of Child Health and Human Development, NIH, DHHS [38]. In this retrospective multi-center study, Nien *et al*. provided the normal values of adiponectin during various time frames of pregnancy in normal weight women as well as obese women. They also demonstrated a slight but significant decrease in adiponectin concentrations with advancing gestational age among normal weight women but not obese pregnant women. Our study differs from the NIH study in that our data were collected prospectively, and subjects were followed-up closely throughout their pregnancy after specimen collection according to the study protocol. Our specimens were freshly sent for analysis to the same laboratory and not frozen specimens as used in previous studies. Moreover, the NIH study defined normal BMI as < 25, but we did not include underweight women < 18.4 kg/m^2. Our sample size is relatively smaller than the NIH study but provided adequate power to compare our three groups.

Our study confirms that adiponectin levels do not change early in pregnancy but significantly decrease towards the end of normal pregnancy. We demonstrated a 21% reduction in adiponectin levels during the second half of pregnancy which may contribute to the increase in insulin resistance during this period. The cause of this reduction is not well understood. Catalano *et al*. demonstrated a 2.5-fold reduction of adiponectin mRNA levels in white adipose tissue in the third trimester [35]. Whether the regulation is at the transcriptional or translational level or at the level of secretion into the systemic circulation is not known. On the other hand, a dilutional effect can not be excluded due to pregnancy-associated increase in plasma volume [24]. The present study was intended to be a pilot study to determine if the aforementioned serum ELISA assay for adiponectin could detect a difference in the first half vs the second half of pregnancies. As mentioned, the serum adiponectin levels have been shown to paradoxically increase after the development of preeclampsia [23, 24]. Since the pilot study found that the ELISA assay for adiponectin could detect a decrease in the second half of pregnancy, we plan to evaluate serum adiponectin longitudinally during pregnancy to determine if failure of the serum adiponectin levels to decrease in a given individual may be associated with a greater risk to subsequently develop preeclampsia.

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