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Adipokinins in Pregnancies at Risk for Preterm Delivery

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Abstract

Objective—To compare adipokinins between women experiencing preterm labor (PTL) and prior preterm deliveries (PTD)

Study Design—In this prospective observational cohort, 110 women with a singleton <35 weeks at increased risk for PTD were studied. Serum leptin, adiponectin, and resistin were obtained at three times (23–34 weeks, 35–36 weeks, at delivery) and analyzed via ELISA assays. The adipokinins were compared across time and between PTL (n=59) and prior PTD (n=51) groups using Generalized Estimated Equation models.

Results—There were no differences in leptin, adiponectin or resistin levels over the three times between the PTL and PTD groups. There was a trend towards higher leptin levels (p=0.06 unadjusted analysis, p=0.09 adjusted analysis) at 23–34 weeks. When stratified by body mass index (BMI), there were differences in leptin (p<0.001 for BMI<30; p=0.77 for BMI ≥30) and adiponectin (p=0.04 for BMI<30; p=0.09 for BMI ≥30), but not in resistin over the three times between the PTL and prior PTD groups.

Conclusion—There were no significant differences in adipokinins in women with PTL and a prior PTD. The trends towards higher leptin levels at 23–34 weeks in women with PTL may represent a compensatory response and requires further evaluation in the study of treatments for PTL.

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Declarations of Interest

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Reprints will not be available.

Keywords

adipokinins; preterm delivery; obesity; pregnancy

Introduction

Preterm birth, a delivery occurring prior to 37 weeks gestation, accounted for 11.6% of live births in 2012 in the United States.[1] Thus far, efforts to predict, prevent, and delay preterm births have had some, but limited success. This includes identifying high risk patients via risk factors and scoring systems, applying advanced techniques (e.g., cervical lengths, fetal fibronectin), and treatment (e.g., progesterone, antibiotics, tocolytics).[2–10] The pathophysiology of preterm birth also differs between spontaneous and medically indicated deliveries and likely involves several different molecular pathways in both the mother and fetus (e.g., stress, inflammation, hemorrhage, uterine distention). In terms of identifying high risk women for preterm delivery, it is interesting to note that the risk for spontaneous preterm delivery decreases as maternal body mass index (BMI) increases in several studies. [11–14] Obese women also have fewer contractions, longer cervical lengths, and are more likely to deliver after their due date.[11, 15] The reason for this protective effect is not known and is understudied.

It is possible that an alteration in the maternal endocrine or metabolic status, a novel pathway to explore in the study of preterm delivery, can explain the differences in preterm delivery amongst different weight groups. Leptin, a protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism, is well-characterized with respect to physiologic variations during pregnancy and its role in fetal and neonatal growth. Longitudinal studies have revealed that maternal leptin levels increase with gestational age and body mass index in uncomplicated pregnancies.[16–19] In contrast, leptin is also linked to mechanisms affecting pregnancy specific pathologies such as preeclampsia, gestational diabetes, and abnormal fetal growth.[20–23] However, maternal leptin levels have not been studied with respect to preterm labor and delivery. We theorized that alterations in adipokinins may be responsible for mechanisms related to preterm delivery and potentially explain the differences between preterm deliveries between non-obese and obese women.

The purpose of this pilot study was to gain a better understanding of leptin and other adipokinins throughout gestation in women at high risk for preterm delivery. We aimed to compare these levels between women experiencing preterm labor and those with a prior preterm delivery and hypothesized that women with preterm labor would have decreased leptin levels. Secondly, we aimed to compare these levels in women who ultimately had a preterm delivery to term deliveries.

Methods

This was a prospective observational cohort study conducted in 2010–2012. The goal was to study women at high risk for preterm delivery. As such, pregnant women with a singleton gestation identified at < 34 weeks with either an inpatient admission for preterm labor

(defined by cervical change over at least two exams) in the current pregnancy or a prior spontaneous preterm delivery < 37 weeks were recruited to participate either from the high risk outpatient clinics or the inpatient antepartum service after informed consent was obtained. Women < 16 years of age and those requiring emergent delivery were excluded. Participants were compensated for any blood sampling that was done for research purposes. Non-fasting serum levels of leptin, adiponectin, and resistin were obtained at three time points (A: 23–34 weeks, B: 35–36 weeks, C: at delivery) The time points were chosen to not only provide longitudinal data, but to capture changes in adipokinins that were occurring in the late preterm period. Some participants had only two serum samples collected if they delivered < 35 weeks gestation. Maternal demographics, height, weight (prepregnancy and at each blood sampling), co-morbidities, and delivery outcomes were abstracted from the electronic medical record.

The blood samples were immediately spun and the serum was then frozen at -70°C until the ELISA assays were completed in duplicate (R&D Systems, Inc., Minneapolis, MN) according to the manufacturer's instructions. The reported intra-assay variances in our lab for adipokinins is 3.2%. [24]

The maternal data was compared between preterm labor and prior preterm delivery groups with t-tests, Chi-square, and Fisher exact tests as appropriate. The adipokinin levels were compared across time and between preterm labor and prior preterm delivery groups using Generalized Estimated Equation (GEE) models. Covariates for the GEE models included prepregnancy body mass index, nulliparity, prior preterm delivery, progesterone use, and corticosteroids for fetal lung maturity. The adipokinin analysis was repeated after stratification by body mass index (<30 or $\geq 30 \text{ kg/m}^2$). In a secondary analysis, mean adipokinin levels were compared between pregnancies that resulted in preterm delivery (< 37 weeks) and term delivery (≥ 37 weeks) at each of the three time points using t-tests. A p-value <0.05 was considered statistically significant for all analysis. Previously published data on leptin levels in the late 3rd trimester (mean value of $25.8 \pm 14.7 \text{ ng/ml}$) was used to calculate sample size. [17] To observe a 30% difference in the mean leptin levels at this gestational age, with a power of 80%, an alpha of .05, and a two sided test of significance, 55 subjects were needed for each group, for a total of 110. Institutional review board approval was obtained from the University of Illinois at Chicago.

Results

Of the 119 women recruited to participate in this study, 9 were excluded due to missing data. Of the remaining 110, there were 59 women with preterm labor and 51 women with a prior preterm delivery. The preterm labor group was younger with more nulliparas and corticosteroid use, but had less progesterone use compared to the prior preterm delivery group, $p<0.006$ (Table I).

There were no differences in leptin, adiponectin or resistin levels over the three time points between the preterm labor and preterm delivery groups (Figure 1). There was a trend towards higher leptin levels ($p=0.06$ unadjusted analysis, $p=0.09$ adjusted analysis) at time point A.

When stratified by BMI, there were differences in leptin ($p<0.001$ for BMI<30; $p=0.77$ for BMI ≥ 30) and adiponectin ($p=0.04$ for BMI<30; $p=0.09$ for BMI ≥ 30), but not in resistin over the three time periods between the preterm labor and prior preterm delivery groups (Figure 2). Perinatal outcomes (e.g., pregnancy complications, gestational age at delivery) were available for 93 (84.5%) of the final sample whereby 38 women had a preterm delivery and 55 had a term delivery. There were no differences in the adipokinin levels for each of the time points ($p>0.05$) for all comparisons between preterm and term deliveries (Table II).

Discussion

In this longitudinal pilot study of women at high risk for preterm delivery, we did not demonstrate a significant difference in adipokinins in women with preterm labor and a prior preterm delivery. Furthermore, there also were no differences in adipokinins in women who eventually had preterm vs. term deliveries. An in vitro study which evaluated leptin effects on human myometrium found that leptin had a physiologic inhibitory effect on contractility. [25] It is also possible that leptin plays a role in the dysfunctional labor process at term associated with maternal obesity. Because of its effects on smooth muscle, other investigators have proposed to use leptin as a tocolytic in women with preterm labor, [26] yet studies regarding the relationship between preterm labor and adipokinins remain sparse.

A secondary analysis of participants in the Pregnancy Outcomes and Community Health (POUCH) study measured leptin levels at 16–27 weeks gestation.[27] They found that women who delivered a preterm infant that was either appropriate for gestational age (AGA) or small for gestational age by birth weight had lower leptin levels compared to term AGA infants and the results did not change significantly after controlling for prepregnancy BMI. The authors speculated that this may reflect the underlying pathology related to preterm delivery, but they only evaluated leptin at a single time point. Conversely, leptin levels were higher in women who ultimately delivered preterm or term large for gestational age infants, but the geometric means were attenuated after adjusting for prepregnancy BMI. If the majority of the increase in leptin during pregnancy derives from the placenta, then a decrease in leptin in women with a preterm delivery suggests a greater role of the placenta in the mechanisms of preterm labor.[21] Leptin measurements taken directly from the placenta appear to be the next logical step in the study of adipokinins and preterm delivery. The trends towards higher leptin levels at 23–34 weeks in women with preterm labor in our study may represent a compensatory response and requires further evaluation in the study of preterm labor treatment. Other studies have evaluated adiponectin levels from second trimester amniotic fluid specimens, but have found no differences in leptin between preterm and term deliveries.[28, 29]

Of the 63 (57%) women who received corticosteroids for prematurity in the total cohort, 37 in the preterm labor group (62%) received them before the blood sampling for the study purposes. Corticosteroid administration, which has also been linked to increases in leptin, but not adiponectin in women receiving betamethasone for threatened preterm delivery, may also explain the trend towards increased leptin in the preterm labor group we observed, but our analysis also controlled for corticosteroid administration.[30] As expected, leptin levels were higher in women with a BMI ≥ 30 compared to those with a BMI < 30 (Figure 2), but

differences between preterm labor and prior preterm delivery groups were only seen in women with a BMI < 30. We can speculate that this occurred because the leptin concentrations had already reached their peak and no further leptin expression was possible in women with a BMI ≥ 30.

We recognize several limitations to this study. The intended sample size was reached for this pilot study, but the mean leptin values were higher than previous studies of leptin in the third trimester. The higher proportion of obese women in our study (40%) likely accounts for the higher leptin levels and contributes to the lack of differences in all the adipokinins. There was also further attrition in sample size when several of the participants did not ultimately deliver at our institution, thereby limiting the number of other outcomes available to study. In the total cohort, women developed gestational diabetes (n=7) and gestational hypertension or preeclampsia (n=10), but the numbers were too few to make meaningful statistical comparisons between the two groups. We recognize that cervical shortening is also a high risk factor for preterm delivery, but we did not include this group of women in the study as transvaginal cervical length measurements were not standard practice at our institution at the time of the study. The strength of the study includes a longitudinal analysis of adipokinins in a high risk population, but future studies that also include a low risk populations and adipokinin levels in the first trimester will be needed to further characterize these findings.

New investigations into leptin and other adipokinins and their associations with preterm labor may further clarify their use as predictor of preterm birth, but also their role in the treatment or prevention of adverse perinatal outcomes.

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Figure 1. Comparison of Adipokinin Levels (ng/mL) in Preterm Labor (PTL) vs. Prior Preterm Delivery (PTD) Groups across Time. Analysis adjusted for prepregnancy body mass index, nulliparity, prior preterm delivery, progesterone use, and corticosteroids for fetal lung maturity.

Figure 2.
Leptin and Adiponectin Levels (ng/mL) in Preterm Labor (PTL) vs. Prior Preterm Delivery (PTD) by Body Mass Index (BMI) across Time.

Table I

Participant demographics and characteristics

Variable (n,% or mean $\pm$ SD)	Preterm labor (n=59)	Prior preterm delivery (n=51)	P-value
Age (years)	24.9 $\pm$ 5.5	28.5 $\pm$ 5.3	<0.001
Race			0.40
African American	45 (76)	34 (67)	
Hispanic	9 (15)	11 (22)	
White	5 (9)	4 (8)	
Asian/Pacific Islander	0	2 (4)	
Body mass index 30kg/m ²	22 (37)	22 (43)	0.69
Nullipara	19 (32)	0	<0.001
Prior preterm delivery	26 (44)	51 (100)	<0.001
Prior cesarean	5 (8.5)	19 (37)	<0.001
Tobacco use	6 (10)	8 (16)	0.41
Chronic hypertension	6 (10)	5 (10)	0.99
Pregestational diabetes	2 (3)	1 (2)	0.99
Asthma	12 (20)	9 (18)	0.81
Antenatal corticosteroids	47 (100)	5 (11.1)	<0.001
17 hydroxyprogesterone treatment	15 (31.9)	31 (68.9)	<0.001
Transvaginal cerclage	12 (25.5)	8 (17.8)	0.37

Table II

Leptin, Adiponectin, and Resistin in Preterm vs. Term Deliveries

Variable (ng/mL; mean $\pm$ SD)	Sample Time Point ^I	Preterm delivery (n=38)	Term delivery (n=55)	P-value
Leptin	A	57.9 $\pm$ 36.9	48.7 $\pm$ 35.6	0.80
	B	53.6 $\pm$ 29.4	54.8 $\pm$ 41.1	0.94
	C	38.9 $\pm$ 24.5	46.5 $\pm$ 46.2	0.44
Adiponectin	A	5380 $\pm$ 3717	5137 $\pm$ 3073	0.74
	B	4548 $\pm$ 1643	4865 $\pm$ 2621	0.75
	C	5577 $\pm$ 4676	5252 $\pm$ 4158	0.77
Resistin	A	17.7 $\pm$ 17.7	18.8 $\pm$ 16.8	0.77
	B	23.0 $\pm$ 20.9	13.6 $\pm$ 8.2	0.04
	C	17.7 $\pm$ 9.8	20.9 $\pm$ 21.2	0.45

^ITime point A = 23–34 weeks, B = 35–36 weeks, C = at delivery