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SERUM LEPTIN MEASURED IN EARLY PREGNANCY IS HIGHER IN WOMEN WITH PREECLAMPSIA COMPARED TO NORMOTENSIVE PREGNANT WOMEN

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Abstract

Leptin, an adipocyte-derived hormone, plays an important role in reproduction and angiogenesis. Studies examining leptin in preeclampsia are inconsistent, possibly due to small sample sizes and variability in sampling and outcome. We conducted a nested case-control study to examine associations between serum leptin (measured: 9–26 weeks gestation) and preeclampsia among 430 primiparous preeclamptic women and 316 primiparous normotensive controls from the Danish National Birth Cohort. Median [interquartile range] leptin concentrations were calculated. Associations between leptin and preeclampsia (blood pressure ≥ 140/90mmHg), term preeclampsia (preeclampsia and delivery ≥ 37 weeks gestation), or preterm (preeclampsia and delivery < 37 weeks gestation) preeclampsia were examined using generalized linear models adjusting for body mass index, gestational age at blood draw, maternal age, smoking, and socio-occupational status. As leptin is increased in obese women and the risk of preeclampsia increases with body mass index, we used the Sobel test to examine if leptin is a mediator of this relationship. After adjustments, leptin concentrations were significantly higher in women with

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preeclampsia [30.5(24.6) p=0.0117] and term preeclampsia [30.4(24.9) p=0.0228] compared to controls [20.9(28.3)]. There was no significant difference between preterm preeclampsia [30.6(23.4) p=0.2210] and controls. Leptin is a possible mediator of the association between body mass index and preeclampsia (p=0.0276). Leptin concentrations are higher in women with preeclampsia compared to normotensive controls and may mediate some of the relationship between body mass index and preeclampsia.

Keywords

Body Mass Index; Hypertension; Leptin; Preeclampsia; Pregnancy

Introduction

Leptin is a hormone that plays an important role in several physiological processes including the regulation of endocrine function, immune function, inflammation, reproduction, and angiogenesis.[1] The main source of leptin is adipose tissue but during pregnancy leptin is also produced by the placenta.[2] In normal pregnancy, placental leptin expression is increased compared to non-pregnant women and suggested to support implantation, human chorionic gonadotrophin production, placental growth, amino acid uptake, and mitogenesis.[3] Thus, a dysregulation in leptin levels may indicate or lead to maternal disease. For example, placental leptin expression [4, 5] and circulating leptin levels [4, 6–9] are exaggerated in preeclampsia, a systemic maternal disease characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation.[10] As the only treatment for preeclampsia is delivery of the placenta,[10] which is often preterm, there is a need to identify biomarkers for early prediction or to identify women with severe subtypes who require different clinical management.[11] Thus, leptin could be a potential biomarker for preeclampsia.

Elevated placental leptin expression in preeclampsia is consistent with the accepted model that placental dysfunction leads to an increase in placental-associated factors resulting in maternal systemic disease.[12] One hypothesis is that leptin is increased as a result of placental stress to increase nutrient delivery to the fetus.[13] Alternatively, excessive maternal inflammation coupled with other placental factors mediates excessive leptin expression in preeclamptic women.[14] In both scenarios, increased placental leptin could be a valuable proxy for disease. In addition, there is evidence that leptin may play a direct role in preeclampsia pathogenesis. Increased leptin leads to hypertension in mouse models[15] and has been shown to increase blood pressure through sympathetic activation and nitric oxide synthesis.[16] Furthermore, leptin may have pro-inflammatory properties,[17] and inflammation is associated with preeclampsia.[18]

Although epidemiologic studies have shown significant associations between leptin and preeclampsia, some studies have found no association after adjustment for maternal characteristics including body mass index (BMI). [19–21] Indeed serum leptin is increased with obesity[6] and increasing BMI has been shown to be linked with preeclampsia.[22, 23] However, it is possible that leptin partly mediates this association. This may occur due to an increase in placental leptin resistance and a dysregulation of leptin function which is observed in

obese women.[24] We aimed to examine the association between serum leptin in early pregnancy (9–26 weeks gestation) and preeclampsia defined by severity among 430 preeclamptic women and 316 normotensive controls from the Danish National Birth Cohort. In addition, we explored whether leptin mediated the association between maternal BMI and preeclampsia.

Methods

Study Population

This study was part of a previously completed nested case control study of 562 primiparous women with preeclampsia, singleton pregnancies, and no gestational diabetes and 377 primiparous normotensive controls with singleton pregnancies and no gestational diabetes selected from the Danish National Birth Cohort (DNBC).[25] Our subset has similar characteristics compared to primiparous/singleton women in the DNBC. For example, in both groups most women had a maternal age between 26–30 (52.9% vs. 52.2%) and a high socio-occupational status (67.5% vs. 64.9%). There were slight differences in body mass index (BMI) (normal: 70.6% vs. 62.5%) and smoking (25.3% vs. 18.8%), due mainly to the larger percentage of preeclamptic women in our cohort who are more likely to have increased BMI and less likely to smoke.[10] The DNBC is a longitudinal population-based cohort of 101,033 pregnancies and their offspring. Details on the methods of recruitment, retention, and data collection have been published elsewhere.[26] Briefly, between 1996 and 2003 women who were receiving prenatal care were recruited at first prenatal visits by their general practitioners. At the first study visit pregnancy was confirmed and a blood sample was obtained. Telephone interviews were administered at recruitment (median 16 weeks, range 6–40 weeks), at 30 weeks gestation, and twice after delivery. For this study, cohort members were merged with National Birth Register and National Hospital Discharge Register via a unique personal code given to citizens of Denmark. Gestational age was determined by last menstrual period reported but corrected with an early ultrasound if the subject reported use of contraception four months prior to conception, had irregular periods, or had an abnormal last menstrual cycle. The DNBC was approved by the Danish Ethics Central Committee.

For this substudy, leptin results were available for 512 cases and 339 controls. Women with a history of hypertension (n=75) and those with samples obtained in the third trimester (n=30) were excluded from the analyses, yielding 430 cases and 316 controls with markers assessed at recruitment dates ranging from 9 to 26 weeks of gestation. The majority of samples in our study were collected in the second trimester (n=675; median 17 weeks). An additional 71 samples were from women recruited in the first trimester (median 12 weeks). The main analyses were conducted pooling these samples together, since inclusion of the relatively small number of first trimester samples was not expected to significantly influence the results. Furthermore, median leptin levels were similar in the first and second trimester samples [29.6 (IQR 27.25) vs. 24.9 (IQR 26.3); p=0.5432). This study was approved by the University of Pittsburgh Institutional Review Board and the Danish Data Protection Agency.

Preeclampsia definition

Women with preeclampsia were identified by a positive report of preeclampsia at the postnatal interview and confirmed by an *International Classification of Diseases* (ICD) code and discharge diagnoses in the National Hospital Discharge Registry of 637.03, 637.04, 637.09, 637.19 (ICD-8) or D014 to D015 (ICD-10). Preeclampsia was determined if a women had either systolic or diastolic blood pressure ≥140/90mmHg measured twice with an interval of 6 hours and the presence of proteinuria (≥0.3 g/24 hours or 1+ urine dipstick measured twice with an interval of 4 hours). A chart abstraction study within the DNBC shows that compared to a chart review using American College of Obstetrics and Gynecology (ACOG) criteria, the Danish National Discharge Registry yields a highly specific diagnosis of preeclampsia (99%).[27] Preeclampsia is heterogeneous disease.[28] For example, early and late onset preeclampsia are known subtypes with different pathophysiological pathways and clinical presentation.[28] In this analysis, we further classified preeclampsia resulting in either a term birth (≥37 weeks gestation) or a preterm birth (< 37 weeks of gestation) as separate outcomes. Preeclampsia with preterm birth was used as a proxy for disease severity and early onset of disease.

Leptin Measurement

Whole blood samples obtained at the first study visit were mailed to the Statens Serum Institute in Copenhagen and were separated and stored at −80°C. The average time from collection to processing was 28 hours. Leptin was measured in duplicate with an in house assay[29, 30] using the multiplex flow cytometric assay system Luminex MultiAnalyte Profiling Technology (LabMap, Luminex Corporation, Austin Texas). The calibration curve was calculated by the Bio-Plex 3.0 software (BioRad, US). A 5-parameter logistic regression equation was used to determine leptin concentrations. The working range for leptin was assessed from the precision profile and defined as the concentration range where the coefficient of variation was less than 20%.[30]

Maternal Characteristics

During the first study interview women reported the following: gravidity/parity; occupation; cigarette use during pregnancy; prior medical conditions, prior spontaneous abortions, and pre-pregnancy weight and height. Maternal age was self-reported at delivery and grouped as ≥ 25, 26–30, and 31+. Socio-occupational status was based on a women's job classification or education. High status was assigned to women in management or jobs that required more than 4 years of post-high school education. Mid status was assigned to those with office, service, or skilled manual workers or women in the military. Low status included unskilled or unemployed women. Pre-pregnancy BMI was determined using reported height and weight at the first study interview and was categorized as underweight or normal (<25), overweight (≥25 and <30), or obese (≥30).

Statistical Analyses

Baseline variables including gestational age at blood draw, maternal age, BMI, smoking, and socioooccupational status were compared between all preeclamptic cases and controls. In addition, we compared rates of preterm birth between cases and controls. Logistic regression

was used to examine associations between variables and preeclampsia. A p-value <0.05 was used to determine statistical significance. The median and interquartile range for leptin was compared between preeclampsia, preeclampsia defined by gestational age of delivery and normotensive controls by Wilcoxon rank-sum test. To determine if leptin concentrations and preeclampsia were significantly associated, p-values were calculated using generalized linear models. As leptin is not normally distributed, the logarithm of leptin with base 2 was used (this represents a doubling of intensity). Additionally, leptin was dichotomized (≥ median) and logistic regression was used to calculate ORs (as an estimate for relative risk) and 95% CI were calculated. Dichotomizing by the median is one method to analyze biomarkers with limits of detection (LOD).[31] However, we chose to also examine the data in the continuous models in order to determine if there was consistency among both modeling approaches. Maternal age, gestational age at blood draw, BMI, smoking, and socio-occupational status were included in all regression models. Lastly, we explored whether leptin mediated the relationship between BMI and preeclampsia using Sobel test.[32] Statistical significance was determined as a p-value < 0.05. Although adequately powered for our main analyses, a post hoc power analysis reveals that our power was reduced (60%) to detect significant differences in leptin levels between preterm preeclampsia and normotensive controls (based on calculated medians). All analyses were conducted using SAS V9.2 (Cary, NC).

Results

Table 1 compares characteristics between all women with preeclampsia and normotensive controls. The majority of women in our cohort were between the ages of 26 and 30, had a BMI <25, did not smoke during pregnancy, had a high socio-occupational status, and delivered a term infant. When we compared baseline variables between cases and controls, we found that overweight women (OR 1.9, 95% CI 1.3–2.8), obese women (OR 4.1, 95% CI 2.4–7.4), and women with low socio-occupational status (OR 2.8, 95% CI 1.1–7.1) were significantly more likely to have preeclampsia. Women who smoked at the time of enrollment were significantly less likely to have preeclampsia (OR 0.6, 95% CI 0.3–0.9). In addition, preeclamptic women were significantly more likely to have a preterm infant less than 37 weeks gestation (OR 6.8, 95% CI 3.7–12.7) and less than 34 weeks gestation (OR 4.2, 95% CI 1.5–10.9).

Compared to normotensive controls [n=316; median 20.9 (IQR 28.3)], leptin concentration levels were higher in women with preeclampsia [n=430; 30.5 (24.6); p<0.0001]. Results were similar for women with preterm preeclampsia [n=91; 30.6 (23.4); p=0.0192] and term preeclampsia [n=339; 30.4(24.9); p<0.0001]. After adjustments for maternal age, gestational age at blood draw, BMI, smoking, and socio-occupational status there was a significant association between leptin and preeclampsia (p=0.0058) where each unit increase in leptin increased the log odds of having preeclampsia vs. being normotensive (Table 2). Results were similar in women with term preeclampsia (p=0.0228). Leptin was not significantly associated with preterm preeclampsia (p=0.2210). Median leptin concentrations in early pregnancy were higher among women with preeclampsia resulting in a preterm birth <34 weeks [41.0(23.1)] as compared to controls, although the sample size of these cases was limited (n=27) and multivariate models did not show a significant association (p=0.7646).

We conducted our analysis in second trimester samples only (n=675) and found that leptin remained significantly associated with preeclampsia (p=0.0061). Similarly, if we examine a smaller gestational age range between 15 and 18 weeks (n=308), prior to the diagnosis of preeclampsia and when the majority of samples were collected, leptin remains significantly associated with preeclampsia (p=0.0332).

Dichotomized models examining associations between elevated leptin (≥ median) and preeclampsia yielded similar results (Table 3). Elevated leptin increased the risk of preeclampsia (OR 1.4, 95% CI 1.0–2.0). Results were similar for preterm (OR 1.8, 95% CI 1.1–3.0) and term preeclampsia (OR 1.4, 95% CI 1.0–2.0).

In our cohort, lean women [18.9 (23.1)] had lower median leptin levels than overweight or obese women [41 (3.7)]. Furthermore, increasing BMI was significantly associated with increased leptin levels independent of gestational age at blood draw, maternal age, smoking, or socio-occupational status (p<0.0001). We evaluated whether leptin may mediate the relationship between BMI and preeclampsia using the Sobel test. Leptin was a potential mediator of BMI and preeclampsia (p=0.0276) and accounted for 19.6% of the total effect.

Discussion

Our results demonstrate that serum leptin concentrations measured in early pregnancy are significantly higher in women with preeclampsia compared to normotensive controls after adjusting for known confounding factors including BMI. Furthermore, examining leptin in a smaller gestational age range prior to 20 weeks when preeclampsia would be diagnosed shows similar results. Therefore, leptin may be elevated in women who will subsequently develop preeclampsia. Our results are consistent with several small studies conducted in the third trimester that have found elevated maternal leptin in preeclamptic women compared to healthy pregnant controls.[4, 6–9] In contrast, a longitudinal study of 71 preeclamptic women and 71 age, parity, and BMI matched controls reported lower leptin levels at 18 weeks of gestation in women who developed subsequent preeclampsia.[33] A study of 126 preeclamptic women found that first trimester free leptin index was significantly elevated compared to 289 controls (p<0.001).[34] The largest study to date was nested within a study of pregnancy outcomes which included 12,804 births in Norway.[35] This study included 256 cases of preeclampsia and 607 controls and reported that umbilical cord leptin levels were significantly higher in women with preeclampsia compared to controls after adjustment for gestational age.

Leptin is suggested to play a role in angiogenesis, immunomodulation, and fatty acid metabolism in early placentation.[36] Reduced placental perfusion is hypothesized to increase placental expression of leptin which may increase nutrient delivery to the fetus.[13] Studies show that leptin released from the placenta can stimulate system A amino acid transport[37,38] possibly influencing fetal growth. Thus, leptin may be a coping mechanism for reduced placental perfusion and a marker of placental insufficiency. Alternatively, an increase in maternal leptin expression may be a result of other stimuli. Leptin has been shown to play a role in immunity,[17] although its function is not completely understood. As an altered immune response is one pathway which may lead to preeclampsia,[39] it's possible that

inflammatory stimuli or immune dysfunction could alter maternal leptin expression. Once increased, leptin may have direct effects on the development of preeclampsia. In pregnant rats, leptin has been shown to increase blood pressure.[16] Leptin has also been shown to be correlated with systolic and diastolic blood pressure in pregnant women, independent of BMI.[40] Although up to 98.4% of placental leptin may be released into the maternal circulation,[41] in our study we cannot determine the proportion placental leptin measured in maternal serum. As placental leptin expression and placental leptin protein are increased in preeclampsia and correlate with circulating levels,[13, 42] it is suggested that the placenta contributes substantially to serum leptin concentrations. Additionally, leptin is reported to increase throughout pregnancy and then drastically reduces postpartum.[43] However, placental leptin expression is similar in obese and lean women suggesting that adiposity may increase circulating leptin concentrations during obesity.[24]

As leptin has been indicated to be a possible marker for early onset preeclampsia (<34 weeks),[44] we examined associations between leptin and preeclampsia subtypes. We found that leptin concentrations were significantly higher in term preeclampsia but not preterm preeclampsia. The effect sizes as well as median leptin levels were similar for term and preterm cases. Among 27 cases of preterm preeclampsia less than 34 weeks gestation no significant associations with leptin were observed. We were underpowered to examine the associations with preterm preeclampsia. Larger cohorts with well-defined subtypes are needed to examine these associations.

Obesity is associated with an increased risk of mild and severe forms of preeclampsia,[22, 23] as well as hyperleptinemia.[24] The role of obesity in the pathogenesis of preeclampsia is not clear. It has been suggested that increased leptin, inflammation, and metabolic markers may lead to preeclampsia in obese women.[45] We found that leptin could be a possible mediator of BMI and preeclampsia. However it only accounted for a small percent of the total effect. This suggests that other factors such as increased inflammation in addition to leptin may play a role in obesity related preeclampsia. Obesity may lead to dysregulation in leptin function that result in maternal disease. Placental leptin resistance is present in maternal obesity due to syncytiotrophoblast down regulation of leptin receptor during states of maternal hyperleptinemia.[24] Alternatively, an increase in leptin during obesity may have direct effects on inflammation and blood pressure. The relationship between BMI, leptin and preeclampsia is likely very complex. Future work is needed to explore these relationships.

We obtained data from a large well defined cohort and were able to adjust for several known risk factors for preeclampsia. This is one of the largest studies examining relationships between serum leptin and preeclampsia. We did not have data on time of diagnosis of preeclampsia. Therefore, some women in our study may have had preeclampsia at the time of blood sampling. However, our results were the same when we examined a smaller gestational age window between 15–18 weeks, prior to when preeclampsia would have been diagnosed by a clinician. Still, we cannot rule out the presence of subclinical disease at the time of blood sampling. Diagnostic codes to classify women as having severe or mild preeclampsia were not available for all women in the DNBC. We used gestational age of delivery as a proxy for severe disease as well as disease onset. This is a common approach[11] but may have limited our ability to assess the role of leptin in preeclampsia severity. As the

placenta grows during pregnancy, placental derived products may increase and thus leptin levels may vary by the gestational age of sampling. However, we did not find significant differences in gestational age at sampling between cases and controls. We relied on self-reported BMI which may be lower than true BMI[46] and may bias results of our mediation analysis. Although the in-house assay used to measure leptin was previously validated, a CV was not calculated specifically for our study.

Perspectives

Our observational study suggests that serum leptin levels measured in early pregnancy are elevated in women with preeclampsia compared to normotensive controls. Leptin may be a useful biomarker for predicting preeclampsia and could be used clinically as a screening tool in early pregnancy. However, additional studies are needed prior to assessing its clinical utility. First, these results need to be replicated in an independent cohort. Studies utilizing both circulating and placental expression of leptin would be useful in order to gain more insight into the role of leptin in preeclampsia pathogenesis. Additionally, further prospective studies with larger samples of women recruited prior to or early in gestation are needed to confirm if this relationship is temporal. Lastly, the relationship between leptin, BMI and preeclampsia requires further examination.

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Novelty and Significance

What is new?

- This is the largest study to examine serum leptin in early pregnancy (9–26 weeks gestation) and its relationship to preeclampsia defined by severity.

What is Relevant?

- Serum leptin measured in early pregnancy (9–26 weeks gestation) is elevated in preeclampsia.
- Serum leptin may mediate some of the relationship between body mass index and preeclampsia.

Summary

- Elevated maternal serum leptin measured in early pregnancy is associated with preeclampsia.

Table 1

Comparison of baseline variables between preeclamptic women and normotensive controls

Baseline and pregnancy outcome data	Controls N (%) N=316	* Cases N (%) N=430	† P-value
Gestational age at sampling [Mean(SD)]	16.9±3.5	16.4±3.5	0.7827
Maternal age			
≤25	67 (21.2)	119 (27.7)	Reference
26–30	183 (57.9)	209 (48.6)	0.0160
31–35	59 (18.6)	88 (20.5)	0.4422
36+	7(2.2)	14 (3.3)	0.8076
Body mass index			
<25	245 (77.5)	253 (58.8)	Reference
≥25 and <30	55 (17.4)	108 (25.1)	0.0006
≥30	16 (5.1)	69 (16.1)	<0.001
Smoking in pregnancy			
No	246 (77.9)	350 (81.4)	Reference
Yes, past	25 (7.9)	44 (10.2)	0.4203
Yes, current	45 (14.2)	36 (8.3)	0.0158
Socio-occupational status			
High	209 (66.1)	270 (62.9)	Reference
Mid	101 (32.0)	137 (31.9)	0.7609
Low	6 (1.9)	22 (5.1)	0.0263
Preterm birth			
No	304 (96.2)	339 (78.4)	Reference
<37 weeks	12 (3.8)	91 (21.2)	<0.0001
<34 weeks	5 (1.6)	27 (6.3)	0.0038

* Cases include all women with preeclampsia.

† P-values were calculated using multivariate logistic regression models.

Table 2

Associations between leptin concentrations and preeclampsia subtypes

Leptin concentration	Outcome group				Estimate (β) and P-value	
	All Preeclampsia		*Normotensive controls*			
	n	Median (IQR)	n	Median (IQR)		
Leptin (ng/mL)	40	30.5(24.6)	31	20.9(28.3)	0.06	†0.0117
	Preterm preeclampsia		*Normotensive controls*			
	n	Median (IQR)	n	Median (IQR)		
Leptin (ng/mL)	91	30.6(23.4)	31	20.9(28.3)	0.03	0.2210
	Term preeclampsia		*Normotensive controls*			
	n	Median (IQR)	n	Median (IQR)		
Leptin (ng/mL)	33	30.4(24.9)	31	20.9(28.3)	0.06	*0.0228

P-values were derived from generalized linear models and based on log transformed leptin to the base 2.

*P<0.05,

†P<0.01. Models were adjusted for maternal BMI, gestational age at blood draw, maternal age, smoking, and socio-occupational status.

Table 3

Associations between elevated leptin dichotomized above the median and preeclampsia subtypes

Leptin Concentration	Outcome group N(%)		Odds ratio (95% CI)
	All preeclampsia	*Normotensive controls*	
Leptin elevated > median	246(57.2)	127(40.1)	1.2 (1.0–2.0)
	Preterm preeclampsia	*Normotensive controls*	
Leptin elevated > median	48(59.3)	127(40.1)	1.8 (1.1–3.0)
	Term preeclampsia	*Normotensive controls*	
Leptin elevated > median	174(56.6)	127(40.1)	1.3 (1.0–2.0)

Odds ratios were calculated by logistic regression. Models were adjusted for maternal BMI, gestational age at blood draw, maternal age, smoking, and socio-occupational status.