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Leptin and Adiponectin as markers for preeclampsia in obese pregnant women, a cohort study

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ABSTRACT

Objective: Preeclampsia (PE) is a serious complication of pregnancy, the pathogenesis of which is largely unknown. We hypothesize that adipocytokines may play a role in the pathogenesis of PE, particularly in obese women, and evaluate leptin and adiponectin as potential first trimester markers for predicting PE.

Study design: A cohort of 2503 pregnancies, containing 93 PE pregnancies, was divided into women with normal weight, moderate, or severe obesity. All pregnancies had serum adiponectin and leptin measured in first trimester. Logistic regression was used to model PE with maternal characteristics and concentrations of the biomarkers.

Results: In obese women a lower concentration of adiponectin was found in PE pregnancies; the concentration was lowest in the severely obese ($p = 0.005$). No association was found in normal weight women ($p = 0.72$). Leptin concentration had no association with PE in normal weight and moderately obese ($p = 0.175$–0.072), however in women with severe obesity a lower level of leptin was found ($p = 0.049$). The AUC was 0.73 for the ROC curve of combined maternal characteristics and adiponectin. Using adiponectin in women with moderate to severe obesity the sensitivity was 72.9% and the specificity was 49%.

Conclusions: In severely obese women, PE is associated with low serum adiponectin and leptin concentrations in first trimester. This indicates that the inability of adipokine regulation to adapt to severe obesity may play a role in the pathogenesis of PE. Adipocytokines may contribute in identification of risk pregnancies among severe obese.

1. Introduction

Hypertensive disorders during pregnancy are serious conditions with a prevalence of 3–9% [1]. Risk factors for developing a hypertensive disorder are nulliparity, advanced maternal age, chronic hypertension and pre-pregnancy diabetes mellitus (DM) [2]. Several studies have identified pre-pregnancy body mass index (BMI) as a risk factor for preeclampsia (PE), obese mothers have a three times greater risk of developing PE than normal weight mothers [3] with a prevalence of up to 14.5%. However, the mechanism behind this association is unknown.

One of the many theories behind the development of PE is that an abnormal placentation, due to abnormal trophoblastic invasion of uterine spiral arteries, leads to placental ischemia and subsequently systemic maternal inflammatory response due to activation of the maternal endothelium [4–6]. There is also an association between insulin resistance and preeclampsia, which might partially underlie the association between obesity and PE [7,8].

Adiponectin and leptin are adipocytokines, hormones mainly produced by the adipose tissue, and responsible for regulation of lipid

Abbreviations: AGA, Appropriate for gestational age; AUC, Area under the curve; BMI, Body mass index; Coef, Regression coefficient; DBT, Diastolic blood pressure; DM, Diabetes mellitus; GA, Gestational age; HELLP, Hemolysis, elevated liver enzymes and low palates; NNT, Number needed to treat; PE, Preeclampsia; ROC, Receiver operating characteristic; SBT, Systolic blood pressure; SD, Standard deviation; SGA, Small for gestational age; SSI, Statens Serum Institut

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metabolism, angiogenesis, insulin sensitivity and inflammatory processes [9]. Adipocytokines seem to be involved in the complex mechanisms of implantation and early pregnancy, and thereby play a potential role in the development of PE [10]. Leptin concentration is increased during pregnancy [11], primarily due to leptin production by the placenta [12,13]. Furthermore, leptin levels are found to be higher in preeclamptic placentas [9]. Adiponectin is inversely related to obesity, insulin resistance, and hypertension [14,15]. The association between adiponectin, leptin and PE are conflicting in the literature, some studies has found an association and others have not [8,14,16].

Several studies have reported that treatment with low-dose aspirin, initiated ≤ 16 weeks' gestation, effectively prevents PE [17,18]. Consequently, it is clinically relevant to identify high-risk pregnancies in first trimester [18]. Women with BMI > 30 kg/m^2 are found to have a high risk of developing PE, in patients with this risk profile the number needed to treat (NNT) with aspirin prophylaxis is < 250 to prevent a single case, which may justify preventive treatment to all women in this group [2]. However, improved selection of high risk women using biomarkers would reduce the NNT and better justify preventative use of aspirin in these selected high risk cases.

We hypothesize that adiponectin and leptin concentrations characterize a metabolic or inflammatory state within both obese and normal weight women, and therefore may be relevant markers of risk for developing hypertensive disorders in first trimester. We aimed to evaluate the potential of adiponectin and leptin as screening markers for PE.

2. Materials and methods

The Holbæk mother cohort was used for this trial [19]. The cohort was generated from a population of 14,591 women attending their first routine visit at the ultrasound unit in Holbaek Hospital, Denmark during a 6-year period (from January 2006 to December 2011). In this study, we included women who had a serum sample from first trimester stored frozen at the Danish National Biobank at Statens Serum Institut (SSI), Copenhagen, Denmark. All obese women (BMI ≥ 30 kg/m^2) were identified and matched randomly with normal-weight women; underweight and overweight women were excluded, as the focus of the study was obesity.

The study was reported according to the STROBE recommendations and approved by the Danish Data Protection Agency (6 June 2013 reg. no. SJ-HO-01) and the regional Research Ethics board (3 April 2013 SJ-335).

3. Outcome measures

The primary outcomes were hypertensive disorders of pregnancy i.e. pregnancy related hypertension, PE or HELLP. Pregnancy related hypertension was defined as hypertension diagnosed after 20 weeks of gestation with a systolic blood pressure (SBT) > 140 mmHg and/or diastolic blood pressure (DBT) > 90 mmHg. Light to moderate PE was defined as hypertension accompanied by proteinuria (≥ 0.3 g, or ≥ +1 on a urine dip). Severe PE was defined by SBT ≥ 160 and/or DBT ≥ 110 mmHg, subjective symptoms or eclampsia or abnormal levels of platelets < 100 × 10^9/l, aspartate aminotransferase (ASTO) > 70 U/l, alanine aminotransferase (ALT) > 70 U/l, urate > 45 mmol/l and or creatinine > 110 mmol/l. Hemolysis, elevated liver enzymes and low platelets (HELLP) was defined as lactate dehydrogenase (LDH) > 600 U/l and/or haptoglobin > 0.3 g/l, ASTO/ALT > 100 U/l, low platelets < 100 × 10^9/l. The three later diagnoses of hypertensive disorders of pregnancy were referred to as PE in this article. All pregnancies with recorded diagnoses were validated by reviewing the hospital charts validated the diagnoses.

Gestational ages were defined from first trimester ultrasound of CRL. Early onset of PE was defined as birth before GA 34^{+0} or GA 37^{+0}; we tested two definitions due to inconsistency in the literature [20,21]. Birth weight deviations were calculated as the ratio between the actual birth weight and the expected birth weight defined according to the GA and gender specific weight formula of Marsal et al [22]. We considered both Marsal et al's definition of small for gestational age (SGA) (weight deviation < −22% (−2 SD, < 2.3 percentile)) [22]; as well as the Danish national guidelines suggested definition of SGA (weight deviation < −15% (< 10th percentile)) [23]. Appropriate for gestational age (AGA) were all children with a birth weight that was ≥–22% or ≥ −15%, when SGA were defined as −2SD or < 10th percentile respectively.

BMI was calculated from height and weight measured at the first prenatal visit < 10 weeks of gestation. Obesity was classified according to WHÓs definition of BMI categories as normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), moderately obese (30–34.9 kg/m^2), and severely obese (≥ 35 kg/m^2) [24].

All data were registered prospectively and stored in a database (Astraia) that comprises information on all ultrasound measurements, mothers' medical history, parity, maternal age, pre-pregnancy maternal weight and height and smoking habits. The data were merged with the maternal birth register in Denmark containing information on complications during pregnancy, date of birth, birth weight and length of the child.

4. Sample analysis

The serum samples were collected at gestational age (GA) 8^{+0}–14^{+6} weeks, processed, and stored at −20 °C at the Danish National Biobank at SSI. Plasma adiponectin concentrations were determined using the DuoSet® ELISA Development System for human adiponectin/Acrp30 (Catalogue no.: DY1065, R&D System, TX, USA). The detection range of the assay was 62.5 pg/mL–4000 pg/mL. Intra- and inter-assay coefficients of variations were < 5% and the analyses were stable for 3 months at −20 °C and for 10 freeze–thaw cycles [25]. Plasma leptin concentrations were determined using the Human Leptin Elisa Development Kit, DuoSet (DY398, R&D Systems, Minneapolis, MN, USA). The lower limits of detection of the assays was 0.03 μg/L. Leptin's intra- and inter-assay coefficients of variations were < 5% and the analyses were stable for 3 months at −20 °C and for 10 freeze–thaw cycles [26].

5. Statistical analysis

Descriptive statistics are presented as mean, standard deviation (SD), median, interquartile range, and percentages. Comparisons between groups were done by chi-square test for categorical variables and the Kruskal–Wallis test for continuous or ordinal variables for skewed distributions with a *post hoc* Bonferroni correction. The Pearson or Spearman correlation coefficients were used as measurements of correlation for continuous normally or not normally distributed variables.

The following maternal characteristics were considered in the analyses; Smoking habits (smoker, non-smoker), maternal age (years), parity (1–9), GA at blood sample (days), ethnicity (Caucasian/other), and BMI (kg/m^2) or BMI groups (women with normal-weight, moderate obesity and severe obesity).

Adiponectin and leptin concentrations were logarithmically transformed into a Gaussian distribution. The adiponectin/leptin ratio was also investigated.

Multiple regression analyses were performed to determine which factors predicted the log concentrations of the adipocytokines, accounting for clustering induced by the same mother giving birth several times using random effect models. The variables affecting the log-transformed concentrations of adiponectin and leptin were used to calculate the median values for the levels of leptin and adiponectin. The results for all subjects were then transformed to multiple of the median (MoM) values. Multivariable ordered logistic regression and regular logistic analyses were used to determine the factors predicting PE. In ordered logistic regression PE was divided into its subgroups;

pregnancy related hypertension, light to moderate-, severe PE and HELLP. Early and late PE was also considered. Additionally, PE pregnancies with SGA and AGA children were evaluated. PE was the dependent variable, while BMI/BMI groups, smoking habits, age of the mother, and parity were used as independent variables. Interactions between BMI groups and biomarker were added if significant. Results were reported as odds ratios with 95% confidence intervals (CI). To evaluate the predictive power of the identified predictors of PE, we used receiver operating characteristic (ROC) curves and the associated area under the curve (AUC). The performance of the biomarkers that were significantly predictive of PE was described using likelihood ratio, sensitivity, specificity, positive and negative predictive values. The cut-off levels of the biomarkers were set using the mean, SD and after visual evaluation of the distribution of the concentrations of the biomarkers in the PE groups and the unaffected pregnancies. $P < 0.05$ was considered statistical significant. The statistical package STATA (version 14.2) was used for data analyses.

6. Results

The cohort was composed of 2205 obese women and 2205 normal weight randomly selected women, of which, serum samples were available for 2644 (60%). We excluded samples which were collected at GA $< 8^{+0}$ (N = 7) and $> 15^{+0}$ (n = 18), samples for which GA defined by first trimester ultrasound was missing (n = 107) and samples from women with pre-pregnancy hypertension (n = 9). Ultimately, 2503 pregnancies were available for analysis. Hypertensive disorders of pregnancy developed in 93 (3.7%) of the pregnancies analyzed. Maternal characteristics of the cohort are described in Table 1, divided into pregnancy related hypertension, PE and unaffected pregnancies.

The effect of maternal characteristics and GA at sampling on the concentrations of adiponectin and leptin have been described in an earlier publication [27]. Outcomes were considered categorical (pregnancy related hypertension, light to moderate, severe PE and HELLP, or early/late PE, or SGA/AGA PE) or binomial (unaffected/PE). There were no differences in the coefficients and significance levels of the results for log adiponectin and log leptin using different categories of PE. Consequently, the final model was a logistic regression (unaffected/PE); the coefficients for leptin, adiponectin and adiponectin/leptin ratio within the different BMI groups are presented in Table 2. Log concentrations of adiponectin had a negative association with PE in moderately (p = 0.004) and severely obese (p = 0.005) but not in the normal weight women (p = 0.727) (Table 2). Log leptin had no significant association with PE in women with normal weight and moderate obesity (p = 0.205 and p = 0.173, respectively), however, in women with BMI ≥ 35 kg/m^2 a lower log leptin level was found in PE pregnancies (p = 0.049) (Table 2). There were significant interactions between the different BMI groups and the log concentrations for both adiponectin and leptin. Adiponectin/leptin ratio did not have any association with the development of PE, in any of the BMI groups (p = 0.352–0.618) (Table 2). When adjusting for maternal characteristics BMI > 30 kg/m^2 (p = 0.02) and a lower parity (< 0.001) had an influence on the development of PE. DM before or during pregnancy, smoking habits, maternal age and maternal height did not have any significant effect on development of PE.

Fig. 1A–D illustrated the log concentrations of adiponectin and leptin in the different BMI groups in the PE and unaffected group. The MoM values of adiponectin and leptin are displayed in Figs. 2 and 3.

The AUC (CI) for maternal characteristics was 0.701 (0.648–0.754). Combining maternal characteristics with log adiponectin or MoM adiponectin increased the AUC to 0.733 (0.680–0.785) and 0.732 (0.680–0.785), respectively. The combinations were all significantly different from maternal characteristics alone (p = 0.02–0.04). Transforming log concentrations to MoM values for adiponectin did not improve the prediction models. The MoM values for Leptin and Adiponectin and their relationship to PE are displayed in Figs. 2 and 3. The ROC curves for the different predictive models are presented in Fig. 4.

The highest sensitivity was achieved using a log adiponectin cut off level of < 8.35. In the total population the sensitivity was 63.4%, the specificity was 60.1%, PPV was 6.21%, NVP was 97.5% and the likelihood ratio was 1.59 when using adiponectin alone as a predicator.

Table 1
Maternal and fetal characteristic and concentrations of biomarker in the three PE groups.

	Unaffected (n = 2410)	Hypertension (n = 29)	Preeclampsia (n = 64)
Maternal age in years, mean (SD)	29.3 (5.1)	29.2 (4.6)	28.2 (5.6)
Gestation at sampling in days, median (IQR)	69.2 (63.8–76.4)	69.7 (63.4–76.8)	68.3 (62.8–75.5)
Gestation at delivery in days, median (IQR)	280.3 (272.9–286.7)	279.8 (270.0–284.7)	270.6 (261.5–279.7)*
Birth weight in g, median (IQR)	3580 (3230–3912.5)	3420 (3200–3870)*	3090 (2645–2652.5)*
Small for gestational age (−22%)	36 (1.5)	1 (3.5)	3 (4.7)
Small for gestational age (−15%)	227 (9.4)	3 (10.3)	18 (28)*
Preterm birth GA < 34 + 0	37 (1.5)	0 (0)	4 (6.3)*
Preterm birth GA < 37 + 0	101 (4.2)	1 (3.5)	11 (17.2)*
Parity:			
Nulliparous, n (%)	968 (40.2)	15 (51.7)*	46 (71.9)*
Parous 1, n (%)	924 (38.3)	8 (27.6)*	13 (20.3)*
Parous ≥ 2, n (%)	518 (21.5)	6 (20.7)*	5 (7.8)*
Cigarette smoker, n (%)	438 (18.2)	2 (6.9)	13 (20.3)
BMI groups			
18.5–24.99, n (%)	1233 (51.2)	9 (31.0)*	14 (21.9)*
30–34.99, n (%)	800 (33.2)	13 (43.8)*	35 (54.7)*
≥ 35, n (%)	377 (15.6)	7 (24.1)*	15 (23.4)*
Conception			
Spontaneous, n (%)	2353 (97.6)	26 (89.6)*	57 (89.0)*
Ovulation drugs only, n (%)	18 (0.7)	2 (6.9)*	3 (4.7)*
In vitro fertilization, n (%)	39 (1.6)	1 (3.4)*	4 (6.3)*
Ethnicity			
Caucasian	2272 (94.3)	29 (1 0 0)	62 (96.9)
Other	138 (5.7)	0 (0)	2 (3.1)
log adiponectin mean (SD)	8.43 (0.42)	8.32 (0.51)*	8.22 (0.48)*
log leptin mean (SD)	9.92 (0.73)	10.18 (0.57)*	10.15 (0.64)*
log adiponectin/leptin, mean (SD)	−1.49 (0.90)	−1.86 (0.92)*	−1.93 (0.78)*

Table 2
Effect of log adiponectin, log leptin and log adiponectin/leptin ratio for development of preeclampsia (final models of ordered logistic regressions, including parity and BMI groups).

BMI group	18.5–24.99 (n = 1298)				30–34.99 (n = 870)				≥35 (n = 422)			
	B	p	Exp (B)	95% CI for Exp (B)	B	p	Exp (B)	95% CI for Exp (B)	B	p	Exp (B)	95% CI for Exp (B)
Log adiponectin	0.06	0.727	1.06	0.38–3.00	−1.03	0.004	0.35	0.18–0.72	−1.61	0.005	0.20	0.06–0.61
Log leptin	0.51	0.205	1.66	0.76–3.65	−0.40	0.173	0.67	0.38–1.19	−0.94	0.049	0.39	0.15–1.00
log adiponectin/leptin ratio	−0.29	0.352	0.69	0.40–1.38	−0.21	0.385	0.81	0.50–1.33	−0.21	0.618	0.81	0.36–1.83

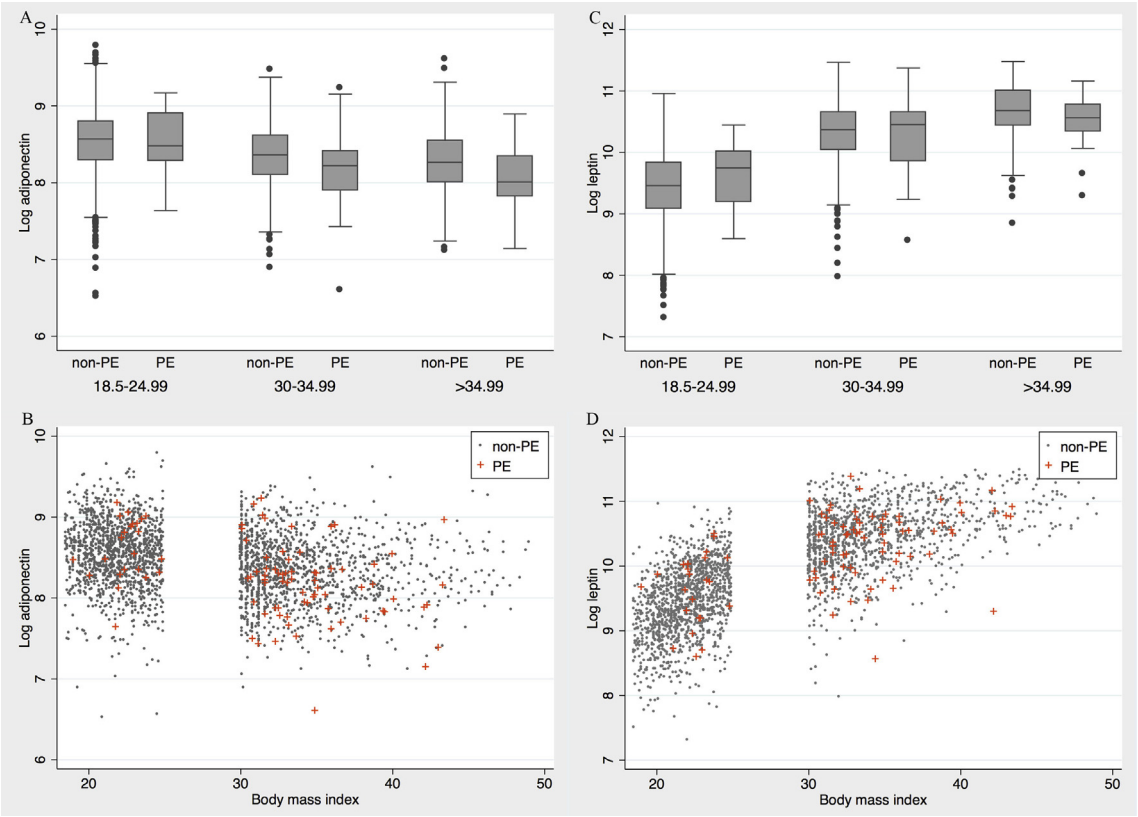

Fig. 1. A–D: The log concentrations of adiponectin (A–B) and leptin (C–D) depending on BMI in PE and non-PE.

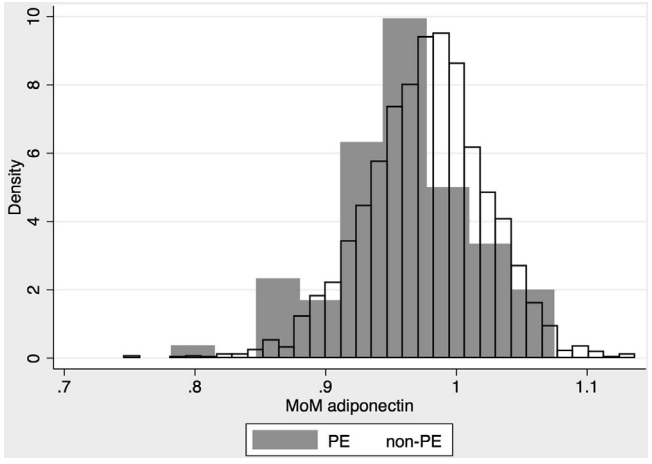

Fig. 2. The distribution of MoM values of adiponectin in the total population divided into PE and non-PE pregnancies.

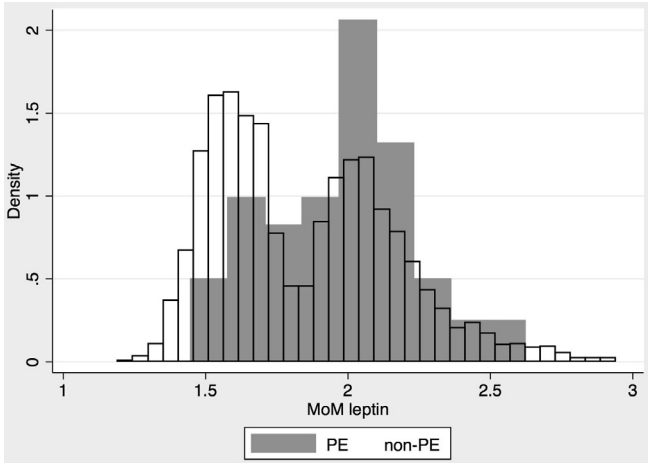

Fig. 3. The distribution of MoM values of leptin in the total population divided into PE and non-PE pregnancies. PE and non-PE.

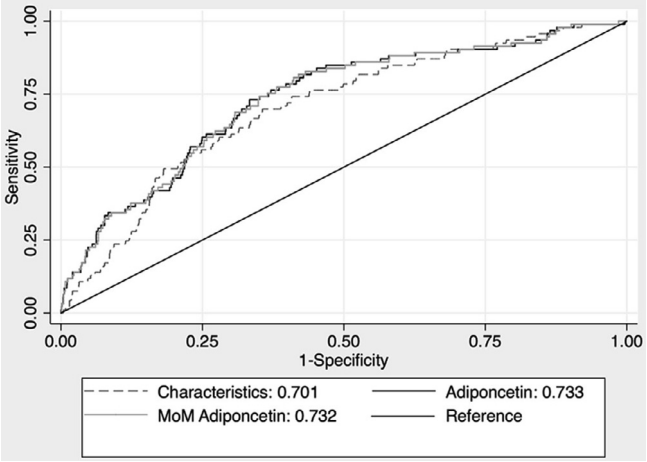

Fig. 4. The ROC curves for the different predictive models.

Women of moderate-severe obesity had a sensitivity of 72.9%, a specificity of 49%, a PPV of 12.3%, a NPV of 94.8%, and a likelihood ratio of 1.42.

7. Discussion

In this examination of a large population of obese and normal weight pregnant women attending routine pregnancy care, we have explored the association between first trimester maternal serum levels of adiponectin and leptin in obese pregnancies and later development of PE. Using detailed recording of maternal characteristics and pregnancy outcomes we have identified circulation levels of adiponectin as a marker for PE in women with moderate to severe obesity. Leptin is strongly dependent of BMI and when adjusting for BMI there were no association between the concentration of leptin and the development of PE, except for women with severe obesity where an inverse relationship was found.

Understanding the pathogenesis of the overrepresentation of PE among obese women is essential to effectively predict and prevent PE. Others have found a relationship between DM before pregnancy, gestational DM (GDM), obesity and PE [1,28]. We found a strong association between BMI and PE but did not find an association between PE and DM/GDM in our material, probably due to the small number of DM and GDM pregnancies (N = 104). We have previously explored adiponectin as a marker for GDM where BMI did not affect the predictive effect [27]. Our findings of a significant association between BMI and a lower concentration of adiponectin, along with a lack of association between PE and adiponectin/leptin ratio (a surrogate marker for insulin resistance) [29–31], in PE pregnancies suggest that adiponectin represents an alternate process to insulin resistance in PE pregnancies. This role of adiponectin might be a consequence of adiponectin's anti-inflammatory- or vasodilatory effects [32,33]. In obese women a higher degree of inflammatory mediators are found; IL-6, C-reactive peptide, TNF-alpha, and macrophages in the placenta [34], supporting the theory that adiposity creates a state of chronic inflammation [10]. Furthermore, human and experimental studies have shown that endothelial and vascular dysfunction caused by pro inflammatory factors from the placenta leads to hypertension and ultimately PE. Earlier studies found that tumor necrosis factor alpha (TNF-alpha), soluble fms-like tyrosine kinase-1 (sFlt-1), vascular endothelial growth factor (VEGF), placental growth factor (PGF) were markers for PE [35]. However, their efficiency as a predictor in obese women in first trimester has, to date, not been investigated.

Different sub classifications of the disease have proved useful in the predictive efficacy of PE; obesity in particular has been associated with late onset and more severe PE [36], which in turn has been associated with a fetal and placental overgrowth, and consequent hypoxia of the fetus [37]. Immaturity of the villous tree of the placenta and angiogenesis abnormalities might explain this phenomenon [38]. Different sub classifications of hypertensive disorders of pregnancy (pregnancy related hypertension, light to moderate PE and severe PE) did not affect the results in the predicative effect of adiponectin in our study. We also stratified patients into early and late PE as well as SGA and AGA, which did not improve the efficacy. A larger number of PE cases would be needed to investigate differences between PE types in relation to BMI, e.g. Dust et al. reported an investigation of 1119 PE cases [36].

The relationship between leptin and PE pregnancies is not well understood and several studies have reported discrepant results [39–43]. Most of these studies are performed on serum samples from late pregnancy [39–41,43]. Thus, it is difficult to distinguish between pathogenic changes in first trimester and possible epi-phenomena of PE when approaching term. Anim-Nyame et al have done a longitudinal study describing how leptin levels rise consistently after week 20 in PE pregnancies compared to normal controls [44]. The increase in leptin level at the end of pregnancy is aligned with the finding of increased expression of the leptin gene in PE placentas at birth [45]. Few studies have investigated the association in first trimester leptin concentrations and subsequent development of PE or its utility as a predictor of disease [16,42]. Samolis et al [42] found an association with high leptin in normal weight PE pregnancies and we have previously found a similar association in a larger PE population [16]. However, none of these studies investigated the interaction between BMI and leptin concentration in PE pregnancies. Adjusting for this we found no association of leptin concentration in first trimester and later development of PE in normal weight and moderate obese women. On the other hand, an inverse, marginally significant ($p = 0.049$), relationship was found in women with severe obesity. Transforming leptin to MoM values did not alter the nature or the significance of the relationship. In Fig. 3, the association between PE and MoM values of leptin are shown, giving a bimodal curve for both PE cases and normal pregnancies. The bimodality effect might represent a physiological effect in the function of leptin in early pregnancy.

As this study was focused on women with moderate to severe obesity, we excluded women who were underweight or overweight. While we do not expect underweight and overweight women to differ from the relationship seen in the levels of adiponectin and leptin in Fig. 1 it is a limitation of the study that we cannot illustrate where the difference between normal weight and moderate obesity occurs.

Our study sought to understand the increased prevalence of PE in obese women and possible effects of adipocytokines on its development. In severely obese pregnancies, PE was associated with decreased maternal serum levels of both leptin and adiponectin. This suggests that adipokine dysregulation in severe obesity might contribute to the pathogenesis of PE. We have identified adiponectin in first trimester as a maternal serum marker of the development of PE in pregnant women with obesity, and suggest that this is due to its inflammatory effect. Adiponectin could be useful in screening obese pregnant women in order to evaluate risk of developing PE with the option of initiating early preventative treatment with aspirin. However, the performance of the adipokine markers is not – when looking at the whole population of obese women – very effective. Further studies to identify additional markers that can improve screening performance in obese women are needed.

Contributions

IT analyzed the data and wrote the draft of the paper. TL helped with the statistical analysis. LK, J-C H, TL, and MC conceived of the research idea and designed the study. MC and PH helped with the clinical interpretation of the findings. All authors contributed to the writing of the final draft of the paper.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2018.12.002.

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