Eur J Nutr (2010) 49:83–90
DOI 10.1007/s00394-009-0052-8

ORIGINAL CONTRIBUTION

Dietary sucrose intake is related to serum leptin concentration in overweight pregnant women

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Received: 2 March 2009 / Accepted: 14 August 2009 / Published online: 29 August 2009

Abstract
Background Overweight, characterized by low-degree systemic inflammation, predisposes women to impaired glucose metabolism during pregnancy. Adipokine leptin participates in the regulation of energy balance and immune action.
Aims of the study Objective of the study was to evaluate if aberrations in glucose metabolism during pregnancy are related to leptin concentration and whether serum leptin concentration is affected by diet composition.
Subjects and methods Normal-weight ($n = 61$) and overweight or obese (BMI > 25, $n = 42$) pregnant women visited study clinic at third trimester of pregnancy and one month postpartum. Serum fasting leptin and insulin as well as plasma glucose concentrations were measured, insulin resistance (HOMA) and sensitivity (QUICKI) calculated, and dietary intake from food records determined.
Results In overweight women leptin concentration was significantly higher both in pregnancy, 45.27 (95% CI 39.40–51.14) ng/ml, and postpartum, 31.84 (27.38–36.30) ng/ml, than in normal-weight women, 31.09 (95% CI 27.80–34.37) ng/ml and 16.23 (13.93–18.53) ng/ml, respectively. Equally, blood glucose concentration during pregnancy was higher, 4.82 (4.67–4.97)mmol/l, and insulin concentration, 15.34 (12.00–18.68) mU/l, more pronounced in overweight compared to normal-weight women, 4.51 (4.42–4.61) mmol/l and 8.28 (7.21–9.36) mU/l, respectively. Significantly higher HOMA and lower QUICKI were also detected in overweight compared to normal-weight women. At third trimester of pregnancy, leptin concentration correlated positively with insulin concentration in normal-weight ($r = 0.561$, $P = 0.002$) and overweight women ($r = 0.736$, $P < 0.001$), as well as with HOMA ($r = 0.568$, $P = 0.002$ and $r = 0.731$, $P < 0.001$, respectively) whereas negative association was found with QUICKI in normal-weight ($r = -0.484$, $P = 0.011$) and overweight women ($r = -0.711$, $P < 0.001$). Importantly, serum leptin concentration was affected by dietary sucrose intake both as quantitatively ($r = 0.424$, $P = 0.009$) and relative to energy intake ($r = 0.408$, $P = 0.012$) in overweight but not in normal-weight pregnant women.
Conclusions Overweight-related elevation in serum leptin is associated with impaired regulation of glucose metabolism during pregnancy. The novel finding that dietary sucrose intake is related to serum leptin concentration is in line with the current dietary recommendations to overweight pregnant

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women with impaired glucose metabolism advising the lower intake of sucrose during pregnancy.

Keywords Leptin · Pregnancy · Overweight · Glucose · Sucrose

Introduction

Obesity is a worldwide public health concern with considerable comorbidity, including atherosclerosis, diabetes, and asthma [23, 39]. It is characterized by low-grade systemic inflammation resulting from the production and secretion of a variety of pro-inflammatory and anti-inflammatory factors, such as adipokines, cytokines, and chemokines [17]. Equally, inflammation markers in the circulation, for example, C-reactive protein, interleukin 6, and tumor necrosis factor α, are raised in obesity and decrease with weight loss [17, 18].

Pre-pregnancy overweight and excess weight gain during pregnancy increase the risk of gestational diabetes and hypertension [36]. Also increased birth weight as well as other complications in the newborn is associated with maternal obesity [15, 36]. Further, maternal overweight may carry long-term sequelae, since the early life environment has been proposed to program susceptibility to degenerative diseases [4]; children of overweight mothers have an increased tendency to obesity in their adult life, this contributing to a continuous vicious cycle of obesity [34].

Adipokine leptin regulates food intake [3] and participates in glucose metabolism via regulation of insulin secretion and action [13, 16, 22] and glucose uptake to cells [5]. Concomitantly leptin acts as an immunoregulator influencing cytokine production by switching the phenotype of naïve T-cells toward Th1 response, activating monocytes, and stimulating phagocytosis [7, 40]. Leptin concentration in serum is dependent on the amount of body's fat mass and is, therefore, increased in obesity [17].

We hypothesized here that leptin would provide a link between overweight-related inflammation and glucose homeostasis during pregnancy. In order to test our hypothesis, we studied overweight-associated aberrations in glucose metabolism during pregnancy. Specifically, we assessed the extent to which leptin is related to glucose metabolism during pregnancy and the possibility that leptin concentration would be affected by diet composition. This may be particularly important in the case of overweight pregnant women, who commonly manifest impaired glucose metabolism during pregnancy [36].

Subjects and methods

Subjects and study design

The study population comprised 103 pregnant women and their infants. Overweight women were consecutively recruited from maternal welfare clinics in the city of Turku and neighboring areas, the prenatal outpatient ward at Turku University Central Hospital, or from an ongoing mother–infant nutrition follow-up study [1, 35], from which controls were selected. Inclusion criteria were pregnancy at third trimester and no metabolic diseases. The participants visited the study clinic at the third trimester of pregnancy and with their infants one month after delivery. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Written informed consent was obtained from volunteers and the study was approved by the Ethical Committee of the Hospital District of South-West Finland.

Clinical evaluation

Information on age, parity, education, and breastfeeding was obtained by interview. Weight prior to pregnancy was recorded at first visit to maternal welfare clinics and used in calculation of pre-pregnancy BMI as weight (kg) divided by the square of the height (m^2).Women were identified as normal-weight, if pre-pregnancy BMI was less than 25 ($n = 61$), or overweight if pre-pregnancy BMI exceeded 25 ($n = 42$). Obese women with BMI more than 30 ($n = 14$) were also included in the group of overweight women. Heights and weights at third trimester and one month postpartum were measured by a research nurse. Last weight information before the labor was recorded at maternal welfare clinics and used for determination of total weight gain during pregnancy. Birth weight and height of the infants were obtained from hospital records. Infants' weight at one month of age was measured by the research nurse.

Food records

The women's food and nutrient intakes were evaluated using 3-day food records with household measures at third trimester of pregnancy and one month postpartum. Written instructions were given and records reviewed by a nutritionist. Daily energy and nutrient intakes were calculated using the Micro-Nutrica® computerized program version 2.5 (Research Center of the Social Insurance Institution, Turku, Finland).

Sampling and analytical methods

Blood samples were taken at the third trimester of pregnancy (mean 33.6, range 29.4–37.1 weeks) and one month postpartum (mean 1.2, range 0.9–2.6 months) after overnight fasting and used for glucose, insulin, and leptin concentration measurements. The glucose concentration was measured from plasma on the day of sampling using an enzymatic method utilizing hexokinase. Analyses were made with a Modular P800 automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Insulin concentrations were determined from serum (stored at −70 °C until analysis) with an immunoelectrochemiluminometric assay on a modular E170 automatic analyzer (Roche Diagnostics GMbH, Mannheim, Germany). Serum leptin concentrations were measured using a I-radioimmunoassay (Human leptin RIA kit, 125 tubes, LINCO Research Inc, St. Charles, MO, USA.). All assays were conducted, according to manufacturer's instructions, with appropriate quality controls included. Insulin sensitivity was determined using the quantitative insulin sensitivity check index (QUICKI), as previously described by Katz and co-workers [25] and insulin resistance by homeostasis model assessment (HOMA), according to Matthews and co-workers [29].

Statistical analyses

Results are shown as mean values with 95% confidence intervals (CI) and clinical characteristics as means with ranges. Study numbers are shown in separate figures and vary slightly between time points due to lack of sample volume to carry out all analyses. The independent samples *t*-test was used to compare differences between normal-weight and overweight women and paired samples *t*-test, when comparing changes from pregnancy to postpartum separately for normal-weight and overweight women. Chi-Square or Fisher's test was used to analyze differences in categorical variables. Correlations were assessed by Pearson's correlation coefficients. Statistical analyses were performed using the Statistical Package for the Social Sciences version 14.0 (SPSS Inc. Chicago, IL, USA). The threshold of significance was set at $P < 0.05$.

Results

Clinical characteristics

The clinical characteristics of the women and their infants in both groups were similar except for weight and BMI (Table 1). All women were Caucasian. Of normal-weight women, 77 and 83% of overweight women had college or university education ($P = 0.437$).

Glucose metabolism during and after pregnancy

In normal-weight women, the mean fasting glucose concentration during pregnancy, 4.51 (4.42–4.61) mmol/l, was lower, when compared to the situation one month postpartum, 4.97 (4.88–5.00) mmol/l; $P < 0.001$ (Fig. 1a). The insulin concentration, in turn, was significantly higher during pregnancy, 8.28 (7.21–9.36) mU/l, when compared to that after pregnancy, 4.32 (3.61–5.04) mU/l; $P < 0.001$ (Fig. 1b). QUICKI, the index for insulin sensitivity, was lower ($P < 0.001$) and HOMA, the index for insulin resistance, higher ($P < 0.001$) during pregnancy, when compared to the postpartum period (Fig. 1c, d).

Differences in glucose and insulin metabolism between normal-weight and overweight women

In general, pregnancy-related alterations in glucose metabolism were more pronounced in overweight women. This was manifested in statistically significantly higher mean fasting glucose, 4.82 (4.67–4.97) mmol/l; $P = 0.001$ and insulin concentrations, 15.34 (12.00–18.68) mU/l; $P < 0.001$ (Fig. 1a, b), as well as decreased QUICKI ($P < 0.001$) and increased HOMA ($P < 0.001$) indices during pregnancy compared to those in normal-weight women (Fig. 1c, d). This notwithstanding, the mean fasting glucose concentration was within the normal reference limits (Word Health Organization, Laboratory Diagnosis and Monitoring of Diabetes Mellitus 2002) in both normal-weight and overweight women during and after pregnancy. The elevated insulin concentration, the weaker insulin sensitivity indicated by lower QUICKI, and the increased insulin resistance indicated by higher HOMA in overweight women were still manifesting postpartum (Fig. 1b–d). Instead, the significant difference in fasting glucose concentration between normal-weight and overweight women was not sustained beyond pregnancy most likely due to elevation in glucose concentration at postpartum, when compared to third trimester in normal-weight women (Fig. 1a).

Leptin in relation to glucose metabolism and diet

In normal-weight women, the mean leptin concentration was higher during pregnancy, 31.09 (27.80–34.37) ng/ml, when compared to one month postpartum, 16.23 (13.93–18.53) ng/ml; $P < 0.001$ (Fig. 2). In order to evaluate the function of leptin as a possible regulator of glucose metabolism, its associations with insulin concentration, insulin sensitivity, and insulin resistance indices were

Table 1 Clinical characteristics of normal-weight and overweight women and their infants

	Normal-weight ($n = 61$)	Overweight ($n = 42$)
Women		
Age (years)	29.8 (18.3–41.4)	31.1 (19.3–42.2)
BMI before pregnancy (kg/m^2)*	22.0 (18.0–24.7)	30.0 (25.0–44.8)
Weight before pregnancy (kg)*	61.1 (45.0–86.0)	83.9 (60.0–125.0)
Weight gain during pregnancy (kg)	14.9 (7.1–26.1)	12.8 (−1.7–20.7)
BMI postpartum (kg/m^2)*	24.1 (18.6–28.2)	30.9 (24.3–45.1)
Weight postpartum (kg)*	66.9 (48.3–91.3)	87.5 (64.8–125.8)
Height (cm)	166.6 (153.2–188.4)	167.4 (154.0–187.2)
Number of children (%) 0	60.7	50.0
1–2	37.7	40.5
≥3	1.6	9.5
Duration of pregnancy (weeks)	40.1 (34.9–42.1)	39.6 (33.1–41.6)
Infants		
Male (%)	50.0	60.5
Birth weight (kg)	3.523 (2.090–4.660)	3.650 (1.930–4.500)
Birth height (cm)	50.9 (44.0–55.0)	50.9 (44.0–57.0)
Breast-fed 1 month of age (%)	98.1	100.0
Exclusively breast-fed 1 month of age (%)	76.5	73.0

Data presented as means (range)

* Statistically significant difference between normal- and over-weight women (independent samples t-test, $P < 0.001$)

studied by correlations. During pregnancy, the leptin concentration was found to correlate positively with the insulin concentration and HOMA, but negatively with QUICKI (Table 2). After pregnancy, the leptin concentration correlated positively with HOMA, but not with insulin concentration or QUICKI.

The elevation in leptin concentration during pregnancy compared to postpartum was also seen in overweight women. The concentration was nevertheless significantly higher in overweight, when compared to normal-weight women both during, 45.27 (39.40–45.27) ng/ml; $P < 0.001$ and after pregnancy, 31.84 (27.38–36.30) ng/ml; $P < 0.001$ (Fig. 2). Further, correlations between leptin and insulin concentrations and HOMA and QUICKI indices during pregnancy were stronger in overweight women and also appeared postpartum (Table 2).

In order to evaluate the impact of diet to serum leptin concentration, the intake of energy and energy-yielding nutrients were assessed by food records. We found that intakes of energy, fat, carbohydrates, and sugar were higher in normal-weight women when compared to overweight women, while no difference in protein intake was detected at the third trimester of pregnancy (Table 3). The proportion of energy yielded from carbohydrates or sucrose was similar in normal- and overweight women, whereas energy% for protein was significantly higher and for fat lower in overweight compared to normal-weight women (Table 3.) No differences in diet between normal-weight and overweight women were transferred to the postpartum period. At the third trimester of pregnancy, leptin concentration was found to correlate positively with sucrose both quantitatively ($r = 0.424$, $P = 0.009$) and as proportion of energy intake ($r = 0.408$, $P = 0.012$) in overweight, but not in normal-weight women ($r = 0.156$, $P = 0.264$ and $r = 0.128$, $P = 0.362$, respectively; Fig. 3a, b). This association did not continue beyond pregnancy and no correlations with other nutrients were detected either during or after pregnancy (data not shown).

Discussion

Our results point to the role of leptin as a regulator of glucose metabolism during pregnancy; serum leptin is linked to insulin concentration, as well as to insulin resistance, and insulin sensitivity. Importantly, in overweight pregnant women, an exaggerated serum insulin concentration was found to coincide with a highly elevated leptin concentration. Our finding of a relationship between sucrose intake and serum leptin is in line with the current dietary recommendations for overweight pregnant women advising the lower intake of sucrose during pregnancy.

Our results reflect the comprehensive regulatory role of leptin in insulin metabolism during pregnancy. In agreement with previous findings [10, 37, 41], we detected an elevated leptin concentration in pregnancy. Particularly, in overweight women, a significantly higher serum insulin concentration was found when compared to normal-weight women, concomitant with elevated leptin concentration, and apparent leptin resistance. Also, in a line with previous

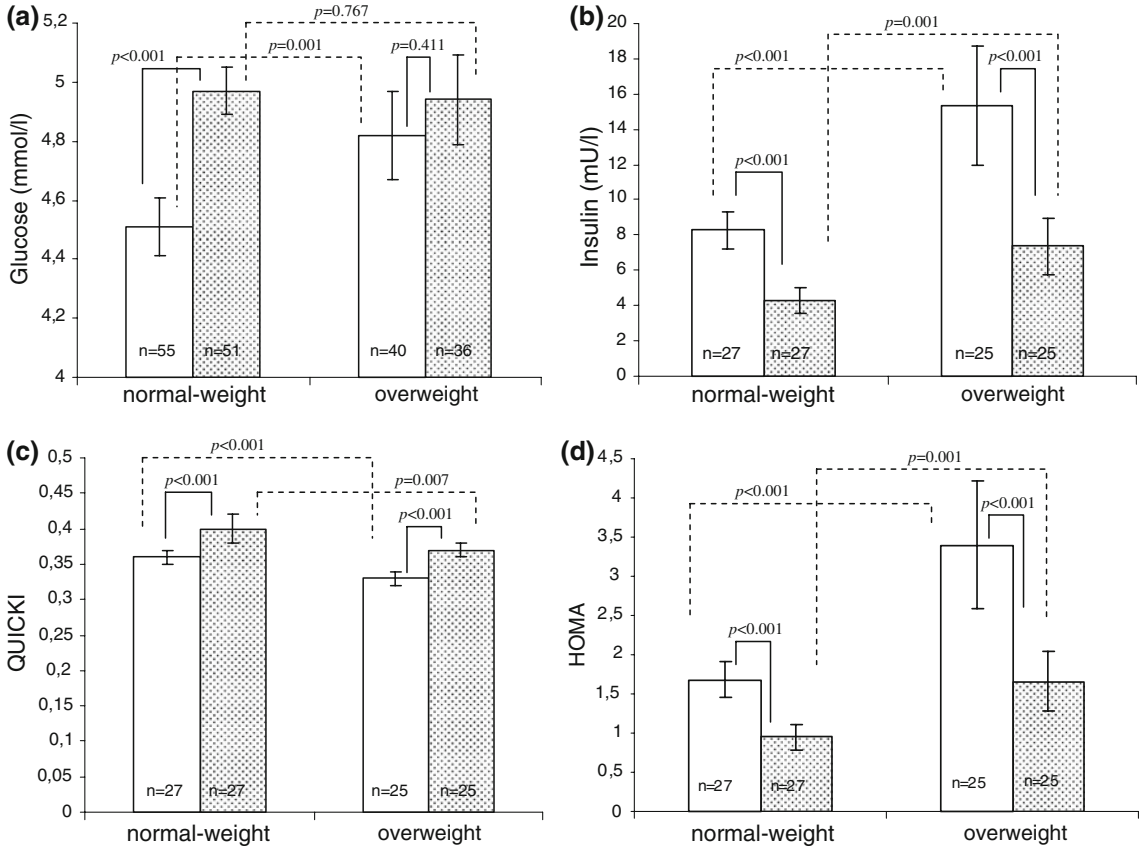

Fig. 1 Fasting plasma glucose (**a**) and serum insulin (**b**) concentrations, QUICKI (**c**), and HOMA indices (**d**) at third trimester and one month postpartum in normal- and over-weight women. *White bars* represent third trimester of pregnancy and *dotted bar* one month postpartum. *Error bars* represent 95% confidence interval for mean. *P*-values for statistical significance are shown

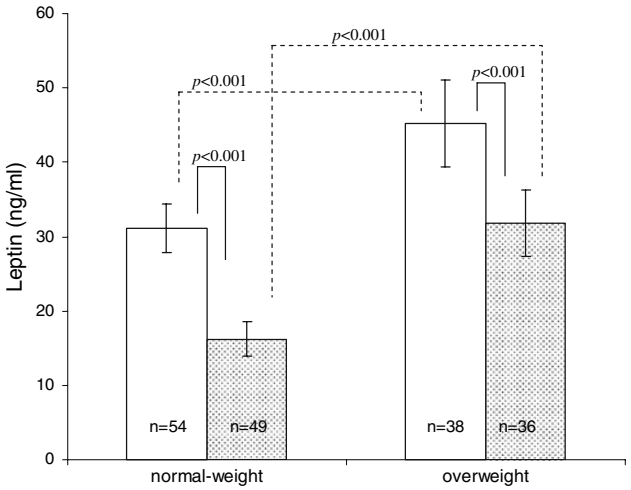

Fig. 2 Leptin concentration at third trimester and one month postpartum in normal- and over-weight women. *White bar* represents third trimester and *dotted bar* one month postpartum. *Error bars* represent 95% confidence interval for mean. *P*-values for statistical significance are shown

studies, we detected pregnancy-related adjustment in fasting glucose concentration in normal-weight women [8, 30], but not in overweight women [30]. Based on our findings, we hypothesize that leptin resistance [2, 32] which is typically related to obesity and pregnancy would appear extensively in overweight women leading to impaired insulin regulation and consequent aberrant glucose metabolism. In accord with our observations, animal and in vitro cell model systems reflect that leptin may modify insulin secretion through its receptors in pancreatic islets [13, 16] and further down-regulate insulin action through insulin receptor substrate 1 [22]. Leptin itself, again, has been suggested to down-regulate the expression of leptin receptors [28], contributing to the development of leptin resistance. During pregnancy, placental leptin secretion has also been reported to participate in the development of leptin resistance [19] ensuring adequate energy intake for both mother and child. This, together with the overweight-related increase in leptin concentration, could silence the function of the leptin receptors and, consequently, leptin signaling providing a mechanism which could lead to elevated secretion of insulin in overweight pregnant women in present study. In normal-weight pregnant women, it may be assumed that despite leptin secretion by the placenta, the serum leptin concentration remains moderate, allowing appropriate leptin signaling for

Table 2 Pearson's correlation coefficients between leptin and other variables at third trimester and one month postpartum in normal-weight and overweight women

	Leptin							
	Normal-weight women				Overweight women			
	Third trimester		One month postpartum		Third trimester		One month postpartum	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Insulin concentration	0.561	0.002	0.368	0.065	0.736	<0.001	0.548	0.005
Fasting glucose concentration	0.203	0.141	0.215	0.139	0.244	0.146	0.238	0.161
HOMA	0.568	0.002	0.393	0.047	0.731	<0.001	0.519	0.008
QUICKI	−0.484	0.011	−0.357	0.074	−0.711	<0.001	−0.516	0.008

Table 3 Daily dietary intakes of energy and energy-yielding nutrients in normal-weight and overweight women at third trimester of pregnancy and one month postpartum

		Normal-weight women		Overweight women		*P*-value	
		Third trimester	One month postpartum	Third trimester	One month postpartum	Third trimester	One month postpartum
Energy (kJ)		8,982 (8,420, 9,546)	9,010 (8,398, 9,622)	7,850 (7,060, 8,640)	8,563 (7,925, 9,201)	0.005	0.308
Protein	g/day	87.3 (81.4, 93.2)	88.2 (81.9, 94.5)	83.1 (74.5, 91.7)	83.4 (76.1, 90.7)	0.163	0.317
	E%	16.4 (15.8, 17.1)	16.5 (15.8, 17.4)	18.0 (17.0, 19.0)	16.3 (15.4, 17.3)	0.022	0.706
Fat	g/day	75.4 (69.1, 81.7)	78.4 (71.1, 85.8)	60.4 (51.3, 69.5)	69.4 (62.6, 76.1)	0.001	0.093
	E%	31.5 (29.9, 33.2)	32.6 (30.5, 34.6)	28.3 (26.1, 30.5)	30.5 (28.4, 32.6)	0.004	0.165
Carbohydrates	g/day	269.5 (249.5, 289.6)	264.9 (242.8, 286.9)	242.0 (219.0, 264.9)	265.4 (242.8, 288.0)	0.044	0.974
	E%	50.4 (48.5, 52.3)	49.1 (47.1, 51.1)	52.2 (49.9, 54.5)	51.7 (49.7, 53.8)	0.075	0.069
Sucrose	g/day	50.5 (44.0, 57.0)	46.2 (39.7, 52.7)	39.9 (32.4, 47.4)	43.8 (35.5, 52.0)	0.027	0.643
	E%	9.2 (8.2, 10.1)	8.3 (7.4, 9.1)	8.4 (7.1, 9.8)	8.4 (7.1, 9.7)	0.500	0.873

Figures in brackets represent 95% confidence interval for mean and *P*-values statistical difference between normal- and over-weight women (independent samples *t*-test)

inhibition of insulin secretion. Nevertheless, it must be taken into account that based on correlative data conclusions about causal relationships cannot be drawn and other pregnancy-related hormones [21] may also participate in the regulation of glucose metabolism during pregnancy.

The present study showed that the leptin concentration is related to sucrose intake in overweight pregnant women. This finding together with current dietary recommendations suggest lower sucrose intake for overweight pregnant women who commonly manifest impaired glucose metabolism, and have an increased risk for gestational diabetes during pregnancy [43]. It must be acknowledged that underreporting is a well-recognized methodological limitation in overweight populations when assessing dietary intakes [33]. In this study, the intake of energy was recorded to be lower in overweight when compared to normal-weight women. This could suggest underreporting, but importantly, congruent to the intake data, also the weight gain during pregnancy was lower in overweight women. It may, thus, be concluded that underreporting of food intake is not causing a significant skew to the results but may rather reflect the awareness of overweight women of the risks associated with high weight gain during pregnancy to the well-being of the fetus. Further, in previous study, underreporting has been shown to be uncommon among pregnant women [42]. Contradictory to our results, earlier study in children, did not found relationship between diet and leptin concentration [20]. Instead, animal studies have shown that rats consuming high amount of sucrose, glucose, or fructose solutions had elevated leptin concentrations compared to water drinking controls [27, 31]. In addition, chronic fructose consumption has proposed to induce leptin resistance prior to body weight, adiposity, or increases in serum leptin, insulin, or glucose concentrations in rats [38]. The discrepancy to previous study in children and difference in present study between the normal- and over-weight women is likely to be caused by co-existence of overweight-related low-degree inflammation with stressful and demanding metabolic time period of pregnancy. In line with previous animal experiments, our results reflect that sucrose intake impact on serum leptin concentration, although the causal connection remains to be shown. Interestingly, based on experimental studies, an innovative hypothesis has recently been

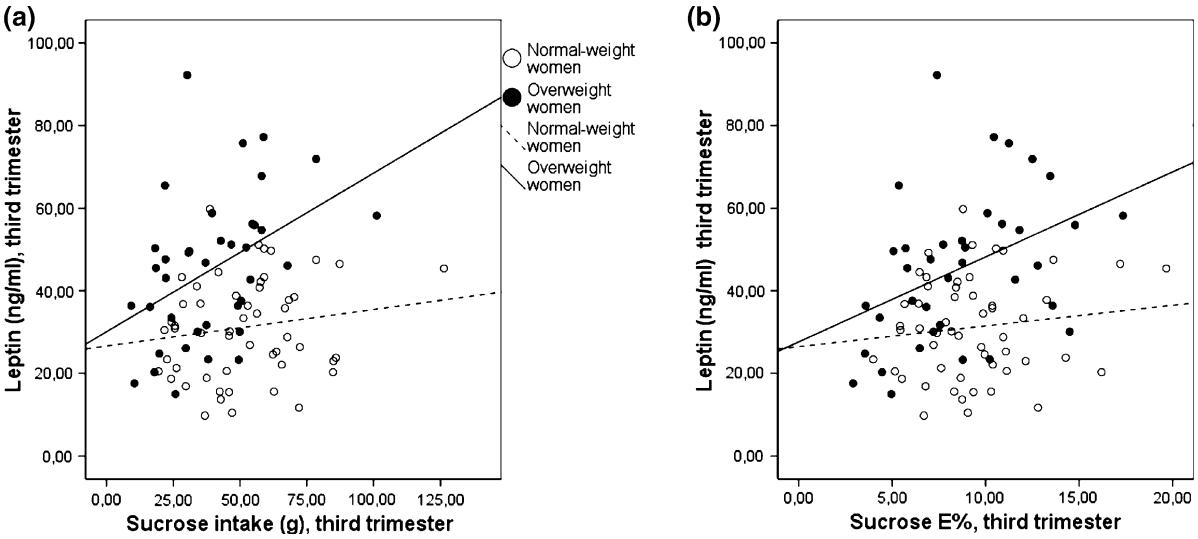

Fig. 3 Correlation between leptin concentration and sucrose intake as quantitatively (**a**) and as proportion of energy intake (**b**) at third trimester of pregnancy in normal-weight ($r = 0.156$, $P = 0.264$ and $r = 0.128$, $P = 0.362$, respectively) and overweight women ($r = 0.424$, $P = 0.009$ and $r = 0.408$, $P = 0.012$, respectively). Regression lines are included separately for normal- and over-weight women

proposed whereby the composition of the gut microbiota could influence energy homeostasis by inducing excessive harvest and storage of nutrients [9]. We have recently provided evidence of higher *Bacteroides* and lower *Bifidobacterium* numbers in overweight pregnant women [11]. Such intestinal microbiota composition induces metabolic endotoxemia manifested as high lipopolysaccharide (LPS) concentration and related activation of the immune system [9]. The role of leptin in overweight-related low-degree inflammation has been demonstrated by experimental studies showing elevation in leptin concentration by LPS injection [26]. These observations taken together with the results of the present study invite a hypothesis that dietary carbohydrates via gut microbiota composition induce the metabolic changes of obesity.

In summary, we suggest that leptin has a central role in glucose metabolism during pregnancy through the regulation of insulin. In women, overweight and consequent high leptin concentration and resistance are associated with pronounced impairments of insulin concentration, sensitivity, and resistance although life-style-related factors and genetic background may contribute to disease susceptibility. Taking into account that higher than optimum blood glucose levels are more common than anticipated [14] and further an impaired glucose metabolism during pregnancy may have long-term detrimental health consequences on both women and children [6, 12, 24], our finding of the influence of dietary sucrose intake on serum leptin concentration is of considerable significance in the nutrition counseling of overweight pregnant women. Further evaluations of diet–leptin inter-relationships with an eye to preventive and therapeutic strategies for glucose metabolism in pregnancy are encouraged.

Acknowledgments The study was supported by the Social Insurance Institution of Finland, the Sigrid Juselius Foundation, Juho Vainio Foundation, and the Academy of Finland.

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