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Maternal Serum Leptin at 11-13 Weeks Gestation in Normal 1 and Pathological Pregnancies

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Abstract

Objective: To examine maternal serum levels of leptin at 11-13 weeks gestation in normal and pathological pregnancies.

Methods: Serum leptin, PAPP-A and uterine artery pulsatility index (PI) at 11-13 weeks were measured in 480 singleton pregnancies, including 240 with normal outcome, 60 that subsequently developed preeclampsia (PE), 60 that developed Gestational Diabetes Mellitus (GDM), 60 that delivered Large for Gestational Age (LGA) neonates and 60 that delivered small(SGA) neonates. Regression analysis was used to determine factors affecting maternal serum leptin concentration and from this model each value was expressed as Multiples of the Median (MoM). The median MoM values in the outcome groups were compared.

Results: In the normal group serum leptin levels increased with maternal weight and decreased with maternal height. In the PE group, the median leptin (1.18 MoM, p=0.027) and uterine artery PI (1.25 MoM, p<0.0001) were increased and serum PAPP-A (0.72 MoM, p<0.0001) was decreased. There was no significant association between serum leptin and either uterine artery PI (p=0.983) or serum PAPP-A (p=0.403). In the SGA, LGA and GDM groups serum leptin MoM was not significantly different from the controls (p=0.621, p=0.385 and p=0.722, respectively).

Conclusion: In conclusion, in pregnancies that develop PE, maternal serum leptin concentration at 11-13 weeks is increased in a manner not related to altered placental perfusion or function. In pregnancies complicated by the development of GDM or delivery of SGA or LGA neonates, serum leptin is not significantly altered.

Keywords: Preeclampsia; Gestational Diabetes Mellitus (GDM); Small for gestational age; Large for gestational age; First-trimester screening

Abbreviations: β-HCG: β- Human Chorionic Gonadotrophin; CRL: Crown-rump length; CV: Coefficient of Variation; ELISA: Enzyme-linked Immunosorbent Assay; GDM: Gestational Diabetes Mellitus; LGA: Large for gestational age; MoM: Multiples of Median; NT: Nuchal Translucency; PAPP-A: Pregnancy-associated Plasma Protein A; PE: Preeclampsia; PI: Pulsatility Index; SGA: Small for Gestational age

Introduction

Leptin, an adipose tissue derived polypeptide hormone, is thought to play an important role in metabolism by reducing insulin secretion and through an action on hypothalamic receptors to decrease food intake and increase energy expenditure [1,2]. 75 Additionally, leptin has anti-inflammatory and angiogenic properties and is involved in immune response and T cell activation [3].

In pregnancy the maternal serum levels of leptin start rising in the first trimester prior to significant maternal weight gain, increase with gestation to reach a peak during the second or third trimester and decline shortly after delivery [4]. Although the main determinant of circulating maternal leptin is visceral fat [5], an additional source is the placenta [6]. Indeed, studies at 7-10 weeks' gestation reported that the concentration of leptin is four times higher in coelomic fluid than maternal serum reflecting the high production of the protein by trophoblast [7].

Previous studies have reported that levels of maternal serum or plasma leptin are altered in pathological pregnancies, including Gestational Diabetes Mellitus (GDM), Preeclampsia (PE) and pregnancies delivering Small for Gestational Age (SGA) neonates. Although most studies have reported on pregnancies with established disease some have also examined circulating levels in the first and second trimester before the clinical onset of the disease and reported contradictory results [8-14].

The aim of our study was to establish a normal range of maternal serum levels of leptin at 11-13 weeks' gestation and to examine whether the levels are altered in pregnancies that subsequently develop PE or GDM and those resulting in delivery of SGA and Large for Gestational Age (LGA) neonates.

Methods

Study population

This study was drawn from a large prospective observational study for early prediction of pregnancy complications in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. In this visit, which was held at 11+0-13+6 104 weeks of gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies by measurement of the fetal Crown-Rump Length (CRL) and Nuchal Translucency (NT) thickness and maternal serum free ß-hCG and PAPP-A [15,16]. In addition, transabdominal Doppler studies were carried out and the mean uterine artery pulsatility index (PI) was measured [17]. Women

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attending for this visit were invited to participate in research and from those who agreed serum and plasma samples were stored at -80°C for subsequent biochemical analysis. The study was approved by King's College Hospital Ethics Committee (02-03-033).

Women were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian and East Asian), parity (nulliparous, parous), cigarette smoking during pregnancy (yes or no), mode of conception (spontaneous or after use of assisted reproduction technologies), medical history, including chronic hypertension and diabetes mellitus. The questionnaire was then reviewed by a doctor together with the patient and the maternal weight and height were measured.

In this study we measured maternal serum leptin concentration in 240 singleton pregnancies with no medical complications, such as hypertensive disorders or diabetes mellitus, resulting in the birth after 37 weeks' gestation of a phenotypically normal neonate with birth weight between the 5th and 95th 124 percentiles for gestational age [18]. The values were compared to those from 60 pregnancies that subsequently developed PE, 60 that developed 125 GDM, 60 that delivered LGA neonates with birth weight above the 95th 126 percentile and 60 that delivered SGA neonates with birth weight below the 5th 127 percentile. The cases of PE, GDM, SGA and LGA were selected at random from our database of stored samples for these conditions. Each case was matched to one control that was sampled on the same day.

Preeclampsia was defined according to the criteria by the International Society for the Study of Hypertension in Pregnancy [19]. Screening for GDM in our hospital is based on a two-step approach. In all women random plasma glucose is measured at 24-28 weeks of gestation and if the concentration is more than 6.7 mmol/l, a 100 g oral glucose tolerance test is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is at least 6 mmol/L or the plasma glucose level 2-hours after the oral administration of 75 g glucose is 7.8 mmol/l or more [20].

Sample analysis

Maternal serum leptin was measured by a quantitative Enzyme-Linked Immunoassay (ELISA) technique using Quantikine Human Leptin ELISA kit (Catalogue no. DLP000, R and D Systems Europe Ltd., Abingdon, UK). The lower limit of detection of the assay was 0.01 ng/ml. The intra assay and inter-assay coefficient of variation (CV) varied from 3.0% to 3.3% and 3.5% to 5.4%, respectively. All samples were done in duplicates and samples with a CV exceeding 10% were reanalyzed. None of the samples in this study were previously thawed and refrozen.

Statistical analysis

Comparisons between outcome groups were by X^2-test or Fisher's exact test for categorical variables and by Mann Whitney-U test for continuous variables. Data are presented as median and Interquartile Range (IQR).

The distribution of serum leptin, PAPP-A and uterine artery PI were logarithmically transformed and probability plots and Kolmogorov-Smirnov test (p=0.153, p=0.061 and p=0.075, respectively) were used to confirm Gaussian normality. In the normal outcome group, multiple regression analysis was used to determine the factors from maternal characteristics and gestation that provided significant contribution in the prediction of log10 leptin. Each value in both the normal and pathological outcome groups was expressed as a multiple of the normal median (MoM), after adjustment for those characteristics found to be significant in the multiple regression analysis. Similarly, the measured values of uterine artery PI and serum PAPP-A were converted into MoMs as previously described [21,22]. The median MoM values of serum leptin, serum PAPP-A and uterine artery PI in the outcome groups were compared. The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL) was used for data analyses.

Literature search

We searched MEDLINE and EMBASE from 1994, when leptin was first described [23], to July 2012 to identify English language articles reporting on circulating maternal levels of leptin in pregnancy. We included case-control and cohort studies, which reported data regarding the outcome measures of PE, GDM, and birth of SGA or LGA neonates. We used the reported data in each paper and excluded duplicate publications.

Two independent reviewers extracted the data from each article, which was then examined by a third reviewer. Standardized Mean Difference (SMD) with 95% Confidence Intervals (CI) was calculated

Maternal	Characteristics	Control PE	GDM	LGA	SGA
Sample size, n	240	60	60	60	60
Maternal age in years, median (IQR)	33.0 (27.3-35.9)	32.9 (27.4-37.0)	32.0 (28.5-35.6)	32.5 (29.0-36.9)	30.4 (24.8-35.8)
Maternal weight in kg, median (IQR)	64.0 (58.9-70.0)	71.5 (63.0-85.7)*	76.5 (64.3-94.0)*	75.5 (69.0-89.2)*	63.0 (54.3-77.3)
Maternal height in cm, median (IQR)	165 (159-169)	162 (158-167)	163 (159-168)	167 (163-172)*	162 (157-165)*
Crown rump length in mm, median (IQR)	63.2 (58.5-69.7)	59.8 (55.4-65.4)	63.7 (58.1-71.6)	65.1 (60.1-71.7)	60.7 (56.0-67.4)
Gestation at sampling in days, median (IQR)	88.9 (86.1-91.2)	87.1 (84.8-90.0)	89.1 (86.2-93.1)	89.9 (87.3-93.2)	87.6 (85.1-91.0)
Racial origin					
Caucasian, n (%)	172 (71.7)	31 (51.7)*	30 (50)*	32 (53.3)*	33 (55.0)
African, n (%)	51 (21.3)	21 (35.0)	19 (31.7)	28 (46.7)*	22 (36.7)
Asian, n (%)	17 (7.1)	8 (13.3)	11 (28.3)	0	5 (8.3)
Parity					
Nulliparous, n (%)	102 (42.5)	39 (65.0)*	19 (31.7)	24 (40.0)	36 (60.0)
Parous, n (%)	138 (57.5)	21 (35.0)*	41 (68.3)	36 (60.0)	24 (40.0)
Cigarette smoker, n (%)	22 (9.2)	2 (3.3)	2 (3.3)	2 (3.3)	20 (33.3)*
Chronic hypertension, n (%)	1 (0.4)	11 (18.3)*	0 (0)	1 (1.7)	1 (1.7)
Birth weight percentile, median (IQR)	50.6 (30.9-67.0)	15.4 (6.21-46.3)*	67.9 (38.3-89.2)*	97.8 (96.7-98.9)*	0.5 (0.0-2.2)*

Table 1: Maternal and pregnancy characteristics in the outcome groups.
Comparison between outcome groups by Mann-Whitney U-test with post hoc Bonferroni correction and 2-test or Fisher's exact test for categorical variables; Adjusted significance level p=0.0125.

for each outcome in each study. Forest plots were constructed and a random-effects model, which takes into account the random variation within studies [24], was used to calculate weighted summary SMDs by taking into account the weight of each study. Forest plots were generated using Medcalc software version 9.6.2.0 (MedCalc Software, Mariakerke, Belgium).

Results

The maternal characteristics of the study groups are presented in table 1.

Normal controls

In the normal outcome group multiple regression analysis demonstrated that serum leptin increased with maternal weight and decreased with maternal height but there was no significant association with fetal CRL (p=0.652), maternal age (p=0.196), racial origin (p=0.081), cigarette smoking (p=0.558), mode of conception (p=0.606) or parity (p=0.597). Log10 leptin expected=1.264 + 0.017 × maternal weight in kg – 0.007 × maternal height in cm;

R2196 =0.298, p<0.0001.

Preeclampsia

In the PE group, compared to the unaffected controls, there was a significant increase in median serum leptin (1.18, IQR 0.75-1.84 MoM vs 1.00, IQR 0.68-1.37 MoM, p=0.027) and uterine artery PI (1.25, IQR 1.05-1.48 MoM vs 1.00, IQR 0.83-1.15 MoM, p<0.0001) and decrease in serum PAPP-A (0.72, IQR 0.46-1.14 MoM vs 1.01, IQR 0.76-11.35 MoM, p<0.0001) (Figure 1).

The median gestation at delivery of the PE group was 36.0 (range 206, 28-41) weeks. There was a significant association between gestation at delivery and uterine artery PI (r=-0.289, p=0.038) and serum PAPP-A (r=0.274, p=0.036) but not serum leptin (p=0.868). There was no significant association between serum leptin and either uterine artery PI (p=0.983) or serum PAPP-A (p=0.403).

Gestational diabetes mellitus

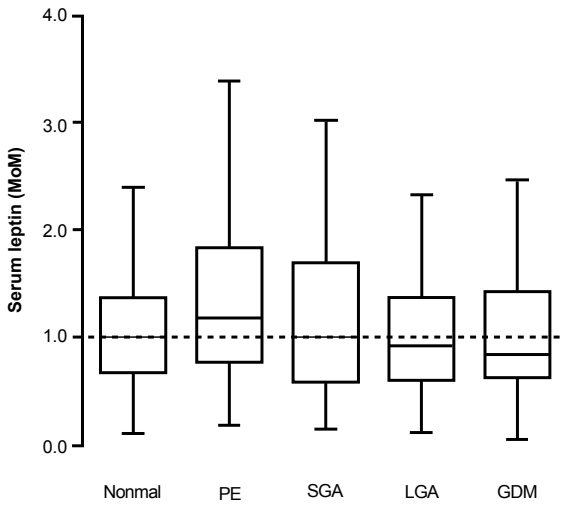

Figure 1: Box (median, interquartile range) and whisker (range) plot of maternal serum leptin Multiple of the Median (MoM) in normal and pathological pregnancies.

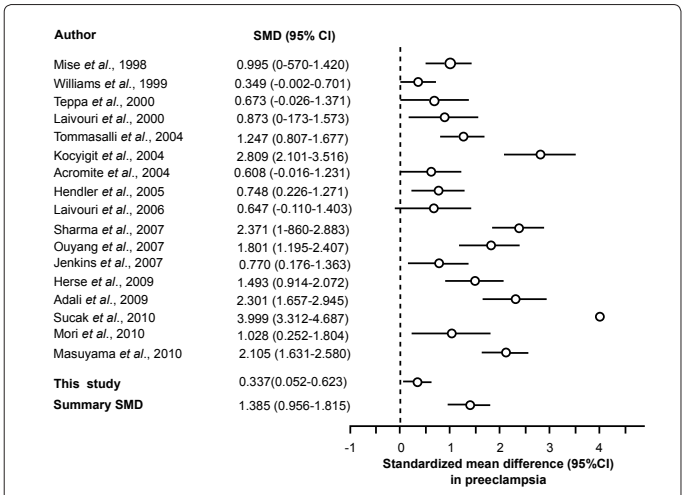

Figure 2: Forest plot of standardized mean difference with 95% confidence interval from previous reports and current study reporting on the association of maternal serum or plasma leptin concentration and established preeclampsia. In our study the samples were obtained before the clinical onset of the disease.

In the GDM group, compared to the unaffected controls, there was no significant difference in median serum leptin (0.89, IQR 0.62-1.45 MoM vs 1.00, IQR 0.68-1.37 MoM, p=0.722), uterine artery PI (0.96, IQR 0.86-1.22 MoM vs 1.00, IQR 0.83-1.15 MoM, p=0.535) or serum PAPP-A (0.99, IQR 0.75-1.41 MoM vs 1.01, IQR 0.76-11.35 MoM, p=0.779) (Figure 1).

Small for gestational age

In the SGA group, compared to the unaffected controls, the median serum PAPP-A was decreased (0.70, IQR 0.44-0.89 MoM vs 1.01, IQR 0.76-11.35 MoM, p<0.0001) and uterine artery PI was increased (1.24, IQR 0.94-1.49 MoM vs 1.00, IQR 0.83-1.15 MoM, p<0.0001) but there was no significant difference in median serum leptin (1.02, IQR 0.58-1.71 MoM vs 1.00, IQR 0.68-1.37 MoM, p=0.621) (Figure 1).

Large for gestational age

In the LGA group, compared to the unaffected controls, the median serum PAPP-A was increased (1.26, IQR 0.92-1.77 MoM vs 1.01, IQR 0.76-11.35 MoM, p=0.003) but there was no significant difference in median serum leptin (0.92, IQR 0.59-1.38 MoM vs 1.00, IQR 0.68-1.37 MoM, p=0.385) or uterine artery PI (0.95, IQR 0.68-1.19 MoM vs 1.00, IQR 0.83-1.15 MoM, p=0.280) (Figure 1).

Literature search

Forest plots of SMDs from previous reports and our study for PE, GDM, and delivery of SGA-neonates are shown in figures 2-4. PE [25-42]; GDM [11,12,43-50]; SGA [13,33,36,51-55].

Discussion

This study has demonstrated that maternal serum leptin concentration at 11-13 weeks' gestation in pregnancies that subsequently develop PE is increased. In pregnancies that develop GDM and those that result in delivery of SGA and LGA neonate's serum leptin is not significantly different from pregnancies with normal outcome.

In normal pregnancies, serum leptin concentration increased with maternal weight and decreased with maternal height but was not affected by other maternal factors including age, racial origin, and

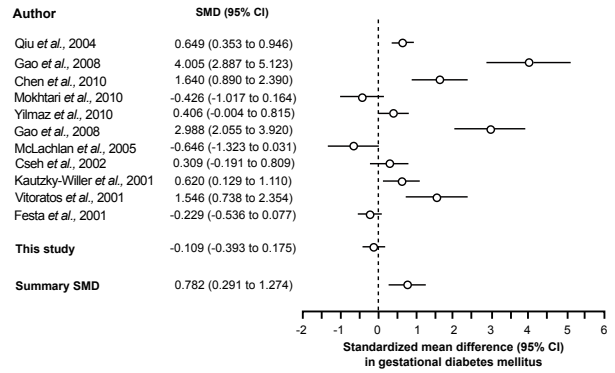

Figure 3: Forest plot of standardized mean difference with 95% confidence interval from previous reports and current study reporting on the association between maternal serum or plasma leptin concentration and gestational diabetes mellitus. In the top two studies and in our study the samples were obtained before the clinical onset of the disease.

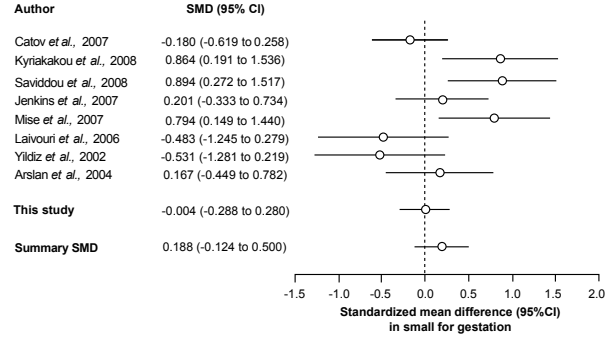

Figure 4: Forest plot of standardized mean difference with 95% confidence interval from previous reports and current study reporting on the association between delivery of small for gestational age neonates and maternal serum or plasma leptin concentration. In the top study and in our study the samples were obtained before the clinical onset of the disease.

parity, smoking status or mode of conception. The association with maternal weight is the inevitable consequence of the main source of this adipocytokine, which is fat tissue, and is compatible with the results of previous studies in both pregnant and non-pregnant individuals[56].

Previous studies in pregnancies with established PE have consistently reported that maternal circulating leptin concentration is increased (Figure 2). It was suggested that leptin is a marker of placental hypoxia [25] and the increased serum levels observed in PE may be due to the underlying impaired placental perfusion and oxygenation. Our findings indicate that the increased leptin precedes the clinical onset of the disease and is apparent from the first trimester of pregnancy. Previous studies in pregnancies before the onset of PE provided conflicting results. Samolis et al. [8] reported that the median maternal plasma leptin concentration at 13 weeks' gestation was approximately twice as high in 37 pregnancies that subsequently developed PE than in normotensive controls. In contrast, two other studies reported no significant differences in leptin levels at 7-13 and 18 weeks' gestation in 30 and 71 cases, respectively, that subsequently developed PE compared to controls [9,10]. In our study the increase in serum leptin concentration was unrelated to the severity of PE, reflected in the gestational age at delivery and was also unrelated to biophysical and biochemical evidence of impaired placentation reflected in increased uterine artery PI and decreased serum PAPP-A [57]. Two previous studies examining serum leptin levels in patients with established PE reported that the levels were higher in those with severe than mild disease [38,39] but in two other studies the opposite was true [41,42].

In pregnancies that developed GDM the serum concentration of leptin at 11-13 weeks was not significantly different from normal controls. Previous studies in patients with established disease reported contradictory results with levels that were either increased or not significantly altered (Figure 3). Our findings did not confirm the results of two previous studies, which reported increased leptin levels at 13 and 14-20 weeks' gestation, respectively, in women that subsequently developed GDM [11,12].

In the pregnancies delivering SGA neonates, there was evidence of impaired placentation reflected in increased uterine artery PI and decreased serum PAPP-A but serum levels of leptin at 11-13 weeks were not altered. Previous studies in pregnancies with SGA fetuses reported contradictory results with levels that were either increased or not significantly altered (Figure 4).

Our findings are consistent with one of the two studies examining serum leptin levels prior to the onset of SGA, in the absence of PE. In one study, there was no significant difference in leptin levels at 8-13 weeks between pregnancies delivering SGA and non-SGA neonates [14] but another longitudinal study reported decreased levels of leptin at 18 weeks' gestation in pregnancies that subsequently delivered SGA neonates [13]. In pregnancies delivering LGA neonates, there was a significant increase in serum PAPP-A at weeks' gestation as reported previously [58], but maternal serum levels of leptin were not altered. These findings are consistent with those of Horosz et al. [59] who reported that maternal serum leptin levels at 27 and 32 weeks' gestation in pregnancies delivering macrosomic neonates were not altered in either diabetic or non-diabetic women.

Conclusion

The findings of this study indicate that the reported altered maternal levels of leptin in pregnancies with established GDM and those delivering SGA neonates are not apparent at 11-13 weeks' gestation and therefore measurement of this adipocytokine is unlikely to be useful in early screening for these pregnancy complications. In the case of PE we found that increased levels of leptin, previously reported in cases of established disease, are apparent from early pregnancy but the levels are unrelated to the severity of PE.

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Ethics Approval

Ethical approval was granted by the King's College Hospital 25 Ethics Committee (02-03-033).

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