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Leptin and pre-eclampsia in Black African parturients

G.E. Kafulafula[a,b], J. Moodley[a,b,*], P.J. Ojwang[c], H. Kagoro[d]

Objective To measure serum concentrations of the hormone leptin during late pregnancy in Black African women with pre-eclampsia, healthy normotensive pregnant women as controls and healthy normotensive non-pregnant women; secondly, to explore the relationship between leptin and obesity.

Design Observational, cross sectional study.

Setting Antenatal clinics, antenatal wards, gynaecology out patient and family planning clinics of a tertiary hospital, Durban, South Africa.

Population Pregnant and non-pregnant Black African women.

Method Serum leptin was measured by a homologous radio-immunoassay technique. Simple anthropometric parameters were used to explore the relationship between leptin and obesity. In each group, leptin levels were compared between obese (body mass index, BMI $\geq$ 30 kg m^{-2}) and lean women.

Main outcome measures Serum leptin concentrations, anthropometric parameters, mean blood pressures and proteinuria.

Results There were 68 women with pre-eclampsia, 92 healthy normotensive pregnant women (controls) and 32 healthy normotensive non-pregnant women. Serum leptin levels were higher in pregnant compared with non-pregnant women [26.66 (1.96) and 25.89 (1.65) *vs* 17.97 (2.11) ng/mL, $P = 0.02$]. Weight and BMI showed the greatest correlation with leptin both in pregnant ($r = 0.61$ and $r = 0.58$, respectively) and non-pregnant women ($r = 0.74$ and 0.79, respectively). There was no significant difference in the mean concentrations of leptin between women with and those without pre-eclampsia [26.66 (1.96) *vs* 25.89 (1.65) ng/mL, respectively, $P = 0.95$].

Conclusion Pregnancy is a hyperleptinaemic state. There is no difference in serum leptin levels between Black African women with pre-eclampsia and healthy normotensive pregnant women. Serum leptin concentration is largely determined by the degree of adiposity.

INTRODUCTION

Ever since the discovery of the hormone leptin, as the obese (*ob*) gene product[1], much has been learnt regarding its physiology and association with several human disorders. Leptin may have a wider place in human physiology and pathophysiology than its initial role in the maintenance and regulation of body weight. Leptin shares structural similarities with cytokines[2]. This may explain its potential role in some human diseases that have a (sterile) inflammatory basis such as pre-eclampsia[3].

Obesity is a relatively common problem in pregnancy. Its complications such as hypertension are also commonly associated with pregnancy. Genetic and racial factors are also known to influence the occurrence of both obesity and hypertension. The demonstration of human placenta as a non-adipocyte source of leptin[4] implicates it in obstetric disorders of placental origin such as pre-eclampsia.

The role of leptin in the development of hypertensive disease is further suggested by several studies. Narkiewicz *et al.*[5] recently measured serum leptin levels in men with established essential hypertension. Although they found a positive correlation between leptin and pulse rate, they failed to show a correlation between leptin and blood pressure. In a study on animals, Tartaglia *et al.*[6] demonstrated the presence of central nervous system leptin receptors and their role in the control of circulatory function. Villarreal *et al.*[7] studied the renal effects of leptin in rats and showed that exogenous leptin increases sodium loss, thus suggesting that leptin may be a potential factor in the regulation of salt excretion and indeed play an important role in the pathophysiology of hypertension.

[a]*Department of Obstetrics and Gynaecology, Nelson R. Mandela School of Medicine, University of Natal, Durban, South Africa*
[b]*MRC/UN Pregnancy Hypertension Research Unit, Nelson R. Mandela School of Medicine, University of Natal, Durban, South Africa*
[c]*Department of Chemical Pathology, Nelson R. Mandela School of Medicine, University of Natal, Durban, South Africa*
[d]*Nelson R. Mandela School of Medicine, University of Natal, Durban, South Africa*

* **Correspondence**: Dr J. Moodley, Department of Obstetrics and Gynaecology, Nelson R. Mandela School of Medicine, Private Bag 7, Congella 4013, South Africa.

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Table 1. Clinical characteristics. Values are given as mean (SD).

	Group 1	Group 2	Group 3	*P*
Age (years)	28.1 (5.5)	30.5 (5.6)	29.5 (5.1)	0.56
Parity	1.8 (1.5)	2.3 (1.5)	2.2 (1)	0.12
Gestation (weeks)	34.4 (8.3)	35.5 (4.6)	not applicable	0.44

Group 1 = women with pre-eclampsia; Group 2 = pregnant women without pre-eclampsia (controls); Group 3 = non-pregnant women.

Women with chronic hypertension are more likely to develop pre-eclampsia but the possible aetiologic role of leptin has not been fully investigated[8]. Shek *et al.*[9] studied the influence of leptin in the development of essential hypertension in African-Americans. They concluded that leptin does not seem to play an important role in the development of essential hypertension in this racial group.

Indeed, the role of leptin in pre-eclampsia remains unresolved. Sattar *et al.*[10] found that pre-eclampsia did not affect serum leptin levels. On the contrary, Kokot *et al.*[11] demonstrated significantly higher levels of leptin in women with pre-eclampsia. These conflicting findings underlie the need for further research in the relationship between leptin and pre-eclampsia, as leptin may play a role in the management of pre-eclampsia in future. Leptin research has mainly involved Caucasians and very little is known about leptin in pregnant Black African women in whom both pre-eclampsia and obesity are common.

Our aim, in this study, was to determine serum leptin levels in pregnant Black African women with pre-eclampsia and obesity and to evaluate the correlation between simple (clinical) anthropometric measurements of obesity with serum leptin levels in pregnancy.

METHODS

Institutional ethical permission was obtained for the study and all participating women gave informed written consent. Pregnant Black African women receiving antenatal care at King Edward VIII Hospital, Durban, were enrolled. They were categorised to either Group 1 (pregnant women with pre-eclampsia) or Group 2 (pregnant normotensive healthy women, controls). Non-pregnant healthy women were similarly enrolled from the family planning and general gynaecology out patient clinics. These were allocated to Group 3 (non-pregnant women). Obesity was defined as a BMI of at least 30 kg m^{-2})[12]. Pre-eclampsia was defined as a blood pressure of at least 140/90 mmHg recorded at least 6 hours apart after 20 weeks of gestation with proteinuria of 0.3 g or more in 24 hours[13]. The highest blood pressure reading and degree of proteinuria for each woman with pre-eclampsia were recorded.

For all groups, basic demographic data were obtained. Women with diabetes mellitus, multiple pregnancy, known polycystic ovary syndrome and smokers were excluded from the study. The following anthropometric measurements were taken: total body weight in kilograms, height in metres and circumferences of the mid-upper arm, waist, hip and thigh in centimetres. The mid-upper arm was taken with a plastic tape measure at a midpoint between the olecranon and the acromion process of the right arm. Similarly, the hip circumference was measured at the level of the iliac crest. The waist circumference was taken at the level of the umbilicus and thigh at the midpoint between the anterior superior iliac spine and the medial femoral condyle. Venous blood (5 mL) was obtained by venepuncture in heparinised containers from each woman, at 0800 hours following an overnight fast, for leptin measurement. The blood samples were transported on ice to the chemical pathology laboratory and immediately centrifuged at 4 °C for 10 minutes. The plasma was stored at −20 °C pending batch analysis.

Serum leptin concentrations were determined in the plasma samples by radio-immunoassay using a commercial Human Leptin RIA kit (LINCO Research, Missouri, USA). This assay utilises radioactive ^{125}I-labelled human leptin antiserum to determine the concentration of human leptin in the serum or plasma samples by a double antibody/PEG technique. The assay has a sensitivity limit of 0.5 ng/mL and its specificity is 100%.

The BMI and mean blood pressure were calculated using the formulae: BMI = wt/h^2 where wt is the pregnant

Table 2. Anthropometric parameters and serum leptin levels in the three groups. Values are given as mean (SD).

	Group 1	Group 2	Group 3	*P* (*F* test)
Weight (kg)	88.7 (18.9)	91.1 (21.3)	85.1 (19.7)	0.16
Height (m)	1.62 (0.25)	1.57 (0.08)	1.61 (0.07)	0.26
BMI (kg m^{-2})	35.0 (7.5)	37.1 (8.5)	38.5 (9.7)	0.18
MAC (cm)	30.9 (4.3)	31.2 (4.8)	30.7 (5.8)	0.42
WC (cm)	104.8 (15.5)	106.9 (14.6)	83.6 (13.8)	<0.01*
HC (cm)	111.4 (12.9)	115.8 (14.5)	107.8 (11.6)	0.27
WHR	1.05 (0.09)	0.92 (0.05)	0.78 (0.08)	<0.01*
TC (cm)	58.2 (10.6)	60.4 (8.1)	56.5 (7.7)	0.34
Leptin (ng/mL)	26.66 (1.96)	25.89 (1.65)	17.97 (2.11)	0.02*

Group 1 = women with pre-eclampsia; Group 2 = pregnant women without pre-eclampsia (controls); Group 3 = non-pregnant women; BMI = body mass index; MAC, WC, HC and TC are circumferences of upper arm, waist, hip and thigh, respectively; WHR = waist/hip ratio.

* Statistically significant difference.

Table 3. The correlation (r) between leptin and the anthropometric parameters in the three groups.

Parameter	Pearson's correlation coefficient (r)		
	Group 1	Group 2	Group 3
Weight	0.55*	0.58*	0.74*
BMI	0.61*	0.56*	0.79*
MAC	0.57*	0.42*	0.71*
WC	0.52*	0.56*	0.77*
HC	0.52*	0.54*	0.49*
WHR	0.04	0.12	0.71*
TC	0.34*	0.50*	0.63*

Group 1 = women with pre-eclampsia; Group 2 = pregnant women without pre-eclampsia (controls); Group 3 = non-pregnant women; BMI = body mass index; MAC, WC, HC and TC are the circumferences of upper arm, waist, hip and thigh, respectively; WHR = waist/hip ratio.

* Statistically significant correlation.

body mass in kilograms and h is the height in metres; MBP = 1/3 [SBP + 2 (DBP)], where MBP is the mean blood pressure and SBP and DBP are the systolic and diastolic blood pressures, respectively. The waist/hip ratio was computed. Statistical analysis was performed using the statistical programmes Epi Info Version 6 and 2000 and Statistical Package for the Social Sciences (SPSS). Using the same programme, the appropriate sample sizes to detect a 5.8-ng/mL difference in leptin levels between the two paired groups are 70 in each (pregnant) group and 30 in the non-pregnant group ($\alpha = 0.05$, $\beta = 0.1$). One-way ANOVA was employed to test significance among the groups. Correlation between serum leptin and the anthropometric parameters were performed by the Pearson's test. Leptin concentration values are presented as means (SEM). All other values are presented as means (SD) unless otherwise stated. All statistical tests were done at $\alpha = 0.05$.

RESULTS

One hundred and ninety-two women were enrolled in the study: 68 in Group 1 (pre-eclamptics), 92 in Group 2 (normotensive pregnant controls) and 32 in Group 3 (non-pregnant normotensive women). The demographic parameters between the groups were similar (Table 1). Age, parity and gestation did not show significant correlations with serum leptin levels. The mean proteinuria level for women with pre-eclampsia was 0.761 [range 0.300–3.800] g in 24 hours. The mean blood pressure was higher in Group 1 than Group 2 [116.4 (8.9) *vs* 89.9 (3.8) mmHg, $P < 0.001$]. Table 2 gives a summary of the anthropometric parameters and serum leptin levels in the three groups. Of the anthropometric parameters, waist and waist/hip ratio showed statistically significant difference in the three groups. Serum leptin concentration was higher in pregnant women (Groups 1 and 2), than in non-pregnant women (Group 3) (Table 2).

Although the mean serum leptin level was higher in women with pre-eclampsia [26.66 (1.96) ng/mL] than the control group [25.89 (1.65) ng/mL], this difference was not statistically significant ($P = 0.95$). The mean blood pressure and proteinuria correlated weakly with leptin ($r = 0.3$, $P = 0.002$ and $r = 0.41$, $P = 0.001$), respectively.

All anthropometric parameters showed a positive correlation with serum leptin concentration in all three groups and this was generally stronger in Group 3 than Groups 1 and 2 (Table 3). BMI showed the greatest correlation in Groups 1 and 3 ($r = 0.61$ and $r = 0.79$, respectively), while in Group 2 it was greatest for weight ($r = 0.58$) followed by BMI and waist circumference ($r = 0.56$). The BMI–leptin relationships are shown in Fig. 1.

Anthropometric parameters were higher for the obese compared with the lean women (Table 4). The waist/hip ratio was similar for obese and lean women.

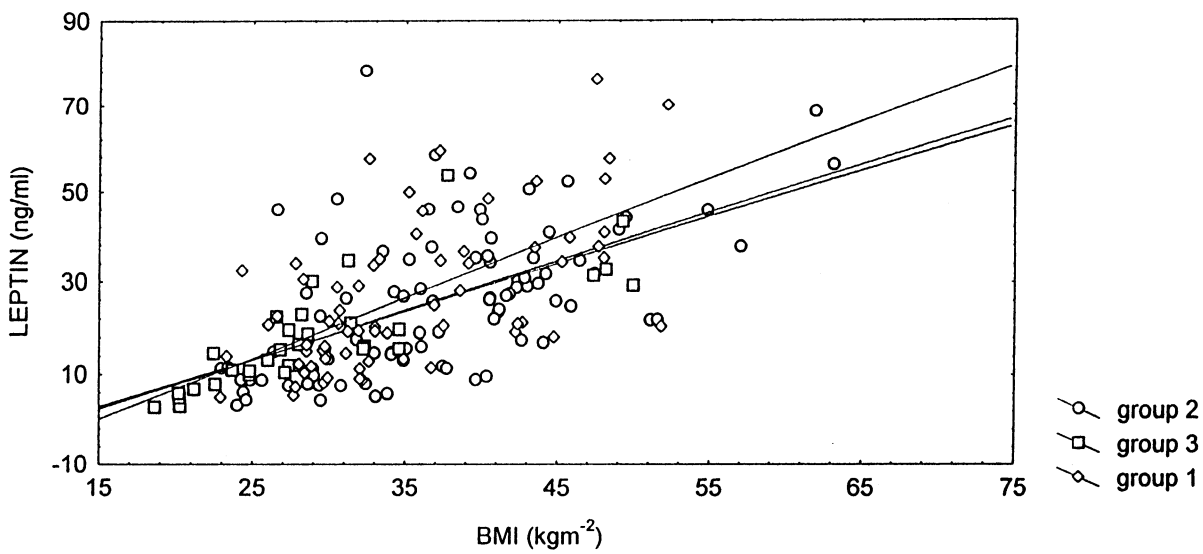

Fig. 1. Scatterplot of BMI (kg m^{-2}) against leptin (ng/mL). Group 1 = women with pre-eclampsia; Group 2 = pregnant women without pre-eclampsia (controls); Group 3 = non-pregnant women.

Table 4. Clinical characteristics and leptin levels of obese and lean women in the pregnant control group. Values are given as mean (SD).

Clinical characteristics	Obese	Lean	*P* (Student's *t* test)
Age (years)	31.3 (4.8)	29.8 (6.2)	0.32
Parity	2.6 (1.2)	2.3 (0.9)	0.18
Gestation (weeks)	34.9 (5.1)	35.4 (4.6)	0.08
Weight (kg)	100.4 (16.5)	66.8 (8.1)	<0.001*
Height (m)	1.61 (0.2)	1.59 (0.3)	0.74
BMI (kg m^{-2})	40.54 (7.1)	27.3 (2.4)	<0.001*
MAC (cm)	32.48 (4.65)	26.8 (1.98)	<0.001*
WC (cm)	113.0 (11.7)	90.7 (8.6)	<0.001*
HC (cm)	120.2 (10.4)	99.6 (7.7)	0.001*
WHR	0.94 (0.6)	0.91 (0.2)	0.72
TC (cm)	65.6 (6.0)	52.4 (3.8)	<0.001*
Leptin (ng/mL)	30.15 (1.84)	13.79 (2.15)	<0.001*

BMI = body mass index; MAC, WC, HC and TC are the circumferences of mid-upper arm, waist, hip and thigh, respectively; WHR = waist/hip ratio.
* Statistically significant difference.

Leptin levels in all the three groups were significantly higher for obese compared with lean women. The correlation between the anthropometric parameters and leptin in obese women was strongest for weight ($r = 0.39$) and least for mid-upper arm and waist/hip ratio ($r = 0.18$). In lean women, the anthropometric parameter that showed the greatest correlation with leptin was the thigh circumference ($r = 0.58$), and BMI in this group also correlated weakly ($r = 0.24$) with leptin.

DISCUSSION

In this study, we measured the serum leptin levels in both pregnant and non-pregnant Black African women. The results of serum leptin levels in late pregnancy are similar to our earlier study in obese Black African parturients[14] using the same radio-immunoassay technique of leptin assay, and the level is much higher than in non-pregnant women. The first report on the concentration of leptin in pregnancy by Geary *et al.*[15] found a maternal serum level of 13.4 (8.13) ng/mL. This is much lower than our finding. The difference may be explained in two ways. Firstly, their sample size was small ($n = 20$). Secondly, they measured serum leptin at 20 weeks of gestation. This same group of researchers found similarly lower maternal leptin levels (11.8 ng/mL) at 10–20 weeks of gestation in a subsequent report[16]. It is clear from longitudinal studies that leptin levels in pregnancy increase with advancing gestation[17].

Our result is, however, in keeping with other numerous studies on leptin levels in late pregnancy. Butte *et al.*[18] found a serum leptin level of 29.8 (17.0) ng/mL in late pregnancy. Although there are variations in the reported levels of serum leptin in late (uncomplicated) pregnancy in other, mainly Caucasian, population groups, most studies are consistent in finding mean serum levels between 25.2 and 38.4 ng/mL[17–19]. Our finding being consistent with these reports suggests that there are no racial differences in leptin levels in late pregnancy.

The resemblance between the trend of maternal leptin concentration[17] and the pattern of maternal adipose tissue accumulation[20] suggests a possible role of leptin in metabolic regulation during pregnancy. Alternatively, the elevated leptin levels may simply be a reflection of total accumulated fat mass in pregnancy. Indeed, the causal–effect relationship between leptin and adipose tissue in pregnancy is not resolved at the moment. Pregnancy hormones may well modulate maternal serum leptin levels[18].

Normal pregnancy is a state of insulin resistance. Chronic hyperinsulinaemia can induce hyperleptinaemia[21]. Therefore, the hyperleptinaemia of pregnancy may be secondary to this resistance. In a cross sectional study such as ours, it is not possible to explore these possible explanations regarding the observed elevated leptin levels associated with pregnancy. The placenta is an additional source of leptin during pregnancy[4]. Therefore, the association between elevated leptin and adipose tissue in pregnancy may be casual rather than causal. However, this is rather unlikely in view of the strong correlation between leptin and measures of obesity, as demonstrated in this and other studies, which holds true both in pregnancy and the non-pregnant state.

Elevated leptin levels may either reflect the normal physiology of pregnancy or indicate a pathophysiologic state, such as pre-eclampsia. Kratzsch *et al.*[22] propose that the hyperleptinaemia of late pregnancy may cause uncoupling of feeding behaviour and diminished responsiveness of leptin receptors as fat reserves are amassed for fetal growth and lactation. The rapid decline in leptin levels postpartum will then stimulate eating behaviour[23] suggesting that leptin may play a role in the excessive postpartum weight gain experienced by some women. Of further interest is the observation that abnormally low levels of leptin in the first trimester have been associated with increased risk of spontaneous miscarriage[23]. Therefore, increased knowledge in the function and regulation of leptin in pregnancy may have an impact on the management of pre-eclampsia, postpartum weight gain and miscarriages.

Obese women had much higher serum leptin levels compared with the lean women in all three groups in our study. This is in agreement with previous studies conducted both in men and women and in pregnancy and outside pregnancy[24,25]. The association of leptin with adiposity explains the observed higher leptin levels in the obese compared with the lean women in all the groups. The relevance of simple anthropometric measures of obesity to explore this association is adequately covered in our previous work[14]. In pregnancy, weight and BMI showed the greatest correlation with leptin levels. This was true for both pre-eclamptic and normotensive women and is in keeping with previous studies[18,24].

The syndromes of pre-eclampsia and obesity share certain clinical and metabolic characteristics. These include

hyperlipidaemia, insulin resistance and glucose intolerance[26]. Thus, it may be expected that the hyperleptinaemia observed in obese women may also be realised in women with pre-eclampsia. It is therefore conceivable that the prediction and/or management of pre-eclampsia may lie in leptin research. The women with pre-eclampsia in our study had similar serum leptin level as healthy pregnant normotensive women. This is in contrast with a report by McCarthy *et al.*[27] who found markedly elevated serum leptin level in Caucasian women with pre-eclampsia compared with the control group. Several reasons may explain this difference.

Firstly, the criteria used to define pre-eclampsia do vary. While proteinuria in our study was defined as total protein of 300 mg or more in a 24-hour urine collection, McCarthy *et al.*[27] used a cut off of 500 mg or more in a 24-hour urine collection. This might have contributed to the difference between the results in the two studies. Secondly, the trend in serum leptin during the third trimester is not well established. While some authors report a continuing rise, others found that the levels plateau and yet others have found that leptin levels actually decline just before delivery[28]. The mean gestation age in our study was 34.5 weeks compared with 38 weeks in the study by McCarthy *et al.*[27]. Furthermore, they used pre-pregnancy BMI while we computed and utilised the pregnancy BMI. This may also have contributed to the lack of correlation between BMI and leptin levels in their study. Pre-pregnancy BMI may not correlate with leptin as well as pregnancy BMI[28]. A small sample size ($n = 24$) in their study may also explain this lack of correlation.

Williams *et al.*[28] found that mid-trimester pre-eclamptic women had either higher or lower leptin levels than controls depending on whether the BMI was 25 kg m^{-2} and below or was above 25 kg m^{-2}, respectively. They concluded that the normal leptin–adiposity relationship during pregnancy is disrupted by pre-eclampsia and that factors other than adiposity determine leptin levels in pregnancies complicated by pre-eclampsia. This possibility and the fact that they measured leptin in the second trimester (we studied leptin in the third trimester) may explain the disparity between our results and theirs.

Anim-Nyame *et al.*[29] recently conducted a longitudinal study to determine the timing of the elevation in serum leptin during pregnancy. Eight women went on to develop pre-eclampsia and it was noted that in this group the concentration of leptin was consistently higher compared with another group of seven women who did not develop pre-eclampsia. They also noted that from 20 weeks of gestation, leptin concentration rose gradually in both groups up to 32 weeks. Subsequently, there was a slight decline in the normal group as opposed to a clear increase in the pre-eclampsia destined group. The increase occurred before clinical manifestation of pre-eclampsia. This is an important and interesting finding. If these results were confirmed by other studies with greater numbers, then the clinical value of assaying serum leptin in the prediction of pre-eclampsia would be established. Their study design and its findings are different from ours.

However, our data are similar to those of Sattar *et al.*[10] who found that, although the level of leptin in the third trimester was higher than in non-pregnant controls, the levels between pre-eclamptic and normotensive controls were similar. Despite the observed inconsistency of both blood pressure and proteinuria in the diagnosis and progression of pre-eclampsia, the weak correlations between mean blood pressure and proteinuria with leptin in this study are in keeping with these findings.

The hyperleptinaemia of pregnancy may be due to the increased adiposity in pregnancy, placental source of leptin, pregnancy hormone-induced modulation of leptin synthesis/secretion or a combination of these factors. It was not possible to explore these mechanisms in our study because of its cross sectional design.

We did not find higher serum leptin concentrations in women with pre-eclampsia compared with pregnant normotensive controls. This may be due to the fact that adiposity has the predominant influence on serum leptin levels overriding all other factors both in and outside pregnancy. The strong correlation, demonstrated in this study, between the various anthropometric parameters and leptin levels both in pregnancy and outside pregnancy appears to be consistent with this explanation. Indeed, studies that have demonstrated hyperleptinaemia in pre-eclampsia[27] are limited by small sample sizes and failure to replicate the well-established correlation between BMI and leptin.

Nonetheless, possible explanations for this observation have been proposed. Pre-eclampsia may be complicated by reduced renal clearance and reduced intravascular volume. Both of these can cause hyperleptinaemia. The other possibility of course is that leptin may be the cause (similar to other cytokines) rather than the result of pre-eclampsia[28,30]. Thus, there is need to explore further the cause–effect relationship between leptin and pre-eclampsia.

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