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Maternal Leptin and Glucose: Effect on the Anthropometric Measurements of the Saudi Newborn

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ABSTRACT

To investigate the influence of maternal leptin and glucose on umbilical cord leptin levels and anthropometric measures in Saudi newborn.

Maternal blood samples (10ml) were drawn in ACD tubes and umbilical cord blood was collected from 151 mothers at the time of delivery of full term normal infants, at King Khalid University Hospital (KKUH), Riyadh. Informed consent was recorded for each female. Maternal height (ht), weight (wt), age and baby's length and weight were recorded and ponderal index (wt/ht^3), wt/ht ratio and body mass index (wt/ht^2) were calculated. Leptin level was estimated in plasma by RIA. Maternal blood glucose level was estimated using an autoanalyser at the KKUH Laboratory in a blood sample collected in fluoride tube. Maternal and umbilical cord blood leptin levels were compared and correlated. Maternal leptin, glucose, weight and BMI were correlated with each other and with the anthropometric variables of the baby.

Maternal leptin levels were significantly higher (19.79± 13.84 ng/ml) compared to the umbilical cord blood (10.36 ± 8.08 ng/ml) leptin (P<0.0001). No significant differences were seen in umbilical cord leptin from male and female babies. Similarly, maternal leptin level did not differ for male and female babies. Maternal leptin correlated with maternal weight (r=0.310; p=0.0001) and maternal BMI (r=0.254; p=.006). It also correlated positively with umbilical cord leptin (r= 0.287; p=0.0001), but not with baby's weight or BMI or ponderal index. Maternal glucose level showed a strong positive correlation with umbilical cord leptin (r=0.435; p=0.0001) and the baby's weight (r=0.307; p=0.008), BMI (r=0.334; p=0.004) and ponderal index (r=0.324; p=0.005).

However, umbilical cord leptin correlated significantly with the weight of the baby (r=0.330; p=0.0001) wt/ht (r=0.182; p=0.034) and ponderal index (r=0.209; p=0.015) . In two large-for-gestational age babies (>4 kg), the leptin level was significantly higher (>25 ng/ml) compared to the rest of the normal-for-gestational age babies.

The results of this study discard the hypothesis of a non-communicating two-compartment model of feto-placental leptin regulation and shows that maternal leptin level correlates with umbilical cord leptin. It is not affected by weight and BMI in the mothers but increases significantly as the maternal blood glucose level increases. This may be one of the causes for large babies in diabetic mothers.

Key words: Leptin, Body Mass Index, Obesity, Cord Blood, Pregnancy.

INTRODUCTION

Leptin is the protein product of the obesity gene and is synthesised in the adipose tissues and placenta[1-2]. It seems to function as a link between adiposity, satiety and activity and regulates body weight and energy expenditure through central nervous system feedback mechanism[3-4]. Since its discovery in 1994, extensive studies have been carried out on leptin both in animals and humans

and have provided new insight in weight regulation and obesity development[5-6]. Studies have shown that leptin synthesis starts *in utero* and circulating leptin levels may provide a growth promoting signal for fetal development during late pregnancy [7]. Umbilical cord leptin levels are generally lower than adult levels [8-9] and play a role in regulation of infancy weight gain[10-11].

A strong correlation has been demonstrated between umbilical cord leptin concentration and birth-weight reflecting a close relationship between leptin, birth-weight and body fat mass in newborn infants[12-15]. Hence leptin is considered as a possible growth factor in intrauterine fetal development (16). Some studies report similar levels of leptin in male and female newborn infants[9], while others show higher levels in female newborns compared to male newborns[17-20]. Other contradictory reports regarding effect of gender of the baby on the leptin level of the mother also exist in the literature[18-20]. It is shown that both leptin and insulin like growth factor are independent predictors of fetal growth[21] and are low in pregnancies with growth restriction[22-23]. The umbilical cord leptin is restricted in several conditions and is considered as a marker of intrauterine growth restriction[23]. Variable leptin levels are reported in different pathological states such as diabetes mellitus and hypertension[24-25]. It is also regarded as a potential marker of placental insufficiency[26].

In an attempt to study maternal leptin and glucose levels at the time of delivery and to investigate correlation between maternal leptin level, umbilical cord leptin levels and anthropometric measures in the new born, we carried out this study on healthy Saudi mother/baby pairs at the time of normal full term delivery.

Materials and Methods

One hundred and fifty one (151) randomly selected healthy mother/newborn pairs at delivery of full term infants were included in this study. The study was approved by the ethical committee of the institution. All females signed an inform consent. The age, parity, height (length of baby), weight was recorded and body mass index (BMI) was calculated using the formula:

$$BMI = \frac{Weight(kg)}{Height^2(m^2)}$$

Ponderal index (wt/ht^3) (Kg/m^3) and ratio of weight (kg) / height (m) were also calculated for the baby.

Ten ml blood was drawn by venepuncture from healthy females having normal deliveries of live born babies at full term. In addition, blood sample was collected from umbilical cord at birth, immediately after delivery from the placental end (discarding the first 2 mls) after early ligation of the cord and after raising the baby to the level of the placenta to avoid feto-placental transfusion and vice versa.

The blood was centrifuged at 1000 RPM for ten minutes and the plasma was carefully removed from the cells and stored frozen at $-70^{o}C$ until required for analysis. Leptin level in the maternal plasma and umbilical cord plasma was determined by radioimmunoassay (RIA) using kits from Linco. Glucose was estimated using autoanalysers at KKUH hospital Lab.

The data obtained were entered on the computers and analyzed using SPSS (version 15) program for windows. Correlations studies and regression analysis were carried out using the General Linear Model Program. The relationship between leptin and anthropometric parameters was assessed by Pearson's and Spearman correlation. Students 't' test was applied to determine the significance of the difference between any two groups and between different parameters. P value < 0.05 was considered statistically significant.

RESULTS

Demographic details of the mothers are presented in Table 1. The gestational age, birth-weight, birth length of the newborns were 36 – 42 weeks, 3.20 ± 0.524 kg and 0.486 ± 0.024 cm. The mean, standard deviation, standard error of the mean (SEM) values for maternal age, leptin, weight, height, BMI and glucose, umbilical cord leptin, baby's length, weight, BMI, wt/ht and ponderal index are presented in Table 2.

Table 1: Mother's Demographic Data

No.	**154**
Age (Yrs):	29.73 ± 6.406 yrs
Weight (kg):	73.36 ± 16.7 Kg
Height (m):	1.54 ± 0.05
BMI (kg/m^2):	30.6 ± 7.47
Parity:	3 ± 2
Gestational age (wks):	36 – 42

Table 2: Age, leptin and anthropometric measures in the mothers and their babies

	Maternal						**Baby**					
	Age Yrs	**Leptin ng/ml**	**Height m**	**Weight Km**	**BMI Kg/m^2**	**Glucose Mmol/l**	**Umbelical Cord Leptin ng/ml**	**Height m**	**Weight Kg**	**BMI Kg/m^2**	**Wt/Ht Kg/m**	**Ponderal Index Kg/m^3**
Mean	29.73	19.79	1.54	72.9	30.5	4.93	10.36	48.64	3.42	14.11	0.71	19.7
SEM	0.47	1.11	0.088	1.4	0.63	0.208	0.80	0.61	0.18	0.72	0.04	0.216
SD	6.40	13.84	0.10	17.6	7.5	1.8	10.08	7.86	2.34	9.30	0.05	2.78

Table 3: Levels of leptin and anthropometric measures in male and female babies

Babies	**Sex of the baby**	**Mean**	**SD**	**SEM**	**P***
Leptin	M	8.88	8.98	1.09	NS
(ng/ml)	F	11.66	10.95	1.20	
Height	M	48.77	3.03	0.34	NS
(Cm)	F	48.56	1.78	0.19	
Weight	M	3.41	1.23	0.14	NS
(Kg)	F	3.44	3.03	0.32	
BMI	M	13.67	1.91	0.21	NS
(Kg/m^2)	F	14.65	1.25	1.37	
Wt/ht	M	0.71	0.040	0.004	NS
Kg/m	F	0.71	0.062	0.006	
Ponderal	M	20.08	2.64	0.300	NS
Index(Kg/m^3)	F	19.37	2.89	0.311	

*The difference in the results in the male and female babies is not statistically significant.

Table 4: Correlation between leptin, weight, glucose and BMI in mothers and their babies

Parameter	Signifi-cance	Maternal				Umbi cal cord Kg	Baby			
		Leptin ng/ml	Weight mmol/l Weight	Glucose Kg/m²	BMI Leptin		Weight Kg/m²	BMI Kg/m²	Wt/ht Kg/m	Ponderal Index Kg/m³
Leptin	r	1	.310**	-.164	.254**	.287**	-.153	-.096	.075	-.148
ng/ml	p		.000	.156	.006	.000	.074	.267	.384	.086
Weight	r	.310**	1	-.113	.940**	.151	.238**	.209*	.048	.216*
Kg	p	.000		.361	.000	.083	.004	.013	.573	.011
Glucose	r	-.164	-.113	1	-.077	.435**	.307**	.334**	.113	.324**
mmol/l	p	.156	.361		.568	.000	.008	.004	.341	.005
BMI	r	.254**	.940**	-.077	1	.109	.209*	.195*	.001	.193*
Kg/m²	p	.006	.000	.568		.240	.017	.030	.991	.031
Umbilical	r	.287**	.151	.435**	.109	1	.330**	.166	.182*	.209*
cord	p	.000	.083	.000	.240		.000	.055	.034	.015
Leptin ng/ml										
Baby	r	-.153	.238**	.307**	.209*	.330**	1	.779**	.182*	.936**
Weight	p	.074	.004	.008	.017	.000		.000	.019	.000
Kg										
Baby	r	-.096	.209*	.334**	.195*	.166	.779**	1	.035	.942**
BMI	p	.267	.013	.004	.030	.055	.000		.652	.000
Kg/m²										
Baby	r	.075	.048	.113	.001	.182*	.182*	.035	1	.050
Wt/ht	p	.384	.573	.341	.991	.034	.019	.652		.524
Kg/m										
Baby	r	-.148	.216*	.324**	.193*	.209*	.936**	.942**	.050	1
Ponderal	p	.086	.011	.005	.031	.015	.000	.000	.524	
IndexKg/m³										

*Statistically significant
r = Pearson correlation coefficient

Table 5: Value of maternal leptin, weight, BMI and glucose in mothers giving birth to male or female babies

Maternal	Sex of the baby	Maternal values			
		Mean	SD	SEM	P value
Leptin	M	20.53	12.61	1.53	NS
(ng/ml)	F	19.13	14.84	1.63	
Weight	M	76.82	14.96	1.83	0.020
(Kg)	F	70.57	17.82	1.93	
Glucose	M	4.60	0.88	0.16	NS
(mmol/l)	F	5.19	2.28	0.34	
BMI	M	32.39	7.29	0.94	0.015
(Kg/m²)	F	29.28	7.45	0.84	

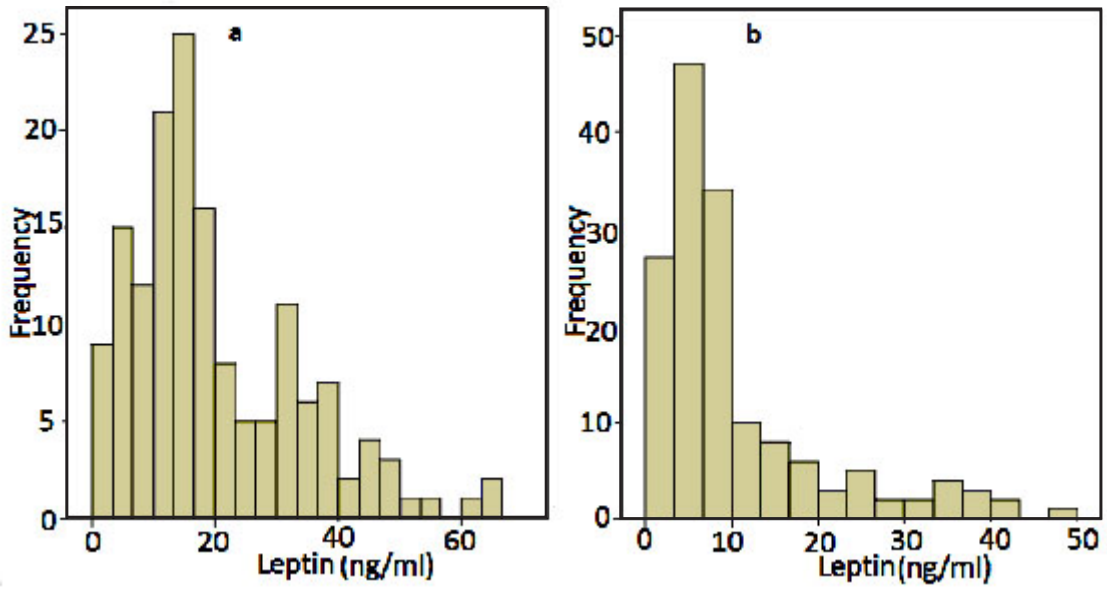

Fig. 1: Frequency distribution histogram of (a) maternal leptin and (b) umbilical cord leptin

Mean value of leptin was significantly higher in the mothers compared to the cord blood leptin level and the difference in the level of leptin in maternal blood and the cord blood was highly significant ($p<0.0001$). In the mothers the lowest leptin level was 1.0 ng/ml and highest was 64.6 ng/ml compared to 0.6 ng/ml and 49.0 ng/ml, respectively, in the cord blood, as shown in the frequency distribution histogram (Figure 1). The male babies were separated from the female babies and the leptin levels and anthropometric values were separately analysed for each gender, and the results are presented in Table 3. No significant differences were seen in values of these parameters in male and female infants.

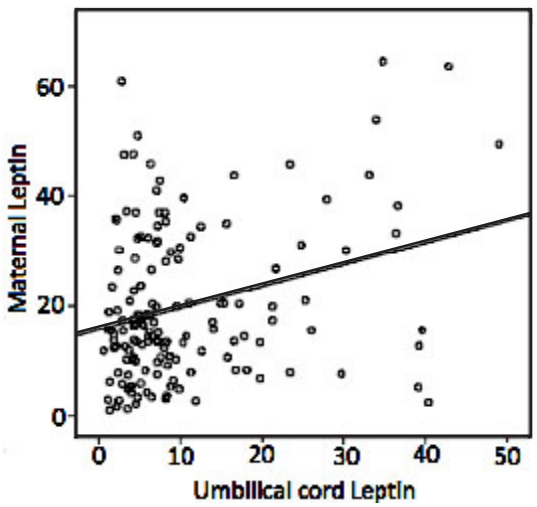

Fig. 2: Correlation between maternal and umbilical cord leptin

Correlation studies were conducted and Pearson correlation coefficient was obtained between the maternal parameters, the umbilical cord leptin and the anthropometric variables of the baby and Table 4 presents the Pearson correlation coefficient (r) and p value between the different correlated parameters ($p<0.05$). Maternal age was seen as an important factor affecting the weight and BMI of the mother and umbilical cord leptin ($r=0.229$; $p=0.005$). Maternal leptin correlated positively with maternal weight, BMI, and umbilical cord leptin ($p<0.0001$). Figure 2 presents the positive and significant correlation between maternal and umbilical cord leptin ($r=0.287$; $p=0.0001$). No correlation was seen with any of the anthropometric measures of the baby. Maternal glucose correlated significantly with umbilical cord leptin and baby's weight, BMI and ponderal index. Figure 3 presents the significant increase in umbilical cord leptin level with increase in maternal

glucose. The babies with the highest leptin were born to the mothers with high blood glucose level. Umbilical cord leptin showed a significant correlation with weight of the baby, weight/height ratio and ponderal index ($p < 0.05$).

Mothers who delivered male babies (no.= 68) were separated from those who delivered female babies (no.=83) and leptin level in the two groups was calculated separately (Table 5). The former group had slightly higher mean leptin (20.53 ng/ml) compared to the latter (19.13 ng/ml) but the difference was not statistically significant ($p>0.05$).

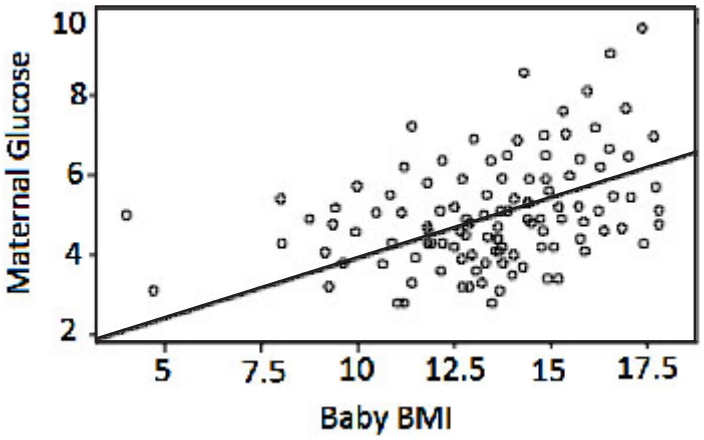

Fig. 3: Correlation between maternal glucose and babies BMI

DISCUSSION

During the last decade several studies have been carried out on umbilical cord leptin in an attempt to elucidate its role in fetal growth and development [8,11-14]. All studies have shown that leptin is present in umbilical cord blood and its levels vary depending on several factors. These include the fetal body weight[27], ponderal index[28], BMI[29], fetal gender[18,20,28], and maternal illnesses[24,25,30,31]. Several studies have shown that the level of umbilical cord leptin is significantly lower than the maternal leptin[10], though a few studies have reported umbilical cord leptin level to be the same as adult level[32]. Our study on healthy Saudi full-term maternal/baby pairs has confirmed the presence of leptin in umbilical cord blood which shows a wide range of distribution both in maternal plasma and umbilical cord sample. This study has also shown that the mean umbilical cord leptin is significantly lower compared to the maternal leptin level ($p<0.0001$) and there is a statistically significant positive correlation between the maternal and umbilical cord leptin. Studies report that leptin level increases in maternal blood during pregnancy and plays an important role in providing a growth-promoting signal for fetal growth and metabolism and fetal fat mass during pregnancy[19,20,33,34]. In addition, it is confirmed that placenta is one of the major sources of leptin production, however, the level of leptin in umbilico-placental circulation is independent of the weight of placenta[10,29,35]. It has been suggested that during pregnancy, placental production of leptin is one major source of higher levels in maternal circulating leptin other than maternal gain of fat mass[34]. Data obtained in pregnant females has reinforced the idea that circulating leptin may provide a growth promoting signal for fetal development during late pregnancy[10] and that an 'adipo-insular axis' exists and is functional before 34 weeks of gestation[35].

The results of this study show a close and statistically significant correlation between umbilical cord leptin and the birth weight, weight/height ratio, ponderal index of the baby. However, no differences were seen in the umbilical cord leptin level of the male and female babies. This is in agreement with several other studies that report no gender differences at birth in leptin levels[37-39], though in

some studies newborn females have been reported to have higher cord blood leptin compared to the male newborns[17,18, 20,39,40]. Hytinantti *et al.,*[30] showed that leptin correlates with adiposity at birth in females, but not in male newborn infants. This led to the suggestion that sexual dimorphism in adipose tissues already exists *in intero*[28]. In adult females there is significantly higher leptin levels compared to the males and extent of adiposity and BMI seem to be important determinants of adult leptin level[41]. However, it is not clear why in some studies there are no differences in the leptin levels of umbilical cord blood of male and female newborns, while in others the difference is statistically significant. This point requires further more carefully controlled larger investigations to identify the possible factors which predispose to such differences in different studies. In addition, there are reports in literature, of differences in leptin levels of mothers depending on the gender of the baby[38]. In this study on Saudis, we did not encounter any difference in the maternal leptin level depending on the gender of the baby. This point also requires further clarification.

The umbilical cord leptin levels are reported to be higher in large for gestational age infants compared to the appropriate for gestational age infants[41-44] and it is suggested that fatness of the fetus is the major determinant of circulating leptin levels[45]. In addition, it is confirmed that circulating leptin concentration relates to the intrauterine growth pattern. A very high umbilical cord leptin has been considered as an independent risk factor for fetal macrosomia[46]. In our study there were 2 babies over 4 kg in weight and their leptin levels were significantly higher (>25 ng/ml) than the infants less then 4 kg in weight.

Maternal health also plays a role in altering umbilical cord leptin level, where higher leptin levels have been demonstrated in the newborn infants of diabetic mothers and mothers with preeclampsia[24,25,30,31], thus suggesting that any condition leading to intrauterine growth changes would also result in variation in umbilical cord leptin levels[47]. Interestingly, glucose level in the maternal plasma showed a significant correlation with umbilical cord leptin, baby weight, BMI and ponderal Index. Though the women included in this study were now diabetic, but elevation was glucose occurred in some near the time of delivery and this glucose level showed a significant correlation with the anthropometric measures in the baby.

In this study we correlated the maternal leptin level in healthy females with the umbilical cord leptin, and observed a positive correlation. This finding is in disagreement with some of the previous reports which show that maternal leptin does not correlate with umbilical leptin level[10,38]. However, maternal leptin level can be considered as a reliable marker of fetal growth, while umbilical cord leptin correlates positively with fetal growth in all studies reported so far[11]. The lack of correlation between maternal and cord blood leptin level seen in some studies had led to a hypothesis of a non-communicating, two compartment model of feto-placental leptin regulation, which our study refutes.

In conclusion, the results of our study refute the hypothesis of a non-communicating two-compartment model of feto-placental leptin regulation and shows that umbilical cord leptin level correlates with maternal leptin level significantly. In addition, the *in utero* production of leptin is not influenced by the gender of the baby, but correlates positively with birth weight, height, BMI and ponderal index of the baby. Thus, both umbilical cord leptin, and the maternal leptin, may be an important factor for growth of the fetus.

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Disclosure of competing interests

Authors declare that they do not have any competing interests with any group.

Authors' contributions

[1]ASW designed the experiment, analyzed the data and wrote the manuscript. [2] ZB and MA collected samples from their patients and contributed to discussion of results and preparation of the manuscript. SD and MA helped in data analysis, discussion of results and preparation of the manuscript. All authors read and approved the final manuscript.

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