

# Leptin concentration during different stages of pregnancy

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## Summary

**Objectives:** To determine the levels of leptin in pregnant females during different stages of pregnancy and to correlate these levels to maternal weight, body mass index (BMI), neonate weight and neonate BMI.

**Material & Methods:** A case control study was carried out in which 60 pregnant females were enrolled, but only 36 completed the study and 30 non-pregnant females were used as controls. Blood samples were collected at the 1<sup>st</sup> trimester, 2<sup>nd</sup> trimester and 3<sup>rd</sup> trimester, and after delivery. Serum was used for the estimation of leptin (by radioimmunoassay).

**Results:** The results showed that the levels of leptin were significantly higher in pregnant females compared to non-pregnant females, but significantly decreased after delivery. In pregnant females with gestational diabetes the leptin level was insignificantly higher.

**Conclusion:** The increase of leptin levels may be due to the stimulatory effect of insulin on leptin secretion from adipose tissue.

**Key words:** Leptin; Pregnancy; Gestational Diabetes.

## Introduction

Leptin is a recently discovered polypeptide hormone, encoded by the *ob* gene and is the first hormone to be released from adipocytes [1, 2]. It has important effects in controlling body weight, metabolism and reproductive functions [3, 4]. The function of leptin in resisting obesity and promoting leanness led to the choice of the name "leptin" from the Greek root leptos, meaning thin [5]. During embryonic development leptin may play a role in the regulation of bone metabolism [6], brain development [7] and it stimulates proliferation and development of fetal islet cells [8] and fetal growth and development [9]. This study was carried out to determine the leptin levels in pregnant females during different stages of pregnancy and to correlate these levels to maternal and fetal body mass index (BMI).

## Materials and Method

### Subjects

The study included 60 Saudi pregnant females regularly attending the antenatal clinic at the King Khalid University Hospital, Riyadh, Saudi Arabia in the year 2001. Thirty non pregnant healthy females of the same age attending the gynecology clinic were used as a control. All women gave informed consent before recruitment. Data including age, gestational age at entry to the study, past obstetric and medical history was recorded on specially designed forms.

Five of the 60 pregnant females aborted during the first trimester whereas two others aborted during the second trimester. Of the total group 14 females withdrew from the study after the first trimester, three withdrew from the study after the second trimester and 36 pregnant females completed the third trimester. Twenty-six of the 36 pregnant females delivered in King Khalid University Hospital, Riyadh, Saudi Arabia, whereas the remaining ten pregnant females delivered in other hospitals.

Gestational age of the pregnant females was calculated from the first day of the last menstrual period and was confirmed by mid-trimester ultrasound scan. The height of the female was measured at entry to prenatal care and weight was measured at each visit. BMI was calculated by dividing the weight in kg by the height in meters squared and the patients were followed till delivery.

Fetal growth was evaluated clinically and by ultrasonography. Outcome of pregnancy, mode of delivery, sex of neonate, length and weight were recorded at delivery.

Blood samples for estimation of leptin levels were obtained from pregnant females at four different times; at booking time (first trimester), second trimester, third trimester and postnatally (on the second day after spontaneous vertex delivery, and on the third day after cesarian section delivery). Only a single sample was obtained from non-pregnant females. The collection of blood samples was between 8 a.m. and 5 p.m. without overnight fasting. Blood samples (5 ml) were drawn by venepuncture in plain tubes (red top tubes). The serum samples were stored frozen at -20 °C until required for analysis.

Serum leptin concentrations were estimated in duplicate by human leptin RIA (RIA, Linco Research, and St Charles, MO, USA). The within batch CV for leptin ranged from 1.6%-13.0%, while the between batch CV was 3.9%.

### Statistical Analysis

The results and the laboratory data of the pregnant females and controls were entered in a personal computer and data analysis was carried out using SPSS Program version 10. Data are presented as the mean  $\pm$  SD. The Student's t-test was used to determine the statistical significance of the difference in the means of the pregnant females and non-pregnant females.

The Students t-test was also applied to determine the significance of the difference of the means in any two trimesters and after delivery. Bivariate correlation studies were carried out between all the studied parameters in the different groups and Pearson's correlation coefficient (r) and p values were obtained;  $p \leq 0.05$  was considered statistically significant.

Multiple regression analysis was conducted to determine the influence of the different parameters on the level of leptin.

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## Results

The demographic characteristics of the pregnant females and non-pregnant controls are presented in Table 1. The ages of the pregnant and non-pregnant females were similar. In the pregnant females, the weight and BMI showed a gradual increase during the three stages of pregnancy, while a reduction was observed after delivery.

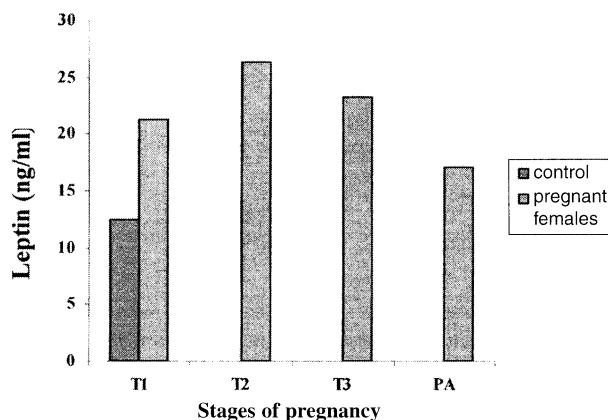
The mean  $\pm$  SD of leptin in the pregnant females during different stages of pregnancy and after delivery compared to the non-pregnant controls are presented in Table 1 and Figure 1.

In the pregnant females, mean level ( $\pm$  SD) of leptin during the 1<sup>st</sup> trimester was  $22.05 \pm 9.54$  ng/ml, while in the control group it was  $12.4 \pm 7.155$  ng/ml. The leptin mean during the 1<sup>st</sup> trimester, 2<sup>nd</sup> trimester, 3<sup>rd</sup> trimester and postnatal stage were significantly higher in pregnant females compared to the non-pregnant controls ( $p < 0.05$ ).

Serum concentration of leptin increased significantly ( $p = 0.01$ ) in the pregnant females from  $22.05 \pm 9.54$  ng/ml during the 1<sup>st</sup> trimester to  $26.89 \pm 9.27$  ng/ml during the 2<sup>nd</sup> trimester, but insignificantly decreased from  $26.89 \pm 9.27$  ng/ml during the 2<sup>nd</sup> trimester to  $23.29 \pm 8.62$  ng/ml during 3<sup>rd</sup> trimester ( $p = 0.073$ ). After delivery leptin concentration significantly decreased from  $23.29 \pm 8.62$  ng/ml during the 3<sup>rd</sup> trimester to  $17.36 \pm 7.95$  ng/ml at postnatal stage ( $p = 0.0025$ ).

The pregnant females were grouped on the basis of maternal health status into a normal pregnancy group and pregnant females with gestational diabetes (GD). Further grouping of the females with GD was made on the basis of whether they were being treated with diet (i.e. GDD) or insulin (i.e. GDI). The demographic characteristics of each group are summarized in Table 2.

The maternal age did not differ significantly between the three groups. The maternal BMI was higher in the pregnant females with GDD and GDI compared to the normal pregnant females, similarly, the placenta weight,



Key: T1 = 1<sup>st</sup> trimester; T2 = 2<sup>nd</sup> trimester; T3 = 3<sup>rd</sup> trimester; PA = postnatal.

Figure 1. — The mean level of circulating leptin in non-pregnant controls and among the pregnant females during different stages of pregnancy and after delivery.

neonate weight and BMI were also higher in the pregnant females with either GDD or GDI compared to the normal pregnancies.

Leptin levels were compared in the GDD and GDI patients with the leptin levels in normal pregnant females during the three trimesters and after delivery. The results are presented in Table 3 and Figure 2.

The leptin levels showed exactly the same pattern of variation, where an increased occurred during the 2<sup>nd</sup> trimester followed by a decrease in the 3<sup>rd</sup> trimester and a further decrease after delivery. During each trimester non-significant differences were seen between GD females treated with insulin (GDI) or diet (GDD) compared to the normal pregnant females. After delivery all three groups showed a significant decrease in leptin levels and between these groups the difference was not statistically significant.

Table 1. — Demographic characteristics and laboratory finding of pregnant females during different trimesters and after delivery compared to non-pregnant controls.

Variable	Pregnant females (mean $\pm$ SD)				Controls (n = 30)
	1 <sup>st</sup> Trimester (n = 60)	2 <sup>nd</sup> Trimester (n = 41)	3 <sup>rd</sup> Trimester (n = 36)	PA (n = 26)	
Maternal age (years)	29.0 $\pm$ 5.0	—	—	—	28.0 $\pm$ 3.0
Maternal height (m)	1.57 $\pm$ 0.1	—	—	—	1.62 $\pm$ 0.35
Maternal weight (kg)	69.3 $\pm$ 14.4	72.55 $\pm$ 14.6	75.5 $\pm$ 13.7	72.2 $\pm$ 15.1	53.89 $\pm$ 16.47
Maternal BMI (kg/m <sup>2</sup> )	30.1 $\pm$ 12.34	31.5 $\pm$ 13.01	32.77 $\pm$ 12.93	28.7 $\pm$ 5.26	29.54 $\pm$ 13.69
Gestational age (weeks)	10.4 $\pm$ 2.57	20.82 $\pm$ 3.3	33.67 $\pm$ 2.57	38.9 $\pm$ 1.9	—
Placental weight (g)	—	—	—	578.5 $\pm$ 131.84	—
Neonatal height (cm)	—	—	—	48.45 $\pm$ 3.1	—
Neonatal weight (kg)	—	—	—	2.75 $\pm$ 0.52	—
Neonatal BMI (kg/m <sup>2</sup> )	—	—	—	13.6 $\pm$ 1.72	—
<i>Laboratory findings</i>					
Leptin (ng/ml)	22.05 $\pm$ 9.54*	26.89 $\pm$ 9.27*	23.29 $\pm$ 8.62*	17.36 $\pm$ 7.95*	12.4 $\pm$ 7.155
Non parametric range (2.5 <sup>th</sup> -97.5 <sup>th</sup> ) ng/ml	8.4-49.57	12.7-54.98	8.33-53.1	5.16-41.35	3.5-23.2

\*Statistically significant difference ( $p < 0.05$ ) compared to control.

Table 2. — Demographic characteristics of females with normal pregnancies and those with GD.

Variables	Normal pregnancies (mean $\pm$ SD)	GD (mean $\pm$ SD)	Significance
Number	28	8	
Maternal age (years)	26 $\pm$ 12	29 $\pm$ 10	NS
Maternal height (m)	1.59 $\pm$ 0.006	1.53 $\pm$ 0.21	NS
Maternal weight (kg)	64.17 $\pm$ 11.6	81.9 $\pm$ 12.4	NS
Maternal BMI after delivery	28.09 $\pm$ 12.6	30.59 $\pm$ 11.57	NS
Placental weight (g)	561.76 $\pm$ 142.22	654.36 $\pm$ 116.30	NS
Neonatal height (cm)	48.7 $\pm$ 3.1	49.6 $\pm$ 0.55	NS
Neonatal weight (kg)	3.17 $\pm$ 0.58	3.6 $\pm$ 0.42	NS
Neonatal BMI (kg/m <sup>2</sup> )	11.99 $\pm$ 2.2	13.18 $\pm$ 1.33	NS

NS = Not Significant.

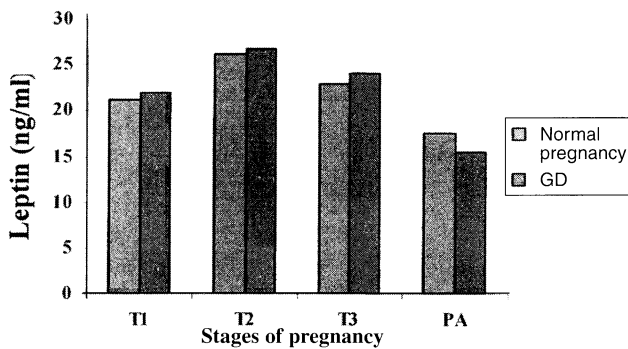
Key: T1 = 1<sup>st</sup> trimester; T2 = 2<sup>nd</sup> trimester; T3 = 3<sup>rd</sup> trimester; PA = postnatal.

Figure 2. — Leptin level during different trimesters and after delivery in normal pregnant females compared to those with GD

The results of correlation studies between leptin and other parameters during each trimester and at postnatal stage are presented in Table 4. A significant correlation was observed between maternal BMI and leptin concentration during the 1<sup>st</sup> trimester ( $r = 0.362$ ,  $p = 0.01$ ) and 2<sup>nd</sup> trimester ( $r = 0.304$ ,  $p = 0.034$ ).

On the other hand, the correlation between leptin and BMI during the 3<sup>rd</sup> trimester and at postnatal stage was not statistically significant. Maternal age and leptin concentration correlated positively only during the 3<sup>rd</sup> trimester ( $r = 0.426$ ,  $p = 0.0025$ ), and the correlation was statistically significant.

Interestingly, after delivery maternal leptin showed no correlation with either neonate weight, height, BMI or placenta weight ( $p > 0.05$ ).

### Discussion

Leptin, the adipocyte hormone, has been the subject of considerable investigations during the last decade due to its possible role in regulation of body weight and reproductive functions [3, 4]. Leptin levels are shown to correlate with the amount of body fat in non-pregnant subjects.

In present study, we attempted to investigate leptin levels during the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> trimesters of pregnancy and after delivery in relation to maternal weight, maternal BMI, neonate weight and BMI, and placental weight.

Results of our studies showed that serum leptin concentrations are significantly elevated in pregnant females at all stages of pregnancy compared to non-pregnant females. In the pregnant females serum leptin levels are the lowest during the 1<sup>st</sup> trimester, but increase significantly from the 1<sup>st</sup> trimester to the 2<sup>nd</sup> trimester, while a slight insignificant decrease occurs during the 3<sup>rd</sup> trimester. After delivery the plasma leptin levels decrease

Table 3. — Mean levels ( $\pm$  SD) of leptin in normal pregnancies and pregnancies with GD.

Parameter	Trimester	n	Normal pregnancies	n	Pregnancies with GDD	n	Pregnancies with GDI	Significance
Leptin ng/ml	1 <sup>st</sup> trimester	28	21.2 $\pm$ 9.6	3	21.5 $\pm$ 3.4	5	22.13 $\pm$ 8.6	NS
	2 <sup>nd</sup> trimester	28	26.2 $\pm$ 9.2	3	25.1 $\pm$ 5.8	5	27.77 $\pm$ 8.1	NS
	3 <sup>rd</sup> trimester	28	23.04 $\pm$ 9.6	3	23.6 $\pm$ 3.6	5	24.5 $\pm$ 4.01	NS
	Postnatal	20	17.5 $\pm$ 8.3	3	16.63 $\pm$ 5.9	3	14.4 $\pm$ 9.5	NS

NS = Non-Significant.

Table 4. — Pearson's correlation coefficient ( $r$ ) and significance of correlation ( $p$ ) between serum leptin concentrations and other parameters during different trimesters and after delivery.

Parameters	T1		T2		T3		PA	
	$r$	$p$	$r$	$p$	$r$	$p$	$r$	$p$
Age	0.21	0.16	0.19	0.225	0.426*	0.005	0.92	0.33
Maternal height	-0.13	0.21	0.001	0.5	0.078	0.33	0.21	0.16
Maternal weight	0.42*	0.003	0.32*	0.027	0.265	0.059	0.245	0.20
BMI	0.36*	0.01	0.3*	0.03	0.18	0.14	0.117	0.29
Neonatal height	—	—	—	—	—	—	-0.09	0.34
Neonatal weight	—	—	—	—	—	—	-0.1	0.32
Neonatal BMI	—	—	—	—	—	—	-0.18	0.21
Placental weight	—	—	—	—	—	—	-0.12	0.3

\*Statistically significant. Key: T1 = 1<sup>st</sup> trimester, T2 = 2<sup>nd</sup> trimester, T3 = 3<sup>rd</sup> trimester, PA = postnatal.

significantly, reaching almost the non-pregnant levels within a few days after delivery. These results confirm the previous reports by Hardiel *et al.* [10] and Sivan *et al.* [11] that also showed elevated leptin levels during pregnancy and a significant decrease after delivery.

Several factors may contribute to the elevation in leptin concentrations during pregnancy in females. *First*, a significant rise of serum leptin is probably due to the increase in body weight, which accompanies the pregnant state and the accumulation of body fat in the first two trimesters of pregnancy [12–14]. This is confirmed by our results as they showed that there is a positive correlation between leptin level, body weight and BMI during the 1<sup>st</sup> and 2<sup>nd</sup> trimesters of pregnancy. In addition, our study showed that the peak leptin concentration occurs during 20–30 weeks of gestation. Interestingly, this coincides significantly with the peak of maternal fat accumulation during pregnancy. On the other hand, from the late second trimester to the early third trimester, skin fold thickness begins to decrease at all sites as fat is mobilized to support fetal growth [15].

This observation can explain the slight though insignificant decrease observed, during our study in leptin concentrations during the 3<sup>rd</sup> trimester. *Second*, this may be a consequence of an influence of  $\beta$ hCG on the leptin level. A stimulatory effect of  $\beta$ hCG on the production of leptin has been shown *in vitro*, and studies have confirmed that when adipose tissue is incubated with  $\beta$ hCG there is an induction of leptin secretion [11].  $\beta$ hCG is produced in large amounts during pregnancy, particularly the early stages. It increases initially in pregnancy but starts to decrease slowly during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. During the 1<sup>st</sup> trimester the increase in leptin and  $\beta$ hCG levels occur concomitantly. This may explain the increase of leptin concentrations in early pregnancy before the occurrence of any notable increase in body weight.

*Third*, the feto-placental unit may contribute to the circulating maternal leptin level. There is a lot of evidence in favor of this suggestion: (i) studies have shown that the obese gene is expressed in human placenta [16, 17]. Thus placenta becomes the source of leptin during pregnancy and with advancement of pregnancy this would lead to an increase in maternal plasma leptin level; (ii) Since leptin is present in amniotic fluid and in arterial and venous cord blood, this points to a feto-placental pathway of leptin secretion, which may add to the leptin level during pregnancy [18]; (iii) Serum leptin concentrations in maternal circulation sharply decreases to below pre-pregnancy levels soon after delivery despite an insignificant change in the maternal weight [10]. This gives further support to the hypothesis that the placenta is one of the major sources of leptin during pregnancy.

*Fourthly*, the increase of leptin levels during pregnancy may be due to a decreased rate of leptin clearance from maternal circulation. The soluble leptin receptor, which is released from the placental membrane, is capable of binding leptin with a high affinity, and subsequent binding of free leptin to this receptor may impair the bioactivity of leptin and protect leptin from degradation which leads to an increase in serum leptin concentrations [19].

A similar finding was reported in GD pregnancies where it was shown that a significantly higher level of soluble leptin receptor occurs in diabetics than in normal subjects [20].

*Fifth*, gestational hormones, most of all progesterone and E2, are also reported to stimulate leptin production by adipose tissue and studies *in vivo* carried out by Messinis *et al.* [21] reported that E2 and progesterone administration to normal cycling women causes a significant increase of plasma leptin concentrations. Furthermore, *in vitro*, 5  $\mu$ g E2 administered to ovariectomized rats for two days significantly enhanced both leptin mRNA levels in adipose tissues and circulating leptin levels, over that of untreated controls [22].

*Sixth*, studies have shown that insulin and cortisol increase with plasma leptin during pregnancy, and are associated with increased maternal lean and fat mass as well as with considerable changes in glucose metabolism [23]. Sivan *et al.* [11] noted a surge in leptin between 12 and 24 weeks of gestation, which correlated positively with cortisol level. Furthermore, in preeclampsia there was a positive correlation between leptin and insulin concentrations [24].

*Seventh*, increase in food intake, which is known to stimulate leptin levels may play a role during pregnancy [25]. As is well known there is frequently an increase in food intake with the advancement of pregnancy and this may lead to elevation in leptin levels with the advancement of pregnancy.

*Finally*, it is believed that there are some unexplained factors which influence leptin levels. This suggestion results from the finding that all the above-mentioned factors cannot fully explain the change in leptin concentrations during pregnancy seen during our study. For example, we found a reversible correlation between maternal leptin concentrations and placenta weight and the same finding has been reported in other studies [11]. However, Yura *et al.* [26] reported that leptin secretion during the first trimester from placental villous tissue is approximately 50-fold greater than that by tissue collected at term, thus suggesting that leptin should be higher initially during pregnancy compared to the later stages. However, we as well as others did not obtain such findings.

In pregnancy, the physiological function of high leptin levels is not clear. However, chronic elevation of leptin levels throughout pregnancy suggests that maternal resistance to leptin occur. This resistance may result from an increase in the soluble leptin receptor from the placental membrane which is capable of binding leptin with a high affinity. This can inhibit leptin binding to a membrane receptor and thereby may be implicated in the development of leptin resistance and may thus play a role in any excessive weight gain seen during pregnancy [19]. Increase of maternal weight may act as an adaptive mechanism to protect the mother during pregnancy.

A possible role of leptin as a regulator of fetal growth has been suggested in intrauterine growth retardation (IUGR) cases and large-for-gestational age fetuses that

presented respectively, lower and higher leptin concentrations compared to normal fetuses [27].

The localization of leptin receptors to the trophoblast may relate to placental function as an endocrine organ. In the placenta it could act as a growth hormone and growth factor for angiogenesis in an autocrine manner [28, 29].

On the other hand, functional leptin receptors are expressed in pancreatic islet cells, as early as the fetal stage of development of these micro-organs. Leptin stimulates proliferation of fetal islet cells and might play a role in determining islet cell mass at birth [8].

During embryonic development leptin may play a role in the regulation of bone metabolism in the developing skeleton and brain [6]. The obese and diabetic mice with low leptin levels share in reduction of brain weight and cortical volume as well as foreshortening of the axial skeleton. While, intraperitoneal administration of leptin to 4-week-old obese mice results in a 10% to 15% increase in brain weight and stimulates femur growth, increasing cortical bone content. Hematological subtypes of the leptin receptor are detectable in blood cells within fetal vessels but not in placental cells [30].

Leptin may promote angiogenic processes by activation of the leptin receptors [28, 29]. This suggests that leptin may play an important role in the formation of the fetal blood system.

In addition, leptin stimulates fetal growth hormone (GH) secretion, which may mediate intrauterine growth promotion. Furthermore, leptin and GH may have interacting roles in intrauterine energy balance and regulation [31].

Finally, leptin may play a role in the regulation of maternal and fetal physiology during pregnancy, ranging from the control of placental anchoring to fetal growth and maturation, fine regulation of uterine blood flow and/or initiation of labor [32].

#### *Effect of gestational diabetes on leptin levels and other pregnancy hormones*

Gestational diabetes is a common metabolic complication during pregnancy and is closely related to Type II (non insulin dependent) diabetes mellitus and obesity in later life. The state of GD is characterized by a combination of marked insulin resistance and insulin secretory impairment. These defects normalize in part after delivery and women with GD frequently regain normal glucose tolerance post-partum [33].

During our study, eight of the pregnant females developed GD. Our results showed that plasma leptin levels were not significantly elevated in pregnant females with GD compared to females with a normal pregnancy. These results are in contrast to some other studies which showed that GD causes an increase level of leptin in serum [20, 33].

However our results are in agreement with some of the other studies that reported no differences in plasma leptin concentrations between subjects with and without diabetes and with a similar body weight [26]. Our results also showed that maternal age, BMI, gestational age, pla-

centa weight and neonate BMI were not statistically different between the two groups. The factors mentioned above may contribute to the differences between our results and previous studies. Several factors may contribute to the difference between our results and previous studies: (i) few subjects in our study, (ii) the blood samples were collected between 8 a.m. and 5 p.m. without overnight fasting and we can not exclude the possibility that the time of sampling may have influenced the leptin concentrations in these pregnancies, (iii) two pregnant women suffering from gestational diabetes were diagnosed during the 3<sup>rd</sup> trimester.

#### **Conclusion**

Our results during this study have shown several interesting findings. It was found that serum leptin levels are significantly higher in pregnant females and increase from the 1<sup>st</sup> trimester to 2<sup>nd</sup> trimester, but beyond this they decrease slightly but insignificantly during the 3<sup>rd</sup> trimester. After delivery a significant decrease in leptin levels takes place and within a few days postnatal stage the non-pregnant levels are reached.

There was an insignificant increase of leptin concentration among pregnant females with GD compared with normal pregnancies. This increase of leptin levels may be due to some stimulatory effect of insulin on leptin secretion from adipose tissue.

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