ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ - ORIGINAL PAPER

ΝΟΣΗΛΕΥΤΙΚΗ 2019, 58(4): 389–395 • **HELLENIC JOURNAL OF NURSING** 2019, 58(4): 389–395

Relationship Between Leptin Levels (in Pregnant Women and Placenta) and Glucose Metabolism and other Metabolic Parametres in Full Term Pregnant Women

Συσχέτιση Επιπέδων Λεπτίνης Εγκύων και Πλακούντα, Γλυκόζης και άλλων Μεταβολικών Παραμέτρων σε Φυσιολογική Εγκυμοσύνη

Abstract at the end of document

Konstantinos Hatziveis,[1] Konstantinos Makris[2]
Konstantinos Tsopelas,[3] Garyfallia Tzifa,[4] Aikaterini Labropoulou,[5]
Christiana Tzamourani,[6] Sofia Zyga[7]

[1]*Hatziveis Konstantinos, MD, PhD, Department of Nursing, University of Peloponnesse, Tripoli,*
[2]*PhD, Eur SpLM, FACB Clinical Biochemist, Clinical Biochemistry Department, KAT General Hospital, Athens,*
[3]*MD, Clinical Biochemistry Department, KAT General Hospital, Athens,*
[4]*MD, Obstetric Clinic, Kalamata,*
[5]*MD, PhD, Obstetric Clinic, Kalamata,*
[6]*MD, Department of Obstetrics and Gynecology, University General Hospital "ATTIKON", Athens,*
[7]*Professor, Department of Nursing, University of Peloponnesse, Tripoli, Greece*

Υποβλήθηκε: 21/10/2019
Επανυποβλήθηκε: 21/11/2019
Εγκρίθηκε: 29/11/2019

Corresponding author:
Konstantninos Hatziveis
65 Aristomenous street,
GR-241 00 Kalamata, Greece
e-mail: khatziveis@gmail.com

Introduction: Letpin is an important hormone for the pregnant woman and for the intrauterine growth. **Objective:** In this study, we aimed to investigate the relationships between leptin levels - from the mother and umbilical cord-and various metabolic parameters as well as anthropometric measurements of in the newborn. **Methods:** Forty mothers and newborns were included in the study. All women had terminated the pregnancy by caesarean section. Leptin levels were measured in mothers and in cord blood. In our study we used a multi variable questionnaire (name, age, gravida, diabetes mellitus, thyroid disease etc.). Anthropometric measurements in the newborn, maternal weight at the end of the pregnancy and the weight of newborn at delivery were recorded. The study data were analyzed using SPSS version 23 statistical package and Pearson correlation and t-test were applied. **Results:** Leptin median value in mother's blood (Lm) (42,7673) was significantly higher than umbilical cord's leptin median value (Lp) (17,7003). Standard deviation values were not significantly high concerning age, weight and mother's leptin values in comparison with placenta values. T-test showed that qualitative parameters did not affect the quantitative ones because the difference among the median levels of quantitative parameters according to the presence of e.g. thyroid disease or diabetes mellitus was statistically insignificant. **Conclusion:** Reference intervals for leptin in maternal serum and in cord blood established in normal pregnancy could be used in clinical practice for interpreting the

differences in leptin concentrations found in normal pregnancy and with glucose metabolism and other various metabolic parameters.
Key words: *Leptin, pregnancy, caesarean section, diabetes mellitus.*

Introduction

Leptin is a protein hormone and its name derive from the Greek word "from Greek λεπτός leptos", "thin". Leptin's molecule was identified in 1995. It is decoded from the human obese gene (ob). It is composed from 146 aminoacids; its molecular weight is 16 KDa and it's structure is similar with that of cytokines.[1] In humans, leptin gene is located in chromosome 7q31. Leptin is secreted, primarily from white adipose tissue. Initially leptin was considered to trigger a negative feedback mechanism regulating adipose tissue mass, in other words, a hormone against obesity.

Leptin is involved in regulation of reproduction, acting through various endocrine and autocrine mechanisms, either stimulating hypothalamus and hypophysis or inhibiting gonads pulsatility.

Body weight is the most significant factor regulating leptin secretion. There is higher positive correlation between the total adipose tissue massand serum leptin levels, with fat percentage and body mass index. (BMI) following.[2–4] Lately leptin has been implicated in endometrium, placenta and mammary gland function thus affecting menstruation, pregnancy and lactation. It has been noted that leptin receptor and specifically it's long isomorph is expressed in endometrium thus playing role in blastocyst implantation.

Leptin levels in healthy women range between 5 ng/ml και 50 ng/mL.[5] After conception, these levels are upregulating until 5th to 6th week of pregnancy.[6] From this point they are increasing till the end of pregnancy especially during second and third trimester.[7–10] After labor leptin's values decrease rapidly.

It is interesting that increased leptin levels cannot be associated only to pregnant increased weight and thus to elevated BMI.[10]

It has been proved that leptin is secreted from placenta,[11] as well that placentas weight is strongly correlated with leptin levels in umbilical cord.[12] Consequently, placentas leptin contributes in rising leptin's concentration in mother's serum, even if its impact is still unknown.

Material and Method

The material consist in a random sample of 40 women, between 21 and 42 years of age in the Obstetric Clinic of Kalamata in Greece from January 2019 to August 2019.Inclusion criteria were: pregnancy achieved by natural conception, gestational age after 38 weeks and termination of pregnancy by caesarean section. For first time and before the delivery a questionnaire was utilized in parallel; such questionnaire included the following data: name, age , parity (and way of delivery: labor or caesarean section), presence or absence (Yes/No) of diabetes mellitus before pregnancy , presence or absence (Yes/No) of thyroid disease before pregnancy, presence or absence (Yes/No) of thyroid disease in present pregnancy, presence or absence (Yes/No) of gestational diabetes in current pregnancy, weight of newborn, weight of placenta and the total number of kilograms gained during pregnancy (the difference between the weight that she had at the beginning of pregnancy and the final weight the day of delivery). In addition, the questionnaire recorded how pre-existing diabetes mellitus or gestational diabetes was treated (use of insulin or diet).

Finally, leptin values were obtained from the maternal serum before childbirth (Lm) and from umbilical cord (Lp) immediately after labor,were recorded.Totally there were 80 samples of blood (40 from the mother and 40 from the umbilical cord) for examination. Finally, mother's leptin value to placenta's one ratio (Lm /Lp) was included in the questionnaire (table 1).

Measurement of Leptin values was performed employing an ELISA (Quantikine® Human Leptin Immunoassay, R&D Systems, Inc. Minneapolis, MN, USA). For this purpose blood samples (10 cc from the pregnant and 10 cc from the umbilical cord after the delivery of the neonate) were collected in the morning after overnight fast using serum separator tube (SST). Samples were allowed to clot for 30 minutes at room temperature before centrifugation for 15 minutes at 1000xg. Serum was aliquoted immediately and samples were stored at -80°C until tested. We avoided any freeze-thaw cycle in our samples.The measurement was done according to manufacturer's instructions. The Quantikine® Human Leptin Immunoassay is a 3.5 hour quantitative sandwich solid phase ELISA designed to measure soluble human Leptin in, serum, plasma and cell culture supernates. It contains E. coli-expressed re-

Table 1. *Questionnaire template.*

Name	Age	Parity	Weight gain	Pre-existing diabetes	Gestational diabetes	Pre existing thyroid disease	Thyroid disease in pregnancy	Fetus weight	Placenta weights	Mother's Leptin (Lm)	Placenta's Leptin (Lp)	Lm/Lp

combinant human Leptin and antibodies raised against this recombinant protein.

In brief, a monoclonal antibody specific for human Leptin has been pre-coated onto a microplate. Serum samples were diluted at 100-fold dilution using a diluent provided in the kit prior to assay. Standards and samples were pipetted into the wells in duplicate and plates were incubated at room temperature for 2 hours. Any Leptin present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for human Leptin was added to the wells and a second incubation for 1 hour followed. A second wash step followed to remove any unbound antibody-enzyme reagent, and a substrate solution was added to the wells and any color develops in proportion to the amount of Leptin bound in the initial step. After half hour incubation the color development is stopped and the intensity of the color is measured at 450 nm.

A standard curve was created by reducing the data using the NCSS computer software to generate a 4 parameter logistic curve-fit. The equation that was produced was used to estimate the sample values from their absorbances. The intra assay precision of this assay in our lab was <5.0% and the inter assay <6.0%. This assay has a sensitivity of 7.8 pg/mL and a linearity up to 1000 pg/ml.

Statistical analysis

Statistical analysis was performed using SPSS version 23. Descriptive statistical analysis was performed in order to present the individual evaluation of every study variable. Pearson correlation coefficient was used in order to investigate relationships between quantitative and qualitative variables and t-test independent samples and dispersion analysis as a factor.

Ethical issues

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Results

Descriptive statistics

In table 2 we are showing that the median value of mother's leptin (Lm) (42,76) is much higher that the median value of that from the umbilical cord (Lp) (17,70). Stan-

Table 2. *Descriptive statistics.*

Variables	N	Minimum	Maximum	Mean	Std. Deviation
Age	40	21	42	32,15	4,944
Weight gained	40	4	25	13,98	4,521
Fetus weight	40	2200	4010	3173,50	411,972
Placenta weight	40	200	900	588,38	131,405
Mother's Leptin (Lm)	40	10,01	140,69	42,7673	32,2721
Placenta's Leptin (Lp)	40	6,83	63,71	17,7003	12,0400
Lm/Lp	40	0,31	13,77	3,1582	2,7379
Valid N (listwise)	40				

dard deviation values about age, weight and mother to placenta leptin ratio are not that high. Standard deviation values for fetus weight (S=411, 97) and placenta's weight (S=131,50) are high, revealing a high spread of values.

Correlations

Pearson coefficient of correlation results (table 3) (r=0,836, P-value<0,001) show that there is a positive linear correlation between mother's leptin value (Lm) and mother to placenta leptin ratio (Lm/Lp) meaning that both variables values increase proportionally. There is a "loose" negative linear correlation between placenta's leptin values and mother to placenta leptin ratio (Lm/Lp) since Pearson correlation coefficient was r=–0,409.

T-test

From One-Sample test table, control value of mother's leptin (Lm) with no pre-existing thyroid disease reported (pre-thyr) equalsμ 42,78. T-statistical value shows that mother's leptin median value (Lm) is not significantly statistically lower than average since mean difference=0,11. Finally 95% of mother's leptin value (Lm) is (–29,19, 29,42).

Studying table 4 one can observe that the above finding applies for mother's leptin media value (Lm) whereas thyroid disease pre-existed. In that case also mother's leptin median value (Lm) is not significantly statistically lower than average (mean difference=0,11). since mean

Table 3. *Correlations.*

		Weight gained	Fetus weight	Placenta weight	Mother's Leptin (Lm)	Placenta's Leptin (Lp)	Lm/Lp
Weight gained	Pearson Correlation	1					
	Sig.(2-tailed)						
	N	40					
Fetus weight	Pearson Correlation	0,189	1				
	Sig.(2-tailed)	0,244					
	N	40	40				
Placenta weight	Pearson Correlation	0,093	0,246	1			
	Sig.(2-tailed)	0,567	0,125				
	N	40	40	40			
Mother's Leptin (Lm)	Pearson Correlation	–0,044	–0,130	–0,020	1		
	Sig.(2-tailed)	0,788	0,426	0,905			
	N	40	40	40	40		
Placenta's Leptin (Lp)	Pearson Correlation	–0,030	0,125	0,241	–0,025	1	
	Sig.(2-tailed)	0,856	0,442	0133	0,877		
	N	40	40	40	40	40	
Lm/Lp	Pearson Correlation	–0,027	–0,256	–0,121	0,836	–0,409	1
	Sig.(2-tailed)	0,871	0,111	0,457	0,000	0,009	
	N	40	40	40	40	40	40

Table 4. *Level of Lm and Lp in Pre-existing Thyroid disease and Thyroid disease in pregnancy.*

Variables		Lm			Lp		
		n	$\bar{x}$±SD	p	n	$\bar{x}$±SD	p
Pre-existing Thyroid disease	No	34	42,78±34,1	0,994	34	17,73±12,4	0,963
	Yes	6	42,67±20,9		6	17,48±11,1	
Thyroid disease in pregnancy	No	32	43,40±34,9	0,806	32	18,14±12,6	0,643
	Yes	8	40,21±19,8		8	15,90±10,0	

difference=0,11. Also 95% of mother's leptin value (Lm) is (–22,77, 23,0).

In general t-test showed that qualitative variables were not affecting quantitative ones, because the difference among the median levels of quantitative parameters according to the presence of e.g. thyroid disease or gestational diabetes was statistically insignificant.

Discussion

There are many studies performed nowadays and during the past years, trying to investigate leptin's role during pregnancy in correlation not only to other metabolic parameters but also with embryo's growth and development.[13–15] In a recent study by Stefaniak et al[16] it was found that there was a statistically significant positive relation between leptin's value in mother and that from the umbilical cord. This finding is supported from our study and it is demonstrated even better when analyzing the relation between mother's leptin values (Lm) (42,7673) and mother's leptin to umbilical cord leptin ratio (Lm/Lp) (17,003). The same positive linear correlation is demonstrated in table 3 where as the values of both variants (Lm) and (Lm/Lp) are proportionally increased and in the end placenta's leptin contributes in rising leptin's concentration in mother's serum.

Serapio et al[17] in a recent study found that mother's leptin levels do not affect neonate's weight. In our study –taking in account that the optimal weight gain during pregnancy is 9–11 kg – there were 28 women that gained 12 to 25 kg during their pregnancy. There was one woman that gained just 4 kg. The woman that gained 25 kg delivered a 4,000 gr newborn while her serum leptin value was 34.01 and the umbilical cord value 27.31. Respectively the woman who gained just 4 kg delivered a 3,200 gr newborn while her serum values were 42.62 and 27.95. Thus, it is been showed here that mother's leptin value does not affect neonate's weight more than BMI.

In current study 5 out of 40 women presented with gestational diabetes and were treated either with diet and insulin administration (3 out of 5) or diet only (2 out of 5).

In a review article Plows et al[18] and Pérez A et al[19] concluded that placenta's leptin levels are increased in cases with diabetes mellitus, probably due to insulin resistance of placenta, leading possibly to fetal macrosomia. In current study, probably due to pharmaceutical and dietary treatment of gestational diabetes, placenta's leptin levels were within normal range (9,11 to 27.95) while fetus weight ranged between 2,600 and 3,620 gr. Likewise in Mosavat et al study[20] pregnant presenting with gestational diabetes showed low levels of leptin. Most characteristically in current study there was gestational diabetes present in women with the lowest value of mother's leptin and umbilical cord leptin as well as the lowest weight gain. Mother'sleptin (Lm) toplacenta'sleptin (Lp) ratiowasthelowest (0.88).

In 2004 Nuamah MA et al[21] studying maternal leptin levels before and after labour concluded that these are reduced whenever delivery was performed by caesarean section. In current study whereas all women delivered through caesarean section, just 10% (4 out of 10) presented with elevated leptin levels (108,19 min – 140,69 max) confirming the older study's results.

Conclusions

The increase of leptin production in increased gestational age and the strong association with anthropometric measurements supports the opinion that leptin behaves as a fetal growth factor. Leptin in intrauterine life is in close association with glucose metabolism and other various metabolic parameters. The above findings need further investigation.

Acknowledgements: The author Konstantinos Hatziveis is thankful to Mrs Konstantina Katsara, mathematic, Msc, for her contribution and assistance instatisticaland data analysis.

Περίληψη

Συσχέτιση Επιπέδων Λεπτίνης Εγκύων και Πλακούντα, Γλυκόζης και άλλων Μεταβολικών Παραμέτρων σε Φυσιολογική Εγκυμοσύνη

Κωνσταντίνος Χατζήβεης,[1] Κωνσταντίνος Μακρής,[2] Κωνσταντίνος Τσόπελας,[3] Γαρυφαλλιά Τζίφα,[4] Αικατερίνη Λαμπροπούλου,[5] Χριστιάνα Τζαμουράνη,[6] Σοφία Ζυγά[7]

[1]PhD, Τμήμα Νοσηλευτικής, Πανεπιστήμιο Πελοποννήσου, Τρίπολη,
[2]PhD, Eur SpLM, Κλινικός Βιοχημικός FACB, Τμήμα Κλινικής Βιοχημείας, Γενικό Νοσοκομείο ΚΑΤ, Αθήνα,
[3]MD, Τμήμα Κλινικής Βιοχημείας, Γενικό Νοσοκομείο ΚΑΤ, Αθήνα,
[4]MD, Μαιευτική Κλινική, Καλαμάτα,
[5]Διδάκτωρ, Μαιευτική Κλινική, Καλαμάτα,
[6]MD, Τμήμα Μαιευτικής και Γυναικολογίας, Πανεπιστημιακό Γενικό Νοσοκομείο "ΑΤΤΙΚΟΝ", Αθήνα,
[7]Καθηγήτρια, Τμήμα Νοσηλευτικής, Πανεπιστήμιο Πελοποννήσου, Τρίπολη, Ελλάδα

Εισαγωγή: Η λεπτίνη είναι μια σημαντική ορμόνη για την έγκυο γυναίκα και για την ενδομήτρια ανάπτυξη. Σκοπός: Σε αυτή τη μελέτη, επιδιώξαμε να διερευνήσουμε τις σχέσεις μεταξύ των επιπέδων λεπτίνης –από τη μητέρα και τον ομφάλιο λώρο– και διάφορες μεταβολικές παραμέτρους καθώς και ανθρωπομετρικές μετρήσεις στο νεογέννητο. **Υλικό και Μέθοδος:** Σαράντα μητέρες και νεογνά συμπεριλήφθηκαν στη μελέτη. Όλες οι γυναίκες είχαν ολοκληρώσει την εγκυμοσύνη με καισαρική τομή. Τα επίπεδα λεπτίνης μετρήθηκαν σε μητέρες και σε αίμα του ομφάλιου λώρου. Στη μελέτη μας χρησιμοποιήσαμε ένα ερωτηματολόγιο πολλαπλών μεταβλητών (όνομα, ηλικία, γρίπη, σακχαρώδης διαβήτης, ασθένεια του θυρεοειδούς κ.ά.). Καταγράφηκαν οι ανθρωπομετρικές μετρήσεις στο νεογέννητο, το βάρος της μητέρας στο τέλος της εγκυμοσύνης και το βάρος του νεογνού κατά την παράδοση. Τα δεδομένα της μελέτης αναλύθηκαν με τη χρήση του στατιστικού πακέτου SPSS version 23 και εφαρμόστηκαν οι στατιστικές δοκιμασίες Pearson correlation και t-test. **Αποτελέσματα:** Η μέση τιμή της λεπτίνης στο αίμα της μητέρας (Lm) (42,76) ήταν σημαντικά υψηλότερη από τη μέση τιμή λεπτίνης του ομφάλιου λώρου (Lp) (17,70). Οι τιμές τυπικής απόκλισης δεν ήταν σημαντικά υψηλές όσον αφορά στην ηλικία, το βάρος και τις τιμές της λεπτίνης της μητέρας σε σύγκριση με τις τιμές του πλακούντα. Η δοκιμασία t-test έδειξε ότι οι ποιοτικές παράμετροι δεν επηρέασαν τις ποσοτικές, επειδή η διαφορά μεταξύ των μέσων επιπέδων των ποσοτικών παραμέτρων σύμφωνα με την παρουσία όπως π.χ. η θυρεοειδοπάθεια ή ο σακχαρώδης διαβήτης ήταν στατιστικά ασήμαντος. **Συμπέρασμα:** Τα διαστήματα αναφοράς για τη λεπτίνη στον μητρικό ορό και στο αίμα του ομφάλιου λώρου που διαπιστώθηκε σε φυσιολογική εγκυμοσύνη θα μπορούσαν να χρησιμοποιηθούν στην κλινική πρακτική για την ερμηνεία των διαφορών στις συγκεντρώσεις λεπτίνης που παρατηρήθηκαν σε φυσιολογική εγκυμοσύνη σε σχέση με τον μεταβολισμό της γλυκόζης καθώς επίσης και με άλλες μεταβολικές παραμέτρους.

Λέξεις-ευρετηρίου*: Λεπτίνη, κύηση, καισαρική τομή, σακχαρώδης διαβήτης.*

✉ **Υπεύθυνος αλληλογραφίας**: Κωνσταντίνος Χατζήβεης, Αριστομένους 65, 241 00 Καλαμάτα, e-mail: khatziveis@gmail.com

References

1. Zhang Y, Proenca R, Maffei M et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* (Lond.) 1994, 372:425–432
2. Wauters M, Considine RV, Van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. *Eur J Endocrinology* 2000, 143:293–311
3. Maffei M, Halaas J, Ravussin E. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Med* 1995, 1:1155–1161
4. Houseknecht KL, Baile CA, Matteri RL, Spurlock ME. The biology of leptin: a review. *J Anim Sci* 1998, 76:405–420
5. Ludwig M, Klein HH, Diedrich K, Ortmann O. Serum leptin concentrations throughout the menstrual cycle. *Arch GynecolObstet* 2000, 263:99–101
6. Laird SM, Quinton ND, Anstie D et al. Leptin and leptin-binding activity in women with recurrent miscarriage: correlation with pregnancy outcome. *Hum Reprod* 2001, 16:2008–2013
7. Linnemann K, Malek A, Sager R et al. Leptin production and release in the dually in vitro perfused human placenta. *J Clin Endocrinol Metab* 2000, 85:4298-4301
8. Hardie L, Trayhurn P, Abramovich D, Fowler P. Circulating leptin in women a longitudinal study in the menstrual cycle and during pregnancy. *Clin Endocrinol* (Oxford) 1997, 47:101–106

9. Chehab FF. The reproductive side of leptin. *Nat Med* 1997, 3:952–953
10. Chien EK, Hara M, Rouard M et al. Increase in serum leptin and uterine leptin receptor messenger RNA levels during pregnancy in rats. *Biochem Biophys Res Commun* 1997, 237:476–480
11. Masuzaki H, Ogawa Y, Isse N et al. Human Obese gene expression adipocyte-specific expression and regional differences in the adipose tissue. *Diabetes* 1995, 44:855–858
12. Schubring C, Kiess W, Englaro P et al. Levels of leptin in maternal serum amniotic fluid, and arterial and venous cord blood: Relation to neonatal and placental weight. *J Clin Endocrinol Metab* 1997, 82:1480–1483
13. Kiess W, Siebler T, Inglaro P, Kratzsch J, Deutscher J, Meyer K et al. Leptin as a metabolic regulator during fetal and neonatal life and in childhood and adolescence. *J Pediatr Clin Endocrinol Metab* 1998, 11:433–496
14. Mantzoros CS, Moschos SJ. Leptin: in search of role(s) in human physiology and pathophysiology. *Clin Endocrinol* 1998, 49:551–567
15. Harigaya A, Nagashima K, Nako Y, Morikawa A. Relationship between concentrations of serum leptin and fetal growth. *J Clin Endocrinol Metab* 1997, 82:3281–3284
16. Stefaniak M, Dmoch-Gajzlerska E, Mazurkiewicz B, Gajzlerska-Majewska W. Maternal serum and cord blood leptin concentrations at delivery. *PLoS One* 2019, 14:e0224863, doi: 10.1371/journal.pone.0224863. eCollection 2019
17. Serapio S, Ahlsson F, Larsson A, KunovacKallak T. Second Trimester Maternal Leptin Levels Are Associated with Body Mass Index and Gestational Weight Gain but not Birth Weight of the Infant. *Horm Res Paediatr* 2019, 25:1–9, doi: 10.1159/000503422
18. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. *Int J Mol Sci* 2018, 19, pii: E3342, doi: 10.3390/ijms19113342. Review
19. Pérez-Pérez A, Maymó JL, Gambino YP, Guadix P, Dueñas JL et al. Activated translation signaling in placenta from pregnant women with gestational diabetes mellitus: Possible role of leptin. *Horm Metab Res* 2013, 45:436–442, doi: 10.1055/s-0032-1333276
20. Mosavat M, Omar SZ, Tan PC, Razif. Leptin and solubleleptin-receptor in association with gestationaldiabetes: a prospectivecase-controlstudy. *Arch Gynecol Obstet* 2018, 297:797–803, doi: 10.1007/s00404-017-4617-0. Epub 2017 Dec 21
21. Nuamah MA, Yura S, Sagawa N, Itoh H, Mise H, Korita D et al. Significant increase in maternal plasma leptin concentration in induced delivery: a possible contribution of pro-inflammatory cytokines to placental leptin secretion. *Endocr J* 2004, 51:177–187