ΛΙΠΩΔΗς ΙΣΤΟς ΚΑΙ ΛΙΠΟΚΥΤΤΟΚΊΝΕς ΣΤΗΝ ΕΓΚΥΜΟΣΎΝΗ

Γεώργιος Βαλσαμάκης

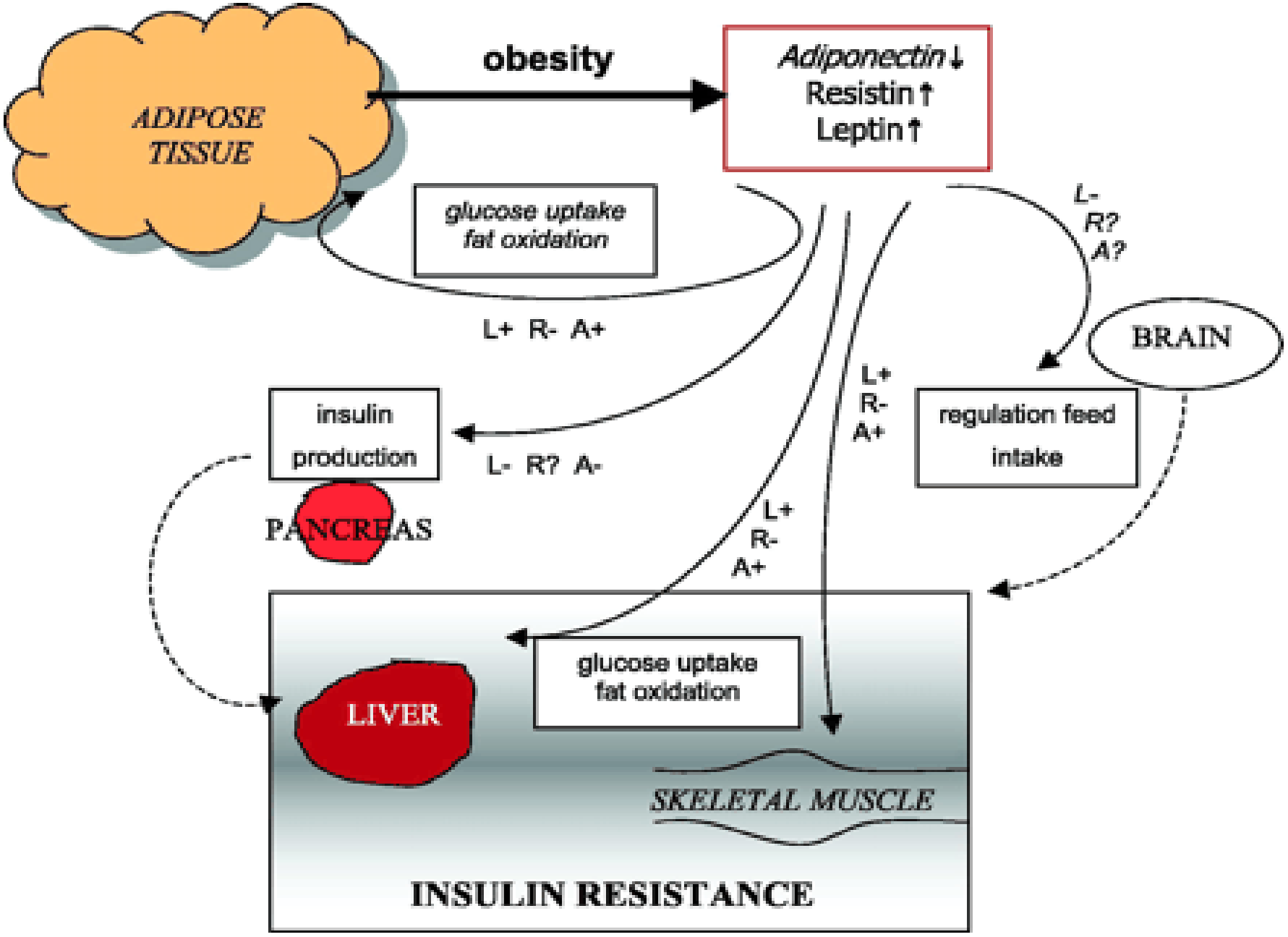
Ενδοκρινολόγος Ευγενίδειο Νοσοκομείο και έμμισθος επιστημονικός συνεργάτης μεταπτυχιακου Αρεταίειο Νοσοκομείο

European SCOPE fellow in Obesity, IASO

Visiting Associate clinical Professor Warwick Medical School, UK

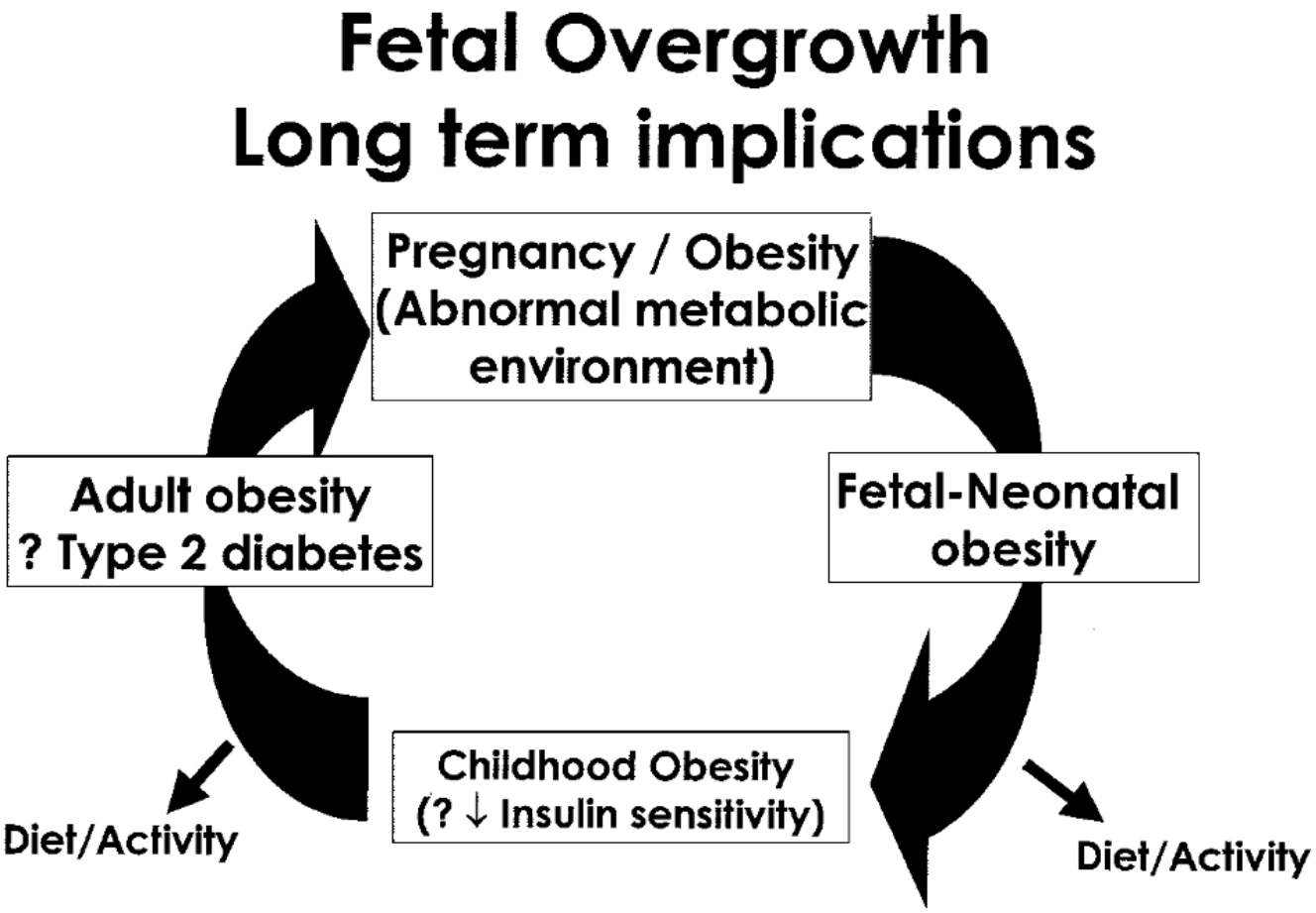
Θέματα

- Λιπώδης ιστός στην εγκυμοσύνη
- (Λιπο) κυττοκίνες, λιπώδης ιστός και μητρικός μεταβ/μός στην εγκυμοσύνη
- (Λιπο) κυττοκίνες, λιπώδης ιστός και ανάπτυξη εμβρύου

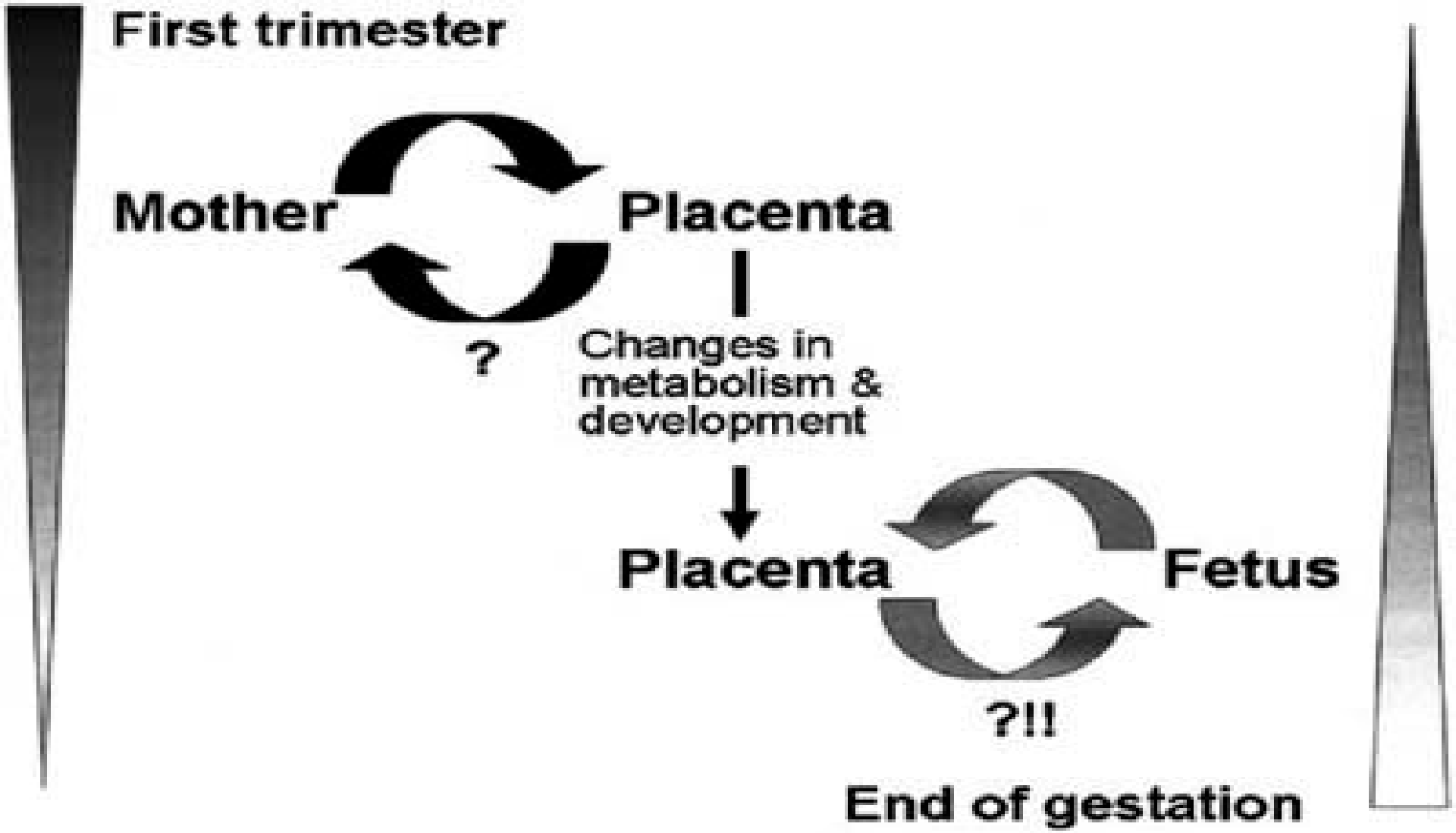

ADIPOSE TISSUE
obesity
Adiponectin↓
Resistin↑
Leptin↑
glucose uptake
fat oxidation
L+ R- A+
L-
R?
A?
BRAIN
insulin
production
L- R? A-
PANCREAS
L+
R-
A+
regulation feed
intake
L+
R-
A+
glucose uptake
fat oxidation
LIVER
SKELETAL MUSCLE
INSULIN RESISTANCE

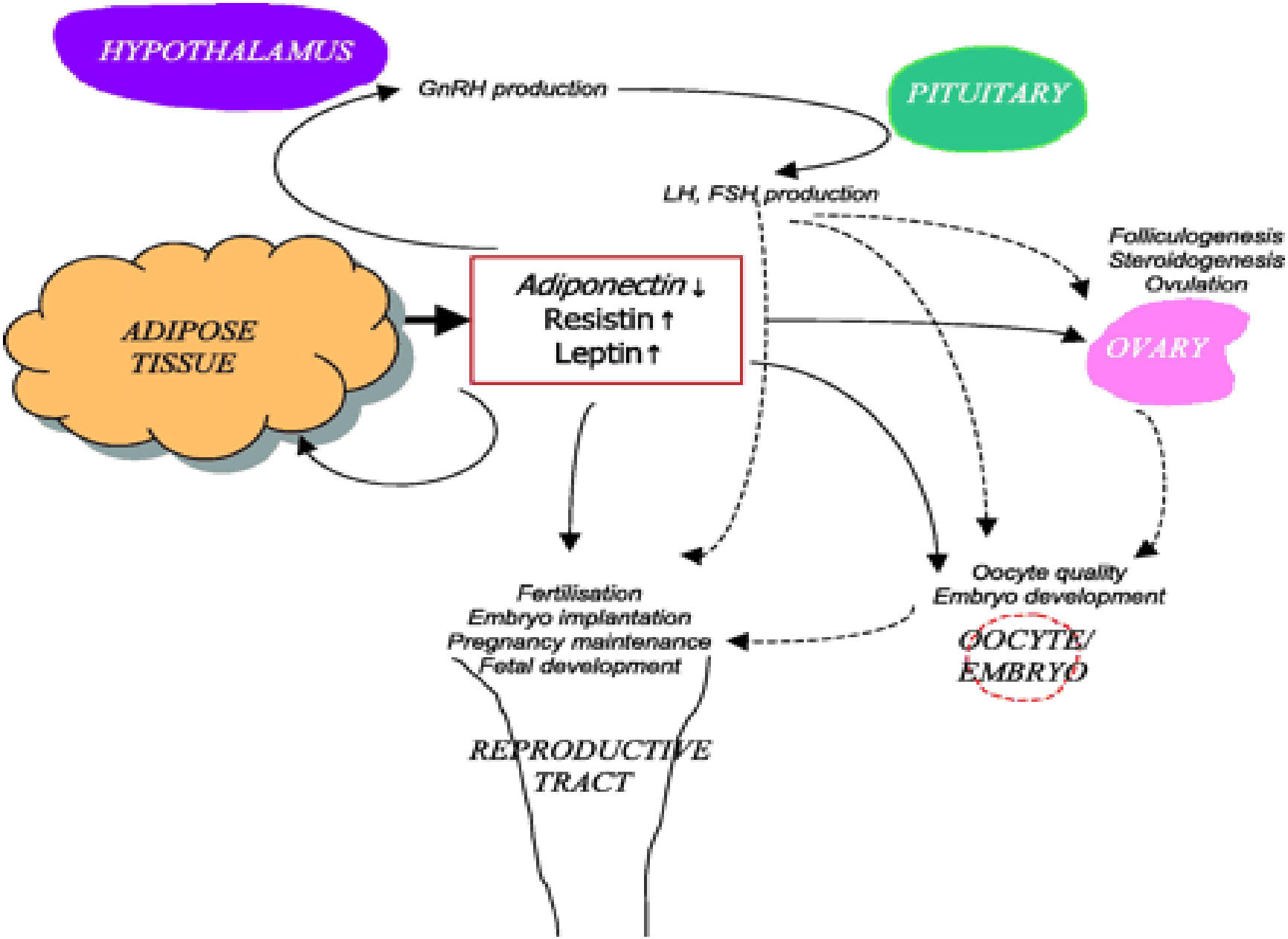
Λιπώδης ιστός στην εγκυμοσύνη

P.M. Catalano, JCEM 2003



Adipose tissue in Pregnancy: Metabolic effects for two

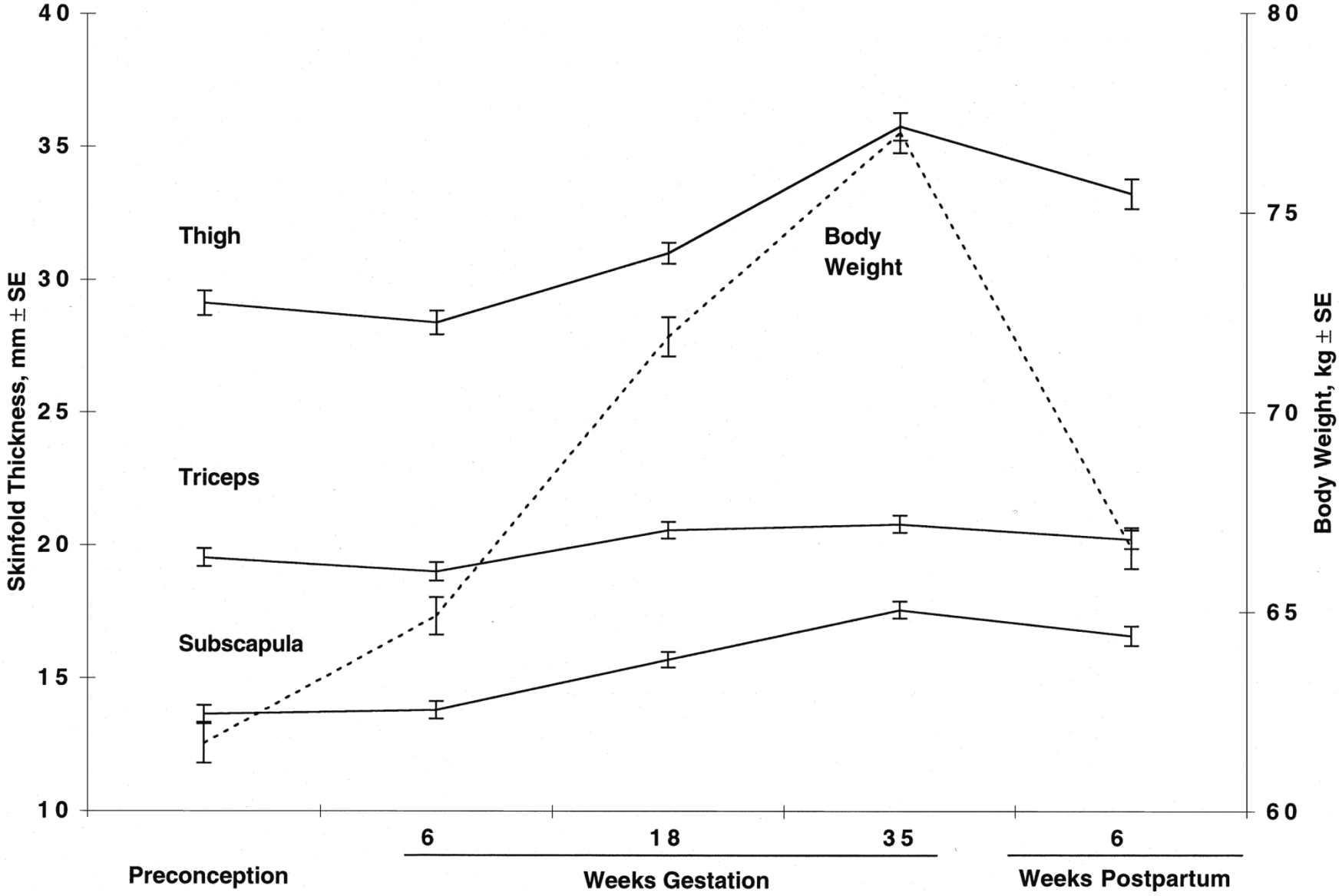



HYPOTHALAMUS
GnRH production
PITUITARY
LH, FSH production
Folliculogenesis
Steroidogenesis
Ovulation
ADIPOSE TISSUE
Adiponectin ↓
Resistin ↑
Leptin ↑
OVARY
Oocyte quality
Embryo development
Fertilisation
Embryo implantation
Pregnancy maintenance
Fetal development
OOCYTE/ EMBRYO
REPRODUCTIVE TRACT

Εναπόθεση του λιπώδους ιστού στην εγκυμοσύνη και τρόποι μέτρησής του

Εναπόθεση του λιπώδους ιστού στην κύηση

N=80	1st trimester	2nd trimester	3rd trimester
weight (kg)	67.6 ± 13.42	76 ± 12.5*	84.4 ±15.6 * #
%fat	30.4 ± 5.2	32.2 ± 4.9*	34.4 ± 6.9* #
Hip circumference (cm)	103.9 ±12.1	107.5 ± 10.2*	116 ±11.8* #
Skinfold (mm)			
biceps	16.5 (11.7-24.2)	20 (14.5-29) *	25.6 (16-29) * #
triceps	16.2 (14-22.7)	21.5 (17-25) *	23 (16-29) *
suprailiac	12.2 (8.5-13)	13.5 (11-15.5) *	16 (12.5-21) * #
subscapular	16.7 (14-26.2)	18 (16-27)	22.2 (14-31) *



Sidebottom et al. Eur. J. Obs. Gyn 2001

Central or peripheral fat is more associated with perinatal outcomes in pregnancy? (1)

McCarthy EA et al Obstet Gynecol Surv 2004

- skinfold caliper thickness and ultrasound assessment remains impractical during pregnancy and cannot distinguish subcutaneous from visceral fat.

- A few studies suggest that central compared with peripheral fat correlates better with birth weight, gestational carbohydrate intolerance, and hypertension

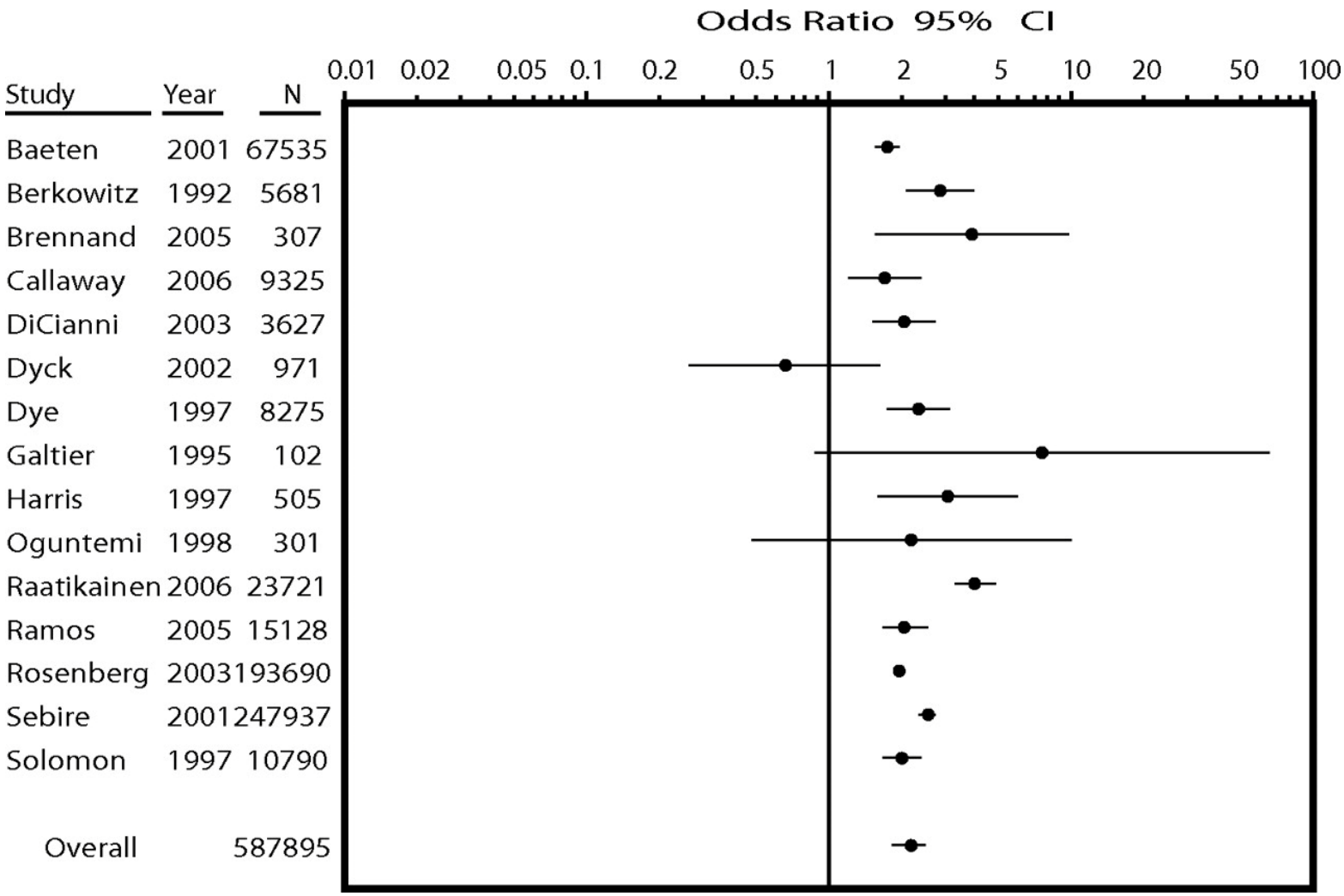
Central or peripheral fat is more associated with perinatal outcomes in pregnancy? (2)

C Stevens-Simon et al, Int J Obes Relat Metab Disord 2001

- study measured subcutaneous adipose tissue thickness at six body sites, first by skinfold caliper and then by ultrasound in 28 primiparous teenagers at 10.7+/-2.8 and 29.6+/-1.8 weeks gestation.
- pregnant women store adipose tissue preferentially on the trunk
- pregnancy-related changes in the regional distribution of maternal body fat based on skinfold caliper measurements should be interpreted cautiously

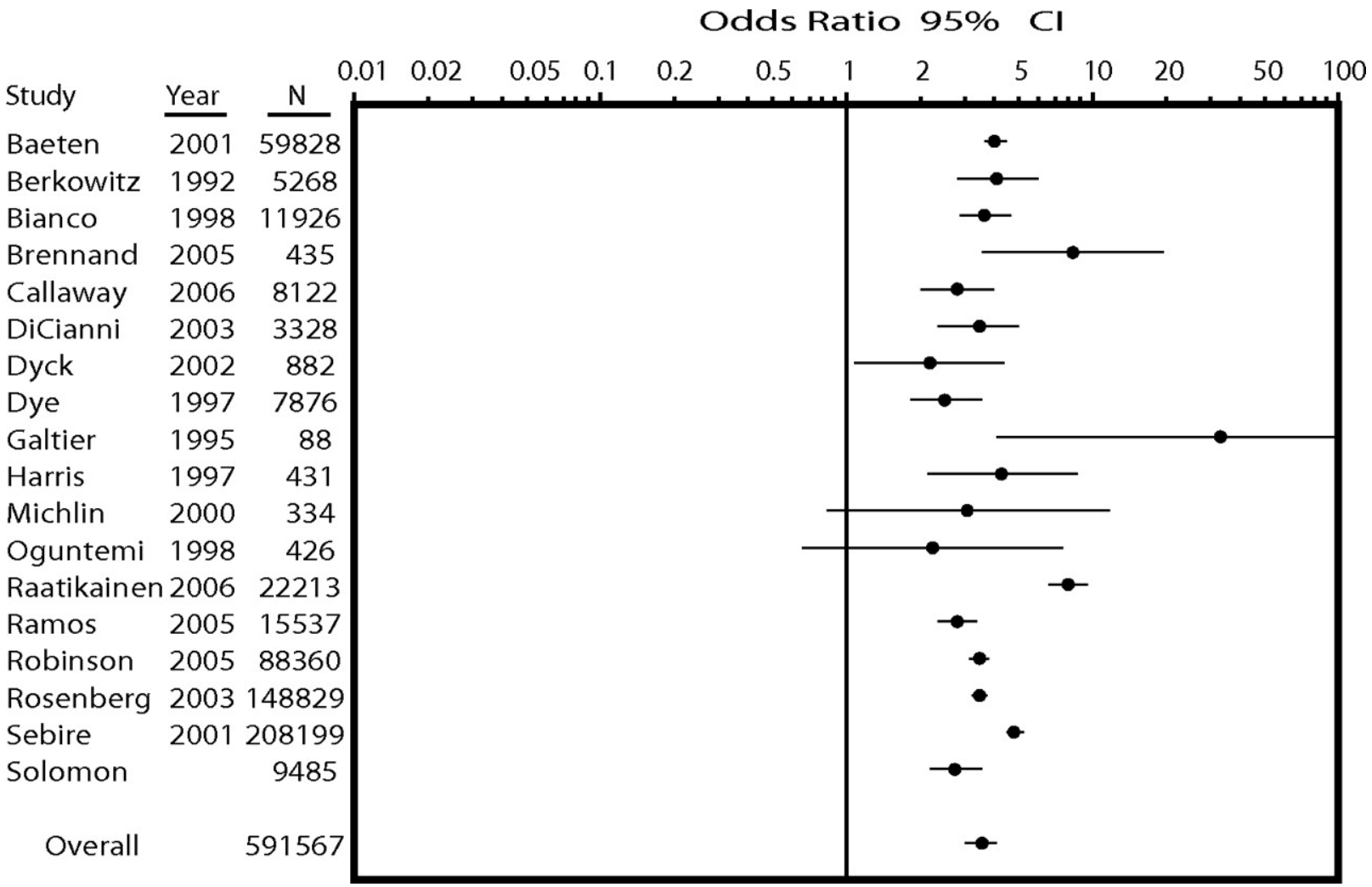
Λιπώδης ιστός στην εγκυμοσύνη και επιπτώσεις

Association of GDM with overweight versus normal maternal BMI.



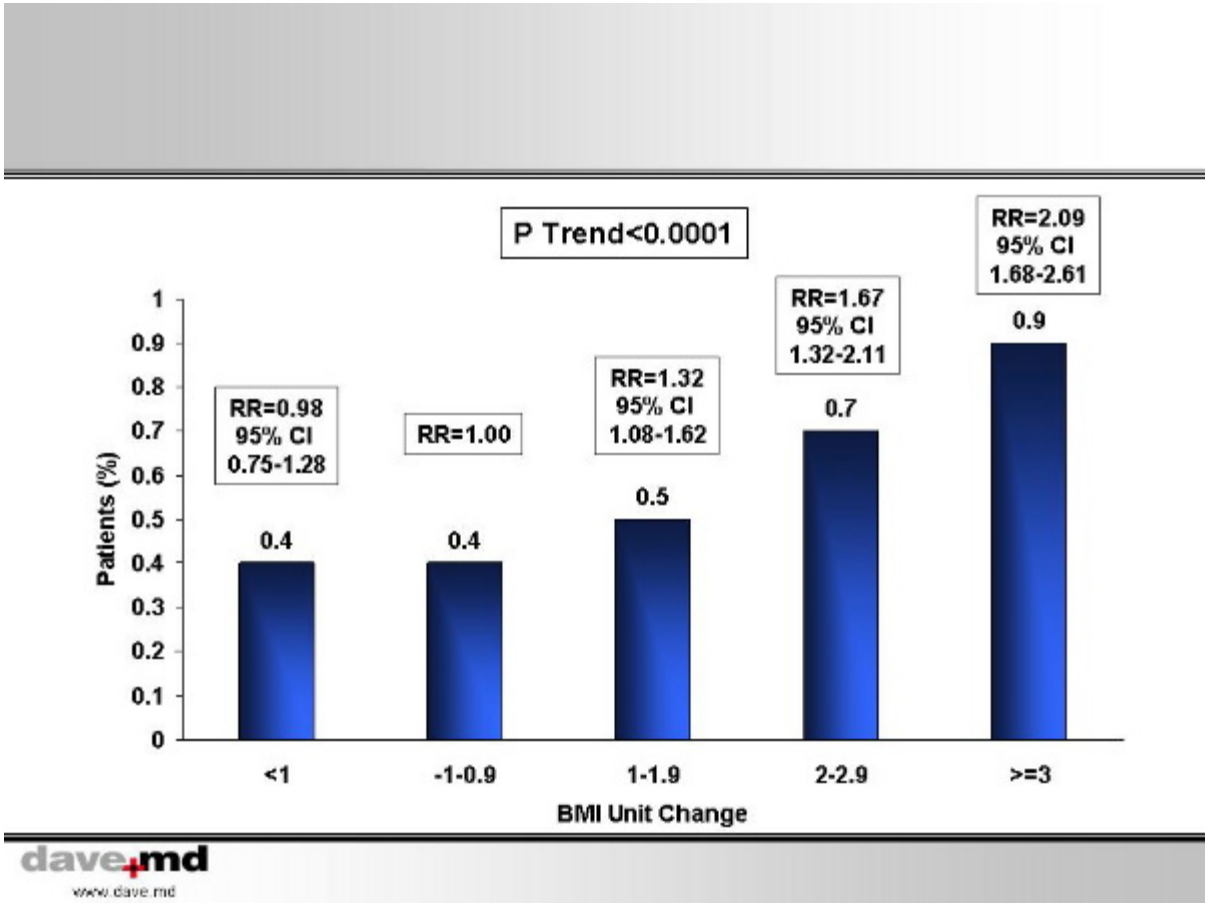
Chu S Y et al. Dia Care 2007;30:2070-2076

Association of GDM with obese versus normal maternal BMI.

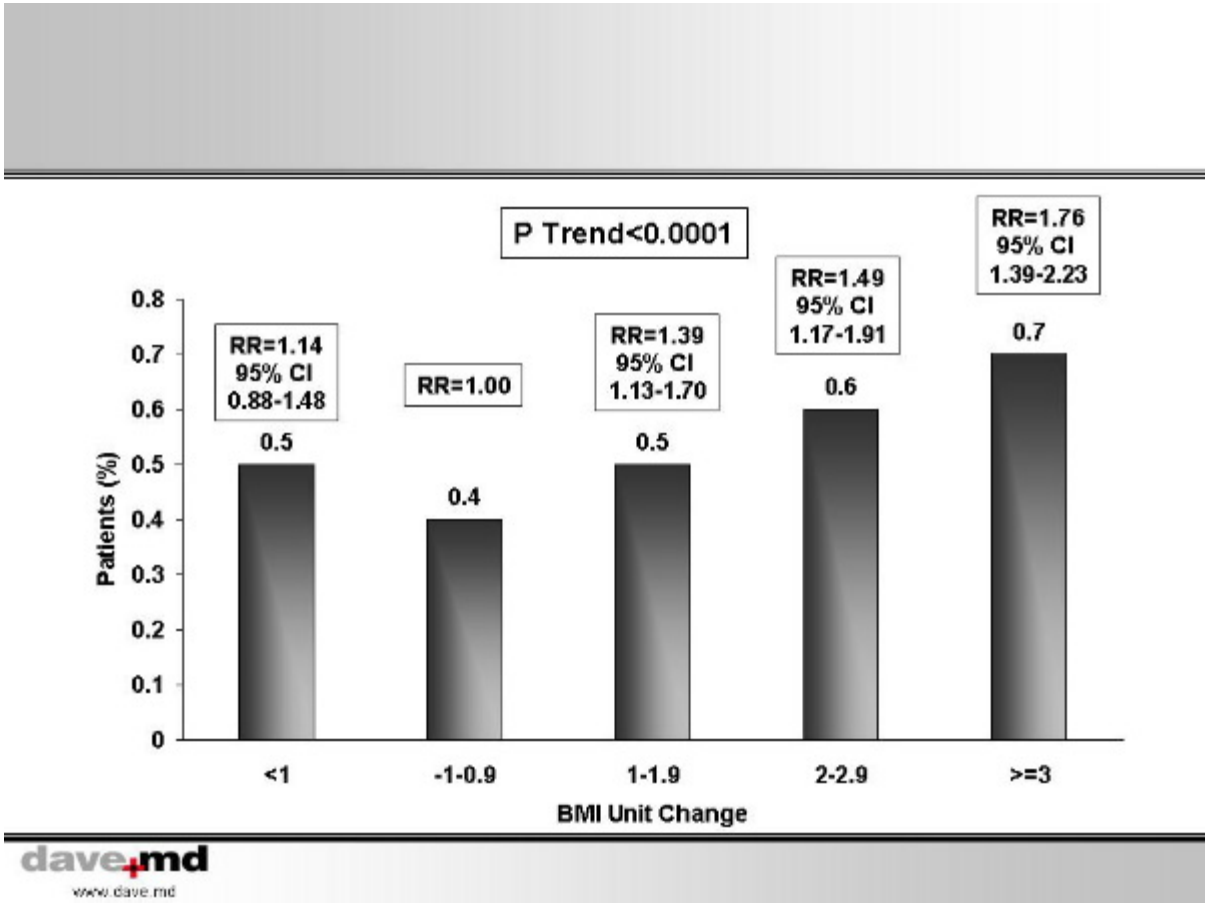


Chu S Y et al. Dia Care 2007;30:2070-2076

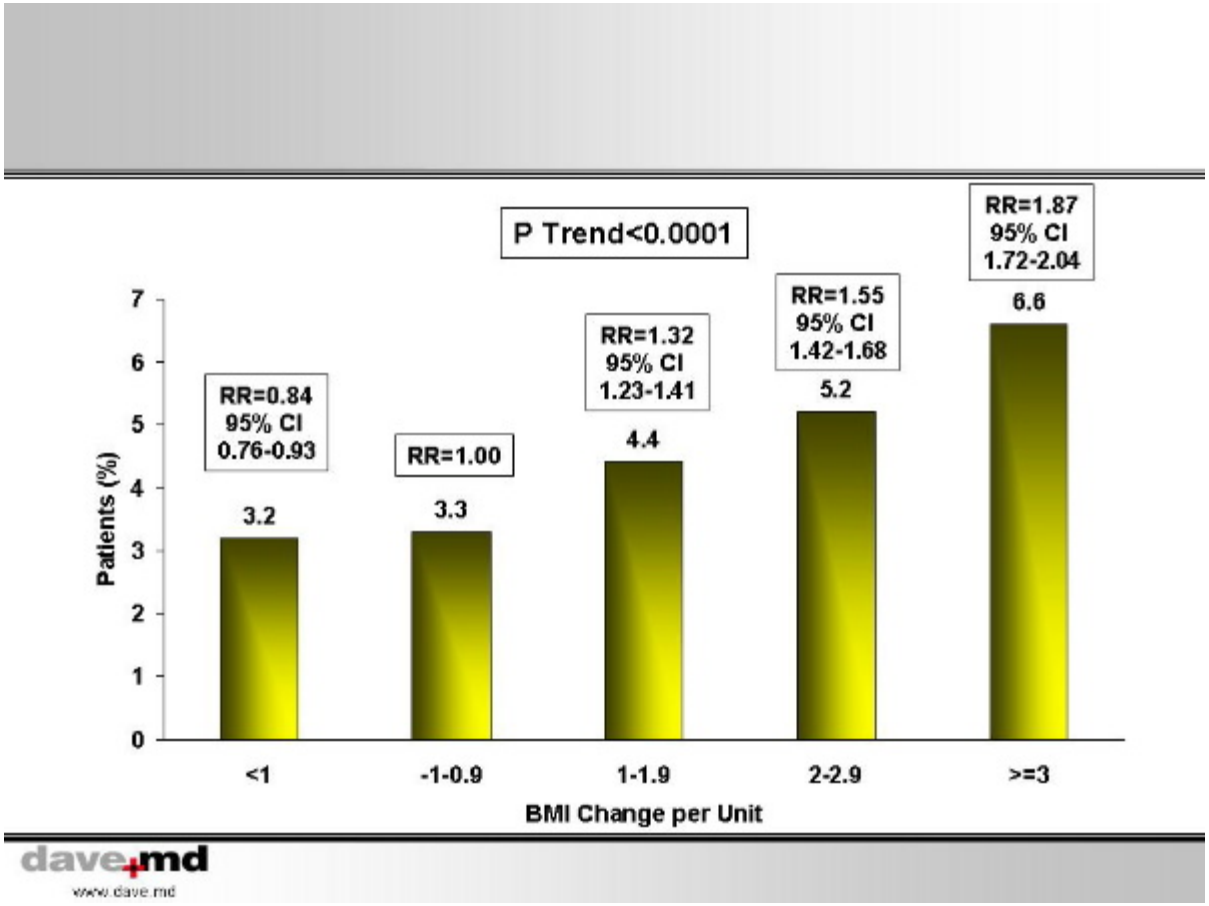
Risk of GDM according to BMI change in pregnancy



Risk of hypertension according to BMI change in GDM



Risk of large fetal gestational weight according to maternal BMI change



Fetal outcomes and maternal pre-pregnancy weight (BMI)

- Large for gestational age
- Birth weight >4000gr
- Neonatal hypoglycemia
- Respiratory distress syndrome
- Jaundice-ικτερος
- Perinatal mortality
- Congenital malformations

Neonatal Body Composition in Obes

Pregravid	BMI < 25	BMI > 25	p-value
Birth weight (g)	3284 ± 534	3436 ± 567	0.051
LBM (g)	2951 ± 406	3023 ± 410	0.22
Fat Mass (g)	334 ± 179	416 ± 221	0.008
Body Fat (%)	9.7 ± 4.3	11.6 ± 4.7	0.006
Weight gain (kg)	6.9 ± 2.4	6.3 ± 3.4	0.001

Sewell, AJ

Factors Relating to Body Composition at Birth (2)

220 Normal Glucose Tolerance, 195 Gestational Diabetes

	r^2	$\Delta r2$	
Fat Mass			
Pregravid BMI	0.066	-	
EGA	0.136	0.070	
Wt. Gain	0.171	0.035	
Group (GDM)	0.187	0.016	p=0.0001
% neonatal Body Fat			
Pregravid BMI	0.072	-	
EGA	0.116	0.044	
Wt. Gain	0.147	0.031	
Group (GDM)	0.166	0.019	p=0.0001

Catalano,

Factors Relating to Body Composition at Birth (1)

220 Normal Glucose Tolerance, 195 Gestational Diabetes

	r^2	Δr^2	
Birthweight			
EGA	0.114	-	
Pregravid Wt	0.162	0.048	
Wt. Gain	0.210	0.048	
Smoking (-)	0.227	0.017	
Parity	0.239	0.012	p=0.0001
Lean Body Mass			
EGA	0.122	-	
Smoking (-)	0.153	0.031	
Pregravid Wt	0.179	0.026	
Wt. Gain	0.212	0.033	
Parity	0.225	0.013	
Maternal Ht.	0.241	0.01	
Paternal Wt.	0.250	0.009	p = 0.0001

Catalano, BJOG;

Pregnancy outcome

Outcome (%)	< 5.0 kg (n=93)	5.0-9.9 kg (n=134)	10.0-14.9 kg (n=134)	>=15 kg (n=122)	P value*
Hypertension (Preecl. + PIH)	9.7	11.4	16.7	20.5	0.014
C-section	15.1	24.6	27.3	27.9	0.030
Induction	20.4	32.9	28.0	36.1	0.039
Birth weight >= 4000 g	19.4	29.1	32.6	35.3	0.011
LGA infant	12.8	25.4	22.7	32.8	0.003
SGA infant	4.3	2.2	0.8	3.3	0.63

logistic regression. Weight gain groups scored 1-4

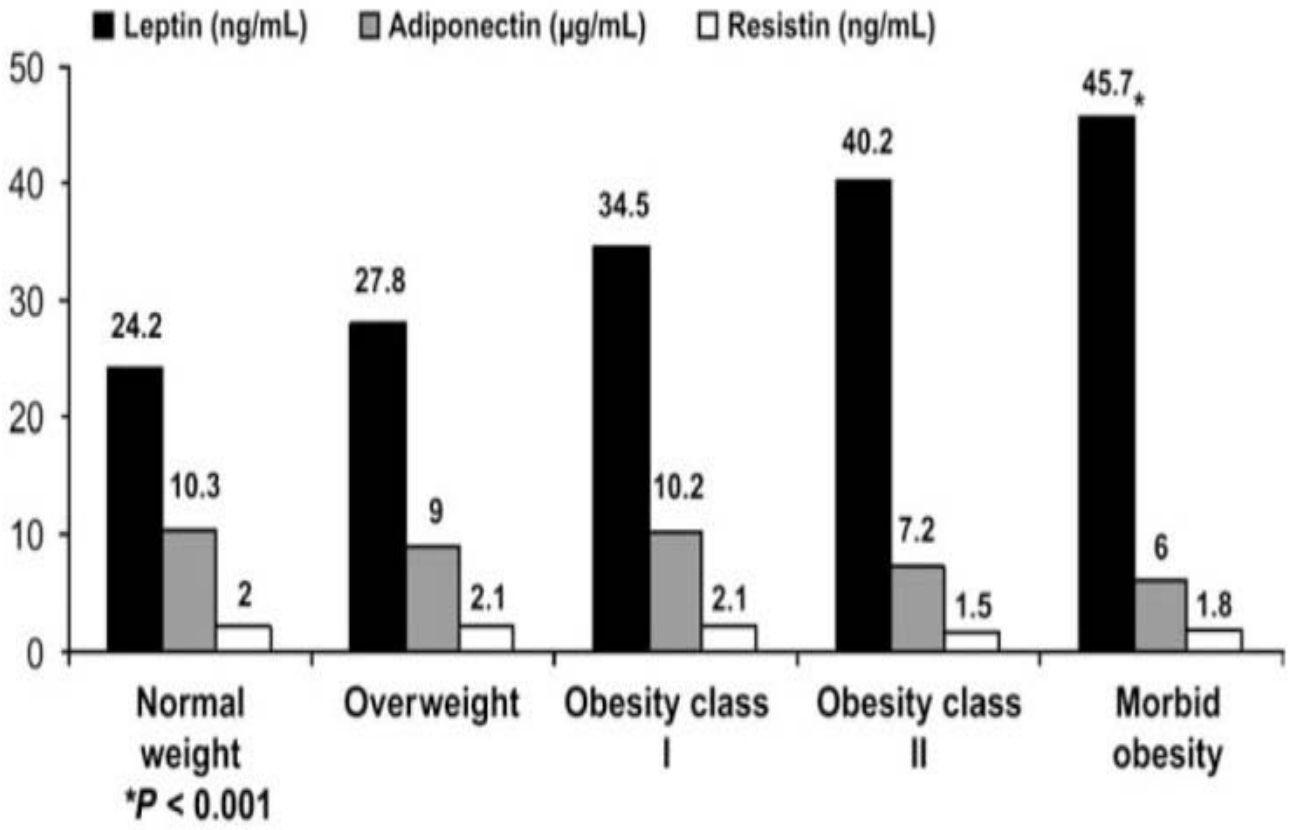
Double Trouble

Frequency of Macrosomia

Maternal BMI	Non obese		Obese	
Glucose tolerance (IADPSG) (n = 23,197)	Non GDM 17,224	GDM 2791	Non GDM 2247	GDM 935
Macrosomia n (%)	1147 (6.7)	286 (10.2)	305 (13.6)	189 (20.2)
Excess macrosomia (Total = 380)	0	100	154	126

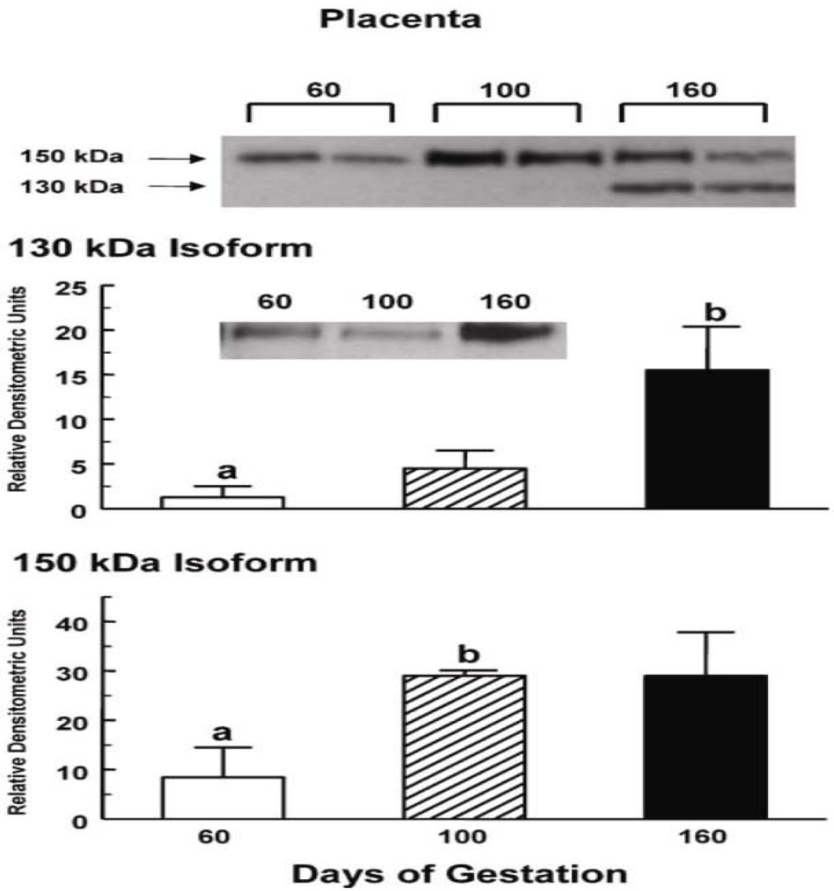
Λιποκυττοκίνες και εγκυμοσύνη

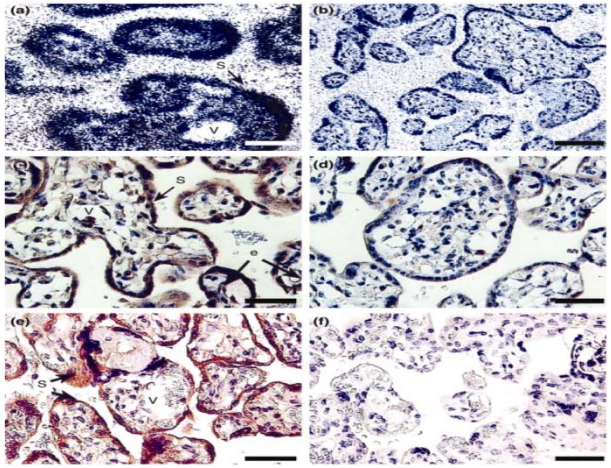
Maternal adipocytokine levels in pregnancy according to pre-pregnancy maternal weight (Hendler I et al. Am. J. Obs. Gyn 2005)



Hauguel-de Mouzon et al. Placenta 2005

	Adipocyte	SVF	Placenta
TNF-α	+	+ + +	+
IL-6	+	+	+
IL-1b		+ +	
IL-8	+	+ +	+
IL-1Ra	+	+ +	+
IL-10	+	+ +	+
Leptin	+ +	0	+
Adiponectin	+ +	0	–
Resistin	0	+ +	+
MCP-1	+	+ +	+
MIF	+ +	+	+
VEGF	+	+ +	+
PAI-1	+	+ +	+
Cathepsin S	+	+ +	+



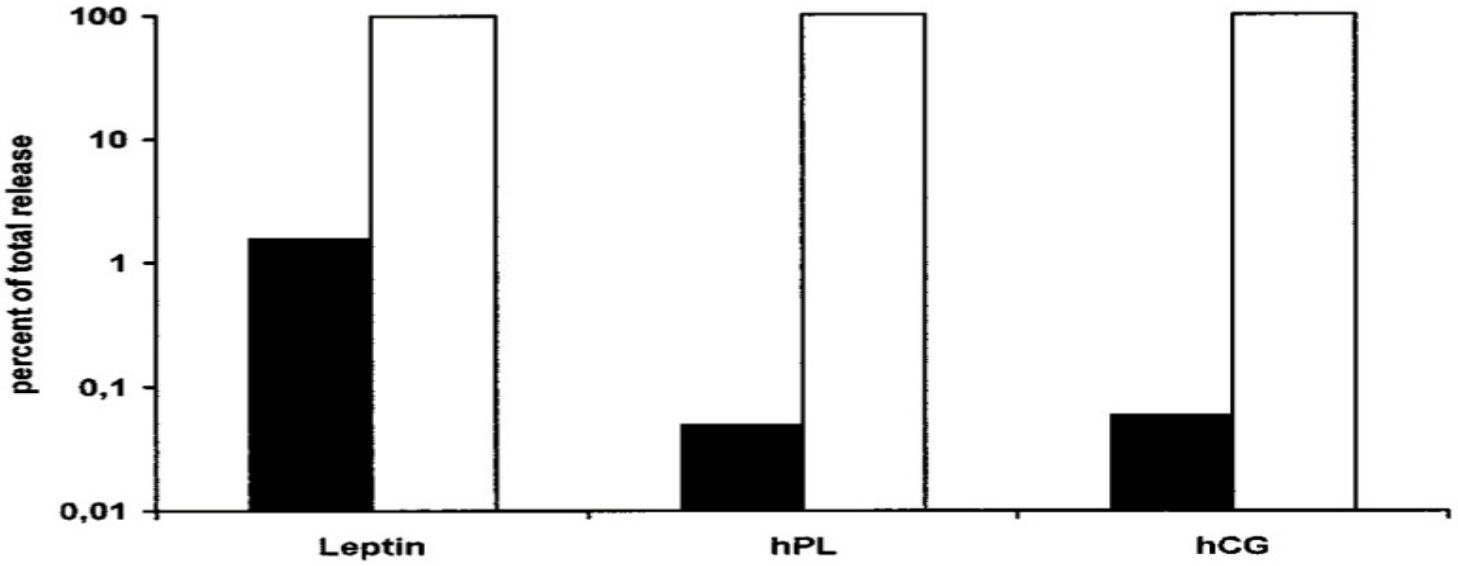


Receptor of Placental Leptin

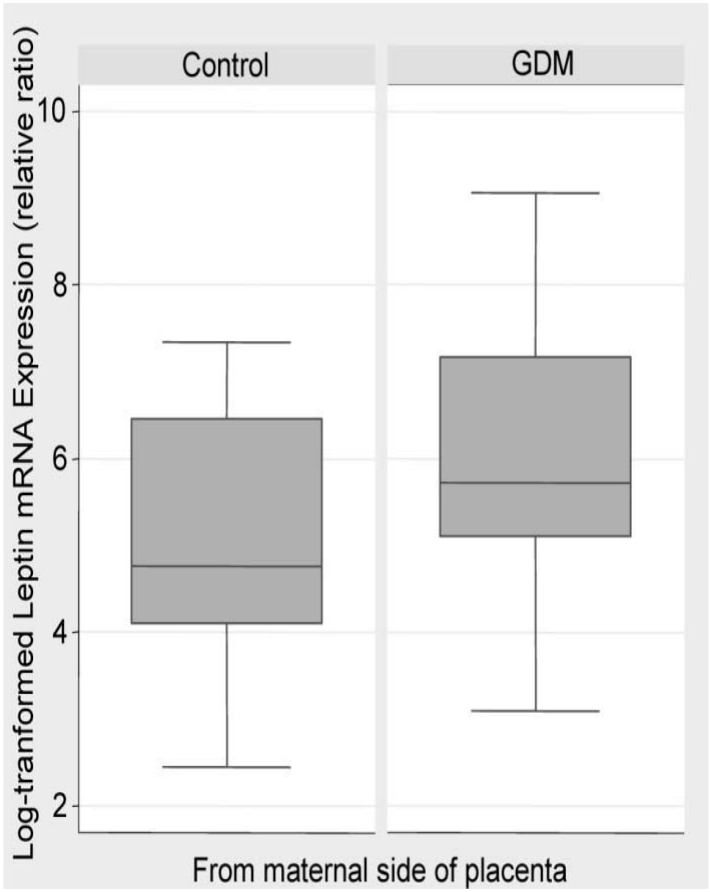
Henson et al. Biol. Of Reprod. 2005
Ashworth Reviews of Reproduction 2000

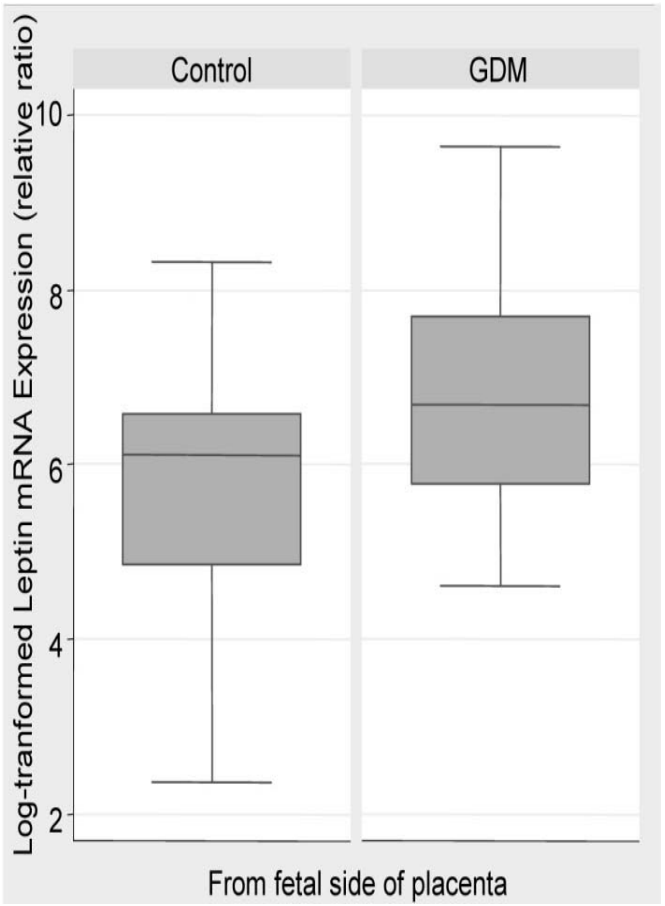
Πλακουντιακή λεπτίνη προς έμβρυο και μητέρα
(Linnemann K et al., Diabetes 2000)

[a] Percent of total release.



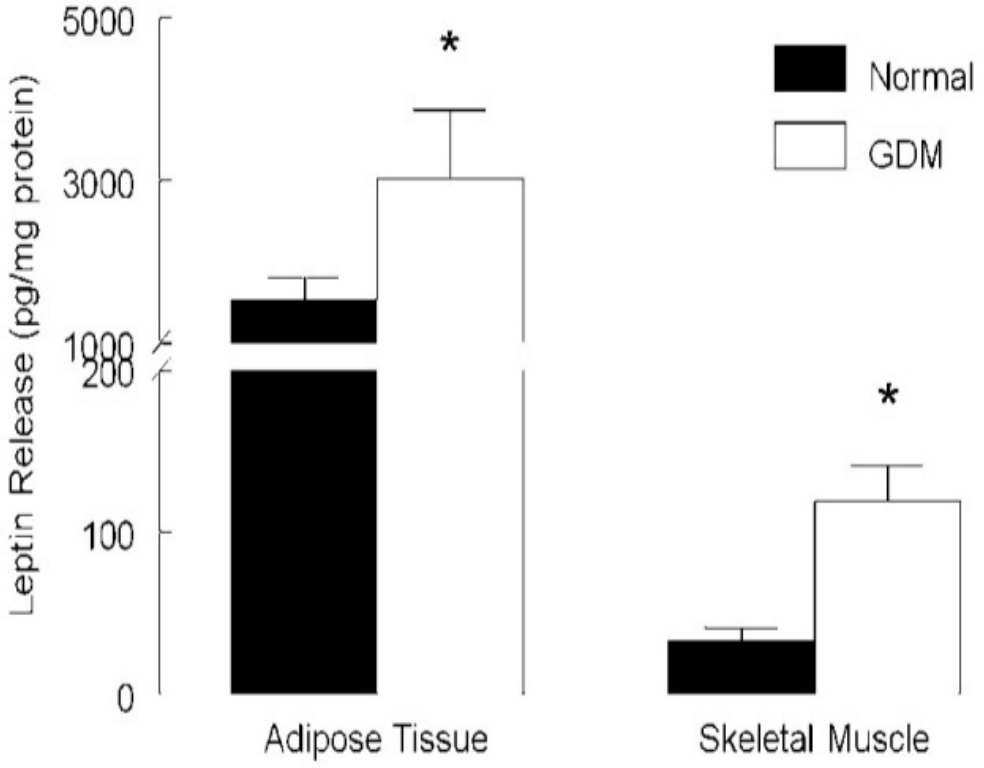
Meller M et al., Physiol Res 2006
Lappas M et al., Journal of Endocrinology 2005

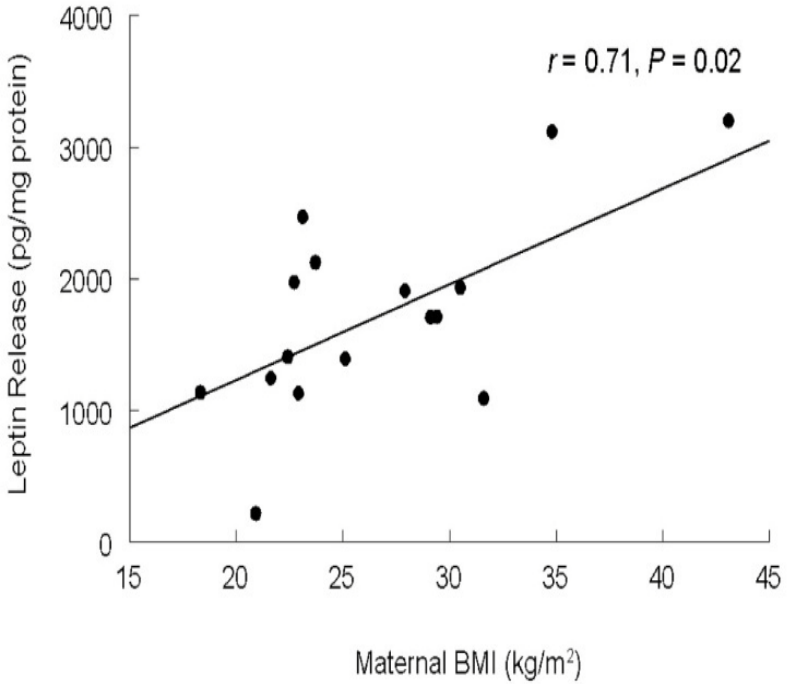




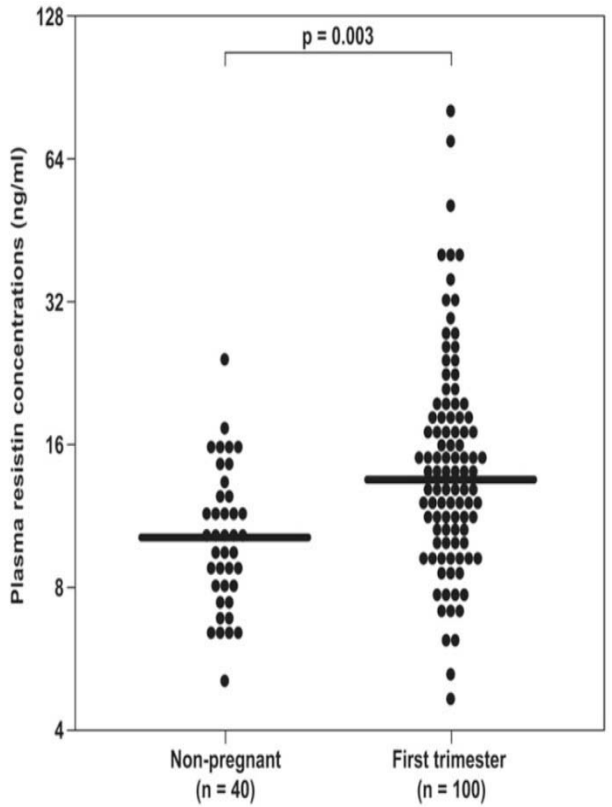
Maternal peripheral leptin in GDM

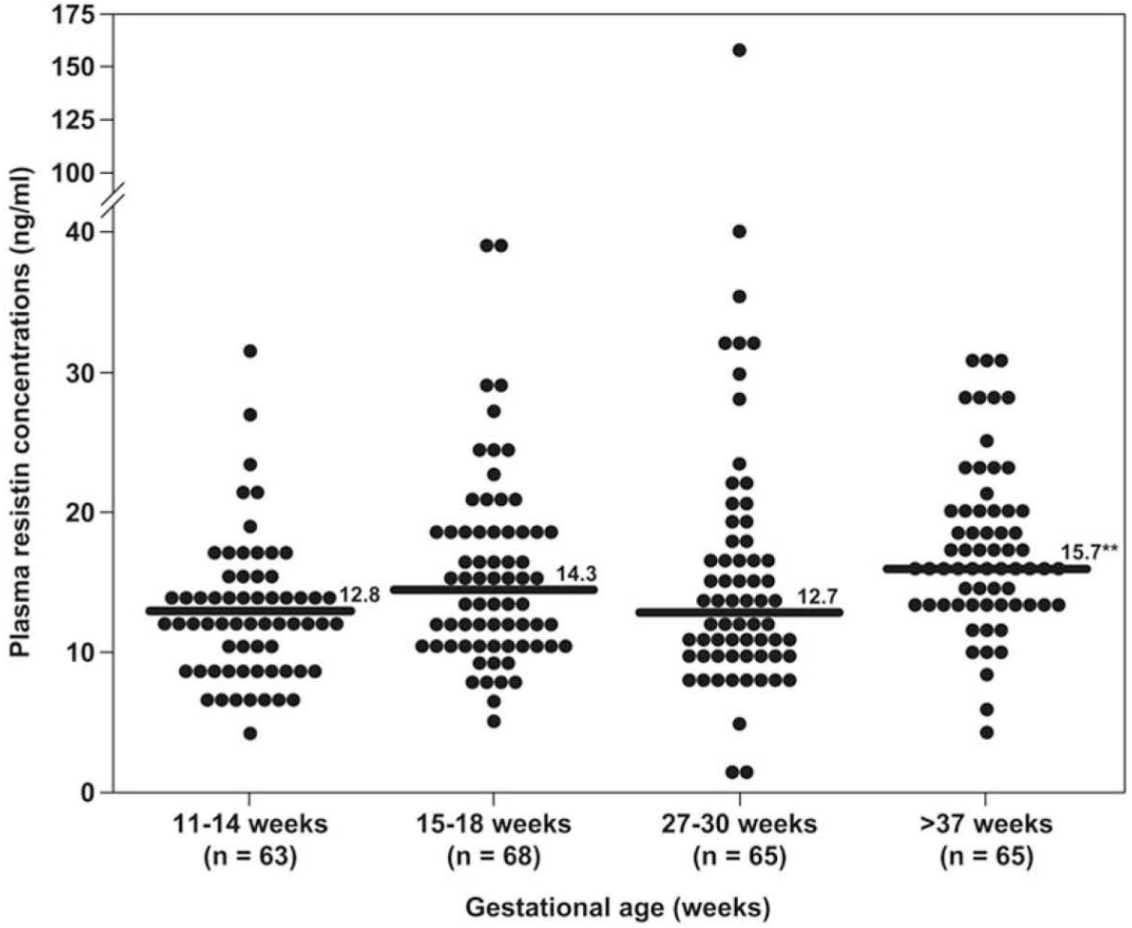
(Lappas M et al., Journal of Endocrinology 2005)





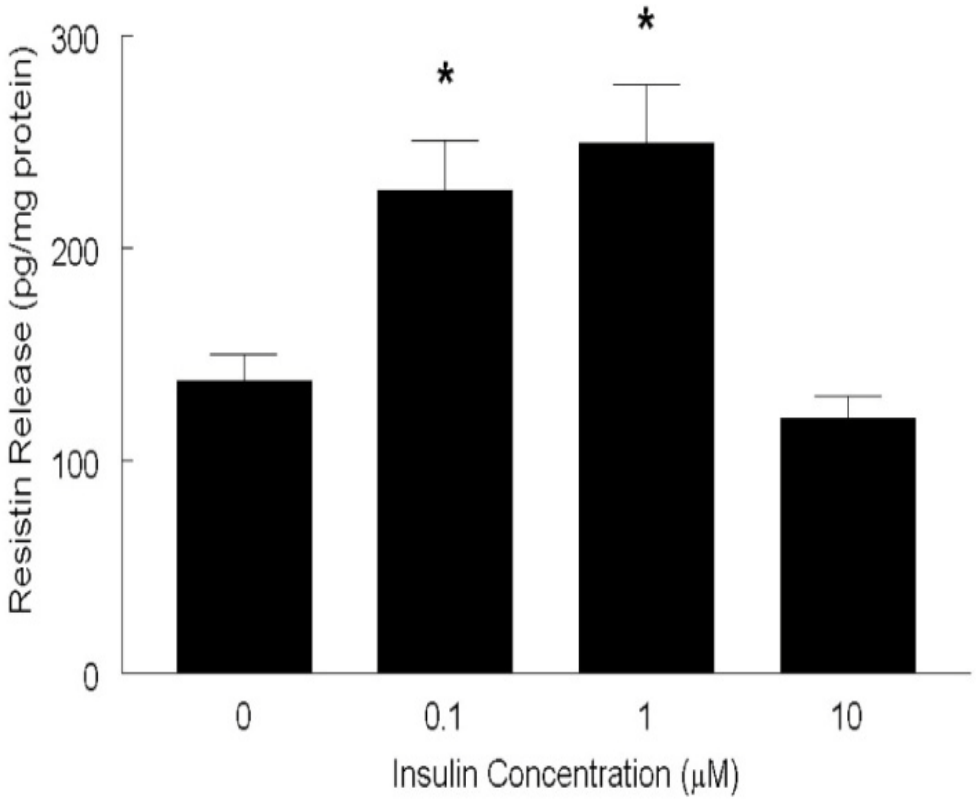
Nien JK et al., J Perinat Med 2007



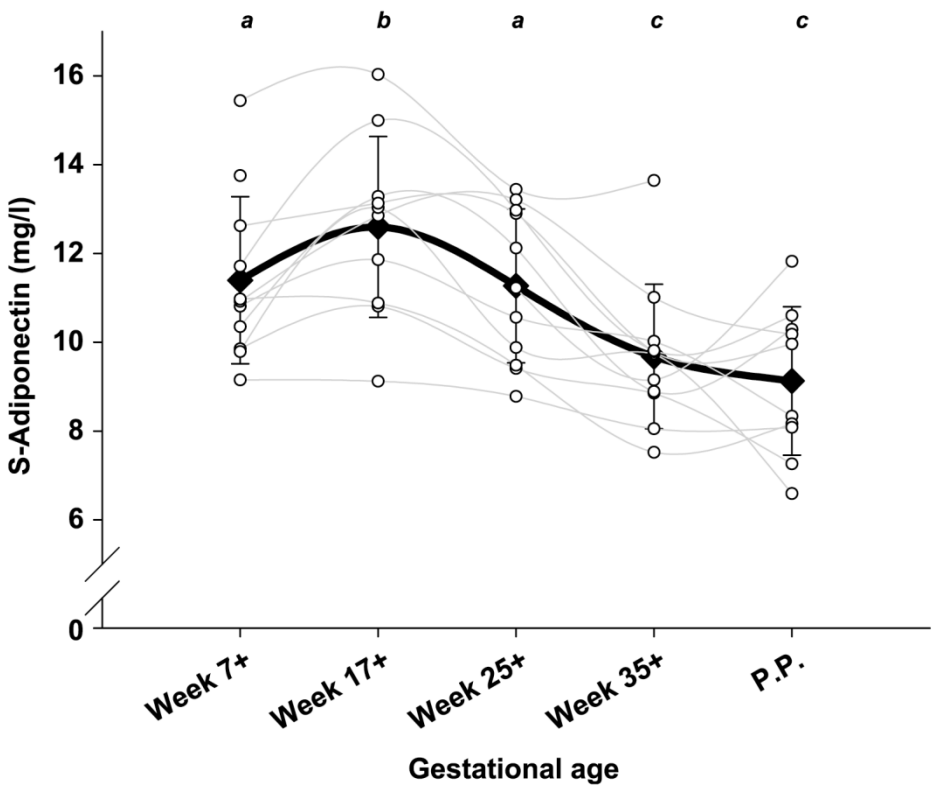


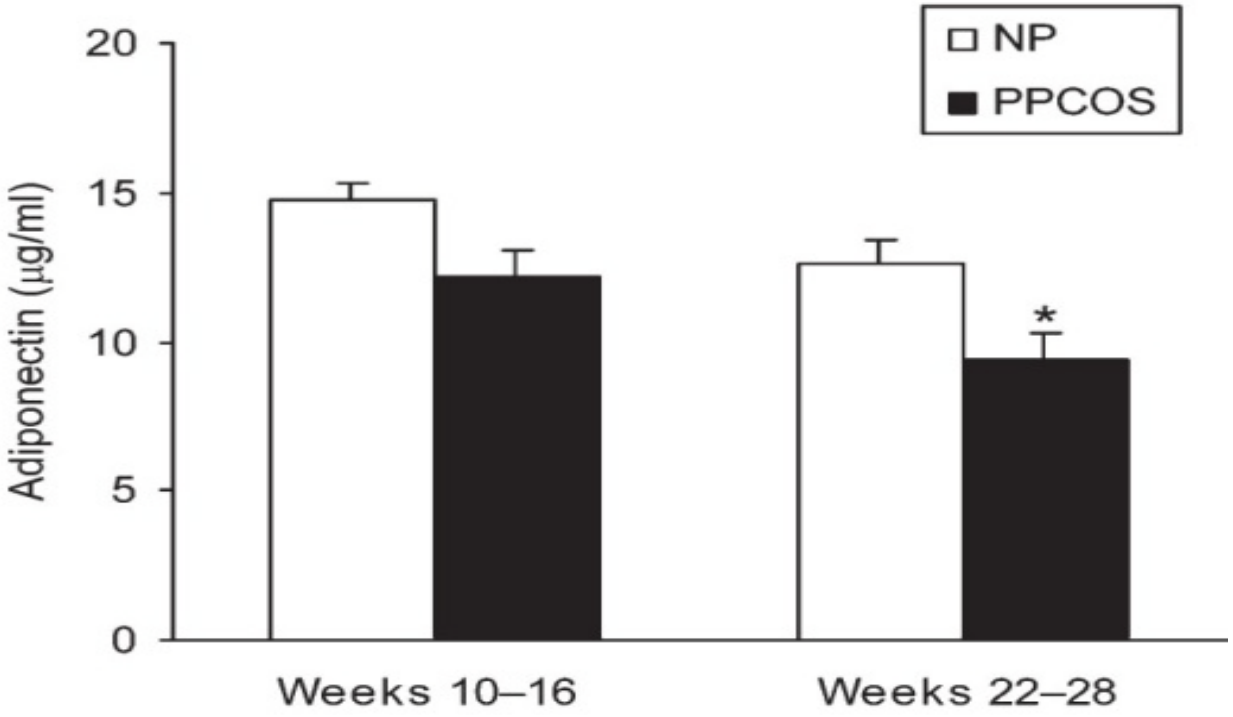
Ρύθμιση πλακουντιακής ρεζιστίνης

Lappas M et al., Journal of Endocrinology 2005



Fuglsang et al. BJOG 2006

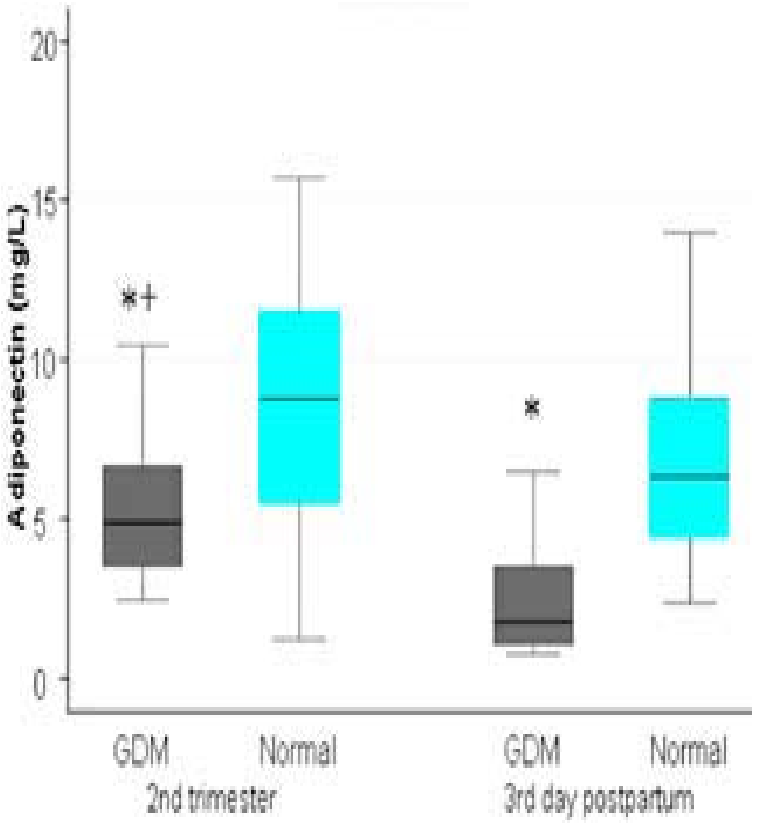


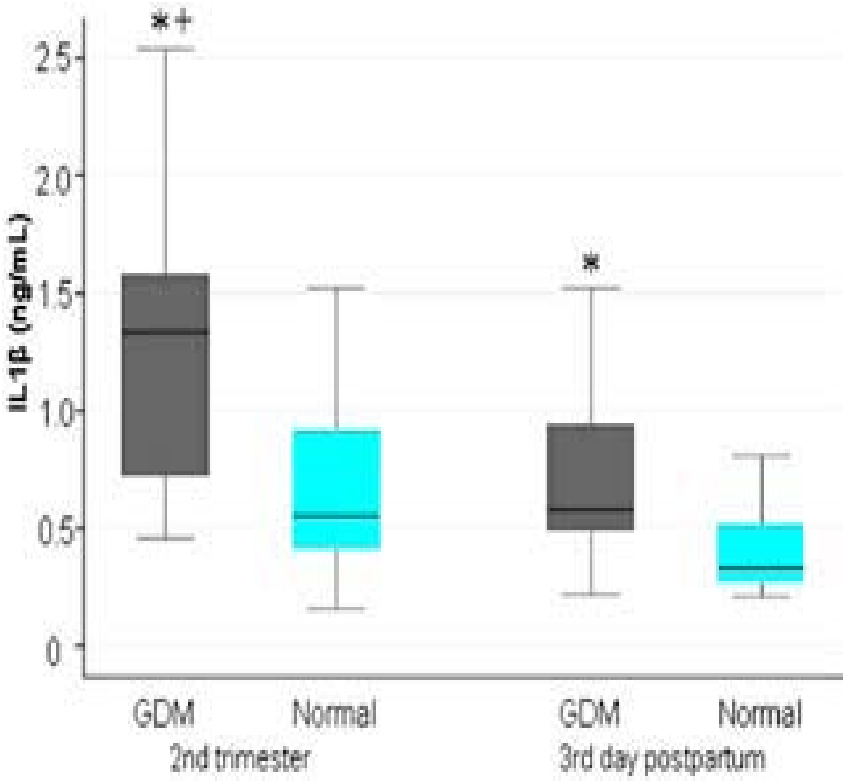


Sir-PetermannT et al., Human Reproduction 2007

Maternal adipocytokines in GDM and postpartum

Vitoratos et al. Hormones 2008



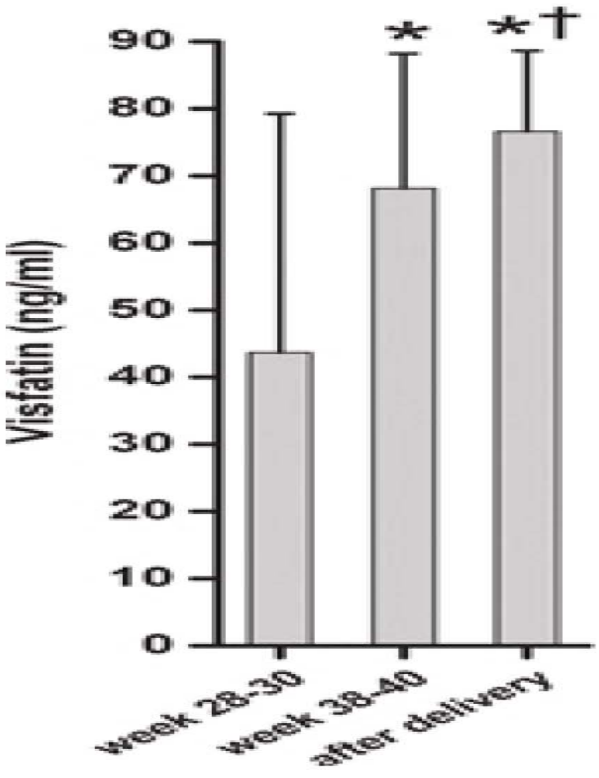


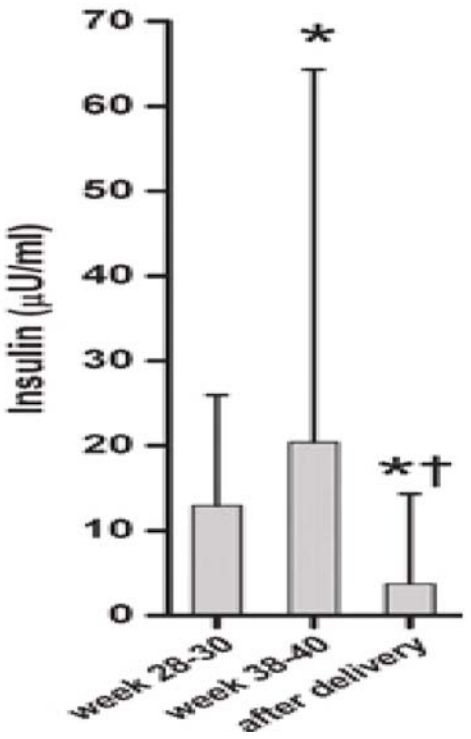
Η βισφατίνη

Lopez et al. Diabetes 2006

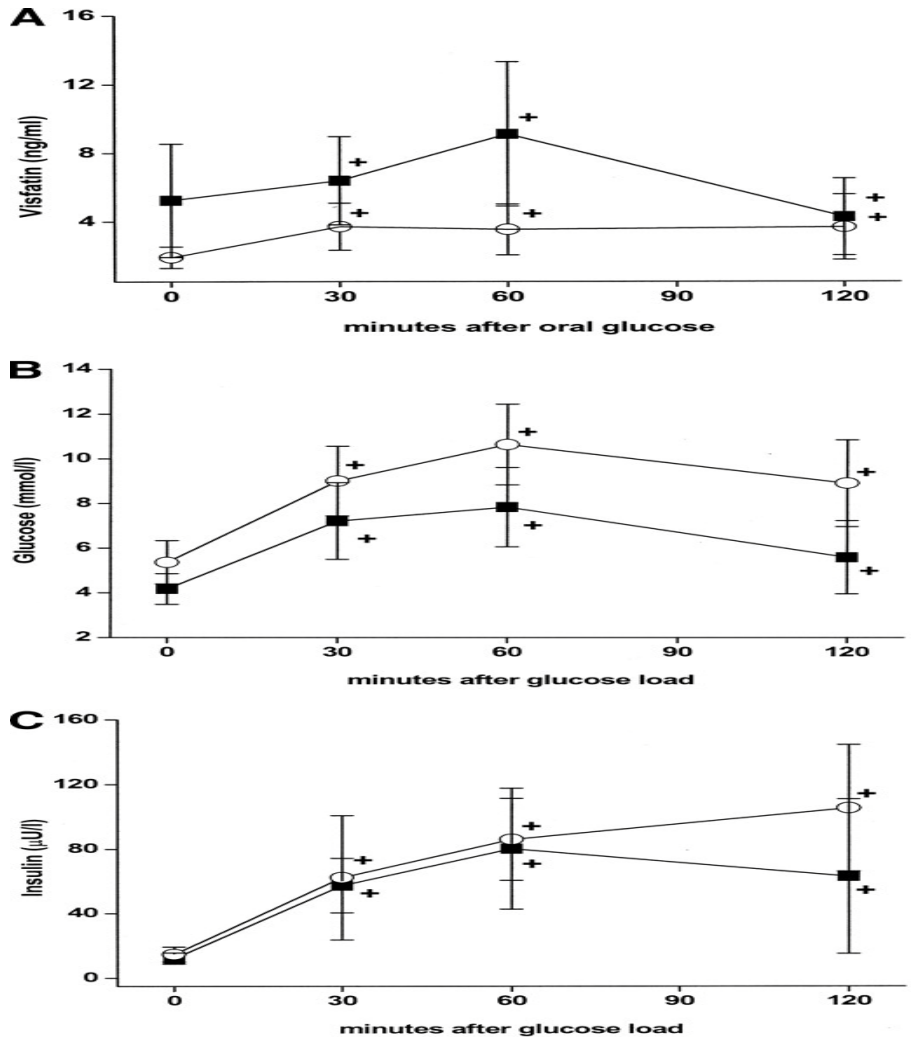
Η βισφατίνη στην κύηση

Krzyzanowska et al. Cl. Science 2006





Plasma concentrations of visfatin (A), glucose (B), and insulin (C) during an OGTT in women with GDM (○) and age-matched healthy pregnant control subjects (▪).



Haider D G et al. Dia Care 2007;30:1889-1891

Mastorakos et al. Clin. Chemistry 2007

Table 1. Anthropometric and metabolic variables during pregnancy.[a]

n = 80	1st trimester	2nd trimester	3rd trimester
Weight, kg	67.6 (13.4)	76 (12.5)*	84.4 (15.6)*†
% Fat	30.4 (5.2)	32.2 (4.9)*	34.4 (6.9)*†
Hip circumference, cm	103.9 (12.1)	107.5 (10.2)*	116 (11.8)*†
Skinfold biceps, mm	16.5 (11.7–24.2)	20 (14.5–29)*	25.6 (16–29)*†
Skinfold triceps, mm	16.2 (14–22.7)	21.5 (17–25)*	23 (16–29)*
Skinfold suprailiac, mm	12.2 (8.5–13)	13.5 (11–15.5)*	16 (12.5–21)*†
Skinfold subscapular, mm	16.7 (14–26.2)	18 (16–27)	22.2 (14–31)*
Visfatin, μg/L	23.7 (19.9–27.6)	26 (21.4–29.3)*	27.1 (22.1–31.1)*
Adiponectin, mg/L	5.2 (3.4–10.9)	5.1 (3.7–8.5)	6.3 (4.3–9.1)
Leptin, μg/L	25.9 (19.4–51.5)	44.5 (26.1–65.9)	53 (38.8–57.9)
IL-6, ng/L	1.8 (1.1–3.1)	2 (1.5–4.3)	1.7 (1.6–1.9)
hsCRP, mg/L	2.3 (1.3–3.4)	2.1 (1.9–4.5)	2.6 (2.3–3.04)
Glucose 0 min, mmol/L	4.5 (0.4)	4.4 (0.4)	4.4 (0.4)
Insulin 0 min, pmol/L	58.4 (43.7–71)	58.8 (48.8–119.8)	115 (86–145)*†
ISI	0.1 (0.09–0.1)	0.08 (0.06–0.1)	0.05 (0.007–0.07)*†
HOMA-R	1.9 (1.4–2.6)	1.8 (1.5–3.8)	3.7 (2.8–4.7)*†
PHIS1	2503 (2009–2809)	2755 (2292–4283)*	4166 (3584–5157)*†
PHIS2	696 (513–768)	764 (626–1120)*	1087 (987–1313)*†
ΔAUCI	9884 (7943–12 680)	16 554 (9332–21 681)	25 018 (16 539–38 354)

[a] Variables expressed as mean (SD) or median (25th–75th interquartile range).

*, Statistically significant change from 1st trimester.

†, Statistically significant change from 2nd trimester.

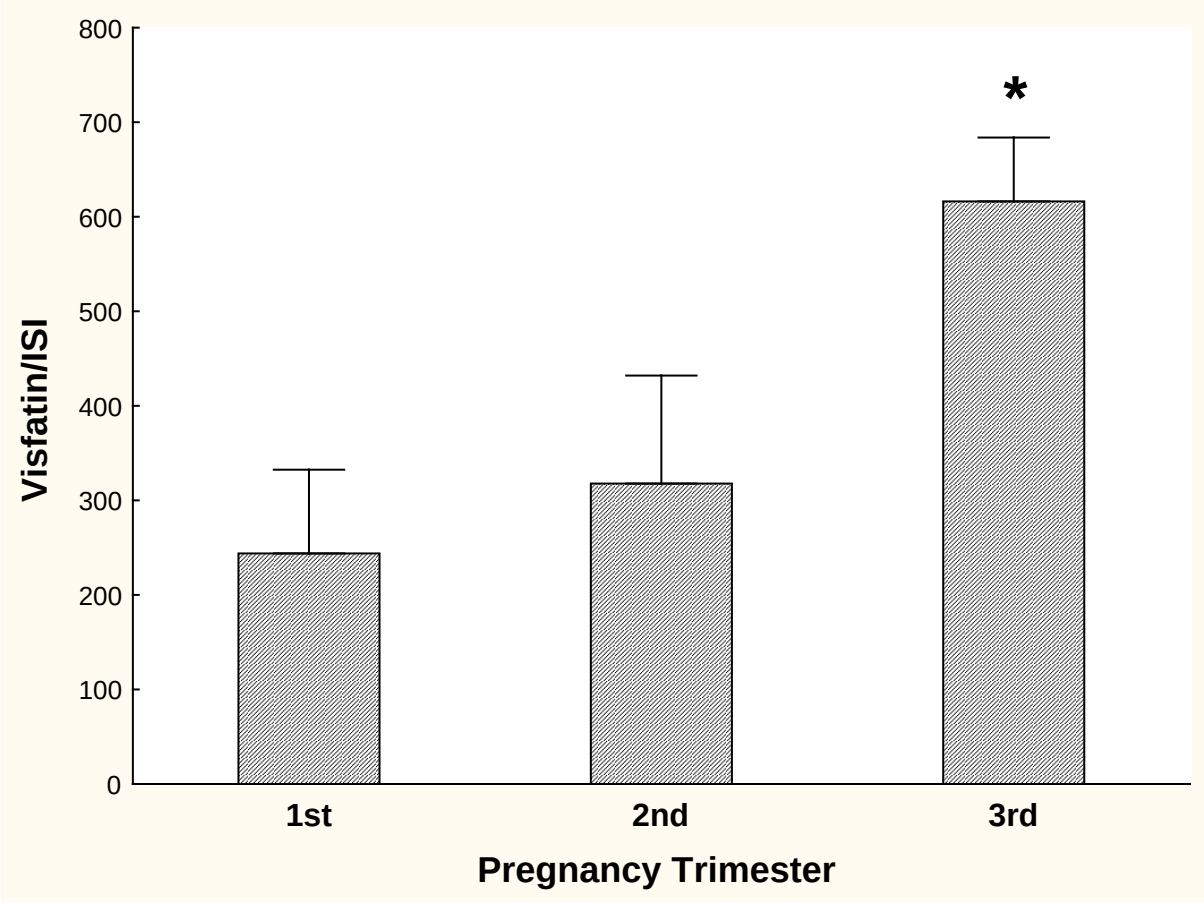

800
700
600
500
400
300
200
100
0
Visfatin/ISI
*
1st
2nd
3rd
Pregnancy Trimester

Table 5. Backwards multiple regression analysis for dependent variable ISI 2nd trimester.[a]

	Coefficient	SE of coefficient	*P* value
Visfatin 1st trimester	1.018	0.024	0.015
HsCRP 1st trimester	0.157	0.024	0.099

[a] The term "coefficient" is the generally used term for the effect of each predictor (independent variable) on the respective dependent variable in a linear regression analysis.

Predictor of insulin resistance (HOMAR) and insulin sensitivity (ISI) change during all trimesters of pregnancy

The longitudinal regression model taking in consideration all three trimesters revealed that maternal fasting visfatin change was the best positive and negative predictor of insulin resistance (HOMAR) (p=0.0002, t-value=4.48) and sensitivity (ISI) (p=0.002, t-value=-3.65) changes, respectively, during pregnancy among leptin, IL6 and adiponectin levels of the three trimesters of pregnancy.

Maternal Serum Visfatin at 11–13 Weeks of Gestation in Gestational Diabetes Mellitus

Table 2. Median (IQR) of maternal serum concentration of adiponectin and visfatin in the outcome groups.

	Nondiabetic controls	GDM
n	300	100
Adiponectin		
μg/L	12 035 (8595–7 085)	7591 (4552–11 059)
MoM	1.02 (0.70–1.29)	0.66 (0.50–0.92)[a]
Visfatin		
μg/L	0.89 (0.47–1.71)	1.20 (0.63–2.55)
MoM	1.00 (0.53–1.92)	1.34 (0.70–2.87)[a]

[a] $P < 0.05$. Comparisons between groups by Mann–Whitney *U*-test.

Table 3. Performance of screening for GDM by maternal factors, maternal serum adiponectin MoM, visfatin MoM, and their combinations.

Screening test	AUROC[a] (95% CI)	Detection rate for false-positive rate of 10% (95% CI)
Maternal factors	0.828 (0.777–0.878)	58.0 (48.2–67.2)
Maternal factors plus		
Adiponectin	0.854 (0.807–0.900)	66.0 (56.3–74.5)
Visfatin	0.825 (0.774–0.876)	64.0 (54.2–72.7)
Adiponectin and visfatin	0.855 (0.808–0.901)	68.0 (58.3–76.3)

[a] AUROC, area under the ROC curve.

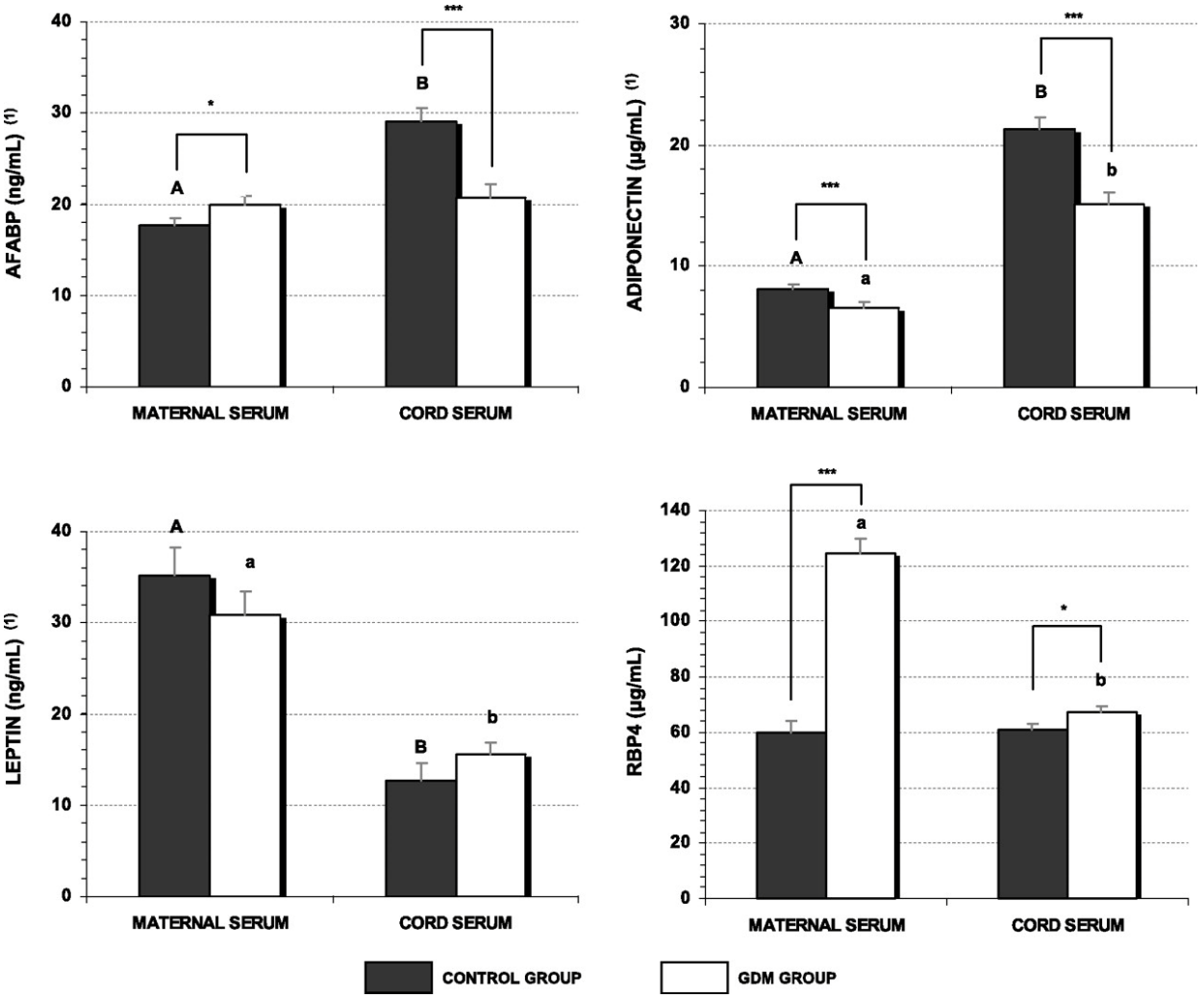
Ferreira AFA et al., Clinical Chemistry 2011

(Λιπο)κυττοκίνες και ανάπτυξη εμβρύου

Vitoratos et al. Hormones 2008

Serum adiponectin in the 2nd trimester of GDM pregnancies correlated negatively with birth weight ($p=0.005$, $r=-0.6$).

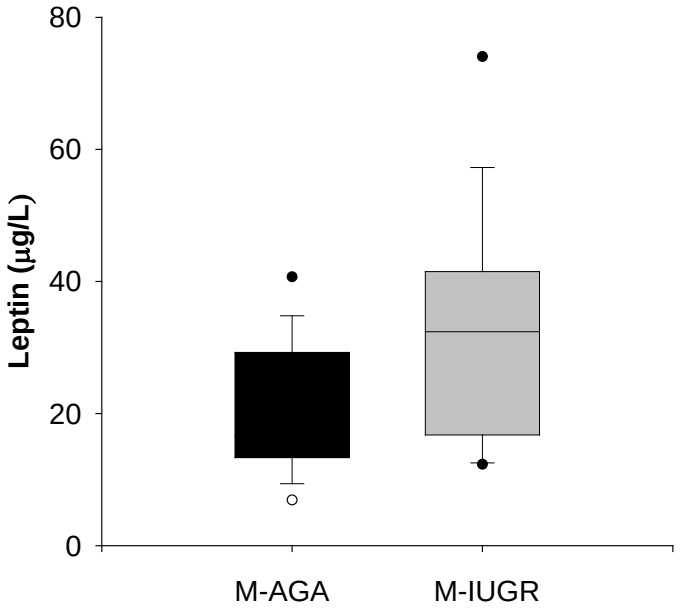
Maternal and cord serum concentrations of AFABP, adiponectin, leptin, and RBP4 in control and GDM pregnant women and their neonates.



Ortega-Senovilla H et al. Dia Care 2011;34:2061-2066

LEPTINEMIA in IUGR and their MOTHERS

	Leptin (μg/L)	Adiponectin (mg/L)	Cortisol (μg/dL)
IUGR	32.5±3.8	5.4±0.9	33.3±3.8
AGA	20.4±2.1	11.8±1.3	33.8±2.7
P values	<0.05	<0.05	NS



Kyriakakou et al. Eur. J. of Endocrinology 2008

Η σημασία του λιπώδους ιστού του 1ου τριμήνου της εγκυμοσύνης

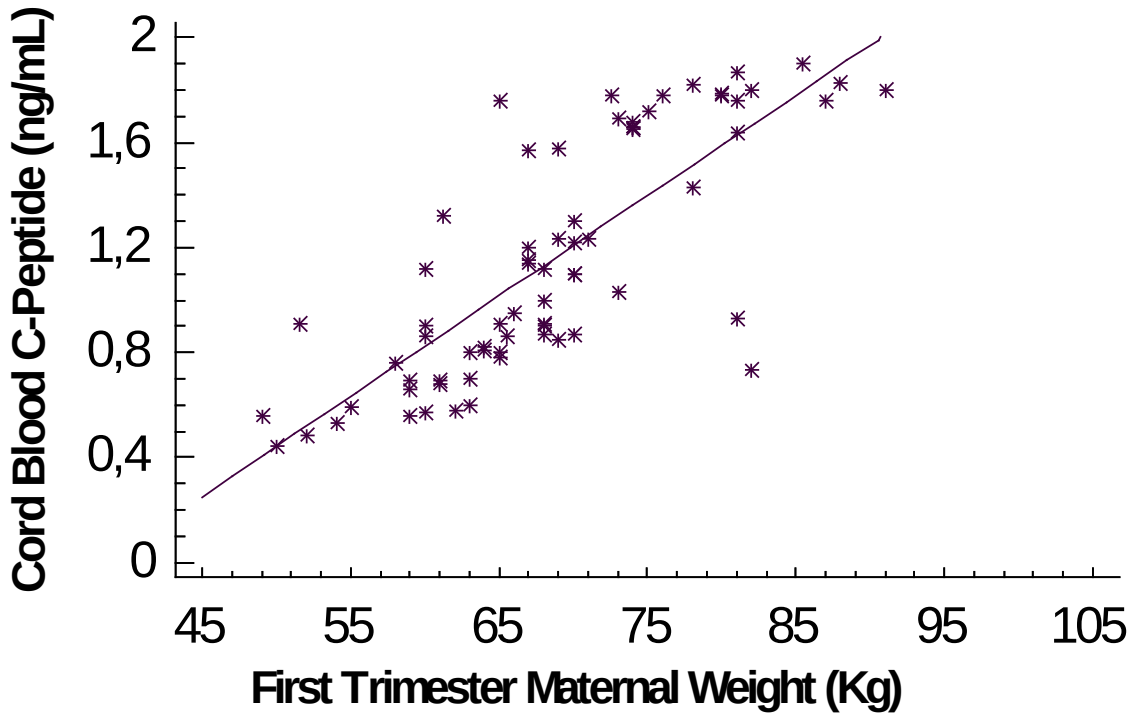
- Recently the HAPO, a large epidemiological study, revealed strong and continuous associations of maternal glucose levels during oral glucose tolerance test (OGTT) performed at 24 to 32 weeks of gestation, below those diagnostic of diabetes, with increased birth weight and cord blood serum c-peptide levels

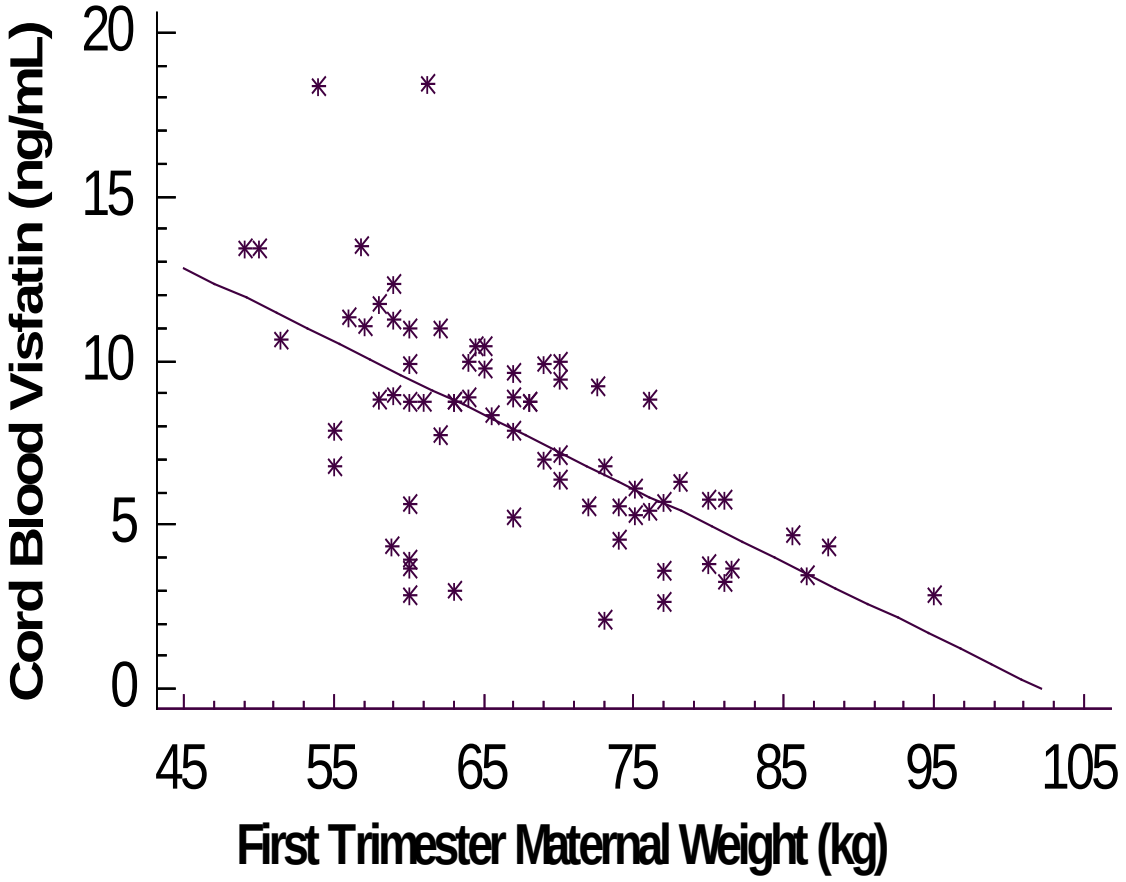
- *(HAPO Study Cooperative Research Group, Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008)*

- In the first trimester maternal adipose tissue is the main source of adipocytokine production and affects glucose metabolism
  - *Mazaki-Tovi S et al. J Perinat Med 2009, Fereira AF Clin Chem 2011)*

- First trimester maternal adiponectin and leptin levels are associated to insulin resistance during pregnancy and to birth weight (Williams MA et al. JCEM 2004, Papastefanou et al. J Mat Fetal Neonat Med 2010

Valsamakis G. et al submitted




Cord Blood Visfatin (ng/mL)
20
15
10
5
0
45
55
65
75
85
95
105
First Trimester Maternal Weight (kg)

	1st trimester				
variable 1	visfatin	visfatin	Leptin	leptin	hip
variable 2	weight before pregnancy	hip Circumference 1st trimester	weight before pregnancy	weight 1st trimester	birth weight
r-Spearman	0.73	-0.61	0.82	0.82	0.52
	3rd trimester				
variable 1	visfatin	ISI	HOMAR	weight	
variable 2	birth weight	birth weight	birth weight	birth weight	
r-Spearman	-0.72	-0.76	0.76	0.59	

	1st trimester				
Variable 1	Maternal weight	HOMAR	Maternal weight	Maternal leptin	HOMAR
Variable 2	Cord c-peptide	Cord visfatin	Cord visfatin	Cord visfatin	Cord leptin
r-Spearman	0.74	-0.90	-0.67	-0.99	0.90
	2nd trimester	**3rd trimester**			
Variable 1	ISI	Maternal weight	Maternal weight	Maternal visfatin	Maternal adiponectin
Variable 2	Cord c-peptide	Cord c-peptide	Cord glucose	Cord IL6	Cord glucose
r-Spearman	r=-0.90	0.67	0.69	-0.90	0.95

Predictor of birth weight

Valsamakis G et al submitted

- Stepwise multiple regression analysis revealed that 1st trimester maternal visfatin levels were the best negative predictor (p=0.017, beta=-1.23) of birth weight among 1st trimester maternal adiponectin, leptin, and IL-6 levels, HOMAR, and weight.

Conclusions

- First trimester maternal adipocytokine levels reflect pre-pregnancy adipose tissue
- First trimester maternal weight predicts fetal insulin and adipocytokine secretion
- First trimester maternal visfatin levels are the best negative predictors of birth weight and of insulin resistance during pregnancy.

Conclusions

- It seems that maternal pre-pregnancy adipose tissue mass and function affect intrauterine insulin resistance possibly *via* genetic predisposition leading to adaptive-προσαρμογή fetal insulin secretion and therefore, influencing birth weight.