

## BACKGROUND

Betatrophin is a member of the angiopoietin-like protein family (ANGPTL), and is also known as ANGPTL8, lipasin, RIFL (Refeeding-Induced Fat and Liver) and hepatocellular carcinoma-associated protein TD26. In human, betatrophin is predominantly produced by the liver, with a smaller amount produced by the adipose tissue. In mice, betatrophin has been shown to significantly improve beta cell function and glucose tolerance. To date, we have evidence to support a relationship between betatrophin and insulin resistance (IR). Increased betatrophin concentrations have been shown in type 2 diabetes, obesity and gestational diabetes mellitus (GDM). During pregnancy, IR is known to increase due to the antagonistic effects of hormones produced by the placenta on insulin action; these hormones include: chorionic gonadotropin, growth hormone, adrenocorticotrophic hormone, placental lactogen, prolactin, estrogens and progesterones. Hyperplasia of beta cells prevents this IR from leading to the development of diabetes. Pregnancy is also a period of remarkably impaired lipid profiles; specifically, in both human and animal models, betatrophin has been shown to be involved in the regulation of lipid metabolism, especially triglycerides (TG)

## AIM

The aim of our study was to evaluate the role of betatrophin in IR and function of beta cells during pregnancy in healthy women.

## SUBJECTS AND METHODS

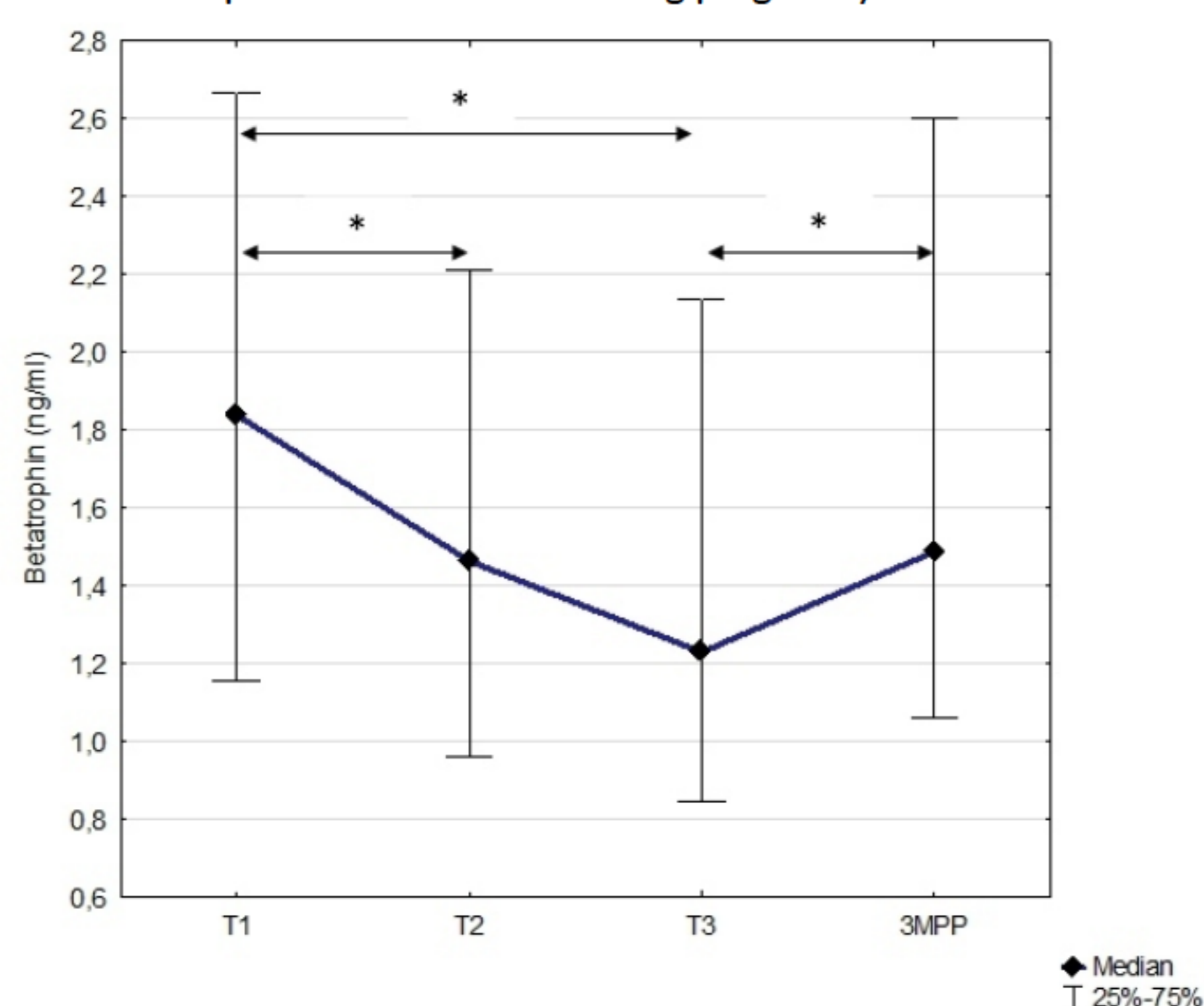
We examined 80 healthy pregnant women in each trimester (T1- first, T2-second, T3-third trimester), with 45 of the cohort also examined 3 months postpartum (3MPP). Our control group comprised 30 non-pregnant healthy women (HW) of reproductive age. We measured the levels of betatrophin (ELISA), glucose (enzymatic method with hexokinase), insulin (IRMA), C-peptide (EASIA), HbA1c (HPLC), and calculated HOMA-IR and HOMA%β.

## RESULTS

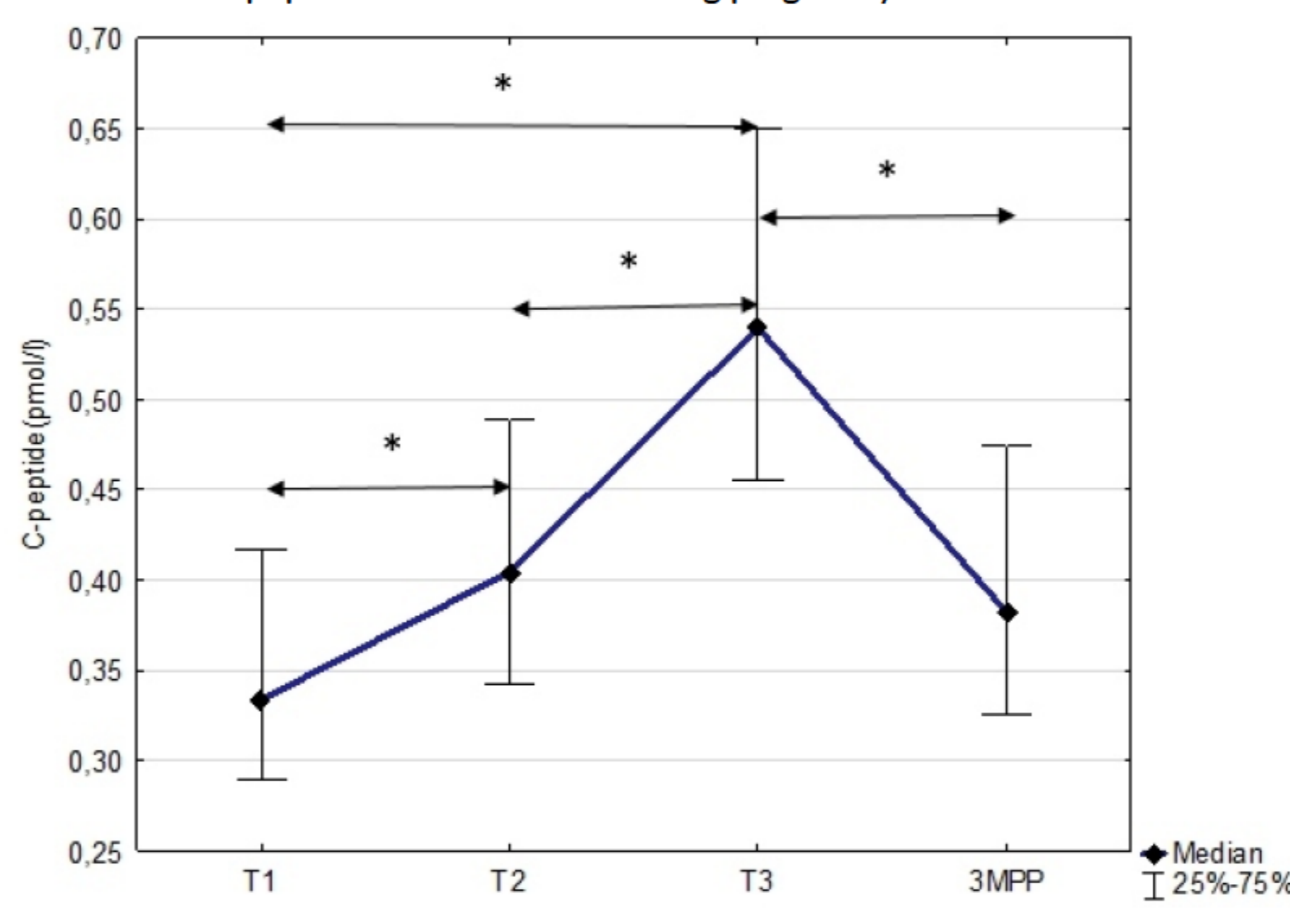
	T1 (n=80)	T2 (n=80)	T3 (n=80)	3MPP (n=45)
Age (years)	30.0 (7.0)			
BMI (kg/m <sup>2</sup> )	Before pregnancy 21.6 (2.9)	N/A	N/A	23.2 (4.0)
Gestational age (week)	11.0 (3.0)	21.0 (3.0)	33.0 (2.5)	N/A
Weight (kg)	63.0 (12.0)*	67.0 (11.0)**	74.8 (11.5)***	64.0 (11.0)
Weight gain (kg)	1.9 (2.8)*	5.5 (3.8)**	12.0 (7.0)***	3.0 (4.0)
Betatrophin (ng/ml)	1.8 (1.5)*	1.5 (1.3)	1.2 (1.3)***	1.5 (1.5)
Fasting glucose (mg/dl)	83.0 (8.5)	80.0 (8.0)	80.0 (7.0)***	87.0 (7.0)****
HbA1c (%)	4.9 (0.4)	4.8 (0.4)	4.9 (0.4)***	5.2 (0.4)****
Fasting insulin (μIU/ml)	8.6 (3.3)	9.0 (3.4)	11.3 (5.3)***	6.2 (2.4)****
C-peptide 0' (pmol/l)	0.3 (0.1)*	0.4 (0.2)**	0.5 (0.2)***	0.4 (0.2)
HOMA-IR	1.8 (0.8)	1.8 (0.7)	2.3 (1.1)***	1.4 (0.6)
HOMA-B (%)	157.7 (84.8)*	206.9 (93.6)	227.7 (140.8)***	92.5 (37.3)****
Cholesterol (mg/dl)	176.5 (40.5)*	234.5 (46.5)**	262.0 (52.0)***	198.5 (49.5)
LDL cholesterol (mg/dl)	92.0 (32.5)*	135.0 (50.0)**	162.0 (59.0)***	110.0 (50.0)****
HDL cholesterol (mg/dl)	70.0 (17.5)*	83.5 (18.5)	79.0 (20.0)***	70.0 (19.0)
Triglycerides (mg/dl)	86.0 (32.5)*	132.5 (60.5)**	193.0 (83.0)***	59.5 (38.0)
TSH (μIU/ml)	0.8 (0.9)*	1.4 (0.8)	1.3 (1.0)	1.2 (0.8)****
fT3 (pg/ml)	3.2 (0.4)*	2.9 (0.4)	2.9 (0.4)	2.9 (0.4)****
fT4 (ng/ml)	1.1 (0.2)*	1.0 (0.1)	0.9 (0.1)***	1.0 (0.1)****

Note: N/A-not applicable. Statistically significant (P<0.05) differences between: \* first (T1) and second trimester (T2); \*\* second (T2) and third trimester (T3); \*\*\* third trimester (T3) and 3 months postpartum (3MPP); \*\*\*\* first trimester (T1) and 3 months postpartum (3MPP). Values for median (interquartile range) are presented.

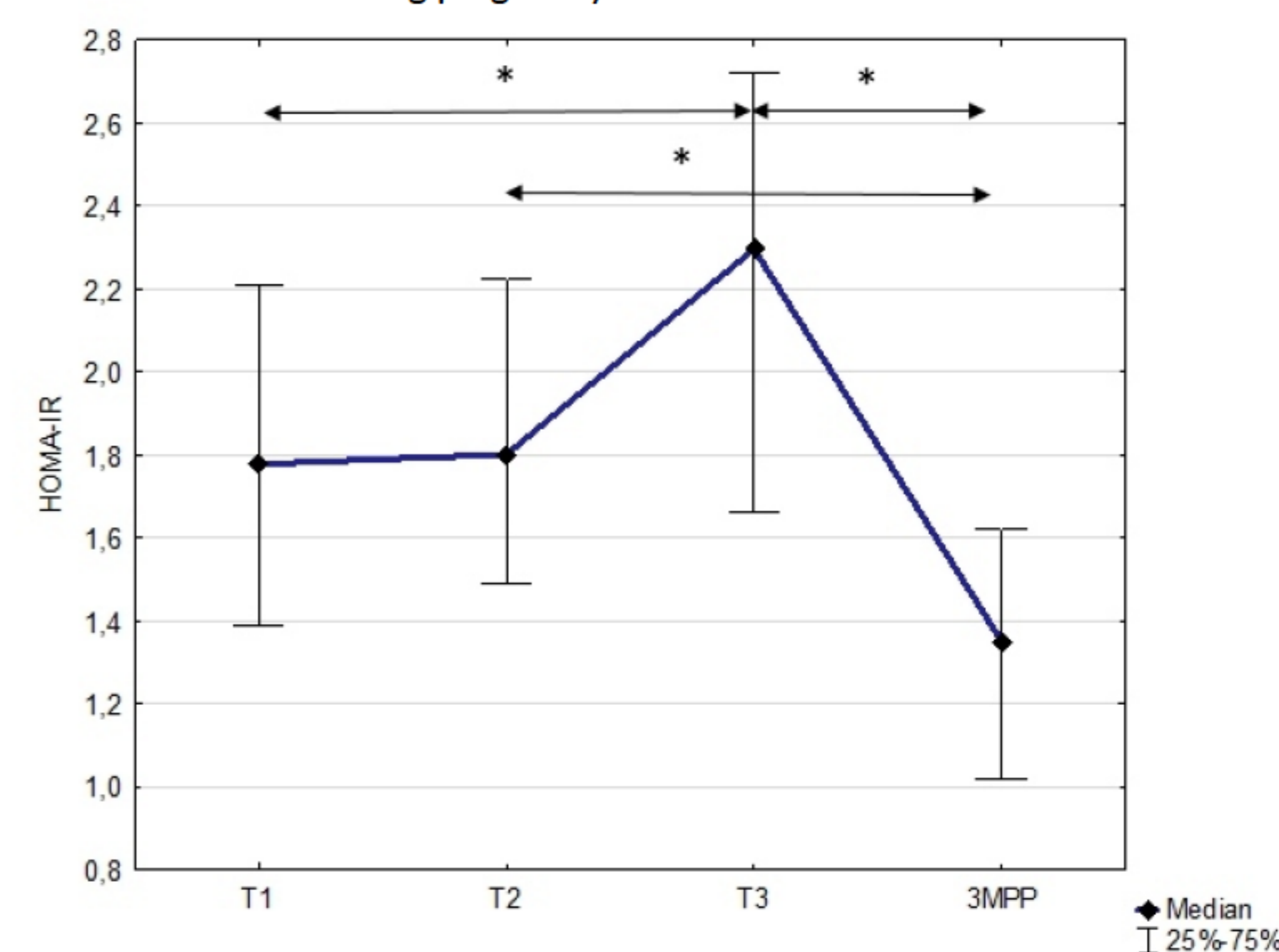
Serum betatrophin concentrations during pregnancy and 3MPP \*P<0.05



Serum C-peptide concentrations during pregnancy and 3MPP \*P<0.05



HOMA-IR during pregnancy and 3MPP \*P<0.05



	3MPP (n=45)	HW (n=30)	p value
Age (years)	30.0 (7.0)	33.0 (14.0)	Ns
BMI (kg/m <sup>2</sup> )	23.2 (4.0)	22.1 (4.5)	Ns
Weight (kg)	64.0 (11.0)	62.0 (11.0)	Ns
Betatrophin (ng/ml)	1.5 (1.5)	1.5 (1.8)	Ns
HbA1c (%)	5.2 (0.4)	5.2 (0.3)	Ns
C-peptide 0' (pmol/l)	0.4 (0.2)	0.5 (0.2)	<b>p=0.001</b>
HOMA-IR	1.4 (0.6)	1.5 (1.3)	Ns
HOMA-B (%)	92.5 (37.3)	88.9 (68.0)	Ns
Glucose 0' (mg/dl)	87.0 (10.0)	86.0 (6.0)	Ns
Glucose 1h (mg/dl)	104.0 (40.0)	121.5 (51.0)	Ns
Glucose 2h (mg/dl)	91.0 (26.0)	94.5 (19.0)	Ns
Glucose AUC	11460.0 (3150.0)	12915.0 (3840.0)	Ns
Insulin 0 (μIU/ml)	7.0 (2.0)	6.7 (6.1)	Ns
Insulin 1h (μIU/ml)	35.6 (31.6)	35.5 (30.6)	Ns
Insulin 2h (μIU/ml)	23.5 (14.5)	21.6 (31.4)	Ns
Insulin AUC	3048.0 (2271.0)	3060.0 (3250.0)	Ns
IS <sub>120</sub>	8.5 (3.7)	8.3 (7.1)	Ns
DI <sub>O<sub>GT</sub></sub>	2.2 (1.0)	2.1 (0.7)	Ns
Cholesterol (mg/dl)	198.5 (49.5)	183.0 (55.0)	Ns
LDL cholesterol (mg/dl)	110.0 (50.0)	105.0 (42.0)	Ns
HDL cholesterol (mg/dl)	70.0 (19.0)	67.5 (24.0)	Ns
Triglycerides (mg/dl)	59.5 (38.0)	60.0 (42.0)	Ns

	T2	3MPP	P value
Glucose 0' (mg/dl)	79.0 (7.0)	87.0 (10.0)	<b>&lt;0.001</b>
Glucose 1h (mg/dl)	114.0 (41.0)	104.0 (40.0)	0.7
Glucose 2h (mg/dl)	105.0 (32.0)	91.0 (26.0)	<b>0.002</b>
Glucose AUC	12540.0 (2910.0)	11460.0 (3030.0)	0.8
Insulin 0 h (μIU/ml)	8.6 (3.3)	7.2 (2.2)	<b>0.004</b>
Insulin 1h (μIU/ml)	60.6 (46.0)	35.6 (26.3)	<b>0.001</b>
Insulin 2h (μIU/ml)	51.5 (46.8)	23.5 (14.6)	<b>&lt;0.001</b>
Insulin AUC	5134.0 (3668.9)	3048.3 (1988.5)	<b>&lt;0.001</b>
IS <sub>O<sub>GT</sub></sub>	6.0 (2.9)	8.5 (3.7)	<b>0.005</b>
DI <sub>120</sub>	2.6 (1.0)	2.2 (1.0)	<b>0.01</b>

## CORRELATIONS

	T1	T2	T3	3MPP
DI <sub>120</sub>	ns	r=0,25 p=0,004	ns	ns
Weight	ns	ns	ns	r=0,23 p=0,03
Weight gain	r=0,25 p=0,03	r=0,27 p=0,01	ns	ns
Age	r= -0,23 p=0,03	ns	ns	ns
TSH	r=0,24 p=0,03	ns	ns	ns
fT <sub>4</sub>	r= -29 p=0,01	ns	ns	ns

## CONCLUSIONS

In conclusion, we observed the level of betatrophin to decrease during pregnancy, despite an increase in IR and beta cell function, as evaluated by C-peptide and insulin concentrations. These results suggest that betatrophin does not play a significant role in the expansion of the beta cell mass and IR during pregnancy. Further studies are needed to establish the factors influencing betatrophin levels during each trimester of pregnancy.

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