Lower Free Thyroxin Associates with a Less Favorable Metabolic Phenotype in Healthy Pregnant Women

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Context: A lower free T_4 (fT4), within the euthyroid range, has been shown in adults to associate with an adverse metabolic phenotype. Thyroid physiology changes significantly during gestation and affects maternal and fetal well-being.

Objective: The aim of the study was to test the hypothesis that a lower serum fT4 in healthy euthyroid pregnant women is related to a less favorable metabolic phenotype and to fetal or placental weight.

Design, Setting, Patients, and Outcome Measures: We examined associations of thyroid function tests (TSH and fT4) and the free T_3 (fT3)-to-fT4 ratio (as a proxy of deiodinase activity) with a metabolic profile [preload and postload glucose, glycosylated hemoglobin (HbA1c), high molecular-weight (HMW)-adiponectin, homeostasis model of assessment for insulin resistance (HOMA-IR), and serum lipids] in 321 healthy pregnant women. All women were euthyroid and had negative anti-thyroid peroxidase antibodies. None received thyroid hormone replacement. Blood tests were performed in women between 24 and 28 wk gestation. Placentas and newborns were weighed at birth.

Results: Circulating TSH did not relate to metabolic parameters, but decreasing fT4 and increasing fT3-to-fT4 ratio associated with a less favorable metabolic phenotype, as judged by higher postload glucose, HbA1c, fasting insulin, HOMA-IR, and triglycerides, and by a lower HMW-adiponectinemia (all $P \leq 0.005$). In multiple regression analyses, fT4 was independently associated with HbA1c ($\beta = -0.135$; $P = 0.038$), HMW-adiponectin ($\beta = 0.218$; $P < 0.001$), and placental weight ($\beta = -0.185$; $P < 0.005$), whereas the fT3-to-fT4 ratio was independently associated with maternal body mass index ($\beta = 0.265$; $P < 0.001$), HMW-adiponectinemia ($\beta = -0.237$; $P < 0.002$), HOMA-IR ($\beta = 0.194$; $P = 0.014$), and placental weight ($\beta = 0.174$; $P = 0.020$).

Conclusion: In pregnant women without a history of thyroid dysfunction, lower concentrations of fT4 and a higher conversion of fT4 to fT3, as inferred by changes in the fT3-to-fT4 ratio, were found to be associated with a less favorable metabolic phenotype and with more placental growth. (***J Clin Endocrinol Metab*** **96: 3717–3723, 2011)**

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Abbreviations: BMI, Body mass index; CV, coefficient of variation; fT3, free T_3; fT4, free T_4; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HMW, high molecular weight; HOMA-IR, homeostasis model of assessment for insulin resistance.

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Thyroid hormones play pivotal roles in metabolic processes. Most effects are related to their pleiotropic effects on energy homeostasis, which include the stimulation of resting metabolic rate, increase in ATP expenditure, and modulation of responsiveness to catecholamines (1). Modulation by thyroid hormone of AMP-activated protein kinase—a conserved regulator of the cellular response to low energy (2)—and of lipid metabolism in the hypothalamus are thought to be major regulatory pathways of whole-body energy homeostasis, including thermogenesis in adipose tissue (3).

Studies in the last decade have shown that even physiological variations in thyroid function are related to markers of metabolic dysfunction (4–9). Whereas these associations are well recognized in euthyroid adults, evidence regarding such a relationship in pregnant women is lacking.

In a homeostatic way to ensure maternal and fetal well-being, TSH decreases transiently during the first trimester of pregnancy and increases thereafter (without attaining pregravid levels), with similar but inverse changes in serum free T_4 (fT4) and free T_3 (fT3) (10, 11). The placenta regulates the amount of thyroid hormones available for the fetus, allowing transfer of both T_4 and T_3 from the maternal into the fetal circulation, and also by actively converting T_4 into T_3 and inactivating both thyroid hormones by tissue deiodinases (12).

We hypothesized that a lower serum fT4 and/or a higher TSH is related in euthyroid pregnant women to a less favorable metabolic phenotype. In the present study, we examined associations of thyroid function tests [TSH and fT4] and the fT3-to-fT4 ratio (as a proxy of deiodinase activity (13, 14) with a metabolic profile, including preload and postload glucose, glycosylated hemoglobin (HbA1c), high molecular-weight (HMW)-adiponectin, homeostasis model of assessment for insulin resistance (HOMA-IR), and serum lipids, in healthy pregnant women. As an additional aim, we studied whether thyroid function associates with weight of both the placenta and the newborn.

Subjects and Methods

Study population and ethics

Subjects were 321 Caucasian women with singleton pregnancies included in a prenatal cohort of cardiovascular risk factors in healthy infants. Cross-sectional data at the end of the second trimester (between 24 and 28 wk gestation; for laboratory variables) and at the end of the third trimester of pregnancy (for clinical characteristics) are presented in this report.

Pregnant women were consecutively recruited among those seen at the prenatal primary care clinics in Alt Empordà, a region in northern Spain. All women were of Caucasian origin and had uncomplicated pregnancy and parturition (no major medical, surgical, or obstetrical complications). Women with multiple pregnancies, gestational diabetes, preeclampsia, and fetal malformations or asphyxia were excluded. Women with self-reported history of thyroid disease, including goiter, overt hypothyroidism or hyperthyroidism, and known thyroid cancer or nodules were also excluded. The final cohort included 370 pregnant women (Fig. 1). Of these, 49 pregnant women with positive anti-thyroid peroxidase antibodies were additionally excluded from the study because thyroid antibodies have been associated with impaired gestational glucose tolerance (15). All women finally included in the present study (n = 321) were euthyroid, and none received thyroid hormone replacement. As part of routine practice in our area, all women were advised to supplement their diet with iodine pills (200 μg iodine per day) across gestation. Smoking was defined as consumption of one or more cigarettes per day during pregnancy.

The protocol was approved by the Institutional Review Board of Dr. Josep Trueta Hospital. Informed written consent was obtained from the women.

Assessments and samples

A close prenatal follow-up, consisting of protocolized clinical exams, ultrasonograms, and laboratory tests (urine and blood), were performed in all subjects. Information on maternal sociodemographic, medical, and reproductive characteristics, and labor and delivery characteristics was abstracted from standardized medical records. Gestational age was based on the last menstrual period and, when possible, was confirmed by ultrasound examination performed before 20 wk gestation.

Maternal weight and height were assessed at the end of the third trimester, before delivery. Body mass index (BMI) was calculated as weight divided by height squared. Systolic and diastolic blood pressure were measured in the sitting position on the right arm after a 10-min rest; an electronic sphygmomanometer (Dinamap ProCare 100; GE Healthcare, Chalfont St. Giles, UK) was used.

Placentas from the studied women were collected and weighed immediately after delivery. Neonates were studied within the

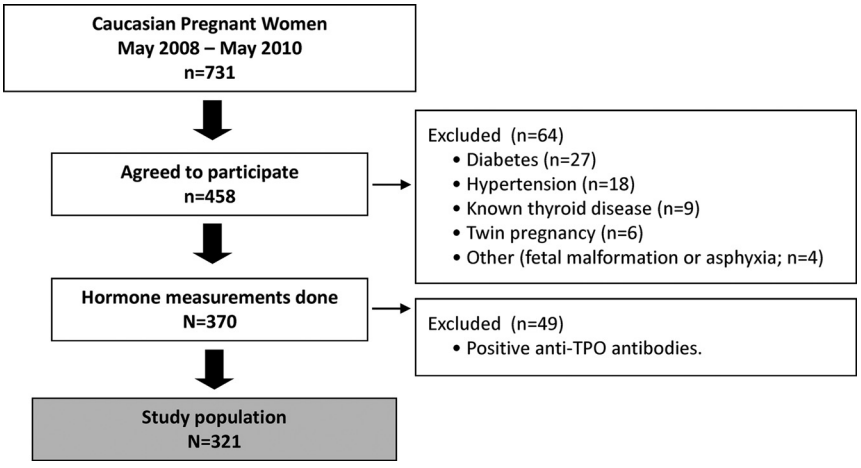

FIG. 1. Recruitment of the study population. TPO, Thyroid peroxidase.

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first hours after birth. Weight and length were measured, respectively, using a calibrated scale for weight and a standardized metal measuring board. Gestational age- and sex-adjusted SD scores for birth weight and length were calculated using regional normative data (16).

Analytical methods

Blood tests were performed in women between 24 and 28 wk gestation. All serum samples were obtained under fasting conditions. Serum glucose was analyzed by the hexokinase method. Serum immunoreactive insulin was measured by immunochemiluminescence (Immulite 2000; Diagnostic Products, Los Angeles, CA). The lower detection limit was 0.4 mIU/liter, and intra- and interassay coefficients of variation (CV) were less than 10%. Fasting insulin sensitivity was estimated from fasting insulin and glucose levels using the following formula: HOMA-IR = (fasting insulin in mU/liter) × (fasting glucose in mM)/22.5. HMW-adiponectin was measured by sandwich ELISA (Linco, St. Charles, MO). The detection limit was 0.5 ng/ml, and CV was less than 4%. Total serum triglycerides were measured by monitoring the reaction of glycerol-phosphate-oxidase and peroxidase. High-density lipoprotein (HDL) cholesterol was quantified by the homogeneous method of selective detergent with accelerator. TSH, fT4, and fT3 serum concentrations were measured by chemiluminescent microparticle immunoassays (Abbott Laboratories, Abbott Park, IL), with detection limits of 0.01 mIU/liter, 5.2 pmol/liter, and 1.5 pmol/liter, respectively; CV were less than 5, 8, and 10%, respectively . Reference values for early third trimester of pregnancy (between 24 and 30 wk gestation) in European women are: TSH, 0.31 to 2.76 mIU/liter; fT4, 9.3 to 13.7 pmol/liter; and fT3, 3.4 to 5.5 pmol/liter (17).

Oral glucose tolerance tests, with fasting and 1-h timed blood glucose measurements after a 50-g oral glucose load, were performed in all participants.

Statistics

Statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL). Results are expressed as mean ± SEM. Nonparametric variables were mathematically transformed to improve symmetry. The relation between variables of interest was analyzed by simple correlation followed by multiple regression in a stepwise manner.

In this study, bivariate analyses were in part exploratory, and therefore a P value of 0.005 (derived from the Bonferroni correction: 0.05/10 variables or groups of highly correlated variables) was deemed significant in these analyses. Multivariate analyses, however, were rather confirmatory, and the conventional significance level of $P < 0.05$ was chosen to avoid type II statistical errors.

Results

Table 1 shows the results of the clinical and metabolic parameters in the studied subjects.

TABLE 1. Anthropometrical and biochemical parameters in healthy pregnant women and neonatal characteristics at birth

Mothers (n = 321)	
Age (yr)	30.5 ± 0.3
Weight (kg)	76.9 ± 0.6
BMI (kg/m^2)	28.9 ± 0.2
SBP (mm Hg)	118 ± 1
DBP (mm Hg)	69 ± 1
Smokers, n (%)	51 (16)
Fasting glucose (mg/dl)	79 ± 1
Postload glucose (mg/dl)	118 ± 2
HbA1c (%)	5.0 ± 0.1
HMW-adiponectin (mg/liter)	5.9 ± 0.2
Fasting insulin (mIU/liter)	5.7 ± 0.3
HOMA-IR	1.15 ± 0.1
Triglyceride (mg/dl)	164 ± 3
Total cholesterol (mg/dl)	260 ± 2
LDL cholesterol (mg/dl)	155 ± 2
HDL cholesterol (mg/dl)	72 ± 1
TSH (mIU/liter)[a]	1.91 ± 0.04
fT4 (pmol/liter)[a]	11.5 ± 0.1
fT3 (pmol/liter)[a]	4.3 ± 0.1
Newborns (n = 321)	
Sex (female), n (%)	151 (47)
Gestational age (wk)	39.6 ± 0.1
Weight (g)	3300 ± 20
Weight SDS	0.1 ± 0.1
Height (cm)	50 ± 1
Height SDS	−0.2 ± 0.1
Placental weight (g)	610 ± 9

Data are shown as mean ± SEM, unless described otherwise. SBP, Systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density-lipoprotein; SDS, SD score.

[a] Reference values for early third trimester of pregnancy (between 24 and 30 wk gestation) in European women are: TSH, 0.31 to 2.76 mIU/liter; fT4, 9.3 to 13.7 pmol/liter; and fT3, 3.4 to 5.5 pmol/liter (Architect System, Abbott Laboratories).

TABLE 2. Bivariate correlations between maternal thyroid function tests and selected parameters in the studied subjects (n = 321)

	fT4		fT3-to-fT4 ratio	
	r	P	r	P
Age (yr)	−0.058	0.33	−0.049	0.41
Maternal BMI (kg/m^2)	−0.136	0.013	0.292	**<0.0001**
Fasting glucose (mg/dl)	−0.094	0.050	0.214	**<0.0001**
Postload glucose (mg/dl)	−0.159	**0.002**	0.200	**<0.0001**
HbA1c (%)	−0.231	**<0.0001**	0.230	**<0.0001**
HMW-adiponectin (mg/liter)	0.276	**<0.0001**	−0.366	**<0.0001**
Fasting insulin (mIU/liter)	−0.159	**0.002**	0.282	**<0.0001**
HOMA-IR	−0.160	**0.002**	0.291	**<0.0001**
Triglyceride (mg/dl)	−0.151	**0.003**	0.181	**0.001**
LDL-cholesterol (mg/dl)	−0.044	0.43	−0.031	0.58
HDL-cholesterol (mg/dl)	0.038	0.57	−0.090	0.13
Placental weight (g)	−0.208	**<0.0001**	0.232	**0.001**
Birth weight-SDS	−0.131	0.019	0.122	0.049
Birth length-SDS	−0.091	0.11	0.062	0.29

To account for multiple comparisons, significance was set at $P \leq 0.005$ (*boldface*) in these results. LDL, Low-density-lipoprotein; SDS, SD score.

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Bivariate analyses

Although TSH was unrelated to metabolic parameters, decreasing fT4 and increasing fT3-to-fT4 ratio were associated with a less favorable metabolic phenotype, as judged by higher postload glucose, HbA1c, fasting insulin, HOMA-IR, and triglycerides, and by a lower HMW-adiponectin (all $P \leq 0.005$; Table 2). Figure 2 shows representative associations for fT4 and fT3-to-fT4 ratio and metabolic variables.

Both decreasing fT4 and increasing fT3-to-fT4 ratio were also associated with larger placentas (both $P \leq 0.005$; Table 2).

Table 3 shows the distribution of metabolic parameters and placental weight according to the lower and upper quintiles of serum fT4 and of the fT3-to-fT4 ratio.

Multivariate analyses

In multiple regression analyses with thyroid function tests as dependent variables (Table 4), fT4 was independently explained by HbA1c ($\beta = -0.135$; $P = 0.038$), HMW-adiponectin ($\beta = 0.218$; $P < 0.001$) and placental weight ($\beta = -0.185$; $P < 0.005$), whereas the fT3-to-fT4 ratio was independently explained by maternal BMI ($\beta = 0.265$; $P < 0.0001$), HMW-adiponectin ($\beta = -0.237$; $P < 0.002$), HOMA-IR ($\beta = 0.194$; $P = 0.014$), smoking ($\beta = 0.182$; $P < 0.013$), and placental weight ($\beta = 0.174$; $P = 0.020$).

In multiple regression analyses with placental weight as dependent variable, placental weight was independently explained by maternal BMI ($\beta = -0.183$; $P = 0.006$; $R^2 = 7.5\%$), postload glucose ($\beta = 0.163$; $P = 0.014$; $R^2 = 4.2\%$), triglyceride ($\beta = 0.150$; $P = 0.024$; $R^2 = 2.1\%$), and fT4 ($\beta = -0.159$; $P = 0.016$; $R^2 = 2.6\%$). Placental weight was also independently explained by fT3-to-fT4 ratio ($\beta = 0.194$; $P = 0.010$; $R^2 = 5.1\%$) when this ratio was computed in the model instead of fT4. Nonpredictive variables in these models were maternal age, HMW-adiponectin, and HOMA-IR.

Discussion

In healthy euthyroid pregnant women, lower concentrations of fT4 and a higher fT3-to-fT4 ratio, as a proxy for

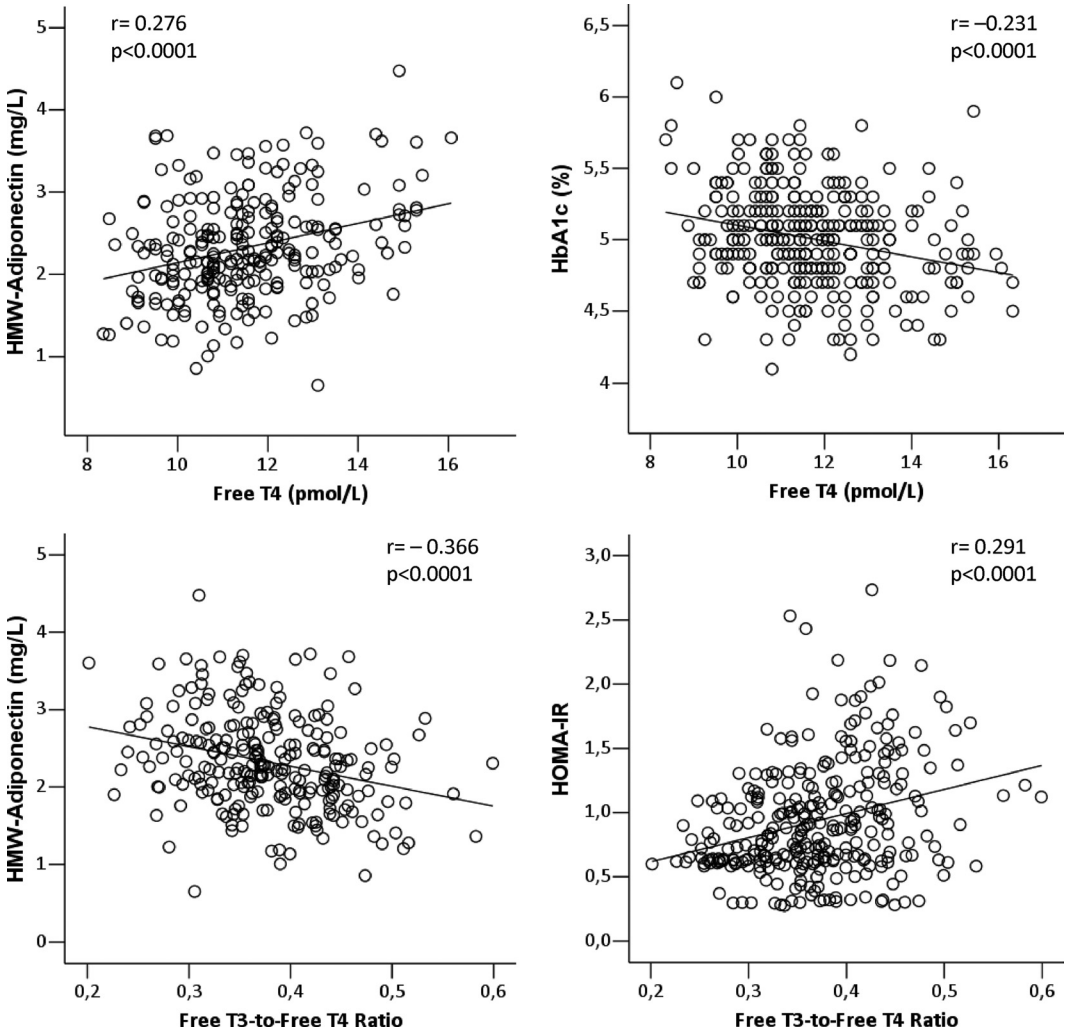

FIG. 2. Correlation graphs of fT4 and fT3-to-fT4 ratio with selected metabolic variables in healthy pregnant women. To improve symmetry, results for HMW-adiponectin and HOMA-IR have been square root-transformed.

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TABLE 3. Distribution of selected parameters according to lower and upper quintiles of serum fT4 and of fT3-to-fT4 ratio in the studied subjects

	fT4			fT3-to-fT4 ratio		
	Lower quintile (8.0 to 10.0)	**Upper quintile (12.9 to 16.3)**	***P***	**Lower quintile (0.2 to 0.3)**	**Upper quintile (0.4 to 0.6)**	***P***
n	65	64		65	64	
Age (yr)	30.5 ± 0.5	30.0 ± 0.6	0.24	30.8 ± 0.5	30.3 ± 0.8	0.52
BMI (kg/m^2)	29.7 ± 0.5	27.8 ± 0.5	**0.005**	27.4 ± 0.5	30.0 ± 0.5	**<0.0001**
Postload glucose (mg/dl)	123 ± 4	110 ± 3	0.008	114 ± 4	132 ± 4	**0.003**
HbA1c (%)	5.1 ± 0.1	4.9 ± 0.1	**<0.0001**	4.9 ± 0.1	5.1 ± 0.1	**0.0001**
HMW-adiponectin (mg/liter)	5.2 ± 0.4	6.8 ± 0.5	**0.0006**	6.9 ± 0.6	4.7 ± 0.3	**<0.0001**
Fasting insulin (mIU/liter)	7.0 ± 0.7	4.6 ± 0.6	**<0.0001**	3.5 ± 0.3	6.9 ± 0.7	**<0.0001**
HOMA-IR	1.42 ± 0.16	0.88 ± 0.10	**<0.0001**	0.66 ± 0.05	1.43 ± 0.15	**<0.0001**
Triglyceride (mg/dl)	173 ± 8	155 ± 8	0.02	148 ± 6	182 ± 9	**0.003**
TSH (mIU/liter)	2.16 ± 0.11	1.76 ± 0.10	0.01	1.88 ± 0.11	1.99 ± 0.11	0.42
fT3 (pmol/liter)	4.1 ± 0.1	4.4 ± 0.1	0.08			
Placental weight (g)	629 ± 10	564 ± 15	0.006	554 ± 19	642 ± 18	**0.0005**

To account for multiple comparisons, significance was set a $P \leq 0.005$ (*boldface*) in these results.

increased conversion of fT4 to fT3, were related to a less favorable metabolic phenotype and with placental growth.

Overt hyperthyroidism and both overt and subclinical hypothyroidism have been associated with deleterious effects in pregnancy (11). To the best of our knowledge, ours is the first study to suggest that normal variations in thyroid function may also influence the course of human pregnancy.

fT4, rather than TSH, and the fT3-to-fT4 were both related to various markers of metabolic dysfunction. Our results are in agreement with the reported negative association of fT4 with several components of metabolic syndrome in euthyroid adult subjects (4–6, 8, 9, 18). TSH may be less reflective of thyroid hormone status in pregnancy because human chorionic gonadotropin is known to act as a TSH agonist. Indeed, the concentration of human chorionic gonadotropin correlates with that of fT4 in pregnant women (11).

Consistent associations were found with HMW-adiponectin. Given that adiponectin and thyroid hormone mediate similar physiological actions, it is conceivable that adiponectin may interact with the thyroid axis. In this respect, serum total adiponectin has been reported to be positively associated with fT4 in healthy euthyroid subjects (19), in patients with chronic renal failure (20), and in thyroid cancer patients after thyroid hormone withdrawal (21). We have recently shown that secretion of HMW-adiponectin is up-regulated by thyroid hormone in human adipose tissue (22). Collectively, these data suggest that thyroid hormone and HMW-adiponectin may be linked together in the regulation of energy metabolism in human pregnancy.

Additional independent associations were found for thyroid hormones and markers of glucose tolerance and insulin resistance. It cannot be excluded that thyroid hormones, even within the euthyroid range, may have an impact on glucose metabolism in pregnant women. Although the present study did not examine causality and therefore cannot support or refute this hypothesis, the suggestion is made based on recently published experimental data. Notably, thyroid hormones are known to improve insulin sensitivity and to decrease hyperinsulinemia and hyperglycemia in animal models of type 2 diabetes (23). Among others, thyroid hormones regulate hepatic gluconeogenesis and modulate mRNA and protein expression of glucose transporters (24, 25). In skeletal muscle and in the brain,

TABLE 4. Multiple linear regression models of maternal thyroid function tests as dependent variables in the studied subjects

	fT4			fT3-to-fT4 ratio		
	β	***P***	***R^2***	***β***	***P***	***R^2***
Maternal BMI (kg/m^2)				0.265	0.001	14.6%
HbA1c (%)	−0.135	0.038	1.4%			
HMW-adiponectin (mg/liter)	0.218	0.001	6.3%	−0.237	0.002	8.7%
HOMA-IR				0.194	0.014	4.5%
Smoking				0.182	0.013	2.6%
Placental weight (g)	−0.185	0.005	3.4%	0.174	0.020	2.9%

Nonpredictive variables are maternal age, fasting or postload glucose, and serum lipids.

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thyroid hormones are known to regulate the activity of AMP-activated protein kinase (3, 26). In a recent clinical study, thyroid hormone at TSH-suppressive doses ameliorated insulin resistance and glucose intolerance in a subject with a mutation in the insulin-receptor gene (27).

We have chosen the fT3-to-fT4 ratio as a proxy for increased conversion of fT4 to fT3 (13, 14). Of note, type 2 iodothyronine deiodinase—which is the major source of plasma T_3 in euthyroid humans (28)—is induced during pregnancy (29). As previously shown, the activity of type 2 deiodinase increases when the availability of T_4 decreases, which seems to depend on a signal from the T_4 molecule *per se* to maintain intracellular and/or circulating T_3 pools (30). Lower concentrations of fT4 could thus be compensated with a higher conversion to T_3 in healthy pregnant women.

It is well known that smoking can affect thyroid hormone levels (31). In multivariate analysis, smoking was an independent explanatory factor of the fT3-to-fT4 ratio. These findings are in line with recent results showing that fT3 is associated with smoking, even after accounting for the effect of obesity, body fat distribution, insulin, and metabolic parameters (18, 32).

Thyroid function within the euthyroid range was also associated with placental growth, independent from common confounders, such as maternal BMI and serum glucose and lipid concentrations (33). Although similar findings have been recently reported (34), the negative association of fT4 and the positive association of fT3-to-fT4 with placental weight were rather unexpected because gestational hypothyroidism has negative effects on the birth weight of offspring (35, 36). However, others have described direct toxic effects of thyroid hormones on fetal development (37). Finally, it cannot be excluded that larger placentas in pregnant women with lower serum fT4 concentrations may result from a compensatory mechanism to ensure adequate thyroid hormone transfer to the fetus. Alternatively, larger placentas may result in increased placental deiodinase activity, which will explain the negative association with fT4 and positive association with fT3-to-fT4 ratio.

We acknowledge a number of limitations in our study. The measurement of free thyroid hormone by commercial assays is limited by the fact that results are highly method- and trimester-specific and are only an estimate of results obtained using more laborious methodologies, such as equilibrium dialysis or ultrafiltration. The assays used in the present study for fT4 and fT3 are two-step immunoassays that may be less prone to artifact (38). Maternal volume expansion in the second trimester of pregnancy may be a confounding factor in association studies of soluble biomarkers (39). Although we did not measure maternal plasma volume in this cohort of pregnant women, all the reported associations in the present study were adjusted for BMI, a common correlate of maternal plasma volume, and were not significantly affected by further adjusting for additional correlates, such as maternal height (data not shown). Although we excluded women with readily detectable thyroid autoimmunity, we cannot rule out the possibility that antibody-positive women were still present in our study because antibody titers may become undetectable toward term due to the general immunosuppressive state of pregnancy. Another study limitation is the normality of our study population. This limitation does not allow us to speculate on the potential link between thyroid status and energy metabolism, for example, in women with gestational diabetes.

In summary, in pregnant women without a history of thyroid dysfunction, lower concentrations of fT4 and a higher conversion of fT4 to fT3, as inferred by changes in the fT3-to-fT4 ratio, are associated with a less favorable metabolic phenotype and with placental growth.

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References

1. **Krotkiewski M** 2002 Thyroid hormones in the pathogenesis and treatment of obesity. Eur J Pharmacol 440:85–98
2. **Lage R, Diéguez C, Vidal-Puig A, López M** 2008 AMPK: a metabolic gauge regulating whole-body energy homeostasis. Trends Mol Med 14:539–549
3. **López M, Varela L, Vázquez MJ, Rodríguez-Cuenca S, González CR, Velagapudi VR, Morgan DA, Schoenmakers E, Agassandian K, Lage R, Martínez de Morentin PB, Tovar S, Nogueiras R, Carling D, Lelliott C, Gallego R, Oresic M, Chatterjee K, Saha AK, Rahmouni K, Diéguez C, Vidal-Puig A** 2010 Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. Nat Med 16:1001–1008

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4. **Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, Jørgensen T** 2005 Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90:4019–4024
5. **Fernández-Real JM, López-Bermejo A, Castro A, Casamitjana R, Ricart W** 2006 Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. J Clin Endocrinol Metab 91:3337–3343
6. **Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH** 2007 Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab 92:491–496
7. **Kim BJ, Kim TY, Koh JM, Kim HK, Park JY, Lee KU, Shong YK, Kim WB** 2009 Relationship between serum free T4 (FT4) levels and metabolic syndrome (MS) and its components in healthy euthyroid subjects. Clin Endocrinol (Oxf) 70:152–160
8. **Ambrosi B, Masserini B, Iorio L, Delnevo A, Malavazos AE, Morricone L, Sburlati LF, Orsi E** 2010 Relationship of thyroid function with body mass index and insulin-resistance in euthyroid obese subjects. J Endocrinol Invest 33:640–643
9. **Garduño-Garcia Jde J, Alvirde-Garcia U, López-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM, Gomez-Perez FJ, Aguilar-Salinas CA** 2010 TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol 163:273–278
10. **Larsson A, Palm M, Hansson LO, Axelsson O** 2008 Reference values for clinical chemistry tests during normal pregnancy. BJOG 115:874–881
11. **Lazarus JH** 2011 Thyroid function in pregnancy. Br Med Bull 97: 137–148
12. **Burrow GN, Fisher DA, Larsen PR** 1994 Maternal and fetal thyroid function. N Engl J Med 331:1072–1078
13. **Nicoloff JT, Lum SM, Spencer CA, Morris R** 1984 Peripheral autoregulation of thyroxine to triiodothyronine conversion in man. Horm Metab Res Suppl 14:74–79
14. **Keck FS, Loos U** 1988 Peripheral autoregulation of thyromimetic activity in man. Horm Metab Res 20:110–114
15. **Fernandez-Soto L, Gonzalez A, Lobón JA, Lopez JA, Peterson CM, Escobar-Jiménez F** 1997 Thyroid peroxidase autoantibodies predict poor metabolic control and need for thyroid treatment in pregnant IDDM women. Diabetes Care 20:1524–1528
16. **Carrascosa-Lezcano A, Fernández-García JM, Ferrández-Longás A, López-Siguero JP, Sánchez-González E (eds)** 2008 Spanish cross-sectional growth study. 1st ed. Barcelona: Pfizer, S.A.
17. **Stricker R, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA, Stricker R** 2007 Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. Eur J Endocrinol 157:509–514
18. **De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R** 2007 Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf) 67:265–269
19. **Fernández-Real JM, López-Bermejo A, Casamitjana R, Ricart W** 2003 Novel interactions of adiponectin with the endocrine system and inflammatory parameters. J Clin Endocrinol Metab 88:2714–2718
20. **Malyszko J, Malyszko J, Wolczynski S, Mysliwiec M** 2006 Adiponectin, leptin and thyroid hormones in patients with chronic renal failure and on renal replacement therapy: are they related? Nephrol Dial Transplant 21:145–152
21. **Lin SY, Huang SC, Sheu WH** 2010 Circulating adiponectin concentrations were related to free thyroxine levels in thyroid cancer patients after thyroid hormone withdrawal. Metabolism 59:195–199
22. **Prats-Puig A, Sitjar C, Ribot R, Calvo M, Clausell-Pomés N, Soler-Roca M, Soriano-Rodríguez P, Osiniri I, Ros-Miquel M, Bassols J, de Zegher F, Ibáñez L, López-Bermejo A** 7 July 2011 Relative hypoadiponectinemia, insulin resistance, and increased visceral fat in euthyroid prepubertal girls with low-normal serum free thyroxine. Obesity (Silver Spring) doi: 10.1038/oby.2011.206
23. **Lin Y, Sun Z** 2011 Thyroid hormone potentiates insulin signaling and attenuates hyperglycemia and insulin resistance in a mouse model of type 2 diabetes. Br J Pharmacol 162:597–610
24. **Shimizu Y, Shimazu T** 2002 Thyroid hormone augments GLUT4 expression and insulin-sensitive glucose transport system in differentiating rat brown adipocytes in culture. J Vet Med Sci 64:677–681
25. **Dimitriadis G, Maratou E, Alevizaki M, Boutati E, Psara K, Papasteriades C, Raptis SA** 2005 Thyroid hormone excess increases basal and insulin-stimulated recruitment of GLUT3 glucose transporters on cell surface. Horm Metab Res 37:15–20
26. **Crunkhorn S, Patti ME** 2008 Links between thyroid hormone action, oxidative metabolism, and diabetes risk? Thyroid 18:227–237
27. **Skarulis MC, Celi FS, Mueller E, Zemskova M, Malek R, Hugendubler L, Cochran C, Solomon J, Chen C, Gorden P** 2010 Thyroid hormone induced brown adipose tissue and amelioration of diabetes in a patient with extreme insulin resistance. J Clin Endocrinol Metab 95:256–262
28. **Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR** 2005 Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest 115:2524–2533
29. **Galton VA, Martinez E, Hernandez A, St Germain EA, Bates JM, St Germain DL** 2001 The type 2 iodothyronine deiodinase is expressed in the rat uterus and induced during pregnancy. Endocrinology 142:2123–2128
30. **Hidal JT, Kaplan MM** 1985 Characteristics of thyroxine 5′-deiodination in cultured human placental cells. Regulation by iodothyronines. J Clin Invest 76:947–955
31. **Asvold BO, Bjøro T, Nilsen TI, Vatten LJ** 2007 Tobacco smoking and thyroid function: a population-based study. Arch Intern Med 167:1428–1432
32. **Shields B, Hill A, Bilous M, Knight B, Hattersley AT, Bilous RW, Vaidya B** 2009 Cigarette smoking during pregnancy is associated with alterations in maternal and fetal thyroid function. J Clin Endocrinol Metab 94:570–574
33. **Herrera E, Ortega-Senovilla H** 2010 Disturbances in lipid metabolism in diabetic pregnancy—are these the cause of the problem? Best Pract Res Clin Endocrinol Metab 24:515–525
34. **Shields BM, Knight BA, Hill A, Hattersley AT, Vaidya B** 2011 Fetal thyroid hormone level at birth is associated with fetal growth. J Clin Endocrinol Metab 96:E934–E938
35. **Alvarez-Pedrerol M, Guxens M, Mendez M, Canet Y, Martorell R, Espada M, Plana E, Rebagliato M, Sunyer J** 2009 Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. Eur J Endocrinol 160:423–429
36. **Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG** 2005 Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 105:239–245
37. **Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S** 2004 Fetal loss associated with excess thyroid hormone exposure. JAMA 292:691–695
38. **Lazarus JH, Soldin OP, Evans C** 2010 Assessing thyroid function in pregnancy. In: Brent GA, ed. Thyroid function testing. New York: Springer; 209–233
39. **Faupel-Badger JM, Hsieh CC, Troisi R, Lagiou P, Potischman N** 2007 Plasma volume expansion in pregnancy: implications for biomarkers in population studies. Cancer Epidemiol Biomarkers Prev 16:1720–1723

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