

Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters

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Abstract

Objective: Subclinical hypothyroidism and isolated hypothyroxinaemia in pregnancy have been associated with an increased risk of gestational diabetes. We aimed to ascertain if these women have a worse metabolic phenotype than euthyroid pregnant women.

Design, subjects and methods: We recruited 956 healthy Caucasian women with singleton, non-diabetic pregnancies from routine antenatal clinics. Detailed anthropometric measurements (including BMI and skinfold thickness) and fasting blood samples (for TSH, free thyroxine (FT₄), free triiodothyronine (FT₃), HbA1c, lipid profile, plasma glucose and insulin resistance (HOMA-IR) analysis) were obtained at 28 weeks gestation.

Results: In comparison to euthyroid women ($n=741$), women with isolated hypothyroxinaemia ($n=82$) had significantly increased BMI (29.5 vs 27.5 kg/m², $P<0.001$), sum of skinfolds (57.5 vs 51.3 mm, $P=0.002$), fasting plasma glucose (4.5 vs 4.3 mmol/l, $P=0.01$), triglycerides (2.3 vs 2.0 mmol/l, $P<0.001$) and HOMA-IR (2.0 vs 1.3, $P=0.001$). Metabolic parameters in women with subclinical hypothyroidism ($n=133$) were similar to those in euthyroid women. Maternal FT₄ was negatively associated with BMI ($r=-0.22$), HbA1c ($r=-0.14$), triglycerides ($r=-0.17$), HOMA-IR ($r=-0.15$) but not total/HDL cholesterol ratio ($r=-0.03$). Maternal FT₃:FT₄ ratio was positively associated with BMI ($r=0.4$), HbA1c ($r=0.21$), triglycerides ($r=0.2$), HOMA-IR ($r=0.33$) and total/HDL cholesterol ratio ($r=0.07$). TSH was not associated with the metabolic parameters assessed.

Conclusions: Isolated hypothyroxinaemia, but not subclinical hypothyroidism, is associated with adverse metabolic phenotype in pregnancy, as is decreasing maternal FT₄ and increasing FT₃:FT₄ ratio. These associations may be a reflection of changes in the thyroid hormone levels secondary to increase in BMI rather than changes in thyroid hormone levels affecting body weight and related metabolic parameters.

European Journal of
Endocrinology
(2016) 174, 51–57

Introduction

Recently, increasing numbers of studies have shown associations between mild maternal thyroid hormone insufficiency (including subclinical hypothyroidism and isolated hypothyroxinaemia) in pregnancy and impaired neuropsychological development of the offspring, as well as several obstetric complications, such as miscarriage,

preterm delivery, gestational hypertension and pre-eclampsia (1, 2, 3). Several of these studies (4, 5, 6), although not all (7, 8) have also shown that subclinical hypothyroidism in pregnancy is associated with an increased risk of gestational diabetes. Isolated hypothyroxinaemia has also been shown to be associated with

gestational diabetes (7), and a recent study found that lower free thyroxine (FT₄) levels and higher free triiodothyronine (FT₃) to FT₄ ratios (suggesting higher peripheral deiodinase activity leading to conversion of FT₄ to FT₃) in pregnant women are associated with several adverse metabolic parameters relating to obesity, glycaemia, insulin resistance and lipid profile (9). It is possible that these adverse metabolic parameters partly explain the poor obstetric outcomes observed in pregnant women with mild maternal thyroid insufficiency (10, 11, 12).

As little is known on whether mild maternal thyroid hormone insufficiency in pregnancy is associated with adverse metabolic parameters, our study aimed to explore the relationship between maternal thyroid hormone levels and metabolic parameters in pregnancy and ascertain if pregnant women with subclinical hypothyroidism and isolated hypothyroxinaemia have worse metabolic phenotype than euthyroid pregnant women.

Subjects and methods

Subjects

A total of 988 healthy non-diabetic Caucasian women with singleton pregnancies were recruited into the Exeter Family Study of Childhood Health between 1999 and 2004 (13). These women had detailed anthropometric measurements, including height, weight and skinfold measures (triceps, biceps and subscapular) and fasting blood samples taken at 28 weeks gestation. After exclusion of women on thyroid-related medications (levothyroxine $n=18$, propylthiouracil $n=3$) and women with overt biochemical hypothyroidism ($n=10$) or hyperthyroidism ($n=1$) on the blood samples, data from 956 women were included in this study.

The study was approved by the North and East Devon Local Research Ethics Committee, and all participants gave informed written consent.

Analysis of thyroid function and biochemical metabolic parameters

Thyroid function tests (thyroid-stimulating hormone (TSH), FT₄ and FT₃) and thyroid peroxidase antibodies (TPO-Ab) were measured on the stored serum samples. Serum TSH, FT₄ and FT₃ were analysed using the electrochemiluminescent immunoassay, run on the Modular E170 Analyzer (Roche). Intra-assay coefficients of variations were as follows: TSH <5.3%, FT₄ <5.3% and FT₃ <5.1%. The manufacturer's population reference

ranges were as follows: TSH 0.35–4.5 mIU/l, FT₄ 11–24 pmol/l, and FT₃ 3.9–6.8 pmol/l. High TSH in this study of women in the third trimester was defined as >3 mIU/l, the generally accepted upper limit of the reference range in the second and third trimesters in Caucasian populations (1, 2). Subclinical hypothyroidism was defined as high TSH (>3 mIU/l) with FT₄ within the reference range (11–24 pmol/l). Isolated maternal hypothyroxinaemia was defined as FT₄ below the 10th centile (<10.4 pmol/l) with TSH within the reference range. TPO-Ab were analysed using the competitive immunoassay (Roche), and a titre above 34 IU/ml was considered positive.

Fasting plasma glucose, serum insulin and lipid profile and glycosylated haemoglobin (HbA1c) were analysed in the fresh blood samples, as previously described (13). We analysed homeostasis model of assessment for insulin resistance (HOMA-IR) to estimate fasting insulin sensitivity using the following formula: fasting serum insulin (mIU/l) × fasting plasma glucose (mmol/l)/22.5.

Statistical analysis

We assessed variables for distribution and log-transformed where they were not normally distributed. We used the independent sample *t*-test to compare metabolic parameters in women with isolated hypothyroxinaemia or subclinical hypothyroidism and women with normal thyroid function, and in euthyroid women with and without TPO-Ab. We used the χ^2 test to assess TPO-Ab-positive proportions in each group. We used Pearson's correlation to assess associations between variables, and multiple linear regression analysis to assess independent associations between variables. As smoking and TPO-Ab are potential confounders affecting thyroid function, we have also included these factors in the regression analysis (14, 15). We used independent samples *t*-test to compare metabolic parameters between women with lower and upper quartiles of FT₄ and between women with lower and upper quartiles of FT₃:FT₄ ratio. We carried out statistical analyses using SPSS (version 22).

Results

Study population

Participants had a mean (s.d.) age of 30.1 (5.1) years and BMI of 27.9 (4.6) kg/m²; 46% were primiparous and 14% smoked during pregnancy.

Metabolic parameters in pregnant women with subclinical hypothyroidism and isolated hypothyroxinaemia

A total of 133 (13.9%) women in our cohort had subclinical hypothyroidism and 82 (8.6%) had isolated hypothyroxinaemia.

There was no difference in metabolic parameters between women with subclinical hypothyroidism and euthyroid women (Table 1). Metabolic parameters in women with subclinical hypothyroidism who had TSH greater than 5 mIU/l ($n=12$) were also similar to those in euthyroid women (data not shown).

When compared to euthyroid women, women with maternal isolated hypothyroxinaemia had significantly increased BMI (29.5 vs 27.5 kg/m², $P<0.001$), sum of skinfolds (57.5 vs 51.3 mm, $P=0.002$), fasting plasma glucose (4.5 vs 4.3 mmol/l, $P=0.01$), triglycerides (2.3 vs 2.0 mmol/l, $P<0.001$) and HOMA-IR (2.0 vs 1.3, $P=0.001$), and borderline increased HbA1c (29.9 vs 28.7 mmol/mol, $P=0.05$) (Table 1).

Association between maternal thyroid hormone levels and metabolic parameters

In bivariate analyses, maternal FT₄ was negatively associated with BMI ($r=-0.22$, $P<0.001$), sum of skinfolds ($r=-0.22$, $P<0.001$), HbA1c ($r=-0.14$, $P<0.001$), fasting plasma glucose ($r=-0.13$, $P<0.001$), triglycerides ($r=-0.17$, $P<0.001$), HOMA-IR ($r=-0.15$, $P<0.001$) but

not Total/HDL cholesterol ratio ($r=-0.03$, $P=0.3$) (Table 2). Maternal FT₃:FT₄ ratio was positively associated with BMI ($r=0.40$), sum of skinfolds ($r=0.37$), HbA1c ($r=0.21$), fasting plasma glucose ($r=0.24$), triglycerides ($r=0.2$) and HOMA-IR ($r=0.33$) ($P<0.001$ for all) and Total/HDL cholesterol ($r=0.07$, $P=0.04$). Maternal TSH in pregnancy was not correlated with any of the maternal metabolic parameters assessed.

Women with the lowest FT₄ quartile and the highest FT₃:FT₄ ratio quartile had significantly higher BMI, sum of skinfolds, HbA1c, fasting plasma glucose, triglycerides and HOMA-IR as compared to women with the highest FT₄ quartile and the lowest FT₃:FT₄ ratio quartile respectively ($P\leq 0.001$ for all) (Table 3). There was no difference in total/HDL cholesterol ratio between groups.

In multivariable regression analyses (Table 4), FT₄ was independently associated with BMI, HbA1c, triglycerides and smoking during pregnancy, but not HOMA-IR. FT₃:FT₄ ratio was independently associated with BMI, HbA1c, HOMA-IR, and borderline associated with smoking during pregnancy, but not triglycerides or total/HDL cholesterol.

Association between maternal TPO-Ab status and metabolic parameters

Amongst the euthyroid women, there was no difference in metabolic parameters between TPO-Ab-positive ($n=37$) and TPO-Ab ($n=696$)-negative women (data not shown).

Table 1 Comparison of thyroid function and metabolic parameters between euthyroid mothers and those with subclinical hypothyroidism and euthyroid mothers and those with isolated hypothyroxinaemia in pregnancy (data presented as mean \pm s.d. or ^ageometric mean (s.d. range) except for TPO-Ab positivity which is presented as percentage). The bold values are statistically significant results.

Metabolic parameters	Euthyroid controls ($n=741$)	Subclinical hypothyroidism ($n=133$)	<i>P</i> value ^b	Isolated hypothyroxinaemia ($n=82$)	<i>P</i> value ^b
TSH ^a (mIU/l)	1.6 (0.9, 2.7)	3.7 (3.1, 4.5)	<0.001	1.8 (1.3, 2.5)	0.001
FT ₄ (pmol/l)	12.5 (1.4)	11.9 (1.5)	<0.001	9.7 (0.5)	<0.001
FT ₃ (pmol/l)	4.2 (0.5)	4.2 (0.5)	0.2	4.1 (0.4)	0.04
TPO-Ab positive (%)	5.0	13.7	0.001	6.0	0.6
BMI (kg/m ²) ^a	27.5 (23.4–32.4)	27.5 (23.7–32.1)	0.7	29.5 (25.1–34.7)	<0.001
Sum of skinfolds (mm) ^a	51.3 (37.2–70.8)	50.1 (33.3–69.2)	0.9	57.5 (40.7–81.3)	0.002
HbA1c (mmol/mol)	28.7 (3.7)	28.5 (3.9)	0.7	29.9 (4.6)	0.05
Fasting plasma glucose (mmol/l)	4.3 (0.4)	4.3 (3.8)	0.8	4.5(0.4)	0.01
Triglycerides (mmol/l) ^a	2.0 (1.5–2.8)	2.0 (1.4–2.8)	0.7	2.3 (1.7–3.3)	<0.001
HOMA-IR ^a	1.3 (0.7–2.0)	1.0 (0.8–2.0)	0.4	2.0 (0.9–2.8)	0.001
Total/HDL cholesterol ratio	3.4 (0.9)	3.3 (0.9)	0.4	3.5 (1.0)	0.1

^aDenotes log-transformed data.

^b*P* values refer to euthyroid controls vs subclinical hypothyroidism and euthyroid controls vs isolated hypothyroxinaemia.

Table 2 Correlations between maternal TSH, FT₄, FT₃:FT₄ ratio and metabolic parameters at 28 weeks gestation. The bold values are statistically significant results.

Metabolic parameters	TSH ^a r (P value)	FT ₄ r (P value)	FT ₃ :FT ₄ ratio r (P value)
BMI (kg/m ²) ^a	0.007 (0.8)	-0.22 (<0.001)	0.40 (<0.001)
Sum of skinfolds (mm) ^a	0.013 (0.7)	-0.22 (<0.001)	0.37 (<0.001)
HbA1c (mmol/mol)	0.007 (0.8)	-0.14 (<0.001)	0.21 (<0.001)
Fasting plasma glucose (mmol/l)	-0.01 (0.8)	-0.13 (<0.001)	0.24 (<0.001)
Triglycerides (mmol/l) ^a	0.006 (0.9)	-0.17 (<0.001)	0.20 (<0.001)
HOMA-IR ^a	0.02 (0.5)	-0.15 (<0.001)	0.33 (<0.001)
Total/HDL cholesterol ratio	-0.04 (0.2)	-0.03 (0.3)	0.07 (0.04)

^aDenotes log-transformed data.

Discussion

In this study of healthy non-diabetic pregnant women, we found that women with isolated hypothyroxinaemia have worse metabolic parameters with increased obesity, glycaemia, triglycerides and insulin resistance compared to euthyroid women. In contrast, subclinical hypothyroidism in pregnancy was not associated with these adverse metabolic parameters. We also identified lower maternal serum FT₄ and higher FT₃:FT₄ ratio (indicating an increased peripheral deiodinase activity leading to conversion of FT₄ to FT₃) associated with adverse metabolic parameters.

Thyroid hormones play key roles in regulating metabolic processes and energy homeostasis in the body (16). It is well known that overt thyroid dysfunction (hypothyroidism or hyperthyroidism) affects body weight, and recent studies have shown that even small variations in thyroid hormone levels within the reference range are associated with significant metabolic consequences and changes in body weight (16, 17). In the mouse model of type 2 diabetes, thyroid hormone has been shown to improve glycaemia and insulin sensitivity (18). Our

finding of the inverse correlation between maternal serum FT₄ and maternal BMI is consistent with previous studies in the pregnant and non-pregnant populations (19, 20, 21, 22, 23). In the general population, low FT₄ as well as high FT₃:FT₄ ratio have also been shown to be associated with adverse metabolic parameters, including less favourable lipid profile, blood pressure and insulin resistance (24, 25, 26, 27, 28). It is thought that lower FT₄ levels are compensated by a higher peripheral deiodinase activity resulting in higher conversion of FT₄ to active thyroid hormone FT₃ and higher FT₃:FT₄ ratio (20). In a recent study of 321 healthy pregnant women without a history of thyroid dysfunction, Bassols *et al.* (9) found that decreasing FT₄ and increasing FT₃:FT₄ ratios are similarly associated with less favourable metabolic profile. In addition to confirming the associations in a larger cohort of pregnant women, our study also demonstrates the presence of worse metabolic parameters in women with maternal hypothyroxinaemia as compared to euthyroid women. In contrast, despite several studies (4, 5, 6), but not all (7, 8), showing association between subclinical hypothyroidism in pregnancy and gestational diabetes,

Table 3 Comparisons between upper and lower FT₄ and FT₃:FT₄ ratio quartiles, and maternal metabolic parameters (data presented as mean ± s.d. or ^ageometric mean (s.d. range)). Bold values are statistically significant results.

Metabolic parameters	FT ₄		P value	FT ₃ :FT ₄ ratio		P value
	Lower quartile	Upper quartile		Lower quartile	Upper quartile	
BMI (kg/m ²) ^a	28.8 (24.6–33.9)	26.9 (22.9–31.6)	<0.001	25.1 (21.9–28.8)	30.2 (26.7–35.5)	<0.001
Sum of skinfolds (mm) ^a	57.4 (41.7–79.4)	47.9 (34.7–66.1)	<0.001	44.7 (32.4–61.7)	63.1 (45.7–87.1)	<0.001
HbA1c (mmol/mol)	29.5 (4.1)	28.1 (3.8)	0.001	27.9 (3.6)	29.9 (4.4)	<0.001
Fasting plasma glucose (mmol/l)	4.4 (0.4)	4.3 (0.4)	<0.001	4.2 (0.3)	4.5 (0.4)	<0.001
Triglyceride (mmol/l) ^a	2.2 (1.6–3.1)	1.9 (1.4–2.5)	<0.001	1.9 (1.4–2.6)	2.2 (1.6–3.1)	<0.001
HOMA-IR ^a	2.0 (1.0–2.6)	1.0 (0.8–2.0)	<0.001	1.0 (0.6–1.6)	2.0 (1.0–2.5)	<0.001
Total/HDL cholesterol ratio	3.0 (1.8)	3.3 (0.7)	0.17	3.3 (0.9)	3.4 (1.0)	0.24

^aLog-transformed data.

Table 4 Multivariable regression analysis to demonstrate the relationships between maternal FT₄ and FT₃:FT₄ ratio with metabolic parameters. Partial *R* is the adjusted correlation coefficient. Bold values are statistically significant results.

Associated metabolic parameters	Partial <i>R</i>	β	95% CI for β	<i>t</i>	<i>P</i>
Maternal FT ₄					
BMI (kg/m ²) ^a	-0.13	-1.55	-2.43, -0.68	-3.47	0.001
HbA1c (mmol/mol)	-0.09	-0.04	-0.07, -0.01	-2.54	0.01
Triglycerides (mmol/l) ^a	-0.10	-0.49	-0.84, -0.13	-2.71	0.007
HOMA-IR ^a	-0.02	-0.06	-0.31, 0.21	-0.43	0.7
Smoking during pregnancy	0.09	0.43	0.10, 0.77	2.52	0.01
TPO-Ab positive	-0.004	-0.02	-0.47, 0.41	-0.10	0.9
Maternal FT ₃ :FT ₄ ratio					
BMI (kg/m ²) ^a	0.26	0.10	0.07, 0.12	7.18	< 0.001
HbA1c (mmol/mol)	0.11	0.001	0.00, 0.002	2.92	0.004
Triglycerides (mmol/l) ^a	0.07	0.01	-0.001, 0.02	1.86	0.06
HOMA-IR ^a	0.14	0.02	0.007, 0.023	3.72	< 0.001
Total/HDL cholesterol	-0.07	-0.004	-0.009, 0.000	-3.52	0.06
Smoking during pregnancy	0.07	0.01	0.00, 0.02	1.98	0.05
TPO-Ab positive	0.02	0.003	-0.01, 0.02	0.80	0.9

^aVariable transformed using natural logs (allowing β coefficients to be interpreted in terms of percentage change).

we were unable to demonstrate that pregnant women with subclinical hypothyroidism have less favourable metabolic parameters than euthyroid pregnant women. The possible explanations for this discrepant observations include differences in study populations (for example, women with gestational diabetes were excluded in our study) and different TSH cut-off levels used to define subclinical hypothyroidism.

As it is a cross-sectional observational study, our study cannot ascertain that the observed less favourable metabolic parameters are caused by changes in the thyroid hormone levels. Indeed, it is possible that the associations between maternal thyroid function and metabolic parameters are mediated by obesity, as glycaemia, insulin resistance and dyslipidaemia are closely associated with obesity. Several lines of evidence support the hypothesis that changes in thyroid hormone levels are the consequence rather than the cause of changes in body weight. Increased subcutaneous fat has been shown to be associated with lower FT₄ and higher TSH levels in euthyroid adults (29). A study in iodine-deficient pregnant women showed that obesity is associated with an increased risk of maternal hypothyroxinaemia (30). It is thought that obesity stimulates peripheral deiodinase activity as an adaptation process to increase energy expenditure resulting in an increased conversion of FT₄ to FT₃ and high FT₃:FT₄ ratio (22). More importantly, weight loss following dietary and life-style interventions have been shown to be associated with changes in thyroid hormone levels, including decreases in FT₃ level

and FT₃:FT₄ ratio (31 32). Together, these observations suggest that pregnant women should be encouraged to avoid excess weight gain to prevent maternal hypothyroxinaemia.

We acknowledge a number of other limitations in this study. First, we carried out thyroid function tests on stored serum samples; however, it has been shown that serum TSH, FT₄, FT₃ and TPO-Ab concentrations remain stable after storage for several years (33). Second, women with gestational diabetes were excluded from the study during recruitment, therefore we were unable to analyse whether the observed association between isolated hypothyroxinaemia and adverse metabolic parameters extended to an increased risk of gestational diabetes. Finally, we were also unable to assess the potential impact of iodine deficiency on our results due to a lack of urinary iodine concentration data.

In conclusion, this study demonstrates that maternal isolated hypothyroxinaemia, but not subclinical hypothyroidism, is associated with adverse metabolic parameters in pregnancy. The association between low serum thyroxine level and adverse metabolic parameters may be a reflection of changes in the thyroid hormone levels secondary to increases in BMI rather than changes in thyroid hormone levels affecting body weight and related metabolic parameters.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The Endocrine Research Fund funded the thyroid function tests. B A Knight, B M Shields and A T Hattersley are funded by the National Institute for Health Research (NIHR) as core members of the NIHR Exeter Clinical Research Facility. Work of B Vaidya is supported by the Research and Development Department of the Royal Devon and Exeter NHS Foundation Trust.

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Received 26 August 2015

Revised version received 3 October 2015

Accepted 14 October 2015