Original Article

Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women

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Abstract

Hypothyroxinaemia early in pregnancy may impair fetal brain development. Increased body weight has been associated with low thyroxine concentrations in non-pregnant women. In pregnant women, morbid maternal obesity is a risk factor for thyroid dysfunction. But whether lesser degrees of overweight that are much more common could be a risk factor for hypothyroxinaemia in pregnancy is unclear. The objective of this study was to investigate if overweight increases risk for thyroid dysfunction, and specifically hypothyroxinaemia, in iodine-deficient pregnant women. We performed a cross-sectional study at first hospital visit among healthy Thai pregnant women. We measured weight and height, urinary iodine concentration (UIC), serum thyroid hormones and thyroglobulin. Pre-pregnancy weight and relevant dietary factors were determined by questionnaire, and body mass index (BMI) was used to classify weight status. Among 514 women (mean gestational age, 11 weeks) with a median UIC of 111 $\mu\text{g dL}^{-1}$, indicating mild iodine deficiency, 12% had low free thyroxine (fT4) concentrations: 3% had overt hypothyroidism; 7% had subclinical hypothyroidism; and 8% had isolated hypothyroxinaemia. Based on pre-pregnancy BMI, 26% of women were overweight or obese. In a multiple regression model, BMI was a negative predictor of fT4 ($\beta = -0.20$, $P < 0.001$). Compared to normal weight women, the prevalence ratio (95% CI) of a low fT4 in overweight women was 3.64 (2.08–6.37) ($P < 0.01$). Iodine-deficient pregnant Thai women who are overweight have a 3.6-fold higher risk of hypothyroxinaemia in the first trimester compared to normal weight women. Targeted screening should consider overweight a potential risk factor for thyroid dysfunction in pregnant women in iodine-deficient areas.

Keywords: iodine deficiency, pregnant women, overweight, hypothyroxinaemia, thyroid dysfunction, obesity.

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Introduction

Adequate maternal iodine status is essential during pregnancy for maternal and fetal thyroid hormone synthesis. Iodine deficiency increases risk of maternal thyroid dysfunction and hypothyroxinaemia, which can adversely affect pregnancy outcome and infant development (Wasserstrum & Anania 1995; Montoro 1997; Davis *et al.* 1998; Smallridge & Ladenson 2001).

Mild to moderate hypothyroxinaemia during pregnancy may impair neurodevelopment of the offspring (Haddow *et al.* 1999; Pop *et al.* 2003; Kooistra *et al.* 2006; Berbel *et al.* 2009; Costeria *et al.* 2011). The iodine requirement is sharply increased during pregnancy to meet increased maternal and fetal requirements. Therefore, the World Health Organization (WHO), the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the

United Nations Children's Fund (UNICEF) recommends a daily iodine intake of 250 $\mu\text{g day}^{-1}$ for pregnant women (WHO/ICCIDD/UNICEF 2007).

In generally iodine-sufficient Western populations, about 2–3% of pregnant women are subclinical hypothyroid and 10–15% are positive for anti-thyroid peroxidase antibodies (anti-TPO Abs) (Stagnaro-Green *et al.* 1990 & Allan *et al.* 2000). The prevalence of these thyroid disorders in iodine-deficient pregnant women has not been well defined. Mild to moderate iodine deficiency remains common in pregnant women in both high- and low-income countries (Zimmermann & Delange 2004). Globally, screening of thyroid disorders in early pregnancy is controversial, and experts generally recommend targeted high-risk case finding (Abalovich *et al.* 2007).

Adiposity is associated with thyroid hypofunction, and overweight adults tend to have higher thyroid-stimulating hormone (TSH) and lower free thyroxine (fT4) concentrations than normal weight adults (Biondi 2010). In iodine-deficient adults without overt thyroid dysfunction, higher body mass index (BMI) predicts a lower fT4 concentration (Knudsen *et al.* 2005), and in pregnant women at mid-gestation, high maternal BMI is positively correlated with the free triiodothyronine (fT3)/fT4 ratio (Bassol *et al.* 2011). Currently, expert guidelines on screening for thyroid dysfunction in pregnancy recommend that women with morbid obesity ($\text{BMI} \geq 40 \text{ kg m}^{-2}$) be screened, but do not recommend screening for overweight women (Stagnaro-Green *et al.* 2011).

Although iodine status of school-aged children in Thailand is adequate, many Thai pregnant women are iodine deficient (Gowachirapant *et al.* 2009). In 2009, the median urinary iodine concentration in pregnant women in the Bangkok metropolitan area was 108 $\mu\text{g L}^{-1}$, and 69% of women had a

UIC < 150 $\mu\text{g L}^{-1}$, (the cut-off indicating iodine deficiency) (Gowachirapant *et al.* 2009). Therefore, our study aim was to measure iodine status and thyroid function in healthy pregnant women in the first trimester in Bangkok and to assess risk factors for thyroid dysfunction. Specifically, we determined if overweight (defined as $\text{BMI} \geq 23 \text{ kg m}^{-2}$) increases risk for hypothyroxinaemia in iodine-deficient pregnant women.

Subjects and methods

Subjects

This cross-sectional study was performed on Thai pregnant women who presented for their first prenatal visit between October 2008 and October 2010 at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand. Inclusion criteria for this study were: (1) confirmed single pregnancy; (2) age 18–40 years; (3) gestational age ≤ 14 weeks; (4) non-lactating; (5) apparently healthy with no history of thyroid disorders; and (6) not taking any iodine supplements. All women gave written informed consent. The ethical review boards of Wageningen University in the Netherlands and Ramathibodi Hospital in Thailand approved the study. The study was registered into the clinical trials database at <http://www.clinicaltrials.gov/> with its identifier: NCT00791466.

Methods

Maternal characteristics, including dietary intakes and pre-pregnancy weight, were recorded by using a questionnaire. Four questions on seafood consumption and salt use were included in the questionnaire for assessing iodine intakes. Weight and height were

Key messages

- This study confirms that pregnant Thai women are facing mild-to-moderate iodine deficiency.
- Most of Thai pregnant women are euthyroid in the first trimester of pregnancy.
- In iodine-deficient pregnant women, overweight women have a higher risk of hypothyroxinaemia than normal-weight women.
- Not only morbidly obese women but also women who are overweight should be screened for thyroid dysfunction.

measured using standard methods. Pre-pregnancy BMI and baseline BMI were calculated. Because the association of BMI and health risk in Caucasian and Asian populations is different, women were classified by weight status using BMI reference ranges for Asian populations: $<18.5 \text{ kg m}^{-2}$ (underweight), $18.5\text{--}22.9 \text{ kg m}^{-2}$ (normal range), $23.0\text{--}24.9 \text{ kg m}^{-2}$ (overweight), and $\geq 25.0 \text{ kg m}^{-2}$ (obese) (WHO/IASO/IOTF 2000).

A spot urine sample was collected, aliquoted, stored at -20°C and UIC was measured using the Pino modification of the Sandell–Kolthoff reaction (Pino *et al.* 1996) at the Institute of Nutrition, Mahidol University. This laboratory successfully participates in the EQUIP external control program for UIC analysis from the CDC in Atlanta, USA. The UIC range indicating optimal iodine nutrition in pregnancy is $150\text{--}249 \mu\text{g L}^{-1}$ (Zimmermann 2008). Salt samples from the households of a subsample of pregnant women in this study were collected ($n = 112$) and analysed for iodine (Sullivan *et al.* 1995).

Whole blood samples were collected by venipuncture into vacutainer tubes without anticoagulant, centrifuged, and the serum aliquoted into cryovials and frozen at -20°C . Serum samples were analysed for TSH, total T4 (tT4), free T4 (fT4), total T3 (tT3), free T3 (fT3), thyroglobulin (Tg), and anti-TPO Abs by enzyme-labelled chemiluminescent competitive immunoassay (IMMULITE 2000, SIEMENS, Munich, Germany) at the Laboratory for Human Nutrition, ETH Zurich, Switzerland. With the exception of TSH, we used the manufacturer's reference ranges: $58\text{--}161 \text{ nmol L}^{-1}$ for tT4, $0.89\text{--}1.76 \text{ ng dL}^{-1}$ for fT4, $1.3\text{--}2.6 \text{ nmol L}^{-1}$ for tT3, $1.8\text{--}4.2 \text{ pg mL}^{-1}$ for fT3, $\leq 55 \text{ ng mL}^{-1}$ for Tg, and $<35 \text{ IU mL}^{-1}$ for anti-TPO Abs. For TSH in the first trimester of pregnancy, we used the reference range of $0.2\text{--}2.5 \text{ mIU L}^{-1}$ (Patil-Sisodia & Mestman 2010).

Maternal thyroid gland volume measurement was performed by a portable echocamera (Aloka, Mure, Japan), using a 7.5-MHz linear transducer. Thyroid volume was calculated by using the following equation: Volume of each lobe (mL) = anteroposterior (AP) diameter (cm) $\times$ mediolateral (ML) diameter (cm) $\times$ craniocaudal (CC) diameter (cm) $\times 0.479$, and

the total lobe volumes from both sides were summed (Brunn *et al.* 1981). Normative thyroid volume was defined as $8.0\text{--}18.0 \text{ mL}$ (WHO/UNICEF/ICCIDD 1993).

Data analyses

Statistical analyses were carried out with SPSS 19.0 (IBM, New York, NY, USA). Normality of data was checked with the Kolmogorov–Smirnov test. Variables were expressed as means $\pm$ SD for normally distributed data and medians (1st, 3rd quartiles) for non-normally distributed data. For data that could not be normalised, Spearman correlation coefficients were calculated and Mann–Whitney *U*-tests were used for comparison. For identifying the predictors and confounders of TSH, fT4, Tg and thyroid volume, first, all parameters (including socio-demographic data, UIC and thyroid function) were analysed using Spearman correlation test in order to assess their correlation. Then, a simple linear regression was applied to identify the possible predictors of TSH, fT4, Tg and thyroid volume. Finally, all possible predictors were used in a stepwise multiple regression for generating the model. Cox regression with time set at 1 for all subjects was performed to determine the prevalence ratios (PR) (Barros & Hirakata 2003) as potential predictors of $\text{UIC} < 150 \mu\text{g L}^{-1}$, $\text{TSH} > 2.5 \text{ mIU L}^{-1}$, $\text{fT4} < 0.89 \text{ ng/dL}$ and $\text{anti-TPO Abs} \geq 35 \text{ IU mL}^{-1}$. Differences were considered statistically significant at $P < 0.05$.

Results

Characteristics of the pregnant women are shown in Table 1 and 514 pregnant women participated at a mean gestational age of 11 weeks. More than half of women had pre-pregnancy BMI (58%) and baseline BMI (54%) within the normal range ($18.5\text{--}22.9$). Pre-pregnancy BMI was strongly correlated with baseline BMI ($r = 0.95$, $P < 0.001$). Twenty-six per cent of the population was overweight or obese as defined by pre-pregnancy BMI ≥ 23 . Despite the fact that fish sauce was used more frequently (74%) as a cooking ingredient than salt (25%), 89% of the pregnant women usually bought iodised salt and 75% used salt

Table 1. Characteristics of pregnant women participating in the study ($n = 514$)

Variables	<i>n</i>	Values*
Age (years) [†]	514	30 ± 5
Pre-pregnancy BMI (kg m ⁻²) [‡]	513	20.9 (19.1, 23.1)
<18.5	87	17
18.5–22.9	295	57.5
23.0–24.9	52	10.1
≥25.0	79	15.4
Baseline BMI (kg m ⁻²) [‡]	513	21.5 (19.5, 23.7)
<18.5	71	13.8
18.5–22.9	279	54.4
23.0–24.9	67	13.1
≥25.0	96	18.7
Parity		
1	224	43.6
2	177	34.4
3	87	16.9
4	20	3.9
>4	6	1.2
Usually buying iodised salt	453	88.5
Salt use		
No	5	1
For cooking	385	75.2
As a condiment	96	18.8
Both	26	5
Use of salt and fish sauce		
More salt	125	24.6
More fish sauce	377	74.1
Equal amounts	7	1.3
Weekly seafood consumption		
None	30	5.9
1–2 times	352	68.8
3–4 times	91	17.8
>4 times	39	7.5

BMI, body mass index. *Values are percentages unless stated otherwise. †Mean ± SD. ‡Median (first, third quartiles).

for cooking. Sixty-nine per cent of women consumed seafood once to twice a week. Salt samples obtained from a subsample of pregnant women ($n = 112$) had a mean ± SD iodine concentration of 60 ± 35 ppm, indicating adequate levels of salt iodisation. There were no statistical differences in the characteristics listed in Table 1 between normal weight and overweight women. With the exception for age, we used chi-square test for all variables: parity ($P = 0.645$), usually buying iodised salt ($P = 0.251$), salt use ($P = 0.571$), use of salt and fish sauce ($P = 0.246$), and weekly seafood consumption ($P = 0.284$). We used independent-samples *t*-test for comparing mean

age between normal weight and overweight women ($P = 0.148$).

Thyroid function tests, UICs and thyroid gland volume are shown in Table 2. In more than 80% of women, all thyroid parameters were within normal ranges. However, 12% of the women had a low fT4 concentration and 17% had elevated anti-TPO Abs. The median UIC was $111 \mu\text{g L}^{-1}$, indicating mild ID: 23% had a UIC $100\text{--}149 \mu\text{g L}^{-1}$, 32% had a UIC $50\text{--}99 \mu\text{g L}^{-1}$, and 10% had a UIC $< 50 \mu\text{g L}^{-1}$. None of the women had increased thyroid volume by ultrasound. The median thyroid volume of overweight women (8.50 mL) was lower than in normal weight women (8.69 mL); however, there was no statistical difference between these two values (Mann–Whitney test, $P = 0.903$). Based on Spearman correlation tests, there were no significant correlations between iodine intake (data from questionnaire) and TFTs ($P > 0.05$) (data not shown).

The median of fT4 among overweight women was significantly lower than among normal weight women ($P < 0.001$) (Fig. 1).

Prevalences of thyroid dysfunctions are shown in Table 3. Three per cent of women had overt hypothyroidism, 7% had subclinical hypothyroidism and 8% had isolated hypothyroxinaemia.

Table 4 shows the adjusted regression models for TSH, fT4, Tg and thyroid volume as dependent variables. In simple and multiple linear regression analysis, there were no significant predictors of anti-TPO Abs (data not shown). There was a significant inverse relationship between pre-pregnancy BMI and fT4 concentration ($P < 0.001$). There was also a significant inverse relationship between baseline BMI and fT4 concentration ($P < 0.001$). In addition, there was a significant inverse association between thyroid size and TSH concentration ($P < 0.01$). In contrast, there was a positive relationship between pre-pregnancy BMI and Tg concentration ($P < 0.05$). Parity was positively correlated with thyroid size ($P < 0.01$).

As shown in Table 5, risk for a low fT4 was significantly increased in women with a pre-pregnancy BMI $\geq 23.0 \text{ kg m}^{-2}$ (3.64, 95% CI: 2.08–6.37). Risk for elevated anti-TPO Abs ($\geq 35 \text{ IU mL}^{-1}$) was significantly decreased in women with a smaller thyroid gland volume (0.40, 95% CI: 0.20–0.83).

Table 2. Thyroid hormones, urinary iodine concentration (UIC) and thyroid volume of pregnant women*

Indicators [†]	Normal weight (n = 296)	Overweight (n = 131)	All [‡] (n = 514)
TSH (mIU L ⁻¹) [§]	1.03 (0.55, 1.60)	1.11 (0.71, 1.89)	1.07 (0.60, 1.73)
<0.2	9.3	7	8.5
0.2–2.5	81.7	82.2	81.5
>2.5	9	10.9	10
Total T4 (nmol L ⁻¹) [§]	119.0 (102.0, 138.0)	116.0 (100.5, 138.3)	118.0 (101.0, 138.0)
<58	0.3	0.8	0.6
58–161	90.4	93.1	91.7
>161	9.2	6.2	7.7
Free T4 (ng dL ⁻¹) [§]	1.08 (1.00, 1.19)	1.00 (0.88, 1.12)	1.08 (0.97, 1.19)
<0.89	7.3	25.4	11.8
0.89–1.76	91.3	73	86.3
>1.76	1.4	1.6	1.9
Total T3 (nmol L ⁻¹) [§]	1.82 (1.51, 2.11)	2.06 (1.61, 2.40)	1.85 (1.54, 2.17)
<1.3	8.5	10.9	8.8
1.3–2.6	84.7	73.6	82.2
>2.6	6.8	15.5	9
Free T3 (pg mL ⁻¹) [§]	3.12 (2.72, 3.60)	3.45 (2.87, 3.90)	3.16 (2.73, 3.64)
<1.8	0.4	–	0.4
1.8–4.2	91.1	83.9	89.6
>4.2	8.5	16.1	10
Tg (ng mL ⁻¹) [§]	9.11 (4.94, 16.15)	10.33 (6.78, 17.15)	9.53 (5.09, 16.7)
≤55	97.6	95.3	96.8
>55	2.4	4.7	3.2
Anti-TPO Abs (IU mL ⁻¹) [§]	18.6 (13.5, 26.9)	21.7 (15.6, 31.4)	19.8 (14.1, 27.4)
<35	84.5	84	83
≥35	15.5	16	17
UIC (µg L ⁻¹) [§]	113.20 (74.69, 172.98)	111.89 (76.25, 169.59)	111.66 (74.72, 169.79)
<50	11.5	6.3	10.4
50–99	29.5	35.2	32.3
100–149	22.4	25	22.6
≥150	36.6	33.6	34.7
Thyroid gland volume (mL) [§]	8.69 (7.23, 10.4)	8.50 (7.53, 10.0)	8.41 (7.18, 10.2)
T3/T4 ratio [§]	0.015 (0.013, 0.017)	0.017 (0.015, 0.020)	0.016 (0.014, 0.018)

Tg, thyroglobulin; TSH, thyroid-stimulating hormone. *Values are percentages unless stated otherwise. [†]Cut-offs to categorise thyroid hormone concentration are based on manufacturer's reference range, except for TSH for which a pregnancy-specific cut-off range was used. [‡]Including underweight women (body mass index <18.5 kg m⁻²). [§]Median (first, third quartiles).

Discussion

The present study confirms that pregnant women living in Bangkok are iodine deficient with median UIC of 111 µg L⁻¹. In an earlier study in pregnant women from the same area, we reported a similar median UIC of 108 µg L⁻¹ (Gowachirapant *et al.* 2009). Other studies have found suboptimal iodine status among pregnant women in Thailand. In 2007, Rajatanavin (2007) reported the median UICs of mothers in Bangkok and six rural provinces in Thailand were 85 and 103 µg L⁻¹, respectively. In southern

Thailand, the median maternal UIC ranges from 51 to 106 µg L⁻¹ (Jaruratanasirikul *et al.* 2009).

There may be several reasons why iodine intakes are low in Thai pregnant women. The salt iodisation program in Thailand, begun in 1995, currently covers only 60–70% of Thai households with adequately iodised salt, below the national goal of at least 90% coverage (World Health Organization, Regional Office for South-East Asia 2004; Division of Nutrition, Ministry of Public Health 2005; UNICEF & National Statistical Office, Thailand 2006; Jaruratanasirikul *et al.* 2009). In many rural areas, salt

Fig. 1. Box plot of free T4 concentration (ng dL⁻¹) and pre-pregnancy body mass index (BMI) (kg m⁻²). Outliers are indicated by *.

Table 3. Thyroid dysfunction of pregnant women (*n*=498) in their first trimester*

Thyroid dysfunction ^{†‡}	<i>n</i>	Percentages
Overt hyperthyroidism	5	1.0
Subclinical hyperthyroidism	34	6.8
Overt hypothyroidism	14	2.8
Subclinical hypothyroidism	34	6.8
Hypothyroxinaemia	42	8.4

*Number of pregnant women who had free T4 concentration. [†]Cut-offs to categorise thyroid hormone concentration are based on manufacturer's reference range, except for thyroid-stimulating hormone (TSH) for which a pregnancy-specific cut-off range was used. [‡]Classified by using the definition of Helfand & Redfern (1998): overt hyperthyroidism: low TSH + high free T4; subclinical hyperthyroidism: low TSH + normal free T4; overt hypothyroidism: high TSH + low free T4; subclinical hypothyroidism: high TSH + normal free T4; hypothyroxinaemia: normal TSH + low free T4.

from local small producers is often not iodised. Moreover, in Thailand and throughout Southeast Asia, fish sauce is a more popular household seasoning than salt, reducing the contribution of iodised salt to dietary iodine intakes. In the present study, three of four women used mainly fish sauce for household seasoning, whereas only one in four used mainly salt. In the urban households of the women in this study, all salt samples analysed were adequately iodised

Table 4. Multiple regression model of predictors for thyroid function in pregnant women*

Model	Predictors	<i>R</i> ²	Beta (95% CI)	Sig.
TSH	Tvol	0.019	-0.137 (-0.114, -0.025)	0.002
FT4	Tvol	0.079	0.222 (0.016, 0.037)	0.000
	BMI	0.079	-0.200 (-0.019, -0.008)	0.000
TG	BMI	0.011	0.105 (0.086, 1.145)	0.023
Tvol	Parity	0.016	0.126 (0.083, 0.441)	0.004

BMI, body mass index; CI, confidence interval. *Stepwise regression.

(≥15 ppm) (Keetman 2010). Thus, use of iodised salt in the production of fish sauce, or, alternatively, direct iodisation of fish sauce, are likely to be the effective dietary interventions to increase intakes in this population. Iodine supplementation during pregnancy could also increase iodine intakes, but most Thai women present for prenatal care near the end of the first trimester. Therefore, prenatal supplementation would likely not be effective in increasing intakes during the first trimester, the period during which the fetus is most vulnerable to ID.

However, despite their low iodine intakes, most pregnant women in this study were euthyroid and all had normal thyroid volume. Glinioer *et al.* (1995) suggested an increased T3/T4 ratio >0.025 reflects

Table 5. Prevalence ratios of predictors in relation to iodine status and thyroid function in first trimester pregnant women

Independent variables	UIC < 150 µg L ⁻¹	Prevalence ratios (95% CI)		
		TSH > 2.5 mIU L ⁻¹	Free T4 < 0.89 ng dL ⁻¹	Anti-TPO Abs ≥ 35 IU mL ⁻¹
Age (years)				
<25	Ref.	Ref.	Ref.	Ref.
25–30	0.87 (0.64–1.19)	1.15 (0.49–2.70)	0.83 (0.39–1.75)	1.21 (0.55–2.68)
>30	0.87 (0.64–1.18)	1.08 (0.46–2.52)	0.90 (0.44–1.87)	1.88 (0.89–4.00)
BMI (kg m ⁻²)				
<18.5	1.11 (0.83–1.48)	1.30 (0.63–2.70)	1.03 (0.41–2.55)	0.74 (0.37–1.46)
18.5–22.9	Ref.	Ref.	Ref.	Ref.
≥23.0	1.04 (0.81–1.35)	1.20 (0.63–2.30)	3.64 (2.08–6.37)**	1.03 (0.61–1.72)
Parity				
1	Ref.	Ref.	Ref.	Ref.
2	0.99 (0.78–1.27)	1.09 (0.59–2.01)	1.60 (0.89–2.87)	1.10 (0.66–1.85)
>2	0.92 (0.69–1.23)	0.83 (0.38–1.81)	1.24 (0.62–2.49)	1.22 (0.69–2.15)
Tvol (mL) [†]				
<7.18	1.08 (0.83–1.40)	0.96 (0.51–1.82)	1.09 (0.62–1.91)	0.40 (0.20–0.83)*
7.18–10.20	Ref.	Ref.	Ref.	Ref.
>10.20	1.11 (0.85–1.43)	0.50 (0.22–1.13)	0.36 (0.15–0.85)*	1.03 (0.62–1.70)
Seafood (times wk ⁻¹)				
None	Ref.	Ref.	Ref.	Ref.
1–2	1.02 (0.64–1.62)	1.43 (0.34–5.98)	1.86 (0.45–7.68)	0.78 (0.31–1.97)
3–4	0.98 (0.59–1.65)	2.02 (0.45–9.04)	2.33 (0.53–10.27)	1.39 (0.52–3.67)
>4	0.82 (0.44–1.53)	1.21 (0.20–7.28)	0.41 (0.04–4.47)	0.77 (0.22–2.66)
Iodised salt use				
Yes	Ref.	Ref.	Ref.	Ref.
No	1.13 (0.79–1.62)	0.90 (0.32–2.49)	1.37 (0.62–3.01)	1.07 (0.49–2.33)

CI, confidence interval; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration; * $P < 0.05$, ** $P < 0.01$ (compared with reference group). [†]Categorised by percentiles.

excessive thyroid stimulation during pregnancy due to iodine deficiency. In our sample, the median T3/T4 ratio was 0.016, evidence that thyroid function was normal in many of these women. Spot UIC is a useful indicator for assessing recent iodine intake of this population because about 90% of daily ingested iodine is excreted in the urine. But this method has large day-to-day variation and should not be used to classify an individual's iodine status. Therefore, a 24-h urine sample collection or repeated spot urine samples may be more useful for categorizing individual status. A combination of UIC and thyroid function tests may provide the most accurate assessment of iodine status of pregnant women.

Because iodine intakes in the general Thai population are adequate, many of these women likely entered pregnancy with ample stores of intrathyroidal iodine, enough to support increased needs for iodine

in the early stages of pregnancy. Although none of the women had evidence of increased thyroid volume, thyroid volume was inversely correlated with TSH and positively correlated with fT4. This pattern, in the first trimester of pregnancy, is thought to be due to high circulating human chorionic gonadotropin that stimulates thyroid hormone production and TSH (Haddow *et al.* 2008). In addition, we found that higher parity was associated with greater thyroid volume, as has been previously reported in iodine-deficient European populations (Rotondi *et al.* 2000; Knudsen *et al.* 2002). Thus, repeated pregnancy may be a risk factor for goitre, particularly in iodine-deficient areas.

Although most women in our study were euthyroid, 12% of women had low fT4 concentration: 3% had overt hypothyroidism; 7% had subclinical hypothyroidism; and 8% had isolated

hypothyroxinaemia. These prevalences are about threefold higher than those reported for iodine-sufficient Western populations, where generally 2–3% of pregnant women are hypothyroid, of whom 0.3–0.5% have overt hypothyroidism and 2–2.5% have subclinical hypothyroidism. In a recent study in iodine-sufficient Asian women early in pregnancy ($n = 2899$) (Wang *et al.* 2011), the prevalence of overt or subclinical hypothyroidism was 7.5% and the prevalence of hypothyroxinaemia was only 0.9%. Thus, our results suggest that low iodine intakes in Thai pregnant women increase risk for hypothyroxinaemia, and thus improving iodine intakes should be a public health priority.

The novel finding in this study is the clear inverse relationship between body weight and fT4 in mildly iodine-deficient pregnant women. In general, overweight adults tend to have slightly higher TSH and, in some studies, lower fT4 concentrations than normal weight adults (Lindeman *et al.* 2003; Biondi 2010). Greater subcutaneous fat is associated with lower fT4 in overweight adults, independent of age, gender and smoking (Alevazaki *et al.* 2009). The link between body weight and thyroid function is less well studied in areas of iodine deficiency. In iodine-deficient Danish adults without overt thyroid dysfunction, higher BMI was associated with lower fT4, but not fT3 (Knudsen *et al.* 2005). In pregnant Spanish women at mid-gestation, higher maternal BMI was directly correlated with the fT3/fT4 ratio, but not with fT4 alone (Bassol *et al.* 2011).

Several mechanisms may contribute to a higher prevalence of thyroid hypofunction in overweight pregnant women who are iodine deficient. Obese adults may be more likely to develop autoimmune hypothyroidism leading to mild thyroid failure (Marzullo *et al.* 2010). However, in our subjects, there was no correlation between anti-TPO Abs and either BMI or fT4. Inflammatory cytokines released by adipose tissue may impair the hypothalamic–pituitary–thyroid axis (Toni *et al.* 2004) but this should result in negative associations between BMI and serum TSH as well as fT4, a pattern not visible in our subjects. Circulating oestrogen metabolites may be increased in pregnant women who are overweight, and 2-methoxyestradiol has been shown to have det-

perimental effects on thyroid cells in culture (Wang *et al.* 2000). A leptin-induced increase in TSH secretion may occur in obesity via hypothalamic effects (Zimmermann-Belsing *et al.* 2003), but this would increase TSH and thyroid hormone secretion, a pattern not found in our subjects. Finally, there may be a higher peripheral conversion of T4 to T3 in obesity due to increased de-iodinase activity as a compensatory mechanism to improve energy expenditure (Biondi 2010). This could accentuate the preferential thyroidal secretion of T3 over T4 in iodine deficiency and lead to lower fT4 levels. However, in our subjects the median T3/T4 ratio was not increased compared to previous reports in iodine-deficient pregnant women (Glinioer *et al.* 1995), and there was no correlation between BMI and the T3/T4 ratio.

Because thyroid dysfunction during early pregnancy is associated with poor offspring development, many expert groups, including the Endocrine Society (Abalovich *et al.* 2007), recommend a case-finding approach where women at high risk for thyroid disorders are screened. But this approach has been questioned. In a recent large Chinese study (Wang *et al.* 2011), despite using a recommended case-finding screening strategy, 82% of pregnant women with hypothyroidism were missed. Thus, the optimal screening criteria to identify women with hypothyroidism in early pregnancy remain uncertain. Current guidelines (Stagnaro-Green *et al.* 2011) recommend targeted screening based on weight status only in morbidly obese women ($\text{BMI} \geq 40 \text{ kg m}^{-2}$). However, our data suggest milder degree of maternal adiposity ($\text{BMI} \geq 23 \text{ kg m}^{-2}$ in Asian populations) should be considered a potential risk factor for thyroid dysfunction, particularly in iodine-deficient areas.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

All the authors contributed to the study design and article writing. SG performed data collection, laboratory work, data entry and analysis under supervision of AMB, PW and MBZ.

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