Hypothyroidism Complicating Pregnancy: A Local Perspective

Chung-Ming CHOR MBChB, MRCOG
Wing-Hung TAM MBChB, MD, MRCOG, MHKCOG, FHKAM (O&G), FHKCOG
Department of Obstetrics and Gynaecology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

Objective: To examine the thyroid status and adequacy of thyroxine replacement at the first antenatal visit in Hong Kong women with a known history of hypothyroidism prior to pregnancy.
Methods: Data were obtained from an electronic database, which registered all medical diseases complicating pregnancy among women attending the high-risk obstetric clinic in a teaching hospital between 1 April 2006 and 31 December 2009.
Results: A total of 136 eligible subjects were identified from 24,424 maternities during the study period. Thyroiditis was the most common cause of hypothyroidism followed by post-radioactive iodine treatment for previous hyperthyroidism. Overall, 96 (70.6%) women were hypothyroid according to the gestational age–specific reference ranges, and 29 (21.3%) were diagnosed with overt hypothyroidism. Furthermore, 63.5% of the women needed a mean dose increment of 44.6 ± 45.1% during pregnancy.
Conclusion: The majority of women with hypothyroidism complicating pregnancy did not receive adequate hormone replacement early in the course of their pregnancy in Hong Kong.
Hong Kong J Gynaecol Obstet Midwifery 2014; 14(1):38-42

Keywords: Hong Kong; Hypothyroidism; Pregnancy

Introduction

Hypothyroidism is a common condition among women in the reproductive age. About 0.5% and 3% of women in the reproductive age reported having overt and subclinical hypothyroidism, respectively[1]. The cause of hypothyroidism varies, but the most common cause appears to be thyroiditis[2].

The association between adverse pregnancy outcomes and maternal hypothyroidism is described since the high prevalence of cretinism in Western New Guinea where there was low dietary intake of iodine[3]. Thyroid hormone receptors can be found in the fetal brain tissue as early as 8 weeks of gestation indicating that the organ has an important role in brain growth[4]. Since the fetus only starts producing sufficient thyroid hormones in the mid-trimester, maternal hypothyroidism in early pregnancy can be detrimental to fetal brain development; other pregnancy complications such as miscarriage, preterm delivery, and pre-eclampsia have also been reported to be associated with maternal hypothyroidism[5].

It has been well known that the demand for thyroxine increases in early pregnancy. Women with hypothyroidism on thyroxine replacement therapy would need a mean of 50% increase in the replacement dosage[6]. It is, therefore, important to monitor the thyroid function test (TFT) and adjust thyroxine dosage as soon as women with hypothyroidism become pregnant to ensure an adequate thyroxine level[7,8]. The present study aimed to investigate the adequacy of thyroxine replacement therapy in the local pregnant women at their first antenatal visit in a teaching hospital in Hong Kong.

Methods

This was a retrospective study of women who required thyroxine replacement or regular monitoring of TFT and attended the high-risk obstetrics clinic at the Prince of Wales Hospital, Hong Kong, between 1 April 2006 and 31 December 2009. The Prince of Wales Hospital is a regional hospital in the Eastern New Territories of Hong Kong that manages an average of 7000 maternities per annum. Data were obtained from an electronic database, which registered all medical diseases complicating pregnancy during the study period, for the purpose of an audit. Pregnant women who had a known history of hypothyroidism requiring regular monitoring of TFT or thyroxine replacement therapy during pregnancy, as well as women who were diagnosed hypothyroidism during

Correspondence to: Dr Chung-Ming Chor
Email: cmchor@cuhk.edu.hk

pregnancy and requiring thyroxine replacement therapy were eligible for the audit. All relevant medical information was retrieved from the case notes and the computerised antenatal record system. The study was approved by The Chinese University of Hong Kong Clinical Research Ethics Committee (CREC 2011.227).

Thyroid status of the pregnant women was classified on the basis of their first TFT results performed in our unit at the first antenatal visit and a gestational age–specific reference range derived from a previous publication (Table 1)[9]. Women were classified as having overt hypothyroidism if the sensitive thyroid-stimulating hormone (sTSH) level was ≥10 mIU/L, or if free thyroxine (fT4) level was below the reference range when sTSH level was above the reference range but <10 mIU/L[10]. Women were classified as having subclinical hypothyroidism if sTSH level was above the reference range but <10 mIU/L while the fT4 level was within the reference range or unavailable. All subjects with normal sTSH level and / or a normal fT4 level were classified as having normal thyroid function.

During the study period, sTSH and fT4 levels were assayed by using Roche Cobas e601 electrochemiluminescence immunoassay analyser (Roche Diagnostics GmbH, Germany) in the laboratory of the Department of Chemical Pathology, Prince of Wales Hospital, Hong Kong. All data were expressed as median and interquartile range (IQR), mean ± standard deviation, or proportions. Between-group differences were compared by Chi-square tests. A p value of ≤0.05 for 2-tailed statistical tests was used to indicate statistical significance. All statistical analyses were performed by using PASW Statistics 18 (SPSS Inc., Chicago [IL], US).

Results

A total of 149 (0.6%) women, at a mean age of 33.5 ± 4.4 years, were identified out of 24,424 maternities during the study period; 78 (52.3%) were primigravida. Of the 149 records that were reviewed, 11 women were non-eligible persons from mainland China without a Hong Kong citizenship, one was from the Philippines who subsequently returned to her home country for delivery, and another woman who had partial thyroidectomy prior to the pregnancy was diagnosed to have miscarriage at 8 weeks of gestation, therefore these 13 women were excluded from analysis.

The sTSH levels in the first TFT performed in our laboratory in the remaining 136 pregnant subjects are shown in Figure. Among them, 96 (70.6%) were hypothyroid at their first antenatal visit according to the gestational age–specific reference ranges, and 29 (21.3%) were diagnosed with overt hypothyroidism. In all, hypothyroidism was diagnosed in 134 subjects prior to the pregnancy, except in two cases who presented with goitre and cold intolerance during pregnancy. The median (IQR) duration between the diagnosis and the pregnancy was 4.0 (1.75-7.00) years. Twelve women with overt hypothyroidism were not on any thyroxine replacement treatment before their first antenatal visit; eight were previously treated in mainland China and were not offered any follow-up, three defaulted their follow-up from the public clinics in Hong Kong,

Table 1. Non-pregnant and gestational age–specific reference ranges of sensitive thyroid-stimulating hormone (sTSH) and free thyroxine (fT4) levels adopted from a previous publication at the Prince of Wales Hospital[9]

Characteristic	Reference range	
	sTSH (mIU/L)	fT4 (pmol/L)
Non-pregnant	0.3-4.2	12-22
Gestational age (weeks)		
<10	0.01-3.1	10-26
≥10 to 14	0.01-2.7	11-33
>14 to 22	0.01-3.9	10-18
>22 to 26	0.01-4.1	8.6-18
>26	0.01-4.3	8.3-22

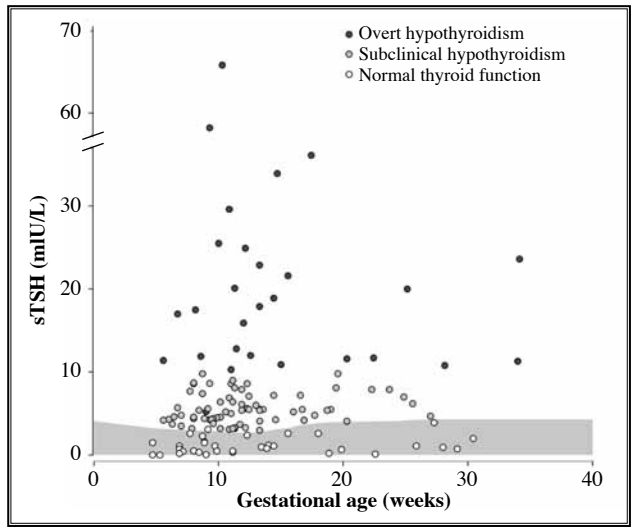

Figure. Dot-plot of sensitive thyroid-stimulating hormone (sTSH) levels in the first thyroid function test against the gestational age when the test was performed

and another one was followed up by general practitioner. Among the 94 women with known hypothyroidism before pregnancy (two cases with hypothyroidism newly diagnosed during pregnancy were excluded), 24 (25.5%) received obstetrician's advice on their condition in the second and third trimester.

Thyroiditis was the most common cause of hypothyroidism followed by post-radioactive iodine treatment for previous hyperthyroidism (Table 2). Causes of hypothyroidism had no association with the patients' thyroid status (p=0.20) nor the gestation period at their first antenatal visits (p=0.85).

Table 3 shows the patient status of previous follow-up and management of their hypothyroidism prior to pregnancy. There was significant association between patient's usual follow-up place with patient's thyroid status (p=0.034) and the gestation period at their first antenatal visit (p=0.031). Patients with no follow-up had significantly worse thyroid function than those followed by family physicians (p=0.014), specialists in public hospital (p=0.029), or private practitioners (p=0.003). Patients who had regular follow-up by public hospital specialists also presented earlier in the antenatal clinic than those who did not have any follow-up (p=0.048) and those who were followed up in the private sector (p=0.009).

Overall, 62.5% (85/136) of the women were on thyroxine replacement therapy during their first antenatal checkup, of whom 54 (63.5%) needed a dose increment during pregnancy. A mean dose increment of 44.6 ± 45.1% was required for this group of patients. The mean final dosage of thyroxine replacement for all women was 107.3 ± 46.3 μg. Of note, 29.1% (39/134) of the women did not have regular follow-up for hypothyroidism prior to pregnancy in spite of a known history of hypothyroidism. Among the 95 women with regular medical attention, 59 (62.1%) had inadequate

Table 2. Thyroid status of the study subjects at their first antenatal visit and their gestation period according to their causes of hypothyroidism*

Cause	No. (%) of patients					
	Thyroid status at first antenatal visit			Trimester at the first presentation in antenatal clinic		
	Euthyroid	Subclinical	Overt	First	Second	Third
RAI (n=45)	9 (20.0)	22 (48.9)	14 (31.1)	32 (71.1)	11 (24.4)	2 (4.4)
Thyroiditis (n=48)	18 (37.5)	24 (50.0)	6 (12.5)	34 (70.8)	12 (25.0)	2 (4.2)
Thyroidectomy (n=39)	13 (33.3)	18 (46.2)	8 (20.5)	30 (76.9)	9 (23.1)	0
Idiopathic (n=2)	0	2 (100)	0	2 (100)	0	0

Abbreviation: RAI = radioactive iodine treatment

* Two patients with hypothyroidism who were newly recognised during pregnancy were excluded from analysis

Table 3. The status of previous follow-up and management among women with known hypothyroidism prior to pregnancy*

Cause	No. (%) of patients					
	Thyroid status at first antenatal visit			Trimester at the first presentation in antenatal clinic		
	Euthyroid	Subclinical	Overt	First	Second	Third
Defaulted FU or no FU (n=39)	4 (10.0)[a,b,c]	22 (55.0)	13 (33.3)	25 (64.1)[d]	11 (28.2)	3 (7.7)
GOPD or family medicine clinic (public) [n=29]	11 (35.5)[a]	14 (45.2)	4 (13.8)	23 (79.3)	6 (20.7)	0
Specialist (public) [n=48]	16 (34.0)[b]	23 (48.9)	9 (18.8)	41 (85.4)[d,e]	7 (14.6)	0
Private doctor (n=18)	9 (56.3)[c]	7 (43.8)	2 (11.1)	9 (50.0)[e]	8 (44.4)	1 (5.6)

Abbreviations: FU = follow-up; GOPD = general outpatient department

* P values of individual group comparison. a, b, and c denote comparisons between euthyroid, subclinical, and overt groups; a: p=0.014, b: p=0.029, c: p=0.003. d and e denote comparisons between different trimesters at the first presentation in antenatal clinic; d: p=0.048 (with Yate's correction), e: p=0.009 (with Yate's correction)

Table 4. Simple outcome measurement among patients who delivered in the maternal unit of Prince of Wales Hospital

Characteristic	Thyroid status at the first antenatal visit (mean ± standard deviation or as otherwise stated)		p Value
	Euthyroid (n=29)	Hypothyroid (n=75)	
Maternal age (years)	34.4 ± 4.7	33.7 ± 3.9	0.358
Maturity (weeks)	38.4 ± 1.4	38.7 ± 2.1	0.537
Male-to-female baby ratio	16:13	38:37	0.680
Birth weight (g)	3076 ± 363	3131 ± 542	0.613
5-Minute Apgar score <7	0	1	0.532
Birth weight <2500 g	2	7	0.545
Delivery before 37 weeks of gestation	2	6	0.532
Delivery before 34 weeks of gestation	0	1	0.731

replacement. Among those patients that delivered in the Prince of Wales Hospital (n=104), there was no significant difference in the pregnancy outcomes between those who were euthyroid and hypothyroid (Table 4).

Discussion

In this short retrospective study, we observed an inadequacy in the counselling and management of subclinical and overt hypothyroidism in pregnant women in Hong Kong. Women with subclinical hypothyroidism are usually asymptomatic while symptoms of overt hypothyroidism, such as cold intolerance and lethargy, may not appear obvious to patients. On the other hand, those who have overt hypothyroidism are usually infertile and seldom achieve pregnancy[11].

Overt hypothyroidism is known to cause adverse maternal and fetal outcomes, hence treatment is recommended for this condition[5,8]. It remains controversial whether routine antenatal screening of subclinical hypothyroidism is beneficial. Most of our experience and practice to manage subclinical hypothyroidism were based on the study by Haddow et al[12] showing that these children had a lower mean intelligence quotient (IQ) and were more predisposed to having learning difficulties compared with those born to euthyroid mothers. However, a recent study[13] did not support routine antenatal screening and thyroxine replacement to mothers with subclinical hypothyroidism in early pregnancy to improve the children's IQ at 3 years of age. Another similar study[14] supported by the National Institute of Child Health and Human Development is ongoing and will provide further information by 2015.

Nonetheless, for mothers with a known history of thyroid disease, in particular those who require thyroxine replacement, it remains a standard practice to monitor the TFT and render mothers euthyroid throughout pregnancy as soon as possible[7,15]. Our study showed that 63.5% of the patients who had already been treated before pregnancy needed a mean 44.6% increment in their thyroxine dosage. This is consistent with findings from a previous study in the western population[6].

There are several limitations in this study. Firstly, the total number of women with hypothyroidism might be underestimated; pregnant women who were not referred to the high-risk obstetrics clinic might have been omitted from the audit. However, the prevalence was similar to that reported in the literature[16]. Secondly, this was a retrospective study, so we could not ascertain whether these women had been counselled on the importance of adequate thyroxine replacement, particularly in the early gestational period when the fetus totally relies on the mother for thyroxine, and whether they knew they should seek medical advice immediately after becoming pregnant. Furthermore, there were no comparison data available on the adverse pregnancy outcomes between mothers who were euthyroid and those who suffered a period of inadequate thyroxine replacement during pregnancy. Moreover, we are uncertain of the underlying cause of the high rate of subclinical hypothyroidism and overt hypothyroidism detected at the first antenatal visit due to lack of data on their thyroid function immediately before conception. It could be due to suboptimal treatment before pregnancy or an increase in demand during pregnancy.

It has been suggested that thyroid function should be evaluated before conception and at least once during

the first trimester. Any inadequacy in treatment should be replaced promptly[15]. In view of the finding that about three-quarters of the subjects with a history of hypothyroidism had abnormal thyroid function at their first antenatal visit, and that more than one-third of them were not recognised until the second trimester, we see an urgent need to advocate pre-conception counselling in Hong Kong in this regard. It would be useful to conduct a survey of women in the reproductive age with known hypothyroidism to evaluate their knowledge about the importance of thyroid function monitoring and thyroxine replacement in the peri-conception period. In addition, it will also be worthwhile to assess the usual practice among clinicians on providing pre-conception counselling to this at-risk group.

References

1. Klein RZ, Haddow JE, Faix JD, et al. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 1991; 35:41-6.
2. Glinoer D. The systematic screening and management of hypothyroidism and hyperthyroidism during pregnancy. *Trends Endocrinol Metab* 1998; 9:403-11.
3. Choufoer JC, Vanrhijn M, Querido A. Endemic goiter in western New Guinea. II. Clinical picture, incidence and pathogenesis of endemic cretinism. *J Clin Endocrinol Metab* 1965; 25:385-402.
4. Bernal J, Pekonen F. Ontogenesis of the nuclear 3,5,3'-triiodothyronine receptor in the human fetal brain. *Endocrinology* 1984; 114:677-9.
5. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. *Obstet Gynecol* 1988; 72:108-12.
6. Mandel SJ, Larsen PR, Seely EW, Brent GA. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med* 1990; 323:91-6.
7. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 381: subclinical hypothyroidism in pregnancy. *Obstet Gynecol* 2007; 110:959-60.
8. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2012; 97:2543-65.
9. Panesar NS, Li CY, Rogers MS. Reference intervals for thyroid hormones in pregnant Chinese women. *Ann Clin Biochem* 2001; 38:329-32.
10. Wartofsky L, Van Nostrand D, Burman KD. Overt and 'subclinical' hypothyroidism in women. *Obstet Gynecol Surv* 2006; 61:535-42.
11. Krassas GE. Thyroid disease and female reproduction. *Fertil Steril* 2000; 74:1063-70.
12. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New Engl J Med* 1999; 341:549-55.
13. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; 366:493-501.
14. Eunice Kennedy Shriver National Institute of Child Health and Human Development. *A randomized trial of thyroxine therapy for subclinical hypothyroidism or hypothyroxinemia diagnosed during pregnancy*. Available from: http://clinicaltrials.gov/ct2/show/NCT00388297. Accessed 15 Feb 2013.
15. Nelson-Piercy C. *Handbook of obstetric medicine*. 4th ed. London: Informa Health; 2010: 101-3.
16. Allan WC, Haddow JE, Palomaki GE, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 2000; 7:127-30.