0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(1):203–207

doi: 10.1210/jc.2006-1748

BRIEF REPORT

Detection of Thyroid Dysfunction in Early Pregnancy: Universal Screening or Targeted High-Risk Case Finding?

Bijay Vaidya, Sony Anthony, Mary Bilous, Beverley Shields, John Drury, Stewart Hutchison, and Rudy Bilous

Department of Endocrinology (B.V., B.S.), Peninsula Medical School, Royal Devon & Exeter Hospital, Exeter EX2 5DW, United Kingdom; and Departments of Endocrinology (S.A., M.B., R.B.), Clinical Biochemistry (J.D.), and Obstetrics (S.H.), James Cook University Hospital, Middlesbrough TS4 3BW, United Kingdom

Context: Maternal subclinical hypothyroidism during pregnancy is associated with various adverse outcomes. Recent consensus guidelines do not advocate universal thyroid function screening during pregnancy but recommend testing high-risk pregnant women with a personal history of thyroid or other autoimmune disorders or with a family history of thyroid disorders.

Objective: The objective of the study was to assess efficacy of the targeted high-risk case-finding approach in identifying women with thyroid dysfunction during early pregnancy.

Design/Setting: This was a single-center cohort study.

Patients/Outcome Measures: We prospectively analyzed TSH, free T_4 and free T_3 in 1560 consecutive pregnant women during their first antenatal visit (median gestation 9 wk). We tested thyroperoxidase antibodies in 1327 (85%). We classified 413 women (26.5%), who had a personal history of thyroid or other autoimmune disorders or a family history of thyroid disorders, as a high-risk group. We examined whether testing only such a high-risk group would pick up most pregnant women with thyroid dysfunction.

Results: Forty women (2.6%) had raised TSH (>4.2 mIU/liter). The prevalence of raised TSH was higher in the high-risk group [6.8 *vs.* 1% in the low-risk group, relative risk (RR) 6.5, 95% confidence interval (CI) 3.3–12.6, $P < 0.0001$]. Presence of personal history of thyroid disease (RR 12.2, 95% CI 6.8–22, $P < 0.0001$) or other autoimmune disorders (RR 4.8, 95% CI 1.3–18.2, $P = 0.016$), thyroperoxidase antibodies (RR 8.4, 95% CI 4.6–15.3, $P < 0.0001$), and family history of thyroid disorders (RR 3.4, 95% CI 1.8–6.2, $P < 0.0001$) increased the risk of raised TSH. However, 12 of 40 women with raised TSH (30%) were in the low-risk group.

Conclusion: Targeted thyroid function testing of only the high-risk group would miss about one third of pregnant women with overt/subclinical hypothyroidism. **(*J Clin Endocrinol Metab* 92: 203–207, 2007)**

MATERNAL SUBCLINICAL hypothyroidism during early pregnancy has been shown to be associated with impaired neuropsychological development of children and several other adverse outcomes, including premature birth, preeclampsia, breech delivery, and increased fetal mortality (1–5). These findings have triggered a debate about whether all pregnant women should be screened for hypothyroidism. The recent consensus guidelines from an expert panel sponsored by the American Thyroid Association, the American Association of Clinical Endocrinologists, and The Endocrine Society did not advocate universal screening of thyroid function during pregnancy but recommended aggressive case finding in high-risk pregnant women who have a family or personal history of thyroid disorders, a personal history of type 1 diabetes or other autoimmune disorders, or clinical features suggestive of a thyroid disorder (6). We examined efficacy of this targeted high-risk case-finding approach in identifying women with thyroid dysfunction during early pregnancy.

First Published Online October 10, 2006

Abbreviations: CI, Confidence interval; FT3, free T_3; FT4, free T_4; RR, relative risk; TPOAb, thyroperoxidase antibody.

Subjects and Methods

Subjects

Between June 2002 and July 2003, we invited pregnant women who were attending the James Cook University Hospital (Middlesbrough, UK) for their first antenatal check-up to have screening blood tests for thyroid function and thyroid antibodies. Their demographic and clinical details were collected as a part of routine antenatal care and were recorded on the local maternity database. We specifically asked the women about personal and family history (in first and second degree relatives) of thyroid disorders; personal and family history of other autoimmune diseases; and current and past treatment with antithyroid drugs, T_4, radioiodine, or thyroid surgery. Duration of gestation was calculated from last menstrual period and verified by ultrasonography.

The local research ethics committee approved the study, and all participating women gave informed written consent.

Analysis of thyroid function and thyroid antibodies

Serum concentrations of TSH, free T_4 (FT4), and free T_3 (FT3) were measured by the fully automated electrochemiluminescent immunoassay, run on the Modular E 170 analyzer (Roche Diagnostics Ltd., Lewes,

UK). The between-batch coefficient of variations for TSH, FT4, and FT3 were 2.9, 4.5, and 5.5%, respectively. Thyroperoxidase antibodies (TPOAbs) were analyzed by a manual semiquantitative microtiter plate agglutination method using the Serodia kit (Fujirebio Inc., Tokyo, Japan). A reactive pattern detected at a final dilution of 1 in 1600 or greater was considered positive.

The manufacturers' population reference ranges for TSH, FT4, and FT3 were 0.27–4.2 mIU/liter, 12–23 pmol/liter, and 4–7.8 pmol/liter, respectively. Women, who were found to have abnormal thyroid function at screening were reviewed in the joint antenatal endocrine clinic. We offered T_4 replacement or increased the dose if already on T_4 replacement for women with TSH greater than 4.2 mIU/liter.

In recent years, it has been suggested that trimester-specific reference ranges should be used for the assessment of thyroid function in pregnancy (7, 8). Therefore, we also carried out a *post hoc* analysis of our cohort to define first trimester-specific reference ranges for TSH, FT4, and FT3. The results of women in the first trimester (up to wk 12) who had no personal or family history of thyroid disease and who were negative for TPOAbs were used for the analysis. The TSH, FT4, and FT3 results were square root transformed to enable normal distribution, and therefore, the reference ranges were based on the squared 95% confidence intervals.

Statistical analysis

We used χ^2 test for statistical comparisons (SPSS version 11.5; SAS Institute, Cary, NC).

Results

Study population

We screened thyroid function in 1560 pregnant women. TPOAbs were checked in 1327 (85%). Demographic characteristics of these pregnant women are shown in Table 1. Mean age of the women was 27 yr and median duration of gestation was 9 wk. The majority (91.4%) were whites; 4% were South Asian (Indian, Pakistani, Bangladeshi, and Sri-Lankan origin). Eighty-nine women (5.7%) reported a history of thyroid disorder; 42 hypothyroidism (overt or subclinical), 25 hyperthyroidism (overt or subclinical), six goiter/thyroid nodule, and 16 unspecified. At screening, 35 (2.2%) were on T_4 (median dose 100 μg; range 50–200 μg); 946 (60.6%) and 59 (3.8%) were taking folic acid and multivitamin tablets, respectively.

TABLE 1. Demographic characteristics of pregnant women (n = 1560)

Characteristics	
Mean (± SD) maternal age (yr)	27 (± 6)
Median (range) gestational age at screening (wk)	9 (6–22)
Gestational age at screening, n (%)	
<9 wk	577 (37)
9 to <12 wk	638 (40.1)
12 to <15 wk	196 (12.6)
>15 wk	112 (7.4)
Ethnicity, n (%)	
Whites	1426 (91.4)
South Asians	62 (4)
Other races	72 (4.6)
Smoking, n (%)	
Total smokers	701 (44.9)
Smokers during pregnancy	424 (27.2)
Pregnancy after fertility treatment, n (%)	30 (1.9)
History of previous pregnancy, n (%)	
None	506 (32.4)
One pregnancy	468 (30)
Two pregnancies	265 (17)
More than two pregnancies	321 (20.6)
History of previous miscarriages, n (%)	340 (21.8)
History of previous stillbirth, n (%)	23 (1.5)
Personal history of thyroid disease, n (%)	89 (5.7)
On T_4 replacement, n (%)	35 (2.2)
Personal history of other autoimmune diseases, n (%)[a]	17 (1.1)
Family history of thyroid disease, n (%)	356 (22.8)

[a] Includes Crohn's disease (n = 7), rheumatoid arthritis (n = 2), celiac disease (n = 2), Addison's disease (n = 1), alopecia (n = 1), lupus (n = 1), Raynaud's disease (n = 1), type 1 diabetes (n = 1), and vitiligo (n = 1).

Based on the expert panel guidelines (6), we classified 413 women (26.5%), who had a personal or family history of thyroid disorder or a personal history of other autoimmune disease, as a high-risk group.

Prevalence of raised TSH

Forty women (2.6%) had raised TSH (>4.2 mIU/liter), 16 of whom also had low FT4 (<12 pmol/liter) (Table 2). Of the 16 women with raised TSH and low FT4, eight had TPOAbs (TPOAbs unknown in four). Overall, eight women had TSH greater than 10 mIU/liter, five of whom had low FT4.

The prevalence of raised TSH (>4.2 mIU/liter) was higher in the high-risk group (6.8 *vs.* 1% in the low-risk group, relative risk (RR) 6.5, 95% confidence interval 3.3–12.6, $P < 0.0001$). Presence of personal history of thyroid diseases (RR 12.2, $P < 0.0001$), personal history of other autoimmune disorders (RR 4.8, $P = 0.016$), TPOAbs (RR 8.4, $P < 0.0001$), and family history of thyroid disorders (RR 3.4, $P < 0.0001$) increased the risk of raised TSH (Table 3). Nonetheless, 12 of 40 women with raised TSH (30%) were in the low-risk group. Of the 12 women with raised TSH in the low-risk group, two had TSH above 10 mIU/liter and three had TPOAbs (TPOAb unknown in one). If the criteria for the high-risk group is extended to include other possible risk factors, such as age older than 35 yr, current smoking, and a history of miscarriage, six of 40 women with raised TSH (15%) would still belong to the low-risk group.

Overall, older age (>35 yr), smoking (all smokers), previous pregnancy, or a history of miscarriage was not associated with raised TSH (Table 3). South-Asian ethnicity was associated with an increased risk of raised TSH (RR 2.8, $P = 0.04$). Interestingly, the prevalence of raised TSH among smokers during the pregnancy was lower than that in nonsmokers (1.2 *vs.* 3.2%, $P = 0.03$). Within the low-risk group, the prevalence of raised TSH was not affected by smoking status or maternal age above 35 yr. There were no significant differences in maternal age; ethnicity; smoking status; and number of previous pregnancies, miscarriages, and stillbirths between the women with raised TSH in the high-risk group, compared with those in the low-risk group (data not shown).

We found that 7.8% of the women with normal TSH had low FT4 (Table 2).

Prevalence of fully suppressed TSH

A fully suppressed TSH level (<0.03 mIU/liter) was found in 29 women (1.9%); 11 of them also had raised FT4 and/or FT3 (Table 2). There was no significant difference in the

TABLE 2. Screening thyroid function in early pregnancy[a]

	Normal TSH[a]				Raised TSH[a]			Low but detectable TSH[a]			Fully suppressed TSH[a]		
	Normal FT4	High FT4	Low FT4	Total	Normal FT4	Low FT4	Total	Normal FT4 and FT3	High FT4 or FT3	Total	Normal FT4 and FT3	High FT4 or FT3	Total
All women (n = 1560)	1274 (81.7)	3 (0.2)	122 (7.8)	1399 (89.7)	24 (1.5)	16 (1)	40 (2.6)	88 (5.6)	4 (0.3)	92 (5.9)	18 (1.2)	11 (0.7)	29 (1.9)
Low-risk women (n = 1147)[b]	959 (83.6)	3 (0.3)	89 (7.8)	1051 (91.6)	8 (0.7)	4 (0.3)	12 (1.0)	62 (5.4)	2 (0.2)	64 (5.6)	12 (1.0)	8 (0.7)	20 (1.7)
High-risk women (n = 413)[c]	315 (76.3)	0	33 (8.0)	348 (84.3)	16 (3.9)	12 (2.9)	28 (6.8)	26 (6.3)	2 (0.5)	28 (6.8)	6 (1.5)	3 (0.7)	9 (2.2)
Women with known thyroid disorder (n = 89)	56 (62.9)	0	3 (3.4)	59 (66.3)	11 (12.4)	6 (6.7)	17 (19.1)	8 (9)	1 (1.1)	9 (10.1)	2 (2.2)	2 (2.2)	4 (4.5)
Women with autoimmune disorders (n = 17)	13 (76.5)	0	1 (5.9)	14 (82.4)	2 (11.8)	0	2 (11.8)	0	1 (5.9)	1 (5.9)	0	0	0
Women with thyroid disorder in family (n = 356)	274 (77)	0	31 (8.7)	305 (85.7)	10 (2.8)	10 (2.8)	20 (5.6)	21 (5.9)	2 (0.6)	23 (6.5)	5 (1.4)	3 (0.8)	8 (2.2)
Women on T_4 (n = 35)	18 (51.4)	0	1 (2.9)	19 (54.3)	6 (17.1)	2 (5.7)	8 (22.9)	4 (11.4)	2 (5.7)	6 (17.1)	1 (2.9)	1 (2.9)	2 (5.7)
Women with TPOAbs (n = 126)	92 (73)	0	8 (6.3)	100 (79.4)	9 (7.1)	8 (6.3)	17 (13.5)	6 (4.8)	0	6 (4.8)	2 (1.6)	1 (0.8)	3 (2.4)

[a] Normal range: TSH, 0.27–4.2 mIU/liter; FT4, 12–23 pmol/liter; FT3, 4–7.8 pmol/liter. Fully suppressed TSH, less than 0.03 mIU/liter. Data represent number of pregnant women (percent).

[b] Low-risk women are those without personal history of thyroid or other autoimmune disorders, and without family history of thyroid disorders.

[c] High-risk women are those with personal history of thyroid or other autoimmune disorders, or with family history of thyroid disorders.

prevalence of fully suppressed TSH between the high-risk and low-risk groups (Table 3).

Prevalence of thyroid dysfunction in women on T_4 replacement

Thirty-five women were on T_4 replacement at recruitment; eight of them (22.9%) had raised TSH (Table 2). Two women had fully suppressed TSH.

First trimester-specific reference ranges for TSH, FT4, and FT3

The *post hoc* analysis of our cohort defined first trimester-specific reference ranges for TSH, FT4, and FT3 as 0.09–3.03 mIU/liter, 10.6–20.4 pmol/liter, and 3.4–7.1 pmol/liter, respectively. An analysis of the data using these trimester-specific reference ranges showed 98 women (6.3%) as having raised TSH (>3.03 mIU/liter); 54 of 413 in the high-risk group (13.1%), compared with 44 of 1147 in the low-risk group (3.8%) had raised TSH (RR 3.41, 95% CI 3.16–3.67, $P < 0.0001$). Overall, 44 of 98 women with raised TSH (44.9%) belonged to the low-risk group. The analysis also showed that 25 of the 1560 women (1.6%) as having hypothyroxemia (normal TSH but a low FT4 level); none of these women were positive for TPOAbs.

Discussion

This prospective screening of thyroid function in a cohort of unselected pregnant women shows that high-risk women (with a personal or family history of thyroid disorders or a personal history of other autoimmune diseases) have more than a 6-fold increased risk of hypothyroidism (subclinical or overt) during early pregnancy. However, testing only the high-risk pregnant women, as the consensus guidelines recommend (6), would miss about one third of women with hypothyroidism. Subclinical hypothyroidism during early pregnancy is common, affecting about 2.5% pregnant women (5, 9). Therefore, with the growing evidence for an association between maternal subclinical hypothyroidism and adverse pregnancy outcomes but lack of intervention trials showing beneficial effect of T_4 in preventing these adverse outcomes, the controversy between targeted high-risk case-finding and universal screening continues (10–12). The consensus guidelines recommend the use of T_4 in pregnant women with subclinical hypothyroidism, justified on the basis of potential benefit to risk ratio (6). Our study shows that, without universal screening, a significant number of such pregnant women with thyroid dysfunction will not be picked up. Furthermore, our previous audit has highlighted the difficulty in implementing targeted screening: despite the development and circulation of local guidelines, less than 20% of the high-risk pregnant women in the district were screened for thyroid dysfunction (13).

Several factors affect thyroid function tests during various stages of pregnancy. FT4 increases with suppression of TSH in response to placental human chorionic gonadotrophin during the first trimester, whereas FT4 tends to decrease in late gestation (3, 14). This is likely to be the cause for the high prevalence of suppressed TSH in our cohort. Furthermore,

TABLE 3. RRs for raised and fully suppressed TSH at screening

Risk factors	Raised TSH (>4.2 mIU/liter)			Full suppressed TSH (<0.03 mIU/liter)		
	RR	95% CI	*P* value	RR	95% CI	*P* value
Personal history of thyroid disease	12.2	6.8–22	<0.0001	0.7	0.1–5.0	0.68
Personal history of type 1 diabetes and other autoimmune disorders	4.8	1.3–18.2	0.016	0		0.568
Family history of thyroid disorders	3.4	1.8–6.2	<0.0001	1.3	1.0–1.9	0.5
TPOAbs	8.4	4.6–15.3	<0.0001	1.3	0.6–2.7	0.67
Older age (>35 yr)	1.4	0.7–2.8	0.551	1	0.5–2	0.99
Smoking (all smokers)	1.0	0.8–1.2	0.993	1	0.8–1.2	0.99
Smoking during pregnancy	0.4	0.25–0.6	0.03	0.6	0.4–0.9	0.23
Previous pregnancy	0.9	0.7–1.1	0.739	1.9	1.2–2.8	0.17
History of miscarriage	1.3	1.1–1.6	0.425	1.1	0.8–1.6	0.78
South Asian ethnicity	2.8	1.6–4.6	0.04	2.8	1.4–5.7	0.08

increased serum thyroid-binding globulin and decreased albumin during pregnancy result in assay-dependent variations in FT4 levels (15). These observations have led to the call for using trimester- and assay-specific reference ranges for thyroid function tests in pregnancy (7, 8). If the trimester-specific reference range is used, 6.3% pregnant women in our cohort will be considered to have hypothyroidism. Whereas there will be less of a controversy to use the trimester-specific reference range in titrating the dose of T_4 in pregnant women on T_4 replacement, further studies are needed to determine the threshold level of TSH at which initiation of T_4 replacement should be considered.

There is also an uncertainty regarding the most appropriate initial screening test for thyroid dysfunction in pregnancy. The consensus guidelines recommend using TSH as the initial test (6), whereas others have stressed the importance of testing FT4 by highlighting the fact that FT4 (and FT3) is responsible for thyroid hormone action and that maternal hypothyroxinemia (normal TSH but low FT4) is associated with neuropsychological deficit in the offspring (16, 17). In our study, 7.8% (1.6% if we use the trimester specific reference ranges) of pregnant women had hypothyroxemia. The cause of maternal hypothyroxemia is not fully understood, but iodine deficiency is thought to be a major factor (18). Although urinary iodine was not analyzed in the present cohort, a previous study in this same population has shown that 7 and 40% pregnant women have urinary iodine excretion of less than 50 μg/liter (suggestive of dietary iodine deficiency) and 50–100 μg/liter (suggestive of borderline iodine deficiency) (19).

Nearly one quarter of hypothyroid women on T_4 replacement in this study had raised TSH at their first antenatal visit. Given the fact that the fetus relies entirely on maternal thyroid hormones for its development until about 13 wk gestation, it is critical to ensure adequate T_4 replacement in pregnant women during the first trimester. Hypothyroid pregnant women on T_4 require an increased dose from as early as the fifth week of gestation to maintain optimum T_4 replacement (20). Some recommend a 30% increase in the T_4 dose as soon as the pregnancy is confirmed, with further dose adjustments based on TSH measurements (20). In addition, through education of all hypothyroid women in the reproductive age, every attempt should be made to ensure an adequate T_4 replacement before a planned pregnancy.

There are several limitations of our study. First, our study was based on single thyroid function test at screening. The data on subsequent thyroid function tests during the pregnancy were not collected systematically. Second, we relied on patients' recall in ascertaining personal and family history of thyroid and other autoimmune disorders and have not verified by reviewing case records. Finally, our cohort may not represent other populations with different ethnic mix and iodine intake.

In conclusion, this study shows that targeted thyroid function testing of only high-risk pregnant women would miss nearly one third of women with overt/subclinical hypothyroidism during early pregnancy.

Acknowledgments

We gratefully acknowledge the help of Patricia Wood and Elaine McGeary in recruitment and Elaine Hall and Barbara Woodward in organizing the databases.

Received August 11, 2006. Accepted October 4, 2006.

Address all correspondence and requests for reprints to: Dr. Bijay Vaidya, Department of Endocrinology, Royal Devon, Exeter Hospital, Exeter EX2 5DW, United Kingdom. E-mail: bijay.vaidya@pms.ac.uk.

This study was presented in part at the 13th International Thyroid Congress, Buenos Aires, Argentina, October 30 to November 4, 2005.

Disclosure: The authors have nothing to disclose.

References

1. **Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ** 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555
2. **Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ** 2000 Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 7:127–130
3. **Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ** 2003 Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 59:282–288
4. **Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG, Vader HL** 2004 Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation? BJOG 111:925–930
5. **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
6. **Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ** 2004 Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291:228–238
7. **Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR** 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 13:3–126
8. **Mandel SJ, Spencer CA, Hollowell JG** 2005 Are detection and treatment of thyroid insufficiency in pregnancy feasible? Thyroid 15:44–53

9. **Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML** 1991 Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 35:41–46
10. **Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT** 2005 Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 90:581–585; discussion 586–587
11. **Ringel MD, Mazzaferri EL** 2005 Subclinical thyroid dysfunction—can there be a consensus about the consensus? J Clin Endocrinol Metab 90:588–590
12. **Surks MI** 2005 Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab 90:586–587
13. **Vaidya B, Bilous M, Hutchinson RS, Connolly V, Jones S, Kelly WF, Bilous RW** 2002 Screening for thyroid disease in pregnancy: an audit. Clin Med 2:599–600
14. **Burrow GN, Fisher DA, Larsen PR** 1994 Maternal and fetal thyroid function. N Engl J Med 331:1072–1078
15. **Roti E, Gardini E, Minelli R, Bianconi L, Flisi M** 1991 Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J Endocrinol Invest 14:1–9
16. **Morreale de Escobar G, Obregon MJ, Escobar del Rey F** 2000 Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? J Clin Endocrinol Metab 85:3975–3987
17. **Pop VJ, Vulsma T** 2005 Maternal hypothyroxinaemia during (early) gestation. Lancet 365:1604–1606
18. **Morreale de Escobar G, Obregon MJ, Escobar del Rey F** 2004 Role of thyroid hormone during early brain development. Eur J Endocrinol 151(Suppl 3):U25–U37
19. **Kibirige MS, Hutchison S, Owen CJ, Delves HT** 2004 Prevalence of maternal dietary iodine insufficiency in the north east of England: implications for the fetus. Arch Dis Child Fetal Neonatal Ed 89:F436–F439
20. **Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR** 2004 Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 351:241–249

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.