Subclinical Hypothyroidism and Pregnancy Outcomes

Brian M. Casey, MD, Jodi S. Dashe, MD, C. Edward Wells, MD, Donald D. McIntire, PhD, William Byrd, PhD, Kenneth J. Leveno, MD, and F. Gary Cunningham, MD

BACKGROUND: Clinical thyroid dysfunction has been associated with pregnancy complications such as hypertension, preterm birth, low birth weight, placental abruption, and fetal death. The relationship between subclinical hypothyroidism and pregnancy outcomes has not been well studied. We undertook this prospective thyroid screening study to evaluate pregnancy outcomes in women with elevated thyrotropin (thyroid-stimulating hormone, TSH) and normal free thyroxine levels.

METHODS: All women who presented to Parkland Hospital for prenatal care between November 1, 2000, and April 14, 2003, had thyroid screening using a chemiluminescent TSH assay. Women with TSH values at or above the 97.5th percentile for gestational age at screening and with free thyroxine more than 0.680 ng/dL were retrospectively identified with subclinical hypothyroidism. Pregnancy outcomes were compared with those in pregnant women with normal TSH values between the 5th and 95th percentiles.

RESULTS: A total of 25,756 women underwent thyroid screening and were delivered of a singleton infant. There were 17,298 (67%) women enrolled for prenatal care at 20 weeks of gestation or less, and 404 (2.3%) of these were considered to have subclinical hypothyroidism. Pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption (relative risk 3.0, 95% confidence interval 1.1–8.2). Preterm birth, defined as delivery at or before 34 weeks of gestation, was almost 2-fold higher in women with subclinical hypothyroidism (relative risk, 1.8, 95% confidence interval 1.1–2.9).

CONCLUSION: We speculate that the previously reported reduction in intelligence quotient of offspring of women with subclinical hypothyroidism may be related to the effects of prematurity. (Obstet Gynecol 2005;105:239–45. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: II-2

The importance of maternal thyroid hormones for fetal central nervous system development is well established. Maternal thyroxine is particularly critical early in pregnancy because the fetal thyroid gland cannot synthesize iodothyronines until after 10 weeks of gestation. From this time onward, maternal as well as fetal thyroid hormones seem to be necessary for normal neurodevelopment.[1] With maternal and fetal thyroid insufficiency caused by severe iodine deficiency, the infant has profound neurologic impairment and mental retardation.[2,3] Overt maternal hypothyroidism from glandular failure, particularly in the first trimester, is also associated with intellectual impairment during childhood as well as pregnancy complications that include preeclampsia, placental abruption, preterm birth, low birth weight, and fetal death.[4,5] The effects of mild maternal thyroid deficiency with a normally functioning fetal thyroid gland are less clear. This is of importance because the spectrum of thyroid deficiency begins with subclinical hypothyroidism characterized by an elevated serum thyrotropin (thyroid-stimulating hormone, TSH) concentration but a normal serum free thyroxine level.[6,7]

Subclinical hypothyroidism has a prevalence of 2% to 5% in pregnant women.[8,9,10] Concerns that mild maternal thyroid hormone deficiency might be harmful to embryofetal brain development were addressed in several recent landmark studies in 1999. Pop and colleagues[11] found that during pregnancy maternal free thyroxine levels less than the 10th percentile at 12 weeks of gestation, but not at 32 weeks, were associated with a significant 5.8-fold risk for impaired psychomotor development in infants evaluated at 10 months of age. These findings were later confirmed through developmental testing of a cohort of these children at ages 1 and 2 years.[12] Haddow and colleagues[13] reported that children of women whose TSH levels were elevated during the midtrimester of pregnancy had a slight but significant reduction in intelligence quotient scores between 7 and 9 years of age when compared with infants of euthyroid women. Women with TSH values more than 10 mU/L also had significantly more stillborn infants.[14] Somewhat related are previous reports that subclinical maternal hypothyroidism might be associated with poor pregnancy outcomes such as placental abruption, preterm birth, and low birth weight infants.[4,5] To further elucidate these observations, we designed this prospective

From the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas.

0029-7844/05/$30.00
doi:10.1097/01.AOG.0000152345.99421.22

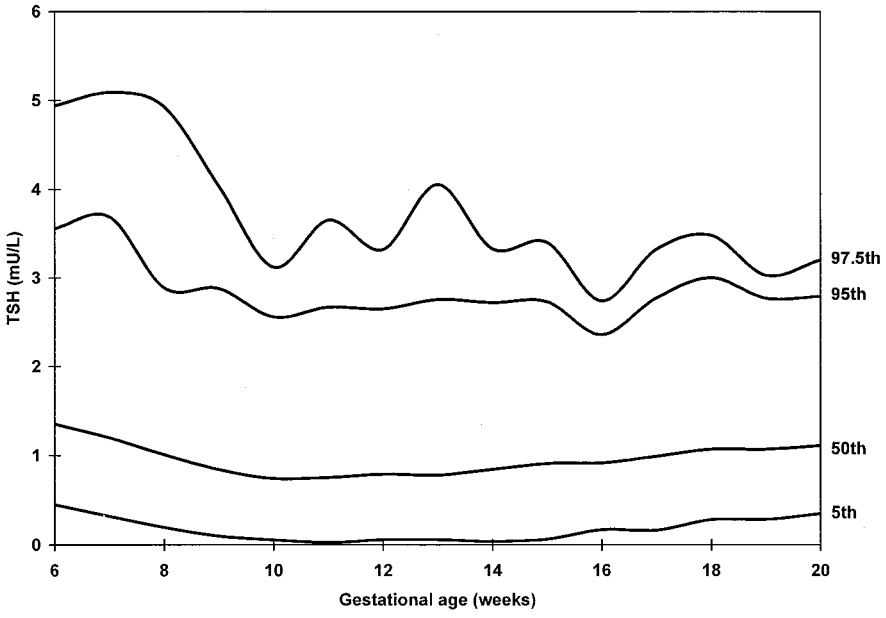

Fig. 1. Median, 5th, 95th, and 97.5th percentile thyrotropin values according to weeks of gestation at screening in 17,298 women who presented for prenatal care at or before 20 weeks. TSH, thyroid-stimulating hormone (thyrotropin).

Casey. Subclinical Hypothyroidism and Preterm Birth. Obstet Gynecol 2005.

screening study of a large obstetric population to evaluate pregnancy outcomes in women with subclinical hypothyroidism.

MATERIALS AND METHODS

Parkland Health and Hospital System is a tax-supported institution serving the medically indigent in Dallas County. The Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical School supervises the delivery of all women's health care at 10 clinic sites throughout Dallas County and at Parkland Hospital. Beginning with enrollment for prenatal care at these sites, obstetric care for women delivered at Parkland Hospital is coordinated throughout pregnancy, delivery, and the puerperium by members of the Division of Maternal Fetal Medicine.

All women who present for prenatal care, regardless of gestational age, undergo immediate prenatal laboratory testing including screening for rubella status. With the approval of the Institutional Review Boards at the University of Texas Southwestern and Parkland Hospital, excess serum from each rubella screen was delivered to an immunochemistry research laboratory in the Department of Obstetrics and Gynecology for thyroid testing. Thyroid function studies were performed using chemiluminescent assays for TSH and free thyroxine. Specifically, these assays were performed using an Immulite 2000 Analyzer (Diagnostic Products Corporation, Los Angeles, CA). The analytical sensitivity of the TSH assay was 0.002 mU/L. The coefficient of variation was 3.8% within a run and 4.6% between runs using specimens in the normal range. The sensitivity limit for free thyroxine was 0.18 ng/mL. The within-run coefficient of variation was 7.1% and was 6.4% between runs.

Serum samples from women screened for a 1-month period (October 2000) were analyzed to estimate the 95th percentile value for TSH (uncorrected for gestational age) in our obstetric population (3.0 mU/L). Serum from women (November 1, 2000 to April 14, 2003) with TSH values above 3.0 mU/L was prospectively assayed for free thyroxine. Those women with both an abnormally elevated TSH and a low free thyroxine ($<$ 0.9 ng/dL) were contacted for referral to a special obstetric complications clinic for evaluation and treatment. The Institutional Review Boards at the University of Texas Southwestern and Parkland Hospital approved this identification and referral of women with clinical hypothyroidism.

Women who were screened at 20 weeks of gestation or less and delivered a singleton infant weighing 500 g or more during the screening period were analyzed. For the purposes of this study, women with TSH values at or above the 97.5th percentile for gestational age at screening and with free thyroxine more than 0.680 ng/dL were retrospectively identified with subclinical hypothyroidism. The free thyroxine threshold of 0.680 ng/dL was established using the 2nd percentile from available free thyroxine values of women in the study cohort. The 97.5th percentile for TSH corrected for gestational age varied between 2.74 mU/L and 5.09 mU/L (Fig. 1). Pregnancy outcomes in women identified with subclinical hypothyroidism were compared with those in

women with TSH values between the 5th and 95th percentiles.

Selected obstetric and neonatal outcomes for all women delivering infants at Parkland Hospital are routinely entered into a computerized perinatal database. Nurses attending each delivery complete an obstetric data sheet and research nurses assess the data for consistency and completeness before electronic storage. Data on infant outcomes are abstracted from discharge records. Results from thyroid function studies (TSH and free thyroxine) were electronically stored and linked to the perinatal and infant databases.

Gestational age at screening was established using the obstetric estimate of gestational age recorded at delivery. This gestational age is based on the woman's certain last menstrual period (LMP), with sonography performed if there are discrepancies between fundal height and LMP or if the LMP is uncertain. This method of gestational age determination has been found to correlate well with sonographic and pediatric estimates in our population.[15] Gestational hypertension was defined as an intrapartum systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg. Severe preeclampsia was diagnosed in women with hypertension who had at least 1 of the following: blood pressure more than 160/110 mm Hg, serum creatinine more than 1.0 mg%, platelet count less than 100,000/μL, serum aspartate aminotransferase level at least twice the upper normal value, persistent headache or scotomata, 2+ or greater proteinuria, or more than 2 g of protein excreted in 24 hours. Preterm birth was defined as gestational age of 34 weeks or less at delivery. Infants with major malformations included those with aneuploidy, an identifiable syndrome, and those with an anomaly involving a principal organ system.[16]

Pearson's χ^2 and Student t tests were used for univariate 2-group comparisons. Logistic regression was applied to examine the significance for preterm birth adjusted for age, race, and placental abruption. The Hosmer-Lemeshow statistic examined the goodness-of-fit for the logistic regression models.[17] Statistical computations were performed using SAS 8.2 (SAS Institute, Cary, NC). A 2-tailed $P < .05$ was judged statistically significant.

RESULTS

As shown in Figure 2, between November 1, 2000, and April 14, 2003, a total of 25,756 women underwent thyroid screening and delivered a singleton infant at Parkland Hospital. Of these, 17,298 (67%) enrolled for prenatal care at 20 weeks gestation or less and 436 (2.5%) had screening TSH values at or above the 97.5th percentile threshold for their gestational age in weeks (Fig. 2). Of these, 32 (0.2%) had a free thyroxine less than or equal to 0.680 ng/dL and were considered to have overt hypothyroidism. These women were referred for evaluation and treatment and thus excluded from this analysis. Therefore, 404 women with TSH values at the 97.5th percentile and normal free thyroxine were considered to have subclinical hypothyroidism and served as the study group. The TSH levels in these women ranged from 2.74 mU/L to more than 75 mU/L. Shown in Figure 3 is the distribution of TSH values for women with either overt or subclinical hypothyroidism. One eighth of women with subclinical hypothyroidism (n = 50) had TSH values greater than 10 mU/L. A significant majority of women with overt hypothyroidism had TSH values of 10 mU/L or greater ($P < .001$).

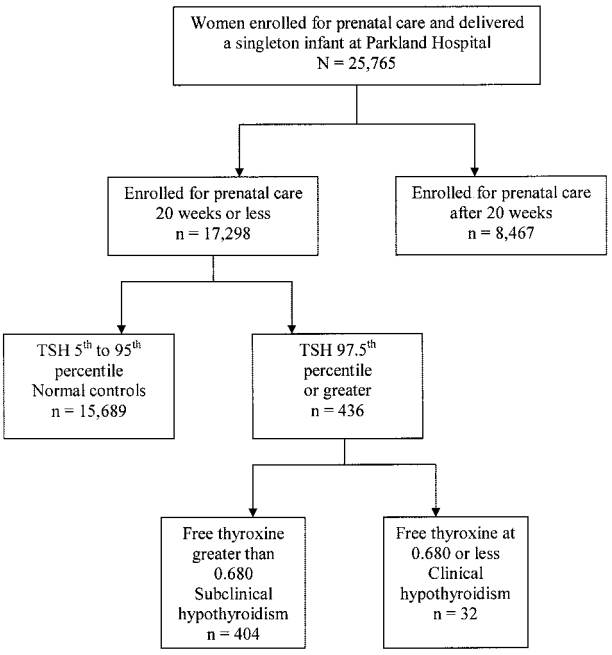

Fig. 2. Outcome of thyroid screening in women who presented for prenatal care and delivered a singleton infant between November 1, 2000, and April 14, 2003. TSH, thyroid-stimulating hormone (thyrotropin).

Casey. Subclinical Hypothyroidism and Preterm Birth. Obstet Gynecol 2005.

Women with subclinical hypothyroidism are compared with 15,689 pregnant controls identified with TSH values between the 5th and the 95th percentiles in Table 1. The incidence of subclinical hypothyroidism was higher in white women and those classified as "Other" ethnicity. Also, women with subclinical hypothyroidism were significantly older than control women. For example, 11% of women with an elevated TSH value were aged 35 years or greater compared with only 7% of

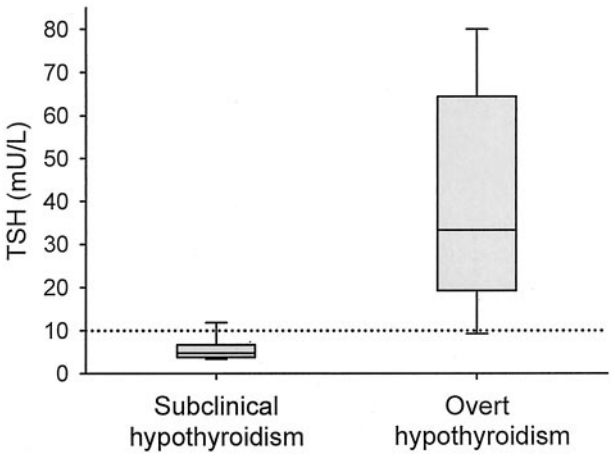

Fig. 3. Thyrotropin values for 404 women diagnosed with subclinical hypothyroidism and 32 women diagnosed with overt hypothyroidism. Boxes represent 25th to 75th percentile. TSH, thyroid-stimulating hormone (thyrotropin).
Casey. Subclinical Hypothyroidism and Preterm Birth. Obstet Gynecol 2005.

healthy controls. ($P = .009$). There was no difference between the groups in relation to parity or body mass index. The gestational age at screening was similar between the 2 groups.

Listed in Table 2 are selected pregnancy outcomes in women with subclinical hypothyroidism compared with controls. The incidence of gestational hypertension and severe preeclampsia was similar between the 2 groups. Pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption when compared with healthy pregnant women. (relative risk [RR] 3.0, 95% CI 1.1–8.2). Although the mean gestational age at delivery was not significantly different between the 2 groups, preterm birth, defined as delivery at or before 34 weeks of gestation, was almost 2-fold higher in women with subclinical hypothyroidism. (RR 1.8, 95% CI 1.1–2.9). Specifically, 18 (4%) women with a TSH at or above the 97.5th percentile and a normal free thyroxine level delivered preterm compared with 385 (2.5%) controls ($P = .01$). These significant differences persisted after adjustment for maternal age, race, and placental abruption (Hosmer-Lemeshow goodness of fit, $P = .97$). Furthermore, preterm birth remained significantly higher in women with subclinical hypothyroidism and a TSH value less than 10 mU/L.

Infant outcomes are compared in Table 3. Neonates delivered of women with subclinical hypothyroidism were similar in birth weight to infants of women with normal TSH values. Other conditions consistent with prematurity were increased in infants of women with subclinical hypothyroidism. For example, admission to the neonatal intensive care nursery and respiratory distress were twice as likely in infants delivered of women with subclinical hypothyroidism (RR 1.8, 95% CI 1.1–2.9 and 1.0–3.3, respectively). Fetal death rates were the same (5/1,000 births) in both groups, and the neonatal death rates, although higher in infants of women with subclinical hypothyroidism (5/1,000 compared with 2/1,000 live births), were not significantly different.

DISCUSSION

There are several important findings from this prospective analysis of more than 17,000 women who underwent screening for abnormal thyroid function during the first half of pregnancy. First, subclinical hypothyroidism was identified in 2.3% of the population tested, and this corresponds with virtually all previous reports.[8,9,14] Second, women with subclinical hypothyroidism had a significant, almost 2-fold higher incidence of preterm delivery at or before 34 weeks of gestation. A third finding was a significant 3-fold increase in the incidence of pla-

Table 1. Maternal Characteristics of Women Who Underwent Thyroid-Stimulating Hormone Screening at or Before 20 Weeks of Gestation

Maternal Demographics	Subclinical Hypothyroidism (n = 404)	Normal TSH (n = 15,689)	*P*
Age (y)	26.9 ± 5.9	25.5 ± 5.6	< .001
≥ 35	44 (11)	1,161 (7)	.009
Race or ethnicity:			< .001
Hispanic	341 (84)	13,472 (86)	
African American	27 (7)	1,588 (10)	
White	16 (4)	321 (2)	
Other	20 (5)	308 (2)	
Nulliparity	145 (36)	5,672 (36)	.915
Weeks at enrollment	12.2 ± 4.0	11.9 ± 3.8	.211
Body mass index (kg/m^2)	32.1 ± 6.3	31.7 ± 5.5	.163

TSH, thyroid-stimulating hormone.
Values are mean ± standard deviation or n (%). Women with a TSH value at or above the 97.5th percentile and normal free thyroxine (subclinical hypothyroidism) are compared with those with a TSH between the 5th and 95th percentiles (normal).

Table 2. Pregnancy Outcomes in Women Who Underwent Thyroid-Stimulating Hormone Screening at or Before 20 Weeks of Gestation.

Pregnancy Outcome	Subclinical Hypothyroidism (n = 404)	Normal TSH (n = 15,689)	*P*
Hypertension			
Gestational	41 (11)	1,400 (9)	.397
Severe preeclampsia	23 (6)	842 (5)	.774
Placental abruption	4 (1)	52 (0.3)	.026
Weeks gestation at delivery	39.3 ± 2.2	39.4 ± 1.9	.226
36 or less	27 (7)	891 (6)	.390
34 or less	18 (4)	385 (2.5)	.011
32 or less	10 (2.5)	218 (1)	.068
Cesarean delivery	108 (27)	3,853 (25)	.316
Repeat	59 (15)	1,923 (12)	.156
Primary			
Dystocia	16 (4)	716 (5)	0.566
Fetal distress	17 (4)	647 (4)	0.933
Other	16 (4)	567 (4)	0.713

TSH, thyroid-stimulating hormone.

Values are mean ± standard deviation or n (%). Women with a TSH value at or above the 97.5th percentile and normal free thyroxine levels (subclinical hypothyroidism) are compared with those with a TSH between the 5th and 95th percentiles (normal).

cental abruption in women in the subclinical hypothyroid group compared with healthy controls. Related to the second 2 findings, the proportion of infants of hypothyroid mothers admitted to the neonatal intensive care unit, as well as those who developed respiratory distress syndrome, was significantly doubled when compared with infants of euthyroid women.

It is important to emphasize that our findings include only infants born to women with subclinical hypothyroidism as contemporaneously defined.[6,7] We excluded women with abnormally elevated serum TSH levels accompanied by abnormally low free thyroxine levels because they were considered to have hypothyroidism. This distinction is important and may explain why our results differ from Allan and colleagues,[14] who reported increased stillbirths in hypothyroid women. Specifically, in their retrospective study they did not distinguish subclinical hypothyroidism from overt disease. This likely accounts for their findings that the incidence of stillbirth was significantly increased only in the group of women whose TSH levels exceeded 10 mU/L, many of whom probably had overt hypothyroidism. (Fig. 3). Importantly, the increased risk for preterm birth in women identified with subclinical hypothyroidism in this study persisted even in those women with TSH values less than 10 mU/L.

Table 3. Neonate Outcomes in Women Who Underwent Thyroid-Stimulating Hormone Screening at or Before 20 Weeks of Gestation.

Neonate Outcome	Subclinical Hypothyroidism (n = 404)	Normal TSH (n = 15,689)	*P*
Birth weight (g)	3,317 ± 599	3,367 ± 567	.081
≤ 1,000	2 (0.5)	70 (0.4)	.884
≤ 1,500	7 (2)	142 (1)	.086
≤ 2,500	26 (6)	839 (5)	.338
Admission to intensive care	16 (4)	347 (2)	.019
Apgar score at 5 minutes ≤ 3	3 (0.7)	109 (0.7)	.909
Umbilical artery blood pH < 7.00	8 (2)	263 (2)	.643
Respiratory distress syndrome*	11 (3)	235 (1.5)	.048
Necrotizing enterocolitis†	0	5 (0.03)	.720
Intraventricular hemorrhage‡	0	11 (0.1)	.594
Major malformations	2 (0.5)	177 (1)	.231
Fetal death	2 (0.5)	78 (0.5)	.995
Neonatal deaths	2 (0.5)	37 (0.2)	.295

TSH, thyroid-stimulating hormone.

Values are mean ± standard deviation or n (%). Women with a TSH value at or above the 97.5th percentile and normal free thyroxine levels (subclinical hypothyroidism) are compared with those with a TSH between the 5th and 95th percentiles (normal).

* Ventilator greater than 24 hours of life.

† Necrotizing enterocolitis requiring surgery.

‡ Grade 3 or 4 intraventricular hemorrhage.

Although it is too early to measure any neurodevelopmental abnormalities that might develop in children of women with subclinical thyroid deficiency, data now presented may help to elucidate the findings of others. Specifically, Haddow and colleagues[13] reported that children of women with abnormally high TSH levels during pregnancy had significantly lower intelligence quotient scores compared with controls born to euthyroid mothers. Similarly, Pop et al[11] reported that abnormally low maternal serum free thyroxine concentrations at 12 weeks of gestation were significantly associated with impaired neurodevelopment in infants at 10 months. In this country, preterm birth is overwhelmingly the most common recognized cause of neuropsychologic dysfunction in children.[18,19] We therefore propose that this significant increase in preterm birth could potentially contribute to these neurodevelopmental abnormalities or may amplify abnormalities caused by thyroxine deficiency. Indeed, Haddow and colleagues attempted to correct for prematurity by excluding births less than 1,500 g. Only long-term follow-up of those children could resolve this issue.

The most cogent question is whether identification and thyroid hormone supplementation of women with subclinical hypothyroidism would prevent or modify any of these adverse outcomes. It may be that therapy beginning after 10 weeks of gestation would not eliminate any already established fetal neurodevelopmental impairment from hypothyroxinemia. Pop and colleagues[11] have provided evidence that treatment may be ineffective only if given after this time. Because the mechanism of disease whereby thyroid hormone deficiency leads to preterm labor, placental abruption, and other pregnancy complications is not known, we can only speculate about any salutary effects of thyroxine replacement. One unifying hypothesis is that thyroid hormone is necessary for normal placental development. Specifically, there is evidence that preterm delivery and vascular diseases such as preeclampsia and placental abruption may be causally linked to faulty early placentation.[20,21] Although our findings may provide further incentive to screen for subclinical hypothyroidism in pregnancy, there are currently no randomized controlled treatment trials to substantiate such a policy. We are of the view that until studies are done to demonstrate that thyroxine supplementation will obviate any of these maternal and fetal morbidities, widespread serum TSH screening and treatment of women with subclinical hypothyroidism during pregnancy is unjustified.

REFERENCES

1. Utiger RD. Maternal hypothyroidism and fetal development. N Engl J Med 1999;341:601–02.
2. Xue-Yi C, Xin-Min J, Zhi-Hong D, Rakeman MA, Ming-Li Z, O'Donnell K, et al. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med 1994;331:1739–44.
3. DeLong GR, Stanbury JB, Fierro-Benitez R. Neurological signs in congenital iodine-deficiency disorder. Dev Med Child Neurol 1985;27:317–24.
4. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol 1988;72: 108–12.
5. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993;81:349–53.
6. Cooper DS. Subclinical hypothyroidism. N Engl J Med 2001;345:260–5.
7. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004; 291:228–38.
8. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, et al. Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 1991;35:41–6.
9. Woeber KA. Subclinical thyroid dysfunction. Arch Intern Med 1997;157:1065–8.
10. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34.
11. Pop VJ, Kuijpens JL, van Baar Al, Verkerk G, van Son MM, de Vijlder JJ, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 1999;50:149–55.
12. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder J. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 2003;59: 282–8.
13. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549–55.
14. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 2000;7:127–30.
15. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999;340:1234–8.
16. Koster EL, McIntire DD, Leveno KJ. Recurrence of mild malformations and dysplasias. Obstet Gynecol 2003;102: 363–6.
17. Hosmer DW, Lemeshow S. Applied logistic regression. New York (NY): Wiley; 1989.

18. Victorian Infant Collaborative Study Group. Anderson P, Doyle LW, Neurobehavioral outcomes in school-aged children born extremely low birthweight or very preterm in the 1990s. JAMA 2003;289:3264–72.
19. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288:728–37.
20. Walker JJ. Pre-eclampsia. Lancet 2000;356:1260–65.
21. Dommisse J, Tiltman AJ. Placental bed biopsies in placental abruption. Br J Obstet Gynaecol 1992;99:651–4.

Address reprint requests to: Brian M. Casey, MD, The University of Texas Southwestern Medical Center, Department of Obstetrics & Gynecology, 5323 Harry Hines Blvd., Dallas, Texas 75390–9032; e-mail: brian.casey@utsouthwestern.edu

Received September 20, 2004. Received in revised form November 12, 2004. Accepted November 18, 2004.