What is a normal thyroid-stimulating hormone (TSH) level? Effects of stricter TSH thresholds on pregnancy outcomes after in vitro fertilization

Using a thyroid-stimulating hormone (TSH) cutoff of 2.5 mIU/L or 4.5 mIU/L, no differences in the rates of clinical pregnancy, delivery, or miscarriage were observed in this large, retrospective cohort study of first-cycle IVF patients from 2005 through 2008, after controlling for age. Although lowering the TSH threshold to 2.5 mIU/L would result in a nearly fivefold increase in the number of women being classified as hypothyroid, the lack of differences in maternal clinical outcomes must be considered in the current controversy regarding the relative merits of lowering the upper limit of normal of TSH. (Fertil Steril® 2010;94:2920–2. ©2010 by American Society for Reproductive Medicine.)

Key Words: Thyroid stimulating hormone, TSH, threshold, pregnancy outcomes, TSH screening, subclinical hypothyroidism, ART

Hypothyroidism has been proposed as an etiology for numerous aspects of reproductive difficulties, including impaired ovulation, fertilization, and implantation, miscarriage, and late pregnancy complications (1–3). Importantly, undiagnosed hypothyroidism in pregnant women may also adversely affect the neurodevelopment of fetuses (4). Because of potentially critical consequences to the mother and fetus, this is a topic of active investigation and controversy. Currently, universal screening in asymptomatic fertile patients is not endorsed by the American College of Obstetrics and Gynecology (5), the US Preventative Task Force (6), or the Endocrine Society (TES) (7). In contrast, the American Association of Clinical Endocrinologists (AACE) recommends that thyroid-stimulating hormone (TSH) be measured in women of childbearing age before pregnancy or in the first trimester (8), and the American Thyroid Association (ATA) recommends screening beginning at age 35 years and then every 5 years thereafter (9). In addition, a committee of six members who had participated in a consensus statement group comprising experts from AACE, ATA, and TES (9) independently articulated a position in a subsequent consensus that diverged from the larger group of panelists, stating that TSH testing "should be performed routinely during the pre-pregnancy evaluation or as soon as pregnancy is diagnosed" (10). Despite these controversies, there is universal agreement that at a minimum, aggressive case finding in pregnant women is warranted, as is obtaining a serum TSH level for those with a history of infertility and/or recurrent miscarriage (7).

Improvements in serum TSH assays have led to better definition of the lower limit of the reference range, but the upper limit of the range for a healthy population is also a topic of active debate (11). Recent guidelines proposed by the National Association of Clinical Biochemistry (NACB) have stated that it is likely that in the future the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 mIU/L for all adults, because more than 95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mIU/L (12). However, the AACE, ATA, and TES consensus panel has continued to recommend that 4.5 mIU/L be maintained as the upper limit of normal, reasoning that although some individuals within the range of 2.6–4.5 mIU/L may have subclinical thyroid disease, there is a lack of evidence of adverse outcome in this group (13). For women with clinical hypothyroidism anticipating pregnancy, new guidelines from TES recommend that optimal preconception levels of TSH be <2.5 mIU/mL (7). They further recommend that if overt hypothyroidism is diagnosed during pregnancy, T_4 doses be rapidly titrated to "reach and thereafter maintain serum TSH concentrations of <2.5 mIU/liter in the first trimester (or 3 mIU/liter in second and third trimesters) or to trimester-specific normal TSH ranges" (of <2.3, <3.1, and <3.5 for the first, second, and third trimesters, respectively) (7). Although routine screening was not recommended, the earlier AACE, ATA, TES consensus group (9) recommended T_4 replacement to restore serum TSH to the reference range in pregnant women found by case finding to have subclinical hypothyroidism (normal free T_4 with TSH above the upper limit of normal) (9). However, it is recognized that the supporting evidence is insufficient, and such recommendations are largely based on expert consensus (14).

Andrea Reh, M.D.[a]
James Grifo, M.D., Ph.D.[a]
Ann Danoff, M.D.[b]

[a] Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, New York University Fertility Center, New York, New York

[b] Department of Medicine, Division of Endocrinology; New York University School of Medicine, New York, New York

Our goal was to determine whether there was a difference in pregnancy outcomes of IVF patients with TSH levels above or below the ATA cutoff of 4.5 mIU/L and at the lower cutoff proposed by the NACB of 2.5 mIU/L. We performed a retrospective cohort study of the first cycle of all fresh IVF patients undergoing ET at a single site from 2005 through 2008 (4 years). All patients had nonstimulated TSH and PRL values measured within 1 year of the studied cycle at one of three laboratories (Enzo, Quest, or New York University fertility center onsite laboratory), depending on patient's insurance. Patients with untreated hyperthyroidism (TSH <0.40 mIU/L), hyperprolactinemia, cycles using donor oocyte, preimplantation genetic diagnosis, any cycle without confirmed delivery follow-up, and/or those with a baseline TSH value measured more than 365 days from the first cycle were excluded. Clinical endpoints were rates of clinical pregnancy (gestational sac on ultrasound), miscarriage (loss after sonographic presence of gestational sac), and live birth (delivery confirmed via Society for Assisted Reproductive Technology and direct patient report). Relative risks were calculated with 95% confidence intervals, with a P value of $<.05$ considered significant, and Pearson's correlations were determined. Statistics were performed using Epi Info 3.4.3 (Centers for Disease Control and Prevention, Atlanta, GA) and SPSS 13.0 for Windows (SPSS, Chicago, IL). Our deidentified study was approved for institutional review board exemption (#10-01447).

We identified 1,055 patients aged 36.7 ± 4.8 years (mean ± SD) with a TSH level of 2.1 ± 1.6 mIU/L (median 3.9; range, 0.4–23.8 mIU/L). There was no correlation between patient age and TSH and no difference in ages between abnormal and normal TSH groups using either threshold. The TSH distribution showed a left skew with a long upper tail. Thyroid-stimulating hormone thresholds of ≥2.5 mIU/L resulted in classification of 24% of patients as abnormal (normal: median [interquartile range] 1.5 [1.2–1.9] mIU/L vs. abnormal: 3.2 [2.8–3.8] mIU/L). Thyroid-stimulating hormone thresholds of ≥4.5 mIU/L resulted in classification of 5.3% of patients as abnormal (normal: 1.7 [1.3–2.3] mIU/L vs. abnormal: 5.1 [4.4–6.7] mIU/L). With TSH ≥2.5 vs. <2.5 mIU/L, there was no difference in the clinical pregnancy (52% vs. 47%), live delivery (39% vs. 34%), or miscarriage rates (13% vs. 13%) (Table 1). With TSH ≥4.5 vs. <4.5 mIU/L, there was no difference in the clinical pregnancy (54% vs. 48%), live delivery (43% vs. 34%), or miscarriage rates (9% vs. 13%). There was no difference in the clinical pregnancy, delivery, or miscar-

riage rates when comparing those with TSH <2.5 mIU/L with those with TSH <4.5 mIU/L. Although PRL levels were statistically higher in the ≥2.5- vs. <2.5-mIU/L group, no difference was noted at the 4.5 mIU/L threshold; it is unlikely that this is of clinical significance.

On the basis of this analysis, introducing stricter TSH cutoff values does not seem to impact IVF outcomes. Such information is important, given that most reproductive endocrinologists routinely perform TSH screening as part of a basic infertility workup. On the basis of the increased future risk of hypothyroidism in individuals with a TSH of >2.0 mIU/L, as identified in the Whickham survey (15), the authors of the NACB guideline proposed that the upper limit of the reference range should be 2.5 mIU/L (12). For those with clinical hypothyroidism, TES practice guidelines have recommended a preconception TSH value of <2.5μU/mL (7) for women with previously diagnosed hypothyroidism. However, the use of this stricter preconception TSH level in previously diagnosed patients, as well as application of that threshold value in formerly undiagnosed patients in the absence of clinical relevant outcomes, could lead to potentially unnecessary workups and a delay in infertility treatment.

We found that the TSH distribution in our infertile population showed a left skew with a long tail, as has been previously described (16). The debate for lowering the upper TSH reference limit assumes that the reference distribution for serum TSH be Gaussian in nature, but the upper tail of the distribution could be skewed by euthyroid outliers, such as may occur in patients recovering from nonthyroidal illness, measurement of bioactive TSH isoforms, or receptor gene polymorphisms, and occult autoimmune thyroid dysfunction (17, 18). Furthermore, TSH values may be affected by the timing of phlebotomy, strenuous exercise, and sleep deprivation (19). Previous studies have also shown that TSH distribution progressively shifts toward higher concentrations with age (20), yet we did not find any correlation between age and TSH values.

Our study is limited by its retrospective design and lack of data regarding late pregnancy complications or child neurodevelopmental outcomes. Although the use of three different laboratories may increase the variability of these results, it does represent the realistic limitations inherent in a clinical practice. With respect to the issue of subclinical thyroid disease, we concur that guidelines should take account of the current limitations of assays,

TABLE 1

No difference in clinical outcomes by different proposed TSH thresholds.

Parameter	TSH ≥2.5 mIU/L (n = 248)	TSH <2.5 mIU/L (n = 807)	P value	TSH ≥4.5 mIU/L (n = 56)	TSH <4.5 mIU/L (n = 999)	P value
TSH (mIU/L), median (IQR)[a]	3.2 (2.8–3.8)	1.5 (1.2–1.9)		5.1 (4.4–6.7)	1.7 (1.3–2.3)	
Age (y), mean ± SD	37.1 ± 4.7	36.7 ± 4.8	NS	36.1 ± 4.8	36.8 ± 4.8	NS
PRL (ng/mL), mean ± SD	12.6 ± 7.2	11.1 ± 6.4	.003	11.4 ± 8.0	11.4 ± 6.6	NS
Clinical pregnancy, %	51.6	46.7	NS	53.7	47.6	NS
Delivery, %	39.1	33.5	NS	42.9	34.3	NS
Miscarriage, %	12.5	13.3	NS	8.9	13.3	NS

Note: IQR = interquartile range; NS = nonsignificant.
[a] Because data did not fit a normal distribution, values are described as medians and IQR.

Reh. Correspondence. Fertil Steril 2010.

particularly with regard to assay bias (21). We did not exclude patients with known thyroid disease from our analysis (such information was not available), but we note that the goal of our study was to investigate TSH cutoffs regardless of treatment.

Although lowering the TSH threshold to 2.5 mIU/L would result in a nearly fivefold increase in the number of women being classified as abnormal, no difference in the rates of clinical pregnancy, delivery, or miscarriage were observed. Previous studies have estimated that lowering the threshold from 4.5 to 2.5 mIU/L would identify an additional 9.7% patients, potentially representing 20.6 million Americans, who would also be identified as subclinical hypothyroid if the upper TSH limit were decreased, many of whom do not have thyroid disease (19). Until definitive evidence is available, debate will continue regarding the relative merits of obtaining screening TSH in the general population or in preconception counseling. Despite agreement for TSH screening in infertile women, there are insufficient data upon which to base recommendations for treatment thresholds and optimal TSH goals during pregnancy. Our data suggested no difference in maternal clinical outcomes at TSH thresholds of ≥2.5 and ≥4.5 mIU/L. However, because the potential benefits to mother and fetus outweigh the negligible risks associated with treatment, we support the recommendations for aggressive case finding and early intervention until additional data are available (22).

REFERENCES

1. Poppe K, Velkeniers B, Glinoer D. Thyroid disease and female reproduction. Clin Endocrinol 2007;66:309–21.
2. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol 1988;72:108–12.
3. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993;81:349–53.
4. 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.
5. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 37, August 2002. (Replaces Practice Bulletin Number 32, November 2001. Thyroid disease in pregnancy. Obstet Gynecol 2002;100:387–96.
6. U.S. Preventive Services Task Force. Screening for thyroid disease: recommendation statement. Ann Intern Med 2004;140:125–7.
7. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2007;92:S1–47.
8. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002;8:457–69.
9. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000;160:1573–5.
10. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. 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 2005;90:581–5.
11. Waise A, Price HC. The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism. Ann Clin Biochem 2009;46:93–8.
12. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003;13:3–126.
13. 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.
14. Cooper DS. Subclinical thyroid disease: consensus or conundrum? Clin Endocrinol 2004;60:410–2.
15. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:55–68.
16. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489–99.
17. Jensen E, Blaabjerg O, Petersen PH, Hegedus L. Sampling time is important but may be overlooked in establishment and use of thyroid-stimulating hormone reference intervals. Clin Chem 2007;53:355–6.
18. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab 2005;90:5483–8.
19. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab 2005;90:5489–96.
20. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 2007;92:4575–82.
21. Beckett G, MacKenzie F. Thyroid guidelines—are thyroid-stimulating hormone assays fit for purpose? Ann Clin Biochem 2007;44:203–8.
22. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63–8.