

Suppressed TSH?

Expanded Hormone Exercise

Assume that the patient is a 34 year-old woman who is gravida 3, parity 1. Her first pregnancy ended with a spontaneous abortion but her second was uncomplicated. She is eight weeks past her last menstrual period and is being seen for her first prenatal visit. Her only complaint is that she has been experiencing vague abdominal discomfort for several days and, this morning, experienced severe nausea and vomiting. Her obstetrician is not overly concerned, especially when he hears that she did not have any significant "morning sickness" during either of her other pregnancies. Physical exam is unremarkable. The obstetrician requests several routine laboratory tests, including human chorionic gonadotropin (hCG). Because he has read about the controversy over whether to screen pregnant women for thyroid disease, he also requests thyroid stimulating hormone (TSH). ECE1-01 was meant to represent this specimen.

It is now recognized that pregnancy is a "stress test" for the thyroid gland. Although iodine crosses the placenta, the fetus does not develop a thyroid gland until the last part of first trimester, and is therefore dependent on maternal thyroid hormone until that time. hCG is actually a major source of thyroid stimulating activity and rising estradiol levels alter the clearance of thyroid binding globulin, creating a larger pool of protein-bound thyroxine. Thyroid glands in women who have subclinical hypothyroidism may not be able to mount an appropriate response and may need thyroid hormone supplementation. This is especially important to ensure normal fetal brain development. Although some have advocated universal screening of pregnant women for subclinical hypothyroidism, most guidelines still recommend against this.

The results that your laboratory obtained for ECE1-01 represent a different problem. The TSH was "suppressed". (Although there was the expected variability in this low range, all of the participants obtained a TSH result between 0.03-0.06 mIU/L, and probably use approximately 0.3 mIU/L as the lower limit of their "euthyroid" reference range.) Does your laboratory have a different TSH reference range for pregnant women? It is generally accepted that the range for TSH should be lower during the first trimester because the stimulatory effect of hCG removes the need for TSH, but several studies have shown that TSH tends to be lower than the non-pregnant range throughout pregnancy as well. In one study which looked at the level of hCG associated with suppression of TSH, investigators determined that hCG seems to lower TSH especially in women whose baseline (non-pregnant) TSH is already low. If you determined that the TSH was abnormally low (even for the patient's gestational age), would you be worried about hyperthyroidism?

Hyperthyroidism appearing during pregnancy is less common than hypothyroidism. If the patient has subclinical hyperthyroidism due to Graves' disease (autoantibody to the TSH receptor), she is more likely to become euthyroid because pregnancy exerts a suppressive effect on autoimmune disorders. The differential diagnosis in this case, given the question of her nausea and vomiting, might be between true hyperthyroidism and what is called gestational or transient hyperthyroidism. The latter disorder usually occurs near the middle of the first trimester, when hCG levels peak and has been linked to especially high hCG levels (as would be seen in a twin pregnancy or in trophoblastic tumors). It may be associated with hyperemesis gravidarum a

condition characterized by extreme vomiting, usually associated with electrolyte abnormalities and central nervous system disturbances. At this point, it is too early to say whether this patient's vomiting is unusual. Also, her hCG level appears consistent with her gestational age. (The gonadotropin levels, which would not have actually been requested in a real case, are appropriately low.)

In all likelihood, this patient's TSH level should not be a cause for concern. It would be appropriate to measure the free T4 and, if this were elevated, follow her closely. If the TSH continued to be suppressed (or undetectable) and the free T4 continued to be elevated, a diagnosis of hyperthyroidism could be made. Because she has no prior history of thyroid disease (and, probably, no enlargement of the thyroid gland), it is more likely that she has gestational hyperthyroidism. Unless she develops symptoms (such as hyperemesis), she should not receive any treatment. If the biochemical abnormalities persist into the second trimester and the question of Graves' disease arises again, it would probably be appropriate to measure the level of TSH receptor antibody. Because it crosses the placenta, it may pose a risk to the fetus.

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Read More About It!

- Lazarus JH, Thyroid function in pregnancy. *Brit Med Bull* 2011; 97:137-148
- Haddow JE et al, Variability in thyroid-stimulating hormone suppression by human chorionic gonadotropin during early pregnancy. *J Clin Endocrinol Metab* 2008; 93:3341-3347

Expanded Hemoglobin A1c Exercise

The samples in this Survey were designed to determine whether the A1c methods in use in laboratories are subject to interference from hemoglobin variants. The samples themselves are prepared from human whole blood and therefore are expected to reliably reflect any bias or interference that would exist with real patient samples having the same variant when analyzed by a given method.

For this exercise, sample ECE3-01 was prepared from a single healthy individual (i.e., with no hemoglobin variants); sample ECE3-02 was prepared from a single individual with hemoglobin C trait (i.e., with Hemoglobin AC). Target values were established for both samples by taking the means of the values from two National Glycohemoglobin Standardization Program (NGSP) Secondary Reference Laboratories (SRLs), whose methods are not affected by Hemoglobin AC and are traceable to the method used in the Diabetes Control and Complications Trial (DCCT). The target values are 6.0% for ECE3-01 and 5.6% for ECE3-02.

Participation in this program is voluntary, so the results are not formally graded. Rather, the information collected and this summary are provided for educational purposes. Based on the current CAP Hemoglobin A1c grading criteria (within 6% of the target value), acceptable performance would be represented by values from 5.6% to 6.4% on ECE3-01 and from 5.2% to 6.0% on ECE3-02.

HbC has a lysine in place of a glutamine at position 6 in the beta chain of hemoglobin. Individuals with HbAC have one normal hemoglobin gene (HbA) and one HbC gene. HbAC has a prevalence of 2-3% among African Americans and as high as 30% in parts of sub-Saharan Africa.¹ Individuals with HbAC have no symptoms.

A total of 33 laboratories submitted results for sample ECE3-01, whereas 29 laboratories submitted results for sample ECE3-02; we do not know the reasons for the discrepancy between the two totals. Because so few laboratories submitted results, we have listed results from all peer groups in the tables below, even though in many cases there was only one participant in the peer group.

From the tables, you can see that, for the normal sample, five methods had participants with unacceptable results; in each case, the values were just 0.1 or 0.2 units above the acceptable upper limit. For the HbAC sample, although eight methods had unacceptable results, four of them were just 0.1 unit and one was just 0.3 units above the acceptable limits. In one case (Roche cobas c500), the result was 0.7% above the acceptable limit; in the other two cases (Abbott Architect and Beckman AU), the results, 7.8% and 7.4%, respectively, were 1.8 and 1.4 units above the acceptable upper limit, 2.2 and 1.8 units above the reference value of 5.6%, and clearly in the frankly diabetic range rather than the normal range.

It is difficult to draw any firm conclusions from such small sample sizes – poor performance might represent a problem in the laboratory in question or a problem with the method itself. An excellent resource for all laboratories is the NGSP website (www.ngsp.org), where a comprehensive list of methods and interferences is maintained. Of note, the Roche cobas c500 method is not specifically listed. However, the Beckman AU and Abbott Architect are listed on the NGSP website, which states that both of these methods are known to give inaccurate results with samples containing HbAC.

This is yet another example of where peer group grading is not adequate.² Laboratories using the Beckman AU or Abbott Architect HbA1c method on samples with HbAC will get results that

match their peers but those results will be inaccurate when compared to the true value and clinically misleading.

The best course of action is for laboratories to check their methods' characteristics on the NGSP website so that they can be aware of any limitations of the methods they use for Hemoglobin A1c.

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1. Beutler E. Disorders of hemoglobin. In: Fauci A, Braunwald E, Isselbacher K, eds. Harrison's Principles of Internal Medicine. 14th ed. New York: NY: McGraw-Hill; 1996:645-652.
2. Miller WG, Jones GRD, Horowitz GL, Weykamp C. Proficiency testing / external quality assessment – current challenges and future directions. Clin Chem 2011; 57(12):1670-1680.