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DIAGNOSTIC SERVICES

MANITOBA ENDOCRINE TESTING GUIDELINES

THE RIGHT TEST FOR THE RIGHT PATIENT AT THE RIGHT TIME

A CLINICAL TESTING GUIDELINE
JANUARY 2022

PART 1
THYROID DYSFUNCTION

SCOPE

This clinical guideline is for the:

1. The detection of thyroid dysfunction in the general population.
2. Monitoring of individuals with known diagnosis of thyroid dysfunction under treatment.

This clinical guideline excludes:

1. Neonates

CHOOSING WISELY CANADA RECOMMENDATION

- ***Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests unless there is a palpable abnormality of the thyroid gland.***

  Thyroid ultrasound is used to identify and characterize thyroid nodules, and is not part of the routine evaluation of abnormal thyroid function tests (over- or underactive thyroid function) unless the patient also has a large goiter palpable nodule. Incidentally discovered thyroid nodules are common. Overzealous use of ultrasound will frequently identify clinically irrelevant nodules, which are unrelated to the abnormal thyroid function, and may divert the clinical evaluation to assess the nodules, rather than the thyroid dysfunction. Imaging may be needed in thyrotoxic patients; when needed, a thyroid scan, not an ultrasound, is used to assess the etiology of the thyrotoxicosis and the possibility of focal autonomy in a thyroid nodule.

- **Don't use Free T4 or T3 to screen for hypothyroidism or to monitor and adjust levothyroxine (T4) dose in patients with known primary hypothyroidism.**

  T4 is converted into T3 at the cellular level in virtually all organs. Intracellular T3 levels regulate pituitary secretion and blood levels of TSH, as well as the effects of thyroid hormone in multiple organs. Therefore, in most people a normal TSH indicates either normal endogenous thyroid function or an adequate T4 replacement dose. TSH only becomes unreliable in patients with suspected or known pituitary or hypothalamic disease when TSH cannot respond physiologically to altered levels of T4 or T3.

- ***Don't routinely test for Anti-Thyroid Peroxidase Antibodies (anti – TPO).***

  Positive anti-TPO titres are not unusual in the 'normal' population. Their presence in the context of thyroid disease only assists in indicating that the pathogenesis is probably autoimmune. As thyroid autoimmunity is a chronic condition, once diagnosed there is rarely a need to re-measure anti-TPO titres. In euthyroid pregnant patients deemed at high risk of developing thyroid disease, anti-TPO antibodies may influence the frequency of surveillance for hypothyroidism during the pregnancy. It is uncommon that measurement of anti-TPO antibodies influences patient management.

CLINICAL BACKROUND

Thyroid dysfunction prevalence rates in the general population are varied. The rate for overt hyperthyroidism is <1.9%. The inclusion of subclinical hyperthyroidism (low TSH and normal T4 and T3 levels) increases the prevalence rate to about 2.7%. The incidence of overt hyperthyroidism is estimated at 2-3 per 1,000 women.

The prevalence of hypothyroidism (elevated TSH and normal or low thyroxine (T4) and triiodothyronine (T3)) in the general population is estimated at 1%-4% with an incidence of 1-2 per 1,000 women. The prevalence for this condition is three times higher in women than men. In geriatics, the prevalence rate for overt hypothyroidism is estimated to be 0.2%-3%. Subclinical hypothyroidism (mildly elevated TSH and normal thyroxine (T4) and triiodothyronine (T3)) prevalence is about 4%-8.5% in a population with no thyroid disease history, and increases with age. Subclinical hypothyroidism in women over the age of 60 years is about 20%. Hypothyroidism is more common than hyperthyroidism.

RISK FACTORS

The risk factors for developing thyroid disease are outlined below.

1. Previous history of thyroid disease
2. Confirmed diagnosis of autoimmune disease
3. Strong family history of thyroid disease
4. A history of neck irradiation
5. Thyrotoxic drug therapies such as lithium and amiodarone
6. Post-partum women (especially 6 weeks to 6 months)
7. Women over age 50
8. Elderly patients, particular over age 60.

SIGNS AND SYMPTOMS

Table 1.1: Signs and Symptoms of Thyroid Disease

Hyperthyroidism	Hypothyroidism
Goitre	Lethargy
Hair loss	Hair loss
Weight loss	Weight gain
Menstrual irregularities (amenorrhea / oligomenorrhea)	Menstrual irregularities (menorrhagia)
Widened pulse pressure	Cognitive impairment
Palpitations / Tachycardia / Atrial fibrillation	Goitre
Nervousness and tremor	Cold intolerance
Heat intolerance, diaphoresis, clammy hands	Constipation
Hypertension	Depression
Muscular weakness	Dry skin

DIAGNOSIS AND MONITORING

The American Thyroid Association (ATA) recommends screening of thyroid disease in adults starting at age 35 years and every five years thereafter. Increased frequency of screening would be appropriate for high risk individuals (see risk factors section). The risk of developing thyroid disease is higher in Caucasians populations.

The diagnosis of thyroid disease in the population (non-hospitalized individuals with intact Hypothalamic-Pituitary-Thyroid Axis) is best done using the algorithm below (figure 1.1). Thus, TSH alone is the best single initial test for the diagnosis of thyroid disease (hyper-and-hypothyroidism). When it is abnormal, appropriate reflex to either Free T4 or/and Free T3 would provide clarity of the nature of the thyroid disease (subclinical or over hypo-or-hyperthyroidism).

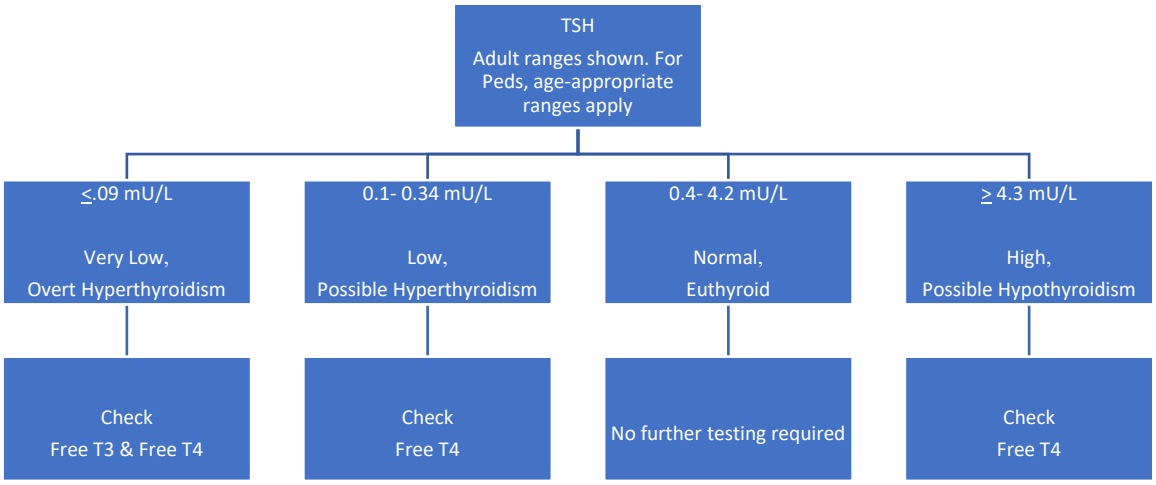

Figure 1.1: Thyroid function testing algorithm. Adult scenario shown. Pediatric algorithm is exactly same using age-appropriate TSH cut-offs.

Free T4 is recommended for monitoring patients with known pituitary disease. TSH, in such conditions, is not of value. TSH also in unhelpful in patients with severe non-thyroidal illness such as in times of critical care and acute severe psychiatric illness. In monitoring of initial therapy (first three months) of hyperthyroidism with radioactive iodine, the combination of both TSH and Free T4 is useful.

PREGNANCY

Some, but not all, observational studies have found subclinical hypothyroidism in pregnancy to be associated with a higher risk of adverse pregnancy outcomes[8-12]. However, new evidence in the form of large randomized controlled trials have failed to demonstrate an improvement in outcomes with treatment of levothyroxine[13-15]. The use of the algorithm in figure 1 will facilitate appropriate diagnosis. The prevalence of an elevated serum TSH in healthy, nonpregnant women of reproductive age is at least 2%–3%. This may be higher in iodine insufficient areas. When iodine nutrition is adequate, the most frequent cause of hypothyroidism is autoimmune thyroid disease (Hashimoto's thyroiditis).

Thyroid autoantibody positivity in pregnancy is common (5-15% in unselected pregnant populations[16-17]) and has been associated with adverse pregnancy outcomes[18-19]. However, given that there is a lack of evidence to support treatment of antibody positivity in women who are planning pregnancy or who are pregnant, we recommend against routine screening of thyroid antibodies in pregnancy[20-23].

Placental human chorionic gonadotropin (hCG) often decreases maternal thyrotropin (TSH) concentrations, especially in early pregnancy, through its stimulatory effect on thyroid hormone secretion. Such transiently suppressed maternal TSH concentrations are often observed and deemed safe. Therefore, mild TSH suppression can be seen in normal early pregnancy and in association with normal FT4. Such an abnormality is not associated with adverse obstetrical outcomes.

PREGNANCY TESTNG RECOMMENDATIONS

1. Women seeking pregnancy, or newly pregnant, should undergo clinical evaluation. If any of the risk factors in table 1.2 are identified, testing for serum TSH should be performed.
2. We recommend against routine thyroid antibody screening in women who are planning pregnancy or who are pregnant as there has been no effective treatment to improve outcomes.

Table 1.1: Risk Factors of Thyroid Disease in Pregnancy

• A history of hypothyroidism/hyperthyroidism or current	• Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
• symptoms/signs of thyroid dysfunction	• Residing in an area of known moderate to severe iodine insufficiency
• Known thyroid antibody positivity or presence of a goiter	• Morbid obesity (BMI ≥40 kg/m^2)
• History of head or neck radiation or prior thyroid surgery	
• Age >30 years	
• Type 1 diabetes or other autoimmune disorders	
• History of pregnancy loss, preterm delivery, or infertility	
• Multiple prior pregnancies (≥2)	
• Family history of autoimmune thyroid disease or thyroid dysfunction	

REFERENCES

1. Choosing Wisely Canada, Endocrinology and Metabolism, https://choosingwiselycanada.org/endocrinology-and-metabolism/

2. U.S. Preventive Services Task Force. Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions. Baltimore MD: Williams & Wilkins; 2004.

3. US Preventative Services Task Force. Screening for thyroid disease: recommendation statement. Ann Intern Med. 2004;140:125-7.

4. Haddow JE et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;341:549-55.

5. Martino E et al. The effects of amiodarone on the thyroid. Endocr Rev. 2001;22:240.

6. Bocchetta A et al. Thyroid abnormalities during chronic lithium treatment. Acta Psychiatr Scand. 1991;83:193.

7. Mazzaferri E, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86:1447-63.

8. Negro R, Stagnaro-Green A. Diagnosis and management of subclinical hypothyroidism in pregnancy. BMJ 2014;349:g4929.

9. Maraka S, Mwangi R, McCoy RG, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ 2017;356:i6865.

10. Maraka S, Singh Ospina NM, O'Keeffe DT, et al. Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women with Subclinical Hypothyroidism. Thyroid 2016;26:980–6.

11. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549–55.

12. Korevaar TI, Muetzel R, Medici M, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 2016;4:35–43.

13. Casey BM, Thom EA, Peaceman AM, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med 2017;376:815–25.

14. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012;366:493–501.

15. Yamamoto JM, Benham JL, Nerenberg KA, et al. Impact of levothyroxine therapy on obstetric, neonatal and childhood outcomes in women with subclinical hypothyroidism diagnosed in pregnancy: A systematic review and meta-analysis of randomised controlled trials. BMJ Open 2018;8:e022837. doi:10.1136/ bmjopen-2018-022837

16. Moreno-Reyes R, Glinoer D, Van Oyen H, et al. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. J Clin Endocrinol Metab 2013;98:3694–701.

17. McElduff A, Morris J. Thyroid function tests and thyroid autoantibodies in an unselected population of women undergoing first trimester screening for aneuploidy. Aust N Z J Obstet Gynaecol 2008;48:478–80.

18. Thangaratinam S, Tan A, Knox E, et al. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ 2011;342:d2616.

19. Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth, Korevaar TIM, Derakhshan A, et al. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: a systematic review and meta-analysis. JAMA 2019;322:632–41.

20. Lau L, Benham JL, Lemieux P, et al. Impact of levothyroxine in women with positive thyroid antibodies on pregnancy outcomes: a systematic review and meta-analysis of

randomised controlled trials. BMJ Open 2021;11:e043751. doi:10.1136/ bmjopen-2020-043751

21. Donovan L, Cockwell H, Tallon N, Yamamoto J. Committee Opinion No. 407: Thyroid Disease and Infertility. J Obstet Gynaecol Can. 2020 Oct;42(10):1279-1282. doi: 10.1016/j.jogc.2020.08.004. PMID: 33059881

22. Wang H, Gao H, Chi H, et al. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: a randomized clinical trial. JAMA 2017;318:2190–8.

23. Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med 2019;380:1316–25.