CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2561226

Available online at: http://www.iajps.com ***Review Article***

AN OVERVIEW OF DIAGNOSIS AND MANAGEMENT OF HYPOTHYROIDISM IN FAMILY MEDICINE

[1]Dr. Ahmed Twafeq [2]Dr. Hesham Alqahtani, [3]Dr. Mohammed Kadasah [4]Dr. Abduallah Alhammad

Abstract:

Hypothyroidism commonly manifests as a slowing in physical and mental activity but may be asymptomatic. The purpose of this review is to present an updated evidence-based framework for the diagnosis, treatment of hypothyroidism in primary care. We Conducted a comprehensive computerized review of literature reporting hypothyroidism assessment in primary care by family physicians published in English language until end of 2018., published in English language up to 2018. Hypothyroidism is dealt with by recommending an oral thyroid hormone prep work (typically levothyroxine, a T4 preparation). The dosage should suffice enough to recover regular thyroid hormone levels without creating poisoning from way too much thyroid hormone. TSH levels are monitored to help optimize the dose of T4. TSH is created by the pituitary gland in reaction to thyroid hormone degrees. So when thyroid hormonal agent degrees are reduced (as in hypothyroidism), TSH levels respond by enhancing, in an effort to "whip" a lot more thyroid hormone out of the thyroid gland. When hypothyroidism is adequately dealt with, TSH levels generally drop back down into the typical range. So, a mainstay in identifying the best dosage of T4 is measuring TSH degrees.

Corresponding author:

Dr. Ahmed Twafeq

QR code

Please cite this article in press Ahmed Twafeq et al., ***An Overview Of Diagnosis And Management Of Hypothyroidism In Family Medicine.,*** *Indo Am. J. P. Sci, 2019; 06(02).*

INTRODUCTION:

Hypothyroidism is the most common disorder occurring from hormone deficiency. Inning accordance with the time of beginning it is divided in congenital and acquired, according to the degree of endocrine disorder in primary and secondary or central and inning accordance with the severity in severe or clinical and mild or subclinical hypothyroidism [1].The difference in between subclinical and clinical hypothyroidism is of major significance as in medical hypothyroidism signs are much more extreme even coma may happen, while in subclinical hypothyroidism signs and symptoms are less significant and could also be absent. The diagnosis could be conveniently executed by the measurement of blood degrees of thyroid hormones [2]. Hypothyroidism is separated in primary, caused by failing of thyroid function and second (central) because of the failure of adequate thyroid-stimulating hormone (TSH) secretion from the pituitary gland or thyrotrophin-releasing hormone (TRH) from the hypothalamus. Secondary hypothyroidism can be differentiated in pituitary and hypothalamic by the use of TRH test. In some cases, failing of hormone activity in peripheral tissues can be identified. Primary hypothyroidism may be clinical, where free T4(FT4) is lowered and TSH is enhanced or subclinical where FT4 is regular and TSH is increased. In secondary hypothyroidism FT4 is lowered and TSH is regular or reduced. Primary hypothyroidism is most commonly triggered by chronic autoimmune thyroiditis, less usual causes being radioiodine therapy and thyroidectomy. Salt iodination, which is carried out consistently in many countries, could increase the occurrence of overt hypothyroidism [3]. Hypothyroidism is defined as failing of the thyroid gland to produce sufficient thyroid hormone to fulfill the metabolic demands of the body. In this review we discuss the proper diagnostic and management methods in primary care. Without treatment hypothyroidism can add to high blood pressure, dyslipidemia, infertility, cognitive impairment, and neuromuscular disorder.

METHODOLOGY:

We conducted a narrative review over the literature using electronic databases as; MEDLINE, and EMBASE for studies involving data on treatment hypothyroidism in primary care by family doctors, published in English language up to 2018. keywords were used in our search as following: “Hypothyroidism”, family physicians”, “management” We then reviewed the references lists of included studies to find more relevant articles to be for additional evidence.

DISCUSSION:

- **Cellular and biochemical pathophysiology**

Thyroxine (T4) and triiodothyronine (T3) are created from the thyroid gland. T4 is produced just from the thyroid, whereas T3 from the thyroid and from T4 deiodination in extrathyroidal tissues. T3 deficiency is responsible for the clinical and biochemical indications of hypothyroidism. Thus, basic intracellular functions such as oxygen usage by the mitochondria and calorigenesis are decreased. The decline in energy metabolism and heat processing is reflected in the reduced basal metabolic rate, reduced appetite, cold intolerance, and a little low basic body temperature.

T4, which is the major item of the thyroid and flows in plasma, is transformed to T3, T4 remaining in lots of aspects thought about as a prohormone for the more effective T3. This is carried out in the cytoplasm and the nuclei of target tissue cells by three specific deiodinases with the reduction of a molecule of iodine from the peripheral ring of T4 [3]. Deiodinases have a diverse localization in tissues, diverse substrates and varied actions in various medications and disorders. It is believed that the result of T3 in target tissues is moderated genomically by T3 binding to one of the T3 receptor isoforms [4].

There is raising proof for non-genomic effects of T3 along with the transcriptional results moderated by the nuclear receptors [5].

- **Aetiology**

The most widespread reasons that are in charge for the development of primary and secondary or central hypothyroidism are revealed in Table 1.

Table 1. Causes of primary and secondary (central) hypothyroidism [3-5].

Primary	**Secondary**
Chronic autoimmune thyroiditis	**a.Pituitary**
Iodine deficiency or excess	Pituitary adenomas
Thyroidectomy	History of pituitary surgery
Therapy with radioactive iodine	History of head trauma
External radiotherapy	History of pituitary surgery or radiotherapy
Drugs	**b.Hypothalamus**
Thyroid agenesis or dysgenesis	Hypothalamus or suprasellar tumors
	History pf hypothalamic surgery or radiotherapy

- **Cellular and biochemical pathophysiology**

Thyroxine (T4) and triiodothyronine (T3) are produced from the thyroid gland. T4 is created only from the thyroid, whereas T3 from the thyroid and from T4 deiodination in extrathyroidal tissues. T3 deficiency is responsible for the clinical and biochemical indications of hypothyroidism. Thus, basic intracellular functions such as oxygen usage by the mitochondria and calorigenesis are slowed down. The decrease in energy metabolism and heat production is shown in the reduced basal metabolic rate, decreased appetite, cold intolerance, and slightly low basal body temperature level.

T4, which is the primary product of the thyroid and circulates in plasma, is converted to T3, T4 being in many aspects taken into consideration as a prohormone for the much more potent T3. This is executed in the cytoplasm and the nuclei of target tissue cells by 3 specific deiodinases with the subtraction of a particle of iodine from the peripheral ring of T4 [8].Deiodinases have a varied localization in tissues, varied substrates and varied practices in different medications and conditions. It is thought that the impact of T3 in target tissues is mediated genomically by T3 binding to one of the T3 receptor isoforms [9].

There is boosting evidence for non-genomic effects of T3 in addition to the transcriptional results mediated by the nuclear receptors [10].

- **Diagnosis**

The diagnosis of hypothyroidism is made from the history, the clinical picture and the laboratory measurements.

History and clinical picture

The symptoms and indications of clinical hypothyroidism are shown in Table 2 [1]. The look of symptoms depends on the degree of its seriousness. This relates to the level of modification in biochemical exams. In the beginning manifestations are mild, could be distinguished with trouble from those of euthyroid patients and might be intensified with time. In a research study, only 30% of hypothyroid patients had several of the signs and symptoms, 17% of euthyroid patients contending the very least one. The assessment of symptoms is performed either when they are freshly developed, or when current aggravation of currently existing symptoms is observed. Many times the question arises regarding whether an increase in body weight is associated with hypothyroidism. This symptom needs to be evaluated under the condition that it is a tiny boost in body weight in the order of 3 to 6 kg and not an excessive weight gain which there are other existing together symptoms. It should be kept in mind that hypothyroid people could likewise exhibit a decrease in body weight in the order of 2 to 13%. In serious hypothyroidism there are various clinical manifestations such as congestive heart failure, pericarditis, pleural effusion, intestinal obstruction and pseudo-obstruction, in addition to coagulation disorders. Neurologic indications might additionally establish such as clinical depression, psychosis, ataxia, seizures and coma. Neurocognitive deficits could likewise develop, especially in memory.

Symptoms commonly connected with hypothyroidism are typically nonspecific (Table 2). These consist of weight gain, tiredness, inadequate focus, clinical depression, diffuse muscle mass ache, and menstrual irregularities. Symptoms with high uniqueness for hypothyroidism consist of irregular bowel movements, cool intolerance, completely dry skin, proximal muscular tissue weakness, and hair thinning or loss [6].

Table 2. Common Symptoms of Hypothyroidism [6].

Arthralgias
Cold intolerance
Constipation
Depression
Difficulty concentrating
Dry skin
Fatigue
Hair thinning/hair loss
Memory impairment
Menorrhagia
Myalgias
Weakness

Signs and symptoms of hypothyroidism might vary with age and sex. Babies and youngsters may offer regularly with sleepiness and failing to thrive. Females who have hypothyroidism might present with menstrual irregularities and the inability to conceive. In older patients, cognitive decrease may be the single manifestation. Examination discoveries connected with hypothyroidism include however are not restricted to goiter, delayed relaxation phase of deep tendon reflexes, slim or brittle hair, dry skin, and peripheral edema (Table 3). Common electrocardiography discoveries include bradycardia, flattened T waves, and low voltage. Patients with serious hypothyroidism might present with pericardial effusion, pleural effusion, megacolon, hemodynamic instability, and coma. The medical discussion is frequently confused with septic shock. Myxedema coma, which stands for serious physiologic decompensation arising from hypothyroidism, occurs rarely, with a yearly incidence of 0.22 per million [7]. Laboratory discoveries in hypothyroidism might consist of hyponatremia, hypercapnia, hypoxia, normocytic anemia, elevated creatine kinase, hyperprolactinemia, and hyperlipidemia [8].

Table 3. Clinical Signs of Hypothyroidism [7],[8].

Bradycardia
Coarse facies
Cognitive impairment
Delayed relaxation phase of deep tendon reflexes
Diastolic hypertension
Edema
Goiter
Hypothermia
Laboratory results
Elevated C-reactive protein
Hyperprolactinemia
Hyponatremia
Increased creatine kinase
Increased low-density lipoprotein cholesterol
Increased triglycerides
Normocytic anemia
Proteinuria
Lateral eyebrow thinning
Low-voltage electrocardiography
Macroglossia
Periorbital edema
Pleural and pericardial effusion

- **Management**

Family doctor ought to examine for thyroid dysfunction in all patients with signs and symptoms of hypothyroidism. The American Academy of Family Physicians does not advise screening for hypothyroidism in asymptomatic adults, and the U.S. Preventive Services Task Force located insufficient proof for routine screening in this population [9]. Testing of asymptomatic patients may be considered in those with risk elements for hypothyroidism, such as a background of autoimmune disorder, background of head or neck irradiation, previous radioactive iodine treatment, visibility of a goiter, family history of thyroid disease, or treatment with medicines understood to affect thyroid function.

The most effective lab evaluation of thyroid function, and the favored examination for diagnosing primary hypothyroidism, is a serum TSH examination [11]. If the serum TSH level is elevated, screening ought to be repeated with a serum free thyroxine (T4) measurement [12]. Obvious primary hypothyroidism is suggested with a raised serum TSH degree and a low serum free T4 degree. An elevated serum TSH level with a typical array serum free T4 level is consistent with subclinical hypothyroidism. A low serum free T4 level with a reduced, or wrongly typical, serum TSH level follows second hypothyroidism and will normally be connected with further evidence of hypothalamic-pituitary insufficiency.

Laboratory evaluation

TSH and FT4 measurement are the laboratory evaluations necessary for the medical diagnosis of hypothyroidism and the differential medical diagnosis in between primary (clinical or subclinical) and secondary one.

When TSH is enhanced and FT4 is lowered or typical hypothyroidism is primary. In this instance raised anti-TPO or anti-Tg antibodies indicate the reason for hypothyroidism, which is autoimmune thyroiditis. Primary hypothyroidism is separated in professional when TSH is boosted and FT4 is lowered and in subclinical when TSH is boosted and FT4 is typical. When TSH is normal or decreased and FT4 is reduced hypothyroidism is second (main). In order to discriminate whether the reason remains in the pituitary or the hypothalamus an examination with the TSH releasing aspect is done (TRH examination). In the first case the response is normal, while in the 2nd it is abnormal. In central hypothyroidism imaging studies of the mind and the pituitary are done aiming at locating its reason.

Normally the reported typical limitations of TSH are between 0.4-4.0 mU/l. When TSH is discovered in the upper regular restrictions it might show moderate hypothyroidism which might progress to hypothyroidism, specifically if antibodies are raised. Michalopoulou et al [20] in people with hypercholesterolemia and TSH in the middle to top normal limits found that the administration of thyroxine lowered cholesterol. Positive antithyroid antibodies predispose to the growth of hypothyroidism

TSH may be increased in euthyroid people in particular circumstances. Enhanced TSH (5-20 mU/l) is observed during convalescence from non thyroidal ailment (euthyroid unwell syndrome), also in pituitary adenomas creating TSH or in separated resistance of the pituitary to thyroid hormones. Ultimately, TSH rise could be observed in chronic kidney failing and in primary adrenal insufficiency.

- **Therapy**

Hypothyroidism treatment is done with the administration of thyroxine, which is transformed by 80% in outer tissues to T3 [16].

The daily dosage of thyroxine in the initiation of substitution treatment depends upon numerous elements, such as body weight, age, the presence of coronary artery disease and cardiac arrhythmias. In grownups the dose has to do with 1.8 µg/ kg body weight, is higher in neonates and young children (3.8 µg/ kg) and lower in the senior (0.5 µg/ kg) [16]. The dose is higher in individuals having undergone thyroidectomy than those with chronic autoimmune thyroiditis, as in those there are remnants of functioning thyroid tissue. In subclinical hypothyroidism the dose is low (0.5 µg/ kg). In maternity, finally, a bigger dose is needed (2 µg/ kg). During pregnancy the increase in dosage that might be required is 25-47% more than the one before pregnancy and it is observed throughout the 4th to 6th week [16].

In young and healthy grownups therapy may be started with the total dosage and not always with tiny doses. However, in the senior or patients with coronary artery illnesses 25-50 µg are administered every day and the dose is enhanced by 12.5 or 25 g every 2 weeks. TSH measurement after the initiation of treatment is executed every 4-6 weeks up until TSH comes to be typical. The follow-up is performed by TSH measurement as soon as annually. In maternity the very first TSH measurement need to be carried out when maternity is detected and thereafter every 3-4 weeks during the initial one-half of the maternity and every 6 weeks afterwards. TSH in primary hypothyroidism on alternative treatment should remain in the mean levels to reduced regular limitations (roughly 1.0 mU/l), whereas in second

TSH dimension does not assist. FT4and occasionally FT3 measurement is performed and the values ought to be in the top one-half of the normal variety.

In congenital hypothyroidism according to Rose et al the measurement and treatment need to be executed throughout the first 2 weeks of life for the avoidance of the repercussions of hypothyroidism [17]. This measurement has been instituted in different places of the world, and in Greece, however not all over. In neonates the preliminary dose is 10-15 μg/ kg. After that regular TSH measurement is required, which should be regular and T4 or FT4, which should remain in the top one-half of normal values during the first 3 years of life.

In subclinical hypothyroidism there is no agreement regarding whether thyroxine should be carried out. In guidelines from numerous organizations and universities of physicians as to whether therapy is required or not for subclinical hypothyroidism, all agree, aside from the American College of Physicians, which does not hold a definitive position, that thyroxine ought to be carried out if antibodies declare [19], [18].

In myxedema coma, which is one of the most serious type of hypothyroidism and happens in long-lasting not treated hypothyroidism the threat of death was 60-70% in 1985 however it has actually reduced to 20-25%, owing to the timely medical diagnosis and the recommendation of patients to acute care units. Intravenous thyroxine is administered at a dose of 200-400 g throughout the initial 2 days and afterwards at normal dosages. During the very first day of therapy hydrocortisone 100 mg every 8 hours is likewise administered and hypothermia, hypoglycemia, hypotension, hyponatremia and hypercalcemia are properly dealt with [18].

Great care is needed in replacement therapy with thyroxine as dosage overestimation has repercussions. It has actually been observed that more than one fifth of the patients have medical or subclinical hyperthyroidism. These effects are atrial fibrillation, aggravation of coronary artery ailment and a decrease in bone mineral thickness, fractures of the spinal column and the hip being observed in women > 65 years.

Hypothyroidism is not always properly dealt with by the administration of thyroxine, as there are distinctions in the activity, stability and bioavailability in between different batches of thyroxine which might also be supplied by the very same manufacturer. Koutrascommenting on the previously mentioned problems suggests the following: a) authorities ought to demand bioavailability studies of thyroxine preparations, b) medical professionals must instruct their patients to take thyroxine while fasting for a minimum of 4 hours, and avoid food for at least 20-30 minutes, in addition to stay clear of other medications for at least 30 min after the thyroxine tablet and know food products or fruit juices that may interfere with thyroxine absorption, c) medical professionals should not frivolously change from one thyroxine brand to one more on the assumption that 100 μg thyroxine from brand name An amounts to 100 μg from brand B d) physicians need to report to the authorities if they have questionable lead to several patients [20].

Hypothyroidism is not always permanent and a percentage of patients exists in whom thyroid function might be regular after thyroxine discontinuation. The normalization of thyroid function may be a lot more related to the antibodies to TSH receptor than to anti-TPO or anti-Tg antibodies, the titles of which extremely little might be affected by thyroxine administration. The portion of hypothyroidism normalization after thyroxine management is between 0-24%, indicate 10%.

- **Complications**

Myxedema coma is a presentation of serious hypothyroidism and is an endocrine emergency. Early recognition and timely treatment in the intensive care unit (ICU) is vital, and even then, mortality reaches 25% to 60% [21].
Myxedema situation should be believed in patients that have encephalopathy, hypothermia, seizures, severe hyponatremia, hypoglycemia, cardiogenic shock and arrhythmias, breathing failing, and symptoms of fluid retention [21]. A mix of couple of or all of these symptoms and various other signs of moderate to extreme hypothyroidism as stated above can be present.

Factors resulting in increased danger of myxedema dilemma consist of poor doses of thyroid hormonal agent, interruption in treatment, undiagnosed hypothyroidism, or existence of acute illness such as sepsis possibly as a result of increased metabolic needs [21].

Encouraging therapy ought to be offered in the intensive care unit with liquid and electrolyte management, ventilator assistance, vasopressors, therapy of co-existing acute illness, and hypothermia [21].

Thyroid replacement treatment is with intravenous hydrocortisone at stress and anxiety doses complied with by intravenous levothyroxine then changed to

oral levothyroxine after scientific enhancement. If effective, this should cause cardiopulmonary and cognitive renovation [22]. There ought to likewise be an associated enhancement in laboratory derangements including a down trending of TSH which needs to be measured every 1 to 2 days during the first therapy period. Intravenous liothyronine (T3) can be considered until first renovation [22].

Endocrinology reference is advised for all patients with believed myxedema coma and other signs listed in Table 4 [23].

Table 4. Reasons for Endocrinology Consultation in Patients with Hypothyroidism [23].

Age younger than 18 years
Cardiac disease
Coexisting endocrine diseases
Myxedema coma suspected
Pregnancy
Presence of goiter, nodule, or other structural thyroid gland abnormality
Unresponsive to therapy

CONCLUSION:

Hypothyroidism is a clinical disorder frequently encountered by the primary care doctor. Untreated hypothyroidism can lead to hypertension, dyslipidemia, inability to conceive, cognitive disability, and neuromuscular dysfunction.
Hypothyroidism is a constant ailment, impacting more females than males. The negative effects of hypothyroidism, which are regular, dictate its prompt medical diagnosis. The measurement of thyroid hormonal agents in females after the age of 50, in maternity and after delivery, in women and males with hypercholesterolemia, in patients having had neck radiotherapy, in patients having actually been offered drugs, such as amiodarone and lithium, shows up suitable. Therapy is long term, typically life lengthy and is performed by the management of thyroxine.

The TSH examination is the primary test made use of for the medical diagnosis and management of hypothyroidism. But various labs usually have slightly various worths wherefore is called the "TSH recommendation variety." At several labs, the TSH reference variety runs from 0.5 to 4.5. A TSH value of less than 0.5 is considered hyperthyroid, while a TSH value of more than 4.5 is considered possibly hypothyroid.

Hypothyroidism is dealt with by recommending an oral thyroid hormone prep work (typically levothyroxine, a T4 preparation). The dosage should suffice enough to recover regular thyroid hormone levels without creating poisoning from way too much thyroid hormone. TSH levels are monitored to help optimize the dose of T4. TSH is created by the pituitary gland in reaction to thyroid hormone degrees. So when thyroid hormonal agent degrees are reduced (as in hypothyroidism), TSH levels respond by enhancing, in an effort to "whip" a lot more thyroid hormone out of the thyroid gland. When hypothyroidism is adequately dealt with, TSH levels generally drop back down into the typical range. So, a mainstay in identifying the best dosage of T4 is measuring TSH degrees.

REFERENCE:

1. Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007. October 9; 116 15: 1725– 35.
2. Vanderpump M. The epidemiology of thyroid diseases. In: Braverman LE, U R, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 9th edn.

Philadelphia, PA: JB Lippincott-Raven; 2005. pp. 398–496.
3. Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol (Oxf) 2016;84(6):799–808.
4. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002;23:38–89.
5. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev. 2001;81:1097–1142.
6. Davis PJ, Leonard JL, Davis FB. Mechanisms of nongenomic actions of thyroid hormone. Front Neuroendocrinol. 2008;29:211–218.
7. Dutta P, Bhansali A, Masoodi SR, Bhadada S, Sharma N, Rajput R. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care. 2008;12(1):R1.
8. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction [published correction appears in Arch Intern Med. 2001;161(2):284]. Arch Intern Med. 2000;160(11):1573–1575.
9. Helfand M; U.S. Preventive Services Task Force. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2004;140(2):128–141.
10. Spencer CA. Clinical utility and cost-effectiveness of sensitive thyrotropin assays in ambulatory and hospitalized patients. Mayo Clin Proc. 1988;63(12):1214–1222.
11. Levy EG, Ridgway EC, Wartofsky L. Algorithms for diagnosis and management of thyroid disorders. http://www.thyroidtoday.com/ExpertOpinions/ThyroidDiseaseAlgorithms.pdf. Accessed February 1, 2012.
12. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228–238.
13. Roelfsema F, Pereira AM, Veldhuis JD, et al. Thyrotropin secretion profiles are not different in men and women. J Clin Endocrinol Metab. 2009;94(10):3964–3967.
14. Soldin SJ, Soukhova N, Janicic N, Jonklaas J, Soldin OP. The measurement of free thyroxine by isotope dilution tandem mass spectrometry. Clin Chim Acta. 2005;358(1–2):113–118.
15. Carle A, Laurberg P, Pedersen IB, et al. Epidemiology of subtypes of hypothyroidism in Denmark. Eur J Endocrinol. 2006;154(1):21–28.
16. Khalid S, Asad-Ur-Rahman F, Abbass A, Gordon D, Abusaada K. Myxedema Ascites: A Rare Presentation of Uncontrolled Hypothyroidism. Cureus. 2016 Dec 05;8(12):e912.
17. American Academy of Pediatrics. Rose SR, Section on Endocrinology and Committee on Genetics, American Thyroid Association. Brown RS, Public Health Committee. Lawson Wilkins, Pediatric Endocrine Society. Foley T, Kaplowitz PB, Kaye CL, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006;117:2290–2303.
18. Anonymous American Association of Clinical Endocrinologists releases clinical guidelines for thyroid disease. Am Fam Physician. 1995;51:679–680.
19. Singer PA, Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. JAMA. 1995;273:808–812.
20. Koutras DA. The treacherous use of thyroxine preparations. Stability of thyroxine preparations. Hormones. 2003;2:159–160.
21. Guglielmi R, Frasoldati A, Zini M, Grimaldi F, Gharib H, Garber JR, Papini E. ITALIAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS STATEMENT-REPLACEMENT THERAPY FOR PRIMARY HYPOTHYROIDISM: A BRIEF GUIDE FOR CLINICAL PRACTICE. Endocr Pract. 2016 Nov;22(11):1319-1326.
22. Hou J, Yu P, Zhu H, Pan H, Li N, Yang H, Jiang Y, Wang L, Wang B, Wang Y, You L, Chen S. The impact of maternal hypothyroidism during pregnancy on neonatal outcomes: a systematic review and meta-analysis. Gynecol. Endocrinol. 2016;32(1):9-13.
23. Baskin HJ, Cobin RH, Duick DS, et al.; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism [published correction appears in Endocr Pract. 2008;14(6):802–803]. Endocr Pract. 2002;8(6):457–469.