Mesut Önal
Ondokuz Mayıs University, mansuat@hotmail.com, Samsun-Turkey
Pervin Karlı
Amasya University, parpi2300@hotmail.com, Amasya-Turkey
Ayşe Zehra Özdemir
İdris Koçak
Ondokuz Mayıs University, Samsun-Turkey
aysezehra.ozdemir@hotmail.com; idrisk@omu.edu.tr

THYROID DISEASES DURING PREGNANCY

ABSTRACT
Thyroid disorders in pregnancy is frequently seen as a statement of endocrinological. Fetus can't produce the thyroid hormone at the especially beginning of the pregnancy. It is necessary to know, track and treat that thyroid hormones is loss or overt in pregnancy. This review article is wrote for importance of thyroid disorders in pregnancy.
Keywords: Thyroid Disorders, Pregnancy, Hypothyroidism, Hyperthyroidism, Endocrinological

1. INTRODUCTION

A healthy course of pregnancy and fetal development is strictly related with a normally functioning thyroid metabolism. The imbalances of maternal thyroid hormones may cause significant adverse outcomes both for the pregnancy and for the fetal development [1]. The metabolic homeostasis of a pregnant woman changes in way to meet the needs of both the mother and the fetus during pregnancy. These changes undoubtedly affect the thyroid metabolism, and the metabolic activity of thyroid gland increases in parallel to these increased needs. The basic changes in thyroid metabolism include increased human chorionic gonadotropin (hCG) secretion by the placenta, which is significantly homologous with TSH and also have biological activity on TSH receptor. Meanwhile, thyroxine binding globulin (TBG) levels also increase during pregnancy, which requires elevated levels of total T4 and T3 to maintain adequate levels of free-hormones. As a consequence, the normal thyroid-stimulating hormone (TSH) level of a pregnant woman is lower than a non-pregnant counterpart. Recommended ranges for TSH are 0.1-2.5 mIU/liter in the first trimester, 0.2-3.0 mIU/liter in the second trimester, and 0.3-3.0 mIU/liter in the third trimester. These fundamental changes show that pregnancy has profound effects on maternal thyroid gland and its functions. The size of the gland increases by 10% to 40% depending on the iodine repletion, with latter figure in iodine deficient populations. Not only the size of the thyroid gland increases, also the functionality of it changes during pregnancy, and the production of thyroid hormones (thyroxine-T4, triiodothyronine-T3) increases by 50% [2]. The primary reason for this increase is to supplement the fetus with maternal thyroid hormones until 18th-to-20th weeks of gestation, in which the fetal thyroid gland gains maturity [3]. The enlargement of the thyroid gland is due to the

increased size of follicles and amount of colloid, and enhanced blood volume. From these aspects, thyroid metabolism is particularly important during pregnancy, and pregnant women should be considered as a special group with increased vulnerability to thyroid diseases. The prevalence for hypo- and hyperthyroidism during pregnancy are estimated to be 2-3% and 0.4-1.7%, respectively [4]. Furthermore, other thyroid diseases including nodular disease and thyroid cancers may become evident during pregnancy, and may require treatment.

2. RESEARCH SIGNIFICANCE
On this background, this review aimed to gather the recent research and evidence about the thyroid diseases during pregnancy.

3. THYROID METABOLISM IN PREGNANCY
Thyroid metabolism alters significantly and complex changes occur during the course of pregnancy [5]. The changes start with the high-estrogen environment in the organism, which increases the production of hepatic TBG after the first few weeks. The levels reach a stable level through the second trimester, and remains high until labor [6]. Increased TBG results with increased total thyroxine (tT4) and total triiodothyronine (tT3) levels [7]. Following increased TBG levels, hCG begins to increase, and exerts agonistic effects to TSH. It is a glycoprotein heterodimer composed of an α-subunit (identical to that of TSH, LH, and FSH) and a specific β-subunit, which has similarity to TSH [8]. The *in vitro* potency of 1 U hCG is equal to 0.7 µU of human TSH, and high hCG concentrations results with elevated free-T4 (fT4) and decreased TSH. The excessive stimulation of TSH receptors in gestational pathologies like choriocarcinoma or molar pregnancy may lead to gestational hyperthyroidism. Nevertheless, hCG levels increase until 10th week of gestation, and reaches a plateau following a decline thru 20th gestational week in normal pregnancies, which causes increased fT4 concentrations [7]. Another physiological change that associated with gestational thyroid changes is the increased maternal glomerular filtration rate (GFR) during pregnancy, and the enhanced renal iodide clearance due to increased GFR indirectly stimulates maternal thyroid gland. Moreover, sharing the iodide resources with the fetus also acts as a stimulant of the maternal thyroid gland [9]. On the fetal side, the thyroid gland begins its caudal migration from anterior pharyngeal floor, takes lateral migrations from the 4th and 5th pharyngeal pouches, and forms as a bilateral gland by the 9th week of gestation. But, T4 production is undetectable until 14th week, and fetal iodine uptake and T4 production increases by 20th week of pregnancy [10]. The changes in T3 is scarce due to placental type-3 deiodinase, which converts T4 rapidly to inactive reverse T3; and, T3-dependent fetal development is supplied by type-2 deiodinase-catalyzed T4 to T3 conversion [11].

4. ASSESSMENT OF THYROID FUNCTIONS DURING PREGNANCY
As the physiological and metabolic alterations above suggests there may be a transient, and generally subclinical hyperthyroidism may be present in the early pregnancy, which should be considered as a normal finding. But, when it comes to measure the changes in thyroid metabolism by biochemical analyses, American Thyroid Association's (ATA) guideline for assessment of thyroid pathologies during pregnancy recommends that trimester-specific and population-based reference ranges for TSH and fT4 should be used [2]. But, if these population-based reference ranges are absent, ATA guideline for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum suggests the following ranges for thyroid function tests:

- 7th to 12th weeks of gestation: Decrease the lower and upper limits of TSH reference ranges by 0.4mU/L and 0.5mU/L, respectively.
- 2nd to 3rd trimester: TSH gradually returns to non-pregnant ranges.
- Starting from the 7th week, increase the upper reference range of T4 by 5% weekly. Approximately at 16th week, tT4 and T3 levels are 1.5-fold higher than a non-pregnant woman.

5. HYPOTHYROIDISM IN PREGNANCY

Until the fetal production of thyroid hormones in small quantities starts at 10th week of pregnancy, the fetus totally depends on the maternal hormones. If mother has hypothyroidism, a wide-range of adverse pregnancy events including, but not limited to, spontaneous abortion, preterm delivery, gestational diabetes, preeclampsia, and even fetal death can be observed. The worse outcomes are more associated with severe hypothyroidism, but subclinical disease may also result with a threefold increased risk of placental abruption and an almost twofold increased risk of preterm labor [12]. According to the 2017 ATA Thyroid and Pregnancy Guideline, most recent definition of gestational hypothyroidism is as the presence of an elevated TSH and a decreased serum fT4 concentration during gestation, which both are outside the trimester-specific reference ranges [2]. Most frequent cause of this hypothyroidism is autoimmune Hashimoto's thyroiditis in regions with adequate iodine nutrition [13 ve 14].

The upper limits of TSH was previously reported as 2.5mU/L and 3.0mU/L for the 1st and 2nd-3rd trimesters, respectively, in the 2011 ATA guidelines, but recent 2017 report published that there are significant variations among populations, which mainly based on the iodine status of populations and the TSH assays used for the analyses. Accordingly, it was reported that determining a universal TSH cut-off value to initiate therapy is not possible, and decisions should be based on individual assessments of patients according to population- and trimester-specific ranges that defined in healthy anti-thyroid peroxidase antibodies (TPOAb)-negative pregnant women with optimal iodine intake and without thyroid illness. In case of these optimal reference values are not present, then pregnancy-specific TSH reference ranges obtained from similar patient populations and performed using similar TSH assays should be used. And, if internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of ~4.0 mU/L may be used. For most assays, this limit represents a reduction in the non-pregnant TSH upper reference limit of ~0.5mU/L. The severity of gestational hypothyroidism is associated with the pregnancy outcomes. In cases with subclinical hypothyroidism, which is defined by an elevated TSH despite normal fT4 levels, risk of severe preeclampsia, preterm delivery, placental abruption, and/or pregnancy loss were found to be increased when compared with the euthyroid women [13, 15 ve 16].

A recent systematic review and meta-analysis of 18 cohort studies also reported that subclinical hypothyroidism during pregnancy is related with placental abruption, premature rupture of membranes, pregnancy loss, and neonatal death [17]. Despite there is paucity of evidence regarding the association between cognitive impairment the offspring and the subclinical hypothyroidism during pregnancy, observational studies revealed a potential association between these conditions [18]. Apart from subclinical hypothyroidism, cases with overt hypothyroidism, which is defined by an elevated TSH and decreased fT4 levels, are rare and occasional cases, because some

hypothyroid women are anovulatory, and gestational severe hypothyroidism is associated with increased 1st trimester spontaneous abortions. But, if pregnancy continues, some of the adverse outcomes are preeclampsia, gestational hypertension, prematurity, low birth-weight, post-partum hemorrhage, perinatal consequences, and neurophysiological and cognitive impairment of the offspring [19 ve 20]. Another subgroup of gestational hypothyroidism is isolated maternal hypothyroxinemia, which is defined as the presence of normal TSH levels, and maternal fT4 levels in the lower 2.5th-to-5th percentile of the reference range. There is no strong evidence about the effects of isolated maternal hypothyroxinemia on pregnancy outcomes, but limited evidence suggests that incidences of preterm delivery, macrosomia, gestational diabetes, and impaired cognitive functions increases occasionally [13 ve 21]. Keeping all the adverse outcomes due to these clinical tables of gestational hypothyroidism in mind, ATA recommends that overt hypothyroidism should be treated, but isolated hypothyroxinemia should not be routinely treated during pregnancy [2]. If a pregnant woman has a TSH level >2.5mU/L, then she should be evaluated for TPOAb status, and a TPOAb-positive woman with TSH> reference range, and TPOAb-negative women with a TSH greater than 10.0mU/L should be treated with L-thyroxine. On the other hand, treatment was not recommended for cases with TPOAb negativity and normal TSH level.

6. HYPERTHYROIDISM IN PREGNANCY

Maternal hyperthyroidism is defined as a low or suppressed serum TSH level in the presence of a high fT4 level based on trimester-specific reference ranges. It must be kept in mind that TSH levels are normally declined in the 1st trimester of gestation, and fT4 should also be measured for an accurate diagnosis. The human chorionic gonadotropin is the most important biochemical agent that underlies the hyperthyroidism in pregnancy. The clinical view of hyperthyroidism due to increased hCG levels is called gestational transient thyrotoxicosis, and it is the most frequent cause of hyperthyroidism during pregnancy. The clinical table of hyperthyroidism is generally mild and resolves spontaneously. Overt hyperthyroidism occurs in 0.4% to 1.7% of pregnant women, and approximately 90% of overt hyperthyroidism in pregnant women is Graves disease. Other important causes of gestational hyperthyroidism are subacute thyroiditis, toxic thyroid adenoma, toxic multinodular goiter, and iatrogenic excessive L-thyroxine intake [22]. The symptoms of gestational hyperthyroidism may overlap with normal pregnancy features like dyspnea, palpitation, anxiety and heat intolerance. In case of a Graves disease diagnosis, goiter is usually palpable, and Graves' ophthalmopathy may be present. Biochemical analyses reveal a TSH level lower than the lower limit of the reference range, high fT4 levels, and generally the presence of TSH-receptor antibodies (TRAb). TRAb are used to discriminate Graves disease from other forms of hyperthyroidism [23].

If hyperthyroidism of pregnancy is left untreated, the potential adverse outcomes may include low birth-weight, severe preeclampsia, miscarriages, maternal congestive heart failure, stillbirth, and fetal growth restriction. The severity of pregnancy complications and adverse outcomes in gestational hyperthyroidism decreases significantly if the treatment initiated as soon as possible, and delivered at an adequate dose. Radioactive iodine uptake is contraindicated in pregnancy, either at diagnostic or therapeutic doses. If medical treatment is necessary, the medication should be selected according to the specific gestational period. Accordingly, during first trimester, propylthiouracil (PTU) should be the choice of

medication, since methimazole is associated with teratogenicity. Nevertheless, PTU is not free-of risk, and associated with hepatotoxicity, and methimazole should be the choice during second and third trimesters [24]. If medication has started for a pregnant woman, then free T4 and TSH should be measured routinely at every 2-to-6 weeks period during labor. Thyroidectomy is an occasional option for the treatment of thyrotoxicosis, particularly if a rapid control of hyperthyroidism is needed and medications are not applicable due to contraindications, allergies, or noncompliance. The optimal time-frame for thyroidectomy operation is during the second trimester; because, first trimester is associated with fetal loss and teratogenicity, and third trimester is associated with preterm labor. Approximately two-weeks of iodine treatment, anti-thyroid drugs, and beta-blockers are among the options for preoperative medications.

7. THYROID NODULES AND CANCERS IN PREGNANCY

Thyroid tumors are the most common endocrine neoplasms. Majority of them are benign hyperplastic nodules, and approximately 5%-to-20% are benign follicular adenomas or carcinomas of follicular or parafollicular (C) cell origin. The diagnosis of both thyroid nodules, and differentiated thyroid carcinoma rises in pregnancy. This is both related with the increased medical attention in pregnancy period, and also with the increased thyroid volume, which also increases the sizes of the nodules [25]. Thyroid cancer mostly present as thyroid nodules. Radionucleotide scanning is contraindicated in pregnancy. But, if a nodule is detected, then neck ultrasonography and fine-needle aspiration biopsy should be performed when indicated to exclude a malignancy. Meanwhile, the serum thyroid hormone levels should be measured to manage the hypothyroidism or hyperthyroidism appropriately to overcome the associated adverse outcomes [26]. The general approach of ATA guidelines to nodules detected in pregnancy is similar with the Endocrine Society guideline and can be summarized as follows [2 ve 27]:

- Nodules ≤1.5 cm: can be followed postpartum.
- Nodules ≥1.5cm: if ultrasound revealed benign characteristics, fine-needle aspiration can be delayed till after delivery; otherwise, it can be performed in pregnancy.
- Pathologically suspicion of papillary cancer: surgery can be performed in 2nd trimester, or delayed after delivery
- Well-differentiated papillary cancer: 2nd trimester surgery if lymph node metastases (+). Close follow-up by ultrasound and thyroglobulin, and 2nd trimester surgery on progression.
- Thyroid hormone therapy for achieving TSH level between 0.1 and 1.5 IU/L.
- Pregnancy should be deferred for 6 months after radioactive iodine treatment, and dosing of levothyroxine should be stabilized before pregnancy.
- If the nodule is suspicious for a follicular or Hurthle cell neoplasm, it usually represents a 10% to 15% risk of malignancy. It is recommended that surgery be performed after delivery.

8. CONCLUSION AND RECOMMENDATIONS

The most recent ATA thyroid and pregnancy guideline 2017 recommends that health care providers should identify all newly pregnant women at high risk for thyroid disease, according to the criteria of:

- history of thyroid dysfunction
- symptoms or signs of thyroid dysfunction
- presence of a goiter
- and known thyroid antibody positivity
- Other risk factors for thyroid disease are:
  - Age >30 years
  - History of diabetes mellitus type 1 or other autoimmune disorders
  - History of pregnancy loss, preterm delivery or infertility
  - History of head or neck radiation or prior thyroid surgery
  - Family history of autoimmune thyroid disease or thyroid dysfunction
  - Morbid obesity
  - Use of amiodarone, lithium, or recent administration of iodinated radiologic contrast
  - Two or more prior pregnancies
  - Residing in area of moderate to severe iodine deficiency

Guideline recommends that measurement of serum TSH should be performed as soon as pregnancy is confirmed, with reflex anti-TPOAb if TSH is 2.5-10mU/L. The flowchart of decision-making process in approach to thyroid disease in pregnancy is summarized in Figure 1.

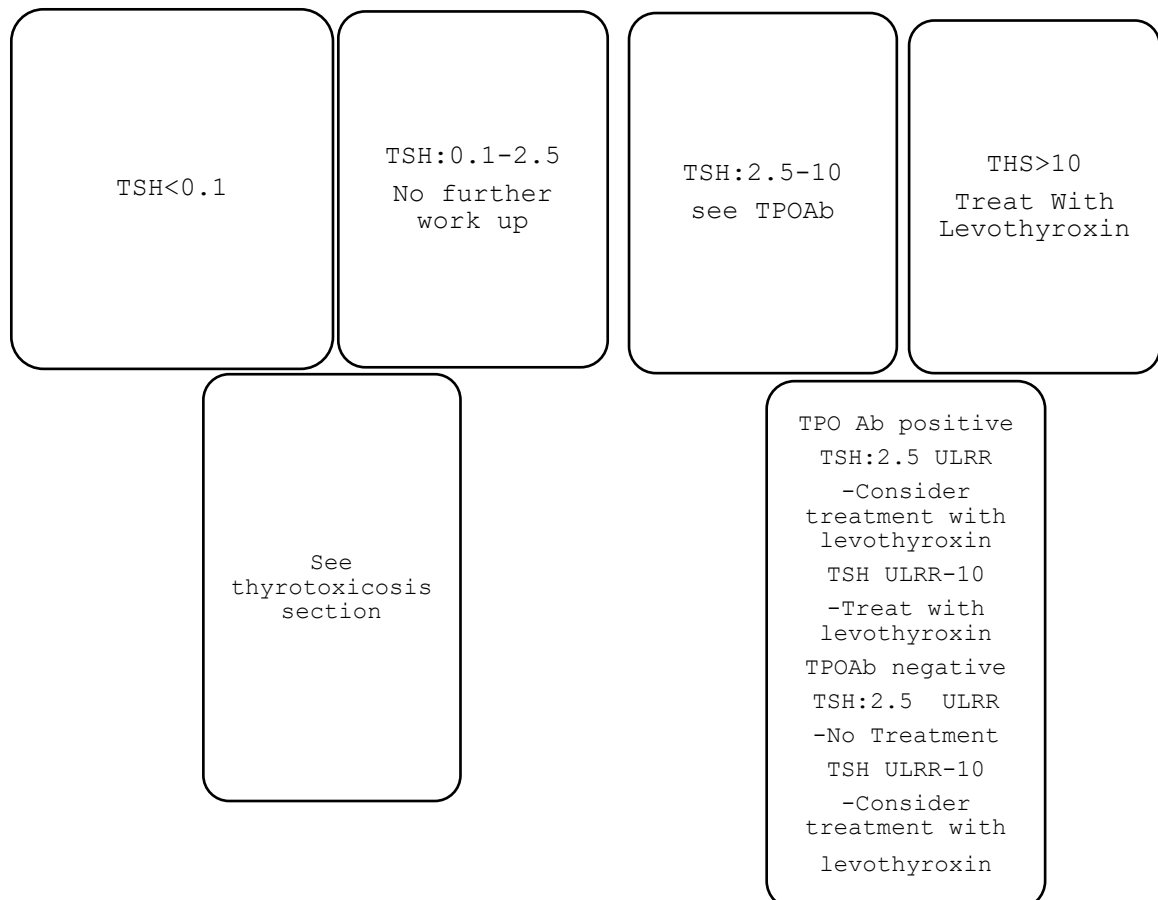In High Risk Women,check TSH a soon as pregnancy confirmed,with reflex TPO Ab if TSH 2.5-10 mU/L

TSH<0.1

TSH:0.1-2.5
No further work up

TSH:2.5-10
see TPOAb

THS>10
Treat With Levothyroxin

See thyrotoxicosis section

TPO Ab positive
TSH:2.5 ULRR
 -Consider treatment with levothyroxin
TSH ULRR-10
 -Treat with levothyroxin
TPOAb negative
TSH:2.5 ULRR
-No Treatment
TSH ULRR-10
 -Consider treatment with levothyroxin

Figure 1. Testing for thyroid dysfunction in pregnancy
(ULRR: upper limit of the reference range)

REFERENCES

1. Krassas, G.E., Poppe, K., and Glinoer, D., (2010). Thyroid Function and Human Reproductive Health. Endocrine Reviews, 31(5), 702-755.
2. Alexander, E.K., Pearce, E.N., Brent, G.A., Brown, R.S., Chen, H., Dosiou, C., and and Peeters, R.P., (2017). 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid, 27(3), 315-389.
3. Korevaar, T.I., Medici, M., Visser, T.J., and Peeters, R.P., (2017). Thyroid disease in Pregnancy: New Insights In Diagnosis and Clinical Management. Nature Reviews Endocrinology, 13(10), 610.
4. Nathan, N., and Sullivan, S.D., (2014). Thyroid Disorders During Pregnancy. Endocrinology and Metabolism Clinics, 43(2), 573-597.
5. Stagnaro-Green, A., (2011). Overt Hyperthyroidism and Hypothyroidism During Pregnancy. Clinical Obstetrics and Gynecology, 54(3), 478-487.
6. Skjöldebrand, L., Brundin, J., Carlström, A., and Pettersson, T. (1982). Thyroid Associated Components in Serum During Normal Pregnancy. Acta Endocrinologica, 100(4), 504-511.
7. Glinoer, D., NAYER, P.D., Bourdoux, P., Lemone, M., Robyn, C., Steirteghem, A.V., and Lejeune, B., (1990). Regulation of Maternal Thyroid During Pregnancy. The Journal of Clinical Endocrinology and Metabolism, 71(2), 276-287.
8. Smits, G., Govaerts, C., Nubourgh, I., Pardo, L., Vassart, G., and Costagliola, S., (2002). Lysine 183 And Glutamic Acid 157 Of The TSH Receptor: Two Interacting Residues with a Key Role in Determining Specificity Toward TSH and Human CG. Molecular Endocrinology, 16(4), 722-735.
9. Burrow, G.N., Fisher, D.A., and Larsen, P.R., (1994). Maternal and Fetal Thyroid Function. New England Journal of Medicine, 331(16), 1072-1078.
10. Glinoer, D., and Delange, F., (2000). The Potential Repercussions of Maternal, Fetal, and Neonatal Hypothyroxinemia on The Progeny. Thyroid, 10(10), 871-887.
11. LaFranchi, S.T.E.P.H.E.N., (1999). Thyroid Function ın The Preterm Infant. Thyroid, 9(1),71-78.
12. Casey, B.M., Dashe, J.S., Wells, C.E., McIntire, D.D., Byrd, W., Leveno, K.J., and Cunningham, F.G., (2005). Subclinical Hypothyroidism and Pregnancy Outcomes. Obstetrics and Gynecology, 105(2), 239-245.
13. Korevaar, T.I., Schalekamp-Timmermans, S., de Rijke, Y.B., Visser, W.E., Visser, W., de Muinck Keizer-Schrama, S.M., and Bongers-Schokking, J.J., (2013). Hypothyroxinemia and TPO-Antibody Positivity are Risk Factors For Premature Delivery: The Generation R Study. The Journal of Clinical Endocrinology and Metabolism, 98(11), 4382-4390.
14. Casey, B.M., Dashe, J.S., Spong, C.Y., McIntire, D.D., Leveno, K.J., and Cunningham, G.F., (2007). Perinatal Significance of Isolated Maternal Hypothyroxinemia Identified in the First Half of Pregnancy. Obstetrics and Gynecology, 109(5), 1129-1135.
15. Liu, H., Shan, Z., Li, C., Mao, J., Xie, X., Wang, W., and Wang, X. (2014). Maternal Subclinical Hypothyroidism, Thyroid Autoimmunity, and the Risk Of Miscarriage: A Prospective Cohort Study. Thyroid, 24(11), 1642-1649.
16. Wilson, K.L., Casey, B.M., McIntire, D.D., Halvorson, L.M., and Cunningham, F.G., (2012). Subclinical Thyroid Disease and the

Incidence of Hypertension In Pregnancy. Obstetrics and Gynecology, 119(2), 315-320.

17. Maraka, S., Ospina, N.M.S., O'Keeffe, D.T., Espinosa De Ycaza, A.E., Gionfriddo, M.R., Erwin, P.J., ... and Montori, V. M. (2016). Subclinical Hypothyroidism in Pregnancy: A Systematic Review And Meta-Analysis. Thyroid, 26(4), 580-590.
18. Fan, X., and Wu, L., (2016). The Impact of Thyroid Abnormalities during Pregnancy on Subsequent Neuropsychological Development of The Offspring: A Meta-Analysis. The Journal of Maternal-Fetal and Neonatal Medicine, 29(24), 3971-3976.
19. Fan, X., and Wu, L., (2016). The Impact of Thyroid Abnormalities during Pregnancy on Subsequent Neuropsychological Development of the Offspring: A Meta-Analysis. The Journal of Maternal-Fetal and Neonatal Medicine, 29(24), 3971-3976.
20. Männistö, T., Mendola, P., Grewal, J., Xie, Y., Chen, Z., and Laughon, S.K., (2013). Thyroid Diseases and Adverse Pregnancy Outcomes in a Contemporary US Cohort. The Journal of Clinical Endocrinology and Metabolism, 98(7), 2725-2733.
21. Finken, M.J., van Eijsden, M., Loomans, E.M., Vrijkotte, T.G., and Rotteveel, J., (2013). Maternal Hypothyroxinemia in Early Pregnancy Predicts Reduced Performance in Reaction Time Tests in 5-to 6-Year-Old Offspring. The Journal of Clinical Endocrinology and Metabolism, 98(4), 1417-1426.
22. Patil-Sisodia, K., and Mestman, J., (2009). Graves Hyperthyroidism and Pregnancy: A Clinical Update. Endocrine Practice, 16(1), 118-129.
23. Barbesino, G., and Tomer, Y., (2013). Clinical Utility of TSH Receptor Antibodies. The Journal of Clinical Endocrinology and Metabolism, 98(6), 2247-2255.
24. Stagnaro-Green, A., Abalovich, M., Alexander, E., Azizi, F., Mestman, J., Negro, R., and Wiersinga, W., (2011). Guidelines of The American Thyroid Association for The Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid, 21(10), 1081-1125.
25. Kung, A.W.C., Chau, M.T., Lao, T.T., Tam, S.C.F., and Low, L.C.K., (2002). The Effect of Pregnancy on Thyroid Nodule Formation. The Journal of Clinical Endocrinology and Metabolism, 87(3), 1010-1014.
26. Kämpe, O., Jansson, R., and Karlsson, F.A., (1990). Effects of L-Thyroxine and Iodide on the Development of Autoimmune Postpartum Thyroiditis. The Journal of Clinical Endocrinology and Metabolism, 70(4), 1014-1018.
27. De Groot, L., Abalovich, M., Alexander, E.K., Amino, N., Barbour, L., Cobin, R.H., and Mestman, J., (2012). Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism, 97(8), 2543-2565.