**ORIGINAL ARTICLE**

# Subclinical Thyroid Disorders during Pregnancy in Saudi women: An update

FAHAD MOHAMMAD ALFHAID[1*]
*[1*]Assistant Professor, Department of Family Medicine, College of Medicine, Majmaah University, Majmaah, Saudi Arabia.*
*Correspondence to: Email: F.Alfhaid@mu.edu.sa; Phone: +966562632662*

## ABSTRACT

After diabetes, thyroid disorder is the most common endocrine dysfunction during pregnancy. Timely findings of most thyroid dysfunction in pregnancy are significant to administer the upshots of unprocessed ailment for the fetus and the mother. Subclinical hyperthyroidism (SHyper) is fundamentally acknowledged largely on laboratory investigation. The widespread clinical entities whose clinical significance is uncertain are subclinical thyroid diseases. Moreover, the status of the condition in Saudi Arabia is not well-established. This update used a search in PubMed, Medline, and Google Scholar for the relevant literature focusing on Saudi Arabia, where available. The purpose of this update is to summarize the updates in the literature about subclinical thyroid disorders during pregnancy in Saudi resident women in the preceding five years of duration.

## INTRODUCTION

In the case of untraceable serum TSH hormone level or TSH, with standard levels of free thyroxine (FT 4), triiodothyronine (TT 3), and free triiodothyronine (FT 3) (1–3), subclinical hyperthyroidism is biochemically observed. Subclinical hypothyroidism (SCH) is a commonly encountered laboratory finding in clinical practice, characterised by elevated levels of thyroid-stimulating hormone (TSH) in serum in the presence of normal serum levels of free thyroxine (FT4), as compared with population-based reference ranges for these values (4).

In pregnant women, the reference value of TSH is lower than in non pregnant cases because of the thyrotrophic upshot of chorionic gonadotropin. It alters through pregnancy. The existing guideline deems a serum TSH level over 2.5 mIU/L as the upper reference limit through the first trimester and a TSH 3.0 mIU/L as the upper limit for the period of the second and third trimesters of pregnancy. (5–8). It is recommended by the American Thyroid Association and the American Association of Clinical Endocrinologists (ATA/AACE) guidelines that using a TSH concentration of 4.12 mIU/l or the age-adjusted definition of SCH to recognize which people should be categorized with SCH (9, 10).

Management of overt thyroid disorder is extremely suggested for pregnant women or for those who are planning pregnancy (11). In the US, researches have revealed a pervasiveness of 3%–15% of subclinical hypothyroidism (12).

In a total of 154 first trimester pregnant Saudi residents women, the frequency of hypothyroidism was observed 40.25% (n=62) with hyperthyroidism 0.6% (n=1) using the cutoff TSH level based on the guiding principle of the American Thyroid Association for the identification and management of thyroid ailment during pregnancy in a study that was carried out at the largest tertiary care hospital in Jeddah, a province in Saudi Arabia. Hussein (2014) came with a viewpoint that dominance of hypothyroidism was established and suggested antenatal thyroid screening through routine testing with serum TSH (13). In her study, she explained the relatively high prevalence of hyperthyroidism by a possible population-specific elevated sensitivity of the thyroid gland to thyrotrophic molecules like HCG, resulting in gestational toxicosis. Price et al. (2001) reported similar differences between Asian and Western Caucasian women in their research evaluating thyroid function tests in expecting as well as in non-pregnant women (14).

In a study comprising of two hundred diabetic sufferers in Al-Jouf, Saudi Arabia, Elmenshawi et al. (2017) observed that 69% had a standard thyroid profile (euthyroid) while 31% displayed thyroid disorder. A total of 3.5% had clinical hypothyroidism, 25% had subclinical hypothyroidism, while 2.5% had clinical hyperthyroidism. No cases of subclinical hyperthyroidism were observed in the study (15).

Clinical hypothyroidism that is above the normal range and a free T4 is below the normal range is slightly more prevalent, occurring in up to 1% of pregnancies. The cure of overt thyroid disorder is extremely suggested for pregnant women or taking pregnancy into consideration. (11)

SHyper might be caused by different conditions such as excessive thyroid hormone replacement therapy, Grave' s disease,thyroid hormone suppressive therapy, or multinodular goiter. In addition, SHyper could be transient due to Subacute thyroiditis, painless thyroiditis, or treatment of overt hyperthyroidism. There are other causes of low serum TSH concentrations apart from SHyper, which include severe non-thyroidal illness, hypothalamic, pituitary insufficiency, and some drugs (16).

Hennesse (2015) has established a viewpoint that the occurrence of SCH diverged by gender, age, race, customs, and location (range, 0.4–16.9%), with higher rates of SCH were time and again observed in women (0.9–16.9%) and older persons (2.7–16.9%) (4).

The term 'subclinical' indicates the nonappearance of indications and signals of thyroid hormone excess or deficiency, correspondingly He also suggested that 'Subclinical' Is a Misnomer and Proposed grading of the disease as grades of hypothyroidism and hyperthyroidism based on the levels of TSH, FT4, and FT3 into categorizing both hyperthyroidism and hypothyroidism in grades (IA, IB, II, III) offers a fairly specific approximation of the sternness of the situation (7).

**Search strategy and selection criteria:** The search terms like "subclinical hyperthyroidism," "SCH," and "subclinical hypothyroidism," AND "Saudi Arabia" were explored

through Medline, PubMed, and Google Scholar for findings and reports published from the period of January 1990, to January 2019, with. The search was constrained to reports published in the English language.

A secondary analysis of a potential cohort of 18–40-year older adults with 1–2 prior pregnancy losses illustrated that subclinical hypothyroidism and thyroid autoimmunity were not connected with an augmented peril of preterm delivery, gestational diabetes mellitus, or preeclampsia (18). For a screening test to be recommended, it must be capable of classifying a preponderance of sufferers with an explicit disease and permit for a clinically advantageous interference to be ratified. Numerous researches have revealed that subclinical hyperthyroidism is not connected with unfavorable obstetrical and neonatal snags (19,20). Therefore, though screening may recognize sufferers with the subclinical ailment, no management is defensible in these persons. (11)

**Physiology of thyroid hormones during pregnancy:** This augments in volume is attended by an almost fifty percent boost in the production of the active thyroid hormones thyroxine (T4) and triiodothyronine (T3), ensuing in a 50% boost in the iodine prerequisite [3]. Alongside, iodine clearance amplifies along with the augmented glomerular filtration rate of pregnancy (11).

Thyroid hormones are significant for fetal brain development, especially in the early embryonic stage. Therefore, thyroid dysfunctions through pregnancy may have unfavorable fetal and maternal results. The fetus relies on maternal thyroid hormones during the early embryonic phase for brain improvement. The fetal thyroid gland commences the emission of both T4 and T3 from about the tenths week of gestation (21). The fetal thyroid is not entirely active until around the twentieth week of gestation, so the fetus depends on the maternal thyroxine (22).

Placental human chorionic gonadotropin (hCG) cross-reacts with the receptors of TSH. hCG stimulates thyroid hormone secretion, especially in early pregnancy, so increases the production of thyroid hormone will lead to a decrease in the production of TSH during pregnancy. The healthy thyroid glands acclimatize to these alterations through the regulation of the hypothalamic-pituitary-thyroid axis, modification in thyroid hormone metabolism, and iodine uptake (23,24). In the occurrence of high hCG levels, which peak around 10 weeks' gestation, thyroid gland activity is considerably augmented. In situations where hCG levels significantly surpass those established during a regular gestation, such as in trophoblastic ailments, or the presence of hCG-secreting tumors, hCG alone may be enough to cause clinical hyperthyroidism (25).

Though these physiological transformations happen efficiently in a vigorous body, thyroid disorder can transfer complications in many. Besides, the elucidation of thyroid lab testing varies from the nonpregnant patient.

In UK thyroid function testing guidelines, it has been advised that using TSH alone may be improper for some patients being screened for the first time and for some specific clinical conditions (26). One of the relatively common clinical situations in diagnosing and monitoring thyroid disorders in pregnancy. Other causes in which measurement of TSH alone can be misleading include central hypothyroidism, non-thyroidal illness, recent treatment for thyrotoxicosis, resistance to thyroid hormone. In pregnancy, measurement of thyroid autoantibodies is not advised 31 except in pregnant who are known to have positive thyroid autoantibodies. In this condition, it is important to have follow-up and TFT measures throughout pregnancy, even if they euthyroid (27).

During pregnancy, the "total" thyroid hormone is changed by alterations in binding proteins. The increasing levels of total T4 but not free T4 15, so it is important to look for freeT4 rather than total T4. Interpretation in patients who are pregnant may be complicated if the total rather than free thyroid hormones are measured.

It has been observed that the thyroid hormone plays a very key function in synaptogenesis, formation of dendrites and axons (28). The development of the fetal pituitary-thyroid system, nevertheless, is not absolute until 12–14 weeks' gestation (29).

Until then, fetal development depends on the transfer of maternal T4 for proper development (30,31).

**Altered reference ranges of TSH in pregnancy:** It is significant to have trimester-specific reference ranges for TSH and serum-free T4 because of physiological alterations in the thyroid through pregnancy. However, regrettably, not all laboratories offer these much-required reference ranges. There is deficient proof to recommend for or against universal screening for abnormal TSH concentrations in early pregnancy (24-27). In the absence of laboratory guidance, the American Thyroid Association currently provides the most specific advice on altered reference ranges during pregnancy (32).

**Weeks seven to 12 of pregnancy:** The upper and lower limit of the reference range of TSH should be reduced by around 0.5 mU/L and 0.4 mU/L, respectively.

**Second and third trimesters of pregnancy:** The upper reference range for total T4 augments by around 5% per week, beginning at week seven. At about 16 weeks, total T4 (and T3) levels through pregnancy are 1.5 times advanced than in women who are not pregnant (33,34).

More recent studies in Asia, India, and the Netherlands have established only an inconspicuous lessening in the higher reference limit (1, 35–40). A study of 4800 pregnant women in China freshly demonstrated that the descending budge in the TSH reference range happened at weeks 7–12. However, the upper reference limit was only concentrated from 5.31 to 4.34 mU/L (39). Separate data from a topical probable intervention trial in the United States holds up this ruling (41).

**Screening for thyroid dysfunction during pregnancy:** Though the preponderance of measures for the screening of thyroid ailment through pregnancy is satisfied founded on the Wilson and Jungner criterion for ailment screening (42), disagreement regarding some criterion still subsists. There is a difficulty over widespread screening and choosy screening at high risk of thyroid disorder before and during pregnancy that stands unsettled. (43) Endocrine Society suggests screening pregnant women at high risk of thyroid disorder by using serum TSH extent (5, 44–46).

There is an ongoing disagreement on the requirement for universal screening for thyroid disorder during pregnancy versus a case-finding approach (47) since an

advanced proportion of thyroid dysfunction in pregnant women is in the form of subclinical hypothyroidism.

Although one study displayed that selectively screening women at high risk would miss 30% of those with subclinical or overt hypothyroidism (26). Another study exhibited that there is no lessening in unfavorable results in those who were collectively screened versus case finding (48).

Table 1 The Wilson and Jungner criteria for screening of ailments (42)

| |
|---|
| The condition should be a significant health difficulty. |
| The natural history of the condition should be understood. |
| There should be an identifiable latent or early suggestive stage. |
| There should be a test that is easy to perform and interpret acceptable, accurate, reliable, sensitive, and specific. |
| There should be an accepted treatment recognized for the ailment. |
| The cure should be more effective if started in the early hours. |
| There should be a policy on who should be treated upon finding, and management should be cost-effective. |
| Case-finding should be an unremitting development. |

Universal thyroid appraisal for every pregnant woman is not recommended by the American Association of Clinical Endocrinologists (AACE), American Thyroid Association (ATA), Endocrine Society, and American College of Obstetrics and Gynecology (ACOG), and recommend the targeted high-risk case finding approach (27,42,49,50). The 2011 ATA pregnancy guidelines (15) recommended screening in high-risk groups (43).

**Adverse Effects of Subclinical Hypothyroidism on Obstetric and Neonatal Outcomes:** Though relations of subclinical hypothyroidism with results such as miscarriage, premature delivery, gestational hypertension, gestational diabetes, and placental abruption have been reported, associations have differed across studies, and some large cohorts (51,52) have not accounted any unpleasant possessions at all. Whether or not researches barred women with positive thyroid autoantibodies may also have predisposed the upshots; confirmation proposes that women with thyroid autoimmunity may undergo elevated jeopardy for miscarriage at lower TSH thresholds (53).

A 2011 meta-analysis of the studies demonstrated an augmented risk of perinatal mortality in women with subclinical hypothyroidism compared to euthyroid controls (OR 2.7, 95% CI 1.6–4.7) (54). However, in the same systematic review, meta-analyses did not exhibit associations between pregnancy-induced hypertension and preterm delivery (55).

In contrast, Jouyandey et al. reviewed 241 articles on case-based screening for thyroid disease in pregnancy, and their meta-analysis displayed poor sensitivity of "case-based screening" when using risk factors such as higher age, BMI, and family history of thyroid dysfunction to predict unknown (overt) thyroid dysfunction: on average, 49% of the cases were missed (56). The study by Pop et al. (2017) accomplished that "indications and symbols at the time of early pregnancy will not aid a clinician to detect women at the peril of thyroid hypofunction and should not be deployed as a menacing feature for a case-finding approach to distinguish women with thyroid function dysfunction that need an instant cure."(57).

This was established by a current large population-based study in the Netherlands, including 3993 men and 5498 women, presenting no important disparity in indication levels between those with and without prominent or concealed TSH levels (58).

**Outcomes of pregnancy with thyroid dysfunction:** Studies exhibited that subclinical hyperthyroidism is not connected with unpleasant pregnancy shots. There are also researches signifying that there might be a peril of diminished intelligence and motor scores also in the issue (60-61). Many studies have accounted a relationship of SCH with an augment in the hazard of unpleasant pregnancy and neonatal ending counting pregnancy loss, preterm delivery, gestational diabetes, gestational hypertension, preeclampsia, placental abruption, premature rupture of membranes, intrauterine growth restriction, low birth weight, small for gestational age, low Apgar score, and neonatal death (19,61–68).

The studies' outcomes point to the recognition of subclinical hyperthyroidism and management during pregnancy is gratuitous (1). Though subclinical hyperthyroidism has long-term squeal on patients that contain osteoporosis, cardiovascular morbidity, and succession to unconcealed thyrotoxicosis or thyroid failure (2,69–73).

In an exposition legion of 14 blatantly hypothyroid pregnant women, accounted difficulty incorporated anemia in 31%, preeclampsia in 44%, placental abruption in 19%, postpartum hemorrhage in 19%, low birth weight in 31%, and fetal death in 12% (74). In another retrospective analysis which included 23 clearly hypothyroid women, overt hypothyroidism was connected with augmented jeopardy for gestational hypertension, preeclampsia, and low birth weight (75).

Currently, there is no persuasive confirmation that subclinical hyperthyroidism should be cured through pregnancy (46). One large study to assess the effects of SHyper on pregnancy showed that SHyper (1.7%) was not connected with unpleasant pregnancy or neonatal upshots (46,76).

While some observational researches demonstrated subclinical hypothyroidism augment to the unpleasant pregnancy results like preterm labor, miscarriage, gestational hypertension, placental abruption fetal distress, preeclampsia, and gestational diabetes (62,85), others accounted no momentous relations (51). The presented literature sustains a connection between subclinical hypothyroidism and unfavorable perinatal outcomes, like preeclampsia, preterm birth, abruption placentae, and gestational diabetes; though, confirmation for a cure benefit is sparse (68).

Given the variance data, universal thyroid screening holds a theme of disagreement. There are contentious

suggestions for screening asymptomatic sufferers through pregnancy and in the preconception period (1). For example, the ACOG does not suggest universal screening in pregnancy (77), while there is no consensus in the Endocrine Society (78), while the AAGE recommends "Aggressive case finding" but not universal screening (9).

A study by Aljohani et al. (2013) showed that patients with subclinical hypothyroidism have higher vitamin D levels than healthy people. Gestational diabetes mellitus (GDM) with normal pre-pregnancy glucose metabolism only occurs during pregnancy (79). The incidence of gestational diabetes (GDM) has increased significantly in recent years (80). For example, as early as 2006, Akbar et al. (2006) have conducted a study that involved 200 Saudi patients has found that subclinical hypothyroidism and hypothyroidism were the commonest thyroid dysfunction and concluded that thyroid autoimmunity and dysfunction were significantly higher in people with diabetes evaluated to controls and that thyroid dysfunction and autoimmunity are frequent in Saudi type 2 diabetics (81).

Recently, Al Shanqeeti et al. (2018) have estimated the prevalence of SCH in pregnant women (13%). However, they found that age, fast blood sugar, systolic blood pressure, obesity, diabetes, and GDM were not significantly associated with subclinical hypothyroidism ($p>0.05$), and a higher prevalence of subclinical hypothyroidism was found in pregnant women (82).

A multi-center randomized trial reviewed the influence of levothyroxine on the cognitive occupation among kids of women who had TSH superior to 97.5$^{th}$ percentile or free T4 lower than 2.5th percentile, or both, during pregnancy (83). The cure had no consequence on the mean offspring IQ at 3 years or the number of children with IQ below 85. A *post hoc* analysis for the subgroup of pregnant women who met the criteria for SCH had the same non-significant outcomes. Maraka et al. (2016) completed that the extant body of substantiation holds up a connection of SCH during pregnancy with manifold unpleasant maternal and neonatal outcomes, but there is a scarcity of confirmation for the value of levothyroxine therapy to alleviate this alliance (83).

Effects of treatment of subclinical hypothyroidism on the fetus and offspring

The Stagnaro-Green et al. study (2011) of two prospective randomized trials reviewing the influence of levothyroxine on offspring IQ in women with subclinical hypothyroidism with TSH values ≥2.5 mIU/L or isolated hypothyroxinemia identified no momentous outcome (15,63). It has been recommended that subclinical hypothyroidism during pregnancy is linked with impaired cognitive progress in offspring, and cure may recover neurocognitive results. Though, data obtainable from RCTs does not hold up this hypothesis.

A well-designed randomized proscribed trial (RCT) of pregnant women was performed by Lazarus et al. to assess the cure effect on the intelligence quotient (IQ) in children at 3 years of age; women were allocated to the screening and control group; all positive screening women were prearranged with 150 µg of LT4 per day; They found that in children at 3 years of age, prenatal screening and maternal hypothyroidism therapy did not affect enhanced cognitive purposes, as the mean IQ and the number of children with IQ levels below 85 did not differ substantially between the children of mothers treated during pregnancy and the children of those not treated. (84). Nevertheless, in exposition examination, adequate levothyroxine cure diminishes rates of preterm delivery and miscarriage (55).

While adequate levothyroxine treatment reduces premature delivery and miscarriage rates in retrospective analyses (85), and animal studies strongly indicate that management of publicly hypothyroid pregnant women is likely to enhance infant neurodevelopment (86). There is general agreement that overt hypothyroidism should be treated with thyroid hormone replacement during pregnancy. Gong et al. (2016) stated in a 2016 meta-analysis of seven studies that the risk of gestational diabetes was amplified in subclinically hypothyroid women (OR 1.558; 95% CI 1.292-1.877). Tong and colleagues have conducted a meta-analysis of seven studies in 2016 and reported a substantial association with intrauterine growth restriction of subclinical hypothyroidism (OR 1.54, 95 percent CI 1.06-2.2.2) (87).

A systematic analysis of 18 trials, which included 3995 pregnant women with subclinical hypothyroidism, was completed in 2016 by Maraka and colleagues (88). Although the pooled studies showed notable associations between subclinical hypothyroidism and loss of a pregnancy, placental abruption, premature membrane rupture, and neonatal death, there were no notable connections with other outcomes such as premature release, preeclampsia, gestational hypertension, and low birth weight. Most recently, Zhang and colleagues conducted a meta-analysis of 7 studies in 2017 that included 3137 unprocessed subclinically hypothyroid women and found that women with subclinical hypothyroidism had an advanced incidence of miscarriage (RR = 1.90, 95% CI1.59-2.27) relative to women with euthyroidism (89).

**Treatment of Hypothyroidism in Pregnancy:** The recommended solution for all women with open hypothyroidism and for those women with subclinical hypothyroidism in whom care is chosen is levothyroxine (47). Thyroid replacement with desiccated thyroid, or with liothyronine alone or in combination with levothyroxine, is not recommended in pregnancy because it is primarily T4, rather than T3, that crosses the placenta in early pregnancy and thus confers a risk of discriminating fetal hypothyroidism even when maternal TSH is normal (31).

Levothyroxine therapy is recommended to be titrated in order to preserve a maternal serum TSH <2.5 mIU/L both during preconception and childbirth (47). A retrospective analysis found that, relative to women with TSH values of 0.2-2.5 mU/L, levothyroxine-treated women with first-trimester TSH values > 2.5 mU/L had a high risk of miscarriage (90). For all females with established hypothyroidism, preconception therapy is necessary. The predominance of women on levothyroxine would need dose boosting to sustain euthyroidism during gestation, even if adequately cured for before beginning (91).

The criteria for thyroid hormones rise from weeks 4-6 of gestation and progressively increase until weeks 16-2020. (92). The criteria for levothyroxine depend in part on the underlying cause of hypothyroidism, with women who are athyroidic more likely to need increased doses during gestation due to thyroidectomy or radioactive iodine

ablation (93). As soon as pregnancy is known, levothyroxine doses are suggested to be empirically increased by 25-30 percent (33,47). Doses of levothyroxine can be reduced to presumption levels after delivery with serum TSH testing conducted at approximately 6 weeks postpartum. Maraka et al. (2016) concluded that the importance of levothyroxine therapy remains unsure in holding off these unfavorable upshots (83).

## CONCLUSION

A thyroid screening program during pregnancy should be based on a systematic evaluation of several factors, counting the burden of the thyroid disorders in pregnant women, the cost efficiency of the screening interference, and how well a given screening test performs in the target inhabitants; its presentation can be arbitrated by how many o the populace must be screened to put off one pregnancy difficulty, balanced with how many pregnant women who undergo screening have a positive or abnormal test consequence when the treatment has no effect (false-positive test). Testing patients defined at higher risk for thyroid disease, however, is more strongly supported by the literature. All of the aforementioned organizational bodies powerfully advise of screening women with any indication that may be attributable to thyroid disorder.

This indicates a need to improve thyroid management both before and during early pregnancy. Primary healthcare providers, who are responsible for prescribing LT4, should inform these women about the need for early adjustment of LT4 treatment during pregnancy and recommend measuring their TSH serum level as soon as pregnancy is confirmed.

Screening pregnant women for maternal thyroid dysfunction as early as possible should be considered, particularly in a country like Saudi Arabia, which has a high prevalence of undiagnosed thyroid dysfunction. In addition, ethnicity and environmental factors may play a role in the varying prevalence of SCH across regions both at the level of Saudi Arabia and globally. The effect of the environmental risk factors that play a role in the development of SCH and result in a higher prevalence of SCH in a specific region.

**Conflict of interests**: The author has no conflicts to declare. This work was not funded by any party.

**Acknowledgment:** I would like to acknowledge Dr.Ghaiath Hussein for his role in reviewing some of the earlier versions of the review.

## REFERENCES

1. 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(2):228–38.
2. Thyrotoxicosis ATA and AA of CET on H and OC of, Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, et al. hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21(6):593–646.
3. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142–54.
4. Hennessey J V., Espaillat R. Subclinical hypothyroidism: A historical view and shifting prevalence. Int J Clin Pract. 2015;69(7):771–82.
5. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid [Internet]. 2011 Oct [cited 2019 Jul 17];21(10):1081–125. Available from: https://www.liebertpub.com/doi/10.1089/thy.2011.0087
6. MONTAZER F, ALIZADEH-NAVAEI R. Expression of GLUT1 in Neoplastic Cells of Papillary Thyroid Cancer. TURKISH JOURNAL OF ONCOLOGY. 2019;34(4)
7. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab [Internet]. 2012 Aug [cited 2019 Jul 17];97(8):2543–65. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2011-2803
8. Akram FH, Johansson B, Möllerström G, Landgren B-M, Stavreus-Evers A, Skjöldebrand-Sparre L. Incidence of Subclinical Hypothyroidism and Hypothyroidism in Early Pregnancy. J Women's Heal [Internet]. 2017 Oct 5;26(11):1231–5. Available from: https://doi.org/10.1089/jwh.2016.6111
9. Garber JR, Cobin RH, Gharib H, Hennessey J V, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012;22(12):1200–35.
10. Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstet Gynecol. 2006;108(5):1283–92.
11. King N, Bernardi LA, Case C. Thyroid Disease and Reproduction. Thyroid Dis Reprod. 2018;69–78.
12. Akram FH, Johansson B, Möllerström G, Landgren B-M, Stavreus-Evers A, Skjöldebrand-Sparre L. Incidence of Subclinical Hypothyroidism and Hypothyroidism in Early Pregnancy. J Women's Heal [Internet]. 2017 Oct 5;26(11):1231–5. Available from: https://doi.org/10.1089/jwh.2016.6111
13. Hussein KS. Prevalence of Thyroid Dysfunction among Saudi Women in Early Pregnancy at King Abdulaziz University Hospital. 2014;6(2):21–5.
14. Price A, Obel O, Cresswell J, Catch I, Rutter S, Barik S, et al. Comparison of thyroid function in pregnant and non-pregnant Asian and western Caucasian women. Clin Chim Acta. 2001;308(1–2):91–8.
15. Elmenshawi I, Alotaibi S, Alazmi A, Alazmi A, Alruwaili F, Alazmi N, et al. prevalence of thyroid dysfunction in diabetic patients. J Diabetes Metab Disord Control. 2017;4:55–6.
16. Pedersen IB, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Laurberg P. Large differences in incidences of overt hyper- and hypothyroidism associated with a small difference in iodine intake: A prospective comparative register-based population survey. J Clin Endocrinol Metab. 2002;
17. Wiersinga WM. Guidance in Subclinical Hyperthyroidism and Subclinical Hypothyroidism: Are We Making Progress? Eur Thyroid J. 2015;4(3):143–8.
18. Plowden TC, Schisterman EF, Sjaarda LA, Perkins NJ, Silver R, Radin R, et al. Thyroid-stimulating hormone, anti-thyroid antibodies, and pregnancy outcomes. Am J Obstet Gynecol [Internet]. 2017 Dec 1 [cited 2019 Jul 17];217(6):697.e1-697.e7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28917612
19. Tudela CM, Casey BM, McIntire DD, Cunningham FG. Relationship of Subclinical Thyroid Disease to the Incidence of Gestational Diabetes. Obstet Gynecol [Internet]. 2012 May [cited 2019 Jul 17];119(5):983–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22525909
20. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the

incidence of hypertension in pregnancy. Obstet Gynecol. 2012;
21. Fisher DA. Fetal thyroid function: Diagnosis and management of fetal thyroid disorders. In: Clinical Obstetrics and Gynecology. 1997.
22. Puig-Domingo M, Vila L. The Implications of Iodine and its Supplementation During Pregnancy in Fetal Brain Development. CurrClinPharmacol. 2013;
23. Korevaar TIM. Evidence-Based Tightrope Walking: The 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;
24. Levy MJ, Koulouri O, Gurnell M. How to interpret thyroid function tests. Clin Med. 2013;
25. Kimura M, Amino N, Tamaki H, Ito E, Mitsuda N, Miyai K, et al. Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. Clin Endocrinol (Oxf) [Internet]. 1993 Apr [cited 2019 Jul 17];38(4):345–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8319364
26. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, et al. Brief report: Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab. 2007;
27. American College of Obstetrics and Gynecology. ACOG practice bulletin. Thyroid disease in pregnancy. Number 37, August 2002. American College of Obstetrics and Gynecology. Int J Gynecol Obstet [Internet]. 2002 Nov [cited 2019 Jul 17];79(2):171–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12481755
28. Bernal J. Thyroid hormone receptors in brain development and function. Nat ClinPractEndocrinolMetab [Internet]. 2007 Mar [cited 2019 Jul 17];3(3):249–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17315033
29. Epstein FH, Burrow GN, Fisher DA, Larsen PR. Maternal and Fetal Thyroid Function. N Engl J Med [Internet]. 1994 Oct 20 [cited 2019 Jul 17];331(16):1072–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8090169
30. Kimura M, Amino N, Tamaki H, Mitsuda N, Miyai K, Tanizawa O. Physiologic thyroid activation in normal early pregnancy is induced by circulating hCG. Obstet Gynecol [Internet]. 1990 May [cited 2019 Jul 17];75(5):775–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2158026
31. Calvo RM, Jauniaux E, Gulbis B, Asunción M, Gravy C, Contempré B, et al. Fetal Tissues Are Exposed to Biologically Relevant Free Thyroxine Concentrations during Early Phases of Development. J Clin Endocrinol Metab [Internet]. 2002 Apr 1 [cited 2019 Jul 17];87(4):1768–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11932315
32. Yan YQ, Dong ZL, Dong L, Wang FR, Yang XM, Jin XY, et al. Trimester-and method-specific reference intervals for thyroid tests in pregnant Chinese women: Methodology, euthyroid definition and iodine status can influence the setting of reference intervals. Clin Endocrinol (Oxf). 2011;
33. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid Hormone Early Adjustment in Pregnancy (The THERAPY) Trial. J Clin Endocrinol Metab [Internet]. 2010 Jul 1 [cited 2019 Jul 17];95(7):3234–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20463094
34. Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, Braverman LE, et al. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol. 2009;
35. Marwaha, R K, Chopra, S, Gopalakrishnan, S, Sharma, B, Kanwar, R S, Sastry, a, et al. Establishment of reference range for thyroid hormones in normal pregnant Indian women. BJOG Anant J Obstet Gynecol. 2008;
36. Korevaar TIM, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SMPF, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab. 2013;98(11):4382–90.
37. H.-W. M, H.-J. C, C.-M. P, M. H, Y.-M. Y. Establishment of trimester-specific reference intervals for thyroid hormones in Korean pregnant women. Ann Lab Med. 2015;
38. Casey B. 2: Effect of treatment of maternal subclinical hypothyroidism or hypothyroxinemia on IQ in offspring. Am J Obstet Gynecol. 2015;
39. Bernadette Biondi, LuigiBartalena, David S. Cooper LH,, Peter Laurberg GJK. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J. 2015;
40. Casey BM. Subclinical hypothyroidism and pregnancy. Obstetrical and Gynecological Survey. 2006.
41. Ginger D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab [Internet]. 1994 Jul [cited 2019 Jul 17];79(1):197–204. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8027226
42. Amouzegar A, Abdi H, Takyar M. Screening for thyroid dysfunction in pregnancy. Ann Thyroid. 2018;3:19–19.
43. Wilson JMG, Jungner G, Organization WH. Principles and practice of screening for disease. 1968;
44. Marqusee E, Haden ST, Utiger RD. Subclinical thyrotoxicosis. Endocrinol Metab Clin North Am [Internet]. 1998 Mar [cited 2019 Jul 19];27(1):37–49. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9534026
45. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;
46. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab [Internet]. 2012 [cited 2019 Jul 17];97(8):2543–2565. Available from: http://www.endo-society.org/guidelines/
47. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid [Internet]. 2017 Mar [cited 2019 Jul 17];27(3):315–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28056690
48. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab. 2010;
49. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–89.
50. 7Davies TF. The ATA, the Endocrine Society, and AACE Confuse Endocrinologists on Thyroid Disease in Pregnancy. Thyroid [Internet]. 2000 Feb [cited 2019 Jul 17];10(2):107–107. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10718545
51. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal Thyroid Hypofunction and Pregnancy Outcome. Obstet Gynecol [Internet]. 2008 Jul [cited 2019 Jul 17];112(1):85–92. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006250-200807000-00016
52. Männistö T, Vääräsmäki M, Pouta A, Hartikainen A-L, Ruokonen A, Surcel H-M, et al. Thyroid Dysfunction and Autoantibodies during Pregnancy as Predictive Factors of Pregnancy Complications and Maternal Morbidity in Later Life. J Clin Endocrinol Metab [Internet]. 2010 Mar 1 [cited

2019 Jul 17];95(3):1084–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20080846
53. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W, et al. Maternal Subclinical Hypothyroidism, Thyroid Autoimmunity, and the Risk of Miscarriage: A Prospective Cohort Study. Thyroid [Internet]. 2014 Nov [cited 2019 Jul 17];24(11):1642–9. Available from: https://www.liebertpub.com/doi/10.1089/thy.2014.0029
54. Van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JAM, Goddijn M, et al. significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update [Internet]. 2011 Sep 1 [cited 2019 Jul 17];17(5):605–19. Available from: http://academic.oup.com/humupd/article/17/5/605/761372/Significance-of-subclinical-thyroid-dysfunction
55. Pearce E. Hypothyroidism in Pregnancy. In: Eaton J, editor. Thyroid Disease and Reproduction. Springer Nature; 2019. p. 101–15.
56. Jouyandeh Z, Hasani-Ranjbar S, Qorbani M, Larijani B. Universal screening versus selective case-based screening for thyroid disorders in pregnancy. Endocrine [Internet]. 2015 Feb [cited 2019 Jul 17];48(1):116–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25173191
57. Pop VJ, Broeren MA, Wiersinga WM, Stagnaro-Green A. Thyroid disease symptoms during early pregnancy do not identify women with thyroid hypofunction that should be treated. Clin Endocrinol (Oxf). 2017;87(6):838–43.
58. Klaver EI, van Loon HCM, Stienstra R, Links TP, Keers JC, Kema IP, et al. Thyroid Hormone Status and Health-Related Quality of Life in the LifeLines Cohort Study. Thyroid [Internet]. 2013 Sep [cited 2019 Jul 17];23(9):1066–73. Available from: https://www.liebertpub.com/doi/10.1089/thy.2013.0017
59. 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 [Internet]. 1999 Aug 19 [cited 2019 Jul 17];341(8):549–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10451459
60. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf) [Internet]. 2009 Oct 31 [cited 2019 Jul 17];72(6):825–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19878506
61. Su P-Y, Huang K, Hao J-H, Xu Y-Q, Yang S-Q, Li T, et al. Maternal Thyroid Function in the First Twenty Weeks of Pregnancy and Subsequent Fetal and Infant Development: A Prospective Population-Based Cohort Study in China. J Clin Endocrinol Metab [Internet]. 2011 Oct 1 [cited 2019 Jul 17];96(10):3234–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21832110
62. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical Hypothyroidism and Pregnancy Outcomes. Obstet Gynecol [Internet]. 2005 Feb [cited 2019 Jul 17];105(2):239–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15684146
63. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased Pregnancy Loss Rate in Thyroid Antibody Negative Women with TSH Levels between 2.5 and 5.0 in the First Trimester of Pregnancy. J Clin Endocrinol Metab [Internet]. 2010 Sep [cited 2019 Jul 17];95(9):E44–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20534758
64. Korevaar TIM, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SMPF, et al. Hypothyroxinemia and TPO-Antibody Positivity Are Risk Factors for Premature Delivery: The Generation R Study. J Clin Endocrinol Metab [Internet]. 2013 Nov 1 [cited 2019 Jul 17];98(11):4382–90. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2013-2855
65. Wang S, Teng WP, Li XJ, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Invest [Internet]. 2012 Mar [cited 2019 Jul 17];35(3):322–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21642766
66. Feldthusen A-D, Larsen J, Pedersen PL, ToftKristensen T, Kvetny J. Pregnancy-induced alterations in mitochondrial function in euthyroid pregnant women and pregnant women with subclinical hypothyroidism; relation to adverse outcome. J ClinTranslEndocrinol [Internet]. 2014 Mar [cited 2019 Jul 17];1(1):e13–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29235583
67. Chen L-M, Du W-J, Dai J, Zhang Q, Si G-X, Yang H, et al. Effects of Subclinical Hypothyroidism on Maternal and Perinatal Outcomes during Pregnancy: A Single-Center Cohort Study of a Chinese Population. Gao C-Q, editor. PLoS One [Internet]. 2014 Oct 29 [cited 2019 Jul 17];9(10):e109364. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25353960
68. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical Thyroid Disease and the Incidence of Hypertension in Pregnancy. Obstet Gynecol [Internet]. 2012 Feb [cited 2019 Jul 17];119(2, Part 1):315–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22270283
69. Selmer C, Olesen JB, Hansen ML, Von Kappelgaard LM, Madsen JC, Hansen PR, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: A large population study. J Clin Endocrinol Metab. 2014;
70. Collet TH, Gussekloo J, Bauer DC, Den Elzen WPJ, Cappola AR, Balmer P, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med. 2012;
71. Gencer B, Collet TH, Virginia V, Bauer DC, Gussekloo J, Cappola AR, et al. Subclinical thyroid dysfunction and the risk of heart failure events an individual participant data analysis from 6 prospective cohorts. Circulation. 2012;
72. Nanchen D, Gussekloo J, Westendorp RGJ, Stott DJ, Jukema JW, Trompet S, et al. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab. 2012;
73. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, Da Costa BR, et al. Subclinical thyroid dysfunction and fracture risk a meta-analysis. JAMA - J Am Med Assoc. 2015;
74. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol [Internet]. 1988 Jul [cited 2019 Jul 17];72(1):108–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3380497
75. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol [Internet]. 1993 Mar [cited 2019 Jul 17];81(3):349–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8437784
76. Salles F, Salles D. Clinical and therapeutic controversies on subclinical hyperthyroidism. Vol. 1, Medical Express. 2014.
77. American College of Obstetricians and Gynecologists. Practice Bulletin No. 148. Obstet Gynecol [Internet]. 2015 Apr [cited 2019 Jul 17];125(4):996–1005. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25798985
78. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab [Internet]. 2012 Aug [cited 2019 Jul 17];97(8):2543–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22869843
79. Aljohani NJ, Al-Daghri NM, Al-Attas OS, Alokail MS, Alkhrafy

KM, Al-Othman A, et al. Differences and associations of metabolic and vitamin D status among patients with and without sub-clinical hypothyroid dysfunction. BMC Endocr Disord [Internet]. 2013 Aug 20 [cited 2019 Jul 17];13:31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23962199

80. Zhou X, Li Z, Li B, Guo S, Yao M. Expression and clinical significance of serum 25-OH-D in pregnant women with SCH (Subclinical Hypothyroidism) and GDM (Gestational Diabetes Mellitus). Pakistan J Med Sci. 2018;34(5):1278–82.
81. Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. ActaDiabetol. 2006;43(1):14–8.
82. Al Shanqeeti SA, Alkhudairy YN, Alabdulwahed AA, Ahmed AE, Al-Adham MS, Mahmood NM. Prevalence of subclinical hypothyroidism in pregnancy in Saudi Arabia. Saudi Med J. 2018;39(3):254.
83. Maraka S, Ospina NMS, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid. 2016;
84. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal Thyroid Screening and Childhood Cognitive Function. N Engl J Med [Internet]. 2012 Feb 9 [cited 2019 Jul 17];366(6):493–501. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22316443
85. Abramovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Leveille O. Overt and Subclinical Hypothyroidism Complicating Pregnancy. Thyroid [Internet]. 2002 Jan [cited 2019 Jul 17];12(1):63–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11838732
86. De Escobar GM, Obregón MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. In: Public Health Nutrition. 2007.
87. Tong Z, Xiaowen Z, Baomin C, Aihua L, Yingying Z, Weiping T, et al. The Effect of Subclinical Maternal Thyroid Dysfunction and Autoimmunity on Intrauterine Growth Restriction. Medicine (Baltimore) [Internet]. 2016 May [cited 2019 Jul 17];95(19):e3677. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27175703
88. Maraka S, Ospina NMS, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid [Internet]. 2016 Apr [cited 2019 Jul 17];26(4):580–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26837268
89. Zhang Y, Wang H, Pan X, Teng W, Shan Z. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: A systematic review and meta-analysis. Li D, editor. PLoS One [Internet]. 2017 Apr 17 [cited 2019 Jul 17];12(4):e0175708. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28414788
90. Taylor PN, Minassian C, Rehman A, Iqbal A, Draman MS, Hamilton W, et al. TSH Levels and Risk of Miscarriage in Women on Long-Term Levothyroxine: A Community-Based Study. J Clin Endocrinol Metab [Internet]. 2014 Oct [cited 2019 Jul 17];99(10):3895–902. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25057882
91. Mandel SJ, Larsen PR, Seely EW, Brent GA. Increased Need for Thyroxine during Pregnancy in Women with Primary Hypothyroidism. N Engl J Med [Internet]. 1990 Jul 12 [cited 2019 Jul 17];323(2):91–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2359428
92. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and Magnitude of Increases in Levothyroxine Requirements during Pregnancy in Women with Hypothyroidism. N Engl J Med [Internet]. 2004 Jul 15 [cited 2019 Jul 17];351(3):241–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15254282
93. Loh JA, Wartofsky L, Jonklaas J, Burman KD. The Magnitude of Increased Levothyroxine Requirements in Hypothyroid Pregnant Women Depends upon the Etiology of the Hypothyroidism. Thyroid [Internet]. 2009 Mar [cited 2019 Jul 17];19(3):269–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19265498