

Thyroid Disease in Pregnancy: A Clinical Survey among Endocrinologists, Gynecologists, and Obstetricians in Israel

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ABSTRACT: **Background:** Previous surveys demonstrated variations in the clinical practices relating to the treatment and screening of maternal thyroid dysfunction.

Objectives: To study the current practices in the management of subclinical hypothyroidism (SCH) and thyroid nodules during pregnancy by obstetricians/gynecologists (OB/GYNs) and endocrinologists in Israel.

Methods: An electronic questionnaire was sent by email to all members of the Israeli Endocrine Society and the Israel Society of Obstetrics and Gynecology. Questionnaires included demographic data and clinical scenarios with questions regarding the screening and management of pregnant women with SCH, hypothyroxinemia, and a palpable thyroid nodule. The questionnaire for OB/GYNs was slightly modified.

Results: We received 90 responses from endocrinologists and 42 responses from OB/GYNs. Among endocrinologists, 39% would repeat a thyroid-stimulating hormone (TSH) test of 2.9 mU/L with normal free thyroxine and treat with thyroxine if the second result was above 2.5 mU/L. Among OB/GYNs, 73% would manage a woman with SCH at the beginning of her pregnancy by themselves and only 22% would start thyroxine after a first TSH result above 2.5 mU/L. Concerning screening, 57% endocrinologists and 71% OB/GYNs recommended screening for thyroid dysfunction in every woman at the beginning of her pregnancy. Among endocrinologists, 54% would order an ultrasound for a palpable thyroid nodule and perform a fine needle aspiration only for suspicious lesions.

Conclusions: The medical approach to thyroid disease in pregnant women remains a matter of controversy. Our results support the need for larger and prospective clinical studies.

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The detection and treatment of thyroid disease in pregnancy is a matter of controversy [1]. Pregnancy affects almost all aspects of thyroid hormone production. There is an estimated increase in the need for thyroxine (T4) of up to 50% during

pregnancy. Thyroid binding globulins rise during pregnancy and cause an increase in the bound fraction of T4. Human chorionic gonadotropin (HCG) can stimulate thyrocytes to produce the hormone and cause suppression of thyroid stimulating hormone (TSH). The fetal placental unit causes acceleration of the clearance of thyroxine, and iodine requirements escalate because of increased renal clearance and transfer of iodine to the fetus. These conditions make the assessment and interpretation of the normal reference range for TSH difficult to determine during pregnancy [2,3].

Although it is accepted that treating overt hypothyroidism is essential for preventing adverse maternal and neonatal outcomes [4], the management of subclinical hypothyroidism (SCH) in pregnancy and its effect on the pregnancy is unclear. Studies have found associations between SCH and pregnancy loss, preterm delivery, eclampsia, placental abruption, gestational hypertension, and gestational diabetes for the mother as well as an increase in rates of hospitalization for the newborn. There is controversy regarding adverse neurodevelopmental outcomes in newborns of mothers with SCH [2,3].

Several guidelines have addressed the problem of treating SCH throughout pregnancy [2,3,5,6] and the management of thyroid nodule and differentiated thyroid cancer in pregnant women [7]. The guidelines are not uniform regarding the reference range for TSH during pregnancy. The Endocrine Society guidelines (2012) and the previous American Thyroid Association (ATA) guidelines (2011) recommended an upper limit of TSH of 2.5 mU/L for the first trimester and 3 mU/L for the second and third trimesters. The 2011 ATA guidelines recommended treatment for women with TSH above 2.5 mU/L only if they had a positive anti-thyroid peroxidase antibody (TPO) test [3], whereas the Endocrine Society made this recommendation for pregnant women who are anti-TPO negative as well, although the recommendation was not strong [5]. According to the American College of Obstetricians and Gynecologists (ACOG), there is no recommendation to identify or treat maternal SCH [2].

Previous surveys demonstrated variations in the clinical practices relating to the treatment and screening of maternal

hypothyroidism. A 2013 survey among clinical members of the Endocrine Society, the ATA, and the American Association of Clinical Endocrinologists (AACE) suggested that pregnant and pre-pregnant TSH levels should be well below 2.5 mU/L [8]. Another survey among the members of the European Thyroid Association found most responders aiming at the same trimester-specific TSH of 2.5 mU/L for the first trimester and 3 mU/L for the second and third trimesters [9]. With regard to isolated hypothyroxinemia, 40% of responders chose treating pregnant women and 40% recommended universal screening for thyroid dysfunction during pregnancy [9]. Another survey conducted in East Asia found that most endocrinologists suggested a target of trimester-specific TSH levels, with half of the clinicians treating isolated TPO positivity and 40% of endocrinologists treating maternal hypothyroxinemia [10].

These common clinical scenarios constitute a common problem in the clinical practice of both obstetricians and gynecologists (OB/GYNs) and endocrinologists. We conducted a clinical survey to study the current practices in the management of SCH and thyroid nodules among OB/GYNs and endocrinologists in Israel.

PATIENTS AND METHODS

Between April 2016 and June 2016, an electronic questionnaire was sent by email to 198 endocrinologists who treat adults and who are members of the Israeli Endocrine Society (IES) and to 800 members of the Israel Society of Obstetrics and Gynecology (ISOG). Of note, members of the ISOG were contacted irrespective of their status in clinical practice. A web-based survey platform service was used to administer the survey (SurveyMonkey, Palo Alto, California). Two reminders were sent after the first email, each 2 weeks apart. The study was approved by our local institutional ethics committee.

QUESTIONNAIRES

The questionnaire was designed by the authors for the purpose of this study (see supplementary data in the electronic version of this article). The authors are familiar with the study population and have experience as clinicians caring for populations with thyroid dysfunction. Questionnaires included demographic data (e.g., gender, work environment, years of practice in endocrinology or OB/GYN with a subspecialty in maternal-fetal medicine) and multiple choice questions regarding clinical scenarios depicting the management of pregnant women with SCH, hypothyroxinemia, and a palpable thyroid nodule. Four yes/no questions dealt with screening data. The questionnaire for OB/GYNs was slightly modified.

STATISTICAL ANALYSIS

Statistical calculations were performed with the SigmaStat 2.03 (Systat Software Inc., Point Richmond, CA, USA) com-

puterized program. The continuous variables are presented as means and standard deviations, and the categorical variables as percentages. Differences in demographic and categorical baseline characteristics were analyzed with chi-square or Fisher's exact test. For continuous variables, we used the independent *t*-test or Mann-Whitney test, as appropriate. Since not every respondent answered the questionnaire fully, the frequencies of every given answer were adjusted on a 100% basis excluding the non-responders. A *P* value of < 0.05 was considered as statistically significant.

RESULTS

DEMOGRAPHICS OF RESPONDENTS

We received 90/198 responses (45%) to questionnaires sent to endocrinologists. Their demographic characteristics are shown in Table 1. Respondents worked as endocrinologists for an average of 13.2 ± 11.3 years and evaluated approximately 70 ± 53 patients with thyroid dysfunction every month. Of the respondents, 53% were female and 23% worked exclusively at community clinics. The most recent ATA guidelines for the diagnosis and management of thyroid dysfunction during pregnancy were read by 76% of endocrinologists who responded to the questionnaire.

We collected 42 responses (5%) from OB/GYNs out of 800 emails sent. Of these, 35 completed the demographic information. The respondents had worked as practitioners for an average of 16 ± 10 years, 55% were females and 48% worked both in a hospital and in the community. Forty percent of all responders were specialists in maternal-fetal medicine. Characteristics of the OB/GYN respondents are presented in Table 1 and Table 2.

THERAPY FOR SUBCLINICAL HYPOTHYROIDISM

As shown in Table 2, 38.9% of endocrinologists would repeat a TSH test of 2.9 mU/L with normal free thyroxine (FT4) and treat with thyroxine if the second result was above 2.5 mU/L, even if anti-TPO antibodies were negative during the first trimester of pregnancy. This response was followed by 35.5% who would initiate treatment only if the anti-TPO antibodies

Table 1. Characteristics of endocrinologists and gynecologists who responded

	Endocrinologists (n=90)	Obstetricians/ gynecologists (n=48)
Females	53%	55%
Hospital practice	27%	26%
Community practice	23%	26%
Both practices	50%	48%
Maternal-fetal medicine	–	40%
Years in practice, mean \pm SD	13.2 ± 11.3	16 ± 11
Thyroid patients per month, mean \pm SD	70 ± 53	–

were positive, 14.5% who would follow-up 1 month later, 7.8% who would not make any further evaluation, and 3.3% who would treat with thyroxine immediately after the first result. More females than males (41 vs. 29%) would repeat the test and start treatment if TPO antibodies were positive, while more males (15 vs. 2%) would not initiate further evaluation ($P = 0.06$). Other parameters, such as work experience or number of thyroid patients per month, had no influence on decision making. In 41% of responders, a goiter or positive family history for thyroid dysfunction would influence their management, and more clinicians would treat those cases with thyroxine immediately (12.5 vs. 3.3%; $P = 0.001$) [Table 3].

If the patient had two abnormal test results above 2.5 mU/L, 70% would treat with thyroxine immediately, whereas 19% would order an anti-TPO test and treat only if the outcome was positive, followed by 8% who would only conduct a follow-up and 3% who would make no further evaluation. Compared to females, male endocrinologists began immediate treatment less frequently and decided on no further evaluation more often (68 vs. 72% and 7.5 vs. 0%, respectively; $P = 0.078$). Endocrinologists with more than 7 years of experience tended to follow women with two TSH results above 2.5 mU/L more often and start thyroxine treatment less often than those with less than 7 years (15 vs. 0% and 67 vs. 72%, respectively; $P = 0.087$).

Among OB/GYNs, 73% would manage a woman's condition with SCH at the beginning of her pregnancy by themselves, whereas 27% would refer her to an endocrinologist. With regard to treatment, 22% of OB/GYNs would start thyroxine, 68% would repeat TSH at 1 month, and 67% would start treatment if TPO antibodies came back positive.

TSH TARGET DURING PREGNANCY

The TSH target level among endocrinologists treating a woman with SCH during the third trimester was found to be < 2.5 mU/L for 21%, < 3 mU/L for 41%, and within normal reference values of non-pregnant women in 38%. For the OB/GYN respondents, the TSH targets were < 2.5 mU/L for 42%, < 3 mU/L for 30%, and within normal reference values of non-pregnant women in 15%. Of all the respondents, 13% would leave the decision to an endocrinologist.

APPROACH TO HYPOTHYROXINEMIA

Among endocrinologists, 42% would neither treat nor monitor women with hypothyroxinemia in pregnancy. Subsequently, 35% of respondents would repeat the test and treat if FT4 was still under normal reference values, 14% would treat without repeating the test, and 9% would treat only if a TPO antibody test came back positive. The OB/GYN approach to pregnant women with hypothyroxinemia was as follows: 44% would offer no further evaluation, 22% would repeat the test and treat if still abnormal, 7% would order TPO antibodies and treat only if positive, and 7% would treat immediately. Only 20% would

Table 2. Endocrinologist management of TSH 3.1 mIU/L during the first trimester in pregnant women with or without goiter and/or a family history of thyroid disease

Family history and/or goiter	No further evaluation	Follow-up	Treat without further evaluation*	Repeat and treat regardless TPO	Repeat and treat if TPO+
Without	7.8%	14.5%	3.3%	38.9%	35.5%
With	2.3%	19.3%	12.5%	35.2%	30.7%

* $P < 0.001$

TSH = thyroid stimulating hormone, TPO = thyroid peroxidase antibody

Table 3. Endocrinologist approach to 1.5 cm palpable thyroid nodule during first trimester

	All* (n=89)	Community* (n=20)	Hospital* (n=69)
Order ultrasound and FNA for any solid lesion	15.5	0	24.6
Order ultrasound and FNA only for suspicious lesions	55.5	50	58
Follow-up by ultrasound and FNA if growth	16.7	30	11.6
Follow-up by palpation only	1.1	5	0
Follow-up by ultrasound only	7.7	15	5.8

*All values are presented as percentage

FNA = fine needle aspiration

consult an endocrinologist. OB/GYNs with a maternal–fetal medicine subspecialty would treat and follow pregnant women with hypothyroxinemia less often than those without (36 vs. 68%; $P = 0.032$). Likewise, they would consult endocrinologists less frequently (0 vs. 31.6%; $P = 0.032$).

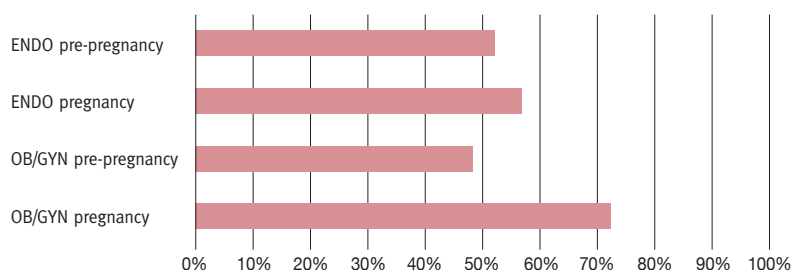
FOLLOW-UP MODALITY

For women with thyroid dysfunction, 64.44% of endocrinologists would monitor TSH at 4–8 week intervals, 11.12% at 2–4 week intervals, and 24.44% only when not appropriate for gestational age. Among OB/GYNs, 48% would follow-up TSH every 6–8 weeks, 22% every 12 weeks, 20% every 2–4 weeks, and 10% only if not appropriate for the gestational age.

SCREENING DURING AND BEFORE PREGNANCY

Among the 90 endocrinologists who responded to the survey, 57% recommend screening for thyroid dysfunction for every woman at the beginning of her pregnancy. Fifty-two percent of respondents recommend screening women who were planning a pregnancy [Figure 1]. Endocrinologists with more than 7 years of practice tended to favor screening more often than those with less than 7 years (67 vs. 43%; $P = 0.075$). The same trend was found in screening women planning a pregnancy. Other parameters, such as gender, working environment, or number of thyroid patients seen per month, had no influence on the results. Among OB/GYN specialists, 71% recommended screening every woman at the beginning of her pregnancy, while only 48% recommended screening women who were planning a pregnancy [Figure 1]. OB/GYNs with a maternal–fetal medicine subspecialty recommended screening less often than those without (51 vs. 90%; $P = 0.043$). FT4 monitoring,

Figure 1. Bars represents the percentage of respondents in favor of screening for thyroid dysfunction



ENDO = endocrinologists, OB/GYN = obstetricians/gynecologists

despite a normal TSH, was recommended by 30% of endocrinologists (40% of female, 18% of males; $P = 0.043$).

PALPABLE THYROID NODULE

Among the endocrinologists, 54% would order an ultrasound for a palpable thyroid nodule of 1.5 cm and perform a fine needle aspiration (FNA) only for suspicious lesions [Table 3]. Others would order an ultrasound and perform FNA for any solid lesion (20%). They would recommend a follow-up with ultrasound and perform FNA only if there was significant growth (17%) and postpone an FNA until after delivery (8%). One respondent would follow-up with palpation alone. Female endocrinologists tended to perform more ultrasounds and FNAs in a suspicious lesion (69 vs. 40%) and male endocrinologists tended to follow-up with more ultrasound and perform an FNA only if the lesion grew (22.5 vs. 10.5%, $P = 0.076$). There was a significant difference in decision making between physicians working in a hospital and those working solely in the community [Table 3]. Hospital workers performed more FNAs for solid lesions (24.6 vs. 0%) and more FNAs in suspicious lesions (58 vs. 50%); whereas, physicians working in the community tended more to delay FNAs until after delivery (15 vs. 6%) or to perform an FNA if the lesion grew (30 vs. 12%, $P = 0.009$).

DISCUSSION

The association between SCH and maternal and fetal complications is unclear. Studies have shown that SCH is associated with gestational diabetes mellitus [11], risk for pregnancy loss [12], gestational hypertension, and pre-eclampsia [13], although others have shown conflicting results [14,15]. The role of anti-TPO positivity vs. SCH and the risk of preterm delivery is also not straightforward [16,17]. There is inconsistency regarding impairment of neuropsychological development in the offspring of pregnant woman with SCH [18,19]. Previous studies have shown a lower reference range for TSH during pregnancy than in the general population [20]. Based on these results, SCH was diagnosed as TSH levels above 2.5 mU/L for the first trimester

or over 3 mU/L for the second and third trimesters. It is possible that this target was set too low and further studies have demonstrated significant variations between ethnic and racial groups and only modest reduction in TSH (of 0.5–1 mU/L) from the pre-pregnancy values [21,22]. Our survey was conducted before the publication of the new 2017 ATA guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum. The new guidelines recommend assessing reference ranges through local population data of pregnant women with no known thyroid disease. If this is not feasible, an upper limit of 4 mU/L during the first trimester with a gradual return toward the non-pregnant range in the second and third trimesters is applicable. There is a strong recommendation to treat women with a negative TPO antibody test with TSH greater than 10 mU/L and a weaker recommendation to consider treatment for women who are TPO negative with TSH levels above the specific reference range. The 2017 ATA guidelines also recommend treatment for SCH in women with TSH above 2.5 mU/L and a positive TPO antibody test, although this is a weak recommendation with only moderate quality of evidence [23].

Our survey demonstrated that most endocrinologists follow previous reference values and 74.5% of responders would repeat a TSH above 2.5 mU/L, with 52% of them starting treatment even if anti-TPO antibodies were negative. With two abnormal TSH results, 70% of respondents would start treatment with thyroxine irrespective TPO antibodies status. This finding corresponds with previous surveys conducted in recent years [8–10].

Among gynecologists, the picture was somewhat different, with 68% of respondents recommending follow-up alone and 67% suggesting treatment only if TPO antibodies were positive. These findings parallel the latest ACOG practice bulletin published in 2015 that did not address the trimester-specific target range or the management of TSH above 2.5 mU/L [2].

Managing hypothyroxinemia of pregnancy is also an issue of debate. Studies have found a correlation between hypothyroxinemia and preterm labor, fetal distress, small for gestational age, and impaired neuropsychological development of the offspring [16]. Other studies found no association between hypothyroxinemia and maternal or fetal adverse events [24,25]. This controversy is manifested also in our survey, as 42% of endocrinologists and 44% OB/GYNs make no further evaluation for this clinical condition, whereas 35% and 22%, respectively, repeat an abnormal FT4 test and treat the condition if results are still low. These percentages are somewhat lower than in previous surveys among members of the European Thyroid Association [9] and Asian endocrinologists [10].

Screening for thyroid disease during and before pregnancy is not recommended by the ACOG [6] or the Endocrine Society [3]. The ATA guidelines recommend against screening for maternal hypothyroxinemia and did not find enough evidence to recommend for or against screening for SCH before or during pregnancy [4]. Our survey found that most OB/GYNs and

over 50% of endocrinologists do recommend screening during pregnancy and about half of endocrinologists and OB/GYNs recommend screening for women planning a pregnancy. This result may come as a surprise, considering the diversity in the treatment decisions we found.

The latest ATA guidelines for the management of thyroid nodules and differentiated thyroid cancer recommends an FNA for every suspicious thyroid nodule in euthyroid and hypothyroid pregnant patients. In the case of thyroid cancer detected by FNA during pregnancy, delaying surgery until after delivery in selected cases does not affect the outcome [7]. Among endocrinologists, 54% would follow the ATA guidelines, 20% would perform an FNA for any solid lesion, and 17% would follow-up with ultrasound and perform FNA only for growing lesions. Interestingly, gender had an influence on decision making. Female endocrinologists tended to be more active in treating SCH and performing FNA for thyroid nodules, and they also tended to monitor FT4 more frequently than males. Less experienced physicians also treated SCH more frequently, but recommended less screening.

LIMITATIONS

There are some limitations to this study. First, this was a small and local study involving a population of physicians in Israel alone. Second, our questionnaires were not validated and were designed solely for the purpose of the study. Third, there was a low response rate among OB/GYNs, probably due to difficulties in selecting our target group among the diverse category of members within that society. Still, our results reflect the controversy in treatment guidelines and correspond well with previous surveys.

CONCLUSIONS

We conclude that the medical approach to thyroid disease in pregnant women remains a matter of controversy, as does the true impact of SCH and hypothyroxinemia on maternal and fetal outcome. Our study supports the need for larger and prospective clinical studies aimed at reaching more consensual, evidence-base clinical practice recommendations on thyroid dysfunction during pregnancy.

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References

1. Soldin OP. When thyroidologists agree to disagree: comments on the 2012 Endocrine Society pregnancy and thyroid disease clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97 (8): 2632-5.
2. American College of Obstetricians and Gynecologists. Practice Bulletin No. 148: Thyroid Disease in Pregnancy. *Obstet Gynecol* 2015; 125 (4): 996-1005.
3. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. *Thyroid* 2011; 21 (10): 1081-125.

4. Stagnaro-Green A. Overt hyperthyroidism and hypothyroidism during pregnancy. *Clin Obstet Gynecol* 2011; 54 (3): 478-87.
5. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97 (8): 2543-65.
6. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014; 3 (2): 76-94.
7. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016; 26 (1): 1-133.
8. Burch HB, Burman KD, Cooper DS, Hennessey JV. A 2013 survey of clinical practice patterns in the management of primary hypothyroidism. *J Clin Endocrinol Metab* 2014; 99 (6): 2077-85.
9. Vaidya B, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K. Treatment and screening of hypothyroidism in pregnancy: results of a European survey. *Eur J Endocrinol* 2012; 166 (1): 49-54.
10. Azizi F, Mehran L, Amouzegar A, et al. Prevalent practices of thyroid diseases during pregnancy among endocrinologists, internists and general practitioners. *Int J Endocrinol Metab* 2016; 14 (1): e29601.
11. Karakosta P, Alegakis D, Georgiou V, et al. Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J Clin Endocrinol Metab* 2012; 97 (12): 4464-72.
12. 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* 2010; 95 (9): E44-8.
13. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 2012; 119 (2 Pt 1): 315-20.
14. Blumenfeld Z. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008; 112 (6): 1390-1; author reply 1391.
15. Van den Boogaard E, Vissenberg R, Land JA, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 2016; 22 (4): 532-3.
16. Su PY, Huang K, Hao JH, 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* 2011; 96 (10): 3234-41.
17. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; 105 (2): 239-45.
18. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; 366 (6): 493-501.
19. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; 341 (8): 549-55.
20. Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. *J Med Screen* 2004; 11 (4): 170-4.
21. Laurberg P, Andersen SL, Hindersson P, Nohr EA, Olsen J. Dynamics and Predictors of Serum TSH and ft4 Reference Limits in Early Pregnancy: A Study Within the Danish National Birth Cohort. *J Clin Endocrinol Metab* 2016; 101 (6): 2484-92.
22. Li C, Shan Z, Mao J, et al. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab* 2014; 99 (1): 73-9.
23. 2016 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum. *Thyroid* 2017; 27 (9): 1212.
24. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol* 2007; 109 (5): 1129-35.
25. Craig WY, Allan WC, Kloza EM, et al. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. *J Clin Endocrinol Metab* 2012; 97 (1): E22-8.

Supplemental material

Questionnaire for endocrinologists**Question 1**

A 29 year old healthy woman is referred to you for evaluation during the tenth week of her first pregnancy. She currently takes no medication and is feeling well. There is no known family history of thyroid disease. Her TSH levels are 3.1 mIU/L, FT4 16 pmol/L. A previous test shows a TSH level of 2.9 mIU/L with FT4 of 18 pmol/L. On neck palpation there is no goiter. What would you do?

- No further evaluation
- Treat with thyroxine
- Follow-up TSH in 1 month
- Repeat TSH, and if above 2.5 mIU/L begin thyroxine only if anti-TPO is positive
- Repeat TSH, and if above 2.5 mIU/L begin thyroxine even if anti-TPO is negative

Question 2

You have decided to repeat blood tests and the results show TSH 3.9 mIU/L with FT4 13.5 pmol/L, antibodies were not measured, what would you do?

- No further evaluation
- Follow-up of TSH in 1 month
- Treat with thyroxine
- Order anti-TPO and treat only if positive

Question 3

A similar 29 year old healthy woman is referred to you for evaluation at the tenth week of her first pregnancy. She currently takes no medication and is feeling well. She has a family history of thyroid disease. Her TSH levels are 3.1 mIU/L, FT4 16 pmol/L. A previous test a year prior to her visit shows a TSH level of 2.9 mIU/L with FT4 of 18 pmol/L. On neck palpation there is a small diffuse soft irregular goiter. What would you do?

- No further evaluation
- Treat with thyroxine
- Follow-up TSH in 1 month
- Repeat TSH, and if above 2.5 mIU/L begin thyroxine only if anti-TPO is positive
- Repeat TSH, and if above 2.5 mIU/L begin thyroxine even if anti-TPO is negative

Question 4

Repeated blood test shows TSH 3.9 mIU/L with FT4 13.5 pmol/L, antibodies were not measured. What is your next step?

- No further evaluation
- Follow-up of TSH in 1 month
- Treat with thyroxine
- Order anti-TPO and treat only if positive

Question 5

You have decided that the patient should receive 25 mcg of thyroxine daily and is currently at the 29th week of her pregnancy. TSH levels are 3.2 mIU/L, what would you do?

- Increase her thyroxine dose to a target of below 2.5 mIU/L
- Increase her thyroxine dose to a target of below 3.0 mIU/L
- Follow-up on the same dose

Question 6

The same patient at the tenth week of her pregnancy is referred to you with a TSH level of 2.3 mIU/L and FT4 levels of 9.8 pmol/L. Your next step would be

- No further evaluation
- Treat with thyroxine
- Repeat test and start thyroxine if FT4 is still below normal
- Order anti-TPO and treat only if positive

Question 7

During her pregnancy TSH levels will be measured

- Every 1–2 weeks
- Every 2 weeks
- Every 4 weeks
- Only if TSH is not appropriate for gestational week

Question 8

The patient is now at her 13th week of pregnancy and a 1.5 cm soft nodule became palpable on the right thyroid lobe. There is no cervical adenopathy and no risk factors for malignancy. Assuming 1.5 cm is the actual size, what would you do next?

- Follow by palpation
- Order an ultrasound and perform FNA in any solid lesion
- Order an ultrasound and perform FNA only if the lesion is suspicious
- Order an ultrasound but postpone FNA to postpartum in any case
- Follow by ultrasound and perform FNA only if significant growth

Question 9

Please answer yes/no

- Screening is mandatory in every woman at the beginning of her pregnancy
- Screening is mandatory in every women planning pregnancy
- I have read the guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum
- I recommend testing for FT4 regardless of TSH results in each blood test

Question 10

Demographics of responder

- Gender
- Year of board certification in endocrinology
- Work environment (hospital, community, both)
- Number of patients with thyroid disease I evaluate monthly (on average)

Questionnaire for OB/GYNs

Question 1

A 29 year old healthy woman is referred to you for evaluation at the tenth week of her first pregnancy. She currently takes no medication and is feeling well. No family history of thyroid disease is known. Her TSH levels are 3.1 mIU/L, FT4 16 pmol/L (normal range 10–20). A previous test showed a TSH level of 2.9 mIU/L with FT4 of 18 pmol/L.

- a. I manage the patient by myself
- b. I send her to an endocrinologist for evaluation

Question 2

Whether you decide to treat yourself or ask for consultation, the next step should be

- a. No further evaluation
- b. Start thyroxine right away
- c. Follow-up TSH in 1 month

Question 3

The patient comes back with a TSH of 2.6 mIU/L and anti-TPO antibodies were ordered

- a. Start thyroxine regardless of antibodies
- b. Start thyroxine only if antibodies are positive

Question 4

It has been decided to treat the patient with 25 mcg of thyroxine daily and she is currently at the 29th week of her pregnancy. TSH levels are 3.2 mIU/L, what should be done now?

- a. Increase her thyroxine dose to a target of below 2.5 mIU/L
- b. Increase her thyroxine dose to a target of below 3.0 mIU/L
- c. Increase her thyroxine dose to a target of below 4.0 mIU/L
- d. Follow-up on same dose
- e. I have no position, the decision is up to an endocrinologist

Question 5

The same patient at the tenth week of her pregnancy is referred to you with a TSH level of 2.3 mIU/L and FT4 levels of 8.9 pmol/L (normal range 10–20). The next step should be

- a. No further evaluation
- b. Treat with thyroxine
- c. Repeat test and start thyroxine if FT4 is still below normal
- d. Order anti-TPO and treat only if positive
- e. I have no position, the decision is up to an endocrinologist

Question 6

During her pregnancy, whether treated or not, TSH levels will be measured

- a. Every 2–4 weeks
- b. Every 6–8 weeks
- c. Every 12 weeks
- d. Only if TSH is not appropriate for gestational week

Question 7

Please answer yes/no

- a. Screening is mandatory for every woman at the beginning of her pregnancy
- b. Screening is mandatory for every women planning a pregnancy

Question 8

Demographics of responder

- a. Gender
- b. Year of board certification in obstetrics/gynecology
- c. Work environment (hospital, community, both)
- d. Maternal fetal medicine specialist (yes/no)