Thyroid Disease in the Perinatal Period

SFOG-Guideline from Endokrin-ARG, 2014-12-28

The reference range for TSH during pregnancy is different compared to the non-pregnant state. Development of local trimester- and laboratory-specific TSH reference ranges in iodine sufficient populations is recommended. In the absence of these, the reference ranges shown below may be used for both women on levothyroxine treatment as well as for those not on treatment.[1]

First trimester:	TSH 0.1– 2.5 mIE/L
Second trimester:	TSH 0.2– 3.0 mIE/L
Third trimester:	TSH 0.3– 3.0 mIE/L

Iodine requirements increase during pregnancy, and the Swedish National Food Agency recommends that pregnant women use iodized salt. The daily recommended iodine intake is 250 µg for pregnant and lactating women.[2]

Thyroid testing DURING pregnancy

When testing for thyroid dysfunction during pregnancy, serum levels of TSH should be primarily assessed. In case of abnormal TSH levels, additional T_4, TPO-Ab or TRAb should be analyzed as described below. Clinical hypothyroidism is defined as an elevated TSH level in combination with a low T_4 level, while subclinical hypothyroidism refers to high TSH levels in combination with normal T_4 levels.
Hyperthyroidism on the other hand refers to low TSH in combination with high T_4 levels. TSH is of the greatest clinical importance and is being used as a guide for assessment, monitoring and treatment of thyroid dysfunction. TPO-Ab positivity does not affect management during pregnancy, but indicates risk of thyroid dysfunction later in life. If hypothyroidism is diagnosed during pregnancy, TPO-Ab positivity should be checked (preferably in the first trimester, or postpartum).

There is currently a scientific debate as to whether universal or targeted screening should be recommended. Despite a somewhat stronger scientific basis for universal screening, screening of high-risk groups of women with risk factors for thyroid disease is still recommended.[3]

Pregnant women should have TSH levels checked as soon as possible if they fulfill any of the following risk factors:

- Age above 35 years of age
- BMI above 35 kg/m^2
- Goiter or clinical evidence of thyroid disease (for example, slow pulse, constipation, muscle weakness, severe tiredness, cold sensitivity, dry skin, inability to gain weight, tachycardia, eye problems, nervousness or fine tremor, and heat intolerance)

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1 Weak recommendation according to GRADE.

2 Strong recommendation/EvidenceÅÅÅ according to GRADE.

3 Universal screening on first visit during pregnancy (weak recommendation/ Evidence ⊕⊕○○according to GRADE), Targeted (weak recommendation/Evidence ⊕○○○ according to GRADE)

- A history of current or previous thyroid dysfunction*, including levothyroxine treatment during pregnancy, thyroid cancer or throat surgery/radiation treatment
- Family history of thyroid disease
- Autoimmune disease (type 1 diabetes, B-12 deficiency, Addison's disease, rheumatoid arthritis, celiac disease, etc.)
- Known TPO-Ab[4]
- Severe hyperemesis gravidarum with clinical signs of hyperthyroidism
- A history of infertility (> 1 year)
- A history of recurrent miscarriages (three consecutive in the first trimester), late miscarriage (at least one in the second trimester) or premature birth

*In the case of current or prior history of hyperthyroidism, see paragraph II B.

Sampling results and further assessment in the first trimester:

- TSH <0.1 mIE/L: Test for fT_4 and TRAb, see section II[5]
- TSH: 0.1-2.5 mIE/L: No further assessment
- TSH >2.5mIE/L: Test for fT_4 and possibly TPO-Ab[6], see section I

Treatment DURING PREGNANCY

I. HYPOTHYROIDISM[7]

A. Newly diagnosed during pregnancy (TSH>2.5 mIE/L in first trimester or >3.0 mIE/L in 2nd-3rd trimester)

- Start treatment (the levothyroxine dose is dependent on TSH levels, body weight, etiology of hypothyroidism as well as individual susceptibility; for example, absorption rate):[8]

- TSH 2.5-4.2 mIE/L: Start levothyroxine treatment, dose 50-100 µg/day (1.2 µg/kg).[9]
  - ≤50-55 kg: 50 µg/day
  - 65 kg: 75 µg/day
  - ≥80 kg: 100 µg/day

- TSH >4.2-10 mIE/L: Start levothyroxine treatment immediately, dose 75–125 µg /day (1,4 µg/kg).
  - ≤50-55 kg: 75 µg/day
  - 65 kg: 87,5 µg/day (Half tablet of 175 µg)
  - ≥80 kg: 100-125 µg/day

4 Patients with known TPO-Ab who are euthyroid in early pregnancy should be sampled with TSH in the first and second trimesters as well as postpartum, as they are at increased risk of developing hypothyroidism later in the pregnancy or after delivery (strong recommendation/Evidence ⊕⊕⊕◯ according to GRADE).

5 Preferably, TSH can be tested at the same time as T_4 and auto-antibodies.

6 In the first trimester or postpartum.

7 Treatment of clinical hypothyroidism (strong recommendation/Evidence ⊕⊕⊕◯ according to GRADE). Treatment of sub-clinical hypothyroidism with positive TPO-Ab, for obstetric outcomes (strong recommendation/Evidence ⊕⊕◯◯ according to GRADE), and child outcomes (weak recommendation/no data); for sub-clinical hypothyroidism with negative TPO-Ab, for obstetric outcomes (weak recommendation/Evidence ⊕⊕◯◯ according to GRADE), for child outcomes (weak recommendation/no data).

8 With a high body weight, there is a greater need for levothyroxine. It is unusual for treatment during pregnancy. The most common symptom is palpitations. If THS is less than 0.1 mIE/L the dose should be reduced.

9 Strong recommendation/Evidence ⊕⊕◯◯ according to GRADE.

• TSH >10 mIE/L: Start levothyroxine treatment immediately, dose 125-150 µg /day and contact prenatal care specialist/ endocrinologist for further therapy and follow-up
  - ≤50-55 kg: 125 µg/day
  - >65 kg: 150 µg/day

- Assess TSH and fT_4 every 4-6 weeks during the first half of pregnancy or until the TSH level is within the reference range for pregnant women.[10,11] Further, TSH should be checked around gestational week 25 and, if normal, no further tests are needed during pregnancy.[12] Note the difference in the reference range during the second and third trimester.
- If TPO-Ab positive, inform the patient about extra controls postpartum.
- For dosage adjustments and checks after delivery, see the respective section.

B. Known levothyroxine-substituted hypothyroidism

Women should be assessed if they plan to get pregnant [13,10] or as soon as pregnancy is known. The levothyroxine dose usually needs to be increased immediately by at least 30% between 4-6 weeks of pregnancy.[14] If a pregnancy is confirmed, the patient can then be recommended to increase dosage from 7 daily doses/week to 9 daily doses/week. It is particularly important to increase the dose in patients with a surgically removed thyroid gland. Sampling and dosage adjustments should be determined by the gynecologist or a general practitioner who has handled the patient before.

During the first visit at the maternity ward, one should:
1. Take a history of prior hyperthyroidism (if prior history of hyperthyroidism, test for TRAb)[15]
2. Inform the patient about the sampling program
3. Test for TSH, fT_4 and possibly TPO-Ab if not earlier assessed

Test results:[16]
• TSH <0.1 mIE/L: Test for TRAb if it is indicated, see above. Consider reducing the levothyroxine dose.

• TSH 0.1-2.49 mIE/L: No further investigation (continue with the same dose)

The increase in the levothyroxine dose is dependent on TSH level, current levothyroxine dosage, body weight, etiology of hypothyroidism as well as individual sensitivity; for example, absorption rate. Usually, one needs to increase the dose by 25-50% during pregnancy. This, in practice, often means an increase of 25 µg for slightly elevated TSH (2.5-4.2 mIE/l) and higher doses accordingly:

10 Strong recommendation/Evidence ⊕⊕⊕⊕ according to GRADE.
11 Many local instruction memos use 2.0 mIE/L as the upper THS limit for the monitoring of levothyroxine treatment, but there is no evidence of these treatment goals in pregnant women.
12 Not enough evidence to recommend for or against (ATA).
13 Adjustment of the dose is recommended, TSH<2.5 mIE/L (strong recommendation/Evidence ⊕⊕◯◯ according to GRADE).
14 Strong recommendation/Evidence ⊕⊕⊕⊕ according to GRADE.
15 Women with levothyroxine-substituded hypothyroidism after previous hyperthyroidism/thyrotoxicosis may have persistent elevated levels of TRAb (antibody that stimulates the thyroid gland into overproduction of thyroid hormone in hyperthyroidism) and should also be sampled for TRAb on the first visit.
16 Note that other levels apply for 2nd and 3rd trimesters, see the first table.

- TSH 2.5-4.2 mIE/L: Raise levothyroxine by 25 µg/day.
- TSH >4.2-10 mIE/L: Raise levothyroxine by 50 µg/day.

- TSH >10-20 mIE/L: Raise levothyroxine by 75 µg/day.
- TSH >20 mIE/L: Raise levothyroxine by 100 µg /day and refer to SMVC/endocrinologist regarding continued therapy and follow-up.

Assess TSH and fT_4 every 4 weeks until the TSH level is within the reference range for pregnant women.[17] Thereafter, assess TSH and fT_4 every 4-6 weeks. If TSH level is within the reference range for pregnancy, assess with an additional test around pregnancy week 25. If TSH is within the reference range for pregnancy, no further testing is needed during pregnancy.[18] Note the changed reference range in the second and third trimesters.

After delivery, the patient can usually return to the pre-pregnancy levothyroxine dosage. Eight weeks after delivery, TSH should be assessed at the antenatal care center and then the patient is referred to (or can seek) a regular health care provider/general practitioner for continued surveillance.[19]

II. HYPERTHYROIDISM

A. Newly discovered sampling during pregnancy (TSH < 0.1 mIE/L in the first trimester)

TSH levels of < 0.1 mIE/L may suggest hyperthyroidism; assess fT_4 and TRAb[15]

- If TRAb levels are elevated, or if the patient has a goiter (palpable) or eye symptoms (endocrine ophthalmology), then autoimmune thyrotoxicosis is likely present. Immediately refer to prenatal specialist/endocrinologist for possible antithyroid treatment, and to prenatal specialist for controls of the fetus.
- If TRAb levels are normal but fT_4 is elevated, consult an endocrinologist.
- If TRAb and fT_4 levels are normal and the patient has neither goiter nor eye symptoms, gestational hyperthyroidism is the common diagnosis. Gestational hyperthyroidism is usually harmless. Awaiting and follow-up is recommended.[20] Test for TSH and fT_4 every 4-6 weeks up until pregnancy week 16. If discrepancies remain, consult an endocrinologist.

- Women with gestational hyperthyroidism and possible severe hyperemesis should be treated symptomatically (fluid therapy, hospitalization and beta blockers, if necessary, such as propranolol 40 mg x 1-3).[21]
- Antithyroid treatment is generally not recommended for the treatment of gestational hyperthyroidism.

17 Strong recommendation/Evidence ⊕⊕⊕⊕ according to GRADE
18 Not enough evidence to recommend for or against (ATA)
19 Strong recommendation/Evidence ⊕⊕⊕⊕ according to GRADE
20 Weak recommendation/ Evidence ⊕⊕◯◯ according to GRADE
21 Weak recommendation/ Evidence ⊕⊕◯◯ according to GRADE

B. History of hyperthyroidism

In women with a history of hyperthyroidism, TSH, fT_4 and TRAb should be tested during the first visit at the prenatal center.[22] (These women can have persistently elevated levels of TRAb).

Concerning TRAb:

- For normal values, thyroid hormones and TRAb do not need to be re-assessed during pregnancy or postpartum.[23] If iatrogenic hypothyroidism is present, see the section concerning hypothyroidism.

- For elevated TRAb values (>1,75 U/L or other values according to local method) refer to prenatal specialist/endocrinologist.

Concerning TSH, with negative TRAb, see section above.

C. Hyperthyroidism with on-going treatment

Immediately refer to an endocrinologist/prenatal specialist.

Thyroid testing POSTPARTUM

Thyroid testing with **TSH** is recommended in the following groups 8-12 weeks postpartum, or earlier if they exhibit symptoms, **as well as** 6 months postpartum:

- TPO-Ab postitivity[24]
- History of[25] or symptoms of postpartum thyroiditis (fatigue and irritability during the hyperthyroidism phase as well as fatigue, weight gain, susceptibility to cold, depression and dry skin during the hypothyroidism phase)
- Type 1 diabetes, chronic viral hepatitis or history of hyperthyroidism[26]
- Postpartum depression [27]
- Levothyroxine treatment initiated during pregnancy or treatment before pregnancy, after appropriate dosage adjustments, see section below.

22 Strong recommendation/Evidence ⊕⊕◯◯ according to GRADE
23 Weak recommendation/Evidence ⊕⊕◯◯
24 Strong recommendation/Evidence ⊕⊕⊕◯ according to GRADE
25 Strong recommendation/Evidence ⊕⊕⊕◯ according to GRADE
26 Weak recommendation/Evidence ⊕⊕◯◯ according to GRADE
27 Weak recommendation/Evidence ⊕⊕◯◯according to GRADE

Treatment POSTPARTUM

A. Levothyroxine treatment initiated during pregnancy:

After delivery,[28] the levothyroxine dose is adjusted according to the following:

Discontinue levothyroxine at parturition if:

- levothyroxine dose is ≤ 50 µg and TPO-Ab is negative or if TPO-Ab was not checked during the first trimester*
- TSH, at the onset of pregnancy, was at most 10 mIE/L and TPO-Ab is negative or if TPO-Ab was not checked during the first trimester*
  (*Assessment of TPO-Ab is recommended 8 weeks postpartum if not assessed during the first trimester)

Assess TSH after 8-12 weeks:

- If TSH is then within the reference range for non-pregnant women, no further assessments need to be planned.
- If TSH is elevated according to the reference range for non-pregnant women, the patient is referred to a general practitioner.

However, if:

1. levothyroxine dose is > 50 µg or
2. TSH at onset was higher than 10 mIE/L or
3. TPO-Ab positive regardless of levothyroxine dose and TSH at onset

- Reduce the dosage by 50 µg after delivery and refer the patient to a general practitioner for follow-up 8-12 weeks postpartum.

B. Levothyroxine treatment before pregnancy

After delivery, the patient can usually return to the pre-pregnancy levothyroxine dosage (if the patient stable at that point).[29] Check TSH around 8 weeks after delivery by means of a regular caregiver.

C. Newly discovered thyroid dysfunction

- If TSH levels 8-12 weeks postpartum are higher than the reference range for non-pregnant women, provide information for the patient and refer them to a general practitioner for a quick follow-up on the basis of suspected postpartum thyroiditis.
- If TSH levels are lower than the reference range for non-pregnant women, test for fT_4 and TRAb and refer patient to an endocrinologist who is responsible for differential diagnosis between postpartum thyroditis and hyperthyroidism.

28 Also applies to women who have not managed to get pregnant after initiation of levothyroxine treatment. Referral to health center for discontinuation of drug.

29 Strong recommendation/Evidence ⊕⊕⊕⊕ according to GRADE

Final comments:

- Women with TPO-Ab as well as those with a history of postpartum thyroiditis should be referred to a general practitioner for continued annual inspections of TSH[30] because of the high risk for developing hypothyroidism later in life.

- If treatment with levothyroxine begins just before or during pregnancy and is subsequently terminated, the patient must be advised to check her thyroid function postpartum as well as early on in the case of a possible new pregnancy. She should also be informed by the maternity center that she has an increased risk of developing hypothyroidism later in life.

- Close collaboration between MVC/SMVC and especially interested endocrinologist in each unit should be encouraged.

Identified gaps in knowledge:

- Lack of trimester-specific reference ranges for TSH in pregnant Swedish women and the different analytical methods used in the country.
- Lack of Swedish studies on possible iodine deficiency among pregnant Swedish women.
- Insufficient evidence that treatment of sub-clinical hypothyroidism has a positive effect on children's cognitive development and pregnancy outcome.

30 Strong recommendation (ATA)

On this guideline:

Thyroid disease is common among pregnant and postpartum women and can have negative consequences for both the mother and the child if it is not diagnosed and treated in a timely manner.

Sweden lacks clear guidelines for the management of thyroid diseases during and after pregnancy. In 2012, Endokrin-ARG was commissioned by SFOG to develop evidence-based guidelines. The latest literature search was made on 2014-01-15.

The commission indicated that the work method should be reported and the GRADE-system (Grading of Recommendations Assessment Development and Evaluation) should be used for grading the scientific evidence as well as for grading the recommendations.

Evidens-ARG was involved in the work, and the document has been reviewed by the consultants in obstetrics who are responsible for the maternity care areas in Sweden.

The group composed a provisional guideline, which was published on June 25, 2014 on SFOG's homepage in order for all the members to have the possibility to review the outline and to propose any changes. The guideline was presented and discussed during SFOG week 2014 (August 28, 2014), and revisions were then made in accordance with the presented feedback. The final version was developed after meetings with the MÖL-group and a presentation at the National SFOG Meeting with endocrinologists and feedback from SFOG's scientific committee.

Revisions of the guideline will be made every three years or more often if necessary.

Grading the strength of evidence according to GRADE, based on the overall scientific evidence:

- Strong scientific evidence (GRADE ⊕⊕⊕⊕). It is unlikely that future research will change the opinion of the results.
- Moderately strong scientific evidence (GRADE ⊕⊕⊕◯). It is likely that future research can have a significant impact.
- Limited scientific evidence (GRADE ⊕⊕◯◯). It is very likely that future research can have a significant impact.
- Insufficient scientific evidence (GRADE ⊕◯◯◯). Estimated effects are very uncertain.

http://sbu.se/sv/Evidensbaserad-vard/Faktaruta-1-Studiekvalitet-och- evidensstyrka/

The recommendation can be strong or weak either for or against an intervention. The recommendation for an intervention is based on the strength of the scientific evidence according to GRADE, the benefit-risk balance of the intervention, potential ethical implications and other considerations such as cost aspects. A weak recommendation may mean that certain conditions must be met or that there is a risk-benefit balance that may be valued differently for different patients.

The document states:
The strength of recommendation / strength of the scientific evidence

Abbreviations:

ATA= American Thyroid Association
T_4= Free Thyroxine
MVC= Maternity Health Care Center
MÖL= Antenatal Care Physician
PPT= Postpartum Thyroditis
SMVC = Specialty Maternity Center
TPO-Ab= Thyroid peroxidase antibodies
TSH= Thyroid-Stimulating Hormone
TRAb (TRAk)= Thyreoglobuline antibodies

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- SFOG's scientific board

The participants' declaration of interest:

None of the participants had any objection or conflict of interest to report on the current issue.