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Thieme

# Recommendations of the AGG (Working Group for Obstetrics, Department of Maternal Diseases) on How to Treat Thyroid Function Disorders in Pregnancy

## Empfehlungen der AGG (Arbeitsgemeinschaft Geburtshilfe, Sektion maternale Erkrankungen) zum Umgang mit Schilddrüsenfunktionsstörungen in der Schwangerschaft

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## ABSTRACT

**Objective** These recommendations from the AGG (Committee for Obstetrics, Department of Maternal Diseases) on how to treat thyroid function disorder during pregnancy aim to improve the diagnosis and management of thyroid anomalies during pregnancy.

**Methods** Based on the current literature, the task force members have developed the following recommendations and statements. These recommendations were adopted after a consensus by the members of the working group.

**Recommendations** The following manuscript gives an insight into physiological and pathophysiological thyroid changes during pregnancy, recommendations for clinical and subclinical hypo- and hyperthyroidism, as well as fetal and neonatal diagnostic and management strategies.

## ZUSAMMENFASSUNG

**Ziel** Diese Empfehlungen der AGG (Arbeitsgemeinschaft für Geburtshilfe und Pränatalmedizin, Sektion maternale Erkrankungen) zum Umgang mit Schilddrüsenfunktionsstörungen in der Schwangerschaft haben das Ziel der Verbesserung der Diagnostik und des Managements von Schilddrüsenanomalien während der Schwangerschaft.

**Methoden** Basierend auf der aktuellen Literatur entwickelten die Mitglieder der Task Force die vorliegenden Empfehlungen und Stellungnahmen. Diese Empfehlungen wurden nach einem Konsens der Mitglieder der Arbeitsgruppe verabschiedet.

**Empfehlungen** Das folgende Manuskript beschäftigt sich mit einem Einblick in physiologische und pathophysiologische Schilddrüsenveränderungen in der Schwangerschaft, Empfehlungen zur klinischen und subklinischen Hypo-, Hyperthyreose sowie fetale und neonatale Diagnose- und Managementstrategien.


# 1. Introduction

Pregnancy has a profound impact on the thyroid gland and its functions. The production of thyroid hormones and the requirement for iodine increase by almost 50% during pregnancy. Some pregnant women may experience significant and pregnancy-related thyroid function disorders, which should be identified during screening examinations. Furthermore, the assessment of materno-fetal thyroid function differs significantly during pregnancy and thus constitutes another challenge in terms of the clinical aspect and laboratory-based tests. Given the emerging body of evidence, the complexity and importance of maternal thyroid diseases, the Working Group for Obstetrics and Prenatal Diagnostics (AGG) decided to prepare a statement of specific recommendations on how to treat thyroid function disorders during pregnancy.

# 2. Method

The basis for the preparation of this statement was the updated version of the 2017 American guidelines for the management of thyroid diseases during pregnancy (19). In addition, we performed a Medline literature review using the search terms “pregnancy AND thyroid”, “pregnancy AND hypothyroidism”, “pregnancy AND hypothyroidism”, and “pregnancy AND subclinical hypothyroidism”, and the filters “meta-analysis”, “systematic review”, and “5 years”. Abstracts were reviewed for relevance before inclusion of the corresponding studies in the current publication. For individual more specific questions, a subject-related literature search was carried out. The formulated recommendations were coordinated with the “Maternal Diseases” department of the Working Group for Obstetrics of the German Society for Gynecology and Obstetrics (DGGG).

# 3. Pathophysiology/Screening and Diagnostics during Pregnancy

## 3.1. Physiological changes during pregnancy

**AGG STATEMENT (1)**

Due to the TSH receptor and LH/β-hCG receptor homology, **TSH values already fall** to 0.1 mU/ml in the first trimester, but then rise with advancing gestational age.

**AGG RECOMMENDATION (1)**

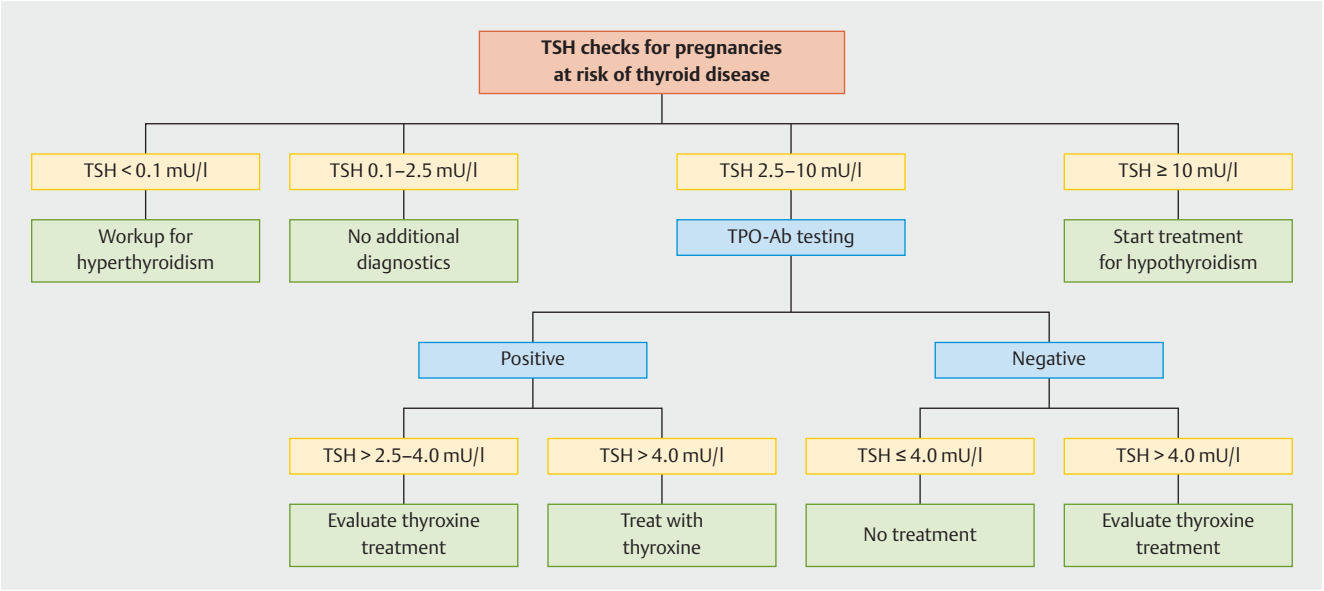
A **daily** intake of **100–150 µg of iodine** should be recommended to pregnant women. It is however debatable whether this actually protects children from iodine deficiency.

**AGG RECOMMENDATION (2)**

The TSH serum concentration should be determined prior to conception in all women who intend to undergo **reproductive medicine measures**.

Physiological changes occur during pregnancy, which must be taken into account when assessing thyroid parameters.

Due to its affinity for the TSH receptor, β-hCG has thyrotropic properties. A negative feedback loop leads to a significant drop in TRH and TSH secretion between 7 + 0–12 + 0 weeks of pregnancy [1 – 11]. The TSH values reach their nadir between 11 + 0 and 14 + 0 weeks of pregnancy [12, 13]. The TSH values between 4 + 0–6 + 0 weeks of gestation are similar to those of non-pregnant women [14]. In the first trimester, the upper threshold drops by approx. 0.5 mU/l and the lower threshold by approx. 0.4 mU/l (standard values: 0.1–2.5 mU/l). As the pregnancy progresses, the values approach the normal range again as they would be in non-pregnant women [15, 16]. With higher β-hCG levels, e.g., in a multiple pregnancy, significantly lower TSH values and higher thyroid hormone values were measured [12, 17 – 20]. The TSH reference range depends on several factors, such as the iodine status of the population, the TSH assay used, BMI, geographic region




▶ **Fig. 1** Treatment algorithm for thyroid function disorder during pregnancy (according to [15]).

and ethnicity [15,21]. Ideally, any available local and trimester-specific reference values should be based on healthy and TPO-Ab negative pregnant women with normal iodine levels. If such data is not available, an **upper TSH threshold of 4.0 mU/l** is currently recommended internationally [15]. This effectively renders any prior trimester-specific threshold values inapplicable. The frequency of a subclinical hypothyroidism diagnosis thus also decreases. Notwithstanding these specifications, the recommendation to carry out further diagnostics from a TSH value of 2.5 mU/l continues to apply (▶ **Fig. 1**).

The thyroid hormones (T3, T4) and thyroxine-binding globulins (TBG) increase with the β-hCG values in the first trimester [11]. After an initial T3 and T4 plateau, in first semester serum, these values steadily decrease during the second and third trimester [11]. Thus, when determining normal values, the trimester of pregnancy must be taken into account [22]. When quantifying fT4 by conventional immunoassays, discrepant results may be obtained in routine practice on account of methodological susceptibilities to interference during pregnancy. Tandem mass spectrometry can reliably quantify fT4 levels during pregnancy. However, as a routine procedure, this method is not cost-effective and is technically complex [23–25]. Alternatively, the fT4 measurement can be replaced by determining the free T4 index or the total T4 value [26]. As a result, the T3 uptake must also be determined by means of a laboratory analysis. The free T4 index is calculated as follows:

$$\mathrm{FTI} = \frac{(\mathrm{total})\mathrm{T4} \times \mathrm{T3\ uptake}}{100}$$

In pregnant women, the estimated daily iodine requirement is 160 µg/d and the recommended daily intake is 220 µg/d [27]. Severe iodine deficiency increases TSH production, which may stimulate materno-fetal goiter formation [28]. There is an association, albeit contentious, between maternal iodine deficiency during pregnancy and increased complications in children, e.g., placenta hypotrophy, smaller neonatal head circumference, attention deficit during childhood, as well as hyperactivity and neurocognitive deficits during childhood [29–33]. Due to regional differences in the availability of iodine from the diet and the environment, a regional iodine supplementation policy for pregnant women is indicated [15]. The German Society for Nutrition (DGE), the Federal Institute for Risk Assessment (BfR) and the Working Group for Iodine Deficiency (AKJ) recommend a daily intake of 100–150 µg iodine for pregnant women and women that are breastfeeding in Germany, where possible starting from three months prior to conception, to prevent subclinical maternal and fetal hypothyroidism (SCH) [34]. A protective childhood effect of iodine supplementation is, however, a matter of contentious debate in the literature [35,36]. Women should avoid an intake of more than 500 µg iodide per day due to its potential for inducing thyroid dysfunction in children [15,37].

## 3.2. Should there be universal screening for thyroid disease during pregnancy?

**AGG RECOMMENDATION (3)**

All pregnant women should be asked about their medical history of thyroid disease and about any risk factors for thyroid disease at their initial examination. It is recommended to carry out a screening for thyroid disease by determining the TSH value during pregnancy if risk factors are present.

A physiological thyroid hormone concentration is essential for a good materno-fetal outcome [38]. The unfavorable outcome of clinical hyperfunction and hypofunction of the thyroid gland is undisputed [38,39]. Manifest ("overt") thyroid dysfunction is signifi-

▶ **Table 1** Risk factors for a thyroid disease during pregnancy (incl. subclinical hypothyroidism) (according to [15, 44]).

| |
|---|
| Condition after miscarriage/premature birth or a medical history of infertility |
| Evidence of a medical history or a clinical suspicion of hypothyroidism/hyperthyroidism |
| A self-reported or family history of thyroid disease |
| Positive antibody status (thyroid peroxidase [TPO-Ab], TSH receptor antibodies [TR-Ab], thyroglobulin antibodies [T-Ab]) |
| Existing goiter |
| Condition after thyroid operation or neck/throat radiotherapy |
| Thyrotoxic medications |
| Age > 30 years |
| BMI > 40 kg/m$^2$ |
| Multiparity (≥ 2) |
| Type 1 diabetes mellitus |
| Autoimmune diseases |
| Residence in an area with pronounced iodine deficiency |

cantly less common than the subclinical variants [40]. A general TSH screening is primarily used to diagnose subclinical/latent thyroid dysfunction. The literature is inconsistent with regards to whether the outlook of subclinical thyroid dysfunction is purely a "laboratory cosmetic effect" or whether it offers fetal neurocognitive protection [41, 42]. In Germany, due to a lack of studies, there is no consensus on the inclusion of thyroid examinations in the catalog of health insurance benefits as part of standard prenatal care [43].

The conflicting results from the literature, with respect to the subclinical forms of thyroid dysfunction, are discussed below. Despite these contrasting results, and in light of the association with miscarriage and premature birth, TSH screening should be carried out if risk factors are present (▶ **Table 1**), particularly in positive antibody cases (thyroid peroxidase [TPO-Ab], TSH receptor antibodies [TR-Ab], or thyroglobulin antibodies [T-Ab]) [15, 44]. An algorithm is shown in ▶ **Fig. 1** and will be discussed in the next subchapters.

## 4. Subclinical thyroid Function Disorder

Subclinical hypothyroidism or hyperthyroidism is correspondingly defined as an elevated (subclinical hypothyroidism) or a reduced/not measurable (subclinical hyperthyroidism) serum TSH concentration, where the serum concentrations of free (unbound) thyroid hormones, triiodothyronine (fT3) and thyroxine (fT4), are within the normal range. Subclinical hypothyroidism (SCH) is particularly important with regards to pregnancy. The clinical symptomatology is vague for the most part, so subclinical thyroid function disorders are largely "laboratory diagnoses".

The most common cause of (latent) hypothyroidism during pregnancy is Hashimoto's thyroiditis, characterized by elevated TPO-Ab and/or T-Ab levels and more rarely inhibitory TR-Ab concentrations.

### 4.1. Subclinical hypothyroidism and pregnancy complications

The prevalence of SCH is specified at 2–3 % [42]. Hypothyroidism and iodine deficiency during pregnancy have an adverse effect on the pregnancy as well as fetal/neonatal development [15, 45]. Numerous observational studies and meta-analyses have demonstrated an association between SCH and both pregnancy complications and fetal/neonatal complications. However, there is no unequivocal association between SCH and the neurocognitive development of the child [45].

Other studies and meta-analyses have not been able to confirm the association between SCH and complications during pregnancy. These discrepancies can to some extent be explained by the different threshold values of the TSH level and the varying definitions of SCH [15].

#### 4.1.1. Miscarriage

**AGG STATEMENT (2)**
Subclinical hypothyroidism is associated with an **increased risk of miscarriage**.

Whilst a recent meta-analysis states that SCH does not appear to be associated with an increased risk of repeat miscarriages – albeit that the available data is limited – [46], a systematic review and a meta-analysis published in 2020 confirms SCH as a risk factor for miscarriages prior to 19 + 0 weeks of pregnancy, irrespectively of the SCH diagnostic criteria applied [47]. A pregnancy loss (defined as a miscarriage, intrauterine death, or neonatal death) is associated with SCH, with the risk increasing as TSH levels increase [48–50]. In SCH, the risk of miscarriage appears to increase in the presence of a positive TPO-Ab status [49, 51].

#### 4.1.2. Premature birth

**AGG STATEMENT (3)**
Pregnant women with subclinical hypothyroidism have an **increased risk of giving birth prematurely**.

According to current studies, SCH is a risk factor for premature births (OR 1.29 [95 % CI, 1.01–1.64] to 4.58 [95 % CI, 1.46–14.4]) [52, 53]. Conversely, women with a medical history of premature births are also more frequently diagnosed with SCH [54].

Although numerous additional studies substantiate the association between SCH and an increased risk of a premature birth – the reverse has also been reported [15, 55]. These conflicting results may arise due to studies "pooling" pregnant women with SCH and with manifest hypothyroidism or because only a very small number of pregnant women were included in the analysis. Differences in cut-off values and TPO-Ab positivity, in particular, may also have contributed [56].

#### 4.1.3. Pregnancy complications (preeclampsia, fetal growth restriction [FGR])

**AGG STATEMENT (4)**
Subclinical hypothyroidism is not associated with an **increased risk of preeclampsia or fetal growth restriction**.

Most studies that investigated an association between SCH and preeclampsia or other hypertensive pregnancy disorders and FGR did not find an increased risk [15, 55].

#### 4.1.4. Subclinical hypothyroidism and neurocognitive outcomes

**AGG STATEMENT (5)**
Subclinical hypothyroidism does not appear to be associated with an increased risk of **adverse neurocognitive outcomes** in children.

The majority of studies do not show an increased risk of adverse neurocognitive outcomes in SCH [15, 55]. At best, a weak association with autism spectrum diseases was demonstrated [57]. However, in these available studies, SD hormone replacement was generally only randomized in the late stages of the second trimester, which means that the effects of earlier SD hormone replacement on childhood cognition remain to be conclusively established.

### 4.2. Management of subclinical hypothyroidism during pregnancy

#### 4.2.1. Screening

**AGG RECOMMENDATION (4)**
For pregnant women with a **TSH concentration > 2.5 mU/l**, the **TPO-Ab status** should be determined.

#### 4.2.2. Therapy

**AGG RECOMMENDATION (5)**
Levothyroxine substitution may be considered in women with subclinical hypothyroidism and infertility problems who are planning to conceive.

**AGG RECOMMENDATION (6)**
For women with a **positive TPO-Ab** status and a TSH concentration **between 2.5 and 4.0 mU/l**, substitution with levothyroxine may be appropriate.

**AGG RECOMMENDATION (7)**
Women that are **TPO-Ab positive,** with a TSH value **above 4.0 mU/l**, should receive levothyroxine substitution.

**AGG RECOMMENDATION (8)**
Women that are **TPO-Ab negative,** with a TSH value **below 4.0 mU/l,** should not receive levothyroxine substitution.

**AGG RECOMMENDATION (9)**
Substitution with levothyroxine may be considered in **TPO-Ab negative** women with a TSH level **between 4.0 mU/l and 10.0 mU/l**.

**AGG RECOMMENDATION (10)**
**TPO-Ab negative** women, with a TSH concentration **from 10 mU/l**, should receive levothyroxine substitution.

The usefulness of screening for SCH depends on the effectiveness of treatment. The treatment goals are, on the one hand, the reduction of maternal complications and, on the other hand, the avoidance of neurocognitive handicaps in the child.

Based on our current understanding, L-thyroxine should be used as treatment when the TPO-Ab and/or T-Ab status is positive, and the TSH concentration is above 4.0 mU/l; manifest hypothyroidism and cases of SCH in which the TSH value is over 10 mU/l definitely require treatment [15].

Levothyroxine treatment may reduce the rate of miscarriages in women that are TPO-Ab positive with TSH values > 2.5 mU/l, or in women that are TPO-Ab negative with TSH concentrations above 4.0 mU/l [15]. However, to what extent SCH treatment prevents an adverse outcome remains unclear [42, 58]. What appears to be important is the early start of treatment in the first trimester [55, 59, 60].

An unequivocal benefit of levothyroxine treatment for SCH could not be proven, neither for pregnancy complications nor for the neurocognitive development of the child.

## 5. Hypothyroidism during Pregnancy

**AGG STATEMENT (6)**
Hypothyroidism is defined as the combination of elevated TSH levels and decreased peripheral thyroid hormone levels.

**AGG RECOMMENDATION (11)**
The dose of LT4 should be adjusted as early as possible to accommodate the increased requirements during pregnancy.

**AGG RECOMMENDATION (12)**
LT4 administration should aim for a TSH target value of < 2.5 mU/l.

**AGG RECOMMENDATION (13)**
Thyroid function should be examined **six weeks postpartum**.

### 5.1. Definition and diagnosis

Hypothyroidism is defined as the **combination of elevated TSH levels and reduced peripheral thyroid hormone levels** [15].

If pregnant women have adequate iodine levels, **Hashimoto's thyroiditis** is the most common cause of hypothyroidism; antithyroid tissue autoantibodies are detected in 30–60 % of pregnant women with elevated TSH levels [61]. Rare causes such as a TSH-secreting pituitary gland tumor, thyroid hormone resistance, or the extremely rare variant of central hypothyroidism due to the biologically inactive form of TSH resulting from a mutation in the TSH gene require further investigation [15]. In cases of newly diagnosed hypothyroidism, the TPO-Ab and TR-Ab status should also be determined. If these yield negative results, the T-Ab status should be redetermined [62].

### 5.2. Consequences

If pregnant women have manifest hypothyroidism, this worsens the prognosis for mother and child because it is associated with a **significantly increased risk of pregnancy complications and negative effects on the neurocognitive and physical development of the child**. Typical complications include increased rates of gestational hypertonia (mother), premature birth, low birth weight, intrauterine fetal death, lower IQ, higher prevalence of asthma, type 1 diabetes, and thyroid disease (child) [15, 55, 63, 64].

### 5.3. Treatment

Treatment with **LT4** should only be administered orally; no treatment with T3 or T3/T4 combinations.

The majority of pregnant women who have already received preconception treatment need to increase their LT4 dose. This should be done **as early as possible** after the pregnancy has been confirmed. Usually, one of the following two options is chosen:

1. Increase the number of doses per week by two, i.e., nine instead of seven administrations per week [65]
2. Increase of the daily LT4 dose by 25–30 % [15]

If LT4 treatment only starts during pregnancy, the daily dose should be **at least 50 µg**. The starting dose depends on the severity of the hypothyroidism, the patient's BMI, and concomitant medical problems. In order to prevent interactions with food and other medication, L-thyroxine should be taken **in the morning on an empty stomach and 4–5 hours before taking other medications, such as vitamins, calcium, or iron** [62]. For pregnant women suffering from emesis gravidarum, taking the medication in the evening before going to bed is recommended.

LT4 treatment should aim for a **TSH target value of < 2.5 mU/l**. The TSH values should be assessed **every four weeks up to about 20 + 0 weeks of pregnancy**, then **at least once at 30 + 0 weeks of pregnancy** [15].

The risk of obstetric complications does not increase with proper medical treatment; the only exceptions are Graves' disease patients who underwent surgery or radioablation. In these cases, TR-Ab monitoring is recommended. Otherwise, there is no indication for additional prenatal testing [15].

After delivery, the LT4 dose is generally reduced to the preconception level [15]. However, one study did prove that this approach was not effective in more than 50 % of women with Hashimoto's thyroiditis, since the postpartum dosage had to be increased beyond the preconception level [66]. Treatment can be stopped after delivery if the required LT4 dose during pregnancy was very low (≤ 50 µg LT4). In all cases, the **thyroid function** must be assessed again **six weeks postpartum** [15].

## 6. Hyperthyroidism during Pregnancy

**AGG RECOMMENDATION (14)**
Women with **manifest hyperthyroidism** should be stabilized to have normal thyroid function prior to pregnancy (euthyroid).

**AGG RECOMMENDATION (15)**
If an attempt is made to discontinue **ongoing thyrostatic treatment** when a pregnancy is diagnosed, care should be taken to ensure that the mother's metabolism is strictly euthyroid.

**AGG RECOMMENDATION (16)**
Women with **hyperthyroidism who wish to conceive** should be informed about the necessary treatment adjustments during pregnancy and should consult their attending gynecologist and/or endocrinologist immediately if pregnancy is diagnosed.

**AGG RECOMMENDATION (17)**
If medication is required to treat **hyperthyroid women during pregnancy**, treatment should be initiated with propylthiouracil in the first trimester and continued with thiamazole from the second trimester.

**AGG RECOMMENDATION (18)**
Women who take antithyroid medications continuously during pregnancy should have interdisciplinary consultations relating to the **birth plan** with the involvement of the pediatricians who will care for the child postnatally.

Hyperthyroidism is characterized by elevated FT4 and FT3 levels, and low or unmeasurable TSH. The most common cause of hyperthyroidism is Graves' disease, in which activating TR-Abs lead to overstimulation of the thyroid gland. The primary symptoms of hyperthyroidism are tachycardia, increased blood pressure, increased sweating, and anxiety. Graves' disease also includes exophthalmos, which is due to the effect of antibodies on the retrobulbar tissue. Radioiodine therapy, antithyroid medication, and thyroidectomy are used as treatments. Graves' disease is a rather rare complication in pregnancy – with a prevalence of only 0.1 to 0.2% in all pregnant women [67].

## 6.1. Manifest hyperthyroidism

Since manifest hyperthyroidism is associated with an increased rate of spontaneous miscarriages, premature births, stillbirths, and preeclampsia, a euthyroid metabolic status should be confirmed prior to conception. For treatment with antithyroid medication during pregnancy, consider: propylthiouracil (PTU) (50 to 300 mg/d), thiamazole (5 to 15 mg/d), or carbimazole (10 to 15 mg/d). In principle, treatment with antithyroid medication during pregnancy is problematic. When taking thiamazole and carbimazole (methimazole), there is an increased rate of malformations in the first trimester. Accordingly, the "Rote-Hand-Brief" dated February 6, 2019, expressly states that carbimazole and thiamazole should only be prescribed during pregnancy after a strict individual risk-benefit evaluation has been carried out. Severe liver dysfunction in mothers as well as newborns have been reported with PTU use, which is why the administration of PTU should also be assessed critically [68, 69]. In the current Anglo-American recommendations, if therapy is necessary in the first trimester, the administration of PTU and a change of medication to thiamazole or carbimazole from the second trimester is recommended [15]. In principle, the pharmacotherapy of hyperthyroidism, as always during pregnancy, should achieve the desired clinical effect with monotherapy and the lowest effective dose possible [15, 67]. It therefore makes sense to attempt to discontinue treatments to achieve this objective if planning to conceive or when a pregnancy is diagnosed.

## 6.2. Latent hyperthyroidism

**AGG RECOMMENDATION (19)**
The **fT4** value should be determined first if the **TSH value** is **< 0.1 mU/l**. If these values are within the **normal range**, there is no need for treatment. In these cases, the thyroid antibody status should be determined, particularly if there is a positive medical history of Graves' disease.

Latent hyperthyroidism (TSH suppressed, fT3 and fT4 within the normal range) affects between 6–18% of all pregnant women. In early pregnancy, the increase in β-hCG, which is very similar to TSH in its molecular structure, leads to an increase in thyroid hormones and the suppression of TSH. TSH levels below the detection limit (< 0.01 mU/l) may still be normal. In patients that are clinically inconspicuous and have normal thyroid hormone levels, this type of subclinical hyperthyroidism does not require treatment [15].

## 6.3. Gestational thyrotoxicosis

**AGG RECOMMENDATION (20)**
Symptomatic treatment (antiemetics, β-blockers) is sufficient for **symptomatic gestational hyperthyroidism** with increased fT3 and fT4 levels.

β-hCG can cause the release of thyroid hormones to increase, which may induce gestational thyrotoxicosis and be associated with hyperemesis. In cases presenting with this type of clinical picture, treatment with β-blockers may be considered; antithyroid therapy is not indicated [70].

## 6.4. TSH receptor autoantibodies (TR-Ab) during pregnancy

**AGG RECOMMENDATION (21)**
If **TR-Ab (or TSH receptor autoantibodies)** are detected, they should be checked every trimester.

**AGG RECOMMENDATION (22)**
If there is an **elevation of TSH receptor antibodies** in the mother (> 5 IU/l or > 3 times above the threshold value), or if there is uncontrolled maternal hyperthyroidism during pregnancy, regular checks should be carried out by a physician experienced in prenatal diagnosis to rule out fetal hyperthyroidism.

**AGG RECOMMENDATION (23)**
If there are signs of **fetal hyperthyroidism**, intrauterine treatment is already carried out by administering antithyroid medication to the mother; this may also be necessary in euthyroid mothers that are TR-Ab positive. In addition, a pediatrician (preferably a pediatric endocrinologist) should be consulted and the diagnostics required for the newborn after delivery should be planned.

If TSH is significantly low and thyroid values are normal, the determination of TSH receptor antibody status is indicated, particularly in the presence of a positive medical history of Graves' disease. TR-Ab pass through the placenta and usually have a stimulating effect on the TSH receptor, but can, in rare cases, also have an inhibitory effect on fetal and neonatal thyroid hormone synthesis. Likewise, both TR-Ab variants may be produced simultaneously in the same patient. Ordinarily, however, there are stimulating TR-Ab that can cause hyperthyroidism in the fetus and even a thyrotoxic crisis in the newborn. The development of hyperthyroidism in the fetus is independent of the mother's symptoms and may occur even if thyroid levels are normal, most notably in thyroidectomized and hormone-substituted pregnant women [15]. If TR-Abs are detected, these should be checked every trimester. Pregnant women with elevated TR-Ab concentrations should be treated in a facility with the appropriate experience during early pregnancy.

If pregnant women have TR-Ab concentrations that exceed the normal value by more than three times, intensified obstetric monitoring of the child should be carried out (see below) [15]. If there are sonographic signs of fetal hyperthyroidism, the mother should be treated with antithyroid medication, which in this case will treat the child transplacentally.

# 7. Fetal and neonatal Diagnosis and Therapy

**AGG STATEMENT (7)**
Treated hypothyroidism alone is not an indication for extended fetal diagnostics during pregnancy.
An exception here is hypothyroidism after treating Graves' disease with persistent TR-Abs (see recommendation 22).

The presence of stimulating TR-Abs and the intake of antithyroid medication by the mother are particularly relevant for the fetus during pregnancy and may result in fetal hyper- or hypothyroidism – even in the euthyroid mother.

Treated latent or manifest maternal hypothyroidism is not an indication for fetal diagnostics during pregnancy that go beyond normal prenatal care [15]. An exception here is hypothyroidism after treating Graves' disease with persistent TR-Abs (see recommendation 27).

## 7.1. TSH receptor antibodies (TR-Abs)

**AGG RECOMMENDATION (22) – REPETITION**
If there is an **elevation of TSH receptor antibodies** in the mother (> 5 IU/l or > 3 times above the threshold value), or if there is uncontrolled maternal hyperthyroidism during pregnancy, regular checks should be carried out by a physician experienced in prenatal diagnosis to rule out fetal hyperthyroidism.

Circulating maternal TR-Abs can increasingly permeate the placental barrier during the course of pregnancy and trigger fetal hyperthyroidism from about 20 + 0 weeks of pregnancy [71]. The incidence of fetal/neonatal hyperthyroidism in pregnant women with Graves' disease is 1–5 % [15]. Congenital neonatal hyperthyroidism has a mortality rate of up to 25 % [72].

Two studies have demonstrated that a cut-off value of maternal TR-Abs in the second and third trimester of > 5 IU/l (or > 2–3-fold increase above the upper limit) had a sensitivity of 100 % for the development of neonatal hyperthyroidism [73, 74].

Signs of fetal hyperthyroidism include fetal tachycardia, fetal growth restriction, fetal goiter, premature ossification, cardiac abnormalities (e.g., tricuspid regurgitation), and hydrops fetalis. Several working groups have published nomograms for assessing the fetal thyroid gland (▶ **Fig. 2**) [75 – 80]. ▶ **Fig. 3** shows the location/size of the fetal thyroid gland.

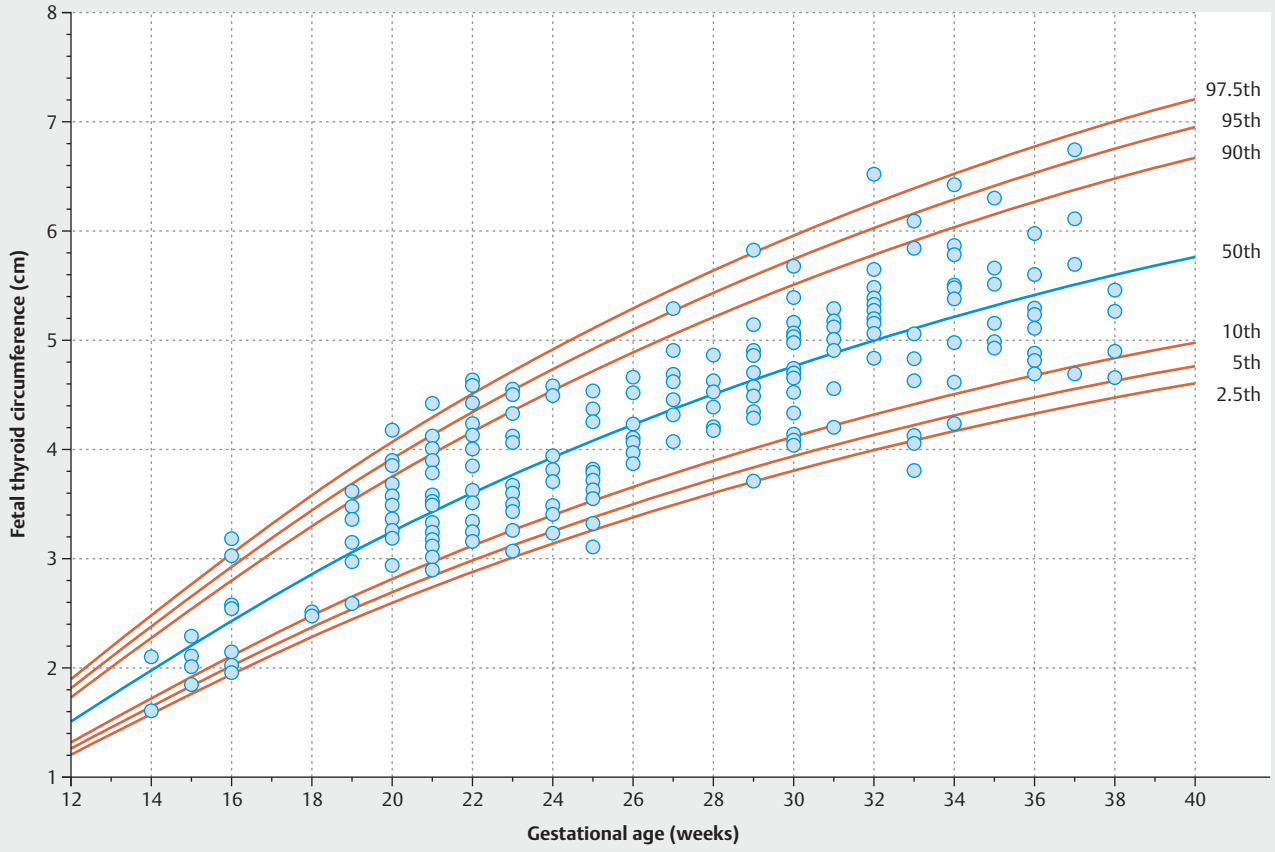
Fetal goiter can develop both in the context of fetal hyperthyroidism with maternal TR-Abs and in fetal hypothyroidism due to maternal antithyroid treatment. Central perfusion on ultrasound is described as a feature of hyperthyroid goiter, in contrast to peripheral perfusion, which is more frequently found in hypothyroid goiter [81, 82].

In the case of fetal goiter that does not have a unclear origin (e.g., simultaneous presence of TR-Abs and maternal use of antithyroid medication), percutaneous umbilical cord blood sampling may be carried out in selected cases to differentiate between fetal hyperthyroidism and hypothyroidism [83 – 85].

## 7.2. Intake of thyrostatic agents

**AGG RECOMMENDATION (24)**
After **taking thyrostatic agents** during the first trimester of pregnancy, the patient should be offered a further **differentiated ultrasound examination**.

**AGG RECOMMENDATION (25)**
If antithyroid medication is taken during pregnancy, **regular examinations should be carried out by an experienced prenatal diagnostician** to rule out fetal hypothyroidism (specifically fetal hypothyroid goiter).




▶ **Fig. 2** Nomogram of the fetal thyroid circumference according to gestational age (Fig. based on data from [76]).

Various studies have reported an increased rate of fetal malformations in pregnant women who were treated with antithyroid medication (carbimazole/thiamazole, propylthiouracil) during the first trimester.

Thiamazole and carbimazole are considered mild teratogens. The typical malformation pattern, which may occur in about 2–4% of children exposed to these medications, consists of aplasia cutis, choanal atresia, esophageal atresia, defects of the abdominal wall, ventricular septal defects and facial dysmorphism [86–89].

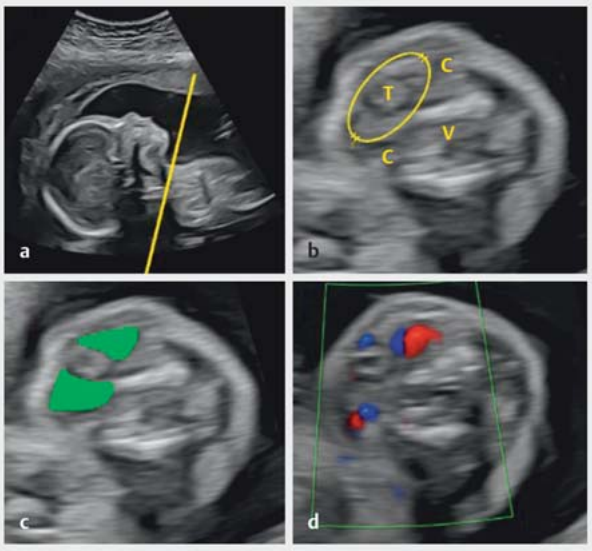
The available data is inconsistent for propylthiouracil with the majority of studies not able to determine an increased risk of malformations, although a slightly increased potential for malformations could not be ruled out [88].

Since antithyroid medications effectively cross the placental barrier, an effect on fetal thyroid gland function is to be expected if medication is taken continuously during pregnancy. Fetal hypothyroidism with the formation of goiter and the risk of complications such as polyhydramnios, tracheal displacement, and FGR may also occur in euthyroid mothers [90]. Therefore, from the fetal point of view, pregnant women should be treated with the lowest possible dose of antithyroid medication and the fetuses should be monitored for any signs of hypothyroidism (particularly fetal goiter).

## 7.3. Treatment options for hyperthyroidism

**AGG STATEMENT (8)**
There is currently limited evidence-based information for the treatment of **fetal hyperthyroidism**.

Case reports and reviews describe the following medication treatment options: the transplacental use of antithyroid medications (thiamazole, PTU) and, if necessary, propranolol via oral intake by the mother. In individual cases, successful intrauterine treatment with potassium iodide was reported [91]. Fetal heart rate, fetal blood analyses by means of percutaneous umbilical cord blood sampling, or a decrease in cardiac changes detected by sonography were used as antepartum outcome measures for treatment [92–96].




▶ **Fig. 3** Treatment algorithm for thyroid function disorders during pregnancy. **a** Transverse section of the fetal thyroid gland. **b** Transverse section of the fetal thyroid gland at 22 + 0 weeks of pregnancy. The thyroid gland is located within the ellipse, lateral to the trachea (T), flanked by the common carotid artery (C), and ventrally by the cervical vertebrae (V). **c** Transverse section showing the fetal thyroid gland (in green), **d** Transverse section of a color Doppler of the normal thyroid gland. Own images, courtesy of M.S. (co-author).

## 7.4. Treatment options for fetal thyroid disease

**AGG RECOMMENDATION (26)**

Intrauterine therapies for **fetal hyper- and hypothyroidism** should only be carried out after careful consideration of the risks and in facilities with prenatal diagnostic and therapeutic expertise.

**AGG RECOMMENDATION (27)**

In case of thyrostatic treatment during pregnancy, uncontrolled maternal hyperthyroidism, or maternal TR-Abs in the second or third trimester, the delivery should take place in a **prenatal center with pediatric staff that have the relevant expertise**.

If there are signs of disfunction of the fetal thyroid gland that have already been diagnosed prenatally, the delivery should take place at a Level I perinatal center.

Case series and reviews describe the reduction of maternal antithyroid therapy and intraamnial injections of LT4 as treatment options for fetal hypothyroid goiter, which resulted in a size reduction of the fetal goiter in more than half of the cases [84, 85, 90, 93].

## 7.5. Peripartum aspects of maternal thyroid disease

Postnatal TSH screening in the newborn is sufficient for newborns who are born to mothers with hypothyroidism and if there is no evidence of TR-Abs. Relating thereto, we refer to the S2k guideline "Diagnostics in newborns of mothers with thyroid function disorder" (12/2018) [97].

Antithyroid treatment during pregnancy may give rise to neonatal hypothyroidism; uncontrolled hyperthyroidism and/or maternal TR-Abs may induce neonatal hyperthyroidism resulting in high mortality rates. It should be noted here in particular that the manifestation of TR-Ab induced neonatal hyperthyroidism can be delayed due to the antithyroid medication that is transferred to the newborn transplacentally. In these cases, it is necessary for pediatric staff to carry out interdisciplinary planning of the birth and postnatal diagnostics (e.g., from cord blood) as well as monitoring of the newborn.

Both the hyper- and hypothyroid fetus can also develop goiter with compression of the airways. In these cases, a cesarean section should be considered with interdisciplinary ex-utero-intrapartum treatment (EXIT) [85].

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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