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EXPERT REVIEWS

Thyroid physiology and autoimmunity in pregnancy and after delivery

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During pregnancy and after delivery, the maternal thyroid gland faces several metabolic, hemodynamic and immunologic changes. In this article we first summarize the current knowledge on the physiologic adaptation of the healthy thyroid to pregnancy, including variations of thyroid-stimulating hormone and free thyroid hormones, as well as variations of thyroid volume. Our second aim is to illustrate the background of thyroid autoimmunity in this period, which characteristically ameliorates during pregnancy and aggravates after delivery. Although rare during pregnancy, Graves' disease is the most frequent cause of hyperthyroidism, while Hashimoto's thyroiditis is the most frequent cause for hypothyroidism. Both types of thyroid dysfunction may lead to detrimental complications in mother and child and therefore timely recognition and treatment is essential. Postpartum autoimmunity most frequently exacerbates in the form of postpartum thyroiditis, which presents with diverse clinical presentations and may lead to permanent hypothyroidism.

Keywords: Graves' disease • Hashimoto's thyroiditis • iodine • postpartum thyroiditis • pregnancy • thyroid function • thyroid size

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Thyroid function & size in pregnancy & after delivery

Iodine in pregnancy & after delivery

Iodine metabolism

Iodine metabolism in pregnancy is marked by several characteristics. Synthesis of thyroid hormones is increased by up to 50% due to estrogen-induced increase in thyroxine-binding globulin (TBG) concentration [1,2]. Renal clearance of iodide increases owing to the higher glomerular filtration rate [1,3]. Iodide and iodothyronines are transported from maternal circulation to the fetus [1]. Fetal thyroid hormone production increases during the second half of gestation [3] and after delivery, iodide is also transported into the breast milk.

Iodine supply

According to the Endocrine Society clinical practice guidelines, iodine intake before pregnancy should be 150 µg/day in order to maintain adequate intrathyroidal iodine stores. During pregnancy and lactation, the recommended iodine intake is 250 µg/day. There is no need to provide more than 500 µg/day. Women, living in countries with adequate and lasting universal salt iodization programs are not at risk of iodine deficiency [4]. When evaluating adequacy of iodine supply in pregnant women, urinary iodine concentration, as a measure of iodine supply, should be seen in light of the fact that the volume of daily urine usually totals 1.5 l and that approximately 10% of iodine is not excreted via urine [5].

Iodine deficiency causes several metabolic changes and goiter in mother and fetus [1]. In mild iodine deficiency, lower levels of free thyroxine (fT_4) and free triiodothyronine (fT_3) and higher levels of thyroid-stimulating hormone (TSH), TBG and thyroglobulin (Tg) were observed in the second and third trimester of pregnancy when compared with the first trimester. In the third trimester, maternal thyroid volume was also larger [6].

In continuation, we will primarily focus on thyroid function and size in healthy pregnant women living in areas with adequate iodine intake.

Maternal thyroid function

Transport proteins

Besides TBG, which is a major thyroid hormone transport protein, transthyretin and albumin are also important. The level of albumin, which has the lowest thyroxine (T_4) affinity and enables a fast release of T_4 [7], gradually decreases during pregnancy [8]. TBG is an active carrier and has a possibility to switch between the high-affinity and the low-affinity form [9]. TBG levels are the highest in the second and third trimester of pregnancy [6] and the same holds true for thyroid-hormone binding ratio [10] and thyroid-binding capacity [11], which decreases as soon as 3–4 days after delivery. In pregnancy, TBG production in the liver is increased and the half-life of TBG is prolonged because of an estrogen-induced increase in sialylation of TBG [1,12].

Variations of human chorionic gonadotropin

The placenta produces human chorionic gonadotropin (hCG) in the first week after conception and the level is the highest at week 10 before it begins to decrease [3] and reach a plateau at week 20 [2]. In twin pregnancies, peaks of hCG values were higher and of longer duration than in single pregnancies (6 weeks and 1 week, respectively) [13]. The hCG and TSH molecules share similarities, as do the hCG and TSH receptors. Consequently, hCG weakly stimulates the thyroid gland. The TSH receptor stimulation depends on the amplitude and duration of the hCG peak. hCG may induce gestational hyperthyroidism, which occurs in 2–3% of pregnancies [1].

Variations of TSH

Most authors agree that in the first trimester, TSH levels may be decreased in some women with otherwise healthy thyroid glands. Approximately 10% of women have TSH levels below normal and up to 10% of women have suppressed levels of TSH [2,14]. In smokers, TSH levels in the first and third trimester were lower than in nonsmokers [15].

During pregnancy, TSH levels increase and reach the highest value in the third trimester, irrespective of iodine supply [6,10,16–18]. At 3–4 days after delivery, TSH levels were the highest [11]. Higher TSH levels in the second half of pregnancy probably mirror hCG and free thyroid hormones levels, being lower in that period of pregnancy. A total of 4 months after delivery, TSH levels were lower than in the third trimester [16]. Similarly, 1-year postpartum they were lower than in the second and third trimester of pregnancy [19], except for one study, where the same TSH levels were established 1-year postpartum and during pregnancy [20].

Relationship between TSH & hCG

The lower TSH level in the first trimester mirrors the highest level of hCG in that period and a negative correlation between these levels is significant [6]. A transient subnormal TSH in the first trimester was associated with hCG levels above 50,000 IU/l [21]. At hCG concentrations above 400,000 IU/l, TSH was suppressed in 100% of women and fT_4 increased in 80%. At hCG levels above 200,000 IU/l, 67% of women had TSH below 0.2 mU/l [22]. From gestational weeks 11–18, only upper deciles of hCG were weakly associated with lower TSH values [23].

Variations of free thyroid hormones

Even in areas with adequate iodine intake, many authors established pregnancy levels of fT_4 and fT_3 to be lower than in nonpregnant individuals. In the last months of pregnancy, fT_4 levels were often below the reference interval [24]. Total thyroxine slightly increased in the first trimester and decreased by approximately 30% to low normal values in the second and third trimester [25]. During pregnancy, fT_4 and fT_3 were also decreased when compared with postpartum levels [20]. fT_4 was lower during pregnancy than 1-year postpartum [19] and lower than those in the nonpregnant state [26].

Several factors may influence the level of free thyroid hormones. Increased hCG at 11–13 weeks was associated with increased median values of fT_4 [23]. Twin pregnancies with higher hCG values of longer duration frequently led to increased fT_4 levels [12]. In smokers, fT_3 levels were higher than in nonsmokers and fT_4 levels did not differ [15]. Despite low iodine supply, Sudanese pregnant women had higher fT_4 and lower TSH than Swedish pregnant women with adequate iodine intake, both in weeks 20–24 and 36–39 [27]. The history of pre-pregnant iodine supply seems to be an important factor influencing thyroid response during pregnancy.

Several authors advocated for the use of gestational specific reference intervals [18,24]. They have already been proposed for Swiss women [18], Indian women [17], Chinese women [28], Danish women [29] and others. In all, TSH increased during pregnancy, while fT_4 and fT_3 decreased.

Interpretations of free thyroid hormone variations

The decrease of fT_4 and, less frequently, of fT_3 in the second half of pregnancy remains an unresolved issue. This is not necessarily the reflection of maternal iodine deficiency [5]. That assumption was confirmed by the following study, showing fT_4 in the third trimester below the nonpregnant reference range in 64.5% of women and fT_3 in 10.3%. The values returned to normal 4 months after delivery and were not associated with the urinary iodine concentration, which has been adequate and even lower after delivery than in the third trimester [16].

Beside a decrease in fT_4 and fT_3, an increase in reverse T_3 during pregnancy was found and a resemblance with the nonthyroidal illness was postulated [30]. However, patients with that condition have frequently decreased fT_3 and rarely decreased fT_4 [31], whereas during pregnancy the fall of fT_4 is more pronounced.

Variations of fT_4 and fT_3 are definitely pregnancy-related, since they increased just 3–4 days after delivery [11]. Decreased fT_4 might not be only a consequence of importantly increased TBG concentration, but also of its increased binding affinity. However, there are no reports on binding affinity of TBG during pregnancy. Besides, albumin levels decrease during pregnancy, diminishing the possibility of the quick release of the bound T_4.

Methodological problems are another possible explanation for the observed variations. Negro *et al.* concluded that there are no optimal diagnostic tests for fT_4 during pregnancy [32]. Recently, several attempts have been undertaken to find the most appropriate method for the determination of thyroid hormones during pregnancy. Total T_4 and fT_4 index keep the inverse relationship with TSH during pregnancy and are possibly more reliable for the evaluation of thyroid function in pregnancy [10]. With equilibrium dialysis and with nine immunoassays the levels of fT_4 were in the lower part of the nonpregnant reference interval or below [33]. With direct equilibrium dialysis – liquid chromatography/tandem mass spectrometry – fT_4 and fT_3 reference intervals decreased from week 14 to week 20 of pregnancy [34]. The relationship between log(TSH) and fT_4 was extremely weak for both the tandem mass spectrometry and the immunoassay [35].

Maternal thyroid size

Factors influencing thyroid size

Thyroid size is influenced by different factors, including iodine supply, genetics, gender, age, TSH, anthropometric parameters, parity and smoking [36]. Thyroid volume in individuals in the nonpregnant state increased with bodyweight, age [37], BMI and total body water [38]. Also during pregnancy, a positive correlation between thyroid volume and BMI was found [39]. A negative correlation between thyroid volume and TSH [38] was also confirmed in pregnant women [39]. Thyroid volume was associated with family history of thyroid diseases and therefore with genetics [40].

Iodine supply & thyroid volume

In an area with adequate iodine intake, thyroid volume did not change during pregnancy [30]. In a group of women living in a marginally iodine-deficient area and taking 200 µg of iodide, thyroid volume did not change, whereas in the group of women taking 50 µg of iodide, thyroid volume slightly increased during pregnancy [41]. In iodine sufficiency, thyroid volume did not differ between pregnant and nonpregnant women [42]. Berghout and Wiersinga [25] reviewed that in iodine-sufficient areas, thyroid volume did not increase during pregnancy. However, even in iodine sufficiency, there are reports on the increase of thyroid gland volume during pregnancy [39,43,44]. The increase of thyroid volume during pregnancy was followed by the decrease after delivery and on the basis of this finding it was postulated that the increased vascularity may be the reason for the increase of thyroid volume [20].

Hemodynamic changes

Weight gain during pregnancy is predominantly caused by the increase in total body water from 6 to 8 l, of which 4–6 l are extracellular [45]. Pregnancy is therefore characterized by hypervolemia. In healthy adults, thyroid volume is positively correlated with total body water [38]. Increased water volume increases body weight and BMI [46]. Both factors may also increase thyroid

volume in pregnancy. By color flow Doppler sonography, an increased intrathyroidal blood flow during pregnancy [47] and a decrease of intrathyroidal blood flow in a year after delivery was found [39]. Authors assumed that, to some extent, thyroid volume increased during pregnancy and decreased after delivery because of hemodynamic changes during pregnancy.

Thyroid autoimmunity in pregnancy & after delivery

The role of pregnancy in triggering of thyroid autoimmunity

Immune adaptations in pregnancy

In order to tolerate the fetus during the intrauterine life, the mother's immune system undergoes several adjustments. Both maternal systemic suppression and placental immune suppression are involved in preserving the pregnancy, being induced by significant hormonal changes. The key regulatory role is carried out by regulatory $CD4^+CD25^+$ T cells (Treg), being important not only in peripheral tolerance against both foreign and self-antigens, but also in fetal tolerance. Treg cells were shown to regulate both Th1-type activity, which leads to cellular immunity, and Th2-type activity, being involved in humoral immunity [48]. In pregnancy, the expansion of Treg cells is presumably provoked by fetal antigen presentation and estrogen-induced expression of several chemokines. They occur in early pregnancy and they increase rapidly during pregnancy, peaking in the second trimester [49]. Treg cells, accumulated predominantly in decidual tissue and to a lesser extent in peripheral blood [49], were shown to significantly suppress both Th1-type and Th2-type reactions against paternal/fetal alloantigens. However, Th2 clones seem to be less sensitive to this suppression than Th1 clones, leading to predomination of Th2 cells and cytokines over a Th1 cellular immune response, driving the cytokine balance away from the detrimental effects of Th1-cell activity, which may cause fetal loss [50]. Therefore, the maintenance of pregnancy is enabled by proper balance of Th1/Th2 immunity, with a slight shift towards Th2 immunity. This physiological state of lowered immune responsiveness in pregnancy results in amelioration of some pre-existing autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis or thyroid autoimmune disease [51]. During the weeks immediately prior to delivery a clear decline in Treg cells occurs. After delivery, this imbalance in Treg cells and shift of cytokine profile away from Th2 to Th1 during the return to normal pre-pregnancy state may be reflected in exacerbation or aggravation of autoimmunity [52,53].

In pregnancy and postpartum, different types of autoimmune thyroid disease may occur, including Graves' disease (GD), Hashimoto's thyroiditis (HT) and postpartum thyroiditis (PPT). Characteristically, thyroid autoantibodies decline during pregnancy, which might be explained by Treg-mediated suppression [52]. After delivery, they return to the pre-pregnant values, frequently ending in postpartum exacerbation of thyroid autoimmunity [54–57].

The role of fetal microchimerism

Fetal microchimerism refers to the phenomena of fetal cell leakage into the mother's circulation through the placenta during pregnancy. The presence of chimeric male cells has been established in the peripheral blood and maternal tissues, including thyroid [58], and they have been found circulating in mothers several years after delivery [59]. In GD and HT, intrathyroidal fetal microchimeric cells were detected significantly more often than in nonautoimmune thyroid disease [101]. However, large population-based studies found no association between parity and thyroid autoimmunity, arguing against a key role of fetal microchimerism [60,61].

Female sex

Several large epidemiological studies confirmed the female predominance in thyroid autoimmunity, as they present with positive thyroid autoantibodies approximately two- to three-times more often than males [62–64]. Estimation, based on the largest National Health and Nutrition Examination Survey (NHANES) III study, indicated that 17% of females were positive for thyroid peroxidase antibodies (TPOAb), while 15.2% were positive for Tg antibodies (TgAb). Additionally, the prevalence of antibodies was twice as high in white females compared with black females [62].

Besides fetal microchimerism, higher genetic susceptibility for thyroid autoantibody production in females than in males has been reported in the study of Danish twins [65]. X chromosome genes are essential in determining sex hormone levels, as well as in maintaining immune tolerance. Therefore, the alterations in X chromosome, including monosomy or structural abnormalities, and disturbances in X chromosome inactivation with consequent impaired thymic deletion of autoreactive cells, might contribute to the impaired immune response [66].

Risk predisposing factors

Genes

Appropriate genetic background is needed to allow different endogenous and environmental influences to trigger thyroid autoimmunity. Initial observations of higher incidence of thyroid autoimmune disease in families have been recently confirmed by two reports, showing that risk for developing thyroid autoimmune disease was around 16-fold increased in children and siblings of the affected individuals [67,68]. According to the estimation based on Danish twins, genetic influence seems to contribute 73% to thyroid autoantibody positivity [65]. Until now, several putative genes have been identified. Among immune regulatory genes, *HLA-DR* gene, cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4*) gene, *CD40* gene, protein tyrosine phosphatase-22 (*PTPN22*) gene and *CD25* gene have shown an association with thyroid autoimmune disease. Among thyroid-specific genes, major candidates are the gene for Tg and TSH receptor gene [69]. Besides being involved in clinical disease, genetic susceptibility is crucial also for thyroid antibody production. Among putative genes, *CTLA-4* was confirmed as a major locus for thyroid antibodies [70], being associated with higher thyroid antibody levels in GD, HT and PPT [71–73].

Iodine intake

The enhancing influence of iodine on thyroid autoimmunity has been confirmed by studies on experimental animal models and also by large observational studies of populations with different iodine intake. Among mechanisms, autoantigenic potency

of highly iodinated Tg or iodine toxicity to thyrocytes have been proposed, but the precise mechanism is still unknown [74]. In humans, the improvement of iodine prophylaxis lead to a three–fourfold increase in incidence of thyroid autoimmunity in a population with previously mild iodine deficiency [75]. The prevalence of thyroid antibodies, estimated by large epidemiological studies, was up to 18% in the areas with sufficient iodine intake [62], up to 25% in conditions of excessive iodine intake [63], but only up to 13% in the circumstances of iodine deficiency [64]. High iodine intake in pregnancy was associated with a higher risk of developing PPT [76], but this observation was not supported by other studies showing that iodine supplementation in pregnancy and after delivery is safe even in TPOAb-positive females [41,77].

Other risk factors

Other risk factors, although less frequent in pregnancy and postpartum, might contribute to thyroid autoimmunity in females in the reproductive period. Smokers are at risk for GD [78] and at even greater risk for either development or deterioration of Graves' orbitopathy [79]. In HT, few early investigations implicated the association with smoking [80], while a recent report indicated even negative relation of smoking with both TPOAb and TgAb as well as with hypothyroidism [81]. Also, data regarding PPT are scarce, with only two studies implying the increased risk in association with smoking [80,82]. Triggers such as stress, infections, environmental toxicants or immune-modulating drugs may contribute to thyroid autoimmunity in the reproductive period equally as in the general population [83].

Thyroid autoimmune disease in pregnancy & after delivery

Graves' disease

In females in the reproductive period, GD is the most frequent cause of hyperthyroidism, which occurs in the population with an estimated prevalence of approximately 1% [62]. Among pregnant women the prevalence rate of overt hyperthyroidism is approximately 0.1–0.4% and GD accounts for 85–90% of all cases [53]. In this type of thyroid autoimmunity, the humoral immune response predominates with the characteristic appearance of stimulating antibodies against TSH receptor (TRAbs), causing hyperthyroidism, goitre and nonthyroid manifestations, such as Graves' orbitopathy or dermopathy.

Owing to physiological immunosuppression during pregnancy, the development of GD or relapse of hyperthyroidism in this period is rare, usually emerging in the first trimester of pregnancy. In the second half of pregnancy even the gradual improvement of previously existing hyperthyroidism is frequently observed, being most probably the reflection of the stimulating TRAbs decrease in the second and third trimester [56,57]. In the postpartum period, when the immunosuppression ceases, the increase of stimulating TRAbs [57], together with relapse of GD, is frequently observed, usually between 4 and 8 months after delivery. In the recent study of patients in remission after antithyroid drug treatment, the recurrence of GD was determined in 84% of patients in the postpartum period compared with only 56% of patients not being pregnant [84]. However, as indicated by one single study, the postpartum period itself has not been shown to be a major risk factor for the first onset of GD [85].

Untreated or inadequately treated GD in pregnancy may lead to several detrimental complications. In mothers, hyperthyroidism has been associated with preeclampsia and with the increased risk of congestive heart failure and thyroid storm. In the pregnancy course, hyperthyroidism may increase the risk of miscarriage, stillbirth, preterm delivery and placental abruption. Fetal hyperthyroidism, which occurs in less than 0.01% of pregnancies [86], may lead to tachycardia, fetal goitre, accelerated bone maturation, growth retardation, low birth weight and malformations. In the fetus, the excess of thyroid hormones may be the reflection of the mother's thyroid hormones or the mother's stimulating TRAbs crossing the placenta. Those antibodies have the impact on fetus only after the twelfth week of gestation, when the fetal thyroid starts to respond to the stimulation [56,87]. In late pregnancy they represent a risk of neonatal hyperthyroidism, which occurs in up to 5% of newborns of mothers with GD. It usually persists for up to 12 weeks due to slow clearance of maternal antibodies, having a half-life of approximately 3 weeks [56,87].

Hashimoto's thyroiditis

With the estimated prevalence of 18% in the population, HT is probably one of the most prevalent autoimmune disorders in general. In women in the reproductive period, the prevalence of thyroid antibodies was approximately 10–15% and the prevalence was increasing with age [62]. In contrast to GD, in HT the cell-mediated immune response predominates with consequent gradual destruction of thyroid tissue, which frequently leads to hypothyroidism. Although not playing a significant role in the pathogenesis of the disease, TPOAb and TgAb characteristically appear in the patients' sera in more than 90% and in up to 80% of cases, respectively [88]. In pregnancy, those antibodies were shown to decline gradually with the lowest values in the third trimester, while the increase was observed as soon as 6 weeks after delivery and returning to the pre-pregnant values 12 weeks after delivery [54,55,89].

In HT, both hypothyroidism and thyroid autoantibodies have been implicated to be involved in pregnancy complications. Overt or subclinical hypothyroidism, occurring in approximately 2–4% of apparently healthy women, has been related to two–threefold increased risk of gestational hypertension, placental abruption, postpartum hemorrhage, preterm delivery or miscarriage. Besides increased risk of low birth weight, neonatal respiratory distress and fetal abnormalities, such as hydrocephalus and hypospadias, maternal hypothyroidism during pregnancy has also been demonstrated to affect neuropsychological development of the child [2,90]. However, rapid and adequate correction of hypothyroidism with L-thyroxine therapy has been shown to improve obstetrical outcome [2,4]. In euthyroid pregnant women, elevated thyroid autoantibodies have been associated with two- to four-fold increased risk of miscarriage and with up to threefold increased risk of preterm delivery, although the etiology remains

Table 1. Thyroid physiology and autoimmunity in pregnancy and after delivery.

Parameter	First trimester	Second trimester	Third trimester	After delivery
hCG	↑↑	↘ →	↘	↓↓
TSH	↘↓	↗	↗	↘
fT_4	↗↑	↘	↘↓	↗
fT_3	↗↑	↘	↘↓	↗
Treg	↑	↑↑	↘	↓↓
TAb	↘	↓	↓↓	↑↑

→: No change; ↘: Slight decrease; ↓: Decrease; ↓↓: Marked decrease; ↗: Slight increase; ↑: Increase; ↑↑: Marked increase when compared with the previous period.
fT_3: Free triiodothyronine; fT_4: Free thyroxine; hCG: Human chorionic gonadotropin; TAb: Thyroid autoantibodies; TSH: Thyroid stimulating hormone.
Data taken from [2,3,14,18–24,49,52,55].

unresolved. Those complications may be associated with underlying generalized immune imbalance, with subtle deficiency of thyroid hormones due to thyroid autoimmunity, or with older age of those females [90,91].

Hypothyroidism may also lead to infertility, since menstrual irregularities, including oligomenorrhea, menorrhagia and ovulatory dysfunction may occur and their severity correlates with the elevation of serum TSH levels. Similarly, hypothyroidism may provoke *in vitro* fertilization failure in infertile females, while L-thyroxine replacement has been shown to improve embryo implantation rate and pregnancy outcome [90,92]. However, the clinical importance of thyroid antibodies in infertility remains controversial and underlying pathogenic mechanisms of putative association still need to be clarified [90].

Postpartum thyroiditis

Postpartum thyroiditis refers to thyroid dysfunction within the first year after delivery or miscarriage, when the known immunosuppressive effect of pregnancy disappears. The clinical disease may present with hyperthyroidism alone, only with hypothyroidism, or with hyperthyroidism followed by hypothyroidism. The prevalence varies significantly between studies from 1.1 to 21.1% [93], with estimated pooled prevalence in the general population of approximately 8%, occurring up to six-times more often in females with elevated TPOAb and three-times more often in females with Type 1 diabetes [94]. Therefore, in these two groups screening for thyroid dysfunction is recommended 3 and 6 months after delivery [4]. Females positive for TPOAb in early pregnancy develop PPT in 40–60% of cases, while among patients with PPT 70% present with positive TPOAb, putting them at risk for developing a permanent thyroid dysfunction [54].

The hyperthyroid phase of the disease is only transient, more frequently occurring in TPOAb-negative patients between 1 and 6 months after delivery and lasting 1–2 months. Hypothyroidism may occur with or without a previous hyperthyroid phase, more often in TPOAb-positive patients and between 3 and 8 months after delivery, being caused by destruction of thyroid tissue [54,73]. It may be only transient, lasting 4–6 months and passing within 1 year after delivery or it may be permanent [4]. A few earlier studies reported permanent hypothyroidism in up to 30% of PPT patients [2], but a recent large prospective report demonstrated a significantly higher incidence of approximately 50%. The latter observation might be an overestimation, since owing to limited sampling only 6 and 12 months after delivery a considerable number of patients with transient hypothyroidism may have been missed [95,96]. However, patients with transient hypothyroidism are also at risk for developing permanent hypothyroidism, which is established within 5–10 years after PPT in 20–60% of females [94]. While in the hyperthyroid phase no specific antithyroid therapy is indicated, replacement therapy with L-thyroxine frequently needs to be started in hypothyroid patients [4].

Expert commentary

In pregnancy and the postpartum period, several physiological changes develop, which are reflected in the healthy thyroid gland as well as in autoimmune thyroid disease (Table 1).

Appropriate adaptation of the healthy thyroid gland to metabolic challenges during pregnancy and lactation is assured by adequate iodine supply. When dealing with thyroid biochemical tests, we should also keep in mind that levels of TSH and free thyroid hormones may vary outside the normal reference ranges both with adequate iodine supply and in the healthy pregnant state. TSH levels, being lower in the first trimester and increasing in the second and third trimester, probably mirror hCG levels. Additionally, higher TSH in the second half of pregnancy may be the reflection of lower free thyroid hormones in this period, although the reason for the latter observation has not yet been established. Several explanations have been proposed, including increased binding capacity for thyroid hormones or methodological problems. In order to reduce the interpretation difficulties in daily clinical practice, the use of gestational-specific reference intervals proposed by several authors seems plausible. Beside biochemical changes, thyroid volume changes in pregnancy remain an open issue. Despite contradictive reports, in our experience thyroid volume increases in pregnancy and decreases after delivery even with sufficient iodine intake, most probably being associated with anthropometric and hemodynamic changes.

Pregnancy represents a challenge not only for thyroid function and size, but also for the immune system. It is important to consider the high prevalence of thyroid autoimmune disease in the reproductive period, being significantly influenced by the modification of immune response in pregnancy and after delivery. Given this view, the understanding of the pathophysiology of this condition is essential for the management of thyroid disorders in this period. Although immunotolerance in pregnancy frequently leads to amelioration of thyroid autoimmunity, the recognition and treatment of thyroid dysfunction is of crucial importance to avoid detrimental complications in mother and child. On the other hand, the exacerbation of thyroid autoimmunity after delivery, when the immune responsiveness increases, is expected and therefore screening for thyroid dysfunction in women with known

thyroid disease in this period is required. Nevertheless, the warranty for the universal screening through TSH or even antibody testing in pregnancy remains an unsettled question. By the current evidence, case finding by TSH measurement is recommended in women at risk, including those with thyroid disease or family history of thyroid disease, those with symptoms and signs, women who other autoimmune disorders, like Type I diabetes, women who are infertile or with a history of miscarriage, and those with a history of neck irradiation [4].

Five-year view

It is likely that within the next 5 years more accurate measurements of free thyroid hormones and implementation of gestational-specific reference intervals will enable realistic estimation of thyroid function in pregnancy. Grounds for low free thyroid hormones in that period will probably be experimentally elucidated. Further progress in the evaluation of thyroid volume changes in pregnancy is expected, based upon physiological characteristics of pregnancy with the emphasis on hemodynamic changes. With regards to thyroid autoimmunity during pregnancy and postpartum, a immense progress has been achieved in the understanding of pathophysiological mechanisms in the past decade. In the near future, further evidence will hopefully enable better recognition of women at risk in order to avoid the harmful effects of unrecognized thyroid dysfunction for mother and child.

Key issues

- In normal pregnancy, thyroid-stimulating hormone levels may decrease in the first trimester due to human chorionic gonadotropin action, while the low level of free thyroxine in the third trimester remain a matter of debate.
- Thyroid volume may increase during pregnancy even in areas with adequate iodine supply, which does not represent an important clinical problem. However, in our opinion, such an observation and novel explanations for this occurrence represent a valuable contribution to the better understanding of thyroid physiology in pregnancy.
- Pregnancy itself causes significant variation in immune tolerance, which may trigger thyroid autoimmunity in susceptible individuals with appropriate genetic background, excessive iodine intake and other environmental risk factors.
- Graves' disease rarely occurs in pregnancy and frequently relapses between 4 and 8 months after delivery. If untreated, several detrimental consequences may develop in the mother, fetus and in the pregnancy course.
- Hashimoto's thyroiditis, present in approximately 10–15% of females in the reproductive period, may cause hypothyroidism, associated with several complications for the mother, fetus and the pregnancy course.
- Postpartum thyroiditis, occurring in 8% of females in the first year after delivery, usually presents with transient thyroid dysfunction and less frequently ends with permanent hypothyroidism.

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. A 25-year-old woman presents for her first prenatal visit. Based on the review by Drs. Gaberšček and Zaletel, which of the following thyroid changes are you **most likely** to expect during her pregnancy?

- ☐ **A** Thyroid-stimulating hormone (TSH) levels may increase in the first trimester
- ☐ **B** Free T_4 (fT_4) levels may be low in the first trimester
- ☐ **C** Thyroid volume may decrease
- ☐ **D** Synthesis of thyroid hormones increases by up to 50% because of estrogen-induced increase in thyroxine-binding globulin (TBG) concentration

2. Based on the review by Drs. Gaberšček and Zaletel, which of the following changes in immune tolerance would you most likely expect in the patient described in question 1?

- ☐ **A** Regulatory $CD4^+$ $CD25^+$ T cells (Treg) rapidly decrease during pregnancy
- ☐ **B** As pregnancy progresses, T-helper 1 (Th1) cellular immune response predominates over Th2 cells and cytokines
- ☐ **C** Lowered immune responsiveness in pregnancy may result in amelioration of pre-existing rheumatoid arthritis, multiple sclerosis, thyroid autoimmune disease, or other autoimmune disorders
- ☐ **D** During the last few weeks of pregnancy there is a sudden increase in Treg cells

3. Based on the above review by Drs. Gaberšček and Zaletel, which of the following statements about characteristics and complications of thyroid disorders during pregnancy is most likely correct?

- ☐ **A** Graves' disease is common during pregnancy
- ☐ **B** Hashimoto's thyroiditis is the most frequent cause of hyperthyroidism during pregnancy
- ☐ **C** Postpartum thyroiditis occurs in about 8% of women in the first year after delivery
- ☐ **D** Postpartum thyroiditis usually results in permanent hypothyroidism