

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Hypothyroidism in Pregnancy

Baha Zantour, Wafa Alaya, Hela Marmouch and
Wafa Chebbi

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/54745>

1. Introduction

Changes in thyroid function tests occur during pregnancy as a result of physiologic alterations in several factors controlling thyroid homeostasis. Urinary iodine excretion increases along with the increase in thyroxine binding globulin (TBG) concentrations. Human chorionic gonadotrophin (hCG) having structural homology with thyroid stimulating hormone (TSH), stimulates thyroid cells. Thus, during pregnancy, functional activity and size of the thyroid gland are increased. Pregnancy is a stress test for the thyroid resulting in hypothyroidism in women with limited thyroidal reserve or iodine deficiency [1].

Thyroid dysfunction is common during gestation. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3-0.5% for overt hypothyroidism (OH) and 2-3% for subclinical hypothyroidism (SCH). Thyroid antibodies are found in 8-14% of women in the child-bearing age, and chronic autoimmune thyroiditis is the main cause of hypothyroidism during pregnancy, apart from iodine deficiency [2,3].

Given the rapidity of advances in this field, it is not surprising that controversy surrounds optimal detection and management of thyroid disease in pregnant women. It is now well established that OH is associated with an increased risk of adverse pregnancy complications, as well as detrimental effects upon fetal neurocognitive development [4]. However, data regarding SCH are controversial [4,5]

In the past several years, there has been a debate about the universal screening of thyroid disorders. There is until now insufficient evidence to recommend for or against evaluating thyroid function in all pregnant women. OH should be treated in pregnancy. However, due to the lack of randomized controlled trials, there is no evidence to recommend universal treatment of SCH or isolated hypothyroxinemia [6,7]

Central hypothyroidism will not be discussed in this chapter

2. Physiology

Pregnancy profoundly influences thyroid function. This influence is due to many events which are specific to the pregnant state: the changes in thyroid hormone transport protein particularly in TBG, the effects of hCG on the maternal thyroid, the rise in the iodine requirement, the role of the placental deiodinase, and the modifications in the autoimmune regulation. These events occur at different time points during gestation, resulting in complex effects that may be seen only transiently or, by contrast, that persist until term [8]. Hence, pregnancy is a real test for thyroid gland.

2.1. Thyroid hormones transport proteins

Thyroid hormones (TH) circulate in plasma, mainly bounded to 3 transport proteins: TBG, albumin and prealbumin. Despite its smaller concentration compared with albumin and prealbumin, the TBG is the main transport protein of TH, because of its extremely high affinity to these hormones. In serum of normal subjects, TBG carries about two thirds of TH [9]. This bound hormone fraction is in equilibrium with a free unbound fraction, which is in contrast with its smaller amount (0.04% for T₄ and 0.5% for T₃), represents the active fraction of TH [10].

In pregnant women, serum TBG rises sharply few weeks after the beginning of pregnancy, and reaches a plateau around midgestation, 2.5-fold higher than the initial value [11]. Subsequently, the TBG concentration remains stable until term (Figure 1) [12]. This increase in TBG level is due to the increase in estrogen concentration, resulting in a rise of TBG production and release by the liver, site of synthesis of the protein [11]. Furthermore, the circulating levels of both albumin and prealbumin remain stable, with only a discrete tendency to decrease near term, consequently to the hemodilution [13]. The respective affinities of the three binding proteins for TH are not significantly modified. Hence, the proportion of T₄ carried by TBG reaches 75% during gestation [14].

In addition to its increased production, TBG has a longer half-life during gestation. Indeed, the TBG is more sialylated during pregnancy than in other conditions. This higher sialylation confers to the protein a longer half-life. However, the more sialylated fraction of TBG represents a small amount of the total circulating protein (10–15%), and can't explain alone the prolongation of the TBG half-life. This extension of half-life is promoted by the stabilization of the TBG due to the proportional increase in its binding to T₄.

Thus, the major change for thyroid hormone-binding proteins involves TBG, with:

- An increase in its production and release by liver
- An extension of its half-life due to the increase in the degree of its sialylation and its stabilization consequently to the proportional increase in its binding to T₄.

2.2. Thyroid hormones

2.2.1. Total thyroid hormones

In pregnancy, the total TH level increases consequently to the TBG increase. Since the affinity of TBG to T₄ is 20 fold higher than that of TBG to T₃, changes of total T₄ level follow more

closely changes of TBG, and the T3/T4 molar ratio remains unaltered during pregnancy. Total T4 level increases rapidly and markedly between the 6th and the 12th week of gestation and then progresses more slowly, until it stabilizes around midgestation when total T3 level increases more progressively [15].

2.2.2. Free thyroid hormones

Consequently to the increase of the bound fraction of TH, and to maintain free TH homeostasis, an increase in TH production is expected. This production enhancement is thought to be regulated primarily through the normal pituitary-thyroid feedback mechanisms; TSH stimulation of the thyroid gland. However, in healthy pregnant women, without thyroid autoimmunity or iodine deficiency, no increase in serum TSH is commonly observed [16], and free TH levels fluctuations differ in the early gestation than in its second half.

In the first trimester (as it will be discussed later), free T4 (FT4) level rises transiently in response to the peak of production of hCG. This increase in FT4 level is totally independent of the action of TSH which production decreases, in contrast, as a result of its down-regulation by high hCG levels during early pregnancy [17].

In the second half of gestation, longitudinal recent studies based on reliable methodology, carried out on large numbers of pregnant women without iodine deficiency, have showed that serum free TH levels are lower by an average of 10–15% at delivery, in comparison with nonpregnant female subjects, while remaining within reference range of these latters [18,19] (Figure 1). This decrease in free TH level during the second half of gestation in healthy pregnant women, considered euthyroid and without iodine deficiency, remains incompletely explained. Some authors suggest that high estrogen levels over a prolonged period of time may modify the regulation of both basal and TRH-stimulated TSH release by the pituitary gland [20]. Also, an increased nuclear binding capacity for TH in target cells may compensate for this decrease in free TH [21].

2.2.3. Peripheral metabolism of free thyroid hormones and role of placenta

Three enzymes catalyze the deiodination of thyroid hormones. Type I deiodinase, by deiodination of T4, is responsible for the production of most of the circulating T3. Type II deiodinase, is expressed in certain tissues (pituitary gland, brain, brown adipose tissue) and also in the placenta. Its activity increases when the availability of T4 decreases. So, it ensures the maintenance of T3 production in the placenta as maternal T4 levels are reduced [22]. Placental type III deiodinase has an extremely high activity during fetal life. It converts T4 to reverse T3 and T3 to T2, and remarkably increases TH turn-over [23].

Thus, placenta is a selective barrier for the different constituents of thyroid metabolism: it regulates free TH transfer by deiodinases, allows the materno-fetal iodine transfer, and is impermeable to TSH. Placenta is also permeable to thyroid and TSH receptor antibodies and antithyroid drugs.

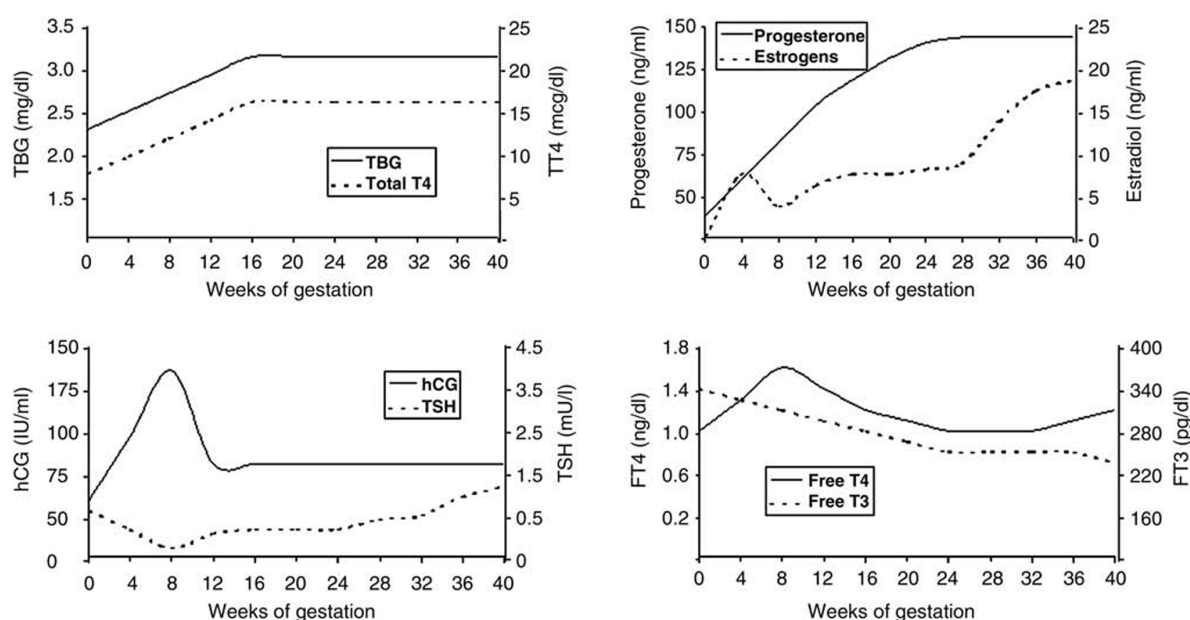


Figure 1. Variation in serum levels of thyroid function test and pregnancy-related hormones according to course of gestation. [19]

2.3. Hypothalamic-pituitary-thyroid axis in pregnancy and the effect of hCG

As it has been already mentioned, previous studies concluded that elevated estrogen levels in pregnancy may influence the hypothalamic-pituitary-thyroid axis (HPTA), perhaps by acting at different levels (and not yet clearly defined) in the thyroid gland feedback-regulatory mechanisms, resulting in a blunting of the TSH response. In normal pregnant women who have no evidence of thyroid autoimmunity and who reside in areas with a sufficient iodine supply, serum TSH remains stable and comparable to pregestational levels, after the transient fall due to high hCG in the first trimester. Conversely, when the iodine intake is restricted, an increase in serum TSH during late gestation (generally remaining within the reference range in normal pregnant women) reflects the stimulated thyroid state. Thus, iodine insufficiency is then revealed by pregnancy and explains the progressive increase in serum TSH observed after 16 weeks of gestation.

Concerning the effect of hCG on thyroid gland, it has been evoked from cases of thyrotoxicosis observed in pathological conditions accompanied by extremely high circulating hCG levels, such as molar pregnancy or other trophoblastic diseases [24]. Therefore, many studies have been carried out to better clarify the real effect of hCG on TH production and its consequences on TSH secretion. The results showed that the profiles of changes in serum TSH and hCG were clear mirror images, with a linear relationship between hCG and FT4 concentrations during early gestation (Figure 2). Thus, the lowering of TSH corresponds to a transient and partial blunting of the pituitary-thyroid axis associated with an increased hormonal output by the thyroid gland under hCG stimulation [18]. The thyrotropic action of hCG is explained by the structural homology between the hCG and TSH molecules, and between LH/hCG and TSH receptors. Thus, hCG is able to bind to the TSH receptor of thyroid follicular cells and exert its stimulatory effects [25]. However, it should be remembered that hCG behaves as a weak

thyroid stimulator *in vivo*. It is estimated that a 10,000 IU/liter increment in circulating hCG corresponds to a mean FT4 increment in serum of 0.6 pmol/liter (*i.e.* 0.1ng/dl) and, in turn, to a lowering of serum TSH of 0.1 mIU/liter. Hence, a transient increase in serum FT4 during the first trimester will only be observed when hCG levels reach or exceed 50,000 –75,000 IU/liter. Some studies assessed from a clinical stand point how often partial TSH suppression may occur in early pregnancy. In up to one fifth of normal pregnancies, serum TSH may be transiently suppressed in the first trimester to values below the lower limit of normal [26].

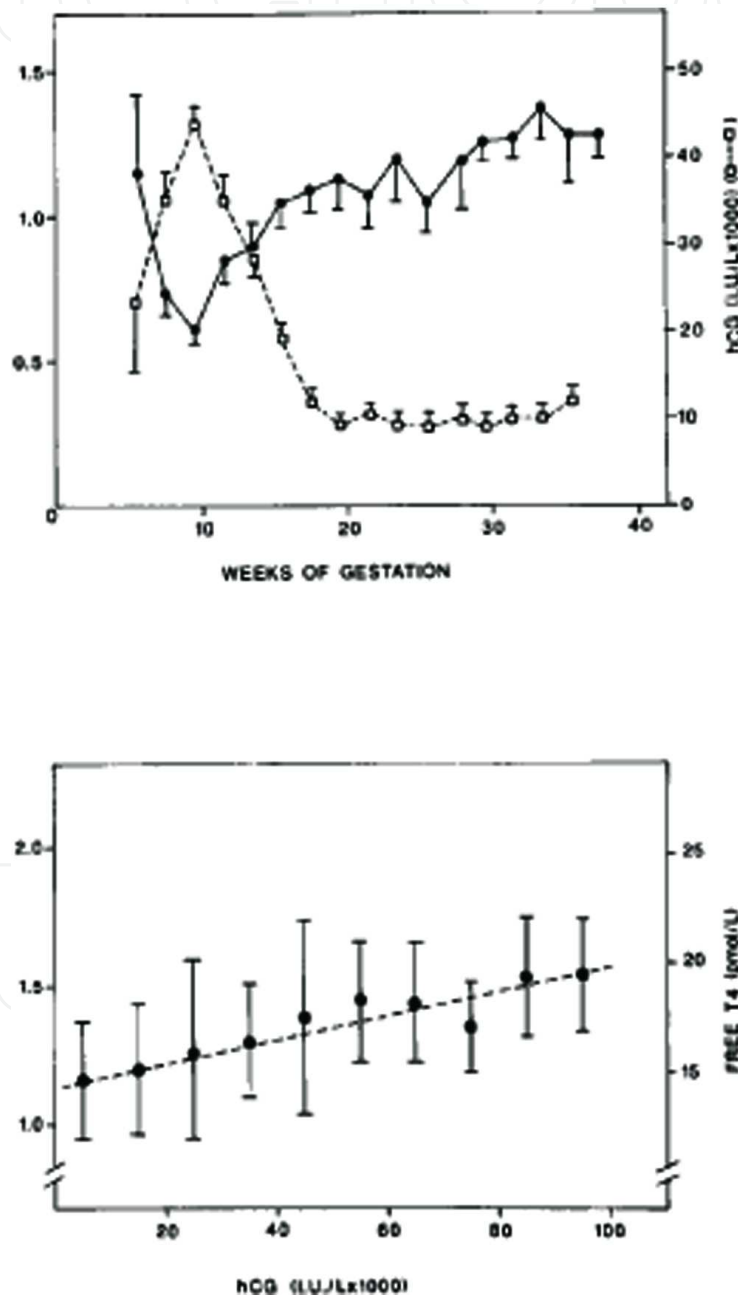


Figure 2. Upper graph, Serum TSH and hCG as a function of gestational age. Lower graph, Scattergram of free T levels in relation to hCG concentrations in the first half of gestation. [28]

In addition to the importance of the hCG peak amplitude on hCG effects on thyroid stimulation and TSH suppression, the duration of exposure to this peak is also important in modulating hCG effects. Thus, in twin pregnancies, where not only the peak hCG values are significantly higher than in single pregnancies (in fact, almost double), but also of much longer duration (6 weeks vs 1 week), more profound and frequent lowering in serum TSH is observed. Among these cases, FT4 levels in the hyperthyroid range accompanied by clinical manifestation of thyrotoxicosis have even been described [27].

2.4. Iodine physiology during pregnancy

During pregnancy, dietary iodine requirements are higher than in nonpregnant women. Three main mechanisms explain this requirement increase: rise in TH production, increase in renal iodine filtration, and passage of a part of the available iodine from maternal circulation to the fetal-placental unit. Beginning in early pregnancy, the glomerular filtration rate of iodide increases by 30% to 50% [29], thus decreasing the circulating pool of plasma iodine. This induces in turn an increase in thyroidal iodine clearance, which reaches 60 ml/mn (versus 17 ml/mn behind pregnancy in sufficient iodine region) [30]. A comparison of pregnant women from various countries demonstrated that peak gestational urinary iodine levels vary, suggesting differences in renal excretion thresholds by regional dietary iodine intake [31]. In addition to the renal leakage of iodine, at midgestation, the fetal thyroid gland has already started to produce thyroid hormones, using iodine pumped in maternal circulation, which exacerbates mother iodine deprivation [32].

The consensus recommendation of the World Health Organization is that the iodine supply should be increased in pregnant and lactating women to at least 200 microg/day [33]. In pregnant women who reside in countries with an iodine sufficient environment (a daily iodine intake of more than 150 mg), iodine losses in the urine and from transfer to the fetus are probably of little importance. In iodine deficient regions, an increase in maternal TSH levels and consequently in thyroid size is observed. If iodine deficiency is severe, TSH increase is insufficient to ensure adequate TH production and hypothyroidism develops (Figure 3).

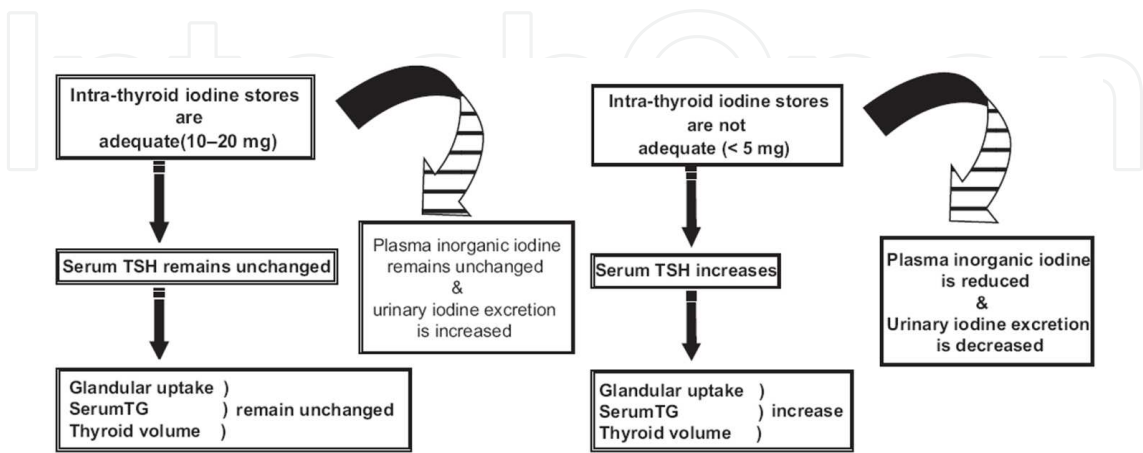


Figure 3. Conceptual models of adequate (left panel) and inadequate (right panel) iodine nutrition and thyroid function [34].

2.5. Gestational modifications of the autoimmune regulation

For a successful pregnancy outcome, the maternal immune system must tolerate the fetus. Therefore, placental trophoblast cells secrete a variety of cytokines and molecules having an immunomodulatory action (table 1). The result is an attenuation of immune responses with a general improvement in autoimmune diseases, including thyroid immune disease [35]

2.6. Fetal thyroid development

Fetal thyroid ontogeny begins at 10-12 weeks of gestation, and is not accomplished until delivery. T4 starts being secreted by 18-20th week of gestation [36]. Before this time, the fetus is dependent on a supply of maternal TH which is essential for early fetal development and, in particular, early central nervous system (CNS) development.

Place event	Adaptation	Result
Local	Trophoblast cells express several immune-modulating molecules (Fas-L, HLA-G and indoleamine 2,3-dioxygenase) as well as secreting a variety of cytokines	- Fas-L induces apoptosis on fetal antigen-reactive maternal lymphocytes -HLA-G inhibits both NK cell function and maturation of dendritic cells -Indoleamine 2,3-dioxygenase catalyzes triptophane in lymphocytes, which is critical in the maintenance of allogenic pregnancy
	T cell	-Decreased CD4, increased CD8 T cells and increasing activity of T regulatory cells -The immune response is turned from Th1 (cellular) to Th2 (humoral), with an increase in Th2 cytokine production
	B cell	Despite the shift to Th2, the relative B cell production and activity are downregulated, leading to a reduction in antibody production
Systemic	Hormonal changes	-Increase in plasma levels of estrogen, progesterone, and corticosteroids -Estrogen produces negative regulation of B cell activity -Progesterone generates variation in cytokine profiles -Corticosteroids induce immune cell apoptosis and immunosuppression
	Recovery of prepregnancy immune function	-Increased titers of serum antibodies, reversed ratio CD4+/CD8+ T cells, and change in cytokine profiles favor Th1 responses

Fas-L, Fas-Ligand; HLA-G, Human leukocyte antigen-G; NK, natural killer; Th1, T helper cell 1; Th2, T helper cell 2

Table 1. Immune Adaptation to Pregnancy [19]

3. Epidemiology

In women of childbearing age, the prevalence of overt hypothyroidism is estimated at 0,3- 0,5% and that of subclinical hypothyroidism at 2-3%. Prevalence rates are similar during pregnancy [2,5]. Three large studies have assessed the prevalence of hypothyroidism in pregnant women. They have concerned respectively 1900, 2000 and 9403 pregnant women. The prevalence of hypothyroidism was similar in the three studies ranging from 2,2 to 2,4%. In the study carried out on 9403 pregnant women, subclinical hypothyroidism was detected in 0,4% of cases [37].

The prevalence of hypothyroidism in pregnancy is strongly linked to the TSH cut-off value used. In a Czech study on more than 5000 women, this prevalence reached 5.6 % if a cut-off at 3.67 mIU/l was used. However, using a cut-off at 2.5 mU/l, the proportion of pregnant women with TSH elevation increased to 16.7 % [38]. The large American study of Blatt et al. showed similar numbers [39].

Defining the true incidence of isolated maternal hypothyroxinemia is rather difficult, because of the differences in diagnostic criteria used to define the condition. In addition, the epidemiological data presently available are somewhat sparse. The issue of the epidemiological impact of isolated hypothyroxinemia was very recently reviewed by Krassas et al. [3], who estimated an overall incidence of approximately 2% in unselected pregnancies. However, there are wide differences among the studies, related mainly to differences in iodine nutrition status. Indeed, in regions where iodine intake is sufficient, as is the case in the United States, the prevalence of isolated hypothyroxinemia ranges between 1.3% [40] and 2.3% [41]. In contrast, in mildly to moderately iodine deficient regions, isolated hypothyroxinemia affects a much higher percentage of women, reaching values up to 25–30% [42,43]. Interestingly, in a very recent study by Henrichs et al. [44] carried out in The Netherlands on a cohort of 3659 women, the prevalence of mild hypothyroxinemia ($FT4 < 10$ th percentile) was 8.5% and that of severe hypothyroxinemia ($FT4 < 5$ th percentile) 4.3%. These figures are significantly higher than those reported in previous studies conducted in iodine sufficient regions [40,42].

4. Causes of hypothyroidism in pregnancy

Worldwide, particularly in mountainous regions and in Central Africa, South America and Northern Asia, the most common cause of hypothyroidism is iodine deficiency [45]. Because of increased thyroid hormone production, increased renal iodine excretion, and fetal iodine requirements, dietary iodine requirements are higher in pregnancy than they are for non pregnant adults [29]. Women with adequate iodine intake before and during pregnancy have adequate intra-thyroidal iodine stores and have no difficulty adapting to this increased demand. In these women, total body iodine levels remain stable throughout pregnancy [46]. However, in areas of even mild to moderate iodine deficiency, total body iodine stores, as reflected by urinary iodine values, decline gradually from the first to the third trimester of pregnancy [47].

It is difficult to determine the severity of iodine deficiency in pregnant women. The commonly used index for assessing iodine status in a population is the median urinary iodine concentration (MUIC) as determined from a casual or spot urine sample. A MUIC > 100 microg/l is indicative of adequate iodine status in children, men and non pregnant women. A MUIC of 50-99 microg/l, 20-49 microg/l and < 20 microg/l are indicative of mild, moderate and severe iodine deficiency respectively [48]. The World Health Organization estimates that about two billion people are iodine deficient [48].

In areas of iodine sufficiency, the most common cause of hypothyroidism in pregnant women is chronic autoimmune thyroiditis [49]. Anti-thyroid antibodies were found in 18% of Australian women in the late first trimester and were associated with subtle effects on thyroid function [50]. In a prospective population study of 9471 pregnant women in the United States in whom serum TSH was measured during the second trimester, hypothyroidism was diagnosed in 2.2% of the cohort, and autoimmune thyroiditis was present in 55% of women with SCH and more than 80% in women with OH [37].

Thyroidectomy, ablative iodine therapies or anti-thyroid drugs are other important causes of primary hypothyroidism [6].

5. Consequences of maternal hypothyroidism

Thyroid diseases are common in women of childbearing age and it is well known that untreated thyroid disturbances result in an increased rate of adverse events. Evaluation of thyroid status in pregnancy requires an understanding of pregnancy-associated changes in thyroid function tests and how they vary by trimester. The spectrum of hypothyroidism in pregnancy includes subclinical and overt hypothyroidism, and also isolated thyroid peroxidase antibody positivity and isolated hypothyroxinemia. These patterns, in some situations, may be related to iodine status, selenium status, or underlying thyroid disease.

5.1. Consequences of maternal hypothyroidism

Abnormal maternal thyroid parameters are associated with adverse pregnancy outcomes, with consequences for both mother and child. Although various studies evaluated maternal thyroid parameters during the first half of pregnancy, little is known about their relations with thyroid parameters of the child. There are correlations between maternal thyroid parameters and gestational age during the first half of pregnancy and a substantially increased risk of SCH in TPOAb-positive mothers [51]

5.1.1. Influence of maternal thyroid disease on fetal development

Any thyroid disease of the mother with disturbances in the functional state of the gland could induce an adverse influence on the course of pregnancy. Furthermore, it can be associated with adverse consequences on fetal development [37].

Enough evidence has been accumulated over the years about the role of T4 in normal development of the fetal brain. The presence of specific nuclear receptors of thyroid hormones in fetal brain at 8 weeks of gestation, the presence of FT4 in the coelomic and amniotic fluids and demonstration of the transfer of maternal thyroid hormones across the placenta, underline the role of thyroid hormones in fetal brain development. Complex interactions between the type II and type III iodothyronine deiodinases during gestation help to fine tune the supply of adequate amounts of T3 required for normal brain development [52].

Because thyroid hormones are crucial to fetal brain and nervous system development, uncontrolled hypothyroidism, especially during the first trimester, can affect the fetal's growth and brain development and can alter the neurocognitive development of the offspring [4].

Maintaining maternal euthyroidism during pregnancy is important for growth and development, in particular neurodevelopment of the fetus. Even subtle changes in thyroid function of the pregnant woman can cause detrimental effects for the fetus. In the first trimester, the foetus relies solely on the thyroid hormones T4 and T3 and iodine from the mother. Later in pregnancy and during lactation, maternal TH still contribute significantly to fetal thyroid homeostasis [32]. The impact of overt maternal hypothyroidism on pregnancy is profound. The severity, timing of onset and duration, as well as postnatal management, all influence fetal and neonatal brain development. It is now believed than even mild maternal hypothyroidism (from mild iodine deficiency, thyroid autoimmunity, or thyroid under-replacement) may affect fetal brain development [5,6]

Adequate thyroid hormone is critical for cerebellar development. Developmental hypothyroidism induced by iodine deficiency during the perinatal period results in permanent impairments of cerebellar development with an unclear mechanism [52].

Hypothyroidism during pregnancy has been also associated with impaired cognitive development and increased fetal mortality [37].

5.1.2. b-Obstetrical complications of maternal hypothyroidism

Women with hypothyroidism have decreased fertility; even if they conceive, risk of abortion is increased, and risk of gestational hypertension, anemia, abruption placenta and postpartum hemorrhage is increased [49]

The association between overt maternal hypothyroidism, particularly in early pregnancy, and adverse obstetric outcomes is well-established. In a study of women during the second trimester of pregnancy, the prevalence of fetal death was over 4-fold higher in mothers with a TSH concentration ≥ 6 mIU/L, compared to those whose mothers had a TSH < 6 mIU/L (3.8% vs. 0.9%) [37]

Untreated hypothyroidism is associated with increased risk of preeclampsia, low birth weight, placental abruption, miscarriage, and perinatal mortality [53,54]. In addition to an increased risk of low birth weight, hypothyroidism (as defined by increased serum TSH) early and late in pregnancy may also increase the rate of caesarean section [55].

Raised maternal serum TSH in the second trimester is also associated with an increased rate of fetal death after 16 weeks' gestation [37]. Other studies have found that although women treated for hypothyroidism may have higher rates of preeclampsia and caesarean section than euthyroid women, they are not at any higher risk for adverse outcomes such as fetal anomalies, fetal demise, or preterm birth. In hypothyroidism there are placental hypoxic changes. This may be responsible for thick meconium, stained liquor and/or fetal distress [37].

5.1.3. Neonatal and long-term complications of maternal hypothyroidism

In addition to adverse obstetrical outcomes, maternal hypothyroidism is associated with adverse neonatal outcomes. As the fetus does not begin to produce its own TH until approximately 12 weeks' gestation, it is solely dependent on maternal T4 during early gestation [56,57]. After 12 weeks, thyroid hormone in the fetus continues to be partly supplied by the mother [58].

Untreated maternal hypothyroidism can lead to preterm birth, low birth weight, and respiratory distress in the neonate.

Many studies [4,59] have conclusively proved that children born to mothers with hypothyroidism had a significantly increased risk of impairment in IQ scores, neuropsychological developmental indices and learning abilities. This risk applies to children born not only of untreated women, but also women with suboptimal supplementation.

Children born to uncontrolled hypothyroid mothers are at increased risk of psychomotor development alterations and diminished school performance, reaching recognition and IQ scores [60]

5.1.4. Subclinical hypothyroidism

The risk of pregnancy complications is greater in women with overt, rather than subclinical hypothyroidism [49].

Wang et al. reported an association between SCH and increased risk of spontaneous abortions, but not with gestational hypertension, premature delivery, anemia, postpartum hemorrhage, low APGAR scores, and low birth weight [61].

During pregnancy, TSH levels higher than 4.5 mIU/l have been related to impaired fetal neurological and psychomotor development and an increased risk of premature labor, preeclampsia, and abruption placenta [53,59]

Although the majority of large-scale, well-designed studies depict a consistent adverse impact from mild to moderate to moderate maternal hypothyroidism, some studies are contradictory [49,62]

5.2. Thyroid auto-immunity

Multiple observational studies [63,64,65] and 2 meta-analyses [66,67] have confirmed a 2-4 fold risk of miscarriage among euthyroid TPO antibody-positive women, compared to euthyroid

TPO antibody-negative women. Some studies [68,69] but not all [70,71], have also found associations between thyroid autoimmunity and increased rates of recurrent miscarriage.

The presence of maternal thyroid antibodies has also been associated with a 3-fold risk for premature delivery before 37 weeks gestation [72], postpartum thyroiditis [73], thyroiditis after pregnancy loss [74], and placental abruption. Moreover, the positivity for thyroid autoantibodies in euthyroid pregnant women affects neuropsychological development of the offspring per se [75].

The reasons for the associations between anti-thyroid antibodies and obstetric complications remain unclear. They may be related to a direct effect of the anti-thyroid antibodies, or the anti-thyroid antibodies may serve as a marker for other causative autoimmune syndromes. Alternatively, anti-thyroid antibodies may simply indicate limited thyroid functional reserve [1], suggesting that the association between TPO antibody positivity and obstetric complications may be confounded by even mild hypothyroidism obtained during pregnancy.

Although positive association exists between the presence of thyroid antibodies and pregnancy loss, universal screening for antithyroid antibodies and possible treatment cannot be recommended at this time. However, women with elevated anti-TPO antibodies are at increased risk for miscarriage, preterm delivery and progression of hypothyroidism. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy.

5.3. Isolated maternal hypothyroxinemia

Isolated maternal hypothyroxinemia is defined as a low FT4 and normal TSH, which can be found in approximately 1% to 2% of pregnancies. In some studies, infants and toddlers whose mothers had isolated maternal hypothyroxinemia during gestation (12 to 20 weeks) had lower mean intelligence, psychomotor, or behavioral scores compared with children born to women with normal thyroid function during gestation [60].

In another study, risks of adverse pregnancy outcomes were not increased in over 200 pregnant women with isolated hypothyroxinemia [40].

However, till date, no study has shown benefit from levothyroxine treatment of isolated hypothyroxinemia during pregnancy, on pregnancy outcome or subsequent infant development.

6. Diagnosis

Clinical semiology of hypothyroidism may be confused or changed by signs of the pregnancy. Tachycardia and cardiovascular erethism, so frequent during pregnancy can mask some signs of pregnancy. On the contrary, other common symptoms during pregnancy can be mistaken for signs of hypothyroidism: fatigue, fluid retention, muscle cramps, constipation, dry skin and hair. Obvious signs such as bradycardia, cold sensitivity, hyporeflexia, paresthesia of extremities, are present in frank hypothyroidism where fertility rate is so small that the possibility of pregnancy is quite unlikely [76].

Because many women may remain asymptomatic, particular attention is required from obstetrical care providers for this condition to be diagnosed and to evaluate more systematically thyroid function when women attend the prenatal clinic for the first time. Only thyroid function tests confirm the diagnosis [77]. Their results differ in healthy pregnant women from those of healthy non pregnant women. This calls for pregnancy-specific and ideally trimester-specific reference intervals for all thyroid function tests but in particular for the most widely applied tests, TSH and FT4 [78]. If a non pregnant reference range is used, many maternal thyroid diseases could be potentially misclassified [79]. Some researchers have established trimester-specific reference intervals for a local population (table 2)

1 st author [reference]	1 st trimester	2 nd trimester	3 rd trimester
Stricker R [79]	1.04 (0.09–2.83)	1.02 (0.20–2.79)	1.14 (0.31–2.90)
Haddow JE [80]	0.94 (0.08–2.73)	1.29 (0.39–2.70)	-
Panesar NS [81]	0.80 (0.03–2.30)	1.10 (0.03–3.10)	1.30 (0.13–3.50)
Soldin OP [82]	0.98 (0.24–2.99)	1.09 (0.46–2.95)	1.20 (0.43–2.78)
Bocos-Terraz JP [83]	0.92 (0.03–2.65)	1.12 (0.12–2.64)	1.29 (0.23–3.56)
Marwaha RK [84]	2.10 (0.60–5.00)	2.40 (0.43–5.78)	2.10 (0.74–5.70)
Wang QW [85]**	1.00 (0.02–3.65)	1.26 (0.36–3.46)	1.50 (0.44–5.04)

*Median TSH in mIU/l, with parenthetical data indicating 5th and 95th percentiles [80,81,84] or 2.5th and 97.5th percentiles [79,82,83,85]. **Self-sequential longitudinal reference intervals

Table 2. Sample trimester-specific reference intervals for serum TSH*

The reference range for TSH is lower throughout pregnancy; both the lower normal limit and the upper normal limit of serum TSH are decreased by about 0.1-0.2 mIU/l and 1 mIU/l respectively, compared with the customary TSH reference interval of 0.4-4 mIU/l of non pregnant women. Serum TSH and its reference range rise gradually in the second and third trimesters, except for the study of Marwaha et al. [84], but it is noteworthy that the TSH reference interval remains lower than in non pregnant women [80,81,85].

There are slight but significant ethnic differences in serum TSH concentrations. Black and Asian women have TSH values that are on average 0.4 mIU/l lower than in white women, these differences persist during pregnancy [86]. Pregnant women of Moroccan, Turkish or Surinamese descent residing in the Netherlands have TSH values 0.2-0.3 mIU/l lower than Dutch non pregnant women [87]. TSH concentrations are lower in multiple pregnancies since hCG concentrations are higher [88].

A serum TSH elevation suggests primary hypothyroidism, and serum T4 levels further distinguish between SCH and OH. Only 0.03% of serum total T4 (TT4) content is unbound to serum proteins and is the free T4 available for tissue uptake. Measuring FT4 in the presence of high concentrations of bound T4 has proved challenging especially in abnormal binding-protein states such as pregnancy [78]. According to the recommendations of the American Thyroid Association [78], the optimal method to assess serum FT4 during pregnancy is the measurement of T4 in the dialysate or ultrafiltrate of serum samples employing on-line

extraction/liquid chromatography/tandem mass spectrometry (LC/MS/MS). If this method is not available, the free T4 index (adjusted T4) appears to be a reliable assay during pregnancy [77]. The normal ranges for FT4 index are calculated by TT4xT3 uptake or a ratio of TT4 and TBG, but trimester-specific reference intervals for FT4 index have not been established in a reference population [78]. Reference ranges provided by the manufacturers of most T4 measurement kits have been established using pools of non pregnant normal sera [2] and such reference ranges are not valid during pregnancy. The Endocrine Society in 2012 recommended caution in the interpretation of serum FT4 levels during pregnancy and that each laboratory establishes trimester-specific reference ranges for pregnant women [77]. The non pregnant TT4 range (5-12 microg/dl or 50-150 nmol/l) can be adapted in the second and third trimesters by multiplying this range by one and a half-fold [77].

A TSH of 2.5 mIU/l is now accepted as the upper limit of normal for TSH in the first trimester [77]. OH is defined as an elevated TSH (>2.5 mIU/l) in conjunction with a decreased FT4 concentration. Women with TSH levels of 10.0 mIU/l or above, irrespective of their FT4 levels are also considered to have OH. SCH is defined as a serum TSH between 2.5 and 10.0 mIU/l with a normal FT4 concentration. Isolated hypothyroxinemia is defined as a normal maternal TSH concentration in conjunction with FT4 concentrations in the lower 5th or 10th percentile of the reference range [78].

7. Specific interventions

Over the last decade there has been enhanced awareness of the appreciable morbidity of thyroid dysfunction, particularly thyroid deficiency.

Well controlled hypothyroidism does not usually pose major problems in pregnancy and there may be good evidence that the benefits of appropriate interventions largely outweigh the potential risks associated with treatment. Uncertainty exists about the benefits of treatment of women with subclinical hypothyroidism. The overall lack of evidence precluded a recommendation for universal screening [77].

We present here main interventional studies, that compared an intervention for hypothyroidism and/or subclinical hypothyroidism in pregnancy with another intervention, no treatment or placebo, and those that evaluated effects of iodine supplementation during pregnancy, and their effects on maternal and fetal outcomes (Table 3)

7.1. Interventions using Levothyroxine (LT4)

Levothyroxine was compared to no treatment or to no change in treatment during the pregnancy in four randomized controlled trials studies:

- *Negro Ret al*, in a study published in 2006 [72] evaluated 984 pregnant women for autoimmune thyroid disease. Were excluded pregnant women with pre-existing thyroid dysfunction. 11.7% (115 participants) were TPO antibody positive (TPOAb+). They were divided into two groups. Group A (n:57) was treated with LT4, and group B (n:58) was not treated.

The 869 TPOAb- patients (group C) served as a control group. The dosage of LT4 varied dependently on TSH and TPOAb titers. The rates of obstetrical complications including gestational hypertension, pre-eclampsia, placental abruption, miscarriage, and preterm birth as well as serum TSH and FT4 were measured. Other outcomes included clinical characteristics of new borns (weight, height, cranial perimeter, Apgar score).

At baseline, TPOAb+ women had higher TSH compared with TPOAb- throughout gestation, FT4 values were lower and TSH higher in group B compared with groups A and C. Groups A and C showed a similar miscarriage rate which was lower than group B. Rate of premature deliveries was higher in group B than groups A and C. Substitutive treatment with LT4 was than able to lower significantly the chance of premature delivery with a trend to a reduced risk miscarriage. Main limitations of this study were the absence of placebo group, the blinding of the outcome assessor was unclear.

- *Rotondi M et al.* [89] in a study published in 2004 conducted a prospective parallel randomized trial. 25 patients with compensated hypothyroidism of different etiology (thyroidectomized and Hashimoto's thyroiditis) and anticipating pregnancy were assigned into two groups. In group 1 (modified n:14), the LT4 dose was adjusted to maintain low-normal TSH levels. Group 2 (unmodified n:11) continued the same treatment. Thyroid function tests were performed pre-conception (at least 60 days from the LT4 increase for the group 1 participants) and at the first post-conception endocrinological visit.

Pre-conception thyroid function evaluation demonstrated significantly higher FT4 and lower TSH in group 1. At the first post-conception thyroid function evaluation, all women in group 1 showed adequate serum FT4 levels while in group 2, three patients had low-normal FT4 levels and one had low FT4 level. The difference was statistically significant between the two groups. None of the Hashimoto's affected patients showed low or low-normal FT4 levels. This study suggests that in hypothyroid women anticipating pregnancy, the pre-conception adjustment of LT4 doses may result in adequate maternal thyroid function up to the first post-conception evaluation. The main limitation of this study was the absence of blinding of the participants, the blinding of the clinicians and outcome assessors was unclear.

- *Negro R et al* [7] in a trial published in 2010 randomly assigned 4562 women in the first trimester to the universal screening or case finding group. Women in both groups were stratified as high risk or low risk based on risk factors for thyroid disease. All women in the universal screening group (n:2280) and high risk women (n:454) in the case-finding group (n:2282) were immediately tested for FT4, TSH and TPO Ab. Low risk women in the case-finding group had their sera tested post-partum. Women with TSH above 2.5 mIU/l and TPOAb+ were given LT4. Women with undetectable TSH and elevated FT4 were given anti-thyroid medication. The rates of obstetrical complications and neonatal outcomes were evaluated.

No significant differences were seen in adverse outcomes between the case-finding and universal screening groups. However, low-risk women in the universal screening group had fewer overall adverse outcomes than low-risk women in the case-finding group. Moreover, more low risk women in the universal screening group with abnormal thyroid function (so

treated) avoided adverse outcomes more often than low risk women in the case finding group with abnormal thyroid function (who were not detected and therefore not treated). Main limitation of the study was the lack of direct comparison of treatment and of treatment and non-treatment among the high risk women, and that a power analysis was not performed to determine the sample size

- *Lazarus JH et al.* [90] in a study published in 2012 conducted a randomized trial of antenatal hypothyroidism screening with selective treatment, and assessment of childhood cognitive function. 21846 pregnant women at a median gestational age of 12 weeks 3 days, provided blood samples for measurement of TSH and FT4. Women were assigned to a screening group (n:10924), in which measurements were obtained immediately, or a control group (n: 10922) in which serum was stored and measurements were obtained shortly after delivery. Women with TSH levels >97.5th centile and/or FT4 levels <2.5th centile were designated positive and women in the screening group were prescribed LT4. The primary outcome was IQ at 3 years of age in children of women with positive results, as measured by psychologists who were unaware of the group assignments.

The proportions of women classified as having positive screening results were 4.6% in the screening group and 5% in the control group. 19% of women required LT adjustment. There were no significant difference between IQ scores in the screening and control positive groups, by intention-to-treat analysis. There were no differences between the proportions of children with IQ of less than 85 between the screening and control group. An on-treatment analysis showed no significant difference.

In this study, antenatal screening and treatment for hypothyroidism from about 12 weeks of pregnancy showed no benefit in childhood cognitive function assessed at age three.

Main limitations of this study were: about 24% of the women were lost to follow-up with similar proportions, but 19 women from the screening and 41 from the control group declined to have their child assessed, screening was performed too late in gestation to have a major influence on brain development, childhood cognitive assessment was performed early, and IQ is not sufficient to evaluate cognitive function

7.2. Interventions using selenium

Negro R et al. [91] in his placebo controlled trial published in 2007, examined whether selenium supplementation during and after pregnancy reduces the rate of postpartum thyroiditis and permanent hypothyroidism. Of the 2143 euthyroid pregnant women studied, 7.9% were TPOAB+. During pregnancy and the postpartum period, 77 TPOAb+ women received Selenomethionine 200 microg/d (group S1), 74 TPOAb+ women received placebo (group S0) and 81 TPO Ab- age-matched women were the control group (group C). All the women were advised to use iodized salt. Thyroid function tests were performed at 20 and 30 weeks, at delivery and months 1-2, 5,9 and 12 postpartum. Selenium concentrations were measured at the first visit (mean 9.4 ± 2.7 gestation), at 20 and 30 weeks' gestation, at delivery and 6 and 12 months postpartum. Participants also underwent thyroid ultrasound scanning to assess for thyroiditis at the first visit, at delivery and at 12 months postpartum. Postpartum thyroiditis and permanent hypothyroidism were significantly lower in group S1 compared with S0 (p<0.01).

Main limitation was the loss to follow-up data; in the selenium group 8/85 and in the placebo group 10/84.

7.3. Interventions using iodine

- In severe iodine deficiency areas

Cao XY et al. [92] in a study published in 1994 examined the effect of iodized oil given during pregnancy on neurological outcomes in a severely iodine-deficient area of China (n = 295). Babies were followed for two years. Three independent measures of neural development were used: the results of neurologic examination, the head circumference and indexes of cognitive and motor development. Children of mothers given iodine earlier in pregnancy had improved all neurologic outcomes compared to mothers given iodine later in pregnancy. Treatment later in pregnancy may improve brain growth and developmental achievement slightly, but it does not improve neurologic status.

O'Donnell KJ et al. [93] in their study published in 2002 evaluated growth and development of 689 children (range 4 to 7.3 years whose mothers received iodine during pregnancy, and children who received iodine first in their 2nd year) in a part of China's Province which has the lowest levels of iodine in water and soil ever recorded. Head circumference but not height was improved for those whose mothers received iodine during pregnancy (compared with those receiving iodine at age 2) and for those supplemented before the end of the 2nd trimester (relative to those supplemented during the 3rd trimester). Iodine before the 3rd trimester predicted higher psychomotor test scores for children relative to those provided iodine later in pregnancy or at 2 years. Results from the test for cognitive development resulted in trend only differences between those children supplemented during pregnancy versus later.

- In moderate to mild iodine deficiency areas

In 2009, two randomized trials were published investigating the effect of iodine supplementation in moderately iodine deficient pregnant women on neurodevelopment of their children. *Berbel P et al.* [94] recruited three groups of pregnant women living in Spain at different phases of gestation; the first group of women had T4 concentrations >20th percentile at recruitment (>0.92 ng/dL at 4–6 weeks gestation), while the second and third groups of women had T4 concentrations <10th percentile (<0.83 ng/dL) at 12–14 weeks gestation and near term, respectively. All three groups of women were supplemented with 200 µg of iodine until the end of lactation. When the children were 18 months old, the development quotient of children in mothers supplemented in the first group was significantly higher than that of children whose mothers received supplements from 12–14 weeks gestation and near term. A limitation of this study was the small numbers of children tested, with less than 20 children in each of the three groups. Furthermore, the women supplemented later in pregnancy or at term were specifically selected because they had low FT4 in pregnancy, while the women supplemented earlier in pregnancy had a higher FT4, thus a difference in FT4 rather than the iodine supplementation may account for the findings. A second Spanish study conducted in an area of moderate iodine deficiency by *Velasco I et al.* [95], evaluated the psychological development of infants aged 3 to 18 months whose mothers (n:133) had received 300 microg of potassium iodide during the first

trimester of their pregnancy and compared with infants whose mothers had received no iodine supplements (n:61). Were evaluated the neuropsychological status of the children and levels of TSH, FT3, FT4, and urinary iodine. Those children whose mothers had received iodine supplement had a more favorable psychometric assessment than those of the other group of mothers. A limitation of this study was that children were tested at different ages in this study (5.5 months *vs.* 12.4 months), and the possible presence of confounding variables not controlled for in this study. Finally, both studies were not randomized, double-blind, placebo-controlled trials, and although they suggest that neurodevelopment in the child may be adversely affected by moderate iodine deficiency, they are certainly not definitive

Author (year)	Country	n	Methods	Outcome measures
Negro R (2006) [72]	Italy	984	Pregnant women TPOAb+ randomized to levothyroxine vs no treatment	Miscarriage, gestational hypertension, pre-eclampsia, preterm birth, placental abruption
Rotondi M (2004) [89]	Italy	25	Women with overt hypothyroidism anticipating pregnancy randomized to adjusted dose of LT4 to have TSH low-normal or unmodified treatment	FT4, FT3, TSH
Negro R (2010) [7]	Italy	4562	Women in first trimester pregnancy randomized to universal screening group or case-finding group. LT4 was given if TSH"/>2.5 mIU/l and TPOAb+	Obstetrical complications (miscarriage, gestational hypertension, preeclampsia..) and neonatal outcomes (weight, preterm delivery, Apgar score...)
Lazarus JH (2012) [90]	United Kingdom, Italy	21846	Pregnant women at 15weeks 6days or less provided blood samples for TSH and FT4, randomized to screening group or control group. Women with TSH"/>97.5 and/or FT4<2.5 th centile in the screening group were given LT4	IQ of children at age 3 years
Negro R (2007) [91]	Italy	2143	Euthyroid pregnant women studied. TPOAb+ randomized to receive selenomethionine 200 microg/d or placebo	Thyroid function tests, thyroid antibodies, thyroid ultrasound
Cao XY (1994) [92]	China	295	Pregnant women in severely iodine deficient area given iodized oil	Neurologic examination, head circumference, indexes of cognitive and motor development
O'Donnel KJ (2002) [93]	USA	689	A group of pregnant women received iodine during pregnancy and a group of children received iodine during their 2 nd year	Head circumference, height, psychomotor and cognitive development
Berbel P (2009) [94]	Spain	96	Women 4–6 weeks gestation with FT4 "/>20th percentile (Group1) vs. women with FT4 < 10th percentile at 12–14 weeks (Group 2) or at 37–40 weeks (Group3) given iodine 200 microg /d until end of lactation.	Brunet-Lezine developmental quotient
Velasco I (2009) [95]	Spain	191	Women <10 weeks gestation (Group 1) vs. last month of pregnancy (Group 2) given iodine 300 microg /d until end of lactation	Bayley Psychomotor Development Index

Table 3. Interventional studies for clinical and subclinical hypothyroidism in pregnancy

8. Screening

In the past several years, there has been considerable discussion about whether all pregnant women should be screened in order to identify and treat thyroid dysfunction. Screening is defined as 'the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not' [96]. Ideally all the following criteria should be met: The Condition should be an important health problem, its epidemiology and natural history should be well known. The test should be a simple, safe, precise and validated with agreed reference range. The treatment should be effective, there should be agreed evidence based policies covering which subjects need treatment and the appropriate treatment to be offered. The Screening Program should be effective in reducing mortality or morbidity (evidence from high quality Randomized Controlled Trials); should be clinically, socially and ethically acceptable to health professionals and the public. The benefit from the screening program should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment). The opportunity cost of the screening program should be economically balanced in relation to expenditure on medical care as a whole (cost benefit and/or cost effectiveness analyses) [97].

In the case for thyroid screening in pregnancy, most of the above points are satisfied. Both OH and SCH are prevalent. Serum TSH is relatively inexpensive, widely available and is a reliable test in pregnancy, assuming that trimester-specific reference ranges are applied [78]. The adverse maternal and fetal effects associated with OH have been clearly demonstrated. The problem is still represented by the halo of uncertainty that surrounds clinical entities such as SCH and isolated hypothyroxinemia. The lack of high quality randomized controlled trials in these two conditions had led to mixed viewpoints among members of the American Thyroid Association [78] and the Endocrine Society [77]. Both agree that there are not enough data for or against universal screening but also acknowledge that lack of evidence of benefit doesn't mean that there is no benefit.

In their recent guidelines, the American Thyroid Association [78], and the Endocrine Society [77] recommend prenatal measurement of serum TSH in women at high risk for thyroid illness on the basis of their medical history, physical exam, or prior chemical data. (Table 4)

There is insufficient evidence to recommend for or against screening all women for thyroid antibodies in the first trimester of pregnancy [78]. Universal screening for the presence of anti-TPO antibodies either before or during pregnancy is therefore not recommended [77]. However, women with elevated anti-TPO antibodies are at increased risk for miscarriage, preterm delivery, progression of hypothyroidism, and postpartum thyroiditis. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy.

Women over age 30 years
Women with a family history or autoimmune thyroid disease or hypothyroidism
Women with a goiter
Women with thyroid antibodies, primarily thyroid peroxidase antibodies
Women with symptoms or clinical signs suggestive of thyroid hypofunction
Women with type 1 diabetes mellitus, or other autoimmune disorders
Women with infertility
Women with a prior history of miscarriage and preterm delivery
Women with prior therapeutic head or neck irradiation or prior thyroid surgery
Women currently receiving levothyroxine replacement
Women living in a region presumed with iodine deficiency

Table 4. Recommended patient profiles for targeted thyroid disease case finding in women seeking pregnancy, or newly pregnant [77]

9. Management

Hypothyroidism is treated with synthetic thyroid hormone called Levothyroxine (LT4), a medication which is identical to the T₄ made by the thyroid. Synthetic thyroxine is safe and necessary for the well-being of the fetus if the mother has hypothyroidism. It is strongly recommended not to use other preparations such as T3 or desiccated thyroid [78]. There are a variety of approaches to the management of thyroxine replacement in known hypothyroid women at the time of pregnancy that are all effective for maintaining a normal range during pregnancy. Women with preexisting hypothyroidism will need to increase their prepregnancy dose of thyroxine to maintain a normal thyroid function.

Thyroid function should be checked every 6 to 8 weeks during pregnancy.

9.1. Overt hypothyroidism and pregnancy

9.1.1. Pre-pregnancy

Physicians should consider diagnosis of hypothyroidism in patients with infertility or menstrual disorders, medical therapy should be optimized and pregnancy delayed until good control is achieved [98].

9.1.2. Pregnancy

In a newly diagnosed hypothyroid patient, a full replacement thyroxine dose should be instituted immediately, assuming there are no abnormalities in cardiac function.

Thyroxine requirement increases in pregnant patients as early as fifth week of pregnancy [98]. Hypothyroid women who are already on thyroxine prior to pregnancy need to increase their daily dosage, on an average, by 30-50% above preconception dosage as soon as pregnancy is diagnosed [77]. The adjustment is based on results of thyroid function tests. Thyroxine replacement should be given at a dose that insures a serum FT4 level at the upper end of normal range for each trimester of pregnancy and a serum TSH level < 2.5 mIU/L in the first trimester or 3 mIU/l in the second and third trimesters. In women who have had a thyroidectomy for thyroid cancer, it is necessary to suppress TSH secretion [77].

Treatment should be initiated at a dose of 100–150 microgm/day or titrated according to body weight (2.0–2.4 micrograms/kg body weight/day). In diagnosed cases, as thyroxine requirements increase, dosage adjustments are required. Suggested mechanisms for this increased requirement include an elevated extrathyroidal pool of T4; the need to saturate large quantities of TBG; increased degradation of T4; reduced absorption of T4, especially if taken with iron supplements; and increased transfer of T4 from mother to fetus. Because a similar increased requirement is seen in hypothyroid post menopausal women who are given estrogen replacement, this increased demand in pregnancy may be caused by increased estrogen production [99].

Dose of thyroxine also depends on the etiology of hypothyroidism. In disorders with very little residual tissue, like radioiodine ablation or extensive thyroid surgery, increment in thyroxine dosage is greater than women with Hashimoto's thyroiditis, who usually have some residual thyroid tissue. Women should be followed up every 4–6 weeks with serum TSH value, till delivery, to facilitate periodic adjustment of LT4 supplementation. [77]

Thyroxine absorption is decreased by certain drugs including iron and calcium supplement. Thyroxine is best taken on an empty stomach and four hours apart from iron supplements or soy products. [32].

When adequate control is achieved, no specific measures are needed for labour and delivery. However, when large goiter causes respiratory compromise, anesthetic or surgical advice may be required [100].

c-After delivery, hypothyroid women need to decrease the LT4 dosage they received during pregnancy to prepregnancy dose and have their serum TSH level re-evaluated after 6 weeks [77].

9.1.3. Post-partum follow-up: At post-partum, two patterns of thyroid dysfunction can be discerned

- Postpartum thyroiditis characterized by transient hyperthyroidism or transient hyperthyroidism followed by transient or rarely permanent hypothyroidism,
- Postpartum exacerbation of chronic Hashimoto's thyroiditis leading to transient or permanent hypothyroidism.

The hyperthyroid phase of postpartum thyroiditis is treated with a beta-adrenergic antagonist drugs. Transient hypothyroidism is treated with LT₄, which may be continued till six months and then tapered to determine if the hypothyroidism is permanent. Thyroid function tests should be monitored for at least 6 months after delivery [78].

9.2. Subclinical hypothyroidism and pregnancy

Since maternal morbidity as well as prenatal morbidity and consequences on the neuropsychological development of the child have been reported in subclinical hypothyroidism, most guidelines recommend thyroxine replacement in women with subclinical hypothyroidism. Association studies have yielded conflicting results regarding outcomes such as miscarriage, hypertension, placental abruption, and preterm delivery, and to date, one single center has demonstrated a significant reduction in obstetrical and neonatal complications when subclinically hypothyroid women are treated from the first trimester [3,7].

The endocrine guidelines 2012 confirm the suggestion of treating subclinical autoimmune hypothyroidism with LT₄ because the potential benefits from treatment outweigh the risk of potential adverse events [77]. The panel also recommends treating antibody-negative women who have subclinical hypothyroidism. Despite the absence of relevant single center, this recommendation seems reasonable given that independent of thyroid autoimmunity, an increased TSH level is associated with a miscarriage risk, and an elevated TSH at the beginning of pregnancy may predispose the mother to further impairment of thyroid function in the following months [77].

9.3. Isolated hypothyroxinemia

Its management is controversial and requires further study. “Partial replacement therapy” with LT₄ may be initiated at the discretion of the physician, with continued monitoring [77]. This recommendation directly leads to another point examined in the guidelines: awareness about the possible inaccuracy of serum FT₄ measurement in pregnancy.

The absence of a universally accepted trimester-specific reference range (and the common absence of each single laboratory-specific reference range) is an issue that makes defining cutoff values difficult and complicates clear identification of isolated hypothyroxinemia as a clinical entity. [77]

9.4. Iodine intake during pregnancy

Iodine is an essential nutrient required for thyroid hormone production and is primarily derived from the diet and from vitamin/mineral preparations. The Institute of Medicine recommended dietary allowances to be used as goals for individual total daily iodine intake (dietary and supplement) are 150 microg/d for women planning a pregnancy, 220 microg/d for pregnant women, and 290 microg/d for women who are breastfeeding [101]. WHO recommends 250 microg/d for pregnant women and for lactating women [102]. Iodine intake during pregnancy should not exceed twice the daily recommended nutrient intake for iodine,

i.e. 500 microg iodine per day [77]. To reach the daily recommended nutrient intake for iodine, multiple means must be considered, tailored to the iodine intake level in a given population.

Different situations must therefore be distinguished:

1. Countries with iodine sufficiency and/or with a well-established universal salt iodization (USI) program;
2. Countries without a USI program or with an established USI program where the coverage is known to be only partial
3. Remote areas with no accessible USI program and difficult socioeconomic conditions.

The Endocrine Society recommend once-daily prenatal vitamins containing 150–200 microg iodine, in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant women taking prenatal vitamins are protected from iodine deficiency. Ideally, supplementation should be started before conception.

10. Conclusion

Thyroid hormone production increases in pregnancy and requires increased iodine intake. Serum TSH concentrations should be interpreted in the context of pregnancy physiology. Thyroid function and thyroid antibody screening during pregnancy is controversial. Further research is needed to determine whether mild maternal hypothyroidism or positive thyroid antibodies are associated with obstetric complications.

Maternal hypothyroidism is a disorder with great potential to adversely affect maternal and fetal outcomes. If the condition is detected early, it is easy to treat, with very little detriment to the mother and the fetus. Hence, this condition needs early detection, prompt initiation of treatment, adequate follow-up and most importantly, sufficient education of the doctors and the patients regarding these objectives, the importance of this condition and the ease and advantages of prompt management.

Author details

Baha Zantour^{1*}, Wafa Alaya¹, Hela Marmouch² and Wafa Chebbi¹

*Address all correspondence to: bahazantour@yahoo.fr

1 Department of Endocrinology, Tahar Sfar Hospital, Mahdia, Tunisia

2 Department of Endocrinology, Fattouma Bourguiba Hospital, Monastir, Tunisia

References

- [1] Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocrine Reviews* 1997; 18(3): 404-433. <http://edrv.endojournals.org/content/18/3/404.full.pdf+html>
- [2] Abalovich M, Amino N, Barbour LA, Cobin RH, Degroot LJ, Glinoe D, Mandel SJ, Stagnaro-Green A. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2007; 92 (8 suppl): S1-47. <http://www.ncbi.nlm.nih.gov/pubmed/17948378>
- [3] Krassas GE, Popper K, Glinoe D. Thyroid function and human reproductive health. *Endocrine Reviews* 2010; 31(5): 702-755. <http://edrv.endojournals.org/content/31/5/702.full.pdf+html>
- [4] Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine* 1999; 341(8): 549-555. <http://www.nejm.org/doi/pdf/10.1056/NEJM199908193410801>
- [5] Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. *Obstetrical Gynecology* 2005; 105(2): 239-215. <http://www.ncbi.nlm.nih.gov/pubmed/15684146>
- [6] Reid SM, Middleton P, Cossich MC, Crowther CA. Interventions for clinical and subclinical hypothyroidism in pregnancy. *Cochrane Database of systematic reviews* 2010, Issue 7. Art. N°: CD007752. DOI: 10.1002/14651858. CD007752.pub2. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007752.pub2/pdf>
- [7] Negro R, Schwartz A, Gismoudi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *Journal of Clinical Endocrinology and Metabolism* 2010; 95(4): 1699-1707. <http://jcem.endojournals.org/content/95/4/1699.full.pdf+html>
- [8] Glinoe D, De Nayer P. Thyroid and its diseases in pregnancy. In: Monaco F, Satta MA, Shapiro B, Troncone L. *Thyroid Diseases: Clinical Fundamentals and Therapy* 1993; 517-527.
- [9] Robbins J. Thyroid hormone transport proteins and the physiology of hormone binding. In: Braverman LE, Utiger RD. *The Thyroid*, JB Lippincott, Philadelphia, 1996, 96-111
- [10] Robbins J. Thyroxine transport and the free hormone hypothesis. *Endocrinology* 1992; 131(2): 546-547. <http://www.ncbi.nlm.nih.gov/pubmed/1639006>

- [11] Glinoe D, McGuire RA, Gershengorn MC, Robbins J, Berman M. Effects of estrogen on thyroxine-binding globulin metabolism in Rhesus monkeys. *Endocrinology* 1977;100(1): 9–17. <http://www.ncbi.nlm.nih.gov/pubmed/401485>
- [12] Sparre LS, Brundin J, Carlstro° m K, Carlstro° m A. Oestrogen and thyroxine-binding globulin levels in early normal pregnancy. *Acta Endocrinologica (Copenh)* 1987;114(2): 298 –304. <http://www.ncbi.nlm.nih.gov/pubmed/3103363>
- [13] Robbins J, Nelson JH. Thyroxine-binding by serum proteins in pregnancy and in the newborn. *The journal of clinical Investigation* 1958; 37(2):153–159. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC293071/pdf/jcinvest00323-0029.pdf>
- [14] Robbins J, Cheng S-Y, Gershengorn M, Glinoe D, Cahnmann HJ, Edelhoch H. Thyroxine transport proteins of plasma: molecular properties and biosynthesis. *Recent Progress in Hormon Research* 1978; 34:477–519. <http://www.ncbi.nlm.nih.gov/pubmed/216060>
- [15] Hotelling DR, Sherwood LM. The effects of pregnancy on circulating triiodothyronine. *The journal of clinical endocrinology and metabolism* 1971;33(5):783–786. <http://www.ncbi.nlm.nih.gov/pubmed/5001493>
- [16] Glinoe D. Thyroid regulation during pregnancy. In: *Iodine Deficiency in Europe: A Continuing Concern*. NATO ASI Series (Vol 241). Plenum Press, New York, 1993; 181–190
- [17] Ballabio M, Poshyachinda M, Ekins RP. Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. *Journal of Clinical Endocrinology and Metabolism* 1991;73(4):824 –831. <http://www.ncbi.nlm.nih.gov/pubmed?term=Pregnancy-induced%20changes%20in%20thyroid%20function%3A%20role%20of%20human%20chorionic%20gonadotropin%20as%20putative%20regulator%20of%20maternal%20thyroid>
- [18] Ball R, Freedman DB, Holmes JC, Midgley JE, Sheehan CP. Low-normal concentrations of free thyroxine in serum in late pregnancy: physiological fact, not technical artefact. *Clinical Chemistry* 1989;35(9): 1891–1896. <http://www.clinchem.org/content/35/9/1891.long>
- [19] Juan C. Galofre, Terry F. Davies. Autoimmune Thyroid Disease in Pregnancy: A Review. *Journal of women’s health* 2009;18(11):1847-1856 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2828163/pdf/jwh.2008.1234.pdf>
- [20] Ylikorkala O, Kivinen S, Reinila M. Serial prolactin and thyrotropin responses to thyrotropin-releasing hormone throughout normal human pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1979;48(2): 288 –292. <http://jcem.endojournals.org/content/48/2/288.long>
- [21] Kvetny J, Poulsen HK. Nuclear thyroxine and 3,5,39-triiodothyronine receptors in human mononuclear blood cells during pregnancy. *Acta Endocrinologica (Copenh)* 1984;105(1):19 –23. <http://www.ncbi.nlm.nih.gov/pubmed?term=Nuclear%20thyro->

xine%20and%203%2C5%2C39-triiodothyronine%20receptors%20in%20human
%20mononuclear%20blood%20cells%20during%20pregnancy

- [22] Hidal JT, Kaplan MM. Characteristics of thyroxine 59-deiodination in cultured human placental cells: regulation by iodothyronines. *The journal of clinical investigation* 1985;76(3):947–955. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC423958/pdf/jcinvest00123-0061.pdf>
- [23] Roti E, Fang SL, Emerson CH, Braverman LE. Human placenta is an active site of thyroxine and 3, 39, 5-triiodothyronine tyrosyl ring deiodination. *Journal of Clinical Endocrinology and Metabolism* 1981;53(3):498 –501. <http://www.ncbi.nlm.nih.gov/pubmed?term=Human%20placenta%20is%20an%20active%20site%20of%20thyroxine%20and%203%2C%2039%2C%205-triiodothyronine%20tyrosyl%20ring%20deiodination>
- [24] Lemon M, Bevan BR, Li TC, Pennington GW. Thyroid function in trophoblastic disease. *British Journal of Obstetrics and Gynaecology* 1987;94(11):1084 –1088. <http://www.ncbi.nlm.nih.gov/pubmed?term=Thyroid%20function%20in%20trophoblastic%20disease%20British%20Journal%20of%20Obstetrics%20and%20Gynaecology>
- [25] Kosugi S, Mori T. TSH receptor and LH receptor. *Endocrine Journal* 1995;42(5):587–606. https://www.jstage.jst.go.jp/article/endocrj1993/42/5/42_5_587/_pdf
- [26] Glinoe D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (hCG) and its free a and b subunits, in relation to maternal thyroid 3 stimulation during normal pregnancy. *Journal of Clinical Investigation* 1993;16(11):881–888. [http://www.ncbi.nlm.nih.gov/pubmed?term=Serum%20levels%20of%20intact%20human%20chorionic%20gonadotropin%20\(hCG\)%20and%20its%20free%20a%20and%20b%20subunits%2C%20in%20relation%20to%20maternal%20thyroid%203%20stimulation%20during%20normal%20pregnancy](http://www.ncbi.nlm.nih.gov/pubmed?term=Serum%20levels%20of%20intact%20human%20chorionic%20gonadotropin%20(hCG)%20and%20its%20free%20a%20and%20b%20subunits%2C%20in%20relation%20to%20maternal%20thyroid%203%20stimulation%20during%20normal%20pregnancy).
- [27] Grün JP, Meuris S, De Nayer P, Glinoe D, The thyrotropic role of human chorionic gonadotropin (hCG) in the early stages of twin (vs. single) pregnancy. *Clinical Endocrinology (Oxf)* 1997; 46(6):719–725. [http://www.ncbi.nlm.nih.gov/pubmed?term=The%20thyrotropic%20role%20of%20human%20chorionic%20gonadotropin%20\(hCG\)%20in%20the%20early%20stages%20of%20twin%20\(vs.%20single\)%20pregnancy](http://www.ncbi.nlm.nih.gov/pubmed?term=The%20thyrotropic%20role%20of%20human%20chorionic%20gonadotropin%20(hCG)%20in%20the%20early%20stages%20of%20twin%20(vs.%20single)%20pregnancy)
- [28] Glinoe D, De Nayer P, Bourdoux P, Lemone M, Robyn C, Van Steirteghem A, Kinthaert J, Lejeune B. Regulation of maternal thyroid during pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1990;71(2):276 –287. <http://www.ncbi.nlm.nih.gov/pubmed/2116437>
- [29] Glinoe D. The importance of iodine nutrition during pregnancy. *Public Health Nutrition* 2007;10(12A):1542–1546. http://journals.cambridge.org/abstract_S1368980007360886
- [30] Pochin EE. The iodine uptake of the human thyroid throughout the menstrual cycle and in pregnancy. *Clinical Science* 1952;11(4):441– 445.

- [31] Smyth PP. Variation in iodine handling during normal pregnancy. *Thyroid* 1999;9(7): 637–42. <http://www.ncbi.nlm.nih.gov/pubmed?term=Variation%20in%20iodine%20handling%20during%20normal%20pregnancy>
- [32] Ballabio M, Nicolini U, Jowett T, Ruiz de Elvira MC, Ekins RP, Rodeck CH. Maturation of thyroid function in normal human foetuses. *Clinical Endocrinology (Oxf)* 1989;31(5): 565–571. <http://www.ncbi.nlm.nih.gov/pubmed/2516787>
- [33] Delange F, Dunn JT, Glinioer D. General comments, conclusions and final recommendations. In: Delange F, Dunn JT, Glinioer D. *Iodine Deficiency in Europe: A Continuing Concern*. NATO ASI Series. Plenum Press, New York, 1993;241: 473–478.
- [34] Leung AM, Pearce EN, Braverman LE. Iodine Nutrition in pregnancy and Lactation. *Endocrinology and Metabolism Clinics of North America* 2011;40(4): 765–777. [http://www.ncbi.nlm.nih.gov/pubmed?term=Endocrinology%20and%20Metabolism%20Clinics%20of%20North%20America.%202011%3B%2040\(4\)%3A%20765%E2%80%93777](http://www.ncbi.nlm.nih.gov/pubmed?term=Endocrinology%20and%20Metabolism%20Clinics%20of%20North%20America.%202011%3B%2040(4)%3A%20765%E2%80%93777)
- [35] Skj° ldebrand L, Brundin J, Carlstro° m A, Pettersson T. Thyroid associated components in serum during normal pregnancy. *Acta Endocrinologica (Copenh)* 1982;100(4): 504 –511. <http://www.ncbi.nlm.nih.gov/pubmed/6812340>
- [36] Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *New England journal of Medicine* 1994;331:1072–1078. <http://www.nejm.org/doi/pdf/10.1056/NEJM199503023320919>
- [37] Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *Journal of medical Screening* 2000;7(3):127-130. <http://jms.rsmjournals.com/content/7/3/127.full.pdf>
- [38] Potlukova E, Potluka O, Jiskra J, Limanova Z, Telicka Z, Bartakova J, Springer D. Is age a risk factor for hypothyroidism in pregnancy? An analysis of 5223 pregnant women. *Journal of Clinical Endocrinology and Metabolism* 2012; 97(6):1945-1952. <http://www.ncbi.nlm.nih.gov/pubmed?term=Potlukova%20JCEM%202012>
- [39] Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. *Journal of Clinical Endocrinology and Metabolism* 2012;97(3):777-784. <http://www.ncbi.nlm.nih.gov/pubmed?term=Blatt%20JCEM%202011>
- [40] Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstetrical Gynecology* 2007; 109(5):1129-1135. <http://www.ncbi.nlm.nih.gov/pubmed/17470594>
- [41] Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, Luthy D, Gross S, Bianchi DW, D'Alton ME. Maternal thyroid hypofunction and

- pregnancy outcome. *Obstetrical Gynecology* 2008; 112(1):85-92. <http://www.ncbi.nlm.nih.gov/pubmed/18591312>
- [42] Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, González-Torga A, de Escobar GM. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* 2009; 19(5):511-519. <http://www.ncbi.nlm.nih.gov/pubmed/19348584>
- [43] Moleti M, Lo Presti VP, Mattina F, Mancuso A, De Vivo A, Giorgianni G, Di Bella B, Trimarchi F, Vermiglio F. Gestational thyroid function abnormalities in conditions of mild iodine deficiency: early screening versus continuous monitoring of maternal thyroid status. *European Journal of Endocrinology* 2009; 160(4): 611-617. <http://www.ncbi.nlm.nih.gov/pubmed/19179457>
- [44] Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *Journal of Clinical Endocrinology and Metabolism* 2010; 95(9):4227-4234. <http://www.ncbi.nlm.nih.gov/pubmed/20534757>
- [45] Jameson JL, Weetman AP. Disorders of the thyroid gland. *Harrison's principles of internal medicine*. 17th Edition. USA: Blackwell publishing; 2008: 2224-2247
- [46] Liberman CS, Pino SC, Fang SL, Baverman LE, Emerson CH. Circulating iodide concentrations during and after pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1998; 83(10): 3545-3549. <http://jcem.endojournals.org/content/83/10/3545.full.pdf+html>
- [47] Brander L, Als C, Buess H, Haldimann F, Harder M, Hanggi W, Herrmann U, Lauber K, Niederer U, Zurcher T, Burgi U, Gerber H. Urinary iodine concentrations during pregnancy in an area of unstable dietary iodine intake in Switzerland. *Journal of Endocrinological Investigations* 2003; 26(5): 389-396. http://www.jendocrinolinvest.it/jei/en/abstract.cfm?articolo_id=5638
- [48] 48-WHO, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. Third edition. World Health Organization, Geneva, Switzerland, 2007
- [49] Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002; 12(1): 63-68. <http://online.liebertpub.com/doi/pdf/10.1089/105072502753451986>
- [50] McElduff A, Morris J. Thyroid function tests and thyroid antibodies in an unselected population of women undergoing first trimester screening for aneuploidy. *Australian and New Zealand Journal of Obstetrics and Gynecology* 2008; 48(5): 478-480. <http://onlinelibrary.wiley.com/doi/10.1111/j.1479-828X.2008.00903.x/abstract>

- [51] Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, Hofman A, Hooijkaas H, Steegers EA, Tiemeier H, Bongers-Schokking JJ, Visser TJ. Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R study. *Journal of Clinical Endocrinology and Metabolism* 2012; 97(2):646-652. <http://jcem.endojournals.org/content/97/2/646.long>
- [52] Wang Y, Zhong J, Xu H, Wei W, Dong J, Yu F, Wang Y, Gong J, Shan Z, Teng W, Chen J. Perinatal iodine deficiency and hypothyroidism increase cell apoptosis and alter doublecortin and reelin protein expressions in rat cerebellum. *Archives of medical research* 2012; 43(4): 255-264. [http://www.arcmedres.com/article/S0188-4409\(12\)00127-0/abstract](http://www.arcmedres.com/article/S0188-4409(12)00127-0/abstract)
- [53] LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? *Thyroid* 2005;15(1):60-71. <http://online.liebertpub.com/doi/abs/10.1089/thy.2005.15.60>
- [54] Montoro MN. Management of hypothyroidism during pregnancy. *Clinical Obstetrics Gynecology* 1997;40(1):65-80. [http://www.ncbi.nlm.nih.gov/pubmed?term=LaFranchi%20SH%2C%20Haddow%20JE%2C%20Hollowell%20JG.%20Is%20thyroid%20inadequacy%20during%20gestation%20a%20risk%20factor%20for%20adverse%20pregnancy%20and%20developmental%20outcomes%3F%20Thyroid%202005%3B15\(1\)%3A60%E2%80%9371](http://www.ncbi.nlm.nih.gov/pubmed?term=LaFranchi%20SH%2C%20Haddow%20JE%2C%20Hollowell%20JG.%20Is%20thyroid%20inadequacy%20during%20gestation%20a%20risk%20factor%20for%20adverse%20pregnancy%20and%20developmental%20outcomes%3F%20Thyroid%202005%3B15(1)%3A60%E2%80%9371)
- [55] Idris I, Srinivasan R, Simm A, Page RC. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. *Clinical Endocrinology (Oxf)* 2005; 63(5):560-565. <http://onlinelibrary.wiley.com/doi/10.1111/j.13652265.2005.02382.x/abstract;jsessionid=571F2AA67A189EBC2DD6E7004DCF0BDB.d04t03>
- [56] Contempre B, Jauniaux E, Calvo R, Jurkovic D, Campbell S, de Escobar GM. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1993;77(6):1719-1722. <http://jcem.endojournals.org/content/77/6/1719.long>
- [57] Morreale de EG, Obregon MJ, Escobar del RF. Role of thyroid hormone during early brain development. *European Journal of Endocrinology* 2004;151(Suppl 3): U25-U37. http://eje-online.org/content/151/Suppl_3/U25.long
- [58] Utiger RD. Maternal hypothyroidism and fetal development. *New England Journal of Medicine* 1999; 341(8):601-602. <http://www.nejm.org/doi/full/10.1056/NEJM199908193410809>
- [59] Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clinical Endocrinology (Oxf)* 1999;50(2): 149-155. <http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2265.1999.00639.x/abstract>
- [60] Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F. Attention deficit and hyper-

- activity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: A possible novel iodine deficiency disorder in developed countries. *Journal of Clinical Endocrinology and Metabolism* 2004;89(12): 6054–6060. <http://jcem.endo-journals.org/content/89/12/6054.long>
- [61] Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. *Journal of Endocrinology Investigation* 2012; 35(3):322–325. http://www.jendocrinolinvest.it/jei/en/abstract.cfm?articolo_id=7772
- [62] Männistö T, Väärasmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto-Luukkonen E Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *Journal of Clinical Endocrinology and Metabolism* 2009; 94(3):772–779. <http://www.ncbi.nlm.nih.gov/pubmed/19106271>
- [63] Abbassi-Ghanavati M, Casey BM, Spong CY, McIntire DD, Halvorson LM, Cunningham FG. Pregnancy outcomes in women with thyroid peroxidase antibodies. *Obstetrics Gynecology* 2010; 116(2 Pt 1): 381–386. [http://www.ncbi.nlm.nih.gov/pubmed?term=Pregnancy%20outcomes%20in%20women%20with%20thyroid%20peroxidase%20antibodies.%20Obstetrics%20Gynecology%202010%3B116\(2%20Pt%201\)%3A381%E2%80%93386](http://www.ncbi.nlm.nih.gov/pubmed?term=Pregnancy%20outcomes%20in%20women%20with%20thyroid%20peroxidase%20antibodies.%20Obstetrics%20Gynecology%202010%3B116(2%20Pt%201)%3A381%E2%80%93386)
- [64] Bagis T, Gokcel A, Saygili ES. Autoimmune thyroid disease in pregnancy and the postpartum period: relationship to spontaneous abortion. *Thyroid* 2001;11(11):1049–1053. [http://www.ncbi.nlm.nih.gov/pubmed?term=Autoimmune%20thyroid%20disease%20in%20pregnancy%20and%20the%20postpartum%20period%3A%20relationship%20to%20spontaneous%20abortion.%20Thyroid%202001%3B11\(11\)%3A1049%E2%80%931053](http://www.ncbi.nlm.nih.gov/pubmed?term=Autoimmune%20thyroid%20disease%20in%20pregnancy%20and%20the%20postpartum%20period%3A%20relationship%20to%20spontaneous%20abortion.%20Thyroid%202001%3B11(11)%3A1049%E2%80%931053)
- [65] Glinoe D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, Kinthaert J, Robijn C, Grun JP, de Nayer P. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *Journal of Clinical Endocrinology and Metabolism* 1991;73(2):421–427. <http://jcem.endojournals.org/content/73/2/421.long>
- [66] Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *British Medical Journal* 2011;342:d2616. <http://www.bmj.com/content/342/bmj.d2616?view=long&pmid=21558126>
- [67] Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *European Journal of Endocrinology* 2004;150(6):751–755. [http://www.ncbi.nlm.nih.gov/pubmed?term=Thyroid%20autoimmunity%20and%20miscarriage.%20Eur%20J%20Endocrinol%202004%3B150\(6\)%3A751%E2%80%93755](http://www.ncbi.nlm.nih.gov/pubmed?term=Thyroid%20autoimmunity%20and%20miscarriage.%20Eur%20J%20Endocrinol%202004%3B150(6)%3A751%E2%80%93755)
- [68] De Carolis C, Greco E, Guarino MD, Perricone C, Dal Lago A, Giacomelli R, Fontana L, Perricone R. Anti-thyroid antibodies and antiphospholipid syndrome: evidence of reduced fecundity and of poor pregnancy outcome in recurrent spontaneous aborters.

- American Journal Reproduction Immunology 2004;52(4):263–266. <http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0897.2004.00215.x/abstract>
- [69] Bussen S, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. *Human Reproduction* 1995;10(11): 2938-2940.<http://humrep.oxfordjournals.org/content/10/11/2938.long>
- [70] Rushworth FH, Backos M, Rai R, Chilcott IT, Baxter N, Regan L. Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies. *Human Reproduction* 2000; 15(7):1637–1639. <http://humrep.oxfordjournals.org/content/15/7/1637.long>
- [71] Esplin MS, Branch DW, Silver R, Stagnaro-Green A. Thyroid autoantibodies are not associated with recurrent pregnancy loss. *American Journal of Obstetrics Gynecology* 1998;179(6Pt 1):1583–1586. [http://www.ncbi.nlm.nih.gov/pubmed?term=Thyroid%20autoantibodies%20are%20not%20associated%20with%20recurrent%20pregnancy%20loss.%20American%20Journal%20of%20Obstetrics%20Gynecology%201998%3B179\(6Pt%201\)%3A1583%E2%80%93936](http://www.ncbi.nlm.nih.gov/pubmed?term=Thyroid%20autoantibodies%20are%20not%20associated%20with%20recurrent%20pregnancy%20loss.%20American%20Journal%20of%20Obstetrics%20Gynecology%201998%3B179(6Pt%201)%3A1583%E2%80%93936).
- [72] Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *Journal Clinical Endocrinology Metabolism* 2006;91(7):2587–2591. <http://jcem.endojournals.org/content/91/7/2587.long>
- [73] Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *New England Journal of Medicine* 2003; 348(26):2646–2655. <http://www.nejm.org/doi/full/10.1056/NEJMra021194>
- [74] Marqusee E, Hill JA, Mandel SJ. Thyroiditis after pregnancy loss. *Journal of Clinical Endocrinology and Metabolism* 1997;82(8):2455-2457. <http://jcem.endojournals.org/content/82/8/2455.long>
- [75] Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. *Clinical Endocrinology (Oxf)* 2010;72(6):825-829. <http://www.ncbi.nlm.nih.gov/pubmed/19878506>
- [76] Schlienger JL. Hypothyroidie et grossesse. In: Leclère J, Orgiazzi J, Rousset B, Schlienger JL, Wémeau JL. (Ed.). *La thyroïde*. 2nd edition. France: Elsevier; 2001: 503-506
- [77] De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin R, Eastman C, Lazarus J, Luton D, Mandel S, Mestman J, Rovet J, Sullivan S. Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2012; 97(8): 2543-2565. <http://jcem.endojournals.org/content/97/8/2543.long>
- [78] Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersing W. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy

- and postpartum. *Thyroid* 2011; 21(10): 1081-1125. <http://online.liebertpub.com/doi/pdf/10.1089/thy.2011.0087>
- [79] Stricker R, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA, Stricker R. Evaluation of maternal thyroid function during pregnancy: The importance of using gestational age-specific reference intervals. *European Journal of Endocrinology* 2007; 157(4): 509-514. <http://ej-e-online.org/lookup/pmid?view=long&pmid=17893266>
- [80] Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulk-Kinen AJ. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. *Journal of Medical Screening* 2004;11(4): 170-174. <http://jms.rsmjournals.com/content/11/4/170.long>
- [81] Panesar NS, Li SY, Rogers MS. Reference intervals for thyroid hormones in pregnant chinese women. *Annals of Clinical Biochemistry* 2001; 38(Pt4): 329-332. <http://acb.rsmjournals.com/content/38/4/329.long>
- [82] Soldin OP, Soldin D, Sastoque M. Gestation-specific thyroxine and thyroid stimulating hormone levels in the United States and worldwide. *Therapeutic Drug Monitoring* 2007; 29(5): 553-559. <http://journals.lww.com/drug-monitoring/pages/articleviewer.aspx?year=2007&issue=10000&article=00001&type=abstract>
- [83] Bocos-Terraz JP, Izquierdo-Alvarez S, Bancalero-Flores JL, Alvarez-Lahuerta R, Aznar-Sauca A, Real-Lopez E, Ibanez-Marco R, Bocanegra-Garcia V, Rivera-Sanchez G. Thyroid hormones according to gestational age in pregnant Spanish women. *BMC Research Notes* 2009; 2: 237. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2788578/pdf/1756-0500-2-237.pdf>
- [84] Marwaha RK, Chopra S, Gopalakrishnan S, Sharma B, Kanwar RS, Sastry A, Singh S. Establishment of reference range for thyroid hormones in normal pregnant Indian women. *BJOG* 2008;115(5): 602-606. <http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2008.01673.x/pdf>
- [85] Wang QW, Yu B, Huang RP, Cao F, Zhu Z-q, Sun D-c, Zhou H. Assessment of thyroid function during pregnancy: The advantage of self-sequential longitudinal reference intervals. *Archives of Medical Sciences* 2011;7(4): 679-684. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3258790/pdf/AMS-7-4-679.pdf>
- [86] Walker JA, Illions EH, Huddleston JF, Smallridge RC. Racial comparisons of thyroid function and autoimmunity during pregnancy and the postpartum period. *Obstetrical Gynecology* 2005;106(6): 1365-1371. <http://www.ncbi.nlm.nih.gov/pubmed?term=Racial%20comparisons%20of%20thyroid%20function%20and%20autoimmunity%20during%20pregnancy%20and%20the%20postpartum%20period>
- [87] Benhadi N, Wiersing WM, Reitsma JB, Vrijkotte TG, Vanderwal MF, Bousel GJ. Ethnic differences in TSH but not in free T4 concentrations or TPO antibodies during pregnancy. *Clinical Endocrinology (Oxford)* 2007; 66(6): 765-770. <http://www.ncbi.nlm.nih.gov/pubmed/17466012>

- [88] Dashe JS, Casey BM, Wells CE, McIntira DD, Byrd EW, Leveno KJ, Cunningham FG. Thyroid stimulating hormone in singleton and twin pregnancy: importance of gestational age specific reference ranges. *Obstetrical Gynecology* 2005;106(4): 753-757. <http://www.ncbi.nlm.nih.gov/pubmed/16199632>
- [89] Rotondi M, Mazziotti G, Sorvillo F, Piscopo M, Cioffi M, Amato G, Carella C. Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy. *European Journal of Endocrinology* 2004;151(6): 695-700. <http://ejonline.org/content/151/6/695.full.pdf>
- [90] Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, Chem MS, George LM, Perona M, Chen MS, Dall'Amico D, Parkes AB, Joomum M, Wald NP. Antenatal thyroid screening and childhood cognitive function. *New England Journal of Medicine* 2012;366(6): 493-501. <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1106104>
- [91] Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. The influence of selenium supplementation on post-partum thyroid status in pregnant women with thyroid peroxidase autoantibodies. *Journal of Clinical Endocrinology and Metabolism* 2007; 92(4): 1263-1268. <http://jcem.endojournals.org/content/92/4/1263.full.pdf+html>
- [92] Cao XY, Jiang XM, Dou ZH, Rakeman MA, Zhang ML, O'Donnell KJ, Ma T Amette K, DeLong N, DeLong R. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *New England Journal of Medicine* 1994;331(26): 1739-1744. <http://www.nejm.org/doi/pdf/10.1056/NEJM199412293312603>
- [93] O'Donnell KJ, Rakeman MA, Zhi-Hong D, Xue-Yi C, Mei ZY, DeLong N, Brenner G, Tai M, Dong W, DeLong GR. Effects of iodine supplementation during pregnancy on child growth and development at school age. *Developmental Medicine and Child Neurology* 2002;44(2):76-81. <http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2002.tb00291.x/abstract>
- [94] Berbel P, Mestre JL, Santamaria A, Palazon I, Franco A, Graells M, Gonzalez-Torga A, de Escobar GM. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* 2009;19(5): 511-519. <http://online.liebertpub.com/doi/abs/10.1089/thy.2008.0341>
- [95] Velasco I, Carreira M, Santiago P, Muela JA, Garcia-Fuentes E, Sanchez-Munoz B, Garriga MJ, Gonzalez-Fernandez MC, Rodriguez A, Caballero FF, Machado A, Gonzalez-Romero S, Anarte MT, Soriguer F. Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. *Journal of Clinical Endocrinology and Metabolism* 2009; 94(9): 3234-3241. <http://jcem.endojournals.org/content/94/9/3234.full.pdf+html>
- [96] Last JM. A dictionary of epidemiology (4th edition). Oxford university press. Oxford 2001. [http://books.google.tn/books?hl=fr&lr=&id=RPa-QY8cG4N4C&oi=fnd&pg=PR5&dq=Last+JM.+A+dictionary+of+epidemiology+\(4th](http://books.google.tn/books?hl=fr&lr=&id=RPa-QY8cG4N4C&oi=fnd&pg=PR5&dq=Last+JM.+A+dictionary+of+epidemiology+(4th)

+edition).+Oxford+university+press.+Oxford+2001.&ots=GdtDy3k1N8&sig=edwX-BoW6-HXPQ7WKJ7X8Wo5DkXw&redir_esc=y#v=onepage&q&f=false

- [97] UK National Screening Committee criteria. www.nhs.uk/whatscreening/what-screen_ind.htm
- [98] Erik K, Marqusee E, Laurens J, Jarolin P, Fischer GA, Larsen PR. Timing and magnitude of increases in Levothyroxine requirements during pregnancy in women with hypothyroidism. *New England Journal of Medicine* 2004; 351: 241-249. <http://www.nejm.org/doi/full/10.1056/NEJMoa040079>
- [99] Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *New England Journal of Medicine* 2001; 344: 1743. <http://www.nejm.org/doi/full/10.1056/NEJM200106073442302>
- [100] Negro R, Mestman JH. Thyroid disease in pregnancy. *Best Practice and Research Clinical Endocrinology and Metabolism* 2011;25(6):927-43. <http://www.ncbi.nlm.nih.gov/pubmed/22115167>
- [101] Trumbo P, Yates AA, Schlicker S, Poos. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *Journal of the American Dietetic Association* 2001; 101(3): 294–301. <http://www.ncbi.nlm.nih.gov/pubmed?term=Dietary%20reference%20intakes%3A%20vitamin%20A%2C%20vitamin%20K%2C%20arsenic%2C%20boron%2C%20chromium%2C%20copper%2C%20iodine%2C%20iron%2C%20manganese%2C%20molybdenum%2C%20nickel%2C%20silicon%2C%20vanadium%2C%20and%20zinc>
- [102] Berghout A, Wiersinga W. Thyroid size and thyroid function during pregnancy: an analysis. *European Journal of Endocrinology* 1998; 138(5):536–542. <http://ej-e-online.org/cgi/pmidlookup?view=long&pmid=9625365>

IntechOpen