Hormonal changes and metabolic demands during pregnancy result in profound alterations in the biochemical parameters of thyroid function. For thyroid economy, the main events occurring during pregnancy are a marked increase in serum thyroxine-binding globulin levels; a marginal decrease in free hormone concentrations (in iodine-sufficient areas) that is significantly amplified when there is iodine restriction or overt iodine deficiency; a frequent trend toward a slight rise in basal thyrotropin (TSH) values between the first trimester and term; a transient stimulation of the maternal thyroid gland by elevated levels of human chorionic gonadotropin (hCG) resulting in a rise in free thyroid hormones and decrement in serum TSH concentrations during the first trimester; and finally, modifications of the peripheral metabolism of maternal thyroid hormones. Together, metabolic changes associated with the progression of gestation in its first half constitute a transient phase from preconception steady state to pregnancy steady state. In order to be met, these metabolic changes require an increased hormonal output by the maternal thyroid gland. Once the new equilibrium is reached, increased hormonal demands are maintained until term, probably through transplacental passage of maternal thyroid hormones and increased turnover of maternal thyroxine (T\(_4\)), presumably under the influence of the placental (type 3) deiodinase. For healthy pregnant women with iodine sufficiency, the challenge of the maternal thyroid gland is to adjust the hormonal output in order to achieve the new equilibrium state, and thereafter maintain the equilibrium until term. In contrast, the metabolic adjustment cannot easily be reached during pregnancy when the functional capacity of the thyroid gland is impaired because of iodine deficiency. The ideal dietary allowance of iodine recommended by World Health Organization (WHO) is 200 \(\mu\)g of iodine per day for pregnant women. In conditions with iodine restriction, enhanced thyroidal stimulation is revealed by relative hypothyroxinemia and goitrogenesis. Goiters formed during gestation may only partially regress after parturition. Pregnancy, therefore, represents one of the environmental factors that may help explain the higher prevalence of goiter and thyroid disorders in women compared with men. An iodine-deficient status in the mother also leads to goiter formation in the progeny and neuropsycho-intelectual impairment in the offspring. When adequate iodine supplementation is given early during pregnancy, it allows for the correction and almost complete prevention of maternal and neonatal goitrogenesis. In summary, pregnancy is accompanied by profound alterations in the thyroid economy, resulting from a complex combination of factors specific to the pregnant state, which together concur to stimulate the maternal thyroid machinery. Increased thyroidal stimulation induces, in turn, a sequence of events leading from physiological adaptation of the thyroidal economy observed in healthy iodine-sufficient pregnant women to pathological alterations affecting both thyroid function and the anatomical integrity of the thyroid gland, when gestation takes place in conditions with iodine restriction or deficiency: the more severe the iodine deficiency, the more obvious, frequent, and profound the potential maternal and fetal repercussions.

**The Economy of Thyroid Function During Pregnancy**

This article reviews recent studies dealing with thyroid physiology and pathophysiology in the pregnant woman, with a special emphasis on the importance of iodine deficiency for both the mother and the fetus, a condition which is still characteristic today of many areas worldwide. The Recommended Dietary Allowances of iodine, endorsed by the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the World Health Organization (WHO), are that the ideal iodine intake should be 150 \(\mu\)g/d for normal adults and 200 \(\mu\)g/d for pregnant (and lactating) women (1–3).
The regulation of maternal thyroid function

Why does the pregnant state represent a condition associated with profound modifications in the biochemical parameters of thyroid function and the thyroidal economy? Pregnancy can be viewed as a prolonged physiological situation during which a combination of events concurs to modify the thyroidal economy, by exerting stimulatory effects on the glandular machinery (4–6). Three series of events, that take place at different time points during gestation, result in complex effects that may be seen only transiently or persist until term.

The first sequence of events begins during early gestation (6th to 10th week), is completed by midgestation, with its effects persisting until term, and results from the increase in thyroxine-binding globulin (TBG) levels under the influence of elevated estrogen concentrations. The rapid and marked rise in serum TBG (basal levels increased 2.5-fold) is accompanied by a trend toward a reduction in free thyroxine (T$_4$) and triiodothyronine (T$_3$) concentrations, that in turn results in a transient feedback stimulation of the pituitary-thyroid axis. For healthy pregnant women who have a sufficient iodine intake, this decrease in free hormones remains marginal (representing, on average, a 10% to 15% decrement). As will be discussed in more detail later, the decrease in free hormone concentrations is significantly more pronounced, and may potentially lead to actual hypothyroxinemia, when there is iodine restriction (even if it remains moderate) or overt iodine deficiency during pregnancy. Concerning serum thyrotropin (TSH), there is frequently a moderate but clear trend toward an increase in basal TSH values, between the first trimester and term: a slight increase in serum TSH can also be observed in pregnant women without evidence of iodine deficiency, but the TSH changes are strikingly enhanced in iodine-deficient conditions, and serum TSH levels may reach (or exceed) the upper limit of normality.

The second sequence of events also takes place transiently during the first trimester, and results from the direct stimulation of the maternal thyroid gland by elevated levels of human chorionic gonadotropin (hCG). The rise in hCG concentrations, reaching peak values near the end of the first trimester, is accompanied by a partial inhibition of the pituitary-thyroid axis: between 8 and 14 weeks, there is a transient lowering in serum TSH, coincident with peak hCG values, and the profiles of changes in serum TSH and hCG are mirror images of each other. Although in most normal pregnancies, the direct stimulatory effect of hCG on the thyroid remains minor, of short duration, and is not routinely detectable, in approximately 20% of pregnancies, the hCG-induced TSH lowering can transiently “blunt” basal TSH concentrations (as well as the thyrotropin-releasing hormone [TRH]-stimulated TSH responses) to below the lower limit of normality. Furthermore, in approximately one tenth of these women (i.e., 2% of all pregnancies), the thyrotropic action of hCG on the maternal thyroid gland may lead to a medical condition referred to as “gestational transient thyrotoxicosis” (4,5,7,8).

The third series of events occur throughout gestation, but are mainly active during its second half: they are related to modifications in the peripheral metabolism of maternal thyroid hormones. Three enzymes catalyze the deiodination of thyroid hormones in human tissues. The activity of the type 1 monodeiodinase (MID-1), that converts T$_4$ to T$_3$, is probably not significantly modified during pregnancy. Type 2 monodeiodinase activity (MID-2), that also converts T$_4$ to T$_3$, is expressed in the placenta and may represent a regulatory homeostatic mechanism for maintaining T$_3$ production locally, when maternal T$_4$ concentrations are reduced. The placenta also contains large amounts of type 3 monodeiodinase (MID-3), that converts T$_4$ to reverse-T$_3$. By its extremely high enzymatic activity, particularly during the second half of gestation, MID-3 may explain the increased T$_4$ turnover of maternal origin and also the low T$_3$/high reverse-T$_3$ pattern, that is so characteristic of the fetal thyroid hormone metabolism (9).

Together, the metabolic changes associated with the progression of gestation in its first half constitute a transient phase from a preconception steady state to the pregnancy steady-state. In order to be accomplished, such changes require an increased hormonal output by the maternal thyroid gland. Once the new equilibrium is reached, the increased hormonal demands are sustained until term, probably both through transplacental passage of maternal thyroid hormones and increased maternal T$_4$ turnover, and presumably under the influence of placentals MID-3. For healthy pregnant women with iodine sufficiency, the challenge of the maternal gland is to adjust the hormonal output in order to achieve the new equilibrium state, and maintain this equilibrium until term: globally, physiological adaptation to the pregnant state is attained without difficulty by the normal thyroid machinery. This is not the case, however, when the functional capacity of the thyroid gland is altered, for instance because of iodine deficiency. Previous studies have shown convincingly that such alterations may already be manifest when pregnancy takes place in healthy women who reside in areas with only a marginally restricted iodine intake: the more severe is the iodine deficiency, the more pronounced are the consequences for the thyroidal economy (10,11).

The metabolism of iodine

After reduction to iodide, dietary iodine is rapidly absorbed from the gut. Iodide derived from the diet and the peripheral catabolism of thyroid hormones and iodothyronines by deiodination constitutes the extrathyroidal inorganic iodine pool. This pool is in a dynamic equilibrium with two main organs, the thyroid gland and the kidneys. In normal subjects with a daily iodine intake of 150 $\mu$g/d, the thyroid clearance rate for iodide is 10 to 25 mL/min and the renal iodide clearance 30 mL/min, resulting chiefly from glomerular filtration. In pregnancy, the renal clearance of iodide increases significantly because of an increased glomerular filtration rate. Renal hyperfiltration and increased clearance of iodide begin in the early weeks of gestation and persist until term, thereby constituting an obligatory renal iodine “leakage” (12). The iodide loss tends to lower the circulating levels of inorganic iodide and induces, in turn, a compensatory increase in thyroidal iodide clearance, reaching 60 mL/min, and an absolute elevation of iodide entry into the gland. These physiological mechanisms underscore the increased thyroidal activity during pregnancy.

A second mechanism of iodine deprivation for the mother occurs later in gestation, from the passage of a part of the
available iodine from maternal circulation to the fetal-pla- cental unit. The extent of iodine passage from mother to fe- tus has not yet been precisely established. At midgestation, the fetal thyroid gland has already started to produce thy- roid hormones that are indispensable for an adequate de- velopment of the fetus (13). Hence, when iodine deprivation preexists during the first half of gestation, it tends to become more severe in the final stages.

**The Effects of Iodine Deficiency on Thyroid Function During Pregnancy**

The pathophysiological repercussions of iodine deficiency during pregnancy are schematically represented in Figure 1. In the following sections, each step in the “vicious circle” induced by iodine deprivation is discussed, as well as the means proposed for its prevention, detection and correction.

**Definition of an iodine-deficient status during pregnancy**

Iodine deficiency disorders are believed not to present problems in the United States, Japan, and a limited number of European regions (Scandinavian countries, Switzerland, Austria) where national programs of dietary iodine supple- mentation have been in place for many years. This global view is however probably too optimistic. For instance, a re- cent survey has indicated that the iodine intake in the United States has markedly decreased in the last decade (1988 to 1994), compared with a similar survey carried out two decades ago (1971 to 1974); the most recent figure available from the United States reports a median urinary iodine excretion value of 145 μg/L, compared with over 300 μg/L previously (14). Thus, the present iodine intake levels in the United States may, at first glance, appear as almost ideal and “comfortably above the recommended minimum” (15). However, the same U.S. survey showed that as many as 14.9 % of women in the child-bearing age and 6.7% during preg- nancy had iodine excretion levels into the range of iodine deficiency, that is, below 50 μg/L.

A second important concept is that the risk of iodine de- privation during pregnancy needs to be assessed locally and monitored over time, because it may occur in areas that are not globally recognized as iodine-deficient areas. For in- stance, the southwest of France was not particularly known to be iodine deficient because of the relative proximity to the sea, fish-eating habits in the population, etc. Nevertheless, a study performed in 1997 in a cohort of pregnant women in this area clearly showed that the urinary iodine excretion lev- els were low, with more than 75% of pregnant women hav- ing excretion levels below 100 μg/L (Fig. 2) (11). In fact, the distribution frequency of urinary iodine concentrations (broadly corresponding to the iodine intake) found in the southwest of France was similar to that found in Brussels 10 years earlier in an area known to be moderately iodine de- ficient, before iodine supplementation was systematically in- troduced in the diet during pregnancy (16).

Another important concept relates to the possibility and frequency of geographical variations in the iodine intake within a given country, because iodine deficiency in general, and mild to moderate iodine deficiency more specifically (the severity of which, in many western European countries, de- pends upon the natural iodine content in the food) may show significant variations from one place to another. A good ex- ample of this concept was demonstrated by a study carried out in Denmark (17). Pregnant women without iodine supple- mentation had a median iodine excretion level of 62 μg/g creat. in Copenhagen, compared with only 33 μg/g creat. in the countryside (Randers, East Jutland). Furthermore, these striking differences were not alleviated in pregnant women from the same two areas receiving iodine supplementation: 74 μg/g versus 34 μg/g creat. (in Copenhagen and Randers,

**FIG. 1.** The regulation of thyroid function in pregnant women with a restricted or deficient iodine intake, illustrating schematically the formation steps of a vicious circle, unless iodine supplementation is provided to avoid enhanced glandular stimulation. (Adapted with modifications, from Glinoer [6]).
respectively), indicating that the iodine supplementation was either not efficient enough or that it did not "show up" in the urinary excretion because the iodine supplements were entirely taken up by the maternal (and fetal?) iodine-deficient thyroid glands.

In summary, iodine deficiency becomes significant during pregnancy when the iodine intake is below 100 μg daily. Recommended dietary allowance for iodine is 200 μg/d in pregnant and lactating women. The degree of iodine deficiency should be assessed in each concerned area specifically and the local situation correctly evaluated before embarking on medical recommendations for iodine supplementation programs.

Enhanced thyroidal stimulation associated with iodine deficiency during pregnancy

In the early 1990s, the concept was introduced that iodine deficiency during pregnancy, even when considered to be mild, resulted in enhanced or excessive thyroidal stimulation, leading to goitrogenesis in both the mother and the fetus (16). Thus, we proposed that pregnancy should be viewed as an “environmental” factor to trigger the thyroid machinery and induce thyroid pathology in areas with a marginally reduced iodine intake (4,6).

In clinical practice, four biochemical parameters were identified and characterized to represent useful markers (Table 1). The first marker was relative hypothyroxinemia. The total T₃/TBG ratio (i.e., the TBG-saturation level) could be used effectively to detect an inappropriately low rise in total T₄ during the first trimester, in relation with the concomitant rise in serum TBG. When free T₃ concentrations were measured directly, they were often found near the lower limit of normality. A good example of iodine-deficiency associated changes in serum free T₄ concentrations is illustrated in Figure 3, comparing pregnant women from Sudan (with iodine deficiency) and Sweden (without iodine deficiency) (18). The second marker was preferential T₃ secretion, reflected by an elevated total T₃/T₄ molar ratio: the stimulation of the thyroid machinery (by TSH) in iodine-restricted conditions led to increased T₃ production. In Brussels for instance, before iodine supplementation was sys-

![FIG. 2. Frequency distribution of urinary iodine excretion concentrations during the first trimester (A) and the ninth month (B) of gestation, in a group of pregnant women in the southwest of France. (Reproduced with permission from Caron et al. [11]).](image)

**Table 1. Excessive Thyroidal Stimulation When the Iodine Intake is Limited in Healthy Pregnancies**

<table>
<thead>
<tr>
<th>Urinary iodine concentration (μg/L)</th>
<th>T₃/T₄ (×10⁻³)</th>
<th>TSH (mU/L)</th>
<th>TG (μg/L)</th>
<th>Free T₄ (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>15 weeks’ gestation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest tertile (&lt;40 μg/L)</td>
<td>25.0</td>
<td>0.99</td>
<td>36</td>
<td>11.5</td>
</tr>
<tr>
<td>Highest tertile (&gt;62 μg/L)</td>
<td>23.4</td>
<td>0.80</td>
<td>26</td>
<td>12.4</td>
</tr>
<tr>
<td>p value</td>
<td>0.03</td>
<td>0.03</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>32 weeks’ gestation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest tertile (&lt;31 μg/L)</td>
<td>24.9</td>
<td>1.38</td>
<td>50</td>
<td>10.3</td>
</tr>
<tr>
<td>Highest tertile (&gt;60 μg/L)</td>
<td>24.3</td>
<td>1.12</td>
<td>29</td>
<td>10.6</td>
</tr>
<tr>
<td>p value</td>
<td>n.s.</td>
<td>0.04</td>
<td>0.001</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

These data were obtained in a large group of healthy pregnant women investigated in Brussels, before the introduction of systematic iodine supplementation during pregnancy. Women were categorized in tertiles (percentile 1–33 compared with percentile 67–100), based on urinary iodine concentrations (UIC), at 15 and 32 weeks’ gestation. The results compare four thyroid function parameters in the pregnancies from the lowest versus highest tertile UIC categories, and show enhanced glandular stimulation that takes place already during early gestation.

Normal ranges are: 10–22 × 10⁻³ for T₃/T₄ ratio; 0.4–4.0 mU/L for serum TSH; 1–25 μg/L for serum TG; 9–20 ng/L for serum free T₄. T₃, triiodothyronine; T₄, thyroxine; TSH, thyrotropin; TG, thyroglobulin.
levels) near the end of the first trimester, serum TSH levels tended to increase progressively until term, where they reached levels that were twice (or even higher) the preconception serum TSH levels. A good example of iodine-deficiency-associated changes in serum TSH concentrations is illustrated in Figure 4, comparing pregnant women, with and without iodine deficiency, in the south of Italy (19). While serum TSH remained almost unchanged in women from a control area (with a urinary iodine excretion of 95 µg/d), serum TSH increased significantly (almost tripling) in women from an iodine-deficient area (with a urinary iodine excretion of 46 µg/d). The fourth parameter was related to changes in serum thyroglobulin (TG). In mild to moderate iodine deficiency conditions, supranormal TG concentrations were found in as much as one third of pregnancies, and this already during the first trimester. Thereafter, serum TG continued to increase progressively and mainly during the later gestational stages (near term): at delivery, two thirds of women had supranormal serum TG concentrations. It is important to emphasize that monitoring serum TG changes during pregnancy in iodine-deficient conditions was of particular clinical value, because TG increments correlated well with gestational goitrogenesis, hence constituting a useful prognostic marker of goiter formation, and its prevention by iodine supplementation (20).

In summary, relatively simple criteria can be used to assess the regulation of thyroid function in normal pregnancy and help define excessive thyroidal stimulation, based on the routine determinations of serum total T₃ and T₄, TBG, free T₄, TSH, and TG levels. However, it is necessary to correctly interpret the changes occurring for each parameter considered as gestation progresses, with a clear understanding of the underlying mechanisms that lead to an adequate (versus a less than adequate) adjustment of thyroidal economy to the

![Graph](image)

**FIG. 3.** Changes in serum free thyroxine (T₄) concentrations (mean and 95% confidence interval) in relation to weeks of gestation in Sudanese (closed circles), compared with Swedish pregnant women (open circles) taken as control iodine-sufficient subjects. Three stars: \( p < 0.001 \), compared to values at 10 to 13 weeks. **\( p < 0.005 \); ***\( p < 0.001 \) compared to the Swedish group. (Reproduced with permission from Elnagar et al. [18]).

![Graph](image)

**FIG. 4.** Changes in serum thyrotropin (TSH) concentrations in relation to weeks of gestation, in a group of pregnant women from an iodine deficient area in Sicily (closed circles) with a urinary iodine excretion of 46 µg/d, and compared with a group of women from an iodine sufficient area in Sicily (closed triangles) with a urinary iodine excretion of 95 µg/d, and used as controls. **\( p < 0.01 \) between the two groups. (Reproduced with permission from Vermiglio et al. [19]).
alterations associated with pregnancy, particularly in conditions with iodine restriction or overt deficiency.

**Goitrogenesis in mother and progeny associated with iodine deficiency during pregnancy**

In the early 1990s, the concept was also introduced that iodine deficiency during pregnancy was a preponderant causal factor to explain goitrogenesis, affecting both the mother and the progeny. Although goiter formation was not noticeable in pregnant women residing in iodine-sufficient areas, several European studies showed that significant changes in thyroid volume (TV) occurred in association with pregnancy (reviewed in Glinoer [4,5,10]. Together, these studies indicated that TV tended to increase during pregnancy. In European regions with an apparently sufficient iodine intake, results showed TV increments of 10% to 15% on average, consistent mainly with vascular swelling (intumesence) of the gland during pregnancy. In other European regions known to have a lower iodine intake, results showed greater increments in TV, ranging between 20% and 35% on average, with many women exhibiting a doubling in thyroid size between the first trimester and term. As an example in Brussels, before iodine supplementation was systematically prescribed to pregnant women, almost 10% of the women developed a goiter during pregnancy and the goiter was only partially reversible after parturition. Furthermore, precise measurements of TV in newborn infants indicated that, on average, TV values were 40% larger in the newborns from nonsupplemented mothers (compared with the newborns from iodine-supplemented mothers), with glandular hyperplasia already present in 10% of these infants soon after birth (compared with none in newborns from treated mothers) (Fig. 5).

In summary, pregnancy represents a strong goitrogenic stimulus for both the mother and fetus, even in areas with only a moderate iodine restriction or deficiency. Maternal goiter formation is correlated with the degree of prolonged glandular stimulation that takes place during gestation. Also, a goiter formed during gestation may only partially regress after parturition, and pregnancy therefore is one of the environmental factors that may help explain the higher prevalence of goiter and thyroid disorders in women compared with men. Finally, and perhaps most importantly, goiter formation also takes place in the progeny, emphasizing the exquisite sensitivity of the fetal thyroid gland to the consequences of maternal iodine deprivation, and indicating that the process of goiter formation in these conditions may already start during the earliest stages of fetal thyroid gland development.

**Maternal goitrogenesis is correlated with the degree of iodine deficiency and thyroidal stimulation during pregnancy**

Taken from two independent studies, the direct correlation between maternal changes in TV and the degree of iodine restriction during pregnancy is illustrated in Figure 6. In a study from Brussels, Belgium (left panel), healthy nongoitrous pregnant women were categorized, based on TV increment during pregnancy: less than 10% versus higher than 10% TV changes, between the first trimester and term. The results showed that more pronounced TV changes were associated with differences in both serum TG and TSH levels (significantly higher), as well as with iodine excretion values (significantly lower) (6). In a comparable study from Toulouse, France (right panel), the degree of maternal thyroid enlargement during gestation was inversely correlated with the degree of iodine deficiency: in this particular study, 11% of the women developed a goiter during pregnancy (11).

Thus, goiter formation during pregnancy is the hallmark of iodine deficiency. Together, the low intrathyroidal iodine stores that prevail before conception, the increased need for a higher iodine availability once pregnancy begins, and finally, the insufficiency of the daily iodine intake that is maintained throughout gestation constitute the three major components of enhanced thyroidal stimulation and the resulting goitrogenesis in the pregnant state.

**Prevention of goitrogenesis associated with iodine deficiency during pregnancy**

In order to prevent gestational goitrogenesis, women should ideally be provided with an adequate iodine intake (150 μg/d) long before they become pregnant, because it is only by reaching a long term steady state, with comfortable intrathyroidal iodine stores (10 to 20 mg), that the triggering of the thyroid machinery can be avoided once gestation begins. To achieve such a goal, national public health authorities need to develop iodine supplementation programs of the population’s diet. Correcting this public health problem is the aim of a massive global campaign, undertaken 10 to 15 years ago worldwide, and that is showing remarkable progress so far (15,21). Until 1992, most European countries were moderately to severely iodine deficient. A survey carried out in 12 European countries in more recent years using a mobile unit (the ThyroMobil van) equipped with a sonographic device and the facilities for collecting urine samples, allowed for the determination of TV and urinary iodine concentrations in almost 8,000 schoolchildren, ages 7 to 15 years (22). Results indicated that the status of iodine nutrition has markedly improved in many, albeit not all, of the European countries surveyed. For instance, and despite the efforts of several recognized experts in the field, the Belgian iodine status remains a vexing paradox: a recent survey in our country (also based on the ThyroMobil van methodology) indicated that the status of iodine nutrition had slightly improved in the recent years, with a median urinary iodine excretion level of 80 μg/L (compared with 55 μg/L, a few years earlier) and a goiter prevalence of 6% (compared with 11% a few years earlier) in representative 6- to 12-year-old schoolchildren (23). These as well as other available data demonstrate that silent iodine prophylaxis is not sufficient to restore an adequate iodine balance, and that more stringent prophylactic measures need to be taken by public health authorities.

Concerning pregnancy in moderately iodine-deficient areas, the most appropriate therapeutic approach is to systematically increase the iodine supply during gestation and after parturition, particularly in breastfeeding mothers. How much supplemental iodine should be given to prevent goitrogenesis remains a matter of local appreciation and depends mainly on the extent of the preexisting iodine deprivation. The ultimate goal is to restore and maintain a balanced iodine status; this goal can be reached in most instances during pregnancy with 100 to 200 μg of iodine given daily as a supplement. It should be remembered, how-
ever, that with longstanding iodine restriction in the diet before the onset of pregnancy, a lag period of approximately one trimester is inevitable before the benefits of iodine supplementation to improve thyroid function can be observed (10,20).

**The case of pregnancy in severe iodine deficiency**

Because of the difficulties inherent to careful field studies in most areas with severe iodine deficiency, there have been no systematic studies to assess the changes in goiter size during pregnancy. Until a few years ago, it was not feasible to obtain echographic measurements of the thyroid gland on a large and representative scale; it was even more difficult to prospectively observe goitrogenic changes during gestation. This situation may presently evolve rapidly, because of the possibility to adapt and use the ThyroMobil technology to large field studies in remote areas from Eastern Europe, Africa, and Asia. Such attempts are being envisaged, and fascinating results will presumably become available in the years ahead.

In women of child-bearing age and during pregnancy, iodine supplements have been administered in the form of iodized salt, potassium iodide drops and also in the form of iodide oil (given intramuscularly or orally) as an emergency prophylactic and a therapeutic approach in areas with severe iodine deficiency complicated by endemic cretinism. Several such programs have conclusively demonstrated their remarkable efficiency to prevent and treat endemic goiter, as well as to eradicate endemic cretinism (24). Also, the results of these studies have indicated that pregnant women who reside in severely iodine-deficient regions can be adequately managed with iodine supplementation. Except for emergency situations, there is presumably no need to use supra-

**FIG. 5.** A: Distribution frequencies of thyroid volumes (TVs), measured by ultrasonography, in a large number of healthy, nongoitrous pregnant women in Brussels, assessed during the first trimester and again 3 to 5 days after delivery. The graph indicates that: (a) the distribution pattern of initially normal TVs has shifted toward significantly larger TVs (with an average increment in glandular size of 30%) within only a few months; and (b) 20% of the women have developed a goiter by the end of pregnancy, with TVs ranging between 23 mL and 34 mL (the upper limit of normal TVs is indicated by the vertical dotted line at 22 mL). B: Distribution frequencies of TVs in 94 neonates in Brussels, born to mothers without \( n = 48 \) and with \( n = 46 \) iodine supplementation during pregnancy. The graphs show that iodine supplementation given during pregnancy allowed for a marked reduction in newborns’ mean TV and also for the absence of neonates with thyroid hyperplasia (the upper limit of normal TVs in newborns is indicated by the vertical dotted line at 1.5 mL). (Adapted with modifications from Glinoer [6]).
physiological amounts of iodine to improve significantly and even normalize thyroid function parameters. Although it has not been possible, thus far, in the setting of difficult field studies to evaluate quantitatively the reduction in goiter size or goiter prevalence associated with the improvement of thyroid function, it is assumed that goiter reduction was indeed a “side” benefit of the improvement in iodine status (25,26).

Consequences of Iodine Deficiency During Pregnancy on the Neuropsychointellectual Development of the Progeny

The potential consequences of maternal (and fetal) hypothyroxinemia on the progeny have recently been extensively reviewed (13). In conditions of iodine deficiency, both maternal and fetal thyroid functions are affected, and it is therefore primarily the degree of severity and the precocity of iodine deficiency that takes place during pregnancy that will drive the potentially deleterious repercussions for fetal neurological development. Because iodine is required for thyroid hormone synthesis, and thyroid hormones for an adequate brain development both during fetal and early postnatal life, iodine deficiency, if severe enough to impair thyroid hormones synthesis during critical periods of brain development, can induce brain damage with its dramatic consequence of an irreversible deficit in the final neuro-psychointellectual development, including mental retardation (27).

In 1993, almost one-third of the world’s population was affected by iodine deficiency that therefore appeared as the most prevalent cause of avoidable mental retardation (2,28). Severe iodine deficiency (defined as an iodine intake below 20 to 25 μg/d) is accompanied by the occurrence of an abnormally high number of individuals referred to as endemic cretins (with prevalences up to 5% to 15%, in some severely affected populations), who exhibit a variety of anomalies of both intellectual and physical development. In most severe endemic goiter areas of the world, the clinical picture of endemic cretinism is characterized by severe mental retardation together with a neurological picture including deaf-mutism, squint, pyramidal, and extrapyramidal syndromes. There are relatively few clinical signs of thyroid failure, and thyroid function and goiter prevalence are almost similar to those observed in noncretin populations. A remarkable exception to this picture has been reported in Africa, where the cretins have less mental retardation and much less important and frequent neurological signs. In contrast, the clinical picture is dominated by severe thyroid failure with dwarfism, delayed sexual maturation, and myxedema. Thyroid function is grossly impaired and the frequency of goiter is low. The present consensus view is that the neurological picture, characteristic of endemic cretinism, is caused by
insults to the developing brain occurring perhaps already during the first trimester (deafness), and mostly during the second trimester of gestation, while the cerebellar abnormalities may result from a postnatal insult (29–31). This interpretation is supported by the observation that the full neurological picture of endemic cretinism can only be prevented when the iodine deficiency is corrected during pregnancy before the second trimester, and optimally even before conception (32). The particular pattern commonly found in Africa might be explained by the fact that in this area iodine deficiency is complicated by selenium deficiency: selenium deficiency results in the accumulation of peroxide in the hyperstimulated thyroid glands, and excess peroxide induces thyroid cells destruction, leading to parenchymal fibrosis and hypothyroidism (33,34). Selenium deficiency also induces decreased MID-1 activity (a seleno-enzyme) in pregnant women, resulting in a reduced T4 to T3 conversion and, in turn, in increased availability of maternal T4 for the fetal brain. This probably explains the higher serum T4 levels recorded during pregnancy in selenium-deficient pregnant women in Africa compared with New Guinea, despite the similar severities of iodine deficiency in these regions. Such a protective mechanism might prevent the development of neurological cretinism, and the combined iodine and selenium deficiencies that prevail in Africa might help explain the predominance of the myxedematous type of endemic cretinism observed in this continent.

Taken together, the different observations suggest that if severe enough, iodine deficiency may induce maternal hypothyroxinemia from early gestation onwards, and also fetal hypothyroxinemia, with resulting mental retardation and neurological abnormalities that depend ultimately on the timing and the severity of the brain insult. In addition to the characteristic picture of endemic cretinism, severe iodine deficiency is also associated with intellectual deficit in subjects who present no other sign. In a meta-analysis of 18 studies conducted in areas with severe iodine-deficiency disorder, it was shown that iodine deficiency was responsible for an IQ loss of 13.5 points (35). Endemic cretinism therefore only constitutes the extreme expression of a spectrum of abnormalities in the physical and intellectual developments, as well as in the diminished functional capacity of the thyroid gland observed in inhabitants of areas with severe iodine-deficiency disorder.

Finally, it is important to note that the neurointellectual deficits associated with iodine deficiency are not limited to remote areas with severe iodine deficiency and endemic cretinism. In a series of studies conducted in areas with moderate or even mild iodine deficiency, mainly from southern Europe, it was shown that developmental abnormalities may also occur in clinically euthyroid schoolchildren. Even borderline iodine deficiency, as observed in many European countries, may be accompanied by impaired school achievements in apparently normal children (for reviews, see Glinoer and Delange [13], Delange [36], and Delange et al. [37]). Even though the causal relationship between iodine-induced maternal/fetal hypothyroxinemia and the neurointellectual deficits in school-age children has not been fully established, the high frequency of neonatal transient hypothyroidism (and transient hyperthyrotopinemia), reported in moderately iodine deficient European countries, suggests at least that minor brain damage may occur in the perinatal period.

Moreover, postnatally acquired moderate hypothyroidism may also contribute to poorer achievements in cognitive motor and school performances (38).

Conclusions

The main changes in thyroid function associated with pregnancy are related to increased hormone requirements, which begin in the first trimester of gestation. Increased hormone requirements can only be met by proportional increased hormone production, directly depending upon the availability of iodine in the diet. When iodine nutrition levels are sufficient, physiological adaptation takes place. When iodine is restricted or deficient, adequate physiological adaptation is difficult to achieve and is progressively replaced by pathological alterations occurring in parallel with the degree of long-term iodine deprivation, leading to enhanced chronic glandular stimulation, hypothyroxinemia, and goiter formation. Therefore, pregnancy typically reveals underlying iodine restriction and gestation results in an iodine-deficient status, even in conditions with only a marginally restricted iodine intake, such as is observed in many European regions. Iodine deficiency during pregnancy has important repercussions for both mother and fetus, namely thyroid underfunction and goitrogenesis. Furthermore, iodine deficiency may be associated with alterations of the neuropsychointellectual outcome in the progeny, and the risk for an abnormal development of the progeny is further enhanced because both the mother and offspring are exposed to the deficiency not only during the entirety of gestation but also during the postnatal period.

In Europe, because iodine deficiency is still prevalent in many regions and remains the subject of great concern to several important groups of thyroidologists, pediatricians, epidemiologists, etc., maternal hypothyroxinemia and its potential repercussions on the mother and her progeny have been, in the past, and remain today major topics of public health interest. European investigators have therefore proposed for several years that iodine prophylaxis be introduced systematically to women during pregnancy in order to provide mothers with an adequate iodine supply throughout pregnancy.

Concerning iodine-deficiency disorder in areas with severe iodine deficiency, the correction of the iodine lack has proved highly beneficial to prevent mental deficiency disorders: the many actions undertaken to eradicate iodine deficiency have prevented the occurrence of mental retardation in millions of infants throughout the world. In most public health programs dealing with the correction of iodine-deficiency disorders, iodized salt has been used as the preferred strategy in order to supply iodine supplements to the household. Iodized salt, however, is not the ideal vector in the specific instance of pregnant women, breastfeeding mothers, young infants because of the necessity to limit the intake of salt, and therefore, particular attention is required to ensure that pregnant women will have an adequate iodine intake.

Finally, it is with some concern that the results of the recent nutritional survey in the United States has disclosed that iodine deficiency, long thought to have been eradicated for many years, may actually show a resurgence, particularly in women of child-bearing age. This issue will need to be con-
sidered seriously by the medical community and public health authorities.

References


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