Clinical and Biological Consequences of Iodine Deficiency during Pregnancy

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Abstract
The main change in thyroid function associated with the pregnant state is the requirement of an increased production of thyroid hormone that depends directly upon the adequate availability of dietary iodine and integrity of the glandular machinery. In healthy pregnant women, physiological adaptation takes place when the iodine intake is adequate, while this is replaced by pathological alterations when there is a deficient iodine intake. Pregnancy acts typically, therefore, as a revelator of underlying iodine restriction. Iodine deficiency has important repercussions for both the mother and the fetus, leading to hypothyroxinemia, sustained glandular stimulation and finally goitrogenesis. Furthermore, because severe iodine deficiency may be associated with an impairment in the psychoneurointellectual outcome in the progeny, because both mother and offspring are exposed to iodine deficiency during gestation (and the postnatal period), and because iodine deficiency is still prevalent today in several large regions of the world, iodine supplements should be given systematically to pregnant and breastfeeding mothers. Particular attention is required to ensure that pregnant women receive an adequate iodine supply, in order to reach the ideal recommended nutrient intake of 250 μg iodine/day.

Introduction
Iodine deficiency (ID) is a major threat to the health and development of populations worldwide, with preschool children and pregnant women representing the target groups with the highest risks. When requirements for iodine are not met, thyroid hormone (TH) synthesis is impaired, resulting in a series of functional and developmental abnormalities collectively referred to as ID disorders. Depending upon the degree of severity of ID in a given population, clinical conditions associated therewith include goiter (referred to as ‘endemic
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...goiter’), miscarriage and still birth, hypothyroidism, impaired growth, as well as mental and neurological disorders resulting from irreversible brain damage (referred to as ‘endemic cretinism’). Although cretinism is the most dramatic expression of severe ID, more subtle degrees of mental impairment with poor learning abilities in schoolchildren as well as reduced intellectual performance and impaired working capability are also of considerable significance [1].

For the thyroid gland, the pregnant state represents a prolonged condition associated with alterations in the regulation of thyroid function and economy, due to separate physiological events that take place at different time points during gestation, and constitute a challenge for the maternal thyroid, because together these events exert stimulatory effects on the glandular machinery [2]. Until the late 1980s, it was commonly accepted that the thyroid gland was capable of adapting physiologically to the pregnant state without much happening in healthy euthyroid women. The main ‘apparent’ changes in thyroid function tests – that had been identified since the early 1960s – were an increase in serum total T4 and T3 concentrations following the marked increase in serum thyroxine-binding globulin (TBG) concentrations, itself resulting from sustained estrogen stimulation [3]. In these early days, it was also considered that the production of TH was not modified during pregnancy [4]. Nowadays however, this view has been completely modified, as several important metabolic changes are known to take place during pregnancy.

**Regulation of Thyroid Function during Pregnancy**

Beginning already in early gestation, reaching a plateau at midgestation that is maintained thereafter until term, there is a 2- to 3-fold increase in serum TBG concentrations under the influence of a sustained rise in the concentration of estrogen [5]. Also starting in early gestation, there is an increase in renal blood flow and glomerular filtration which leads to an increased iodide clearance from plasma, and thus to an obligatory loss of iodine. Occurring transiently near the end of the first trimester, there is direct stimulation of the maternal thyroid gland by an increase in the concentration of human chorionic gonadotropin that may lead temporarily to a slight increase in the concentration of free T4 [6, 7]. Finally, significant changes occur in the peripheral metabolism of maternal TH during the second half of gestation, mainly under the influence of placental type 3 iodothyronine deiodinase [8, 9]. Together, these events represent a profound metabolic change, associated with the progression of gestation already during its first half, which constitutes a transition from the preconception thyroidal steady state to the pregnancy steady state.
In order to be met, these metabolic changes require an increase in hormone production by the maternal thyroid gland (fig. 1). Once a new equilibrium has been reached, the increased demands of TH are sustained until term. For healthy pregnant women with a sufficient iodine intake, the challenge for the thyroid gland is to adjust the hormonal output in order to achieve the new equilibrium and maintain it until term: this corresponds to physiological adaptation of the thyroidal economy to the pregnant state. When pregnancy takes place in women who are otherwise healthy but reside in an area with a restricted iodine intake, physiological adaptation is progressively replaced by pathological alterations. Thus, pregnancy typically acts to reveal the underlying iodine restriction: the more severe the ID, the more pronounced the maternal (and also fetal) thyroidal consequences [10–15].

**Fig. 1.** The scheme shows the three series of separate events which together concur in exerting stimulatory effects on thyroid function during a normal pregnancy. The first event is linked to the progressive rise in TBG concentrations during the first trimester; the second event takes place transiently near the end of the first trimester and is related to the thyrotropic action of peak hCG concentrations; the third event takes place mainly during the second half of gestation and is related to pregnancy-specific modifications in peripheral metabolism of maternal TH, mainly at placental level. MID = Monoiodothyronine deiodinase (type I, II, III).
After being reduced to iodide, dietary iodine is rapidly absorbed from the gut. Iodide of dietary origin then mixes rapidly with iodide derived from the peripheral catabolism of TH and iodothyronines by deiodination, and together they constitute the extrathyroidal pool of plasma inorganic iodide. This pool exists in a dynamic equilibrium with two organs, the thyroid gland and the kidneys. A schematic representation of the kinetics of iodide in healthy nonpregnant and pregnant adults is shown in figure 2. A normal adult uses some \(80\) \(\mu\)g of iodide/day to produce TH and the system is balanced to fulfil these daily needs. When the iodine intake by nonpregnant women is adequate \((\sim 150\) \(\mu\)g/day), the kinetic balance is achieved by thyroid uptake of \(35\%\) of the available iodine. Of the \(80\) \(\mu\)g of hormonal iodide produced each day by the catabolism of TH, \(15\) \(\mu\)g of iodide is lost in the feces, leaving \(65\) \(\mu\)g to be redistributed between the

**Fig. 2.** Schematic representation of the kinetics of iodide in healthy nonpregnant and pregnant adults. 

- **a** Nonpregnant adult with an adequate iodine intake of \(150\) \(\mu\)g/day.
- **b** Nonpregnant adult with a restricted iodine intake corresponding to \(70\) \(\mu\)g/day.
- **c** The latter condition is compared with an identically restricted level of iodine intake \((70\) \(\mu\)g/day) in a pregnant woman. Daily production of TH was set at \(80\) \(\mu\)g of iodide/day (in nonpregnant adults) and increased by 1.5-fold to \(120\) \(\mu\)g/day during pregnancy.
thyroid gland and irreversible urinary losses. In these conditions the metabolic balance remains in equilibrium and the body is able to maintain abundant intrathyroidal iodine stores ranging from 10 to 20 mg [16]. In contrast, when the iodine intake is restricted before the onset of a pregnancy to 70 μg/day or less, the body must increase iodide trapping through the pituitary-thyroid feedback mechanism to compensate for iodine restriction and maintain the necessary absolute iodine intake. Augmentation of iodide trapping is the fundamental mechanism through which the thyroid gland adapts to changes in the daily iodine supply, and this mechanism is the key to understanding the thyroid adaptation to ID [17, 18]. In such conditions, there is a shortfall of some 10 μg of iodine a day and the thyroid gland uses stored iodine which is therefore progressively depleted to low amounts of 2–5 mg of stable iodine. Over time, if the nutritional situation remains unchanged, the metabolic balance of iodine tends to become negative.

Two fundamental changes take place during pregnancy. First, there is a significant increase in renal iodide clearance by some 30–50%. Since the renal iodide clearance already increases in the first weeks of gestation and persists thereafter, this constitutes an obligatory iodine ‘leakage’ which tends to lower circulating plasma inorganic iodide concentration and, in turn, induce a compensatory increase in the thyroidal clearance of iodide. Second, there is a concomitant and sustained increase in the production of TH by 50%, which corresponds to an incremental requirement from 80 to 120 μg of hormonal iodide/day. These two mechanisms underscore the increased physiological activity of the thyroid gland during the first half of pregnancy [19–23]. Calculations show that when the daily intake is restricted to only some 70 μg of iodine during pregnancy and despite an increment in thyroidal uptake to 60%, the equilibrium becomes more or less rapidly lost, with an absolute iodide entry into the gland that is insufficient to fulfil the increased requirements of TH production. In such conditions, there is a shortfall of some 20 μg of iodine/day. As figure 2 shows, in order to sustain an increased production of TH, the glandular machinery must draw from already depleted intrathyroidal iodine stores [2, 13]. An additional mechanism of maternal iodine deprivation occurs during the second half of gestation, from the passage of a part of the available iodine from the maternal circulation to the fetal-placental unit. The absolute extent of iodine that is transferred from the mother to the fetus has not yet been precisely established but, at midgestation, the fetal thyroid gland has already started to produce TH that are indispensable for the adequate development of the fetus.

In summary, during pregnancy in conditions with ID, the already lowered intrathyroidal iodine stores become even more depleted within one trimester after conception; furthermore, when the iodine deprivation prevails already during the first half of gestation, ID tends to become even more severe with the
progression of gestation to its final stages. This is the rationale for the excessive stimulation of the thyroid gland that is observed during a pregnancy that takes place in conditions with ID. The consequences of this are relative hypothyroxinemia and hypothyroidism with an increased concentration in serum thyroid-stimulating hormone (TSH) and thyroglobulin (TG), and finally an increase in thyroid volume (TV) leading to goiter formation in both the mother and newborn [24–26].

**Epidemiology and Management of ID during Pregnancy**

*Epidemiological Aspects*

Countries such as the United States, Japan, and a limited number of European regions have set up national programs of dietary iodine supplementation in the population that have been in place for many years. Therefore, ID disorders are believed not to present problems. This view is however probably too optimistic. A recent survey in the United States has shown that the average iodine intake has markedly decreased during the period 1988–1994, compared with a similar survey carried out in 1971–1974. The median urinary iodine excretion is presently 150 μg/l compared with over 300 μg/l in the previous period. Even though such a level of iodine intake in the USA may at first glance be considered almost ideal and ‘comfortably above the recommended minimum’, the survey showed that as many as 15% of women of child-bearing age and almost 7% during pregnancy had iodine excretion levels which were in the range of moderate ID, namely below 50 μg/l [27, 28].

A second important epidemiological consideration is that the risk of iodine deprivation during pregnancy needs to be assessed locally and monitored over time, because mild to moderate ID occurs in areas that are not immediately recognized to be iodine-deficient. For instance, the southwestern region of France was not particularly known to be iodine deficient because of the relative proximity to the sea and the fish-eating habit of the population. Nevertheless, a study performed in 1997 in a cohort of pregnant women in the city of Toulouse clearly showed that urinary iodine excretion levels (UIE) were too low, with over 75% of pregnant women having iodine excretion levels below 100 μg/l [29].

A third important concept relates to the notion of unexpected geographical variations in the iodine intake within a given country, because ID in general, and mild-to-moderate ID more specifically, may frequently show significant variations from one area to another. A good example is illustrated by a Danish study. Pregnant women without iodine supplementation had a median iodine excretion level of 62 μg/g creatinine in Copenhagen compared with only 33 μg/g creatinine in another area of Denmark (Jutland). Furthermore, these striking
differences were not alleviated in pregnant women from the same two areas who received iodine supplements, indicating that the supplementation was not sufficient enough, presumably because the iodine supplements were entirely taken up by the maternal (and perhaps fetal?) iodine-deprived thyroid glands [30].

In summary, the degree of ID should therefore be assessed specifically in each area concerned and the local situation correctly evaluated before embarking on medical recommendations for iodine fortification programs [31].

**Managerial Aspects**

In 2001, the World Health Organization has officially endorsed the recommendations made by international organizations such as the ICCIDD (International Council for Control of Iodine Deficiency Disorders) and UNICEF (United Nations Children’s Fund) to eliminate ID disorders, on the basis that ID present at critical stages during pregnancy and early childhood resulted in impaired development of the brain and consequently in impaired mental function. The recommended nutrient intake (RNI) for iodine in adults and children above the age of 12 years is 150 μg/day. While a variety of methods exists for the correction of ID, the most commonly applied method is universal salt iodization (USI), that is the addition of suitable amounts of potassium iodide (or iodate) to all salt for human and livestock consumption [32]. In January 2005, a committee of international experts met in Geneva under the auspices of the World Health Organization, and the 2001 recommendations were revised [33] (table 1). The consensus reached by the panel was that the RNI for iodine during pregnancy and breastfeeding should range between 200 and 300 μg/day, with an average of 250 μg/day. During breastfeeding, the physiology of TH production returns to normal but iodine is efficiently concentrated by the mammary gland into milk. Since breast milk provides approximately 100 μg of iodine per day to the infant, the WHO recommendation is that breastfeeding mothers should continue to take 250 μg of iodine/day. An excessive iodine intake may potentially cause more disease, especially in patients with known (or underlying) autoimmune thyroid disorders or autonomous thyroid tissue [34]. Since there is no strong evidence to define clearly ‘how much more iodine may become too much iodine’, the present consensus is to indicate that there is no proven further benefit in providing pregnant women with more than twice the daily RNI, i.e. 500 μg of iodine/day.

To implement the RNI for iodine in the pregnant state, the natural iodine intake level in a population must be taken into account. Therefore, multiple tailored means must be used to reach the RNI for iodine. The overall consideration is that the sooner the iodine fortification is implemented, the better is the resulting adaptation of thyroid function to the pregnant state. It is also important to
emphasize that USI cannot be used for this purpose in pregnancy because of the necessary salt restriction. Practically for the implementation of iodine fortification during pregnancy, several epidemiological situations must be distinguished. In countries with a long-standing and well-established USI program, pregnancies are not at risk of having ID and, therefore, no systematic dietary fortification ought to be organized in these populations. It can however be recommended individually to pregnant women to use multivitamin tablets prepared specifically for the needs of pregnancy and containing iodine supplements, since it is known that even in such apparently satisfactory iodine intake conditions, a fraction of pregnant women may still have an insufficient dietary iodine intake [27]. In countries without an efficient USI program or an established USI program where the coverage is known to be only partial, complementary approaches are required to reach the RNI for iodine. Such approaches include the use of oral iodine supplements in the form of potassium iodide (100–200 µg/day) or the inclusion of KI (125–150 µg/day) in multivitamin tablets specifically designed for pregnancy. Finally in areas with no accessible USI program and difficult socioeconomic conditions generally, it is recommended to administer orally iodized oil as early during gestation as possible: 400 mg of iodine will cover thyroidal needs for about a 1-year period [35].

Table 1. Recommendations for iodine nutrition during pregnancy

- It is recommended that women take 150 µg of iodine/day before pregnancy
- It is recommended that women increase their iodine intake to 250 µg/day during pregnancy and breastfeeding
- It is recommended to start iodine fortification as early in pregnancy as possible
- The maximum iodine intake should not exceed 500 µg/day to prevent the risk of iodine-induced thyroid disease in women with a predisposition (autoimmune thyroid disease, autonomous thyroid tissue)
- USI cannot achieve target supplementation levels because of salt restriction in pregnant women
- To achieve the RNI level for iodine supplementation, it is recommended to use:
  - Oral iodine supplements with KI (100–200 µg/day) or multivitamin tablets containing iodine (125–150 µg/day) in countries with a partial USI coverage
  - Oral iodized oil (400 mg of iodine once): this dose supplements for a 1-year period and is adequate for pregnant women who cannot afford or adhere to daily supplementation
- To monitor the adequacy of iodine supplementation at a population level, it is recommended to use measurements of urinary iodine excretion
- To monitor the adequacy of iodine supplementation at an individual level, it is recommended to use thyroid function parameters, such as serum TSH, free T₄, TG, T₃/T₄ ratio, and TV measured by ultrasonography
Monitoring the Adequacy of Iodine Intake

The best single test to evaluate the adequacy of iodine nutrition in a population is provided by UIE. In conditions with an adequate iodine intake during pregnancy, the UIE should ideally range between 150 and 250 μg/day (or 100–200 μg/l, based on an average 1.5 liters of daily urine output) [36]. However, although UIE is highly useful for public health estimations of iodine intake levels in populations, it alone is not a valid diagnostic criterion in individuals. Therefore, to assess the situation at the level of an individual, it is recommended to use thyroid function parameters which constitute valid markers of the thyroidal consequences of ID during pregnancy (table 1).

Consequences of ID during Pregnancy

Biological Consequences

The increase in TBG during gestation causes an increase in total serum TH (T_4 and T_3). To estimate the free hormone concentration, a TH binding ratio, free T_4 index, or direct free T_4 measurement must be obtained. Because the reduction in the free fraction of T_3 is approximately equal to that of T_4, the standard approach for these determinations using T_3 as a tracer can still be used. However, it is important to recognize that as the free fraction is reduced, the resin T_3 uptake (and similar assessments of the free hormone fraction) asymptotically approaches a fixed lower limit. This is not linearly related to the increase in unoccupied TBG binding sites [37]. Thus, the decrease in the TH binding ratio usually does not match the quantitative decrease in the T_4- and T_3-free fractions estimated directly, and in some sera the free T_4 index or estimate will end up being slightly elevated relative to the true free T_4 or T_3 [38]. Direct measurements of serum free T_4 using the older ‘analogue’ technologies often resulted in an artifactually decreased free T_4 estimate in euthyroid pregnant subjects. Such artifacts have been attributed to the influence of the physiological serum albumin decrease that commonly occurs in pregnancy. Even nowadays and despite technical progress, these artifacts need to be taken into account in the interpretation of thyroid function tests in pregnant women [39, 40].

In healthy pregnant women with an adequate iodine supply, the increase in total serum T_4 is less marked than the increase in serum TBG. As a consequence, TBG is slightly less saturated with T_4 and the free T_4 concentration decreases physiologically during gestation by 10–15% [2]. To differentiate between the ‘normal’ and an abnormal decrement in free T_4 concentrations, it has recently been suggested to establish trimester-specific ranges for free T_4 measurements in the pregnant state [41]. Concerning serum TSH concentrations, these may be transiently lowered – and hence become infranormal – during
the first trimester in about one fifth of pregnant women in response to eleva-
tions of human chorionic gonadotropin. Thus, such a lowering in serum TSH
should not lead automatically to a diagnosis of thyroid dysfunction. During the
second and third trimester, serum TSH returns to the normal range of
0.4–2.5 mU/l [2, 5, 7, 42] (see table 2).

The main impact of ID occurring before and during pregnancy, even when
it is considered only mild or moderate, is to induce maternal hypothyroxinemia.
Hypothyroxinemia can be defined as any deviation of serum free T4, at any time
point during gestation, that is present for a prolonged period with free T 4 con-
centrations significantly below those considered ideal for a given gestational
age. In these conditions, the abnormal lowering in free T 4 leads, in turn, to
enhanced thyroidal stimulation via the pituitary (TSH) feedback mechanisms
and ultimately to goiter formation in both the mother and fetus (see below). In
clinical practice, enhanced glandular stimulation associated with ID can be
evaluated using simple biochemical parameters [13]. Five biochemical thyroid
parameters have been shown to provide useful markers for evaluating enhanced
glandular stimulation when pregnancy takes place in association with ID. The
first parameter is relative hypothyroxinemia, i.e. free T 4 concentrations that
tend to cluster near (or below) the lower limit of normality. The second param-
eter is preferential T 3 secretion, reflected by an elevated total T 3/T 4 molar ratio.

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<th>Table 2. Thyroid physiology during pregnancy</th>
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<td>Physiological change</td>
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<td>in iodine sufficiency</td>
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<td>Increased renal iodine clearance with obligatory iodine losses</td>
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<td>Decreased plasma iodine and placental transport of iodine to the fetus</td>
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<td>Increased serum TBG</td>
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<td>Increased plasma volume</td>
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<td>Inner-ring deiodination of T 4 and T 3 by placenta</td>
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The third parameter is related to changes in serum TSH. While serum TSH remains unchanged in iodine-sufficient pregnancies, TSH levels show a progressive and steady increase after the first trimester and until term in women with ID. The fourth parameter concerns the changes in serum TG. In iodine-deficient pregnancies, serum TG increases progressively to reach supranormal values, mainly during late gestation. It is important to emphasize that monitoring serum TG changes during pregnancy in conditions with ID is of particular clinical value, because the increment in TG correlates well with goiter formation, hence constituting a useful prognostic marker of gestational goitrogenesis. Finally, as already alluded to above, the fifth parameter is provided by the lowering in UIE, which broadly follow the degree of severity of ID. The successive steps in the formation of a vicious circle associated with ID, and its prevention by the early fortification of dietary iodine intake are schematically represented in figure 3.

**Goiter Formation**

In the early 1990s, the concept was introduced that ID was a preponderant causal factor to explain gestational goitrogenesis, affecting both the mother and the fetus (fig. 4). While goiter formation was not noticeable in pregnant women residing in iodine-sufficient areas, several European studies indicated that significant changes in TV occurred in association with pregnancy. Together, these studies have shown that pregnancy is frequently associated with goiter formation [2, 10, 24]. In regions with a sufficient iodine intake, the increments in TV remain usually minimal, in the order of 10–15% on average above the preconception TV; these minor changes are mainly consistent with vascular swelling (intumescence) of the gland during pregnancy [43, 44]. In other regions known
to have a lower iodine intake, increments in TV are significantly more marked, ranging between 20 and 35% on average, with many women exhibiting a doubling in TV between the first trimester and term. For instance in areas such as Brussels (Belgium) and Toulouse (France), 10% of the women were shown to develop a gestational goiter before iodine supplementation was systematically prescribed, and the degree of glandular hyperplasia was directly correlated to the severity of ID during pregnancy (see fig. 4b) [5, 24, 29]. Thus, goiter formation during pregnancy is the hallmark of ID. Together, low intrathyroidal iodine stores that prevail already before conception, increased needs for a higher iodine availability once pregnancy begins, and finally, insufficiency of daily iodine intake – that is maintained throughout gestation – constitute the three major components of enhanced thyroidal stimulation and resulting goitrogenesis in the pregnant state [45–47].

Concerning the newborns of mothers with ID, precise ultrasonographic measurements of TV in neonates have indicated that thyroid sizes were 40% larger in the newborns from nonsupplemented mothers compared with newborns from iodine-supplemented mothers (see fig. 4e). Moreover, glandular hyperplasia was already present in 10% of these infants soon after birth, compared with none in the newborns from iodine-receiving mothers. These data show that ID is associated with goiter formation in the progeny, and emphasize the exquisite sensitivity of the fetal thyroid to the consequences of maternal iodine deprivation, indicating that the process of goiter formation starts already during the earliest stages of development of the fetal thyroid gland [48].

Long-Term Consequences of Gestational Goitrogenesis

An important question concerns the long-term evolution of a goiter formed during pregnancy, in the absence of iodine supplementation. Both prospective and retrospective studies have shown that maternal goiters due to ID do not revert entirely to baseline TV values after parturition [45, 49]. The women who develop a goiter during gestation are prone to remain goitrous thereafter, and the succession of consecutive pregnancies add to this detrimental effect (see fig. 4d). Gestational goiter formation constitutes therefore one of the environmental factors explaining the preponderance of goiter in the female population, especially in multiparous women (see fig. 4e). In a recent study from Denmark, it was also shown that parity had an influence on thyroid size in conditions with ID, especially in women who smoked (see fig. 4e) [47].

In summary, pregnancy represents a strong goitrogenic stimulus for both the mother and fetus, even in areas with only moderate ID. Several environmental factors may play a role to explain gestational goiter formation, which tend to reinforce each other: ID, successive pregnancies, and finally smoking habits.
Prevention of Gestational Goiter Due to ID

As already discussed, women should ideally be provided with an adequate iodine intake (150 μg/day) long before they become pregnant in order to prevent gestational goitrogenesis, since it is only by reaching a long-term steady state with replenished intrathyroidal iodine stores 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 has been the aim of a massive global campaign, undertaken 10–15 years ago worldwide, and that has shown remarkable progress so far [31, 50–52]. Until 1992, most European countries were moderately to severely iodine deficient. A survey carried out in twelve 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 aged 7–15 years. The main results indicated that the status of iodine nutrition was markedly improved in many, albeit not all, of the European countries surveyed. Silent iodine prophylaxis is not sufficient to restore an adequate iodine balance, and more stringent prophylactic measures need to be taken by public health authorities to achieve an ideal iodine nutrition status in the population [53–55].

In the mean time, the most appropriate preventive and therapeutic approach to avoid gestational goitrogenesis is to systematically increase the iodine supply as early as possible during gestation and continue the nutrition fortification after parturition, particularly in mothers who breastfeed. This can

Fig. 4. a TV in 10 selected healthy pregnant women (numbered from 1 to 10) in Brussels, measured by ultrasonography at initial presentation in the first trimester, then at delivery, and finally 12 months postpartum, and showing goiter formation during pregnancy in 4/10 women and only a partial TV normalization during the postpartum period (adapted from Glinoer et al. [45]). b Inverse correlation between the degree of thyroid hypertrophy and the severity of ID (measured as urinary iodine concentrations) in pregnant women in the southwest of France (adapted from Caron et al. [29]). c Progressive changes in TV (mean ± SD) between group 0 (representing nulliparous women) and group IV (representing women with previous pregnancies: group I had one pregnancy, group II two pregnancies, group III three pregnancies, group IV four or more pregnancies) in a retrospective study of TV in relation to parity in 208 nongoitrous healthy women with a mean age of 42 years from southern Italy (adapted from Rotondi et al. [46]). d The effect of parity and smoking on TV in women in Denmark (adapted from Knudsen et al. [47]). e Distribution frequencies of TVs in neonates born to mothers without (left) and with (right) iodine supplementation during pregnancy. Iodine supplementation allowed for a marked 38% average reduction in mean neonatal TV and for the complete prevention of thyroid hyperplasia at birth. The upper limit of normal TV in newborns is indicated by the vertical dotted lines (adapted from Glinoer et al. [48]).
be achieved by the use of multivitamin pills, containing appropriate amounts of iodine supplements. How much supplemental iodine should be given to prevent goiter formation remains a matter of local assessment, since it depends mainly on the extent of the preexisting iodine deprivation [56–59]. The ultimate goal which is to restore and maintain a balanced iodine status can be reached in most instances with 100–200 μg iodine given daily as a supplement during pregnancy. It should be remembered, however, that with long-standing iodine restriction in the diet before the onset of pregnancy, a lag period (of about one trimester) is inevitable before the benefits of the iodine supplementation improving thyroid function are observed.

**Pregnancy in Regions with Severe ID**

In many regions in the world, ID is not only overtly present, but it is often severe. Large areas remain in Central Africa and Asia, for instance, that still have iodine intakes below 25 μg/day, characteristic of severe ID and endemic goiter [51, 52]. In such regions, the thyroid status of pregnant women and their offspring is frequently impaired. In addition, other factors, such as selenium deficiency and thiocyanate excess (resulting from the staple use of foodstuffs such as cassava) combine with severe ID, tending to complicate the thyroidal situation even further [60]. In terms of thyroid function, the adult populations usually exhibit a mixed pattern encompassing subjects with a normal thyroid function and others who present various degrees of hypothyroidism. In women of child-bearing age, severe ID and hypothyroidism play a role in reducing fertility and increase the rate of spontaneous abortions.

When these women become pregnant, thyroid function tends to deteriorate even further, as gestation progresses. Thus, the thyroidal stress associated with pregnancy in conditions with mild to moderate ID cannot be compared, at least in quantitative terms, with the thyroidal repercussions observed in countries with long-standing and severe ID. Because of the obvious difficulties inherent in careful field studies in most areas with severe ID, there have been only few studies of thyroid function and no systematic study to assess the changes in goiter size in pregnant women [61–63]. 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 investigate prospectively goitrogenic changes during pregnancy. Presently, this situation is rapidly evolving, because of the possibility to adapt the ThyroMobil technology to large field studies even in remote areas [64, 65].

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 iodized oil (given intramuscularly or orally) as an emergency prophylactic and therapeutic approach in areas with severe ID complicated by endemic cretinism. Several such programs have conclusively demonstrated their remarkable efficiency to treat endemic goiter, as well as to eradicate endemic cretinism [31, 60, 66]. Also, the results of these studies have proved that the pregnancy of women who reside in severely iodine-deficient regions can be managed adequately with iodine supplementation. Except for emergency situations, there is presumably no need to use supraphysiological amounts of iodine to improve significantly or even normalize thyroid function parameters. Although it has not been possible so 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 can be assumed that goiter reduction was indeed a ‘side’ benefit of the improvement in the iodine status.

Fetal and Neonatal Consequences of Maternal ID and Thyroid Underfunction

The adequate functioning of both the maternal and fetal thyroid glands plays an important part to ensure that the fetal neuropsychointellectual development progresses normally. Globally, three sets of clinical disorders, schematically illustrated in figure 5, ought to be considered. In infants with a defect of thyroid ontogenesis, leading to congenital hypothyroidism, the participation of maternal TH to the fetal circulating thyroxine environment remains theoretically normal. Therefore, the risk of brain damage results exclusively from the insufficient production of TH by the fetus, and will hence depend on the severity of the defect involved (for instance, total agenesis versus ectopia). In contrast, when only the maternal thyroid gland is functionally deficient (for instance, in hypothyroidism due to chronic autoimmune thyroiditis), both the severity and the temporal occurrence of maternal thyroid underfunction will drive the resulting consequences for an impaired fetal neuronal development. Clinical situations of this type may take place already at early gestational stages (women with untreated or undertreated hypothyroidism), or appear during late gestational stages (women with autoimmunity features who are euthyroid during the first half of gestation). Finally, in conditions of ID, both maternal and fetal thyroid functions are affected. Therefore, it is primarily the precocity and severity of pregnancy-related ID that will drive the potential repercussions for fetal neurological development.

Iodine is required for the synthesis of TH, and TH are crucial for brain development both during fetal and early postnatal life [67–70]. When severe enough, ID induces maternal and fetal hypothyroxinemia from early gestation
Thus, any impairment in hormone availability during critical periods of brain development may induce irreversible brain damage, with mental retardation and neurological abnormalities as the final consequences (i.e. endemic cretinism) that ultimately depend upon the timing and severity of the brain’s insult [71–73]. The characteristic neurological picture of endemic cretinism is presumably directly due to insults to the developing brain, occurring already during the first trimester (i.e. deafness) and mostly during the second trimester, while cerebellar abnormalities may result from a postnatal insult [74–76]. This interpretation is supported by the observation that the full neurological picture of endemic cretinism can only be prevented when ID is corrected before the second trimester of pregnancy, and optimally prior to conception [71]. The particular pattern of myxedematous cretinism that is commonly found in Africa might be explained by the fact that in this area severe ID is complicated by selenium deficiency. Selenium deficiency results in the accumulation of peroxide in the hyperstimulated thyroid glands, and excess peroxide induces thyroid cell destruction, leading to parenchymal fibrosis and hypothyroidism [77]. Endemic

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**Fig. 5.** Schematic representation of the three sets of clinical conditions that may affect thyroid function in the mother alone, the fetus alone, or the fetomaternal unit, showing the relative contributions of an impaired maternal and/or fetal thyroid function that may eventually lead to alterations in fetal thyroxinemia (from Glinoer and Delange [25]).
cretinism, therefore, constitutes the extreme expression of a spectrum of abnormalities in the physical and intellectual development in children, as well as diminished functional capacity of the thyroid gland, observed in inhabitants of areas with severe ID and endemic goiter. In a meta-analysis of eighteen studies conducted in areas with severe ID, it was shown that ID was responsible for an IQ loss of 13.5 points [78].

Neurointellectual deficits associated with ID, however, are not limited to remote areas, known to be severely affected by ID. In recent years, the impact of mild or moderate ID on the fetus has also been recognized. For instance in studies conducted in areas with only a moderate or even mild ID (such as in the southern part of Europe), developmental abnormalities were shown to occur in clinically euthyroid school-age children [79–84] (table 3). Thus, ID is one of the most prevalent causes of mental retardation and reduced learning abilities in children that could easily be prevented and eliminated by adequate iodine supplementation.

**Table 3.** Neuropsychointellectual deficits in schoolchildren born to mothers residing in areas with mild-moderate ID

<table>
<thead>
<tr>
<th>Region</th>
<th>Tests</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Locally adapted tests:</td>
<td>Lower psychomotor and mental development</td>
<td>Bleichrodt et al. [79]</td>
</tr>
<tr>
<td></td>
<td>Bayley</td>
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<td></td>
<td>McCarthy</td>
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<td></td>
<td>Cattell</td>
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<tr>
<td>Italy</td>
<td>Bender-Gestalt</td>
<td>Low perceptual integrative motor ability and neuromuscular and neurosensorial abnormalities</td>
<td>Vermiglio et al. [80]</td>
</tr>
<tr>
<td>Sicily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Wechsler</td>
<td>Low verbal IQ, perception, motor and attentive functions</td>
<td>Fenzi et al. [81]</td>
</tr>
<tr>
<td>Tuscany</td>
<td>Raven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>WISC</td>
<td>Lower velocity of motor response to visual stimuli</td>
<td>Vitti et al. [82]</td>
</tr>
<tr>
<td>Tuscany</td>
<td>Reaction time</td>
<td></td>
<td>Aghini-Lombardi et al.  [83]</td>
</tr>
<tr>
<td>Italy</td>
<td>DSM-IV-TR, validated by subscales for the Italian population</td>
<td>Attention deficit and hyperactivity disorder</td>
<td>Vermiglio et al. [84]</td>
</tr>
<tr>
<td>Sicily</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Modified from Glinoer and Delange [25].
The main changes in thyroid function associated with the pregnant state are due to increased hormone requirements, which begin in the first trimester of gestation. Increased hormone requirements can only be met by proportionally increased hormone production, directly depending upon the availability of iodine in the diet. When dietary iodine is 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 glandular stimulation. Therefore, pregnancy typically acts to reveal the underlying iodine restriction and gestation results in a deficient iodine status, even in conditions with only a marginally restricted intake, such as is observed in many European regions. ID during pregnancy has important...
repercussions for both mother and fetus, namely thyroid underfunction and goitrogenesis. Furthermore, ID 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 the postnatal period. Iodine prophylaxis should be introduced systematically to women during pregnancy and the lactation period. Concerning areas with a severe deficiency, the correction of the lack of iodine has proved highly beneficial to prevent mental deficiency disorders: the many actions undertaken to eradicate ID have prevented the occurrence of mental retardation in millions of young infants throughout the world. In most public health programs dealing with the correction of the ID disorder, iodized salt has been used as the preferred method of conveying iodine supplements to the household. Iodized salt, however, is not the ideal vector in the specific instance of pregnancy and breastfeeding, because of the necessity to restrict salt intake. Finally, it is with some concern that the results of the recent nutritional survey in the United States have disclosed that ID, thought to have been eradicated many years ago, may actually show a risk of a resurgence, particularly in young women. This issue will need to be considered seriously by the medical community and public health authorities, since similar situations may occur in other countries as well (see the main ‘take home messages’ in table 4).

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