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The Regulation of Thyroid Function in Pregnancy: Pathways of Endocrine Adaptation from Physiology to Pathology

DANIEL GLINOER

Hospital Saint-Pierre, Department of Internal Medicine, Thyroid Investigation Clinic, Université Libre de Bruxelles, Belgium

Address reprint requests to: Prof. Daniel Glinoer, University Hospital Saint-Pierre, Department of Internal Medicine, 322, Rue Haute, 1000-Brussels/Belgium.

I. Introduction

THYROID disorders are observed 4- to 5-fold more frequently in women when compared with men, in particular during the childbearing period. It is therefore not unusual to encounter thyroid function abnormalities during a "routine" laboratory evaluation carried out for pregnant women. One of the aims of the present review is to underscore the rationale that allows for a correct interpretation of these alterations. Furthermore, pregnancy is accompanied by profound alterations in thyroidal economy, resulting from a complex combination of factors specific for the pregnant state: the rise in T_4-binding globulin concentrations, the effects of CG on the maternal thyroid, alterations in the requirement for iodine, modifications in autoimmune regulation, and the role of the placenta in deiodination of iodothyronines. Another aim of this review is to discuss the specific role attributed to each factor and delineate the main pathways of thyroidal adaptation, including physiology as well as pathophysiology in the pregnant state. Finally, the third aim is to discuss specific aspects of the management of hypothyroidism (related to established, subclinical, and preclinical hypothyroidism) and hyperthyroidism [both Graves' disease (GD) and gestational nonautoimmune transient thyrotoxicosis] when associated with pregnancy.

II. The Regulation of Thyroid Function in Normal Pregnancy

Hormonal changes and metabolic demands during pregnancy result in profound alterations in the biochemical parameters of thyroid function (1). For the thyroidologist, pregnancy can be viewed as a prolonged physiological condition in which a combination of events concur to modify the thyroidal economy. Such events may act independently, synergistically, or even antagonistically to produce subtle or major thyroidal effects. Furthermore, these events take place at different time points during gestation, resulting in complex effects that may be seen only transiently or, by contrast, that persist until term (2, 3).

A. The thyroid hormone transport proteins

Thyroid hormones (TH) are transported in serum noncovalently bound to three proteins: T_4-binding globulin (TBG),

albumin, and transthyretin (previously called prealbumin or TBPA) (4). The relative distribution of TH among the binding proteins is directly related to both their affinities and concentrations. In steady state conditions the bound hormone fraction is in equilibrium with a free unbound fraction, which represents a minute amount of the total circulating TH: 0.04% for T_4 and 0.5% for T_3 (5). Despite the fact that TBG in serum is by far the least abundant of the three transport proteins, about two thirds of the T_4 in serum of normal subjects is carried by TBG, owing to its extremely high affinity for the hormone (6). In conditions with TBG excess, such as pregnancy, the proportion of circulating T_4 carried by TBG is even greater, in excess of 75%, which indicates that TBG represents the major thyroid hormone transport protein in pregnancy (7). Furthermore, during pregnancy the respective affinities of the three binding proteins for their hormonal ligands are not significantly modified, and the circulating levels of both serum albumin and transthyretin remain stable, with only a slight tendency to decrease near the end of gestation, mainly as a result of passive hemodilution due to the increased vascular pool (8–10). Thus, the major change for thyroid hormone-binding proteins involves the marked and rapid increase in serum TBG levels as a result of estrogen stimulation. Compared with preconception concentrations (average 15–16 mg/liter), serum TBG begins to increase in pregnancy after a few weeks and reaches a plateau around midgestation, 2.5-fold higher than the initial value (between 30–40 mg/liter). Thereafter, the TBG concentration remains practically unchanged until term (Fig. 1) (11–13).

What are the mechanisms underlying the increase in serum TBG observed in conditions with estrogen excess? Earlier experimental animal studies, using both *in vitro* dispersed estrogen-exposed monkey hepatocytes and *in vivo* chronically estrogen-stimulated Rhesus monkeys, have shown that the increase in TBG observed in high estrogen conditions results from increased TBG production and release by the liver, where the protein is biosynthesized (14–16). In 1981, Gärtner *et al.* (17) demonstrated that native TBG, like many other serum glycoproteins, exhibited a molecular microheterogeneity caused by differences in the sialic acid content of the protein carbohydrate moieties (17). The microheterogeneity of TBG was shown, using isoelectric focusing, by separating four main bands with isoelectric point (pI) values between 4.25–4.55. The authors were also the first to report that, with TBG obtained from pregnant serum, the isoelectric focusing pattern showed a distinct anodal shift with more acidic bands (pI 4.15–4.17) corresponding to more heavily sialylated TBG, not seen with TBG from control subjects. A few years later, Refetoff and co-workers (18, 19) presented relevant information on the role of sialic acid terminal residues present on TBG's carbohydrate units in altering the stability and rate of removal of TBG from the bloodstream. Their studies showed that the survival of TBG in the circulation is dependent on its level of sialylation: TBG fractions with the highest sialylation levels are cleared from serum with a significantly longer half-life. However, these more heavily sialylated fractions represent only a small part of the total circulating TBG (~10–15%). Therefore, the net effect of kinetic changes due to highly sialylated estrogen-specific fractions on the global TBG clearance is relatively minor. Also, the work was carried out in a heterologous experimental system, where human TBG was injected into rats to perform the metabolic studies; this probably explains the authors' results of short TBG half-lives (~1 day), compared with the known physiological half-times of TBG determined in the Rhesus monkey (>4 days) and the human (>5 day) (15, 20, 21).

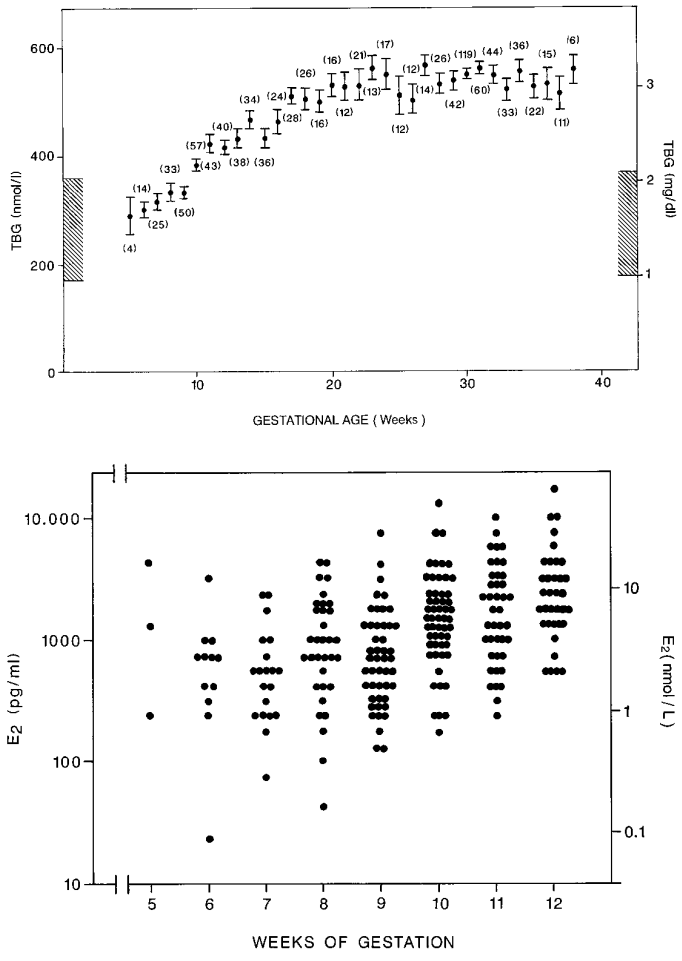

FIG. 1. *Upper graph*, Serum TBG changes as a function of gestational age. The data were obtained from individual serum TBG measurements in 585 euthyroid healthy women with normally progressing pregnancies (after exclusion of women who miscarried later on). Each point represents the mean ± SEM of TBG determinations at weekly intervals in the cohort of pregnant women. There was a significant correlation between serum TBG and gestation time, from the 5th to the 20th gestational week ($r = 0.60$; $P < 0.001$). The reference range of serum TBG in nonpregnant subjects is 10–21 mg/liter. The *numbers given in parentheses* indicate the number of women for whom serum TBG determinations were available, for each time point shown on the graph. *Lower graph*, Serum E_2 levels determined on a weekly basis in 246 normally progressing pregnancies, between the 5th and 12th week of gestation. Even though there was a significant correlation between serum E_2 and gestation time ($r = 0.40$; $P < 0.001$), the figure illustrates the individual variability in the progression of E_2 concentrations in the early stages of pregnancy. Between 5–12 weeks, 21.5% of E_2 levels were below 500 ng/liter and 41.9% below 1,000 ng/liter. [Derived from (34).]

Thus, we infer from these data that a prolonged biological half-time *per se* cannot entirely account for the observation that, at least in primates, serum TBG starts to increase 24 h

after the exposure to high estrogen (15). Ain *et al.* (22) also attempted to demonstrate directly an effect of estrogen on the synthesis and secretion of TBG, using a human hepatoma cell line Hep G2, which produces TBG. The authors failed to show an increase in the cytoplasmic TBG mRNA content after estrogen exposure. It should be kept in mind, however, that Hep G2 cells are not an ideal model for the study of estrogen effects on TBG synthesis because these tumor cells do not react to estrogen stimulation as do normal cells (4). TBG could already be produced at its maximal rate or the cells could simply be unresponsive to estrogen. Hence, until the debate can be solved by more definitive and direct arguments, we consider it safe to propose that the increase in serum TBG found in pregnancy might result from a combination of factors: increased TBG production by liver, prolonged half-life due to increased sialylation, and stabilization of the TBG molecule because more T_4 is proportionally bound to it.

Irrespective of the precise molecular mechanisms that may explain the TBG rise in pregnancy, it is important to note that the serum TBG increase observed during the first part of gestation does not follow a smooth curve. Determinations of TBG levels on a weekly basis in a large number of pregnancies indicates that the overall profile of the TBG rise in blood exhibits wide individual variation until the plateau is attained, and also that the plateau value is variable individually (Fig. 1). Such variation can be partially explained by the fact that preconception TBG levels are variable between 10–22 mg/liter (reference range in a normal female population) (23), but probably also because the effects induced by estrogen require that a certain threshold, estimated to correspond to E_2 concentrations in the order of 500–1,000 ng/liter, be reached. Figure 1 indicates that serum E_2 exhibits wide individual variation in the early stages of gestation, with the threshold range reached after as little as 6 weeks or as long as 12 weeks in healthy, normally progressing pregnancies. A final practical point to remember is that in women with inherited partial TBG deficiency, estrogen stimulation associated with pregnancy leads to variable modifications of TBG levels: no increase is observed in some women, while in others TBG is increased compared with preconception values, albeit to a much lesser extent than in women without congenital TBG aberration (24, 25).

B. The thyroid hormones

1. Total thyroid hormones. In pregnancy, the alterations in total TH levels are the direct consequence of the marked increase in serum TBG: total T_4 and T_3 levels increase significantly during the first half of gestation. Levels of serum T_4 rise sharply between 6 and 12 weeks, progress more slowly thereafter, and stabilize around midgestation; for serum T_3, the rise is more progressive (26). Both total T_4 and T_3 reach their plateau values by 20 weeks and are maintained until term. Because of the 20-fold greater affinity of TBG for T_4 compared with T_3, changes in T_4 levels follow the changes in TBG more closely. It can be expected therefore that the T_3/T_4 molar ratio should remain essentially unaltered during pregnancy (27–29). Later in this review we will discuss the importance of an increased T_3/T_4 ratio, as an indicator of thyroidal alterations due to iodine deficiency during pregnancy.

These modifications represent the necessary adjustment from the "old" (preconception) steady state equilibrium to the "new" (gestational) equilibrium of the thyroidal economy. The changes are initiated by the progressive expansion of the TBG extracellular pool, which increases from ~2,700 to ~7,400 nmol over a trimester, accompanied by a major increase in hormone-binding capacity of the serum (8, 30). In the nonpregnant woman, approximately one third of circulating TBG carries a T_4 molecule; *i.e.* the molar T_4/TBG ratio is 0.35–0.40. To ensure homeostasis of the free hormone concentrations during pregnancy, the extrathyroidal T_4 pool must increase in parallel (31–33). The thyroidal adjustment therefore implies that, in the early stages of pregnancy, a transient period takes place, during which T_4 and TBG concentrations are constantly changing.

This concept is fundamental to understanding the thyroidal alterations that are observed in pathological conditions such as iodine deficiency or hypothyroidism, characterized by the inability to achieve an adequate adjustment by the glandular machinery. Indeed, the adjustment of the thyroidal economy can be achieved only through a steady increase of T_4 output by the gland during this period. To reach the new steady state, the hormonal output must steadily increase over a period of one trimester, with a constant daily enhancement over baseline T_4 production values of 1–3% (34). When the new steady state has been reached, the overall production rate of TH should become similar to that prevailing before pregnancy (35).

How is the required thyroidal adjustment that takes place in the first trimester of gestation regulated? Because the rapid rise in the serum hormone-binding capacity due to increased serum TBG levels tends to induce a trend toward slightly decreased free hormone concentrations, the thyroidal adjustment is regulated primarily through the normal pituitary-thyroid feedback mechanisms, *i.e.* by TSH stimulation of the thyroid gland (Fig. 2). In healthy pregnant women, the "extra load" on the thyroidal machinery is relatively minor, and these physiological changes are unnoticeable: an increase in serum TSH is not commonly observed. On the contrary, as will be discussed later, in women with iodine deficiency or autoimmune thyroiditis and subclinical hypothyroidism, the TSH surge is amplified, and increases in serum TSH can be demonstrated, revealing the underlying mechanisms of adaptation (36).

2. Free thyroid hormones. Numerous publications have indicated that free hormone concentrations decrease during pregnancy; others, however, reported no change or even an increase. In earlier studies, these apparent contradictions could be partly explained by flaws in the methodologies employed for the determinations of both free T_4 and T_3. For example, some techniques did not determine free T_4 concentrations directly and required external calibration; others have been shown to be influenced by modifications occurring in the serum levels of TBG, albumin, and FFA associated with pregnancy; in still others, excessive dilution of serum in the test tube "stripped" T_4 from TBG, producing an artifact (37–45). Figure 3 illustrates an interesting study by Roti *et al.*

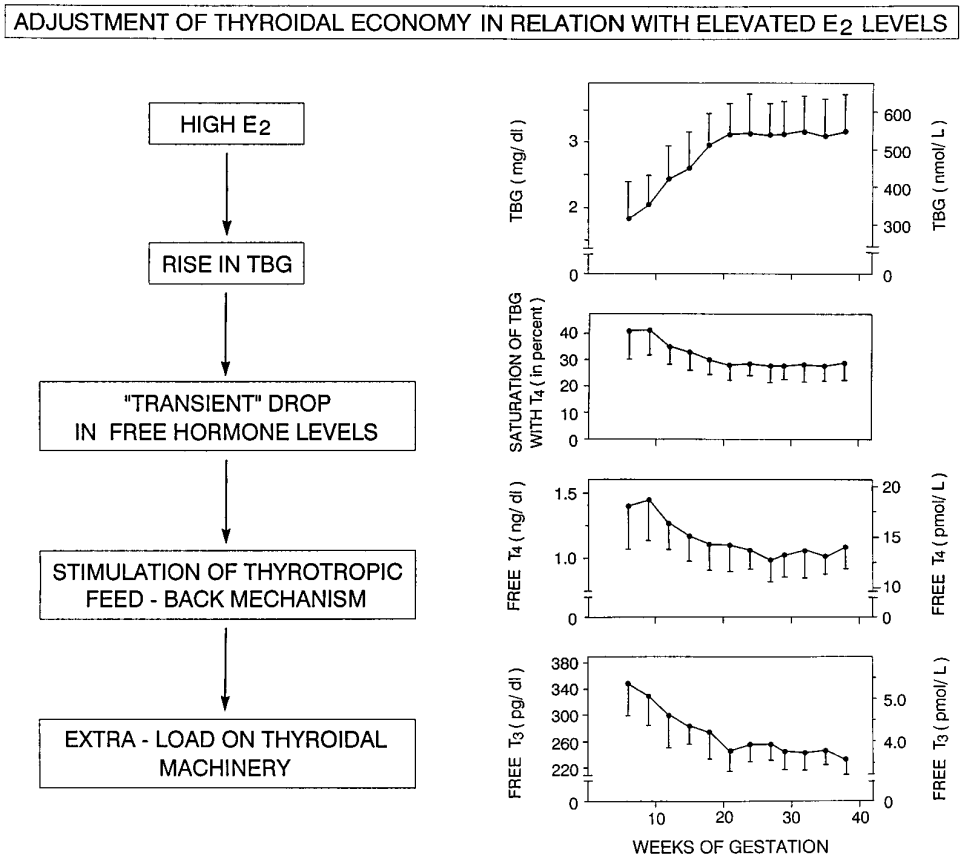

FIG. 2. Schematic representation of the feedback regulatory mechanisms between the rise in TBG levels, the trend toward a reduction in free hormone concentrations, and the stimulation of the pituitary-thyroid axis. In the *right* part of the figure, data collected in 606 normal pregnancies in Brussels are illustrated, showing the progressive rise in serum TBG during the first part of gestation, accompanied by a progressive decrease in the free T_4 index (saturation level of TBG by T_4), and free T_4 and T_3 concentrations. Brussels being in an area with a restricted iodine intake, the quantitative reduction in free hormone concentrations observed in the second part of gestation is more pronounced than in areas without iodine deficiency. [Adapted with permission from D. Glinoer (36) © Plenum Publishing Corp.]

(46) in which the authors compared serum-free thyroid hormones in pregnant women at term and their newborns, using ten different commercially available kits. The data show the variability in free T_4 and T_3 concentrations obtained with different methods, but they also show that free hormone levels are always significantly lower than in nonpregnant women. Longitudinal studies based on reliable methodology (*i.e.* methods that are not influenced by changes in serum TBG and albumin levels) in large numbers of pregnant women without iodine deficiency have confirmed that serum free T_4 levels are lower by an average of 10–15% at delivery, in comparison with nonpregnant female subjects. Changes in free T_3 levels follow a parallel pattern. In most pregnant women, however, free hormone levels are maintained within the nonpregnant reference range (47, 48).

Women are considered to remain euthyroid during pregnancy, and the reason for the reduction (even though of small amplitude) in free hormone levels during the second half of gestation, observed in healthy women who have an adequate iodine supply, is not understood. The more drastic reduction in free hormone levels observed in women with iodine restriction and deficiency during pregnancy has a different meaning that will be discussed in detail later because it signifies true hypothyroxinemia (32, 34, 36, 49). The feedback mechanism through the hypothalamic-pituitary-thyroid axis is thought to function normally in pregnant women because pregnancy serum TSH levels remain similar to those of nonpregnant women when the iodine supply is adequate (50). However in our opinion, this matter is probably more complex than usually considered. For instance, there are arguments to suggest that high estrogen levels over a prolonged period of time may modify the regulation of both basal and TRH-stimulated TSH release directly at the pituitary level (51–55). Also, as will be discussed later, high human CG levels down-regulate the TSH tone during early pregnancy. Finally, an apparent hypothyroid state might be compensated by an increased nuclear binding capacity for thyroid hormones in target cells (56).

The calculation of free T_4 indices (which is still very much in use in many countries) deserves a comment: these indices are established on the basis of the known physico-chemical properties of the thyroid hormone transport proteins, using the T_4/TBG ratio or the T_3 resin uptake test. One should remember that these estimations of free T_4 concentrations from indirect calculations do not always provide reliable results in pregnancy. The free T_4 index based on the T_3 resin uptake test shows only small fluctuations in pregnancy, while the index based on the T_4/TBG ratio yields values significantly lower than those found in nonpregnant women (23, 57).

3. Peripheral metabolism of thyroid hormones. Three enzymes catalyze the deiodination of thyroid hormones in human tissues (58). Type I deiodinase, by outer ring deiodination of T_4, is responsible for the production of most of the circulating T_3. As already discussed, total T_3 levels follow, albeit less tightly, the increase in total T_4 associated with the rise in TBG during the first half of pregnancy. Furthermore, when the

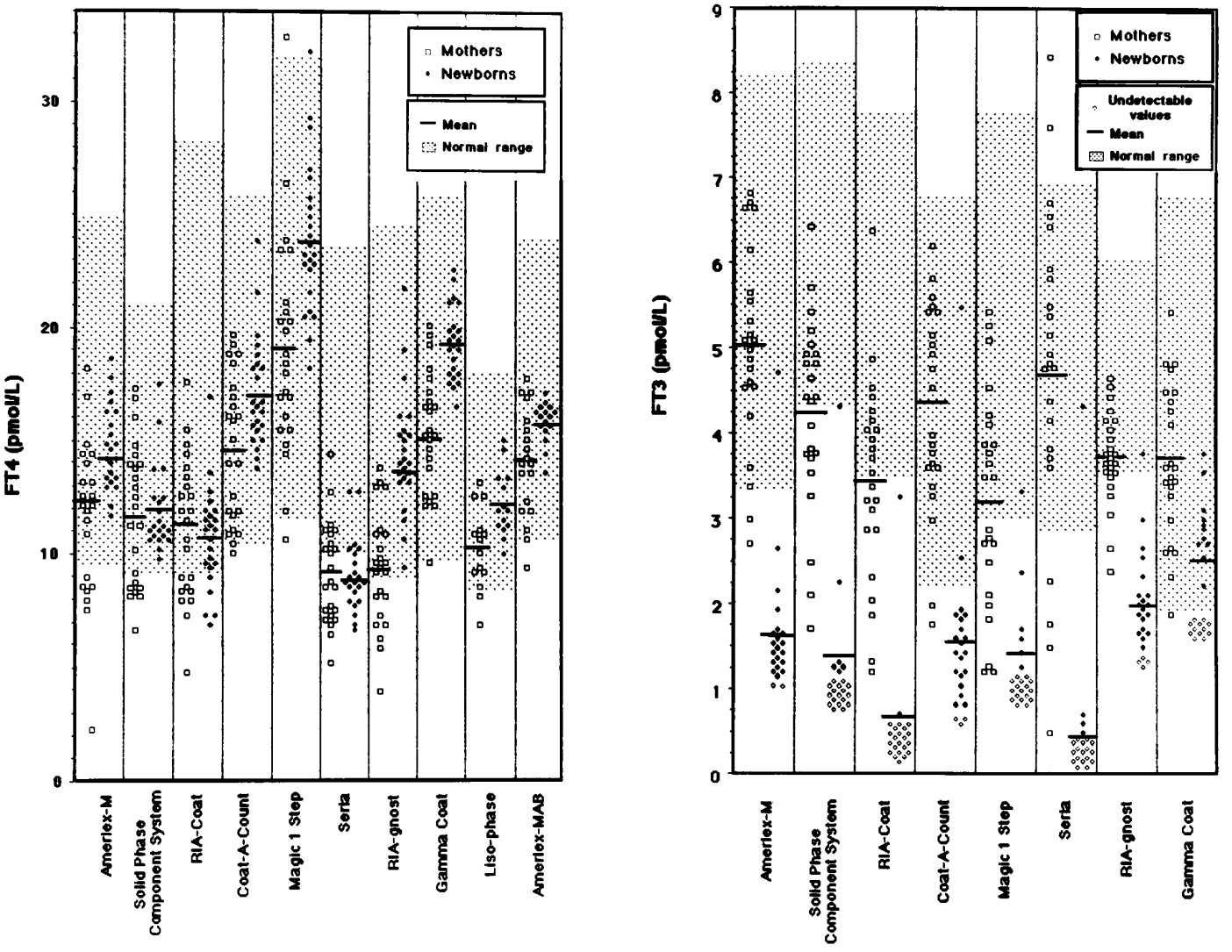

FIG. 3. Free T_4 and T_3 concentrations in at term pregnant women and their newborns, assessed by 10 (for free T_4) and 8 (for free T_3) commercially available kits. [Reproduced with permission from E. Roti *et al.*: *J Endocrinol Invest* 14:1–9, 1991 (46).]

thyroid gland is more stimulated (such as in iodine deficiency) during pregnancy, there is also preferential secretion of T_3 by the gland, presumably under the direct influence of TSH. Concerning reverse T_3 (formed by inner ring deiodination from T_4 or T_4 sulfate as substrates), maternal serum levels increase during pregnancy in proportion to the increase observed for total T_4 (59, 60). Consequently, even though this has not been proven by direct evidence, there is no argument to propose that the activity of type I deiodinase should be altered in pregnant women. Type II deiodinase acts only on the outer ring and prefers T_4 and reverse T_3 as substrates. The enzyme is expressed in certain tissues (*i.e.* pituitary gland, brain, brown adipose tissue) and also in the placenta. Since the activity of type II deiodinase increases when the availability of T_4 decreases, it has been proposed that type II deiodinase activity may represent a homeostatic mechanism for maintaining T_3 production in the placenta when maternal T_4 concentrations are reduced (*i.e.* during hypothyroidism or iodine deficiency) (61). The placenta also contains large amounts of type III deiodinase (62). This enzyme converts T_4 to reverse T_3 and T_3 to T_2. Placental type III deiodinase, by its extremely high activity during fetal life, may explain the low T_3 and high reverse T_3 concentrations, characteristic of fetal thyroid hormone metabolism. The ontogeny of the three deiodinases in the developing fetus involves complex metabolic pathways that are beyond the scope of the present article. For detailed information, readers are referred to two excellent and extensive recent reviews on this important topic (50, 63).

Finally, elevated deiodination activity in the placenta probably plays an important role for the metabolism of maternal thyroid hormones. As was discussed earlier, the metabolic changes associated with the progression of gestation, in its first half, constitute a transient phase from a preconception steady state to a pregnancy steady state. The changes are accomplished through the gland's increased hormonal output to reach and remain at the new equilibrium. Once the latter has been reached, one would expect the hormonal needs to revert to their initial levels. For instance, the increased daily dose of L-T_4 necessary to maintain euthyroid-

ism in hypothyroid-treated pregnant patients should only be transient; however, clinical experience clearly indicates that it is not the case. If the increased L-T_4 dosage is not maintained in those patients during later stages of gestation, they rapidly become hypothyroid. This indicates that once the new steady state is reached, increased hormonal demands are maintained: this could be partially explained by factors such as transplacental passage of maternal hormones and increased turnover of T_4 of maternal origin, due to the high activity of placental type III deiodinase. To date, the quantitative importance of changes in the peripheral metabolism of maternal thyroid hormones and the exact role of the placenta in this mechanism have not been fully elucidated.

C. The serum levels of thyroglobulin (TG)

Thyroglobulin is the protein matrix on which thyroid hormones are synthesized in the thyroid gland. Even though the TG molecule has no peripheral hormonal action, the serum levels of TG represent a sensitive, albeit nonspecific, indicator of the activity or stimulation state of the thyroid gland. Several studies have indicated that TG is frequently elevated during pregnancy: the increase in TG can be observed as early as the first trimester, but by later stages of gestation and particularly near term is significantly more pronounced (64–68). The alterations in serum TG associated with pregnancy were first considered to result from transient thyroidal stimulation due to the thyrotropic action of human (h) CG at the end of the first trimester (69). This hypothesis is probably not correct because, as indicated above, TG changes occur mainly in the late stages of gestation (when hCG levels have decreased) and also because statistical correlation between the increments in TG and peak hCG levels is lacking (70).

Recently, TG changes in pregnancy have been investigated in greater detail. These studies have revealed that the increase in TG is correlated with other indices of thyroidal stimulation, such as slight elevations in serum TSH (usually remaining within the normal range) and an increase in the T_3/T_4 molar ratio, suggesting preferential T_3 secretion (34). Most importantly, changes in TG are also associated with an increase in thyroid volume (TV), and we have proposed that TG alterations may constitute a sensitive biochemical marker to monitor the goitrogenic stimulus frequently occurring during pregnancy in relation with iodine deficiency (71). In the Brussels area, where the iodine intake is only marginally low, between 50–100 μg/day, serum TG was found abnormally elevated in more than 50% of women at delivery with values ranging between 30 and 180 μg/liter, comparable to the TG values observed in conditions of severe glandular stimulation such as GD (Fig. 4).

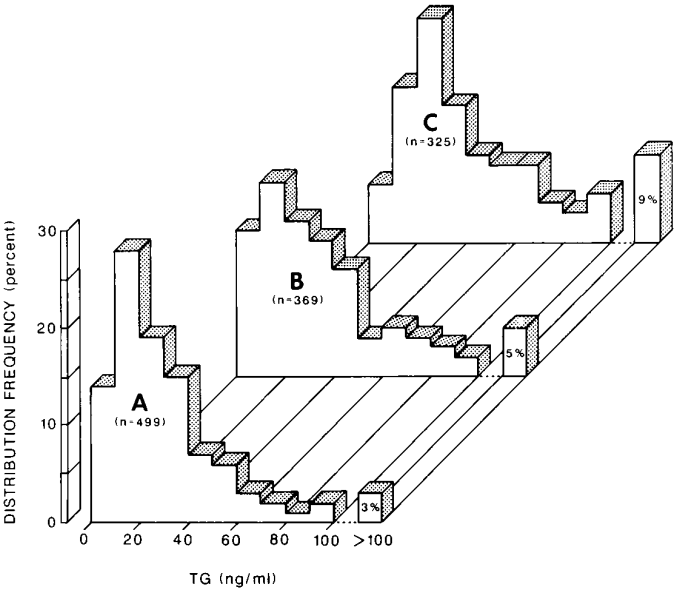

FIG. 4. Distribution frequency of serum TG levels determined at the initial evaluation before 16 weeks (A), during late gestation at 32–33 weeks (B), and immediately after delivery (C) in a cohort of 500 healthy pregnant women in Brussels. The number of determinations for each gestation period is shown in *parentheses*. In this assay for serum TG, the upper limit of the normal range for nonpregnant women was 30 μg/liter. [Reproduced with permission from D. Glinoer *et al.*: *J Clin Endocrinol Metab* 71:276–287, 1990 (34). © The Endocrine Society.]

D. The metabolism of iodine

Dietary iodine after reduction to iodide is rapidly absorbed from the gut. Iodide derived from the diet and from peripheral catabolism of thyroid hormones and iodothyronines by deiodination constitutes the extrathyroidal inorganic iodine pool. The pool is in dynamic equilibrium with two main organs, the thyroid gland and the kidneys. In normal subjects with a daily iodine intake of 150 μg, the thyroid clearance rate for iodide is 10–25 ml/min (average 17 ml/min). The renal iodide clearance is 30 ml/min, resulting chiefly from glomerular filtration, with no evidence for tubular secretion or active transport.

In pregnancy, the renal clearance of iodide increases significantly because of an increased glomerular filtration rate. Renal hyperfiltration and increased clearance, observed for iodide and several other molecules (both smaller and larger) begins in the early weeks of gestation and persists until term, thereby constituting an obligatory renal iodine "leakage" (72–74). The iodide loss tends to lower the circulating levels of inorganic iodide and induces, in turn, a compensatory increase in thyroidal iodide clearance, which reaches 60 ml/min and is accompanied by an absolute elevation of iodide entry into the gland (75, 76). These mechanisms indicate that the thyroidal activity is increased during pregnancy, as has been suggested by early studies using radiolabeled iodine administered to pregnant women, as well as histological studies of thyroid follicular cells obtained during pregnancy and showing marked functional activity (77–79).

A second mechanism of iodine deprivation in the mother occurs later in gestation, from the passage of a part of the available iodine from the maternal circulation to the fetal-placental unit. At midgestation, the fetal thyroid gland has already started to produce thyroid hormones that are indispensable for adequate development of the fetus (80–82). Hence, when iodine deprivation exists during the first half of gestation, it tends to become more severe in the final stages. The extent of the iodine passage from mother to fetus is not precisely established. Another interesting and unresolved question is the role of the placenta in transferring

iodide: does it simply represent passive transfer or is there an "active pump" (83)? In the human the median urinary iodine excretion decreases by 10–15 μg/day in the second half of gestation compared with the first half, perhaps representing the fraction of iodide transferred (34). Since this difference has not been confirmed by other studies, it remains an open question for future work (84).

In the nonpregnant condition an adequate iodine intake is estimated to be 100–150 μg/day. Based on several studies, 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 μg/day (85, 86). For pregnant women who reside in countries with an iodine-sufficient environment with an intake often more than 150 μg/day, the iodine losses in the urine and from transfer to the fetus are probably of little importance. Iodine deficiency disorders (IDD) do not present problems in the United States, Japan, or a limited number of countries in Europe (the Scandinavian countries, Switzerland, Austria), where national programs of dietary iodine supplementation have been in place for many years. In other areas of the world, however, IDD constitutes a serious public health issue (87). Available data indicate that 1 to 1.5 billion people are at risk of IDD. Among them, there are more than 500 million people who live in areas with overt iodine deficiency and a high prevalence of goiter.

Countries like Belgium, on the other hand, are representative of most European countries where systematic programs of dietary iodine supplementation have not been implemented and where the "natural" iodine supply is at, or below, the lower limit of adequacy. The average iodine intake in Belgium is below 100 μg/day (88). Inasmuch as there is no endemic goiter in the population, this restricted level of iodine intake is presumably sufficient to cover the usual needs of thyroid hormone production in normal adult subjects, at least as long as nothing intervenes to disrupt the fragile equilibrium. Pregnancy therefore acts as an indicator of the underlying iodine restriction by its increased hormonal demands and obligatory iodine losses, and gestation results in a relative iodine-deficient state. In countries with a more severe iodine deficiency, the repercussions of iodine deprivation during pregnancy are obviously further enhanced (89).

E. The hypothalamic-pituitary control of thyroid function and the role of hCG

1. Hypothalamic-pituitary-thyroid axis (HPTA). We have already mentioned some arguments suggesting that elevated estrogen levels in pregnancy may influence the HPTA, perhaps by acting directly at different (and not yet clearly defined) levels in the thyroid gland feedback-regulatory mechanisms. In his 1993 review in *Endocrine Reviews*, Burrow (48) analyzed in detail the few available studies in which the HPTA has been assessed, either by the administration of T_4 or T_3 to pregnant women for short periods with the aim of evaluating the TSH responses to induced hormonal changes (75, 76, 90, 91) or after TRH administration (52, 92–94). Unfortunately these studies, performed before 1980, employed the then available assays which were unable to detect subtle serum TSH changes. Overall, the conclusion drawn from this early work was that the responsiveness of the HPTA can be considered to function normally in pregnancy. If the above comments are interpreted with caution, we would certainly agree with Burrow's general conclusion (48).

2. Regulation of serum TSH. A correct interpretation of the modifications in serum TSH concentrations is crucial to correctly assess the alterations in pregnancy-associated thyroid function parameters. In earlier work, conflicting data have been reported: some authors found no change in serum TSH in pregnancy (95, 96), while others observed significant increases in TSH throughout gestation (93, 97). With the introduction 10 yr ago of sensitive immunoradiometric techniques allowing for extremely precise determinations of TSH levels within the normal range, new and important insights have been gained to better define the patterns of serum TSH changes during pregnancy.

In the present review, by examining different periods during gestation, we shall address two main questions related to serum TSH alterations. During the first trimester when hCG levels reach their peak, is there a transient fall in basal and TRH-stimulated TSH?; if so, to what is the TSH decrease related and what is its clinical relevance? During the second half of gestation, do TSH levels remain stable (*i.e.* comparable to before pregnancy and also to before the hCG peak) or are there subtle but significant modifications in serum TSH? If the latter is true, what is the meaning of TSH changes in late gestation?

a. Transient fall in serum TSH in the first trimester. The first observation of a transient fall in serum TSH during the second and third months of pregnancy in normal women was reported in 1976, and the authors at that time postulated that TSH suppression might be related to an intrinsic "TSH-like" activity of hCG. Unfortunately, with the "crude" techniques available, the authors could not show a reciprocal relationship between TSH and hCG levels in individual serum samples, and they concluded that "it was unlikely that hCG alone was responsible for the TSH suppression" (98). At that time, it was commonly believed that the placenta produced large amounts of various chorionic products, distinct from hCG, with thyroid-stimulating activity. Among those, human chorionic TSH (hCT) was a favorite and it was felt that hCT, alone or in concert with hCG, was responsible for the biological thyrotropic activity observed (99). A few years later, however, convincing evidence indicated that hCT was not a significant factor as a thyroid-stimulating agent and that peak hCG levels in normal pregnant women coincided with an important increase in the bioassayable thyroid-stimulating activity (100).

The basis for these early studies on thyroid stimulators of placental origin stemmed from the clinical observations in the 1970s of an association of hyperthyroidism with molar pregnancy (101–103). It has since been amply confirmed that in various pathological conditions, such as molar pregnancy (104, 105), other trophoblastic disease (choriocarcinoma) (106–109), and cancers of various origins (110–113), elevated hCG levels could induce hyperthyroidism, characterized by the rapid appearance of thyrotoxic symptoms and their even more rapid disappearance after the surgical removal of the

mole or cure of the tumor. Taken together, these observations have led to the concept that a substance secreted during pregnancy, and at particularly high levels in moles and choriocarcinomas, could be responsible for hyperthyroidism. Based on physico-chemical analyses of molar or tumor extracts, it was then shown that the thyroidal stimulator most probably was hCG (114–116). It was also suggested that the thyroid-stimulating effects found in these pathological circumstances could be due not only to the extremely high circulating hCG levels, but perhaps also to the presence of molecular variants of hCG with particularly potent thyrotropic activity (117–119).

To date, there is a bulk of compelling evidence to indicate that there is indeed a transient fall in serum TSH near the end of the first trimester in normal pregnancy, and that this partial TSH suppression is associated with the elevation in circulating hCG. In 1985, Guillaume *et al.* (120) reported a significant blunting of the TSH response to TRH in six women who had higher hCG levels (64,000 IU/liter) at the end of first trimester, compared with 19 other pregnant women with a similar gestational age, in whom the TSH response to TRH was unaltered and hCG levels were comparatively lower (45,000 IU/liter). In 1988, Pekonen *et al.* (121) showed a negative correlation between hCG and TSH levels in a small group of pregnant women investigated immediately before and after abortion. These authors were the first to demonstrate clearly, at the level of the individual, a decrease in serum TSH associated with high hCG values. In our prospective studies on maternal thyroid function in pregnancy, the regulatory role of hCG was first investigated in a cohort of several hundred women in whom TSH and hCG levels were systematically determined between 8–14 weeks gestation (34). The results showed that a lowering in serum TSH was coincident with the peak hCG values (Fig. 5). The profiles of changes in serum TSH and hCG were clear mirror images, and there was a significant reciprocal correlation between TSH and hCG in individual samples. The results also indicated a linear relationship between hCG and free T_4 concentrations during early gestation. 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. From these preliminary observations, we concluded that hCG is a thyroid regulator in normal pregnancy (3, 34). Similar conclusions were reached by Ballabio *et al.* (122), who proposed that hCG be considered "a putative physiological regulator" of maternal thyroid function in normal pregnancy.

The clinical relevance of these observations deserves a comment. First, it should be remembered that hCG behaves as a weak thyroid stimulator *in vivo*. We estimated that a 10,000 IU/liter increment in circulating hCG correponds to a mean free T_4 increment in serum of 0.6 pmol/liter (*i.e.* 0.1 ng/dl) and, in turn, to a lowering of serum TSH of 0.1 mU/liter. Hence, a transient increase in serum free T_4 during the first trimester will only be observed when hCG levels reach or exceed 50,000–75,000 IU/liter. Second, for thyroid effects to be significant, such high hCG levels ought to be maintained for sufficiently long periods, but in general the hCG peak is maintained only briefly, lasting less than 1 week. Consequently in the majority of healthy pregnant women,

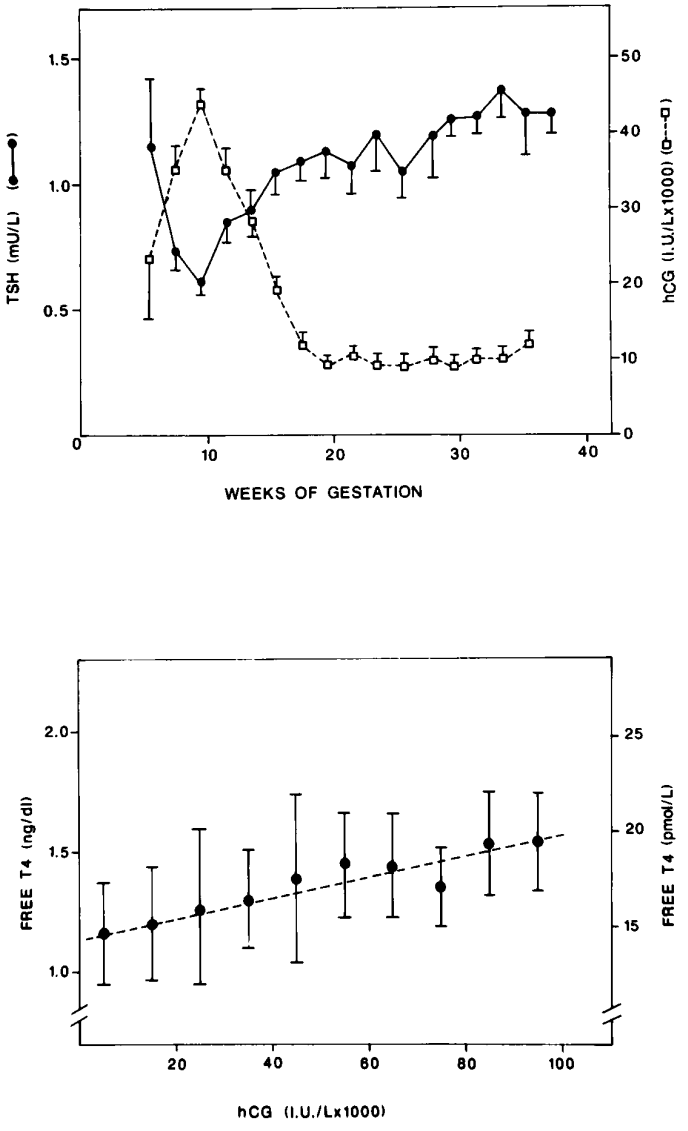

FIG. 5. *Upper graph*, Serum TSH and hCG as a function of gestational age in 606 healthy pregnant women. Between 8 and 14 weeks gestation, the changes in hCG and TSH levels are mirror images of each other, and there is a significant negative correlation between the individual TSH and hCG levels ($P < 0.001$). Each point gives the mean value (± SE) of individual determinations pooled for 2 weeks. *Lower graph*, Scattergram of free T_4 levels in relation to hCG concentrations in the first half of gestation. Each point represents the mean (± 1 SD) free T_4 values, determined between 6–20 weeks, plotted for 10,000 IU/liter increments in hCG. The *dashed line* indicates the linear regression curve ($P < 0.001$). [Reproduced with permission from D. Glinoer *et al.*: *J Clin Endocrinol Metab* 71:276–287, 1990 (34). © The Endocrine Society.]

the stimulatory effects of hCG on the thyroid gland should be minor, of short duration, and not easily detected. Third, it is important from a clinical standpoint to assess how often partial TSH suppression may occur in early pregnancy. To address this question, we analyzed the prevalence of a TSH blunting (*i.e.* basal TSH levels below the lower limit of normality) in a large group of pregnant women during the successive trimesters of gestation (70). The results (Fig. 6) showed that in the first trimester, 18% of the women had a

Trimester	N	TSH (mU/L) ≤0.20 N (%)	TSH (mU/L) 0.21 - 4.00 N (%)	hCG (U/L) (mean ± SEM) in women with TSH ≤0.20	hCG (U/L) (mean ± SEM) in women with TSH 0.21-4.00	P
I	338	62 (18%)*	276 (82%)	52,400 ± 3.900	34,900 ± 1,200	<0.001
II	249	13 (5%)	236 (95%)	20,400 ± 5,300	12,600 ± 1,000	<0.001
III	102	2 (2%)	100 (98%)	ND	13,000 ± 1,400	ND

FIG. 6. Fractional distribution of normal or lowered serum TSH levels in normal pregnancy, in comparison with serum hCG concentrations. The total number of cases in each trimester (N) represents women investigated at initial presentation during the first, second, or third trimester. The percentage of cases with a lowered serum TSH (indicated in *parentheses*) is significantly greater in the first, as compared with second and third trimesters. ND, Not determined. [Adapted with permission from D. Glinoer *et al.*: *J Endocrinol Invest* 16:881–888, 1993 (70).]

TABLE 1. Serum TSH levels during pregnancy

Trimesters I	Trimesters II	Trimesters III (or term)	Control values/comments	First author, year (Reference)
0.39 ↑	0.35 ↑	0.47 ↑	0.25 in postpartum	Lemarchand-Beraud and Vannotti, 1969 (97)
4.20	3.80	4.30	No change; same as controls	Fisher *et al.*, 1970 (95)
3.80 ↑	4.20 ↑	4.50 ↑	2.00 in nonpregnant controls	Kannan *et al.*, 1973 (93)
1.37 ↓	1.74	2.22	2.22 in nonpregnant controls	Braunstein and Hershman, 1976 (98)
0.83 ↓	1.35	1.47	0.80 in nonpregnant controls	Yamamoto *et al.*, 1979 (96)
2.82	2.84	3.03	No change; same as controls	Silva and Silva, 1981 (123)
1.80	2.20 ↑	2.60 ↑	1.80 in postpartum	Weeke *et al.*, 1982 (124)
4.90	5.80	4.80	No change; same as controls	Smith and Bold, 1983 (125)
2.80	2.50	2.60	ND	Gow *et al.*, 1985 (41)
1.30	1.60 ↑	2.10 ↑	0.91 before pregnancy	Pacchiarotti *et al.*, 1986 (126)
2.00	2.00	2.50 ↑	ND	Fung *et al.*, 1988 (127)
1.10	1.40 ↑	2.00 ↑	ND	Price *et al.*, 1989 (128)
1.43 ↑	1.58 ↑	1.71 ↑	1.16 in postpartum	Rodin *et al.*, 1989 (129)
N.D.	1.25	1.25	No change; same as controls	Rasmussen *et al.*, 1989 (130)
0.75	1.09	2.08 ↑	1.00 6 months post partum	Glinoer *et al.*, 1990 (34)
0.72 ↓	1.26	1.09	1.23 in postpartum	Ballabio *et al.*, 1991 (122)
100%	110%	120% ↑	In % of serum TSH at 17 wk	Pedersen *et al.*, 1993 (131)
0.90 ↓	1.10	1.40	1.50 in nonpregnant controls	Berghout *et al.*, 1994 (132)

The values listed represent the mean (or median) TSH concentrations in each trimester and, when available, in the controls. Since actual numbers were not always readily available in all articles, they were recalculated from the data reported to the best possible approximation. The *arrows* illustrate the significant trends for serum TSH during pregnancy, as indicated by the authors in their publication. Irrespective of the TSH trends reported during pregnancy, the variability in mean TSH concentrations when comparing articles (particularly before 1989) is related to the wide variety of the TSH assays used. Articles are classified by chronological order. ND, Not determined.

transient subnormal serum TSH. Moreover in almost half of these cases, serum TSH was transiently undetectable (<0.05 mU/liter). The lowering in serum TSH was still observed in 5% of the women during the second trimester. Women with a blunted TSH level (<0.20 mU/liter) had a circulating hCG concentration significantly higher than in women with normal TSH levels. Confirming our previous estimates, women with a blunted TSH displayed, on average, hCG levels above 50,000 IU/liter. Among the 62 women with a transient suppression of TSH in the first trimester, seven (11%) had free T_4 levels that were transiently increased above the upper limit of normality; among the latter, three women presented symptoms compatible with hyperthyroidism associated with significant vomiting. In this cohort, it should also be noted that nine women with a twin pregnancy were seen in the first trimester, with five of them having transiently undetectable serum TSH levels and two of five women exhibiting overt gestational thyrotoxicosis. Thus, some women may have sufficient thyroid stimulation to cause transient hyperthyroidism, as will be discussed in detail later (see *Sections III.C.2* and *III.C.3*)

b. Serum TSH in the second half of gestation. The patterns of modifications in serum TSH levels in the second part of gestation have been the subject of longstanding controversy. In Table 1 we have collected the serum TSH values reported in 18 studies between 1969 and 1994, in which the authors have examined longitudinal changes in serum TSH according to the trimesters of pregnancy. A note of caution is worthwhile because of the inherent difficulties in the analysis and comparison of such data. First, the techniques employed for the determination of TSH in serum have obviously evolved tremendously in quality and precision over the span of 25 yr. Second, the number of pregnant women investigated in each study was extremely variable, from small numbers to large groups. Third, the actual TSH values were, in some cases, presented in a graph rather than being available directly in the articles; it was therefore necessary in some cases to recalculate the actual TSH values, as precisely as possible, from the original reports. Fourth, it was not always clearly stated whether the women investigated and presented as "normals," were actually normal. For instance, the presence of a goiter and/or thyroid antibodies was not systematically

evaluated, and most studies did not specify whether such women had been excluded from the reports. Finally and most importantly, in many of the studies no comments were made concerning iodine intake, and we can only infer from the authors' geographical locations whether the study was performed in an iodine-replete or -restricted area. Regardless of these inescapable limitations, the table still yields interesting information. First, nine of 18 studies clearly report an increase in serum TSH, within the normal range, near term. Second, the majority of studies that show serum TSH increases during late gestation originate from Europe: they can therefore be considered to have been performed in areas with a restricted iodine intake. In a few studies this question was addressed directly. More specifically, both the Belgian (34) and Danish (131) studies, which showed a systematic increase in serum TSH near term, were carried out in well defined areas with a marginal iodine deficiency. As will be discussed later, the same investigators also showed that iodine supplementation during pregnancy significantly prevented these alterations in serum TSH. Conversely, a Dutch study (132), which failed to show a difference in serum TSH between the third trimester and nonpregnant controls, was performed in an iodine-replete area.

We propose therefore that serum TSH, in normal pregnant women who have no evidence of thyroid autoimmunity and who reside in areas with a sufficient iodine supply, most probably remains stable and comparable to pregestation 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.

3. Thyrotropic action of hCG. The thyrotropic action of hCG is explained by the structural homology between the hCG and TSH molecules, and between LH/CG and TSH receptors. Thus, hCG is able to bind to the TSH receptor of thyroid follicular cells and exerts its stimulatory effects by activating intracellular messengers, such as cAMP (133).

a. In vivo effects of hCG. The role of hCG in regulating maternal thyroid function in the first trimester of pregnancy has already been discussed. The thyroid gland of normal pregnant women may be stimulated by elevated circulating hCG levels to transiently secrete slightly more T_4 and induce in turn a partial suppression of serum TSH. 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.

An interesting question is whether it may be possible to distinguish, among normally progressing pregnancies, those women who are prone to blunt their serum TSH in the first trimester in response to the increase in circulating hCG. We approached this question in two clinical studies. In the first, the serum concentrations of intact hCG and its free α- and β-subunits were measured in two groups of normal pregnant women from the same cohort, subdivided on the basis of whether or not they had a partially suppressed serum TSH (below 0.20 mU/liter) in the first trimester (Fig. 7). The results showed that a low serum TSH was associated with significantly higher levels of both intact hCG and free β-hCG subunit, whereas there was no significant difference in free α-hCG subunit concentrations. Furthermore, in women with a low serum TSH and high hCG production, there was also a 20% increase in mean free T_4 levels during the first trimester (70). The hCG-induced stimulatory effects on the maternal thyroid gland were transient inasmuch as the parameters of thyroid function were similar in both the intially low TSH and the normal TSH groups during the last trimester and at term. In the second study, our aim was to define more precisely the quantitative relationships between circulating hCG and thyroidal stimulation in the first trimester. The levels of hCG, TSH, and free T_4 in early gestation were investigated in two groups of euthyroid women with single or twin pregnancies in whom the gestational age was precisely known because conception was obtained by *in vitro* fertilization techniques (Fig. 8). Results showed that peak hCG values in twin pregnancies were not only significantly higher than in single pregnancies (in fact, almost double), but also of much longer duration. Serum hCG values above 75,000 IU/liter lasted for less than 1 week in single pregnancy, while up to 6 weeks in twin pregnancy. Concerning the thyroidal repercussions, twin pregnancy was associated with a more profound and frequent lowering in serum TSH (blunted TSH values below 0.20 mU/liter were observed 3-fold more frequently). Also,

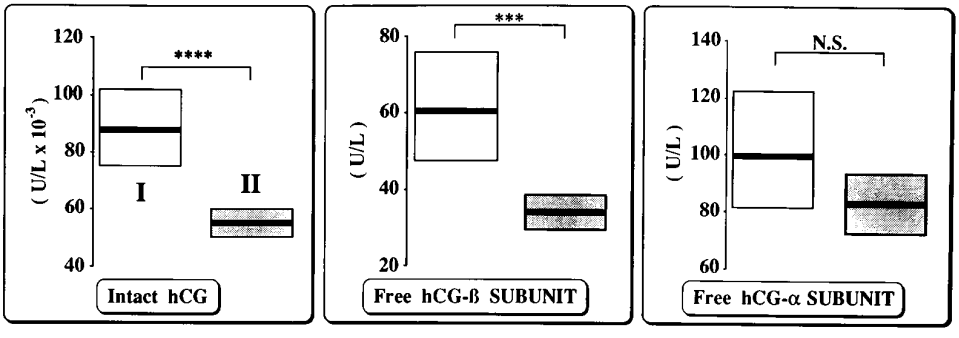

FIG. 7. Serum concentrations of intact hCG, and free α- and β-hCG subunits in 62 women (group I; *open bars*) with blunted serum TSH (<0.20 mU/liter), compared with 338 women (group II; *shaded bars*) in whom serum TSH was between 0.21 to 4.00 mU/liter at the end of the first trimester. The results are given as mean values (represented by the *thick horizontal lines*) ± 95% confidence limits of the mean, calculated after log transformation of the data. Statistical analysis was carried out using one-way ANOVA (***, $P < 0.001$; ****, $P < 0.0001$; NS, not significant). [Reproduced with permission from D. Glinoer *et al.*: *J Endocrinol Invest* 16:881–888, 1993 (70).]

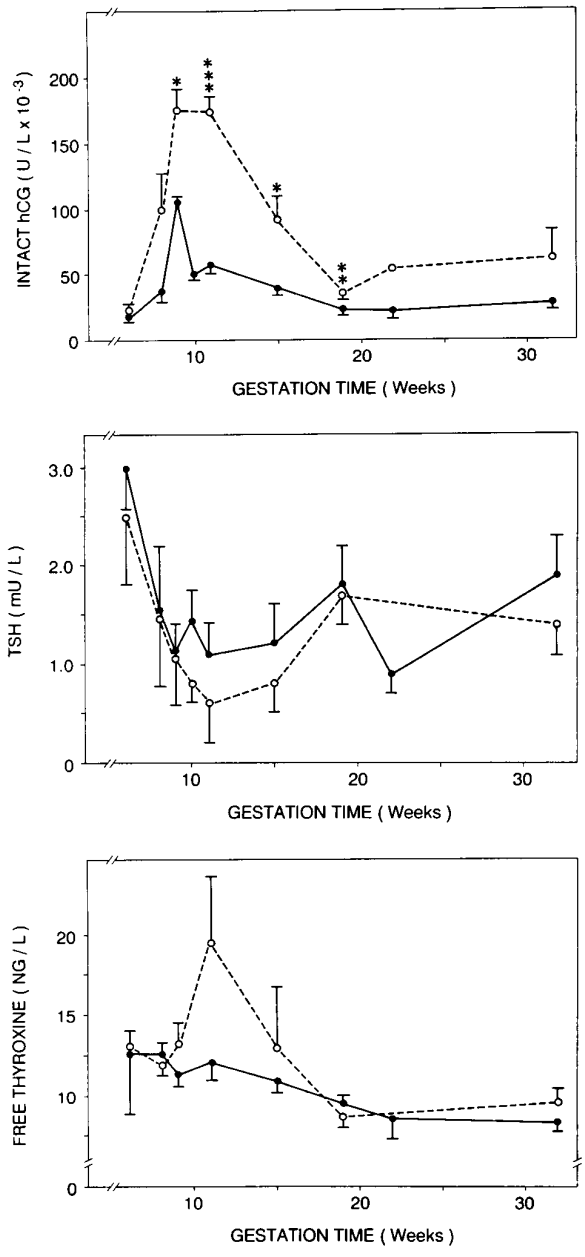

FIG. 8. Profiles of changes in heterodimeric intact hCG (*upper graph*), serum TSH (*middle graph*), and free T_4 (*lower graph*) levels as a function of gestation time in women with single (●) (n = 17) and twin (○) (n = 13) pregnancies. Each point corresponds to the mean ± SD of individual serum samples obtained at each gestational age. Statistical differences were calculated using the nonparametric Mann-Whitney rank test (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$). [Modified with permission from J. P. Grün *et al.*: *Clin Endocrinol (Oxf)*, in press (134). © Blackwell Science Ltd.]

free T_4 values remained unchanged in single pregnancy while transiently rising in twin pregnancy (134).

Taken together these studies indicate that in normal pregnancy it is both the amplitude and duration of the hCG peak (*i.e.* the integrated exposure of the thyroid gland to hCG) that are responsible for the thyroidal stimulation and TSH suppression. Even though the production of a variant hCG molecule cannot be excluded, this hypothesis is not required to explain the data. Finally, these studies show that thyroidal repercussions are generally absent when the hCG peak is of small amplitude and short duration. Thyroid effects may become manifest, however, in a few women in whom the thyroid gland is abnormally stimulated, with free T_4 levels in the hyperthyroid range and suppressed serum TSH, sometimes accompanied by clinical manifestations of thyrotoxicosis (see *Section III.C.2.*).

b. In vitro effects of hCG. Highly purified hCG increases iodide uptake and cAMP production and induces growth in rat FRTL-5 thyroid cells (135–137). Recently, it has also been confirmed that purified hCG interacts *in vitro* with the human TSH receptor, thereby stimulating the human thyroid gland (138–140). Similarly, serum of pregnant women has been shown to exert a thyroid-stimulating activity *in vitro* (141). Thus, there is presently good evidence that the effects of hCG reported *in vivo* correspond to a TSH receptor-mediated thyroid-stimulating action *in vitro* (142).

TSH is a glycoprotein hormone composed of two subunits linked together to form the intact heterodimeric active molecule (143). The TSH receptor located on the surface of thyroid epithelial cells belongs to the family of receptors coupled to G proteins. The structure of the TSH receptor has been identified and consists of three domains, a long extracellular domain representing the N-terminal part of the molecule, a transmembrane-spanning domain of seven peptides joined by intra- and extracellular loops, and finally an intracellular C-terminal domain coupled to the G proteins complex (144, 145). To explain the thyrotropic effects of hCG, it is necessary to compare the structures of the hCG molecule with our present knowledge of the TSH molecule and its receptor. As in the case of TSH, hCG is also composed of two noncovalently linked subunits. The α-subunit is common to all members of this family of hormones, whereas it is the β-subunit that confers its specificity to hCG (146, 147). There is a high structural homology between the β-subunits of hCG and TSH. As is the case for the hormones, there is also a considerable homology between the LH/hCG and TSH receptors (Fig. 9). The homology reaches 70% for the transmembrane-spanning domains and 45% for the extracellular domains of the receptors where the hormones bind (144, 148, 149). These molecular homologies are now part of a novel endocrine concept, referred to as "spill-over" syndromes (142).

In summary, thyroid-stimulating activity found in the serum of pregnant women is correlated with serum hCG levels and can be explained on the basis of molecular homologies between the hCG and TSH molecules as well as between the receptors for these hormones (Fig. 10). Human CG activates the same domain of the TSH receptor as does TSH by a spill-over mechanism related to molecular mimicry. It remains possible, *e.g.* in pathological (tumoral) conditions, that variant hCG molecules or metabolites of circulating hCG, exhibiting a more potent thyrotropic action, may play a role; until now, however, there has been no clear evidence that such variants or metabolites are involved in the hCG effects observed in normal pregnancy.

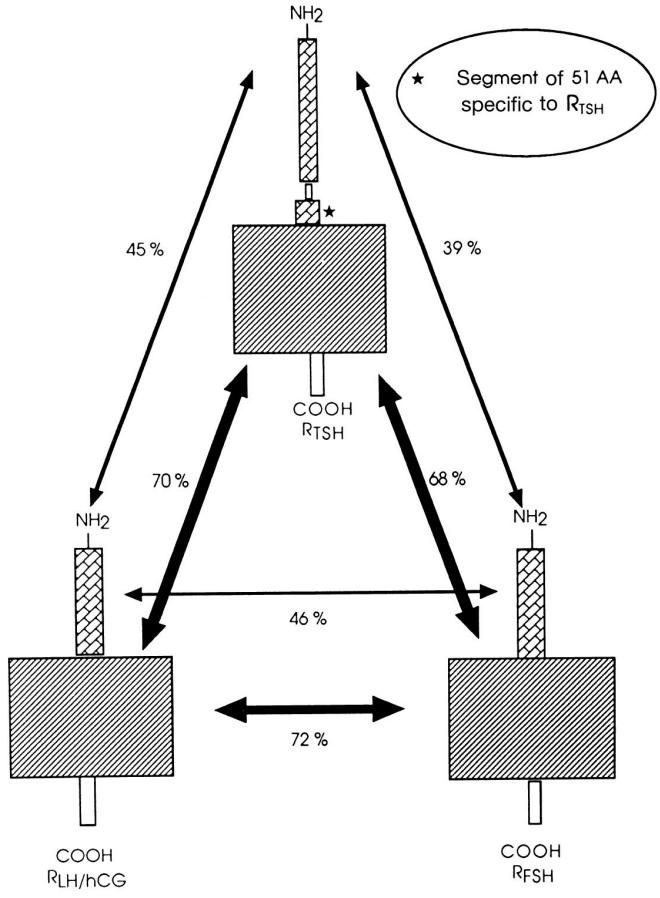

FIG. 9. The graph illustrates schematically the structure of the TSH, FSH, and LH-CG receptors, showing the homology of primary structures between the three receptors for these glycoprotein hormones. The similarities in peptide sequences (indicated as the percentage of homology) are shown by the *thin arrows* for the extracellular N-terminal regions, and the *thick arrows* for the intracellular C-terminal regions (including the transmembrane-spanning domains). [Adapted with permission from G. Vassart and J. E. Dumont: *Endocr Rev* 13:596–611, 1992 (144). © The Endocrine Society.]

F. A global view of thyroidal economy in pregnancy

During a normal pregnancy the changes in maternal thyroid function can be viewed globally as a balance between hormone requirements and the availability of iodine. The increase in hormone demands is due to three independent factors that concur to exert stimulatory effects on the thyroid machinery. The first factor is the adjustment of the thyroidal economy during the first trimester to the marked increase in the circulating levels of TBG, in response to increased estrogen production caused by hCG. The second factor is related to the thyrotropic action of hCG, also occurring in the first trimester, and which tends to transiently elevate free T_4 levels and decrease serum TSH. Thus, hCG has two antagonistic effects on thyroid economy in early gestation, tending to lower free T_4 after the rapid increase in serum TBG, and to increase free T_4 through its specific thyroid-stimulating action. The third factor, which intervenes later in gestation, is related to modifications in the peripheral metabolism of the thyroid hormones, particularly at the placenta level. These events lead to the physiological adaptation of the thyroidal economy when pregnancy occurs in healthy women in geographical areas with iodine sufficiency. A limited availability of iodine during gestation presents an additional challenge to the thyroid gland when hormone requirements are increased (Fig. 11). The same events underlie the pathological repercussions, in both mother and offspring, when pregnancy occurs in iodine-deficient areas (36, 49, 150, 151). These specific circumstances will be discussed in detail in the second part of this review.

III. Pathological Alterations of Thyroidal Regulation Associated with Pregnancy

A. IDD

Iodine deficiency interferes with the capacity of the thyroid gland to meet the metabolic challenges presented by pregnancy, yielding important repercussions for both the maternal and fetal thyroid function. Whereas iodine sufficiency in countries such as the United States presumably explains the failure of US reports to confirm significant changes in thyroidal size associated with pregnancy (152), iodine restriction and deficiency, which are still present in many European regions, are responsible for the formation of gestational goiters, as well as glandular hyperplasia at birth in the newborn.

In Europe where, in the majority of countries, there is usually only a moderate iodine restriction, pregnancy in otherwise healthy women is often associated with goitrogenesis but rarely with hypothyroidism. In other regions of the globe, with a more severe iodine deficiency, however, both maternal and neonatal hypothyroidism is frequently encountered, endemic cretinism representing the most dramatic expression of these alterations.

1. Consequences of iodine deficiency during pregnancy. In most European countries, populations do not benefit from a systematic addition of iodine to the diet, and there is good and recent evidence that nutritional allowances for an adequate daily iodine intake, unanimously recommended by international agencies such as the United Nations International Childrens Emergency Fund, International Council for the Control of Iodine Deficiency Disorders, and World Health Organization are far from being fulfilled: IDD persists and still constitutes a serious public health hazard (85–87). In regions with a marginally low iodine supply, it is particularly difficult to reach firm conclusions concerning the adequacy of iodine intake, mainly because important fluctuations occur in daily intake, both among individuals and also from one day to another. Measuring urinary iodine excretion levels reflects only the iodine intake of the most recent previous days. What really matters, however, is the long-term iodine balance, which determines the extent of intrathyroidal iodine stores. In populations with a chronically reduced iodine supply, it is the decreased availability of iodine that allows a better understanding of thyroidal alterations associated with pregnancy, because borderline iodine nutrition levels lead to increased thyroidal stimulation.

As a representative example of European countries, the average iodine intake in Belgium is limited to between 50–

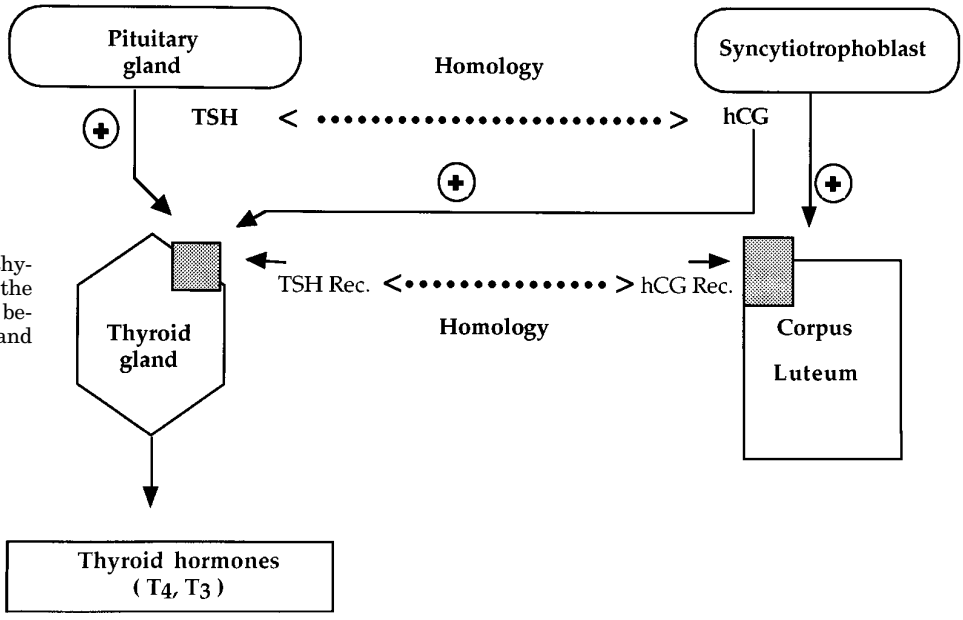

FIG. 10. Schematic representation of the thyroid-stimulating activity of hCG, based on the spill-over mechanism due to the homologies between both the TSH and hCG molecules and between the TSH and LH-CG receptors.

100 μg/day. Figure 12 illustrates urinary iodine excretion levels determined in pregnant women without iodine supplementation from the Brussel's area, showing that 85% of them have iodine intakes clearly below the recommended amount. As a consequence, pregnancy acts to reveal the underlying iodine restriction, and gestation results in a state of increased relative iodine deficiency (153, 154).

In vast regions of the world outside Europe, iodine deficiency is not only overt but is often severe, and in such areas the thyroid status of pregnant women and their offspring is frequently impaired. The degree of iodine deficiency is extremely severe in several areas of Central Africa and Asia for instance, with iodine intake levels below 25 μg/day. Moreover, severe iodine deficiency is often associated with the presence of goitrogens in the diet (*e.g.* from Cassava-rich staple foodstuffs) as well as deficiencies in other trace ele-

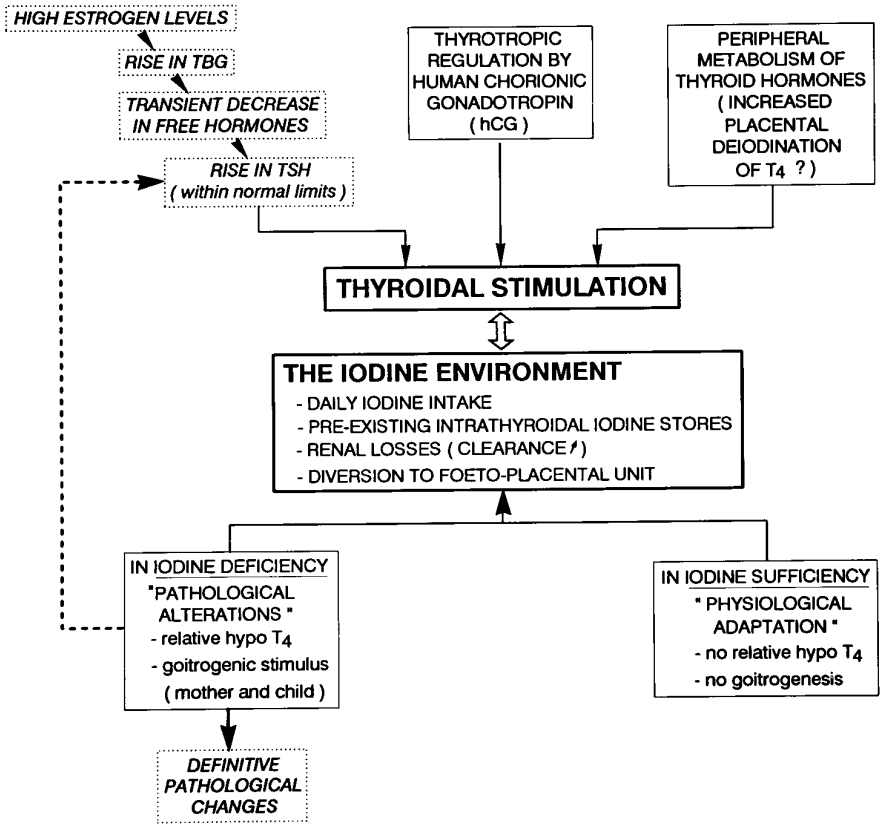

FIG. 11. From physiological adaptation to pathological alterations of the thyroidal economy during pregnancy. The figure illustrates the sequence of events occurring for the maternal thyroid gland, emphasizing the role of iodine deficiency to enhance the stimulation of the thyroidal machinery. [Reproduced with permission from D. Glinoer: *Thyroid Today* 18: 1–11, 1995 (150).]

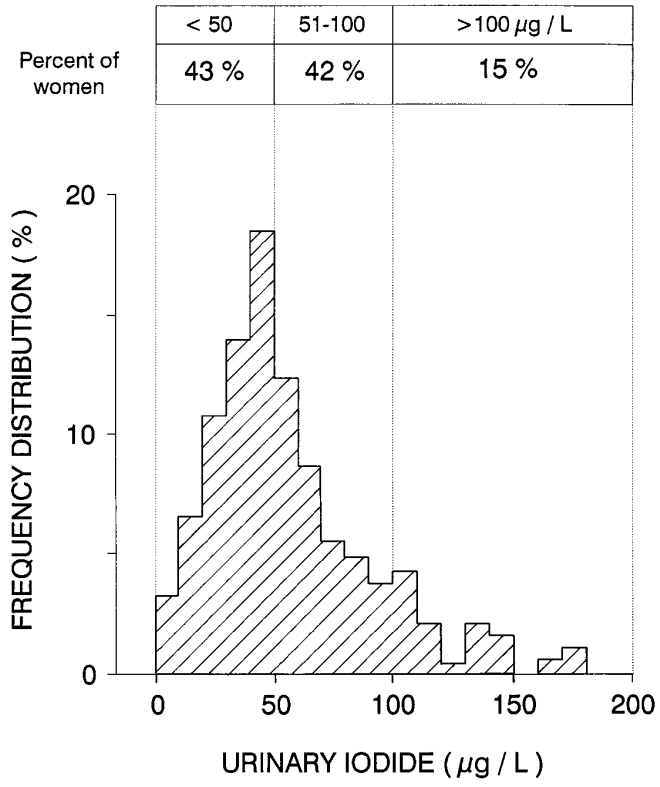

FIG. 12. Distribution frequency of urinary iodine concentrations during the first half of gestation (with a total of 334 urine samples assessed), in women in Brussels who did not receive iodine supplementation during pregnancy. The median urinary iodine concentration was 56 μg/liter. In the *upper* part of the graph, the population is classified as: 1) <50 μg/liter (severe deficiency): 51–100 μg/liter (moderate deficiency); and 101–200 μg/liter (no obvious iodine deficiency). [Reproduced with permission from D. Glinoer (153). © Schattauer.]

ments such as selenium. These factors combined with iodine deficiency tend to enhance the thyroidal alterations (89, 155). Thyroid function, in adults and children in areas with severe IDD varies: some subjects exhibit normal thyroid function parameters and others display variable degrees of hypothyroidism. Also, hypothyroidism plays a major role in reducing a woman's fertility and increasing the rate of miscarriage. When hypothyroid women become pregnant, thyroid function tends to deteriorate even further as gestation progresses. Endemic goiter is the most visible hallmark of severe iodine deficiency in these populations: in some villages, the prevalence of goiter may exceed 60–70% of all adults. Longstanding goiters are usually multinodular, and field observations strongly suggest that goiter sizes often enlarge further during pregnancy. Thus, severe IDD justifies urgent iodination programs to eradicate endemic cretinism and hypothyroidism in women of childbearing age (156–159).

2. Assessment of increased thyroidal stimulation. Since the early 1990s, the concept was developed that increased thyroidal stimulation resulting from iodine restriction may lead to goiter formation during pregnancy. Hence, pregnancy should be regarded as an additional factor during a woman's life (an event that may obviously be repeated at short intervals) that may induce thyroidal pathology when iodine intake is marginally low. It is therefore important that clinicians correctly assess increased thyroidal stimulation (34, 160). In practice, four simple biochemical parameters have been identified and proven to be useful markers.

The first parameter is relative hypothyroxinemia. As already discussed, free T_4 levels tend to decrease slightly, even in pregnant women who have an adequate iodine supply. In women with iodine restriction, however, the early rise in total T_4 (associated with the rise in TBG) was shown to be inappropriately low, with free T_4 and T_3 levels progressively decreasing during the first part of gestation to stabilize at a low level (with an average decrement of 30%) in the second part of gestation (34, 131, 161). Under the environmental conditions that we investigated in Brussels before iodine supplementation was systematically introduced during pregnancy, it was observed that one third of pregnant women had free T_4 values near or below the lower limit of normal (34). It was also shown that there was a tendency for individuals to exhibit variable patterns of glandular adaptation. For instance, a woman whose serum free T_4 was already in the lower tertile of the population's range during early gestation had a greater than 80% risk of remaining in the lower part of the range during late gestation. Conversely, a woman with a serum free T_4 in the upper part of the population's range during the last months of pregnancy had a greater than 90% chance of having a serum free T_4 in the upper part of the range in early gestation, indicating that in this case thyroidal adaptation had taken place during the first trimester (32). That relative hypothyroxinemia was truly related to iodine restriction was confirmed by its partial correction when iodine supplementation was administered early enough during gestation (89, 123, 131).

The second parameter is preferential T_3 secretion, reflected by an elevated molar ratio of total T_3/T_4 in serum. It was mentioned previously that, owing to differences in the respective binding affinities of TBG for T_4 and T_3, the T_3/T_4 ratio tends to remain unchanged during pregnancy. Under conditions of a normal iodine intake, the serum T_3/T_4 ratio ranges between 10–22 ($\times 10^{-3}$) in euthyroid pregnant women (28, 59, 124, 162). In clinical and experimental conditions in which there is an increased stimulation of the thyroid gland, *e.g.* in GD (163) or after acute TSH stimulation (164), the T_3/T_4 ratio increases as the result of preferential T_3 production by the gland. The T_3/T_4 ratio also depends upon the extent of iodine depletion (*i.e.* a small intrathyroidal iodine pool) and has been shown to be useful for evaluating the degree of thyroidal stimulation in endemic iodine deficiency (165).

In the pregnant women that we investigated in Brussels, the T_3/T_4 ratio was significantly increased and remained elevated throughout gestation in women without iodine supplements, whereas the administration of iodine was accompanied by a lowering of the ratio. In our experience, however, iodine supplements given alone (from the 15th week of gestation onward) were not sufficient to normalize the T_3/T_4 ratio, an indication that the intrathyroidal iodine pools remained relatively deprived, probably because the iodine supplements were used immediately for thyroid hormone production, rather than stored (166). It is also of interest to note that after parturition in untreated pregnancies, recovery

of normal thyroid function may take months: at 6 months postpartum the ratio of T_3/T_4 was still elevated (167). These results suggest that the thyroidal alterations associated with pregnancy in iodine-restricted conditions not only persist after term, but may also have long lasting stimulatory effects on the thyroid gland, a consideration that may help explain why features of excessive glandular stimulation are frequently observed again in the same individuals in subsequent pregnancies, especially when the interval between pregnancies is brief.

The third parameter is related to changes in serum TSH. It was already mentioned that iodine restriction is associated with a significant increase in serum TSH after the first trimester. A progressive increase in serum TSH, until term, is observed in more than 80% of pregnancies under iodine-restricted conditions. Serum TSH changes usually remain within the normal range in women who are otherwise healthy. Albeit of relatively small amplitude, these modifications are statistically highly significant, with median TSH concentrations increasing from 0.75 mU/liter in the first trimester to 1.09 in the second, 1.28 in the third, and 2.08 mU/liter at term in Brussels (2, 34). Hence, serum TSH more than doubles during pregnancy when the iodine supply is limited, a clear indication of a sustained thyrotropic stimulation of the thyroid gland. At 6 months postpartum, it was observed that serum TSH levels had generally reverted to pregestational values (167). In comparison, in women who received iodine supplementation during pregnancy, the increment in serum TSH was markedly diminished by 50% or more at term (131, 166).

In areas with severe iodine deficiency such as in Ubangui (Republic of Zaïre), TSH modifications during pregnancy are not restricted to the normal range and are of a much greater amplitude. In such areas, maternal TSH values were found to exceed 100 mU/liter in some women at the time of delivery, confirming the intensity of chronic thyroidal stimulation (168). In comparison, pregnant women from the same villages, who received 1 ml of iodized oil in the second trimester of gestation, had significantly lower mean serum TSH values at delivery, never exceeding 20 mU/liter.

The fourth parameter is related to the changes in serum TG levels. It was already mentioned that serum TG is frequently elevated in pregnancy, particularly during the late stages of gestation near term (34, 68, 160, 169, 170). An illustration that thyroidal stimulation is associated with increased TG concentrations is given in Fig. 13. When we investigated pregnant women (selected because they displayed increased thyroidal stimulation), who were given or not given iodine supplements, a linear relationship was demonstrated between the increments in serum TG and TSH: without iodine supplementation, the relative increment in TSH reached 100% at term (compared with values in the first trimester) and was associated with a 60% relative TG increment. Conversely, with iodine supplementation, TG concentrations remained unchanged or even decreased. Moreover, in a group of pregnant women who received a combination treatment (iodine + L-T_4) during pregnancy, initially elevated TG levels not only decreased but normalized rapidly, in concomitance with a reduction in TSH concentrations (166).

Finally, it is important to mention that changes in serum

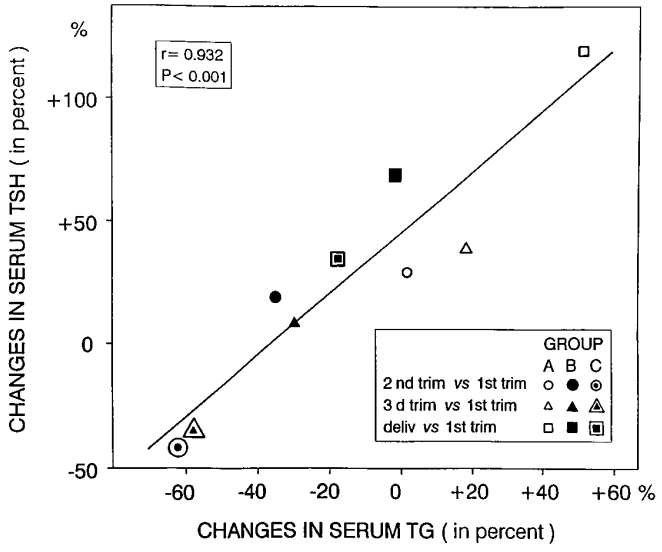

FIG. 13. Linear relationship between the relative changes (given as a percentage) in serum TG and TSH levels in three groups of women who participated in a randomized therapeutic trial during pregnancy: group A received no active treatment (placebo); group B received 100 μg iodide/day; group C received a combination of 100 μg iodide + 100 μg L-T_4/day. The results are presented as the comparison of increments or decrements in TSH and TG concentrations in the second and third trimesters, as compared with the values found in the first trimester before the initiation of treatment. [Adapted with permission from D. Glinoer *et al.*: *J Clin Endocrinol Metab* 80:258–269, 1995 (166). © The Endocrine Society.]

TG are correlated with goiter formation during pregnancy, indicating that TG determinations represent a useful marker to monitor gestational goitrogenesis associated with iodine deficiency.

In summary, relatively simple laboratory tools and standardized criteria can be used to assess excessive thyroidal stimulation, based on the routine determination of serum total T_4 and T_3, free T_4, TSH, and TG levels. Better understanding of the complex mechanisms that intervene to regulate thyroid function during pregnancy and the deviations from physiological adaptation observed in iodine-deficient conditions may be very valuable in assessing the alterations of thyroidal economy associated with pregnancy and also in monitoring their therapy and prevention.

3. Gestational goitrogenesis and its prevention by iodine supplementation. Several investigations have been carried out in Europe in recent years to evaluate the modifications in TV associated with gestation. Together these studies have amply confirmed the original observations by Crooks *et al.* (171), who reported as early as 1967 (in those early days employing palpation) a striking difference in the incidence of goiter in pregnant women between Aberdeen, Scotland (area of lower iodine intake) and Reykjavik, Iceland (area of higher iodine intake) (171). The authors observed that the incidence of gestational goiter was 3-fold greater in Scotland compared with Iceland, and that it doubled during pregnancy in the lower, while remaining virtually unchanged in the higher, iodine area.

Table 2 summarizes seven recent European studies in which TV modifications associated with pregnancy have

TABLE 2. Modifications in thyroid volume (TV) during pregnancy

n	Women without iodine supplementation		Women with iodine supplementation		Study area
	Average increment in TV	Average iodine excretion in urine	Average increment in TV	Average iodine excretion in urine	
21	10%	ND[a]			Finland
20	~30%	ND[b]			Denmark
66	~15%[c]	170 μg/g creat.			Ireland
180	20%	45 μg/liter			Belgium
35	16%	30–55 μg/day	<5%	100–150 μg/day	Italy
54	31%	50 μg/liter	16%	100–110 μg/liter	Denmark
120[d]	30%	40 μg/liter	15%	80–100 μg/liter	Belgium

[a] ND, Not determined, but considered adequate in Finland.
[b] ND, Not determined, but known to be moderately low in this area of Denmark, around 80 μg/day.
[c] Cross-sectional study with TV determined in different pregnant women, between first and third trimester.
[d] Study carried out in euthyroid women with increased thyroidal stimulation (defined by an elevated serum TG, high T_3/T_4 ratio and/or low normal free T_4 index, and normal serum TSH in the first trimester of gestation). [Reproduced with permission from D. Glinoer: *Clin Obstet Gynecol* 40:102–116, 1997 (49). © Lippincott-Raven Publishers.]

been evaluated precisely, employing thyroid ultrasonography. In Finland (172) and Ireland (84), where the iodine intake is considered adequate, the increment in TV was small, on average 10–15%: such changes are probably consistent with vascular swelling of the thyroid gland ("intumescence") during pregnancy. In Belgium (34) and Denmark (130), areas with a restricted iodine intake, the increment in TV was greater, reaching 25% on average. From our work, it became evident that the size of the thyroid gland increases significantly when pregnant women are not supplemented with iodine: an increase in TV was observed in more than 80% of the women investigated and took place gradually with increasing gestation time. Even though the increment in TV, given as an average, may not seem spectacular, it is important to consider the wide individual variation in TV modifications, with many women exhibiting a doubling in TV at term (34, 49, 160). Moreover in our experience, almost 10% of the women developed a goiter during pregnancy (*i.e.* TV > 22 ml by ultrasonography), and volumetric changes in the gland were associated with clear biochemical evidence of increased thyroidal stimulation, hence strongly suggesting that pregnancy truly induces goitrogenesis.

In three European studies (in Italy, Denmark, and Belgium), women were given iodine supplements, and changes in TV were compared between those with the treatment and matched controls (131, 166, 173). The results showed that iodine supplementation was accompanied by a significant increase in urinary iodine excretion levels and a marked reduction in goiter formation. From our data in Belgium, it was apparent that in most women the goitrogenic stimulus of pregnancy could be suppressed with iodine supplementation alone. It should be emphasized, however, that once thyroidal stimulation is triggered, the iodine treatment may not always be sufficient to completely eradicate goitrogenesis, presumably because of the lag period required (approximately one trimester) to partially replenish low intrathyroidal iodine stores. This difficulty probably explains the failure, reported by some authors, to prevent changes in TV, particularly when the study group includes patients who have a goiter before pregnancy (174). For the specific case of goitrous patients, it was shown that combining iodine supplementation with L-T_4 administration during gestation was more efficacious in suppressing the goitrogenic stimulus and also reducing the size of the preexisting goiter (150, 151, 166).

Another important consideration concerns the long term evolution of gestational goiters. To investigate the reversibility of thyroidal alterations after pregnancy, thyroid function parameters and TV were investigated 6 and 12 months after delivery in women who had initially been studied during pregnancy and who had not received iodine supplements (167). Six months after delivery, an overall normalization of thyroid function was noted, except for the T_3/T_4 ratio, which tended to remain elevated, and also serum TG, which was still supranormal in a significant fraction of the cases. TV had only partially reverted to normal 12 months after delivery. More importantly, perhaps, in one half of the women who developed a goiter during pregnancy, the goiter persisted. These results indicated for the first time that thyroidal alterations are not limited to the period of pregnancy. It allowed us to propose the concept that in conditions in which the iodine intake is only marginally reduced, pregnancy constitutes a risk for the maternal thyroid gland. Once formed, goiters tend to persist and therefore the glandular stress associated with pregnancy may provide a clue to understanding the higher prevalence of thyroid disorders in women. Other studies have confirmed the relationship between thyroidal abnormalities and the occurrence of previous pregnancies (175, 176).

Taken together, these observations raise interesting questions concerning the precise role of "environmental" factors such as pregnancy in iodine-restricted conditions in the development of goiter, thyroid nodules, etc. Pregnancy certainly plays a significant pathogenic role, but other predisposing factors must intervene as well. Future studies are needed to delineate such predisposing factors and the ways to monitor and perhaps even treat preventively women who have the highest risk. In the meantime, recent observations on the thyroidal responses associated with pregnancy have provided a strong argument in support of the view that the iodine supply should be increased during pregnancy and also after parturition (in particular in nursing mothers) for all women who reside in areas with a restricted iodine intake (86, 153, 177).

How much supplemental iodine must be given to prevent

gestational goitrogenesis remains debatable. Ultimately, it probably depends on the extent of the deficiency in preexisting intrathyroidal iodine stores. The goal is to restore and maintain an iodine balance; this goal can be reached in most women with 100–200 μg iodine/day given as a supplement during pregnancy, at least in Europe. In regions with a more severe iodine deficiency, iodized oil (given intraperitoneally or by a single oral dose) has been shown to protect pregnant women from hypothyroidism for more than a year without significant side effects (159, 178–180).

4. Consequences of iodine deficiency for the offspring. The functional maturation of the fetal thyroid gland follows a well characterized pattern, with the thyroid acquiring the capacity to concentrate iodine and synthesize iodothyronines by 10–12 weeks, its secretory activity becoming effective by midgestation, and total T_4 levels rising progressively until term (181, 182). Even though maternal and fetal thyroid functions are autonomously regulated, they are not independent of one another. There is evidence of at least some transplacental passage of maternal thyroid hormones, probably important in the early stages of fetal development. Moreover, the fetal thyroid activity depends entirely upon the availability of iodine transferred from the maternal circulation (183–187).

In conditions with only a moderate iodine deficiency, it was reported in 1992 that although the mothers exhibited relative hypothyroxinemia at delivery, this was not the case for the newborn who had total and free T_4 concentrations significantly higher than their respective mothers, which would suggest that the fetus was protected from hypothyroxinemia (188). To achieve protection, and because of the very low intrathyroidal iodine stores in the fetus, the fetal thyroidal machinery is chronically subjected to an intense stimulation (189). In our observations with nonsupplemented mothers, neonatal thyroidal stimulation was reflected by significantly higher TSH and TG concentrations found in cord serum, compared with TSH and TG values in mothers at delivery. These initial studies clearly indicated that only a moderate reduction in the iodine supply was sufficient to constitute a stimulus for both the maternal and neonatal thyroid glands, with relative iodine deficiency representing the common regulatory link (188).

The apparent paradox between subnormal free T_4 in the mothers at term and normal free T_4 concentrations in the newborn can partially be explained by the fact that the fetal thyroid gland is hypersensitive to alterations induced by iodine restriction. In adults with intrathyroidal iodine stores in the order of 10–20 mg and daily needs of 100–200 μg iodine, the turnover rate of used iodine is 1–2%/day. In the newborn, in contrast, intrathyroidal iodine stores are very low, representing, at most, 300 μg when the iodine supply is sufficient, 50–100 μg in Brussels, and as little as 25 μg in severely iodine-deficient areas (190). Therefore, with daily needs of approximately 50 μg iodine, the fetal gland turns over close to 100% of its stores to ensure the required daily hormone production, rendering both fetal and neonatal thyroid economies exquisitely sensitive to fluctuations in the iodine supply from the mother. Hyperthyrotropinemia at birth, before the occurrence of the neonatal TSH surge, reflects the increased fetal thyroidal stimulation. Also, this sensitivity explains why the recall rates after screening for congenital hypothyroidism by TSH determinations on the fifth day of life in Europe was shown to be inversely correlated to maternal iodine intake (87, 190).

The precise mechanism by which the fetus is protected against hypothyroxinemia remains presently unclear; in more severely iodine-deficient areas, however, this protective mechanism is overwhelmed, and the newborn clearly exhibits hypothyroidism. The endemias of Ubangui (northwestern part of Zaïre) and Ntcheu (central part of Malawi) have been extensively investigated by Thilly and co-workers (89, 168, 191). The authors showed that the frequency of severe hypothyroidism, evaluated at birth on the basis of a serum TSH concentration greater than 50 mU/liter, reached up to 25% in Ubangui and affected 7% of the newborn in Malawi. In Ubangui, they observed, in each village, groups of myxedematous cretins and cretinoid subjects exhibiting mental deficiency, neurological symptoms, severe dwarfism, etc. Extreme forms of fetal, neonatal, and juvenile hypothyroidism were less frequently encountered in Malawi, despite a similar degree of severity in the iodine deprivation. The data suggest that the pathogenic mechanisms leading to severe cretinism and hypothyroidism are multifactorial, the role of severe iodine deficiency being amplified by the deleterious effects of thyocyanate overload, selenium deficiency, and also glandular destruction and fibrosis occurring progressively during infancy (89). In contrast, when iodine supplementation is given to pregnant women in such areas, myxedematous cretinism can be eradicated and neonatal hypothyroidism prevented. As an example, Table 3 illustrates the results of a study (A. M. Ermans, unpublished results) in Kivu (Zaïre), in an area where iodine deficiency has previously been known to be extremely severe (167) and where iodine supplementation had recently been introduced. Upon the addition of adequate iodine supplements in the population, both maternal and neonatal thyroid function parameters became the same as the values found in untreated mothers and newborn, respectively, from the Brussels area, strongly showing that the problem had largely been corrected by simple measures (A. M. Ermans, personal communication).

Finally, in Europe, the effects of iodine supplementation

TABLE 3. Thyroid function parameters in mothers at delivery and in cord blood in Kivu (1992) and Brussels (1990)

	Kivu[a]	Brussels[b]
Mothers		
Urinary iodine conc. (μg/liter)	62[c]	55[c]
Total T_4 (μg/dl)	11.8 ± 3.2	11.0 ± 2.3
Total T_3 (ng/dl)	154 ± 42	214 ± 38
TSH (mU/liter)	1.9[c]	1.9[c]
Newborns		
Total T4 (μg/dl)	10.4 ± 2.8	11.8 ± 2.8
Total T3 (ng/dl)	44 ± 23	58 ± 24
TSH (mU/liter)	6.2[c]	6.0[c]

[a] Data from Kivu are unpublished observations collected in 400 subjects and kindly authorized to be included by Prof. A. M. Ermans.
[b] From Refs. 34 and 188.
[c] Median values for urinary iodine and serum TSH. For total T_4 and T_3, mean ± SD are given.

during pregnancy on neonatal thyroid function parameters have been recently investigated in two prospective randomized studies in countries with a moderately low iodine intake in the population, below 100 μg/day (131, 166). In the Danish study, 27/54 healthy euthyroid consecutive women were randomized during pregnancy to receive 200 μg iodine/day, while the other half constituted the control group. In the Belgian study, 60/120 healthy euthyroid but selected pregnant women (exhibiting the biochemical criteria of increased thyroidal stimulation discussed above) were randomized to receive 100 μg iodide/day, while the other half constituted the control group. Parameters of thyroid function were evaluated in cord blood. Both studies yielded essentially comparable results: iodine supplementation did not significantly modify cord TSH levels, which on average were and remained below 10 mU/liter. In contrast, in both the Danish and Belgian studies, iodine supplementation resulted in a marked and highly significant decrease in cord TG concentrations, with mean decrements of 50% compared with the values observed in the newborn from placebo-treated control mothers. Furthermore, in Brussels, we also investigated the TV values, measured by ultrasonography in newborns during the first week of life (Fig. 14). When newborns from mothers with and without iodine supplementation during pregnancy were compared, the study showed an important result: TV was significantly larger at the time of birth in the neonates from nonsupplemented mothers and, moreover, glandular hyperplasia was already present in 10% of the newborns. In contrast, the newborn from supplemented mothers had, on average, a 39% smaller TV with no single occurrence of neonatal goiter formation. The data therefore strongly suggest that the process of fetal goitrogenesis occurs early during fetal development in conditions with a low iodine intake during pregnancy, perhaps as soon as the thyroid gland begins to develop. It remains to be elucidated, however (and this would require long-term investigations that are difficult to set up), whether the newborns who exhibited glandular hyperplasia since birth (or before) will become the cohort of children, then adolescents, and eventually adult subjects that we usually refer to as patients with "sporadic" euthyroid goiter.

In summary, when the iodine intake is marginally restricted or overtly deficient during pregnancy, the adequacy of thyroidal physiological adaptation to the changes associated with pregnancy are not always achieved, and pathological alterations take place in parallel with the severity of chronic iodine deprivation, leading to increased thyroidal stimulation. In the iodine nutrition conditions commonly encountered in Europe, pregnancy therefore acts to disclose the underlying iodine restriction, and gestation results in an iodine-deficient status, with maternal and neonatal goiter formation as the most visible consequence. Both maternal and neonatal alterations can easily be prevented by iodine supplementation given systematically during pregnancy. Finally, in severely iodine-deficient areas, iodine supplementation dramatically improves thyroid functions in both the mother and her infant and largely prevents the spectrum of iodine-deficient disorders.

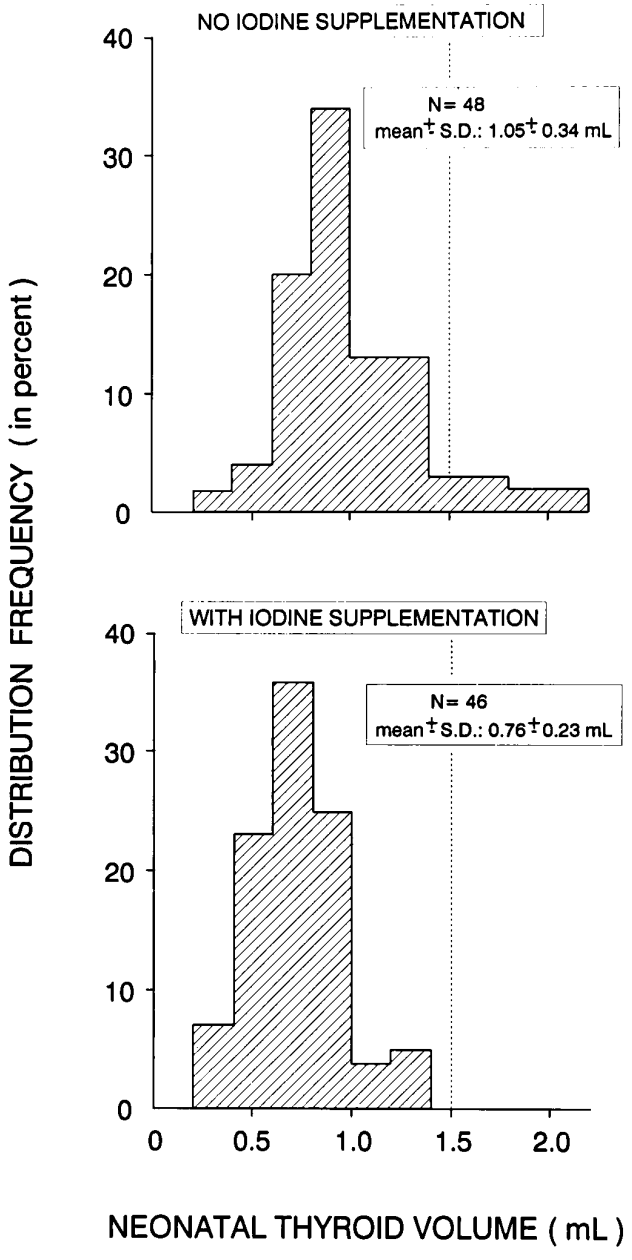

FIG. 14. Distribution frequency of TVs, determined by ultrasonography in 94 neonates born to mothers without iodine supplementation (*upper graph*) and with iodine supplementation (100 μg/day) (*lower graph*) during pregnancy. TV was on average 38% larger in the newborns from untreated mothers, compared with the treated group. The *dashed vertical line* at 1.5 ml shows the upper limit of normality for TV in newborns in the Brussels' area. [Reproduced with permission from D. Glinoer: *Thyroid Int* 5:1–16, 1994 (151).]

B. Hypothyroidism and pregnancy

Over the past decade, important new information has accumulated in relation to primary thyroid insufficiency during pregnancy. In this part of the review, we shall attempt to summarize old and recent data, emphasizing the requirement for the modification of thyroid hormone therapy in women with established hypothyroidism, the importance of adequate detection of autoimmune thyroid disorders (AITD)

and subclinical hypothyroidism in early stages of gestation, and the association of reduced fertility and spontaneous abortion with thyroid dysfunction or positive thyroid antibodies.

1. Fertility and pregnancy outcome in hypothyroid women. There is a known association between hypothyroidism and decreased fertility which, in most cases, is associated primarily with ovulatory disturbances and not with abortion: women who require treatment with thyroid hormone have a 2-fold risk of primary ovulatory infertility (192). Observations in the human species are confirmed by animal investigations showing an association between experimentally induced hypothyroidism and menstrual cycle dysfunctions (193). Also, this association has a well known counterpart in the veterinary sciences. In areas with severe IDD, cattle (like humans) may exhibit various degrees of hypothyroidism, associated with a reduced fecundity. This problem has important consequences for the productivity of cattle raising and dairy farming and therefore constitutes a serious economic issue in some areas (194–196).

Hypothyroid women who become pregnant also carry an increased risk for obstetrical complications such as intrauterine fetal demise, gestational hypertension, placental abruption, and poor perinatal outcome. There are indications that thyroid hormone administration greatly improves, although it does not entirely suppress, the frequency of these abnormalities (197–201). In general, infants of hypothyroid mothers appear healthy without evidence of thyroid dysfunction. In infants born to hypothyroid mothers, some studies have indicated the risk of a higher perinatal mortality and congenital malformations (not confirmed by other investigators), and there is also evidence for an increased frequency of low birth weight (199, 202–204) and a concern about potential long-lasting psychoneurological impairment in the progeny (205).

The most common cause of primary hypothyroidism in young women is chronic autoimmune thyroiditis, which occurs in both goitrous and atrophic forms. It is presently not clearly understood whether diminished fecundity and increased risk of poor pregnancy outcome, observed in hypothyroid women, result from thyroid insufficiency or instead reflect a more generalized autoimmune disturbance affecting both conception and fetal development (206).

2. Thyroid hormone replacement in the hypothyroid pregnant woman. Several recent reports have discussed thyroid hormone replacement during pregnancy in women with a previously established diagnosis of primary hypothyroidism. In the 1980s, the need for a systematic adjustment of the T_4 replacement dose during pregnancy was not recognized, and it was actually stated (surprisingly enough still stated in the 1990s) that women with hypothyroidism rarely required a change in T_4 replacement (207, 208). In fact at that time, only anecdotal reports described isolated clinical cases in which a pregnant woman became severely hypothyroid during gestation when her replacement dose was not adjusted; such cases were thought to represent exceptions, hence justifying publication (209). Newer studies have clearly shown that this is not the case (150). One plausible explanation is that before the development of sensitive TSH assays that permit a more precise titration of T_4 dosage, many patients with hypothyroidism were overtreated before becoming pregnant. Because the L-T_4 overtreatment could not easily be detected with the less sensitive TSH assays, the need for an increased L-T_4 requirement imposed by the metabolic changes associated with pregnancy was not recognized (210). In 1990, Mandel *et al.* retrospectively assessed L-T_4 requirements before, during, and after pregnancy with the use of a sensitive TSH assay (211). The authors showed that all pregnant women on T_4 replacement therapy exhibited an increase in serum TSH, and most also showed a decrease in serum free T_4, changes that indicated the need for increased doses of L-T_4 (Fig. 15). In 1992, Kaplan (212) reported a retrospective analysis of thyroid hormone requirements in a group of 65 women, who were hypothyroid because of Hashimoto's thyroiditis or thyroid ablation for hyperthyroidism. Serum TSH rose markedly when L-T_4 replacement doses were maintained at prepregnancy levels; the free T_4 levels also decreased (on average of 40%) and became subnormal in 13% of the cases. In contrast, raising the daily L-T_4 dosage by 40–100 μg resulted in a reversion of TSH concentrations into the normal range (Fig. 15). After parturition, L-T_4 requirements were approximately the same as before pregnancy.

Taken together, the results of recent work, in which thyroid function has been carefully investigated in pregnant women with established (and hence treated) hypothyroidism, mandate an increase in the daily dose of L-T_4, to avoid gestational hypothyroidism and its potential consequences (213–216). Based on these data and our own experience, the following consensus guidelines have been proposed (150). First, the daily dose of L-T_4 should be increased in at least 80% of hypothyroid women. Pregnant women who do not require an increase in dosage were probably overtreated before pregnancy began. Second, an increased need for L-T_4 is already apparent in the first trimester, concomitant with major changes in the thyroidal economy. Hence, adjustment of L-T_4 dosage should be accomplished in the early stages of gestation. Third, individual increments in L-T_4 dosage vary widely (between 10% and >100%), with a median dosage increment of 40–50% over the pregestational replacement requirement. Fourth, a regular clinical and laboratory follow-up is essential, with periodic determinations of TSH and free T_4 concentrations, indicating the mandatory need for a close collaboration between the endocrinologist and the obstetrician.

3. Subclinical hypothyroidism in pregnancy. As already alluded to above, maternal hypothyroidism is considered uncommon or even rare in pregnancy because hypothyroid women are relatively less fertile (216–218). The frequency of established hypothyroidism in pregnancy is not clearly known, but conservative estimates suggest a prevalence of 0.3–0.7%, compared with 0.6–1.4% in the general population (219). In such women, if hypothyroidism has been diagnosed before gestation starts, appropriate measures to maintain euthyroidism can be implemented.

Perhaps as important (but more subtle) is undisclosed subclinical hypothyroidism in pregnant women. Three sets of studies have addressed this question and are of great value

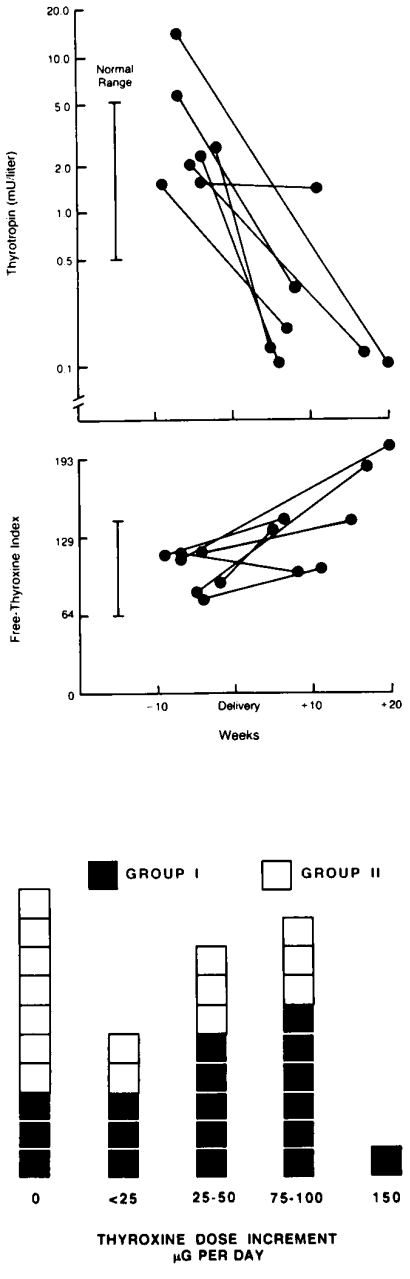

FIG. 15. *Upper graph*, Individual serum free T_4 index and TSH concentration during the third trimester and postpartum in women with hypothyroidism. Results are shown for seven patients whose measurements were made 10 weeks before and 20 weeks after delivery. Each patient is represented by a *single line*. The normal ranges for serum TSH and free T_4 index are indicated by the *vertical bars*. [Reprinted by permission of The New England Journal of Medicine, from S. J. Mandel *et al.*: Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med* 323: 91–96, 1990 (211). © 1990 Massachusetts Medical Society.] *Lower graph*, Increments in daily T_4 dose required for a euthyroid state in women whose optimal doses were known before and during pregnancy. Each *square* represents one woman. T_4 dose increments less than 25 μg/day were achieved by having the patient take one extra 100 μg or 150 μg T_4 tablet each week. Group I represents women who were hypothyroid due to thyroid ablation (after radioiodine or total thyroidectomy); group II represents women who had documented hypothyroidism due to Hashimoto's disease. [Reproduced with permission from M. M. Kaplan: *Thyroid* 2:147–152, 1992 (212).]

to evaluate its clinical relevance. Subclinical hypothyroidism has been shown to occur more frequently in pregnant women with type I diabetes, who had normal serum TSH levels before conception (a significant proportion of them display thyroid antibody positivity) (220, 221). Also, Klein *et al.* (222) carried out a retrospective study on a serum data bank from 2,000 consecutive pregnant women in Maine at 15–18 weeks of gestation. The authors showed that 2.5% of all pregnant women had supranormal TSH concentrations (above 6 mU/liter), with one tenth of them exhibiting overt hypothyroidism. They also found that the prevalence of positive thyroid antibodies in women with subclinical hypothyroidism was 5-fold more frequent than in control pregnant women.

We have investigated prospectively the occurrence of previously undiagnosed subclinical hypothyroidism (150). Among 1,900 consecutive pregnant women who attended the prenatal clinic for the first visit between June 1990 and December 1992 and who were systematically screened by determining serum TSH concentrations and thyroid antibody positivity, 41 women had an elevation of serum TSH, thus yielding an overall prevalence of 2.2% (comparable to the 2.5% prevalence reported by Klein *et al.*). Serum TSH ranged between 4 and 20 mU/liter; in most instances, the TSH elevation was initially mild, below 10 mU/liter. Free T_4 concentrations were not systematically subnormal but tended to cluster near the lower limits of normal. We considered these women as having "asymptomatic" subclinical hypothyroidism. In all women for whom a TRH test was carried out, the TSH response was markedly exaggerated (average increment in TSH: 31 ± 5 mU/liter). These women were systematically given L-T_4(50–125 μg/day) throughout gestation, a treatment that resulted in a clear-cut improvement in thyroid function parameters. In four patients, a spontaneous miscarriage occurred before the therapeutic intervention could be implemented (as will be discussed later, spontaneous miscarriage occurs with a greater frequency in such women). In 16 of the 41 women (40%), the cause of hypothyroidism clearly was related to thyroid autoimmunity, with thyroperoxidase antibody (TPO-Ab) titers between 400 and 5,000 U/ml. In the remainder, the etiology of hypothyroidism could not be determined in the absence of detectable antibody titers or a family history of goiter or hypothyroidism. Thyroid ultrasonography, however, when performed in these women, showed that one quarter of them had a reduced volume, below 7 ml, strongly suggesting thyroid hypotrophy.

Women with thyroid hypotrophy before pregnancy presumably have a sufficient functional reserve for the thyroid gland to function adequately before gestation (hence allowing them to become pregnant), but not after establishment of the pregnant state. An argument in favor of this hypothesis is our observation that, when monitored during the postpartum period, thyroid function reverted to normal despite withdrawal of L-T_4 (personal unpublished information). Thus, at least two population-based surveys, carried out in areas with different iodine intake, suggest a 2.5% overall prevalence of compensated or uncompensated hypothyroidism during pregnancy. Additional studies are warranted because many important questions remain unanswered. For instance, it is not known whether a mild decrease of maternal

thyroid function predisposes to an increased risk of obstetrical complications or impaired fetal brain development. Furthermore, there have been no follow-up studies of thyroid function in affected women after parturition or during subsequent pregnancies.

4. Euthyroid autoimmune thyroid disorders (AITD) and pregnancy. In a cohort study of pregnant women with mild underlying abnormalities published in 1991, it was noted that women who are euthyroid but carry thyroid antibodies at the onset of pregnancy have an increased risk of developing hypothyroidism during gestation (223). We therefore investigated more systematically the role of AITD on thyroid function during pregnancy (224). Among 1,660 consecutive pregnancies with no previous history of thyroid disorder, 87 women (5.2%) at the time of the initial visit showed the presence of thyroid antibodies, but their free T_4 and TSH concentrations were in the normal range. No treatment was given and thyroid function parameters were monitored sequentially during gestation. Despite the expected decrease in the titers of thyroid antibodies during gestation, the parameters of thyroid function showed a gradual deterioration toward hypothyroidism in a significant fraction of the women. During the first trimester, the distribution curve of serum TSH levels shifted significantly to higher (but still normal) values when compared with normal pregnant controls from the same hospital. At the time of delivery, 40% of women with AITD had serum TSH greater than 3 mU/liter, with almost one half of them exceeding 4 mU/liter (Fig. 16). In the early stages of pregnancy, normal thyroid function was maintained due to the sustained thyrotropic stimulation. Three days after delivery, however, the serum free T_4 concentration was significantly lower compared with controls. On the average, there was a 30% reduction in serum free T_4, with almost half of the cases in the hypothyroid range, confirming that such women have a reduced functional thyroidal reserve (225–227). It was also observed that thyroid autoimmunity was associated with obstetrical repercussions such as significantly increased rates of premature deliveries and spontaneous abortion (see below). Finally, it was possible at the individual level to predict progression to hypothyroidism on the basis of serum TSH levels and TPO-Ab titers in the first trimester. Hence, these parameters can be used to provide useful markers to identify those women who carry a higher risk and, therefore, initiate hormone substitution therapy.

It is beyond the scope of the present review to discuss all facets of thyroid autoimmunity and pregnancy, *e.g.* postpartum thyroiditis or the potential role of maternal thyroid autoimmunity on the risk of congenital hypothyroidism. To sum up, pregnant women with asymptomatic AITD carry a significant risk of developing hypothyroidism. Hypothyroidism results from the relative inability of the maternal thyroid gland to adjust to the changes associated with pregnancy. We, therefore, suggest that there may be a justification for proposing a systematic screening for antibodies in the early months of pregnancy, with the following rationale: 1) increased risk of spontaneous miscarriage; 2) risk of progressive hypothyroidism during gestation; 3) risk of postpartum thyroiditis after pregnancy; and 4) finally the well

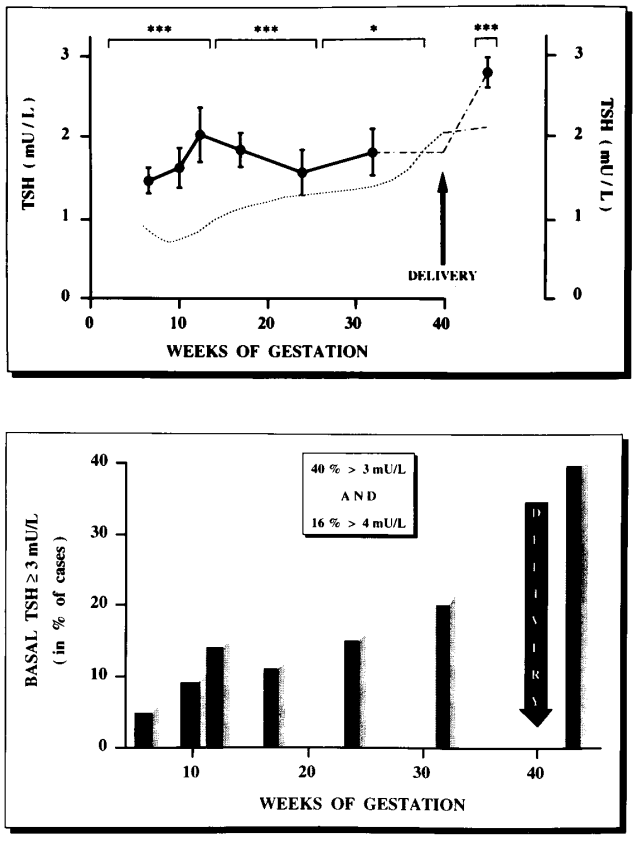

FIG. 16. Serum TSH in pregnant women with AITD. The *upper panel* shows the time course of basal TSH concentrations as a function of gestational time. Each point represents the mean (± SEM) TSH value at 6.5, 10, 12.4, 17, 24, and 32 weeks gestation. TSH was also measured 3 to 4 days after parturition. The *solid line* represents women with positive antibodies, and the *dotted line* indicates healthy subjects, investigated previously and shown as controls. Statistical differences between TSH values in AITD women and controls are indicated by the *asterisks* (*, $P < 0.05$; ***, $P < 0.001$). In the *lower panel*, the *bars* show the proportion of AITD women in whom serum TSH was >3 mU/liter, as a function of gestation time. The last bar shows TSH determinations obtained 3 to 4 days after delivery. [Reproduced with permission from D. Glinoer *et al.*: *J Clin Endocrinol Metab* 79:197–204, 1994 (224). © The Endocrine Society.]

known long-term risk of developing definitive hypothyroidism later on in life (228). All pregnant women with AITD should be monitored closely and jointly by obstetricians and endocrinologists. Moreover, in view of the frequent occurrence of subclinical hypothyroidism and the potentially deleterious obstetrical repercussions of this diagnosis, we have proposed that women with AITD might benefit from L-T_4 administration during pregnancy (150, 224). However, further randomized studies are needed to evaluate whether such treatment is truly beneficial.

5. AITD and the risk of miscarriage. Stagnaro-Green *et al.* in 1990 (229) and Glinoer *et al.* in 1991 (223) were the first to report a strong correlation between positive thyroid antibodies and the risk of spontaneous miscarriage in women who were euthyroid. These results have since been confirmed by other reports, emphasizing the notion that the risk of miscarriage occurs primarily in the first trimester (230) and that women

with a history of consecutive abortions carry an even greater risk (231, 232) (see Table 4). Overall, the data presently available suggest that the relative risk of miscarriage is 2- to 4-fold greater in women with asymptomatic AITD, depending upon the criteria used to define spontaneous abortion and the selection of patients. The presence of thyroid immunity represents an independent marker of an at-risk pregnancy; the higher risk of miscarriage is thought to result from an abnormal stimulation of the immune system (206). It is also possible that mild degrees of thyroid insufficiency may explain, in part, the higher rate of fetal wastage. For instance, in the study of Stagnaro-Green *et al*. (229), the authors indicated that six of 17 thyroid antibody-positive women who miscarried had borderline high TSH levels. In our own studies, we were unable to confirm a statistical difference in TSH concentrations of women who miscarried, either with or without positive antibodies. This is perhaps not surprising, however, because most miscarriages occur in the first trimester, whereas the risk of subclinical hypothyroidism becomes more evident with increasing gestation time. Therefore, in our opinion, the relationship between subclinical thyroid dysfunction, thyroid autoimmunity, and obstetrical outcome needs further study (150).

C. Hyperthyroidism and pregnancy

The major cause of hyperthyroidism in women of childbearing age is GD. Even though the frequency of the disorder is relatively low, occurring in only 0.5 to 2/1000 pregnancies, it constitutes an important clinical entity that has been the subject of several excellent reviews in recent years (for more detailed information see Refs. 35, 48, 202, 204, 216, 218, and 219). Therefore in this review, we elected to emphasize only a few key aspects of GD in pregnancy, dealing mainly with the follow-up and management of the disorder. The main focus of this section will dwell on another aspect of hyperthyroidism and pregnancy, characterized only recently, *i.e.* nonautoimmune gestational transient thyrotoxicosis (GTT) and its relationship with hyperemesis gravidarum.

1. GD in the pregnant woman. As a "condensé" of many references dealing with hyperthyroidism due to GD in pregnancy, and without attempting to be exhaustive, we propose the following general rules of "good clinical practice" for the disorder. First, when the diagnosis of GD has not been established before the start of pregnancy, the disorder is not always readily suspected clinically, mainly because the symptoms and signs of mild to moderate hyperthyroidism may be mimicked by the hypermetabolic state of normal pregnancy (233). Attention should be given to a history of AITD in close family relatives, the presence of a goiter and/or suggestive eye signs, and a variety of clinical manifestations such as heat intolerance, warm and moist skin, tachycardia, wide pulse pressure, weight loss, and excessive vomiting in the early stages of gestation. Thyroid function should also be assessed in all patients with hyperemesis gravidarum. Accurate diagnosis of GD is important, because untreated hyperthyroidism is associated with increased fetal loss, with premature labor, and with low birth weight (234).

TABLE 4. Thyroid antibodies and the risk of miscarriage

% Miscarriage		Stat.	Reference
Positive antibodies	Control subjects		
17%	8%	$P = 0.011$	Stagnaro-Green *et al.* (229)
13.3%	3.3%	$P = 0.005$	Glinoer *et al.* (223)
22%	5%	$P = 0.05$	Lejeune *et al.* (230)
7%	3.3%	$0.05 < P < 0.10$	Glinoer *et al.* (224)
62%[a]	14%[a]	$P = 0.003$	Pratt *et al.* (231)
36%[a]	9%[a]	$P = 0.03$	Bussen and Steck (232)

[a] Women with a history of three (or more) consecutive first trimester abortions. [Modified with permission from D. Glinoer: *Thyroid Today* 18:1–11, 1995 (150).]

Second, the course of hyperthyroidism associated with GD generally tends to improve during pregnancy, for three independent reasons. Due to the immune suppression associated with the pregnancy state, there is a progressive decrease in the titers of thyroid-stimulating antibodies (TSAb), as gestation progresses. Furthermore, as discussed in the first part of this review, the increased hormone-binding capacity of the serum (due to the rise in TBG in the first trimester) tends to decrease the free fraction of thyroid hormones, and hence the free hormone concentrations. Finally, the reduced availability of iodine for the maternal thyroid may also help to improve the course of the disorder, at least when pregnancy occurs in women who reside in areas with a restricted iodine supply. It should be noted, however, that this usual "benevolent" evolution has exceptions, as we and others have witnessed extremely severe forms of hyperthyroidism due to GD in pregnant women. Also, transient exacerbations of hyperthyroidism near the end of the first trimester (associated with peak hCG) are not exceptional (235–237).

Third, concerning the management of patients with GD diagnosed during pregnancy, the general rules of treatment are well defined. Patients should be treated exclusively with antithyroid drugs (ATD), unless the severity of the condition justifies a more radical approach by surgery (which is then preferably carried out in the second trimester) (238–240). The optimal dosage of ATD should be maintained at a minimum, and the drugs withdrawn whenever possible, which is often the case after 4–6 months of gestation. One should not rely on L-T_4 administration to the mother to maintain euthyroidism in the fetus, since the transplacental passage of ATD is high, while it is negligible for thyroid hormones. Preference is usually given to propylthiouracil over methimazole (or carbimazole), although this choice is not mandatory, as long as the minimal dose rule of ATD is implemented (241–245). It is recommended that maternal free hormone concentrations be maintained in the upper third of the normal range, since it has been shown that such levels in maternal blood are associated with free hormone concentrations in the fetus that remain in the midrange of normal values (246–248).

Fourth, if hyperthyroidism is not adequately treated, fetal repercussions are observed with a significantly higher frequency (preeclampsia, premature labor, low birth weight, fetal and perinatal loss) (204, 249–251).

Fifth, it is strongly recommended that TSAb titers be assayed in early pregnancy and in the last trimester, because high TSAb levels predict the risk of neonatal hyperthyroidism and of recurrences of thyrotoxicosis during the postpartum period (235, 252–255).

Sixth, women who require ATD treatment after parturition should be allowed to continue taking ATD, even during breast-feeding, as long as the daily doses required remain relatively small (up to 30 mg carbimazole or 150 mg propylthiouracil). It is recommended that the baby's serum TSH and free T_4 be monitored every 2 to 4 weeks (256–258).

2. GTT. Gestational hyperthyroidism of nonautoimmune origin occurring in women with a normal pregnancy has recently been characterized (70, 104, 142, 150, 259–261). This form of hyperthyroidism differs from GD in that it occurs in women without a past history of GD and without detectable TSAb. Nonautoimmune hyperthyroidism is not always clinically apparent, since it is most often transient. Its etiology is directly related to the thyrotropic stimulation of the thyroid gland associated with hCG. The clinical importance of the disorder has probably been overlooked in the past. As an example, in a 1986 review article on "the thyroid gland and reproduction" for instance, GTT was not even mentioned as a plausible cause of hyperthyroidism in pregnancy (262). From recent studies, it is now thought that the prevalence of GTT may be as high as 2–3% of all pregnancies, if one accepts the concept that, due to its particular etiology, the clinical manifestations of the disorder will not always be apparent or easily detected (150).

To delineate more precisely the clinical relevance of GTT (defined as a biochemical pattern encompassing both subnormal, or undetectable, serum TSH with supranormal free T_4 concentrations), we systematically screened 1900 consecutive pregnant women, at their initial visit, for the presence of a subnormal TSH (<0.20 mU/liter) associated with a supranormal free T_4 concentration (>26 pmol/liter). Among the 40% of women who were tested between the 8th and 14th week of gestation, 18 women were diagnosed with GTT, yielding an overall prevalence of 2.4%. This figure may still be lower than the actual prevalence of the disorder because 60% of the women were screened either before (rarely) or after (more often) the period corresponding to peak hCG (150). Women with GTT were recalled and hCG levels determined 4–10 weeks after initial screening (Fig. 17). Despite the unavoidable delay associated with the recall process, when individual hCG concentrations were plotted as a function of gestation time and compared with the normal hCG profile, circulating hCG was abnormally elevated in every case diagnosed with GTT, with several women having a serum hCG greater than 100,000 U/liter. Serum hCG was determined again 5–13 weeks later in seven women, and it was observed that hCG levels clearly remained abnormally elevated for several weeks during the second trimester. Patients with GTT manifested free T_4 concentrations in the thyrotoxic range, with a mean value of 33 pmol/liter (upper limit of normality: 26 pmol/liter).

From a clinical standpoint, symptoms compatible with hyperthyroidism, *i.e.* weight loss or an absence of weight increase, tachycardia, and fatigue, were present in half of the women. Hyperemesis was uniformly associated with the most severely thyrotoxic cases, and in three women, the symptoms were sufficiently alarming to require hospitalization for 1–2 weeks. Most women required no treatment with ATD and were given β-adrenergic blocking agents for a short

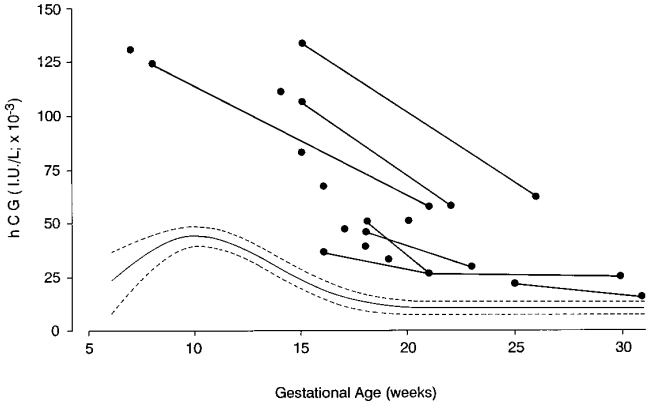

FIG. 17. Human CG levels in women with gestational transient thyrotoxicosis. The *curve flanked by the dashed lines* represents the mean with 95% confidence intervals as previously determined in normal pregnancy. Data for the control pregnancies was computed after log transformation of individual results, pooled for every 2 weeks of gestation. The individual points show serum hCG levels in women with GTT at the time of recall. In seven cases, hCG was determined again during follow-up at a later stage during gestation. [Reproduced with permission from D. Glinoer: *Thyroid Today* 18:1–11, 1995 (150).]

period (up to 2 months), with a noticeable improvement of symptoms; in a few women, we gave propylthiouracil for a few weeks because of the severity of the clinical presentation. In all cases, GTT was transient and the normalization of free T_4 concentrations paralleled the decrease in hCG. GTT was not associated with a less favorable outcome of pregnancy. It is of interest that, while no women had detectable TSAb (and none developed GD in postpartum), the majority of women with GTT also had mild underlying thyroid abnormalities including moderately positive TPO-Ab titers or a micronodular or slightly enlarged thyroid gland, as assessed by ultrasonography.

Our results reinforce the concept that normal women may develop hyperthyroidism associated with abnormally elevated hCG levels, particularly when the hCG elevation is maintained for a prolonged period. The syndrome is not rare (at least 10-fold more frequent than hyperthyroidism due to GD) and is characterized by transient hyperthyroidism, with a blunted or suppressed TSH level in the first trimester and supranormal free T_4 concentrations, and in most cases a marked and prolonged elevation in circulating hCG, which is thought to be responsible for the disorder. It occurs more frequently in women who have mild underlying thyroid abnormalities. The presence of a variant hCG molecule with a potent thyrotropic activity is possible and has been advocated by several authors (140, 260, 261), although this hypothesis is not absolutely required to explain the disorder. The cause of the anomaly in hCG regulation is presently unknown. Obstetricians should be aware of the disorder and monitor thyroid function and hCG levels in women with early gestational emesis.

3. Hyperemesis gravidarum and hyperthyroidism. Pregnant women often exhibit nausea and vomiting, particularly during the first trimester. These symptoms may represent a broad clinical spectrum, from the simple nausea of "morning sickness" to the nausea associated with mild vomiting, and finally to hyperemesis gravidarum, a serious complication

associated with weight loss and severe dehydration, often requiring hospitalization and drastic treatment (263–265). Exceptional cases have even been described with recurrent pregnancy-induced thyrotoxicosis presenting as hyperemesis gravidarum in successive pregnancies (266).

While some studies have suggested that usual morning sickness bears no causal relationship to abnormalities in thyroid function (267), biochemical hyperthyroidism is associated with hyperemesis gravidarum in most women with this condition (268–274). Several important studies have now clearly established a correlation between the intensity of emesis and abnormalities of thyroid function. In 1988, Mori *et al.* (275) compared three groups of pregnant women: those with no symptoms, those with nausea alone, and those with nausea and vomiting. The authors showed that during the first trimester, the severity of morning sickness correlates positively with serum free T_4 and the concentration of plasma hCG and negatively with the level of serum TSH. In 1992, Goodwin *et al.* confirmed these relationships: they suggested that hCG plays a causal role in the hyperthyroidism of hyperemesis patients and that the severity of vomiting among controls and hyperemesis patients varies directly with hCG concentrations and the degree of thyroidal stimulation (259). The same group's experience of 67 hyperemesis patients indicates that the resolution of the hyperthyroidism varies widely, from 1 to 10 weeks, but the disorder is self-limited (204, 259, 276).

Thus, because there is no clear indication of increased vomiting among pregnant women with GD, hyperemesis in pregnancy appears to be significantly associated with hCG-induced thyrotoxicosis. Hyperemesis may be related to the high levels of hCG-induced estradiol in these women, hence providing the potential link between hCG, GTT, and the clinical finding of nausea and vomiting (142). As in the case of GTT without severe vomiting, it seems likely (or at least possible) that certain hCG fractions may be more important than the total hCG as thyroid stimulators (119, 122, 276). As stated by Mestman *et al.* (204): "Hyperthyroidism is a common, self-limited finding in hyperemesis gravidarum. The syndrome of transient hyperthyroidism associated with excessive vomiting should be considered in any woman presenting with biochemical evidence of thyroid function abnormalities suggestive of GTT in early pregnancy".

IV. Conclusions and Perspectives

Our concepts of the complex relationships between pregnancy and thyroid function have evolved importantly over the past several years. The demonstration that relative hypothyroxinemia and goitrogenesis occur in healthy women residing in geographical areas with a restricted iodine intake supports the concept that pregnancy is a potential goitrogenic stimulus and confirms that there is still a state of mild to moderate iodine deficiency in large parts of Europe. Concerning IDD, an effort has been undertaken in recent years to convince the official policy makers, at government levels, to implement iodine supplementation programs in the general population, and particularly in groups with a higher risk, such as children and pregnant women. Pregnancy-induced goitrogenesis actually may constitute one crucial factor responsible, in part, for the so-called sporadic goiter in areas with a limited availability of iodine. Furthermore, relative iodine deficiency constitutes a stimulus not only for the mother's, but also for the newborn's thyroid gland. Because of the recently recognized transplacental passage of thyroid hormones, maternal hypothyroxinemia might have important implications for adequate fetal development.

By stimulating directly but transiently the maternal gland, hCG should now be considered a thyroid-regulating hormone in normal pregnancy. In addition, thyroidal stimulation associated with excess hCG activity may lead to gestational thyrotoxicosis in 2–3% of the pregnant population, a syndrome distinct from classic hyperthyroidism in pregnancy. More research is needed to understand better the regulation of hCG production and metabolism in women who present with GTT and hyperemesis gravidarum.

Undiagnosed subclinical hypothyroidism in pregnant women is probably more prevalent than usually considered. Moreover, pregnancy may precipitate symptomatic hypothyroidism in a significant fraction of women with previously asymptomatic AITD. More work is required to assess the relationships between the risk of spontaneous miscarriage and thyroid function disorders or autoimmunity.

Altogether, thyroid abnormalities, including goiter formation, transient hyperthyroidism, autoimmune thyroiditis, and subclinical hypothyroidism, affect 5 to 15% of pregnant women. Therefore, in our opinion, this justifies the systematic detection of these abnormalities by appropriate laboratory screening and by developing educational programs in this important area for gynecologists, family physicians, and endocrinologists.

Six years ago, when we published our first study on thyroid function during normal pregnancy (34), thyroid changes in pregnancy were generally considered to be minor and attributed only to the increase in TBG (1). We now realize that this assumption is far from the truth. Even though a wealth of new information has been gained in the last decade to improve our concepts of the physiology and pathology of the thyroid gland associated with the pregnant state, more knowledge most certainly needs to be acquired in the near future.

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