

## **The Thyroid and Pregnancy: Historical & Scientific Vignette on The Brussels' Studies**

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*Dr. Glinoer was the recipient of the ETA-Genzyme Prize Award at the ETA Meeting 2009.*

*The Author declares no conflict of interest related to this work.*

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### **ABSTRACT**

The first part of this manuscript is an overview of two successive prospective cohort studies, carried out in Brussels (1988-1998), aiming at evaluating the main changes in thyroid function and the clinical epidemiology of thyroid diseases associated with the pregnant state. Main results were to show the inadequate adaptation of thyroid function in pregnant women with a restricted iodine intake, leading to excessive thyroid stimulation, relative hypothyroxinemia and goiter formation in both mother and fetus. Another finding was the demonstration that CG is a maternal thyroid regulator (especially in 1st trimester), with 2% of the women at risk of developing gestational transient thyrotoxicosis when CG levels remain abnormally elevated during a prolonged period. The second study showed an overall 6.5% prevalence rate of positive thyroid autoantibodies, and women with autoimmune thyroid disorder (AITD) had a significantly increased risk of spontaneous miscarriage. Furthermore in women with AITD whose gestation progressed to term, frequent development of hypothyroidism was evidenced. These results led us to propose that thyroid function screening should be part of the routine management of pregnant women.

The second part outlines the landmarks that allowed to extend our views from the clinical epidemiology of thyroid disorders to their management, in particular iodine deficiency prevention during pregnancy, algorithms for systematic screening of thyroid dysfunction, and the establishment of consensus guidelines for the treatment of thyroid diseases during pregnancy and postpartum.

The third part is a short discussion on unresolved issues, in an attempt to help define some perspectives for future research. (*Hot Thyroidol. 2009: e12*).

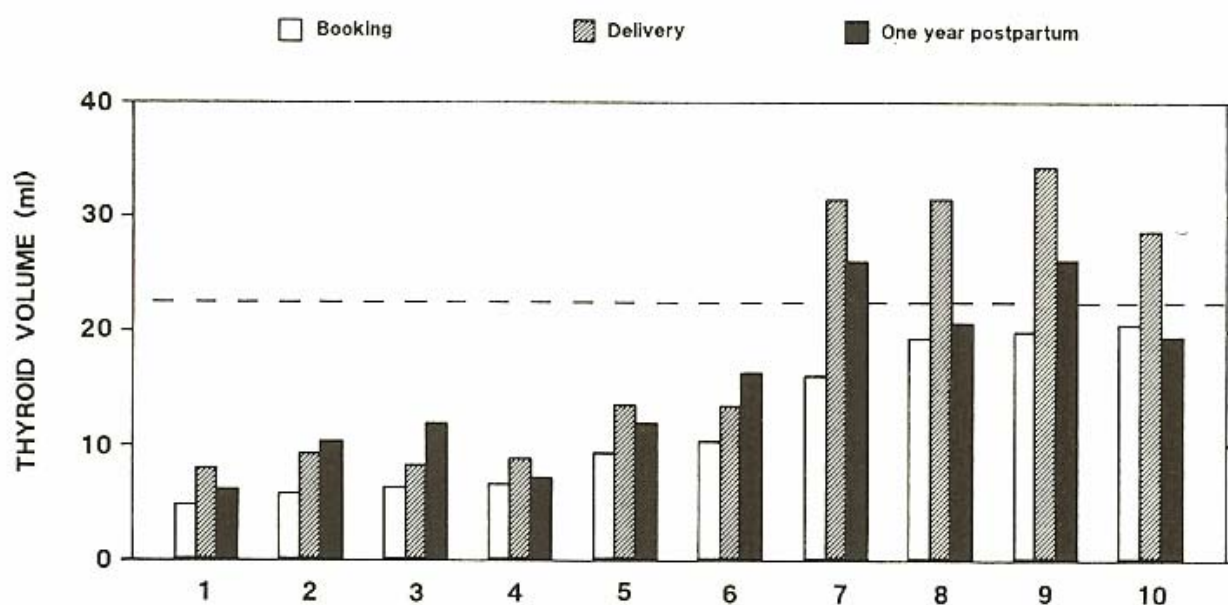
**Key-words:** pregnancy, thyroid disorders, goitrogenesis, fetal development, iodine deficiency, thyroid autoimmunity, screening, consensus guidelines.

## Part 1: Overview of the pioneering observational studies

Two successive prospective studies, carried out in Brussels over the span of a decade (1988-1998), allowed to delineate the main aspects of the clinical epidemiology of thyroid function and disorders associated with pregnancy and present a comprehensive view on how thyroid function is regulated in the pregnant state, in an attempt to delineate the pathways of thyroidal adaptation from physiology to pathology (1).

A cohort of 726 unselected consecutive apparently healthy pregnant women was investigated first in 1988-1989. Among them, 606 women had no known or detectable thyroid abnormality. Thyroid function was evaluated using a double cross-sectional and sequential study design, between first visit at our prenatal clinic and delivery (2). The results showed that iodine deficiency (ID) – considered mild to moderate in our country – was aggravated during pregnancy. As a result of more severe ID, in a context where the thyroid machinery must increase physiologically its hormone production to maintain the homeostasis of thyroid economy, one third of pregnant women presented relative hypothyroxinemia with preferential T<sub>3</sub> secretion and increased serum TG levels, as well as a doubling of serum TSH during the second half of gestation (although TSH remained within the normal range).

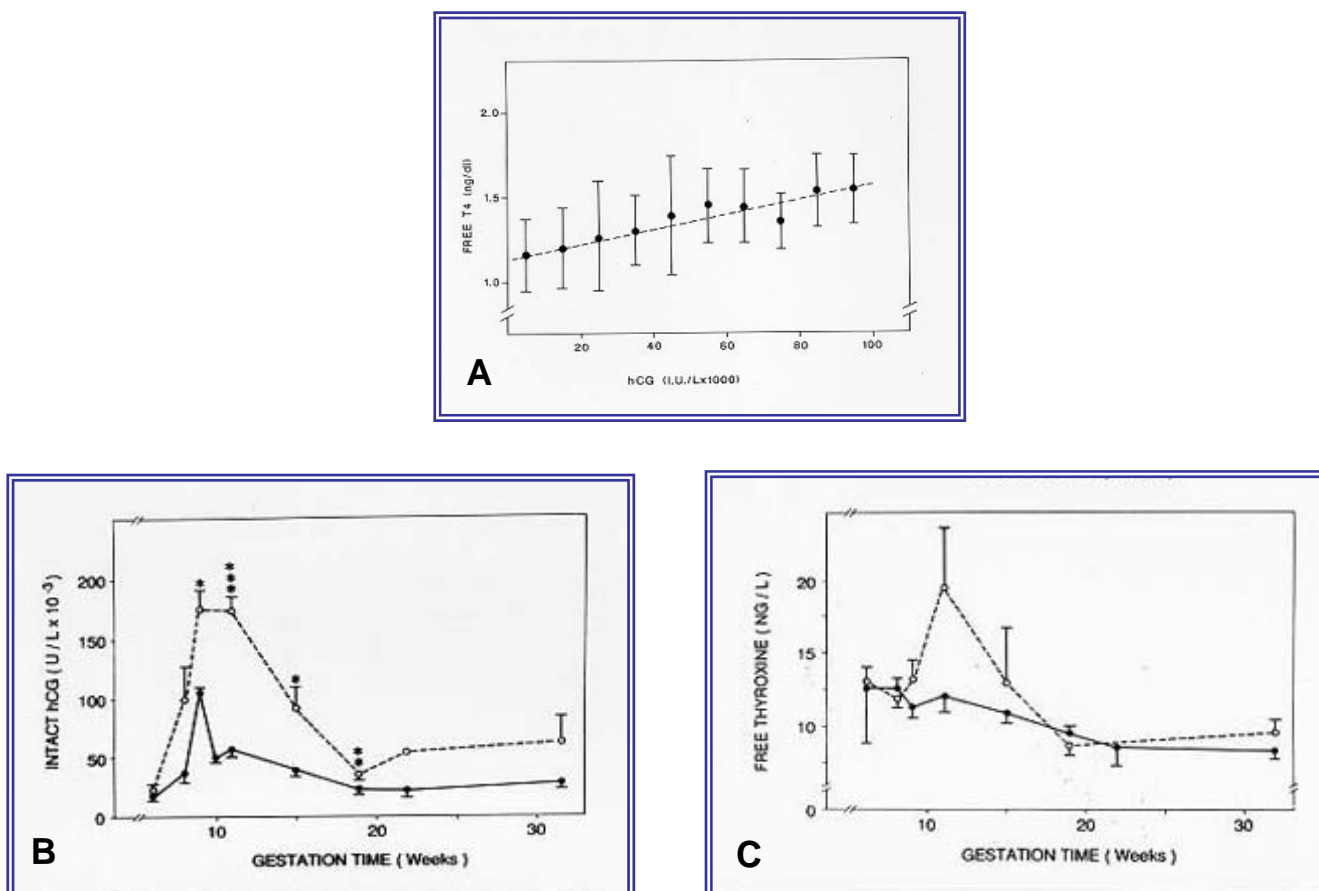
This pattern of changes in thyroid function was compatible with the concept of *excessive and prolonged thyroidal stimulation* including, as its most visible hallmark, development of gestational goiter in 9% of normal pregnant women. Goiter formation did not affect only a small fraction of pregnant women. It was shown that goitrogenesis was a general phenomenon and affected 75% of the women, with a increase in thyroid volume (TV) between early gestation and delivery (3). Furthermore, goiter formation affected also the fetus. This finding provided the first demonstration that goitrogenesis takes already place *in utero* in conditions where normal pregnant women have a restricted daily iodine intake (4). Thus, pregnancy constitutes a stimulus for both the maternal and newborn thyroid glands in conditions with ID. The importance of this notion is that it showed that, although maternal and fetal thyroid economies were regulated independently, the link between them was the iodine nutritional status of the mother. Maternal goitrogenesis was directly correlated to the biochemical indices of excessive thyroidal stimulation due to ID. In a subsequent study, we showed that a gestational goiter may persist one year after delivery, thus allowing us to propose the novel concept of a “*ladder phenomenon*” (Figure 1), whereby each subsequent pregnancy carried an added risk to aggravate goiter formation (5). At the same time already, we recommended that the iodine intake should be fortified as early as possible during pregnancy in our country to reach 150-250 µg/day, in order to avoid such pathologic sequence of events.



**Figure 1.** Thyroid volume (TV) was determined by ultrasonography in 10 women in 1<sup>st</sup> trimester, at delivery, and 1 year postpartum. Women selected for the study had TVs covering the entire normal range (from 5 to 22 mL) at the beginning of their pregnancy and TVs that increased by >25% of the initial size during gestation. Twelve months after delivery, TVs, which had increased by 54% on the average during gestation, had not reverted to initial individual TV sizes. Moreover, a goiter was still evident in 2 of the 4 women in whom a gestational goiter had developed (cases N° 7 & 9).

Another important finding was the blunting of serum TSH due to the thyrotropic action on the thyroid gland of elevated serum concentrations of human chorionic gonadotropin (hCG) near the end of 1<sup>st</sup> trimester, with a mirror image between peak hCG values and a nadir of serum TSH values. Turning our efforts to evaluate more systematically the role of elevated hCG levels on the pituitary-thyroid axis, a study showed that ~20% of pregnant women underwent transiently partial or total suppression of serum TSH levels. In 10% of the latter (i.e., 2% of the female pregnant population), TSH suppression was associated with supranormal free T<sub>4</sub> levels, hence leading to a state of transient biochemical hyperthyroidism of non autoimmune origin, that was coined “GTT” (gestational transient thyrotoxicosis) (6). Normal TSH values were progressively restored during the 2<sup>nd</sup> trimester. In a later study where twin and singleton pregnancies were monitored sequentially during the first weeks of gestation, we showed that it was the both the amplitude and duration of peak hCG values that geared the changes in thyroid function (7). Specifically, peak hCG levels were much higher in twin compared with singleton pregnancy (mean of 170.000 IU/L vs. 65.500 IU/L) and significantly prolonged (~6 weeks vs. <1 week). Thus, GTT results from the abnormal stimulation of the thyroid gland when hCG levels exceed 75.000-100.000 IU/L and when enough time is given for such functional abnormality to develop (Figure 2). In summary, these studies showed that hCG is a maternal thyroid regulator, especially during the first trimester of gestation and also that GTT is the

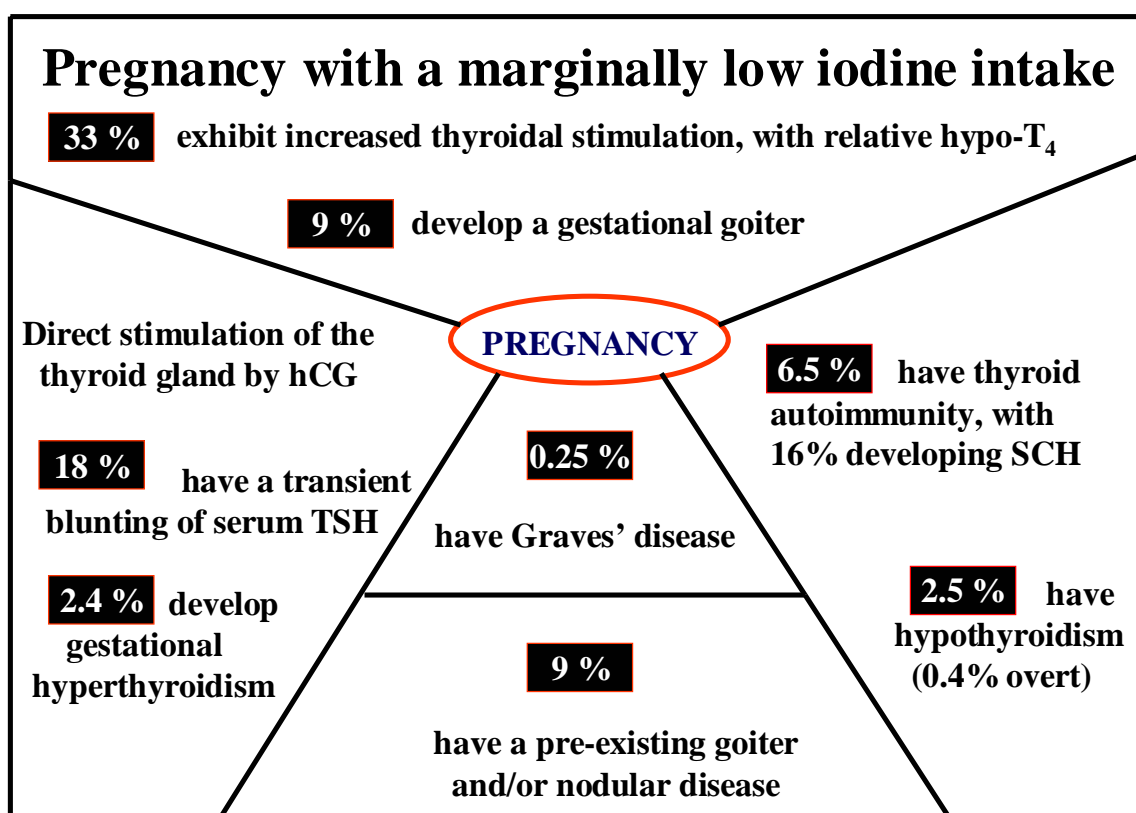
most frequent cause of (non autoimmune) thyrotoxicosis in the pregnant state, as part of the Hyperemesis Gravidarum syndrome (1, 8).



**Figure 2.** A. Direct correlation between increments in peak hCG values (by 10.000 IU/L) and progressively increasing free T<sub>4</sub> levels in normal women with singleton pregnancy near the end of 1<sup>st</sup> trimester. B. Comparison of hCG values between singleton (solid line) and twin (dotted line) pregnancy, showing the marked difference in both the amplitude and duration of hCG peaks. C. Comparison of serum free T<sub>4</sub> concentrations between singleton (solid line) and twin (dotted line) pregnancy, showing the transient burst in serum free T<sub>4</sub> values associated with higher and more prolonged hCG values in twin pregnancy.

After the study of normal pregnant women, we started additional investigations on the outcome of pregnancy in women with preexisting thyroid abnormalities. This group was part of our first cohort and encompassed 120 pregnancies, i.e. 17% of the initial cohort. These women were shown to present subtle, underlying – and hitherto undisclosed – thyroid anomalies: past history of thyroid disease, goiter, nodules, and thyroid autoantibodies (Th-Abs). It was shown that both size and number of these nodules increased during pregnancy. Another finding was that women with positive Th-Abs have a 3-fold increased risk of early spontaneous miscarriage. Finally, the study showed that euthyroid women with Th-Abs frequently develop subclinical hypothyroidism (SCH) as gestation progresses, giving us the first clear indication that asymptomatic autoimmune thyroid disorder (AITD) is a major cause of an impaired thyroid functional reserve, which is revealed by pregnancy (9). To evaluate further the risk of hypothyroidism in euthyroid women with AITD, we initiated a second cohort investigation encompassing 1.660 new consecutive pregnant women. Main results were that

the prevalence of positive Th-Abs (TG-Ab and/or TPO-Ab) reached 6.5% of the population. Despite an overall 50% decrease in Th-Abs titers during gestation, many women developed SCH. The risk of presenting SCH during late gestation was predictable in first trimester already, on the basis of Th-Abs titers and the serum TSH shift toward higher normal values (10). Published in 1994, these data gave us the opportunity to propose for the first time that pregnant women should be screened systematically for thyroid disorders, if such thyroid function abnormalities (both frequent and most usually unknown) were to be diagnosed (11). An overview of the various aspects of the clinical epidemiology of thyroid function abnormalities and diseases associated with pregnancy is illustrated in Figure 3.



**Figure 3.** Overview of the clinical epidemiology of the most prevalent thyroid function abnormalities and thyroid diseases associated with pregnancy, summarizing data obtained in two successive population studies carried out in Brussels between 1988 and 1994.

## Part 2: From the observational studies to the consensus guidelines

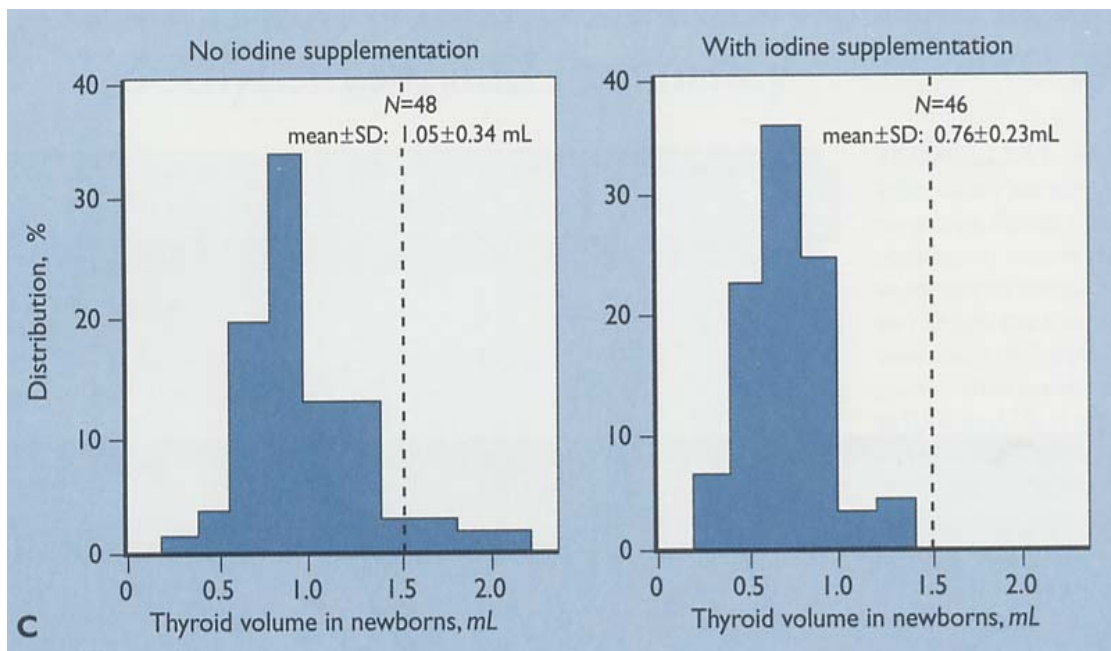
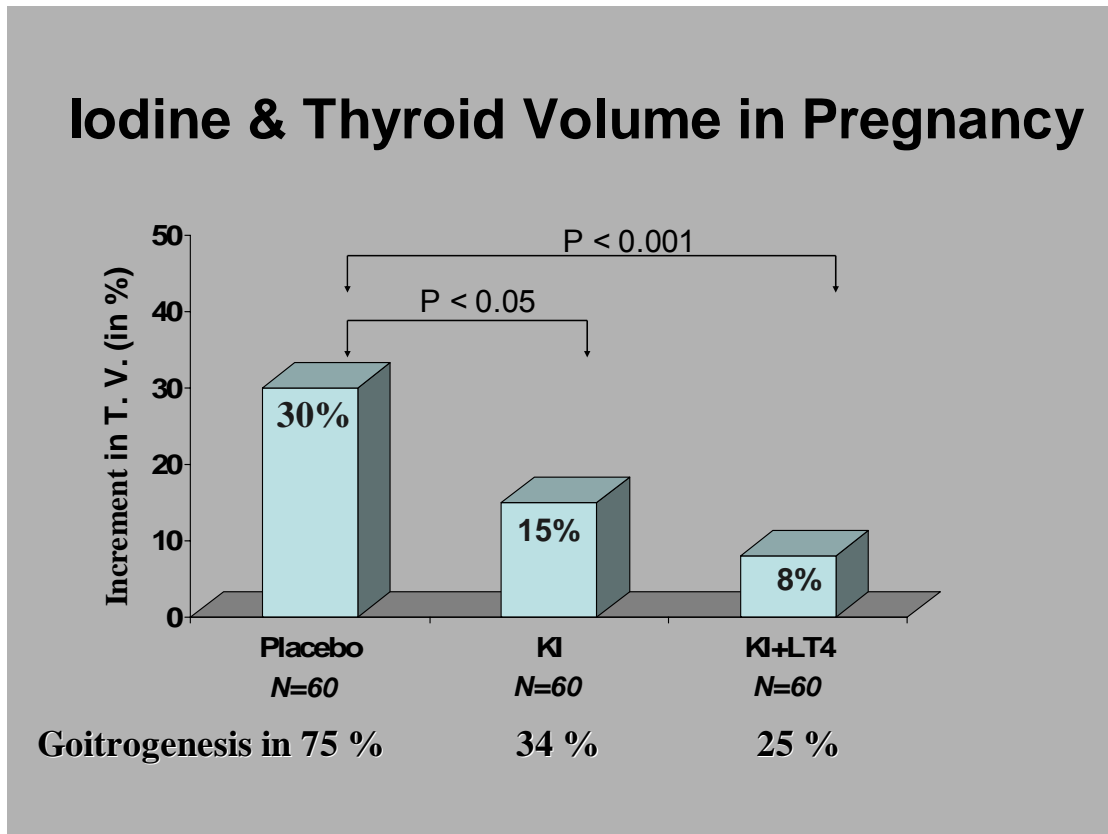
In this section, we outline a number of landmarks that have allowed us – and many other investigators – to extend our views from the clinical epidemiology of thyroid disorders associated with pregnancy to their management.

In 1995, we presented the results of the first prospective double-blind randomized clinical trial for the prevention of ID during pregnancy (12). Women, selected to present biochemical indices of excessive thyroid stimulation in early pregnancy, were subdivided into three groups and treated with either placebo, daily iodine supplementation with KI, or the combination of L-T4 + KI. Main results were that dietary iodine fortification allowed to improve markedly the pattern of thyroid function tests, with a decrease in serum TSH and TG levels, an increase in urinary iodine excretion, and a marked reduction in the risk of maternal goiter formation as well as a complete eradication of neonatal goiter (Figure 4). The study showed also that there was an inevitable lag period of approximately one trimester before the benefits of iodine fortification on thyroid function could be observed, a finding that prompted us to recommend that the iodine supplementation should ideally start before conception and, when this was not feasible, as soon as possible after the onset of pregnancy.

In 1998, we proposed an algorithm for the systematic screening of thyroid disorders during pregnancy, using a 2-step scheme to detect AITD, SCH and OH. With a procedure derived from the screening scheme proposed for the detection of thyroid underfunction, the algorithm could be easily extended to the screening of hyperthyroidism (13).

In 1999, Haddow *et al.* reported the first study showing that school-age children, born to mothers with thyroid insufficiency during pregnancy, presented a risk of impairment in neuro-psychological development (14). Because the design of the study was prospective for the offspring's evaluation, but retrospective for the part that concerned maternal thyroid function, these hypothyroid women had either remained undiagnosed during pregnancy or had been diagnosed before conception and already treated with L-T4, but hormone replacement therapy not correctly adapted, hence leading to more severe thyroid insufficiency during gestation. One of the consequences of this study was to reinforce the proposal to systematically screen pregnant women for thyroid disorders, and particularly for hypothyroidism that constitutes, by far, the most prevalent thyroid disease in this age range (15). Another major consequence of this pioneering study was the launching of several population-based studies thereafter in the U.S. (some of these are still in progress today), especially after the joint meeting organized by CDC and ATA in 2004 and entitled "*The impact of maternal thyroid diseases on the developing fetus: implications for diagnosis, treatment, and screening*" (16).

In 2005, WHO (Geneva headquarters) organized a "Technical Consultation" of world experts to revise the existing programs for iodine supplementation in pregnant and lactating women. This meeting led to the recommendation that the daily iodine intake should be increased to 200-300 µg/day (average: 250 µg/day) during pregnancy and iodine fortification pursued during breastfeeding



**Figure 4.** Upper panel shows that in pregnant women who were given daily supplements of potassium iodide (KI), thyroid volume increments were reduced from 30% in placebo-treated women to 15% in KI-treated women, and TV increases affected only 34% of the latter women compared with 75% in placebo-treated women. With the combination of L-T4 and KI, the beneficial effects were even better.

Lower panel shows that in the offspring of pregnant women, administration of iodine supplements to mothers eradicated entirely the risk of neonatal goiter and resulted in an overall 30% reduction in neonatal thyroid volume.

(Figure 5) (17). Another important result of this meeting was to differentiate three geographical situations for the implementation of iodine fortification, in an attempt to tailor strategies to actual iodine intake levels as well as to the practical possibilities in a given population. First, for those countries considered to have reached iodine sufficiency or with a well-established universal salt iodisation (USI) program (Ex: USA), the recommendation was that there was no need for global public health measures, although individual counselling was still advocated. Second, for those countries without USI program or with a USI program known to have only partial coverage (Ex: several countries in Europe), the recommendation was to provide women with multivitamin pills containing the amount of iodine required to reach the recommended nutritional intake. Third and finally, for those remote areas with no accessible USI program and frequent difficult socio-economic conditions (Ex: several countries in Africa and Asia), the recommendation was to administer orally, as an emergency measure, iodized oil (Lipiodol) in early pregnancy.

**WHO – Geneva 2005**  
**Revision of Recommendations**  
*(Published in Public Health Nutrition, Dec 2007)*

**RNI: 200 – 300 µg/day**

Population Group	Median Urinary Iodine Conc. (UIC)	Category of Iodine intake
Pregnant women	< 150 µg/L	Insufficient
	<b>150 – 249 µg/L</b>	<b>Adequate</b>
	250 – 499 µg/L	More than adequate
	> 500 µg/L	Excessive
Lactating women	< 100 µg/L	Insufficient
	> 100 µg/L	Adequate

**Figure 5.** Median values or ranges in urinary iodine concentrations (UIC) used to categorize the adequacy of iodine intake in pregnant and breastfeeding women (RNI: Recommended Nutritional Intake).

Beginning of 2005, an international *ad hoc* task force was established under the auspices of the American Endocrine Society (TES) to prepare consensus guidelines for the management of thyroid disorders during pregnancy and postpartum. After two years of hard work and thorough discussions within this committee, clinical practice guidelines were published in 2007 (18). These guidelines have been endorsed by TES (The Endocrine Society), AACE (American Association of Clinical Endocrinologists) as well as by the four world regional thyroid associations (ATA, ETA, LATS, & AOTA). Note that ACOG (American College of Obstetricians and Gynecologists) did not endorse the recommendations, essentially because they opposed the screening of pregnant women with the

argument that *“there just isn’t any data to support the routine screening of millions of pregnant women every year because the long term effects are not certain and there is no evidence that any treatment would make a difference in the long run”*.

Finally, and to buckle my personal research buckle, I am pleased that my younger collaborator in Brussels, Kris Poppe, has taken over the challenge to continue working in this field, which he has already nicely prolonged and extended during recent years on specific issues related to thyroid autoimmunity and dysfunction in the context of infertility and assisted reproduction (19).

### **Part 3: The future issues: “Where do we go now, with the presently accepted consensus guidelines?”.**

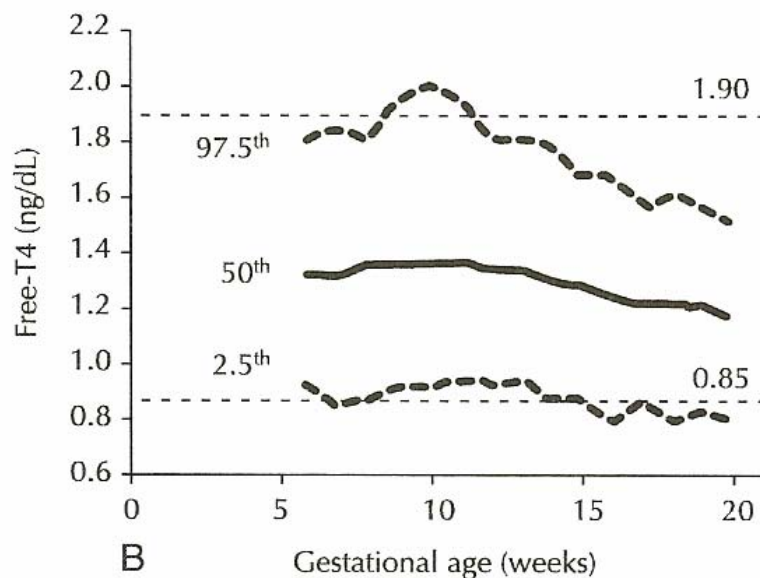
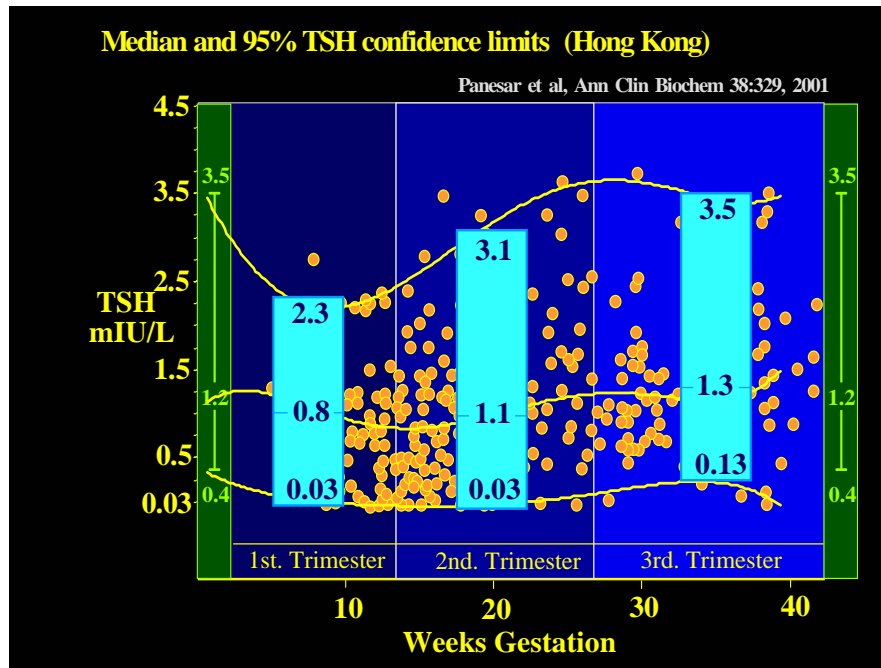
In this section, we discuss shortly some personal views on unresolved issues in an attempt to define perspectives for future research activities in this field.

A first problem concerns the validity and normal reference limits of serum TSH and free T<sub>4</sub> measurements in pregnancy (20, 21). While most TSH assays are intrinsically sturdy and pose no actual validity problems, this is not the case for free T<sub>4</sub> determinations whose intrinsic validity has recently been questioned. Both reference ranges are modified during pregnancy. For serum TSH, there is a downward shift of the entire reference range, which is maximal in first trimester but prolonged during later gestational stages (Figure 6). For serum free T<sub>4</sub>, there is a narrowing and clustering of serum free T<sub>4</sub> estimates near – or just below – the lower normal limit of non pregnant healthy individuals (Figure 6). This difficulty raises an important question, namely that of the correct interpretation of an isolated serum free T<sub>4</sub> lowering, i.e. isolated maternal hypothyroxinemia (hypo-T<sub>4</sub>). It is possible that, in many instances, hypo-T<sub>4</sub> (in the absence of a concomitant TSH rise and absence of detectable thyroid autoantibodies) may primarily reflect dosage interferences. Thus in summary, it will be important to delineate better in the near future a more univocal approach of gestation-specific, trimester-specific, and perhaps also assay-specific reference values for serum free T<sub>4</sub> and TSH determinations in pregnancy.

A second question concerns gestational hypothyroxinemia, with or without concomitant serum TSH elevation. It remains unclear today what degree of maternal T<sub>4</sub> lowering must be reached – and during how long? – for thyroid function abnormalities to be associated – beyond doubt – to detrimental effects on the neuro-psychological development in the offspring. Answering such questions is crucial to help us define the best possible strategies for the detection (by early screening, etc.) and management of these disorders.

A third unresolved issue concerns subclinical thyroid disorders associated with pregnancy (both hypo- “SCH” and hyperthyroidism “SCHR”). There is some evidence that SCHR – which is primarily related to GTT – has no detrimental effect on the pregnancy outcome (22). This is not the case for SCH, as various arguments (more or less direct or indirect) exist to suggest a possible

relationship between mild thyroid insufficiency and a poorer pregnancy outcome (23). If this is so,



**Figure 6.** Upper panel shows the changes in serum TSH reference range in the 3 trimesters of gestation (adapted from Panesar et al., Ref. N° 20). Lower panel shows the gestational-age specific nomogram for upper and lower serum free T4 limits during first half of gestation (adapted from Casey et al., Ref. N° 21).

then systematic screening is required since, in most cases, the diagnosis has not been made before the onset of a pregnancy. A controversy persists today between endocrinologists and obstetricians on whether thyroid screening should be performed in all pregnant women. In the consensus guidelines endorsed in 2007 by the four world Thyroid Associations, a middle-way consensual view was taken in

favour of targeted screening in high-risk groups (18). These included women with a personal or family history of thyroid disease, symptoms of thyroid dysfunction, history of other autoimmune diseases, infertility, type I diabetes, history of head and neck irradiation, and positive thyroid antibodies. Our personal view is that this approach is unrealistic, somewhat hypocritical and will, in any event, prove to be insufficient to solve all the remaining questions. Other colleagues have argued, however, that it was better to reach a consensus (albeit unsatisfactory) than to remain in a quandary with total absence of any consensus.

The last question concerns the future implementation of consensus guidelines. The role of guidelines is to lead the way for the best possible management of patients and their diseases, based on evidence-based medicine combined with common sense. Unfortunately, the evidence is not always available and there is an evident lack of good randomized clinical trials to help us decide on the best attitude. Thus for the moment, the guidelines should essentially be viewed as a guide to help the multiple care providers who intervene in the management of pregnant women. Finally, it is worth mentioning that the existence of guidelines raises the issue of liability and only the future will show how this difficult question may be tackled by both endocrinologists and obstetricians.

## Acknowledgments

The author gratefully acknowledges the friendship and active collaboration of Philippe De Nayer (UCL) and the late François Delange (ULB). These two close colleagues have been major players in this scientific endeavour since its onset and have co-authored most of our studies. We also wish to thank all our colleagues and younger doctors in our institution who have participated into our studies. We wish to thank our international colleagues, with whom so many meetings have been organized, fruitful discussions held, review articles written, and conferences & workshops prepared over the past two decades. Among them, we would like to cite the following: Alex Stagnaro-Green (New Jersey, USA), Susan Mandel (Pennsylvania, USA), John Lazarus (Cardiff, UK), Bob Smallridge (Florida, USA), Joanne Rovet (Toronto, Canada), Marcos Abalovich (Buenos Aires, Argetina), Mario Rotondi (Napoli, Italy), Leslie DeGroot (Rhode Island, USA), Philippe Caron (Toulouse, France), Peter Smyth (Dublin, Ireland), Peter Laurberg (Aalborg, Denmark), Jacques Orgiazzi (Lyon, France), Jorge Mestman (Los Angeles, USA), & Gabriela Morreale de Escobar (Madrid, Spain). Finally, the author wishes to acknowledge the support of the Ministère de la Communauté Française, Administration Générale de l'Enseignement & de la Recherche Scientifique, within the framework of the Actions de Recherche Concertées (ARC: Convention N° 04/09-314).

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