Treatment of subclinical hypothyroidism

in children, in women and in adults

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Presentation

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The IBSA Foundation aims to be an appointment for all and become a point of reference for the diffusion of science, a meeting point for researchers, enthusiasts, students, families, physicians and patients.

It wants to promote the dissemination of scientific culture at international level through meetings, conferences, workshops, books, articles, to tell the science of quality in an innovative and engaging, interactive and transversal way, in a space where the barriers between the different scientific areas are cleared and the research can communicate without boundaries.

A useful tool for enrichment and information exchange on scientific issues is represented by the Forums: meetings of high scientific content involving international experts and aimed at an audience of selected specialists.

The key to the success of these forums is, in our opinion, the choice of a "hot" topic from the point of view of clinic and/or research, presented by people who really have something to say about it.

These were the premises of this first forum focused on "Treatment of subclinical hypothyroidism in children, in women and in adults".

We believe that we do not have disregarded the expectations and a heartfelt thanks to all participants for their enthusiasm, participation, and the scientific level expressed. In order to share the contents of the Forum with a wider audience and to give highlight to the initiatives of our Foundation it was created the publishing project " Papers of IBSA Foundation", of which this paper represents the first act.

We hope, therefore, that represents the launch of a project capable of arousing your interest and your attention.

SESSION 1

INDICATIONS FOR THERAPY WITH LT4 IN SUBCLINICAL HYPOTHYROIDISM IN THE DEVELOPMENTAL AGE

Natural history of subclinical hypothyroidism and effects of therapy in paediatric age: general aspects

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The treatment of subclinical hypothyroidism is a controversial topic in the adult patient and it is even more so in children, because we do not have paediatric guidelines and we cannot simply transfer to the child the findings from studies done on adults. In fact, subclinical hypothyroidism in children can be an expression not only of acquired forms, such as chronic autoimmune thyroiditis, but also of congenital forms. It is therefore of paramount importance to know the natural evolution of the disease in order to assess the possible risk of exposing the child in the early years of life, to physical and mental developmental delays.

Moreover, while we know very well the benefits of the therapy in severe forms of hypothyroidism, the potential risks are not yet fully known, alongside to the benefits of a long-term treatment of "mild" forms in childhood (compliance, behavioural problems, bone mineralization).

From this premise it follows that the fundamental problem concerns the assessment of the actual need of thyroxin therapy and its timing, that is, if and when it is necessary to treat.

Subclinical hypothyroidism is defined by the presence of TSH values above the normal range specific for the age, associated with normal FT4 levels; we speak of isolated hyperthyrotropinemia in the presence of TSH values between 5 and 10 mU/L and levels of FT4 within the normal range.

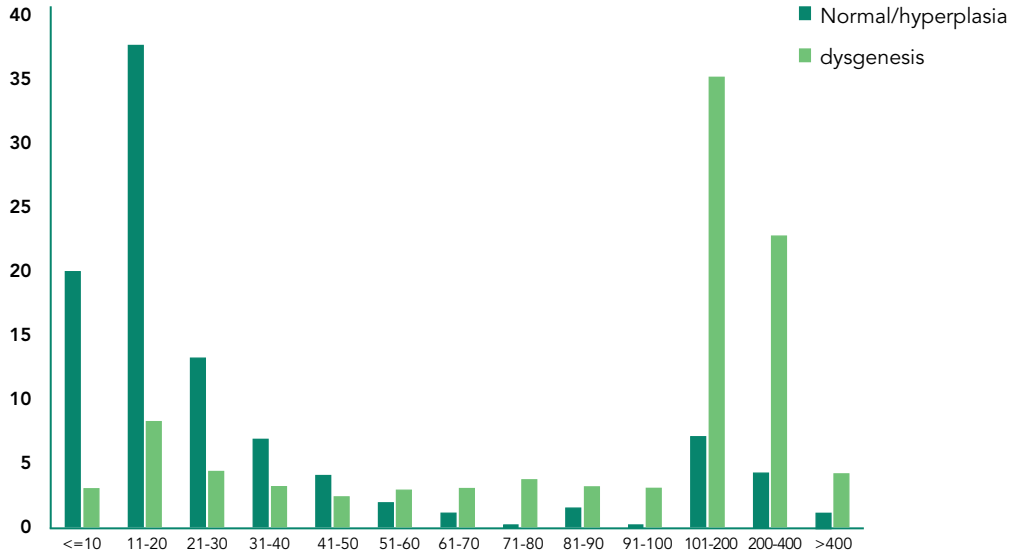
In paediatric, the definition of subclinical hypothyroidism hides in itself a problem: it is not easy to determine which is the reference range age-specific of TSH. There are not many studies in the literature because it is not easy to have an adequate number of healthy children to be recruited into clinical trials, and because we know that there is a biological variability individual and age-related that determines a difference in the sensitivity of the feedback mechanisms, especially in the early months

of life, with obvious implications for the range of TSH. And if this is a problem in the developmental age, it is even more so in the early days and in the first months of life, since it involves other factors, such as the term or preterm birth. In consideration of these variables, it is now widely accepted that in the first year of life the TSH reference range is wider, with values higher than the normal upper limit, and narrows gradually in subsequent phases of development.

Another issue of interest is the frequency of subclinical hypothyroidism in the paediatric population. In the literature there is overall an incidence of 2%, and it is observed an increasing trend of this phenomenon, due, in neonatal and in the first months of life, to the reduction of the threshold-values of TSH. In the first months of life, in screening programs in newborn and subsequent paediatric age, it is expected and more and more frequent the assessment of thyroid function, even in absence of symptoms suggestive of hypothyroidism. This practice is a routine exam in the presence of obesity, fatigue, disorders of puberty, menstrual irregularities and familiarity for thyroid disease [1].

In the first months of life, with the reduction of the threshold of recall for TSH, increases the diagnostic sensitivity of screening programs and the ability to identify

• **Figure 1.** Percent distributions of TSH values at screening in babies with normal/hyperplastic thyroid and in those with thyroid dysgenesis recorded in the INRICH in the period 2000-2006



Source: Olivieri *et al.*, 2013 [2].

"mild" forms of congenital hypothyroidism, which are predominantly characterized by thyroid in place but, according to a recent study published in JCEM [2], are constituted in approximately 10% of cases, by "mild" forms of thyroid dysgenesis (hypoplasia, ectopia, hemiagenesis) [• **Figure 1**]. Especially in the first months of life is therefore important to seek the cause of hypothyroidism even through investigations of image diagnosis in order to be able to make a proper diagnosis and begin, if necessary, treatment.

Despite the absence of specific guidelines, in recent years they have been published some significant paediatric studies on the natural history of subclinical hypothyroidism and the possible effects of hormone replacement therapy in children and adolescents. In a recent review, Monzani *et al.* have collected a set of data with very strict criteria [3]. 9 studies were selected, for a total of 4,018 children examined, the results of which are in part shown in • **Tables 1 and 2**. Despite the studies are heterogeneous in the aetiology of subclinical hypothyroidism (autoimmune and non-autoimmune), number and age of the patients examined and range of TSH levels, the information that results is quite clear. In subclinical hypothyroidism not on autoimmune basis [• **Table 1**], the progression to overt hypothyroidism is very low (0-13%) and a significant percentage of cases, sometimes higher than 50%, has an evolution to euthyroidism. Therefore we have to think about the possibility that they are transitional forms of subclinical hypothyroidism and monitor the situation.

Similar findings have emerged from studies of autoimmune hypothyroidism [• **Table 2**] due to chronic lymphocytic thyroiditis. In this case the evolution towards clinical hypothyroidism is slightly higher (5.5 to 39%), but not high; however, in a significant percentage of cases, there is an evolution towards euthyroidism (21.9

• **Table 1.** Natural history of subclinical hypothyroidism not on autoimmune basis

References	Study design	No of patients	Age (yy)	FW (yy)	Rate of progression to overt hypothyroidism	Rate of reversion to euthyroidism
Wasniewska *et al.*, Eur J Endocrinol 2009, Italy	Long.	92	5-14	2	0	41%
Lazar *et al.*, J Clin Endocrinol Metab 2009, Israel	Retrosp.	3.632	0.5-16	5	0.03-0.2%	76-40%
Leonardi *et al.*, J Clin Endocrinol Metab 2008, Italy	Long.	28	1.3-3.7	7	0	50%
Radetti *et al.*, Clin Endocrinol 2012, Italy	Retrosp.	59	5-13	3	13.5%	40%

Source: Monzani *et al.*, 2012 [3], adapted.

• **Table 2.** Natural history of subclinical hypothyroidism on autoimmune basis

References	Study design	No of patients	Age (yy)	FW (yy)	Rate of progression to overt hypothyroidism	Rate of reversion to euthyroidism
Gopalakrishnan *et al.*, Pediatrics 2008, India	Long.	32	10-15	2	12,5%	21,9%
Moore *et al.*, Arch Pediatr Adolesc Med 1996, USA	Long.	18	5-19	0,6-5	5,5%	39%
Radetti *et al.*, Clin Endocrinol 2012, Italia	Retrosp.	87	0,5-16	3	39%	41%

Source: Monzani *et al.*, 2012 [3], adapted.

to 41%). Even in chronic lymphocytic thyroiditis, therefore, the prevailing attitude must be the monitoring.

Unfortunately, in most of the studies in the literature, there is no evidence of predictors of increased risk of evolving into overt hypothyroidism. Only the study of Lazar *et al*. published in JCEM [1] seems to indicate the presence of values at the upper limit of TSH (>7.5 mU/L), and female gender as a possible rick factor.

But what is the clinical significance of subclinical hypothyroidism? An Italian study conducted by Cerbone *et al*. [4] on 36 children with idiopathic subclinical untreated hypothyroidism (TSH from 4.5 to 10 mU/L), followed at a mean follow-up for 3 years, has not found alterations of growth, bone maturation, BMI and cognitive function, concluding that these forms of non-hyperthyrotropinemia with not evolutionary characteristic have a substantial benign characteristic and generally do not require substitution treatment.

For what concerns possible benefits of substitution treatment, paediatric studies in the literature are even more scarce. The review of Monzani *et al*. [3] selects only 6, for a total of 202 children examined, none of them by randomized controlled trials. Among the various studies the multicenter one conducted by Wasniewska *et al*. [5] is the most comprehensive and rigorous and concludes that in children with idiopathic isolated hyperthyrotropinemia the replacement therapy does not appear to change significantly the auxological parameters and physical and mental development.

For our research it would be important to be able to move from the biochemical level to tissue level and to understand at what degree of hypothyroidism appears the organ damage. The determination of a tissue marker would help us a lot to select patients; unfortunately, however, this marker has not yet been identified for paediatric patients. The only paediatric study appeared in literature, Gottardi *et al*. [6], assessed the endothelial function in 32 hypothyroid children and adolescents compared with a control group, but no differences were found and there is no correlation with TSH levels.

In conclusion, there is insufficient data in children, even more than in the adult, to be able to stratify the risk based on the levels of TSH and/or with reference to the etiology.

At the moment, there is a general indication to treat children with TSH values >10 mU/L, since the data of the literature agree that this situation in adults is associated with an increased risk of progression to clinical hypothyroidism, cardiovascular disease, dyslipidemia, and depression. It remains controversial the attitude in the forms with TSH between 5 and 10 mU/L.

In conclusion, we think there is need in the future of randomized controlled trials on the effects of treatment on neuropsychological sphere, on cardiac function, on lipid profile and bone mineralization.

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Subclinical hypothyroidism in early childhood

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The term "mild subclinical hypothyroidism" (SCH) or "persistent hyperthyrotropinemia" identifies a biochemical profile characterized by TSH values slightly higher compared to the reference values for age and normal FT4 levels, in the absence of specific clinical symptoms.

The SCH in the developmental age represents for the clinical practice an entity extremely topical. At the moment there are few epidemiological data available: a recent study, conducted on a population of 1,327 adolescents aged between 13 and 16 years, revealed the presence of SCH in 1,7% of the subjects [1].

The etiology and the therapeutic approach of the SCH are still under discussion by the specialist literature, as well as the long-term effects on growth and neuromotor development. The SCH, similarly to congenital hypothyroidism, can be divided schematically into autoimmune and non-autoimmune forms (• **Table 1**) and, depending on the time of onset, in congenital forms, already present at birth, and acquired forms

Among the autoimmune forms of SCH, the most common cause, especially in the age of puberty, is the chronic lymphocytic thyroiditis, whose diagnosis in children is on the rise, mainly due to the greater frequency of screening of thyroid function in developmental age. In fact, an evaluation of thyroid function is often recommended in case of positive familiarity for thyroid disease, in case of children of mother with dysthyroidism and/or autoimmune thyroiditis, in the presence of other autoimmune diseases (type 1 diabetes mellitus, celiac disease) or syndromes or chromosomal conditions (Down's syndrome, Turner syndrome, Williams syndrome, Klinefelter syndrome) or in complex malformation syndromes (labiopalatoschisis, heart disease, eye malformations). Autoimmune thyroiditis is the main cause of thyroid dysfunction in the paediatric population with an incidence of 1.3% between 11 and 18 years, and fre-

• **Table 1.** Etiology of subclinical hypothyroidism in the first decade of life

Autoimmune	Not autoimmune
• Autoimmune thyroiditis isolated or associated with polyendocrinopathy, to chromosomal/or syndromes malformations • Trans-placental passage of maternal antibodies (transitional forms)	• Dysgenesis (hemiagenesis, hypoplasia) • Genetics (rTSH, DUOX2, DUOXA) or malformations-syndromic conditions • Specific neonatal conditions - *twinning, prematurity/fertilization in vitro* - *drugs* • Obesity • Deficiency of iodine • Interference of drugs • Chronic diseases (such as thalassemia, transplanted patients)

quently, it may be associated with other autoimmune diseases (autoimmune diabetes mellitus, celiac disease, polyendocrinopathies).

The prevalence in female sex is 4-7 times greater than the male one, and in 30-40% of patients, there is a positive family history for thyroid disease. The sign most frequently associated with autoimmune thyroiditis is goitre, often asymptomatic. The positivity of antiperoxidase antibody, anti-thyroglobulin and the pathognomonic ultrasound data allow us to make the diagnosis. The majority of patients with autoimmune thyroiditis, presents a clinical condition of euthyroidism or SCH and in the paediatric and adolescent population the risk of progression from subclinical form to overt hypothyroidism is less common than in adulthood [2].

Another important cause of SCH tied to autoimmunity is represented by the trans-placental passage of antibodies of maternal origin in particular, antibodies anti-peroxidase and anti-receptor TSH). It is estimated, in fact, that about 10-15% of women in pregnancy present a positivity of antithyroid antibodies and that about 2% of the positivity at neonatal screening for congenital hypothyroidism can be attributed to the inhibitory action exerted by maternally derived antibodies [3]. Our experience in 129 newborn children of mothers affected by autoimmune thyroiditis, showed the presence of mild alterations of thyroid function in the majority of cases of transient nature and spontaneous resolution. Only in a small percentage of these subjects, corresponding to approximately 2.2%, was introduced a drug therapy with L- thyroxine in the first year of life. In addition, our study showed no relationship between the presence of antithyreoperoxidase antibodies and the dosage of maternal L-thyroxine with the alteration of functionality in the neonatal period [4]. Proper management of infants born from mothers with autoimmune thyroiditis should therefore be made in our opinion, as well as the implementation of neonatal screening for congenital

hypothyroidism in third-fifth day of life, the repetition of the screening to the second week of life, as it is currently carried out in some Italian regions.

Among the causes of non- autoimmune SCH (• **Table 1**) there are cases of thyroid dysgenesis (hemiagenesis, hypoplasia), genetic forms (mutation of the receptor TSH, and mutation of DUOX2 DUOXA), emerging realities (twins, prematurity, in vitro fertilization), obesity, iodine deficiency, medications and chronic diseases. It is therefore of paramount importance to collect a thorough history and investigate the presence of hereditary diseases in the family, the use of drugs or possible administration of substances in the neonatal period, the course of pregnancy and the possible hormonal stimulation of the mother. Moreover, in cases of persistent SCH, it is recommended the execution of an ultrasound for a morphological evaluation of thyroid gland.

Conditions such as prematurity, twinning and medically assisted fertilization are risk factors for permanent thyroid dysfunction. Prematurity is an emerging reality of neonatology and paediatrics thanks to the surprising progress in the last thirty years in the field of neonatology and neonatal intensive care (NICU). The improvement of care in NIC resulted in a progressive increase of survival of extremely premature infants. Furthermore, the techniques of assisted reproduction (IVF, IUI, ICSI), increasingly common in recent years, if on one hand have improved the fertility rate, however, have resulted in an increased risk of multiple births and premature deliveries. The latter have a risk 3-5 times greater of congenital hypothyroidism than the ones born at term [5] while, among the ones suffering from congenital hypothyroidism, is 3 times higher the reported incidence of twins (3.5%) compared to the general population (1.1%) [6]. According to a study by Sakka *et al.* [7] 6.6% of the children born from in vitro fertilization (IVF) presented a condition of SCH not autoimmune independently by the gestational age and birth weight.

Multiple factors affect thyroid function in premature infants (• **Table 2**). There are conflicting data in the literature about the clinical and biochemical evolution, however, it is important to carry out the etiological re-evaluation of thyroid function after 2 years of life, to distinguish frequent transitional forms from those permanents, avoiding a substitutive treatment with L-thyroxine, in many cases unjustified.

• **Table 2.** Factors affecting the thyroid function in premature infants

Immaturity of the hypothalamic-pituitary-thyroid axis
Reduced concentration of iodine in the thyroid
Deficiency or excess of iodine
Reduced activity of enzyme MDI type I in the liver
Reduced synthesis of TBG and TG
Non-thyroidal illness
Use of drugs (dopamine, corticosteroids, caffeine)

With the rising incidence of obesity in the paediatric population should be also placed increased attention to the alterations of thyroid function in obese subjects. In the literature it is described a possible reversibility of this thyroid dysfunction with a stable weight loss. In obese children it is possible to find a positivity of thyroid autoantibodies in 15-25% of cases and echographic abnormalities of the thyroid in 37% of obese patients, however, in the absence of antibody positivity [8]. In obese child is not indicated starting a treatment with L- thyroxine in case of absence of autoimmunity, since thyroid dysfunction is often a consequence rather than a cause of obesity; changes in thyroid function may, in fact, be considered as a mechanism of adaptation to the increase weight of the patient and are reversible with weight loss. Moreover, therapy with L- thyroxine showed no benefit on body weight, BMI and lipid profile.

Following the detection of a condition of persistent SCH, especially if there is familiarity for alterations in thyroid function, it is possible to hypothesize genetic alterations that can lead to thyroid dysfunction both transient and permanent. In the literature, have been described mutations in the receptor gene TSH (rTSH) and genes involved in the thyroid hormone genesis DUOX2, DUOXA2, TPO). The latter, expressed in heterozygosity, are frequently associated with clinical conditions characterized by values of TSH borderline or mildly elevated and such patients may be negative at neonatal screening [9, 10]. In the presence of a mutation of the TSH receptor, the phenotype varies depending on the degree of resistance to the action of TSH. The homozygous forms are diagnosed in the neonatal screening because of severe congenital hypothyroidism from complete resistance to TSH and thyroid hypoplasia, while subjects with heterozygous forms of partial resistance to TSH, are usually able to maintain normal levels of thyroid hormones through a slight increase of TSH. The mutation of DUOX2 is one of the most frequent alterations of deficiency of organification of iodine; the clinical condition is very variable and can be characterized by transient or permanent forms of SCH that can sometimes evolve into overt hypothyroidism. However, in 3/4 of the cases the mutation of DUOX2 shows a trend to euthyroidism, so it is necessary to re-evaluate the discontinuation of therapy with L- thyroxine towards 2-3 years of life.

Another risk factor for the development of SCH is represented by chronic diseases. They affect 14% of adolescents and are steadily increasing due to the improving care (transplant).

In the literature there is still no agreement on the necessity of hormone replacement therapy in conditions of SCH and, in children, there are no guidelines in this regard. It has not been scientifically proven that conditions of hyperthyrotropinemia, characterized by TSH values between 5-10 mU/L, cause necessarily adverse effects on the cardiovascular system [11], on the lipid profile [12], on the central nervous system and the musculoskeletal system. In presence of TSH values below 10 mU/L in the subject without morphological alterations of the thyroid gland and thyroid autoantibodies negative, it is recommended to monitor the hormonal trend every six months

for at least 2 years and with particular attention to the adolescent period during which the hormonal demands increase. In addition, some children develop thyroid autoantibodies often only later, so only a thorough follow -up will allow us to make a correct etiological diagnosis.

For the purpose of treatment it is appropriate, in the assessment of each individual case, taking into account all the factors listed above. In subjects in which it is introduced the therapy with L-thyroxine it is opportune to make an attempt of therapeutic suspension to re-evaluate the patient's clinical and hormonal condition and temporary or permanent evolution of the alteration.

These data represent only an introduction to the problem of minor alterations of the thyroid function and require further prospective studies to identify the best diagnostic and therapeutic approach in order to better manage the condition of mild and persistent SCH. New investigations in the genetic field will also enable to clarify the aetiology, still obscure in many cases, offering new perspectives of intervention and care.

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Subclinical hypothyroidism in adolescence

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Subclinical hypothyroidism is a condition characterized by high levels of TSH with normal FT4. Unlike in early childhood, in which the reference range of TSH is wider, in the adolescent age the reference intervals of serum TSH are between 0.4 and 4 mU/L, as in the adult.

The main cause of subclinical hypothyroidism in adolescence is chronic lymphocyte thyroiditis, a chronic inflammatory disease on autoimmune basis, characterized by the presence of autoantibodies directed against thyroid antigens (antibodies anti-thyroperoxidase in 80 to 95% of case, anti-thyroglobulin antibodies in 50% of cases and antibodies anti-receptor TSH in 20-30% of cases). The characteristic echographic appearance is a non-homogeneous and hypoechoic structure. The chronic lymphocytic thyroiditis or Hashimoto's thyroiditis is responsible for 50% of cases of subclinical hypothyroidism in adolescence. In a minority of patients we can have an autoimmune thyroiditis without autoantibodies against thyroid antigens but distinguished by an echographic image with hypoechoic structure.

In the remaining 50% of cases of subclinical hypothyroidism is present a thyroid, normal or slightly reduced in volume, normo-echoic structure, with thyroid autoantibodies negative and the absence of other signs or symptoms of autoimmunity; this condition is often called isolated hyperthyrotropinemia. Causes of isolated hyperthyrotropinemia can be chronic diseases, use of anti-thyroid drugs, lithium, iodine deficiency, obesity, mutations in the TSH receptor, defects in the biosynthesis of thyroid hormones,pseudohypoparathyroidism, genetic disorders or idiopathic forms (• Table 1). In most cases you do not know the cause of the increase in TSH. However, in recent years, part of these idiopathic forms (15%) have been explained thanks to the identification of certain genetic mutations responsible for alterations in the TSH receptor, of thyroid hormone biosynthesis or organification of iodine.

• **Table 1.** Causes of isolated hyperthyrotropinemia

- Chronic diseases
- Medication (antithyroid, lithium)
- Iodine
- Obesity
- Idiopathic
- Mutations of the TSH receptor
- Pseudo-hypoparathyroidism
- Defects in the biosynthesis of thyroid hormones
- Down syndrome, other genetic diseases
- TSH bio-inactivity
- Interference in the TSH dosage for heterophile antibodies

Autoimmune thyroiditis is, together with type 1 diabetes mellitus, the most frequent endocrinopathy in children. It has a prevalence of about 1% and is the most frequent cause of acquired hypothyroidism in children and adolescents. The clinical manifestations are different, depend on the age of the patient and, for this reason, it is important to do a periodical follow-up to assess the kind of evolution of the disease. Often, moreover, it is found a family history of autoimmune diseases.

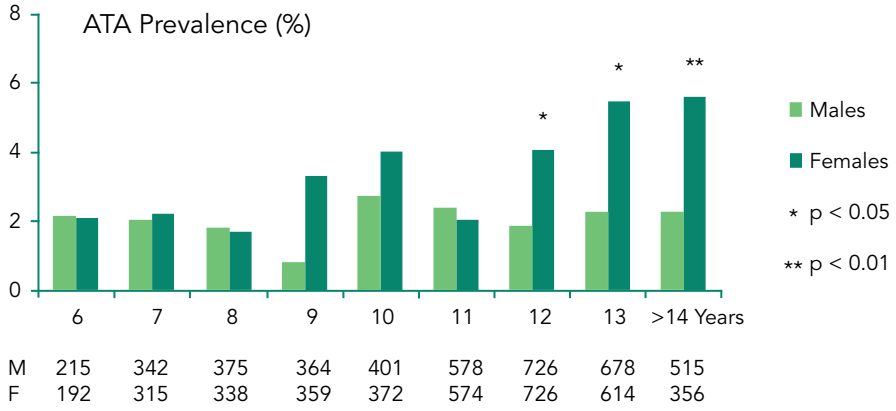
In the study by Rallison *et al.* [1], carried out on 4,819 children in adolescence, it has been highlighted a prevalence of approximately 2% of subclinical hypothyroidism and 1, 2% of chronic lymphocytic thyroiditis.

The study of Hollowell *et al.* [2] has evaluated instead the thyroid function in a wide U.S. population in subjects with age greater than 12 years. Subclinical hypothyroidism was found in 3% of the population aged 12-19 years and to a lesser extent, in the group of 20-29 years, suggesting that often the functional thyroid deficiency in children and adolescents is of transitory nature. The prevalence of autoimmune thyroiditis in adults is rather higher, probably due to the increased incidence in relation with increasing age. The TPO Ab were present in 7% of adult women and 3% of adult males, while the prevalence of Tg-Ab was 7% in adult women and 5% in adult males. These percentages doubled with the increasing age of the population.

In a Italian study carried out by Loviselli *et al.* [3] in a young population in Sardinia, the prevalence of positivity for antibodies against thyroid antigens was 3%, with a huge diversity of geographic distribution within the same region and in the absence of correlations with the iodine intake and with the presence of goiter. In addition, from the study is clear an increase in the prevalence of both thyroid autoantibodies in women, especially from puberty (• **Figure 1**), and subclinical hypothyroidism proportional to the value of thyroid autoantibodies.

A similar study was performed by Kabelitz [4] in a population of 160 children from

• **Figure 1.** Percent antithyroid antibodies (ATA) prevalence in the total Sardinian schoolchildren population subdivided for age and gender



Source: Loviselli *et al*., 2003 [3].

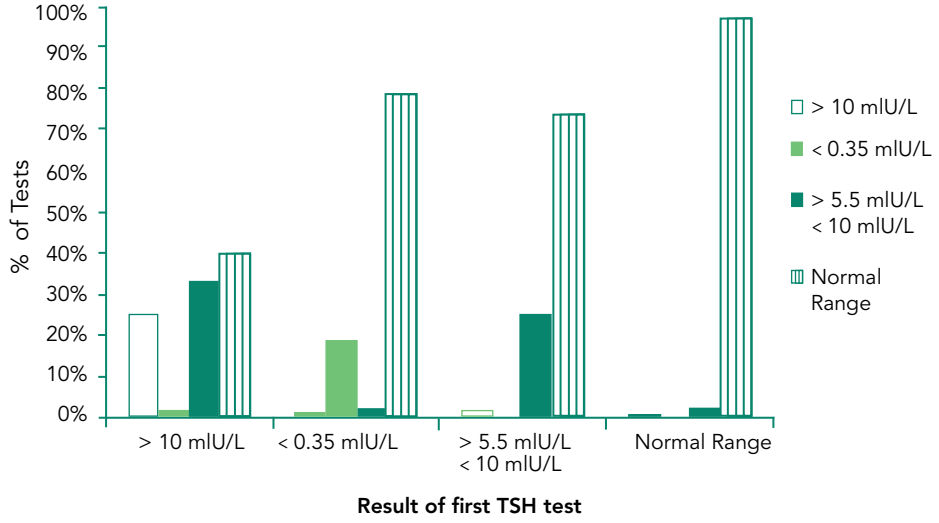
an area with sufficient iodine intake in Berlin, Germany. Even in this population, the prevalence of peroxidase antibodies was 3.4% and the prevalence of subclinical hypothyroidism of 2.5%.

Patients with chronic autoimmune thyroiditis require careful follow-up to monitor the development of thyroiditis and the possible occurrence of other autoimmune diseases. Individuals with autoimmune thyroiditis usually arrive to the observation of the paediatrician or endocrinologist for an increase in the volume of the neck (40%), for the appearance of signs or symptoms of hypothyroidism (30%), family history of thyroid disease (11%) or a an occasional hormonal evaluation in a subject completely asymptomatic (20%). The natural history of chronic lymphocytic thyroiditis tells us that 28% of children goes into remission, 34% becomes clinically hypothyroid and 28% remains subclinical hypothyroid, in the follow-up from 3 to 5 years [1].

The natural history of autoimmune thyroiditis was also examined in the study prospectively performed by Radetti *et al*. [5] of 160 children (mean age 9 years) affected by chronic autoimmune thyroiditis.

The results of this study indicate that 65% of subjects who were euthyroid at the first observation remained euthyroid after 5 years, 25% became clinical hypothyroid and 9.5% evolved towards subclinical hypothyroidism. Among the 55 children with subclinical hypothyroidism to the first observation, 29% of children went into remission, 42% became clinical hypothyroid and 29% remained subclinical hypothyroid, in the follow-up to 5 years. Therefore, since subclinical hypothyroidism of chronic lymphocyte thyroiditis may be reversible even after several years, it is essential to perform a follow-up.

• **Figure 2.** Distribution of TSH results in the second test according to the category of the first TSH measurements in untreated patients (tests were performed between 2002 and 2006)



Source: Lazar *et al.*, 2009 [6].

A large clinical trial [6] on over 121,000 children evaluated the serum TSH with an interval of 5 years (in 2002 and 2007) and, according to previous data showed that a portion of the subclinical hypothyroid goes back to euthyroid while a part evolves in clinical hypothyroidism (• **Figure 2**).

Finally, a recent study of Radetti *et al.* [7] evaluated, through a follow-up of three years, the evolution of thyroid function in patients with autoimmune thyroiditis or isolated hyperthyrotropinemia. The chronic thyroiditis evolves into clinical hypothyroidism in approximately 40% of cases, while the isolated hyperthyrotropinemia only in 13% of cases.

Wasniewska *et al.* [8] evaluated whether the treatment with thyroid hormone changes the natural history of hyperthyrotropinemia. The patients were divided into two groups on the basis of the treatment and were followed for 2 years. The final data have not highlighted differences in the two groups: the thyroid hormonal therapy does not alter the natural history of the disease, does not prevent the risk of a future increase in TSH, does not influence the rate of growth, the body mass index and other metabolic parameters. The final outcome seems to depend exclusively from the baseline TSH.

From some studies in the literature, we learn that the therapy with levothyroxine can reduce the volume of goiter in hypothyroid patients with chronic thyroiditis, but one can not overlook the possibility that this result is in part due to the typical destructive process of autoimmune thyroiditis.

It can be concluded that the predictive factors for progression to clinical hypothyroidis are identified with the presence of autoimmune diseases, high baseline TSH and thyroid autoantibody positivity. The isolated hyperthyrotropinemia in children is often a transient abnormality with low risk of progression to clinical hypothyroidism. In contrast, the presence of thyroid autoantibodies or goiter are associated with a greater chance of evolving into overt hypothyroidism even after many years. There is no clear evidence that treatment with levothyroxine has beneficial effects on the growth and the neuropsychological development. The replacement therapy is not therefore justified in children with TSH between 5 and 10 mU/L, without goitre and without autoimmunity. However, further studies are needed in randomized, double-blind to confirm the present data.

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Hypothyroidism associated to genetic disorders

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Alterations in thyroid function in children recognize multiple causes, including genetic syndromes (• Table 1) Although rare, in their entirety, they are more frequent than congenital hypothyroidism.

From the data in the literature it is learned that approximately 4-10% of the adult population is suffering from subclinical hypothyroidism, while in the developmental age the prevalence is just below 2% [1]. Among the many genetic syndromes, there are many associated to subclinical thyroid hypofunction.

Our group conducted a study of 92 children affected by Williams syndrome with mental retardation and facial deformities and in 73% of cases, a diagnosis of subclinical hypothyroidism (SCH) was made before 3 years of age [2]. 50% of them, moreover, presented ultrasound abnormalities of the thyroid gland, the most frequent of which was hypoplasia of the left lobe. In these patients, monitoring of the thyroid homeostasis showed an initial improvement of subclinical hypothyroidism with the increasing age; however, the functional thyroid deficiency recurred after some time. The ultrasound abnormalities remained rather unchanged. In all subjects with Williams syndrome it is, therefore, necessary a careful morphofunctional follow-up of the thyroid gland in order to initiate thyroxin therapy in those patients whose TSH levels are high or frankly tend to a progressive rise.

Subclinical hypothyroidism in children with Down syndrome is generally a transient disorder of early childhood that goes into remission in more than 70% of cases, especially in the absence of goiter and antibody positivity [3]. In children with Down syndrome there is also an increased risk of thyroid dysfunction on autoimmune basis. Currently, as reported in the review of Rapaport and Graber [4], the optimal timing for the thyroid assessment remains controversial : for some is necessary an annual control, while for others, the monitoring should be carried out every 5 years.

• **Table 1.** Causes of subclinical hypothyroidism in children

• Obesity
•Hashimoto's thyroiditis (TH)
• Iodine deficiency
• hemiagenesis, thyroid hypoplasia, dyshormonogenesis
• Mutations of the TSH-R
• Genetic syndromes (Williams, Down, Turner, PHIP, and more)
• maternal hypothyroidism (for newborns)
• Other (drugs, neck irradiation)

Similarly, there are conflicting data on the clinical effects of subclinical hypothyroidism: some studies have shown a reduction in linear growth and weight while others did not show any alteration. It follows that to date is still contested the appropriateness of thyroxin therapy in subclinical hypothyroid children with Down syndrome.

However, a recent study by Kowalczyk [5] documented that early treatment of subclinical thyroid hypofunction improves the speed of growth of these children, supporting the data of the randomized clinical trial existing in the literature [6], where it was confirmed the existence of statistically significant differences between the group treated with levothyroxine and the group treated with placebo (• **Table 2**).

In addition, a further study [7], carried out on 157 paediatric patients with trisomy 21, showed a higher incidence of hypotonia in the presence of subclinical hypothyroidism compared with euthyroid children (52.6% *vs.* 16.4%), laying the foundation for the therapeutic appropriateness (• **Table 3**).

Alterations in thyroid homeostasis can occur with greater frequency in patients with Turner syndrome. The incidence of hypothyroidism and autoimmune diseases increases in relation to age and regardless of karyotype. Furthermore, unlike the temporal stability of thyroid hormonal profile in case of subclinical not autoimmune hypothyroidism, the others subclinical hypothyroidism are characterized by a progressive deterioration in relation to age.

The pseudo-hypoparathyroidism, due to the receptor resistance to the action of parathyroid hormone, is characterized by hypocalcemia, hyperphosphatemia, and elevated PTH levels.

In these patients the resistance of the receptor may also affect other hormones, such for example, TSH, and then determine a hypothyroid condition that requires drug treatment.

There are several other syndromes that may present subclinical hypothyroidism: the Smith-Lemli-Opitz syndrome, characterized by a defect in the synthesis of cholesterol and consequent impairment of steroidogenesis, associated with dysmorphism,

• **Table 2.** Results of treatment with thyroxine as compared with placebo-treated patients

	Thyroxine group	Placebo group	Difference (95% CI)	*P*
MAIN ANALYSIS	n. 90	n. 91		
Age corrected for preterm birth (months)	23,6 (0,4)	23,7 (0,4)		
Mental				
Raw score	96,1 (10,9)	93,4 (13,7)		
Developmental age delay (months)	9,5 (2,5)	10,2 (3,0)	-0,7 (-1,5 a 0,2)	0,12
Motor				
Raw score	62,2 (5,9)	60,4 (7,4)		
Developmental age delay (months)	12,3 (2,1)	13,0 (2,4)	-0,7 (-1,4 a 0,0)	0,042
ADDITIONAL ANALYSIS	n. 81	n. 87		
Age corrected for preterm birth (months)	23,6 (0,4)	23,7 (0,4)		
Mental				
Raw score	97,9 (8,8)	95,0 (10,4)		
Developmental age delay (months	9,1 (2,1)	9,9 (2,6)	-0,8 (-1,5 a 0,1)	0,032
Motor				
Raw score	63,1 (4,6)	60,9 (6,7)		
Developmental delay (months)	12,1 (2,0)	12,9 (2,3)	-0,8 (-1,5 a 0,2)	0,015

Source: Trotsenburg *et al.*, 2005 [6].

• **Table 3.** Comparison of hypothyroidism-related symptoms and signs between patients with SCH and patients without hypothyroidism

	SCH	Without hypothyroidism	*P* value
Number of patients	20	85	
Girls, %	40	31,8	0,59
Average age, years	4,7 ± 6,3	8,9 ± 8,9	0,04
Average FT4, pmol/l	16,6 ± 3,3	16,0 ± 2,7	0,37
Average TSH, mIU/l	9,0 ± 2,2	3,6 ± 1,5	0,0001
BMI percentile	78,6 ± 22,0	69,9 ± 29,1	0,37
Heart defects, %	35,0 (7/20)	37,6 (32/85)	1,00
Program, %			0,32
Integrative	47,1	27,4	
Special needs	29,4	37,0	
Staying at home	23,5	35,6	
Hypotonia, %			0,002
Without/mild	47,4 (n. 9)	83,6 (n. 56)	
Moderate/severe	52,6 (n. 100)	16,4 (n. 11)	

Fonte: Tenenbaum *et al.*, 2012 [7].

short stature, multiple congenital malformations and mental retardation; syndrome 49,XXXXY characterized by dysmorphism, hypergonadotropic hypogonadism, mental retardation and subclinical not autoimmune hypothyroidism; Angelman syndrome and syndrome of microdeletion of chromosome 12. The hyperthyrotropinemia is not present, instead, in the Prader-Willi syndrome, despite the severe obesity of the patients, probably due to a pituitary damage that prevents the raising of the TSH.

In conclusion, subclinical hypothyroidism is more common in plurimalformative syndromes and the cause is related to the underlying disease. For example, in the syndrome of Williams, there is a morphological abnormality of the thyroid gland; however, the hypofunction may also be partly related to immaturity of the hypothalamic-pituitary axis, considering that TSH tends to normalize with age in some of these genetic forms. In some syndromes, as in that of Down, the presence of hypothyroidism may be associated with a worsening of the clinical condition. Treatment with levothyroxine is still controversial but it seems to be useful in some situations discussed, such as in Down syndrome and in pseudohypoparathyroidism or when there is a clear impairment of the CNS.

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SESSION 2

THYROID HORMONES FOR FERTILITY AND IN PREGNANCY

Selenium and endocrine disorders in pregnancy

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Selenium is an essential non-metallic trace element contained in food and in the soil. It performs many functions in the body: it opposes the proliferation of neoplastic cells, preserves the DNA integrity, reduces oxidative stress, stimulates the immune system and improves the fertility, the brain function and the metabolic profile.

In the world, the availability of selenium is highly variable and the intake which we assume with the diet is below the recommended values in different regions: the Northeast and the South of Italy, in some parts of Europe, England, Africa, USA and Australia (• **Table 1**). In China, in areas with severe selenium deficiency, it has been described the Kashin-Beck syndrome, characterized by bone dystrophy and dilated cardiomyopathy.

A deficiency of selenium must therefore be supplemented; however, it has not yet been made clear what should be the adequate plasma levels of this element.

Some studies have shown that the plasma selenium level may change over time, even depending on the time of year, but still it is not known what significance to attribute to these variations, nor what are the responsible mechanisms.

Today, the recommended plasma level to ensure a proper activity of all the selenoproteins is about 100 g/L. In the body selenium is complexed in many proteins with enzymatic activity, including deiodinase, the glutathione-peroxidase, the membrane proteins responsible for the spermatozoa motility. It has been recently shown a close correlation between selenium, pregnancy and endocrinopathies. Pregnancy brings, in fact, physiological adaptations of the whole endocrine system and metabolic changes that may alter the normal absorption of selenium.

The two main endocrine disorders related to pregnancy are the alterations of the thyroid homeostasis and gestational diabetes. The thyroid autoimmunity is associat-

• **Table 1.** Blood levels (μg/L) of copper, manganese, selenium and zinc in different countries

Reference	Country	Subject	Parameter	Cu	Mn	Se	Zn
Europe							
This study	Italy	215	P5-P95 (GM)	776-1495 (1036)	4.73-17.0 (8.91)	106-185 (140)	4686-8585 (6418)
Minoia *et al.*, Sci Total Environ 1990	Italy	Cu, Se, Zn: ca. 500; Mn: 88	Reference range (mean)	807-1643 (1225)	7.1-10.5 (8.8)	76-140 (108)	4076-7594 (6340)
Alimonti *et al.*, Ann Ist Super Sanità 2005	Italy	110	P5-P95 (P50)	686-1157 (935)	1.53-13.2 (7.85)	nd	5189-8337 (6597)
Gundacker *et al.*, Sci Total Environ 2006	Austria	154	P25-P75 (P50)	nd	nd	74.1-98.1 (83.3)	nd
Beneš *et al.*, Cent Eur J Publ Health 2000	Czech Republic	1216	P25-P95 (GM)	730-1131 (812)	nd	65-114 (74)	5030-8543 (5765)
Beneš *et al.*, Cent Eur J Public Health 2005	Czech Republic	3207	P25-P95 (GM)	F = 840-1510 (999)	nd	M = 72-117 (81) F = 73-113 (81)	M = 6163-9102 (6842) F = 5640-8443 (6315)
Grandjean *et al.*, Scand J Clin Lab Invest 1991	Denmark	200	P2.5-P97.5 (P50)	nd	nd	81.4-134 (102)	nd
Kristiansen *et al.*, Sci Total Environ 1997	Denmark	188	P5-P95 (P50)	nd	5.50-14.9 (8.64)	nd	nd
78 Goullé *et al.*, Forensic Sci Int 2005	France	100	P5-P95 (P50)	nd	5.0-12.8 (7.6)	89-154 (119)	nd
Heitland *et al.*, J Trace Elem Med Biol 2006	Germany	130	P5-P95 (GM)	804-1620 (1020)	5.7-14.6 (8.6)	105-164 (132)	nd
McMaster *et al.*, Clin Chem 1990	Northern Ireland	100	(mean)	nd	nd	M = (90.9) F = (90.9)	nd
Moreno *et al.*, Sci Total Environ 1999	Spain	82	(mean)	M = (1050) F = (1110)	nd	M = (120) F = (115)	M = (7170) F = (6650)
Rosborg *et al.*, Sci Total Environ 2007	Sweden	41 (all F)	min-max (P50)	690-1475 (855)	nd	66.4-137 (105)	3900-7300 (5450)
America							
Nunes *et al.*, J Toxicol Environ Health 2010	Brasil	1125	min-max (mean)	712-1732 (890)	6.9-18.4 (9.6)	68-245 (89.3)	nd
Clark *et al.*, Chemosphere 2007	Canada	43	P50-P95 (GM)	nd	10.7-14.9 (10.8)	nd	nd
Asia							
Liu *et al.*, Biol Trace Elem Res 2010	China	120 (all F)	P2.5-P97.5 (mean)	719-2113 (1081)	nd	nd	5100-8503 (6399)
Raghunath *et al.*, Sci Total Environ 2002	India	35	min-max (GM)	nd	nd	32-178 (99.6)	nd

nd = not determined.

M = male; F = female.

Source: Bocca *et al.*, 2011 [1].

ed with an increased risk of miscarriage and preterm delivery, while the gestational diabetes correlates with increased synthesis of free radicals and a higher frequency of obstetric complications. Based on the data that are emerging in the literature in recent years, the treatment of hypothyroidism, even subclinical in pregnancy reduces the obstetric complications and any selenium supplementation, in case of its deficiency, seems to further improve the outcome of the pregnancy.

During pregnancy, the content of selenium in maternal blood and in the amniotic fluid decreases with the advancing of gestational age, confirming the increase of requirements of this micronutrient in this particular period of life, both for the increase in renal excretion, and for a greater use due to the synthesis of fetal proteins [2].

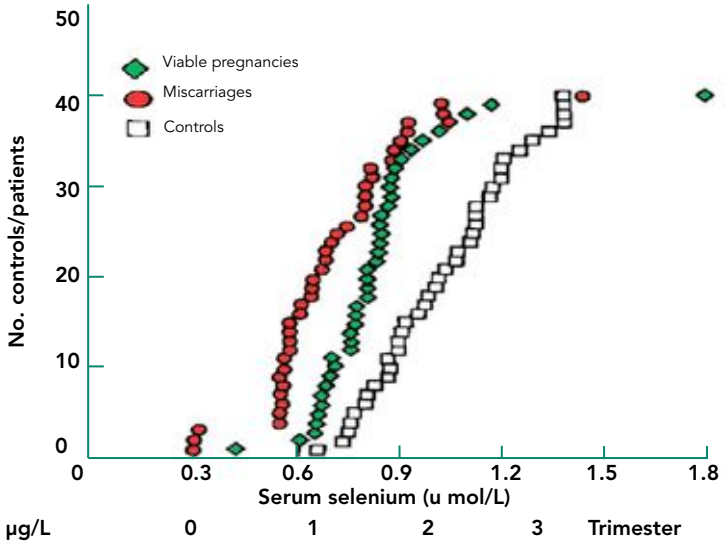
The reduction of selenium level is even more important during pathological pregnancies, probably due to the alteration of oxidative metabolism [3].

The basal levels of selenium in women with gestational diabetes are lower compared to healthy controls [4]. However, no data are available regarding the effects of selenium supplementation on the incidence of gestational diabetes.

Reduced levels of selenium have been associated with various gravidic complications, as miscarriage, premature delivery, pre-eclampsia and low birth weight.

The first study in this regard was in 1996 [5] and showed that women with poliabortivity had lower plasma levels of selenium and therefore less antioxidant activity (• **Figure 1**).

• **Figure 1.** Distribution of serum selenium levels in controls, viable pregnancies and first trimester miscarriage



Source: Barrington *et al.*, 1996 [5].

• **Table 2.** Levels of selenium in the blood from umbilical and maternal cord of newborn at term *vs* preterm

Serum selenium concentrations in newborn infants

Group	Number	Mean concentration	Range
Term	30	124.80 ± 13.72	94-148
Preterm	30	100.30 ± 11.72[a]	75-118

a: = 0.0001, the term infants. (±, µg/L)

Maternal serum selenium concentrations (±, µg/L)

Group	Number	Mean concentration	Range
Term	30	117.03 ± 17.15	89-147
Preterm	30	110.56 ± 17.49	78-144

Source: Iranpour *et al.*, 2009 [6].

It is therefore necessary to assess the levels of serum selenium in case of repeated miscarriages. Did not emerge significant differences of maternal serum selenium between born at term and preterm birth, but it has been found a reduction in the level of this micronutrient in the cord of preterm infants (• **Table 2**)[6].

A prospective study [7] of 1,197 women at the 12th gestational week revealed a statistically significant difference in the level of selenium among women who completed the pregnancy and those which had a preterm delivery. In particular, a value of selenium below the 25th percentile, i.e. <0.92 mol/L (OD 2.18) is a predictor of preterm pregnancy (• **Table 3**).

Supplementation with selenium during pregnancy appears to reduce the risk of premature rupture of placental membrane, as demonstrated by a double-blind randomized clinical trial, [8], which measured a significantly lower incidence in women treated with selenium (8%) compared to the control group (22%).

In the last period, also, there are emerging data that relate the selenium deficiency with pre-eclampsia and low birth weight.

Regarding the correlation between selenium and endocrinopathies, several studies assessed an increase in thyroid volume and a tendency to the development of nodular goiter in women presenting selenium deficiency.

The supplementation of selenium is able to reduce the levels of thyroid antibodies and enhance the echogenicity of the gland in the presence of chronic lymphocytic thyroiditis [9] reduce the incidence of postpartum thyroiditis [10] and strengthen the clinical response and the regression of ophthalmopathy in patients with Graves' disease treated with antithyroid drugs [11].

However, over-physiological supplementation with selenium, ten times higher than the recommended levels, can achieve a degree of toxicity, causing hair loss and

• **Table 3.** Factors associated with increased risk of preterm delivery

Characteristic	Term n = 1069	Preterm n = 60	*p* value
Serum selenium at 12 wk, µmol/L, mean (SD)	1.02 (0.13)	0.96 (0.14)	0.003 †

Factor	OR (95% CI)
Maternal age (unit change per yr)	1.02 (0.94-1.10)
Income < US$ 1500/month	2.34 (0.77-4.68)
Marital status = single	2.08 (0.69-7.81)
Low level of education	1.01 (0.49-2.05)
Smoking	1.09 (0.63-2.37)
Consumption of alcohol > 2 units/wk	0.62 (9.24-1.79)
BMI (unit change per kg/m^2)	1.03 (0.97-1.08)
Low selenium level (< 25th percentile at 12 wk gestation)	2.18 (1.25-3.77)
Primiparity	2.99 (1.59-5.62)
Previous miscarriage	1.52 (0.78-2.99)
Diastolic pressure > 90 mm Hg at 12 wk gestation	1.01 (0.97-1.05)
Preeclampsia	3.19 (1.47-6.91)

† = *t* test; BMI = body mass index; CI = confidence interval; OR = odds ratio.

Source: Rayman *et al.*, 2011 [7].

nail changes. Currently, it is ongoing a multicenter randomized trial (SERENA, NIH: NCT01465867) on selenium supplementation in women with positive thyroid antibodies at the 12th gestational week and women candidates, within 60 days, to embryo transfer. The aim of the study is to evaluate the effects of selenium supplementation alone or in combination with levothyroxine in changing the antibody titer during the pregnancy and in the 3-6 months postpartum, verifying the effects on the function and on the structure of the thyroid and on obstetric and neonatal complications.

Waiting for the results of this interesting work, we remind that in the world today there are still regions, populations and conditions at risk of inadequate intake of selenium with the diet. Several randomized studies indicate that selenium supplementation in pregnancy may improve the rate of thyroid autoantibodies and may reduce some obstetric complications. The measurement of serum selenium level is therefore recommended in case of recurrent poliabortivity.

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Fertility and miscarriages: new roles for the thyroid

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The human reproductive function is regulated by a complex network in which it is involved the thyroid axis. Functional alterations of the thyroid are 4-5 times more frequent in women than in men and are prevalent in the population of reproductive age. All reproductive phases from menstrual cycle to gestational outcome may be altered from the altered thyroid homeostasis (from iodine deficiency to autoimmune thyroid disorders) that is able to influence fertility and gestational homeostasis.

Pathophysiological aspects

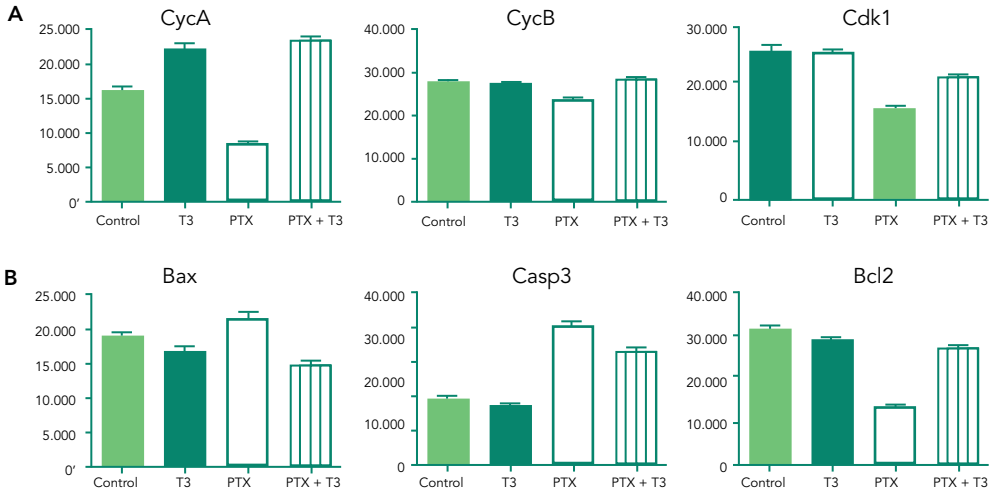
At birth, the woman has millions of primordial follicles, but their number decreases gradually to 300,000 oocytes at the time of puberty; of these only 400-500 reach the ovulation during the fertile period, while the remainder will undergo apoptosis and atresia. The progression of the follicles through the various maturation and differentiation stages requires a series of interactions in which a primary role seems to be played by members of the TGF-β superfamily. Such family includes hormones with endocrine activity, paracrine and autocrine, including inhibin, activin, antimullerian hormone, the ancillary proteins and proteins morphogenetic of the bone, some of which appear to be involved in early ovarian insufficiency. The best known and studied, inhibins and activine, are involved in the modulation of the hypothalamic-pituitary-gonadal axis, inhibiting and stimulating respectively the production of FSH and the expression of its receptors in granulosa cells, and the aromatase activity and thus the production of intrafollicular estrogen and the selection of the dominant follicle. They also represent the actors of some regulatory functions of the hormonal activity of the theca.

The levels of activin and inhibin appear to be affected by thyroid homeostatic alterations; incremented values of activin A were found in women with Graves disease,

while an increase of inhibin B, such as to change towards down the levels of FSH is present in post-menopausal women with abnormal thyroid function.

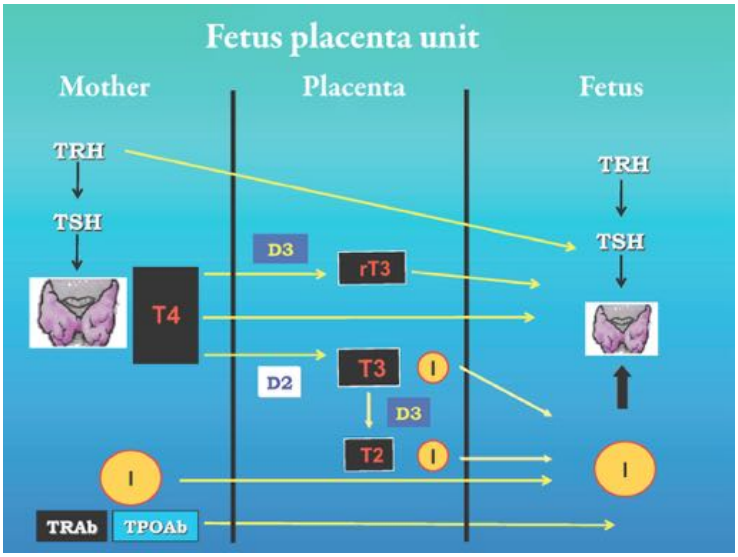
T3 seems to act on the morphogenesis, maturation and differentiation of oocytes. All the receptor isoforms of thyroid hormones are present in the granulosa cells and in those of the cumulus oophorus, for which it is possible a direct action of the iodothyronines on the ovary. Studies on murine models [1] have shown that T3 is able to preserve the granulosa cells from apoptosis induced by chemotherapy (• **Figure 1**). Furthermore, T3 increases the functionality of the follicles and granulosa cells of rat, an effect enhanced by pre-treatment with testosterone thanks to the ability of triiodothyronine to induce aromatase activity. In addition to the receptors for thyroid hormones, also deiodinase are expressed in different entities of the reproductive system and have the utmost importance at the level of the fetus-placenta unit. They are precociously active in the placental tissues: deiodinase isoenzymes type 2 (activating), through their lively and early deiodinase activities of T4, play a trophic role on the trophoblast through T3 produced locally, which stimulates the entire network of placental endocrine secretion. Secondly, the activity of deiodinase type 3 protects the fetus from the powerful metabolic activities of T3, by inactivating the maternal T3 and by providing the unborn child a reservoir of elemental iodine, direct consequence of enzymatic local deiodination. It is realized then, through a network of iodothyronines/deiodinase, the modulation of the passage of T4 and iodine through

• **Figure 1.** Antiapoptotic effect of T3 in granulosa cells of rats exposed to chemotherapy



Source: Verga Falzacappa *et al.*, 2012 [1].

• **Figure 2** Schematic representation of the trans-placental traffic of iodine and iodothyronines

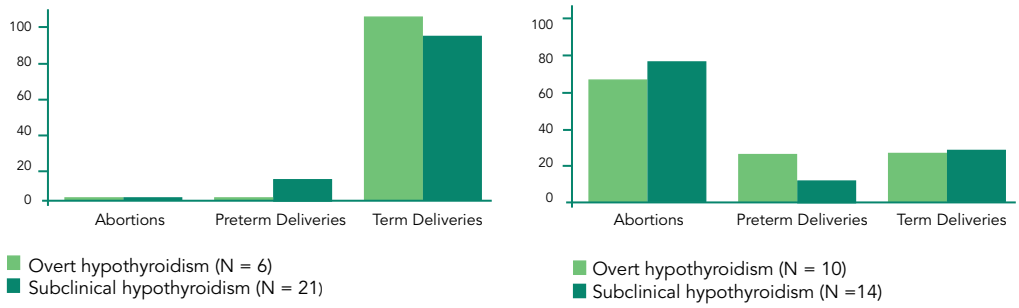


the placental barrier that represents a primary event in the development of the central nervous system of the unborn child. In contrast, the T3 is inactivated by the action of deiodinase 3 and does not reach the circulation and the foetal tissues in amounts physiologically relevant (• **Figure 2**).

Clinical correlates

In view of the numerous interactions between the reproductive system and the thyroid function, it is not surprising that the thyroid alterations, especially if of functional and/or clinical relevance, are highly prevalent in patients with disorders of the menstrual cycle and that the alterations especially hypo-functional triplicate the number of patients with oligomenorrhea. The physiological menstrual cyclicity is in fact the result of a series of regulated events that require the normal function of the hypothalamic-pituitary axis, ovaries and uterus, but also a normal cross-talk with the thyroid axis. In conditions of hypothyroidism, there is an alteration of the pulsatility of GnRH and, therefore, a decrease of the stimulus on the granulosa cells with a series of cascading events that hesitate in many disorders of the cyclicity and sometimes in a reduction of fertility [2]. This assumption is even more true when hypothyroidism results from hyperprolactinemia due to increased stimulation of TRH (able to stimulate both functional axes). The latter is an important cause of oligomenorrhea and amenorrhea, which complicates the perturbative effect of iodothyreonine deficit.

• **Figure 3.** Pregnancy outcome in relation with adequate or inadequate replacement therapy



Eu: 4% Abortions
Ipo: 31,4% Abortions $p < 0.0001$
Eu: 84,5% term pregnancy
Ipo: 58.8% term pregnancy $p = 0.18$ ns

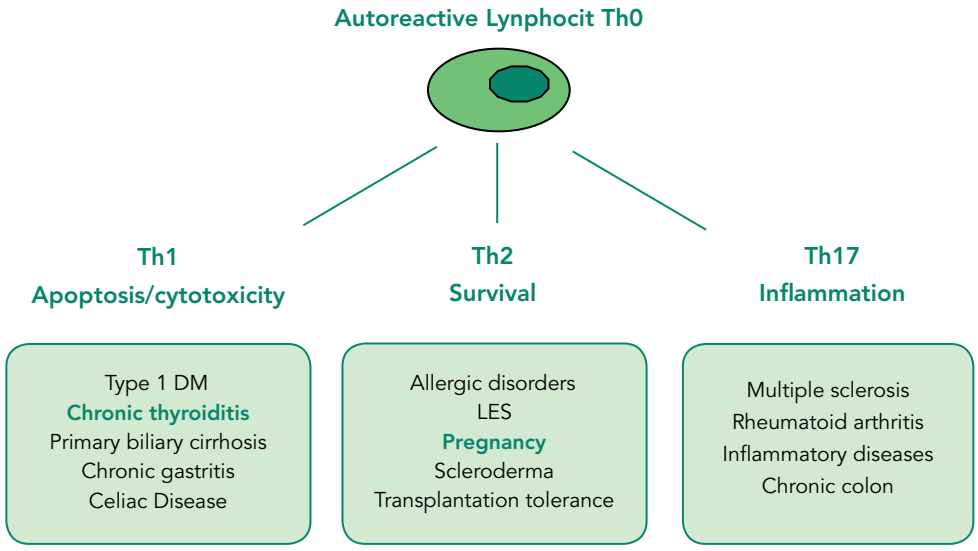
Source: Abalovich *et al.*, 2002 [3].

The availability of micronutrients (especially iodine and selenium), essential for both pregnancy and thyroid gland, the alterations of the immune system that, in some cases, may predispose to prothrombotic states and the incidence of obstetric complications and poliabortivity in women with alteration of thyroid function testify the close clinical correlation between thyroid and pregnancy.

The need for iodine increases significantly during pregnancy and lactation. In conditions of iodine deficiency the risk of miscarriage and premature birth increases, as well as a higher incidence of disorders of the foetal development and infant mortality, correlating with the severity of the deficiency. It is therefore recommended the iodine supplementation in women of childbearing age, possibly years before become pregnant.

Since 1990, several studies have shown an increased risk of spontaneous abortion in women with thyroid disorders. Hypothyroidism in pregnancy is present in 2.5% of pregnant women; the most common cause is autoimmune thyroid disease and has an effect even in the subclinical form. Hypothyroidism in pregnancy causes failure of the corpus luteum, abortions in the first trimester, preterm labours due to gestational hypertension and learning disabilities in children. As the number of abortions and preterm pregnancies is reduced with appropriate treatment, the guidelines establish to treat hypothyroidism, even if present in subclinical form, keeping in mind that the majority of women require an increased need of levothyroxine already in the first trimester of pregnancy (• **Figure 3**). Given the role of concomitant autoimmunity in

• **Figure 4.** Classification of immune, autoimmune and allergic events on the basis of the predominant cytokine milieu



The Th1 structure is associated with poliabortivity
while the Th2 structure is associated with term pregnancies

determining abortivity, the antibody positivity (Ab-antithyreoperoxidase) has been suggested to be responsible of abortivity and poliabortivity and suspicions were also confirmed in medically assisted procreation.

However, the studies of meta-analysis that are the basis of this hypothesis are encumbered by numerous biases, such as to invalidate the linear interpretation of the results: often were not held in account the different maternal ages, the simultaneous presence of the anti-phospholipid antibody syndrome, as well as the different degree of hypothyroidism and its combination with autoimmune phenomena.

In this regard, our group (Centanni *et al*., unpublished observations) has conducted a retrospective study in which selected 288 thyropatic women with clinic abortion; of these, 82 have poliabortions and were divided into two groups on the basis of aetiopathogenesis (autoimmune or not-autoimmune) of the thyroid disease. Women with autoimmune thyroid disease and multiple abortions were further divided on the basis of the presence or absence of another autoimmune disease (polyglandular autoimmune syndrome type III). As expected, it was found that multiple abortions are more correlated with autoimmune thyroid disease compared to not-autoimmune. However, the majority of women with recurrent fetal loss falls within the group of patients with autoimmune polyendocrinopathies (PGAIII), while patients with iso-

lated chronic autoimmune thyroiditis have a frequency only slightly higher than that found in thyreopatic not autoimmune. The poliabortivity is therefore more associated with complex disorders of the immune response that not to the mere presence of antithyroid antibody more epiphenomenal than pathogenetic.

These results are in agreement with those of Raghupathy *et al*. [4], which had stressed the role of the cytokine milieu prevalent in causing recurrent foetal loss. In fact, the effector pathways of CD4 lymphocytes are different in many autoimmune diseases (pro-apoptotic pathway) compared to those antiapoptotic of which pregnancy is part.

It is therefore not surprising that the TH1 lymphocyte structure (lymphocytic structure), typical of chronic lymphocytic thyroiditis, is more associated with recurrent fetal loss, while the TH2 lymphocytes structure is associated with term pregnancies (• **Figure 4**). It was, however, described a hierarchy TH1 >TH2 which proceeds from pluri-abortive women prone to abortion to those pluriabortive who will have a full- term pregnancy to those with multiple normal pregnancies [4] .

In conclusion, ovary and placenta have the entire transductional apparatus of the thyroid hormone signal. The iodothyronines are then able to exercise many functions on the entire female reproductive axis, among which we can highlight three types of action: anti-apoptotic on follicles, trophic in the placenta and differentiative in fetal tissues. The thyroid hormonal action is, therefore, a modulator of the foetus-placenta homeostasis and can affect the pregnancy outcome. The alterations of the thyroid homeostasis, even preclinical, present in pregnancy should therefore always be identified, diagnosed and possibly treated.

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Thyroid and MAP

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Medically assisted procreation (MAP) provides a series of following steps that lead to the in vitro fertilization of gametes and their implantation in the uterine cavity. Because the probability of success of each stage are limited, to ensure a reasonable chance of success, namely the transfer of at least one embryo of good quality in the uterus, it is necessary to start with an optimum amount which corresponds to about 10-15 eggs.

The first phase of the MAP consists of the induction of multiple follicular growth; in other words it is necessary to overcome pharmacologically mechanisms that, in women, are the basis of the selection of the dominant follicle. Next, the oocytes sample is taken through transvaginal ultrasound-guided aspiration and the fertilization in vitro is done. The ovules are fertilized with different techniques (IVF or ICSI), depending on the quantity and quality of the sperm available. The next stage is the in vitro culture of fertilized oocytes. Only 50-80% of them reaches the state of embryo with 4-8 cells after about 48-72 hours and is transferred into the uterus. Since no all oocytes reach the final stage of the procedure, it is necessary to have some more embryo more at the start. The rates of each embryo implantation oscillate between 15% and 20%, so to have a reasonable probability of pregnancy (30%) for many years the tendency has prevailed to transfer 2 or 3 embryos. After about 6-7 days from the fertilization, the embryo, now formed by 120 cells, gets rid of the pellucid zone and is ready for implantation.

A retrospective study conducted by Fumarola *et al.* [1] evaluated the relationship between thyroid function and the outcome of assisted reproduction: 164 patients were stratified on the basis of serum TSH. The results showed as a value of TSH > 2 mU/L was associated with a statistically significant reduction in rates of clinical pregnancy, determined by viewing the gestational room with the embryo inside. If on one hand even mild increases in TSH appear able to reduce the incidence of clinical

pregnancy in cycles of assisted reproduction, it does not seem, on the other hand, that this condition impacts directly on the embryological parameters. In order to verify whether the negative impact on pregnancy rates given by the increase of TSH can be modulated by treatment with levothyroxine (LT_4), the same study also stratified women according to treatment with LT_4 and demonstrated that the therapy cancels the negative effect of subclinical hypothyroidism. The data were confirmed by a further study [2], conducted on 64 patients with subclinical hypothyroidism who did in vitro fertilization; clinical trial has also shown that the women not treated had lower implantation rates and an increased risk of abortion (• **Table 1**).

• **Table 1.** Comparison of the results of controlled ovarian stimulation and IVF/ICSI outcome in patients treated with LT4 compared to untreated controls

Factor	LT4 treatment	Control	*P* value
No. of cycles initiated	32	32	
No. of cycles retrieved	32	32	
No. of ET cycles	32	32	
Cycles with ICSI, n (%)	14 (43.8)	14 (43.8)	NS[a]
Days of rhFSH	9.1 ± 1.2	9.0 ± 1.1	NS[b]
Total dose of rhFSH	1,880.6 ± 425.5	1,919.9 ± 397.7	NS[b]
Days of GnRH antagonist	4.3 ± 1.0	4.3 ± 1.0	NS[b]
On the day of hCG injection			
TSH (mIU/L)	2.9 ± 1.0	6.8 ± 1.9	<.001[a]
FT4 (ng/dL)	1.3 ± 0.1	1.2 ± 0.2	.017 [a]
PRL (ng/mL)	15.8 ± 3.3	16.3 ± 3.5	NS[b]
No. of follicles ≥ 14 mm	8.9 ± 3.4	9.1 ± 3.3	NS[b]
EMT (mm)	10.1 ±1.1	9.8 ± 1.2	NS[b]
On the day of -hCG measurement			
TSH (mIU/L)	2.3 ± 0.4	6.9 ± 2.0	<.001[a]
FT4 (ng/dL)	1.4 ± 0.3	1.0 ± 0.2	<.001[a]
No. of oocytes retrieved	9.3 ± 3.9	9.2 ± 3.2	NS[b]
No. of mature oocytes	8.2 ± 3.4	7.5 ± 2.6	NS[b]
No. of fertilized oocytes	8.1 ± 3.4	7.2 ± 2.3	NS[b]
No. of grade I, II embryos	3.3 ± 1.6	2.2 ± 1.3	.007[b]
No. of embryos transferred	2.9 ± 0.5	2.9 ± 0.4	NS[b]
No. of embryos cryopreserved	2.5 ± 2.7	1.8 ± 2.3	NS[b]
Embryo implantation rate, % (n)	26.9 (25/93)	14.9 (14/94)	.044[b]
Clinical PR per cycle initiated, % (n)	53.1 (17/32)	37.5 (12/32)	NS[a]
Miscarriage rate, % (n)	0 (0/17)	33.3 (4/12)	0.21[a]
Live birth rate per cycle initiated, % (n)	53.1 (17/32)	25.0 (8/32)	0.39[a]

Values are mean ± SD unless otherwise noted; PR = pregnancy rate; NS = not significant; a = Fisher's exact test or χ^2 test; b = student's *t* test.

Source: Kim *et al.*, 2011 [2].

• **Table 2.** Correlation between thyroid autoimmunity and reproductive outcomes in patients subjected to PMA

Variables	ATA + Group	Control Group	*P* value
Stimulation length (days)	11.0 ± 1.8	10.7 ± 1.7	0.074
Total Gn dose (IU)	2302 ± 864	2246 ± 736	0.885
E2 level on the day of HCG (pg/ml)	2290 ± 1101	2342 ± 1173	0.716
Number of retrieved oocytes	10.9 ± 6.1	11.8 ± 6.9	0.166
Fertilization Rate	64.3% (729/1134)	74.6% (8848/11856)	<0.001
Number of available embryos	5.3 ± 3.9	6.0 ± 4.2	0.01
Number of embryo transferred	2.4 ± 0.6	2.3 ± 0.6	0.086
Pregnancy Rate	33.3% (52/156)	46.7% (458/981)	0.002
Implantation Rate	17.8% (66/370)	27.1% (611/2251)	<0.001
Abortion Rate	26.9% (14/52)	11.8% (54/458)	0.002

Source: Zhong *et al.*, 2012 [3].

• **Table 3.** Reproductive outcomes in patients treated with levothyroxine, acetyl salicylic acid and prednisolone

	Group A	Group B	Group C	Group D
IVF cycles	52	56	44	200
Total Gn dose (IU)	3714 +/- 1499 [c]	3430 +/- 1722	3000 +/- 1358 [b]	2755 +/- 1216 [a]
Stimulation length (d)	12.3 +/- 2.1	12.2 +/- 2.5	11.4 +/- 1.6 [b]	11.5 +/- 1.8 [b]
OPU	50	55	44	200
Retrieved oocytes	6.5 +/- 4.3	7.9 +/- 5.4	10.7 +/- 6.4 [b]	8.7 +/- 5.2 [b]
Gn dose/oocyte (IU)	1028 +/- 1141	878 +/- 1045	448 +/- 520 [b]	539 +/- 796 [b]
Fertilization rate (%)	74.2	78.5	82.5	83.0
ET	40	45	39	177
Pregnancies	4	11	14	66
PR/started cycle (%)	7.7 [c]	19.6	31.8 [b]	33.0 [b]
PR/OPU (%)	8.0 [c]	20.0	31.8 [b]	33.3 [b]
PR/ET (%)	10.0 [c]	24.4	35.9 [b]	37.3 [b]
Implantation rate (%)	4.7 [c]	14.4	17.7 [b]	19.0 [a]
Abortions	1	3	4	8
Abortion rate (%	25.0	27.3	28.5	12.0 [a]
Ongoing PR/OPU (%)	6.0 [c]	14.5	22.7 [b]	29.3 [b]
Ongoing PR/ET (%)	7.5 [c]	17.8	25.6 [b]	32.8 [b]

Group A: ATA+, untreated patients. Group B: ATA+ patients treated with LT adjuvant therapy. Group C: ATA+ patients treated with LT+ASA+P adjuvant therapy; Group D: ATA-controls.

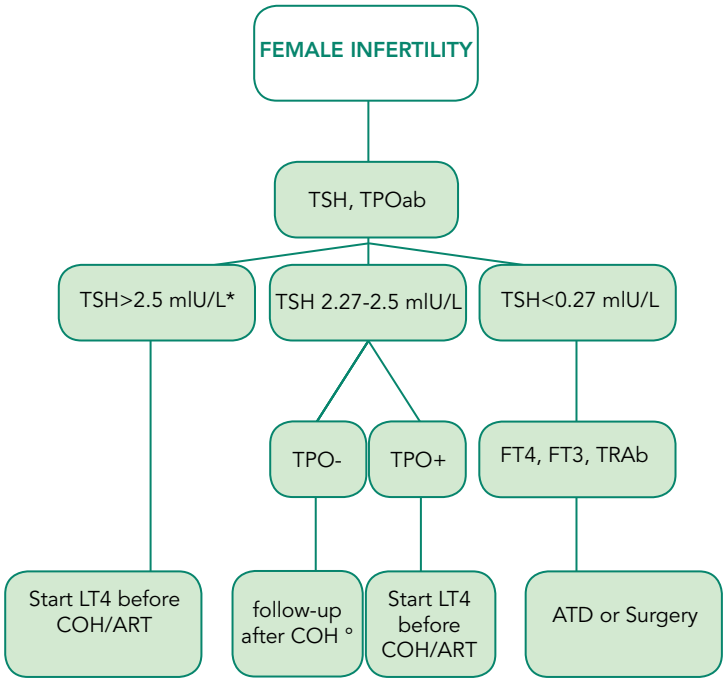
a = $p < 0.01$ *vs* groups A, B and C.

b = $p < 0.01$ *vs* groups A, and B.

c = $p < 0.01$ *vs* group B and C.

Source: Revelli *et al.*, 2009 [4].

• **Figure 1.** Algorithm for screening and management of thyroid and autoimmune dysfunctions in women diagnosed with infertility



* Consider measuring anti-Tg antibodies.
° Consider treatment when altered function aflter Controlled Ovarian Hyperstimulation (COH).
ART: assisted reproductive technology.

Fonte: Unuane *et al.*, 2011 [5].

An adequate thyroxin treatment (TSH <2 mU/L) is, therefore, able to eliminate the negative effects of hypothyroidism and obtain pregnancy rates similar to those of euthyroid patient.

The other aspect that relates thyroid to pregnancy regards the immunological profile. In a retrospective study [3] it has been analyzed the relationship between thyroid autoantibodies and the outcome of assisted reproduction procedures. The presence of thyroid autoimmunity determines an increase in abortions and the reduction of fertilization rate and implantation of embryo, even in the presence of a good hormonal compensation (• **Table 2**). This effect can be cancelled by the therapy, as demonstrated by the increased number of evolutive pregnancies and the reduction of abortions in women with positive thyroid autoantibodies and treated with levothyroxine (• **Table 3**).

Moreover, the presence of TPOAb in the follicular fluid of mothers with positive antibodies has been correlated to a lower in vitro fertilization and reduced embryo quality.

Although it is not yet clear the mechanism through which hypothyroidism impacts on the pregnancy outcome, it is likely that both the increase in TSH and the disorder of the immune system play a key role.

It has been also suggested that the thyroid dysfunction and antibody positivity can act at endometrium level changing the balance of TH1 and TH2 and uterine contractility.

Before starting a cycle of MAP is therefore necessary to ensure that the patient is well compensated, evaluating the thyroid function and the immunological structure. The finding of TSH> 2.5 mU/L requires the initiation of therapy with LT4.The treatment is also recommended in the presence of antibody positivity, even if the TSH <2.5 mU/L (• **Figure 1**).

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Hypothyroidism and planning of pregnancy

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The most common cause of hypothyroidism in adults is chronic lymphocytic thyroiditis. However, in some areas of the world, iodine deficiency still plays a very important etiologic role. The forms of iatrogenic hypothyroidism are due to thyroidectomy and radioiodine therapy. Pituitary or hypothalamic alterations are found in a small minority of hypothyroid.

Signs of thyroid autoimmunity is detectable in 5-15% of women in reproductive age and about a quarter of the population of childbearing age has a value of TSH between 2.4 to 4.5 mU/L.

Hypothyroidism interferes with the female reproductive system in three distinct levels: the hypothalamic -pituitary axis, the gonadal function and the peripheral metabolism of sex steroids.

The lack of thyroid hormones leads to an increase of TRH and then of the stimulus for the production of prolactin. Hyperprolactinemia induces an alteration of the pulsatile secretion of GnRH, resulting in a delayed response of the hormone LH and therefore inadequate ovulation.

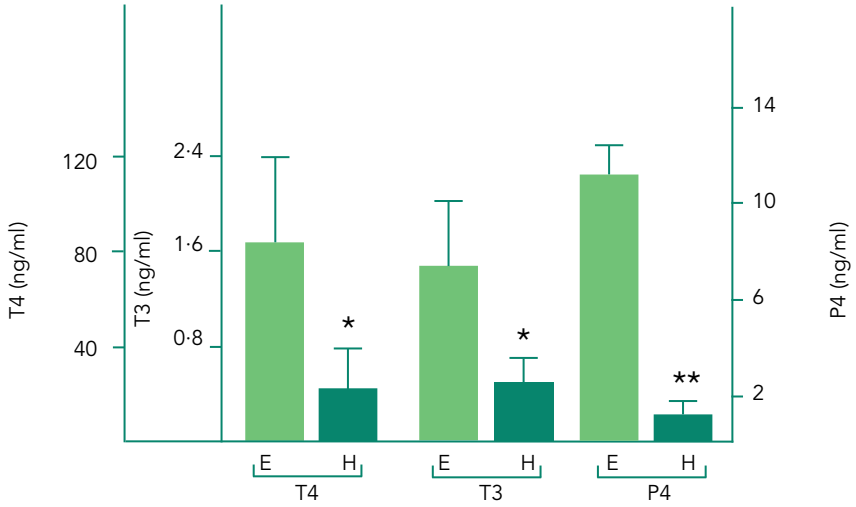
At gonadal level, thyroid hormones act in synergy with oestrogen and progesterone for the maturation of the oocyte and uterine implantation after fertilization (• **Figure 1**) [1].

In hypothyroid subject there is a reduced clearance of androstenedione and oestrone, an increase of peripheric aromatase activity and a decrease in the level of estradiol and testosterone, despite the value of SHBG is reduced.

Hormonal alterations of the thyroid homeostasis and of the reproductive system determine a decrease in fertility and the occurrence of alterations in the menstrual cycle, whose severity is directly proportional to the levels of TSH (• **Figure 2**) [2].

The frequency of menstrual irregularities in hypothyroid women is about 3-4 times

• **Figure 1.** Relationship between hypothyroidism and reduced secretion of prolactin (P4)

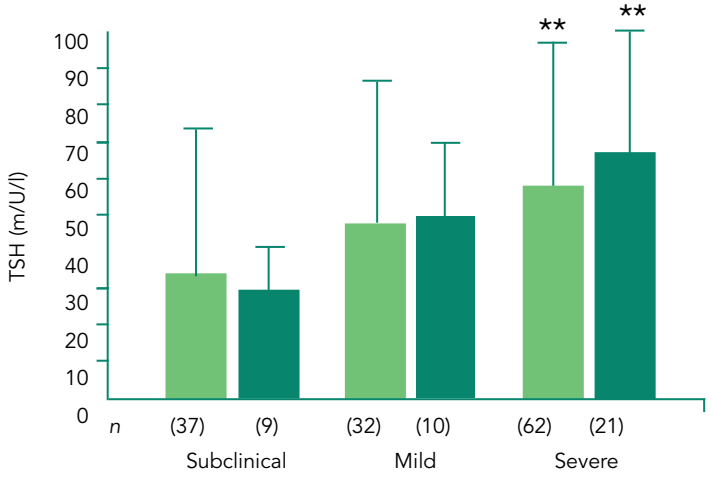


E (Eutyroid) H (Hypothyroid)

* $p < 0.05$; ** $p < 0.01$.

Source: Datta *et al.*, 1998 [1].

• **Figure 2.** Comparison of TSH values in women with and without menstrual irregularities affected by subclinical hypothyroidism, moderate and severe



Patients with menstrual irregularities Patients without menstrual irregularities

** Statistically significant, $p < 0.01$.

Source: Krassas *et al.*, 1999 [2].

higher than in euthyroid women and the main disorder is represented by oligomenorrhea (• **Table 1**) [2].

Data in the literature show varying percentages of the prevalence of hypothyroidism in infertile women.

Numerous scientific studies have confirmed that the presence of chronic autoimmune thyroiditis has a negative impact on the outcome of pregnancy both spontaneous and induced (• **Figure 3**). The aetiology of this association is most likely multifactorial and is mainly due to a primary alteration of the immune system.

In infertile couples the autoimmune thyroid disease is most often present when there is female infertility, especially in women with endometriosis and PCOS (• **Figure 4**).

Ovarian stimulation may represent an event triggering the thyroid imbalance in women with autoimmune thyroiditis. The increase in estradiol determines, in fact, an increase of TBG levels and thus a reduction in the proportion of free thyroxine and an increase of TSH.

Currently, universal thyroid screening is not recommended in all patients planning a pregnancy, but it should be required only in selected women, after a careful history to identify the risk factors : the presence of previous alterations of thyroid homeostasis, signs or symptoms suggestive of thyroid dysfunction or goiter, family history of thyroid disease, signs of autoimmunity, type 1 diabetes mellitus, previous irradiation of the cervical region, infertility, history of recurrent miscarriages or preterm delivery [5].

The AACE/ATA 2012 guidelines [5] recommend treatment with levothyroxine in all women with TSH values >2.5 mU/L at the time of programming a pregnancy and in the first quarter; furthermore, treatment with levothyroxine is recommended for pregnant women or women who are planning a pregnancy with positive TPOAb,

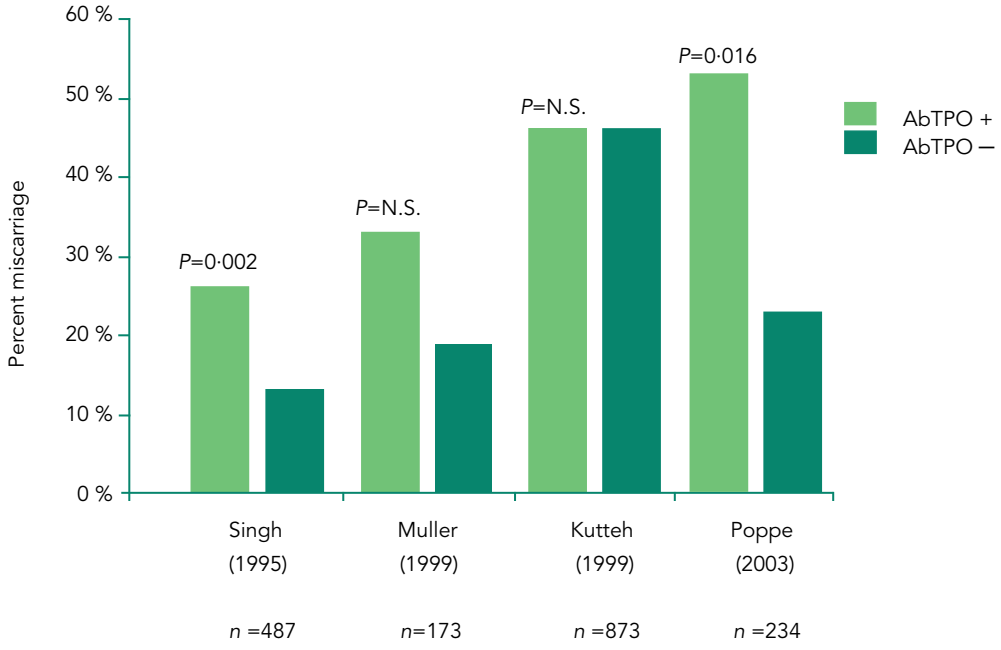
• **Table 1.** Typology of menstrual disorder in hypothyroid subjects before and after treatment and normal subjects

Type of menstrual disturbance	Normal controls (n = 214)		Hypothyroid patients (n = 171)			
			Before LT4		After LT4	
	n	%	*n*	%	*n*	%
Oligomenorrhoea	12	67	17	42.5	8	50
Amenorrhoea	-	-	5	12.5	1	6
Polymenorrhoea	1	5.5	-	-	-	-
Hypomenorrhoea	3	16.5	6	15	4	25
Hypermenorrhoea/menorrhagia	2	11	12	30	3	19
Total	18	8.4	40	23.4*	16	9.3

* Statistically significant percentage in comparison with that of normal controls, P < 0.001.

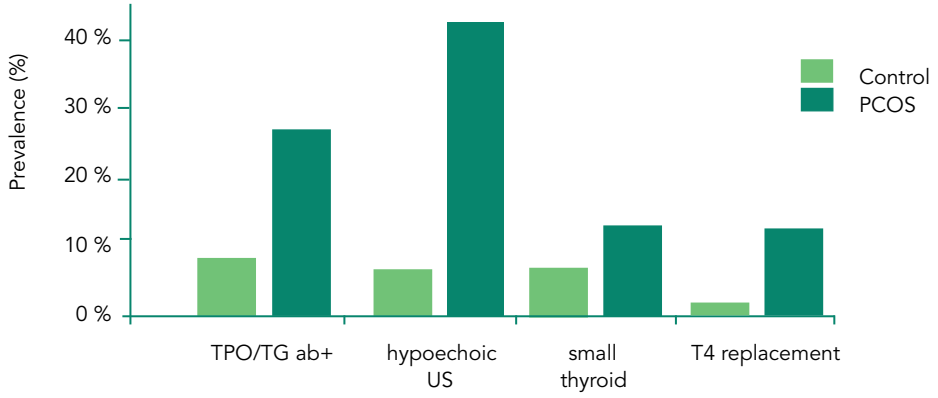
Source: Krassas *et al.*, 1999 [2].

● **Figure 3.** ART (Assisted Reproduction Technology)



Source: Poppe *et al.*, 2007 [3].

● **Figure 4.** Prevalence of thyroiditis in patients with PCOS



Source: Janssen *et al.*, 2004 [4].

even if TSH levels are in the normal range, especially if with a history of previous miscarriages. If they are not currently in therapy, it is useful to monitor them every 4 weeks to diagnose and treat promptly the onset of hypothyroidism.

In conclusion, there is an association between hypothyroidism – subclinical and manifest – and reduction of fertility. The chronic lymphocytic thyroiditis has a negative impact on the outcome of pregnancy, spontaneous or medically assisted. In fact, in infertile women, there is a higher prevalence of chronic thyroiditis. TPOAb and TgAb should always be assayed in the presence of recurrent miscarriages.

However, it is not recommended to perform an universal screening in all women who plan a pregnancy, but only those selected through medical history. The LT4 monotherapy should be considered in women with positive antibodies and repeated abortions and in women with TSH >2.5 mU/L in the first trimester of pregnancy with or without thyroid antibody positivity.

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Hypothyroidism in pregnancy

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The fetal organogenesis occurs in the first three months of gestation, so before the 12th week the maternal provision is the only source of thyroid hormone for the fetus. It stands, then, the extreme importance of having an optimal thyroid homeostasis in the woman who is planning a pregnancy or who is already pregnant.

At the level of the brain tissue, astrocytes metabolize thyroxine and supply the neurons of T3, which instead are cells lacking desiodinase. The thyroid hormone receptors develop early in the embryo; they are inactivated by the binding of repressors and are activated after the interaction with the T3, providing modulation of gene transcription.

The early post-natal treatment of a congenital hypothyroid, born from euthyroid mother, determines a normal neurological development in the infant. There will be, however, severe neurological disorders and severe mental damage (cretinism) if the mother was hypothyroid during pregnancy. Instead, the euthyroid son of a hypothyroid woman (elevated TSH or low FT4) will have a lower intelligence quotient (IQ).

The maternal hypothyroidism during pregnancy, even if mild, may therefore lead to a reduction in neuropsychological performance of the child (• Table 1). However, there are also studies, such as that of Lazarus *et al.* [1], in which there was no difference of IQ among children born to hypothyroid treated women and those born to women with hypothyroidism untreated.

Hypothyroidism in pregnancy has an impact not only on the product of conception, but also on the woman. Gestational hypertension, placental detachment, premature birth, postpartum haemorrhage, low birth weight, perinatal mortality, birth defects and abortion are possible consequences of maternal hypothyroidism untreated.

In pregnancy the dose of LT4 should generally be increased by 30-50% due to the

• **Table 1.** Maternal hypothyroidism during pregnancy and neuropsychological performance in the baby

Test	Children of treated women with hypothyroidism (n = 14)	P Value†	Children of untreated women with hypothyroidism‡ (n = 48)	P Value§	Control Children (n=124)
Intelligence					
WISC-III full-scale IQ score	111	0.20	100	0.005	107
WISC-III full-scale IQ score ≤85 (%)	0	0.90	19	0.007	5
Attention					
WISC-III freedom-from-distractibility score	103	0.80	97	0.03	102
Continuous Performance Test score >8 (%)	50	0.01	33	0.04	19
Language					
Test of Language Development score					
Word articulation	10.5	10.6	10.0	0.6	10.2
Word discrimination	11.4	0.90	10.3	0.02	11.4
WISC-III verbal IQ score	111	0.30	101	0.006	107
School performance					
PIAT-R reading-recognition score	101	0.80	95	0.05	100
PIAT-R reading-comprehension score	105	0.40	96	0.09	101
School difficulties and learning problems (%)	29	0.08	21	0.09	11
Repeated a grade (%)	7	0.50	8	0.3	4
Visual-motor performance					
Score on Developmental Test of Visual-Motor Integration	102	0.30	94	0.1	97
WISC-III performance IQ score	109	0.30	99	0.01	105
Pegboard-test score					
Dominant hand	79	0.40	88	0.06	83
Nondominant hand‡	87	0.70	96	0.04	89

† The P values are for the comparison of the children of the treated women with the children of the untreated women.

‡ One woman received treatment before, but not during, the pregnancy under study.

§ The P values are for the comparison of the children of the untreated women with the children of the control women.

Source: Haddow *et al.*, 1999 [2].

increased weight, presence of deiodinase placental activity, fetal transfer of part of the maternal thyroid hormones, increase in the volume of plasma distribution and plasma levels of TBG and due to the reduced intestinal absorption for the possible presence of nausea.

However, the adjustment of the therapy is often late since most of the women go

to the gynecologist during the 2nd-3rd month of pregnancy. The risk of precocious maternal hypothyroidism could then be prevented, according to Yassa *et al.* [3] adding 2 tablets of LT4/week, which would correspond to an increase of about 29% of the dose.

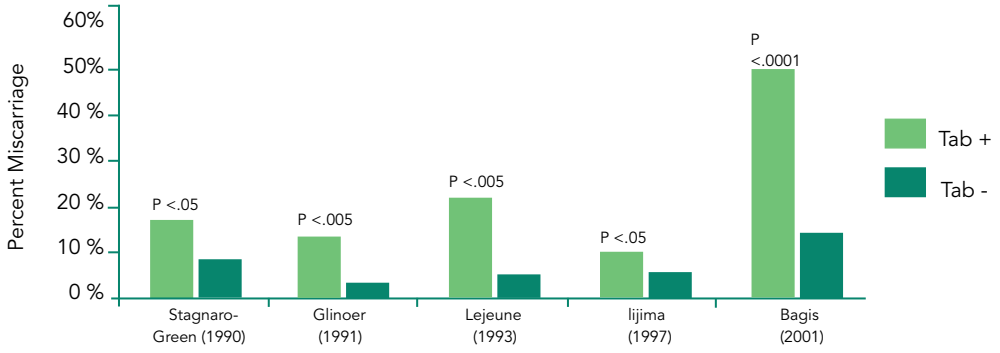
In hypothyroid women being treated and in euthyroid women with chronic thyroiditis, the thyroid function should be monitored every 4 weeks in the first half of pregnancy, at least once between the 26th and 32nd week of gestation, 2 weeks after each dose adjustment of LT4 and 6 weeks after childbirth. The achieving and maintaining of optimal thyroid homeostasis are essential because hypothyroidism, subclinical and clinical, if treated, is associated with an increased number of pregnancies to term and a reduction of the rates of abortions and preterm delivery [4].

It should be noted that the reference range of TSH changes with the variation of the gestational age. In the first trimester of pregnancy the thyroid homeostasis occurs in presence of a TSH value comprised between 0.1 to 2.5 mU/L; in the second quarter it is considered physiological a TSH value between 0.2-3 mU/L, while in the third quarter the reference range of TSH corresponds to 0.3-3 mU/L. [5]. There are even those who, like David Glinoer [6], recommends to arrive at the pregnancy with a TSH <1.5 mU/L to prevent that the increase in requests for thyroid hormones, typical of this period, may induce a condition of hypothyroidism.

The 2012 guidelines of the Endocrine Society [7] recommend to treat subclinical hypothyroidism regardless of the cause in order to improve the pregnancy outcome. Even euthyroid pregnant women positive for TPOAb show an increased risk of miscarriage and premature birth. The LT4 replacement therapy appears to reduce this risk, both in spontaneous pregnancies and in medically assisted procreation (• **Figures 1 and 2**).

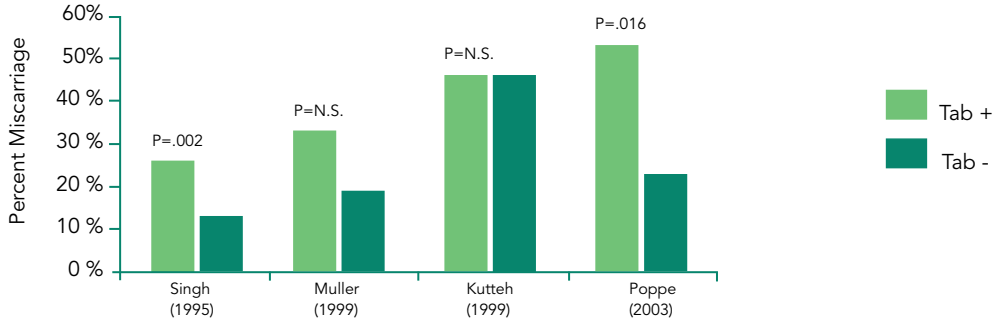
It is obvious that there is an association between the presence of thyroid auto-antibodies, alterations of thyroid homeostasis and recurrent fetal loss. However, antibody

• **Figure 1.** Thyroid autoimmunity and risk of miscarriage



Source: Stagnaro-Green, Glinoer, 2004 [8].

• **Figure 2.** Artificial insemination: Thyroid autoimmunity and the risk of miscarriage



Source: Stagnaro-Green, Glinoer, 2004 [8].

• **Table 2.** Patients to be screened for gestational hypothyroidism according to ATA 2011 guidelines

• Previous thyroid disease
• Age older than 30 years
• Symptoms of hypo/hyperthyroidism
• AbTPO +
• Type 1 diabetes or other autoimmune diseases
• History of recurrent fetal loss or preterm deliveries
• Previous irradiation of the neck
• Family history of thyroid disease
• Severe obesity (BMI> 40)
• Infertility
• Coming from areas with iodine deficiency
• Recent use of amiodarone, lithium or iodinated contrast media

Source: Stagnaro-Green *et al.*, 2011 [9].

screening is not recommended for all women who begin a pregnancy, but only in the presence of certain risk factors (• **Table 2**). Taking into consideration that today, most of the women who are about to begin a pregnancy have more than 30 years and that in Italy many areas are still deficient in iodine, the thyroid screening, while it is not universal, involves almost all women of childbearing age.

Because of the probability of development of gestational hypothyroidism in persons with signs of autoimmunity, there is need of a close follow-up throughout the pregnancy. The guidelines do not recommend, however, thyroxin treatment in euthyroid pregnant women with antibody positivity.

The occurrence of maternal hypothyroidism, subclinical or clinical, must be immediately correct. Although it is known that there is an inverse correlation between the levels of maternal thyroxin in the early weeks of gestation and alterations of neuropsychological development of the unborn child, the guidelines do not indicate treatment of isolated hypothyroxinemia because of the paucity of data available in the literature.

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Postpartum thyroiditis

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The thyroid dysfunction of postpartum are mainly due to Postpartum thyroiditis (PPT) [1], and only in a minority of cases to one of these conditions: subacute thyroiditis, Graves-Basedow's disease (whether an onset or a relapse), iatrogenic hyperthyroidism due to failure to reduce the gravidic dose of levothyroxine, and more rarely, to lymphocytic hypophysitis and pituitary necrosis (Sheehan's syndrome). According to a classic Canadian work of nearly 1,400 women, 6% developed thyroid dysfunction within 12 months after delivery [2]. The postpartum thyroiditis was about 30 times more frequent than Graves' disease (95.8% versus 3.6%).

The average prevalence of PPT in the world is 8,1%, according to a review of the literature done in 2006 [3], but more than 5% according to a recent review of 2012 [4], with wide geographical variation. The • Table 1 shows the data of the PPT prevalence in presence of certain risk factors. Indeed, the best serum marker of the risk for post-

• Table 1. Data on the prevalence of PPT (risk factors)

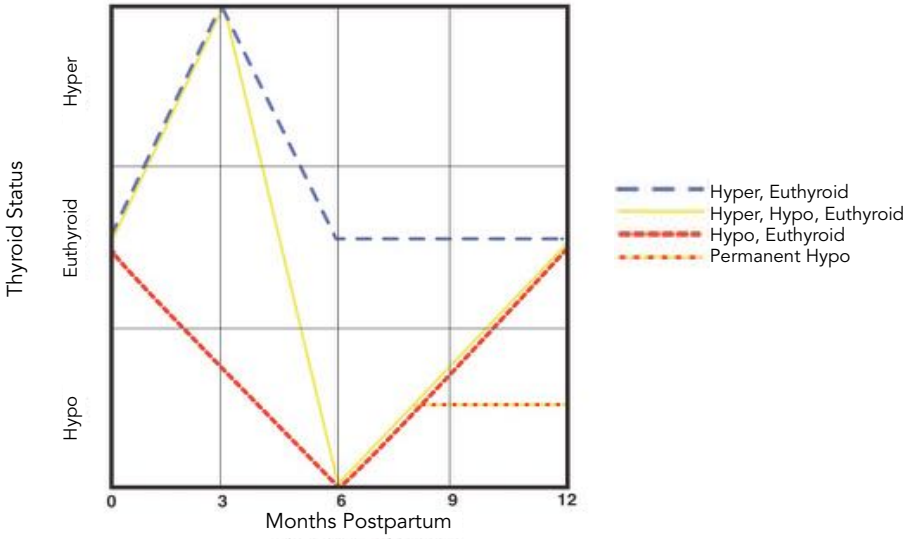
Parameter	Frequency (%)
General population	about 5
Women with diabetes mellitus type 1	10-25
Women TPOAb + (first trimester of pregnancy)	33-52
Women TPOAb neg. (first trimester of pregnancy)	0-5
Recurrent PPT after 2nd pregnancy	70
After second pregnancy in women who were TPOAb + / PTT neg. after first pregnancy	25
Women with non-organ-specific autoimmunity	↑ Undefined
Women after an abortion	↑ Undefined
Women smokers	↑ Undefined

partum thyroiditis is positivity for autoantibodies antithyreoperoxidase (TPOAb), since about half of the women with such positivity during pregnancy or delivery then develop postpartum thyroiditis within the following 12 months.

Among the extra thyroidal autoimmune disorders, type 1 diabetes mellitus is considered what confers the greatest risk (10-25%); however, in the same interval there are women suffering from viral hepatitis C (25%) [5], or from systemic lupus erythematosus (14%) [6].

Postpartum thyroiditis is a silent inflammation of the thyroid gland, an autoimmune pathogenesis, which occurs during the first year after childbirth, in women who had thyroid functional alterations before and during pregnancy. The onset may occur as biphasic, i.e. hyperthyroidism followed hypothyroidism (21%) or monophasic, i.e., only in the form of hyperthyroidism (34%) or hypothyroidism (45%). Classically thyroiditis, both biphasic and monophasic, is transient, with a return to euthyroidism usually within 12 month from delivery (• **Figure 1**) [7]. The episode of thyrotoxicosis should always come to spontaneous resolution; on the contrary, the phase of hypothyroidism may be transient (and therefore be followed by return to euthyroidism), or be permanent (• **Table 2**).

• **Figure 1.** Variability of functional presentation of PPT. The classic form is transient hyperthyroidism followed by transient hypothyroidism with consequent return to euthyroidism within the 12th month postpartum (yellow line)



Source: Stagnaro-Green, 2002 [7].

• **Table 2.** Evolution of the PPT in permanent hypothyroidism

Authors	Average duration (in years) from follow-up	Prevalence of permanent hypothyroidism
Lucas, 2000	3,4	11%
Nikolai, 1987	3	12%
Othman, 1990	3,5	23%
Tachi, 1988	8,7	29%
Jansson, 1988	5	30%
Premawardhana, 2000	6,7	46%
Barca, 2000	2	61%
Stagnaro-Green, 2011	1	54%

From the clinical point of view, the symptoms are typical of thyroid dysfunction of the other periods of life, although minor, so as to pass clinically undetected because the symptoms are attributed to the stress associated to the status of new mothers. The clinical picture consists of: palpitations, intolerance to the heat, sweating, nervousness, irritability, tremors, weight loss in hyperthyroid woman; fatigue, difficulty in concentrating, and depression in hypothyroid women.

According to the guidelines of the American Thyroid Association (ATA) 2011 [8], during the thyrotoxicosis phase of PPT, symptomatic women can be treated with propranolol at the lowest dose that is effective in relieving symptoms. After the resolution of thyrotoxicosis, TSH should be measured every 2 months during the first year post-partum to assess the evolution of thyroid function and identify patients who tend toward hypothyroidism [8].

Hypothyroid women with PPT and with the intention of becoming pregnant should be treated with LT4 (Recommendation 68) [8]. If the treatment with LT4 was undertaken to treat the PPT, it would be advisable to try to perform a gradual reduction of therapy over time. This can be done 6-12 months after the start of the treatment. The reduction of LT4 should be avoided if the woman is planning a subsequent pregnancy, when breastfeeding or if already pregnant (Recommendation 69) [8].

Women with a previous history of PPT should perform annually a TSH test to evaluate the permanent hypothyroidism (Recommendation 70) [8].

According to the guidelines of Endocrine Society, 2012, data on the usefulness of recommending the screening for postpartum thyroiditis in all women are insufficient.

In presence of serum positivity for TPOAb we should dose the TSH in first trimester of pregnancy and at 6 months postpartum. The same indications are recommended for women with type 1 diabetes mellitus, Graves' disease in remission or with chronic viral hepatitis, due to the increased prevalence of postpartum thyroid-

itis in these cases. Women who had a postpartum thyroiditis have a very high risk of becoming hypothyroid in the next 5-10 years, reason why they should be monitored annually [9].

An asymptomatic postpartum thyroiditis and with TSH <10 mU/L in a woman who is not planning a subsequent pregnancy should not be treated with LT4; However, the patient should be monitored every 4-8 weeks in order to start the treatment if the TSH elevation proves stable. Instead, symptomatic patients with transient hypothyroidism or plans to become pregnant should initiate thyroxin therapy [9].

Finally, since hypothyroidism is a potential cause of depression, patients with postpartum depression should be screened for hypothyroidism and, if necessary, appropriately treated [9].

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SESSION 3

REPLACEMENT THERAPY WITH THYROID HORMONE IN THE ADULT

Thyroxin metabolism in the adult

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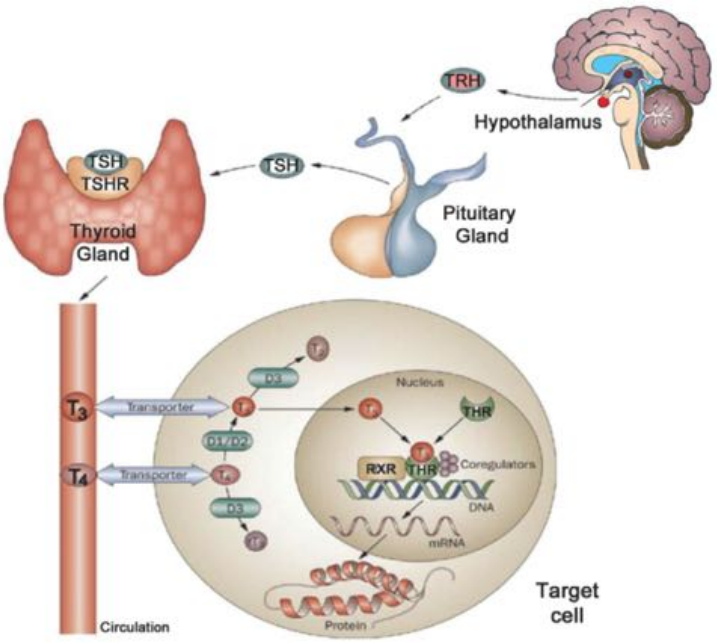
Sodium levothyroxine (LT4) is one of the ten most active principles more prescribed in the world and the drug of choice for hormonal therapy based on thyroid hormone. Absorbed in the intestine, the LT4 is metabolised to triiodothyronin (T3), the biologically active form (• **Figure 1**). This reaction of activation is catalysed by deiodinase, selenoenzymes that remove molecules of iodine from thyroxine (T4) and its derivatives to activate or inactivate these hormones. The dehalogenation reaction, ie removal of an iodine atom from the outer ring, transforms T4 in T3, hormone more metabolically active because it is able to bind with greater affinity the nuclear receptor. T4 can also be inactivated by the removal of one atom of iodine from the inner structure of the hormone producing a molecule metabolically inactive reverse T3 (rT3) (• **Figure 2**). The fate of a T4 molecule then depends on which enzyme encounters in its path: the deiodinase type 1 and type 2 (D1, D2) ensure the production of about 80% of the circulating T3, while the deiodinase type 3 (D3) inactivates the thyroxine.

The cell is therefore able to modulate the action of thyroid hormones through the deiodinase. The tissue and peripheral metabolism of T4 occurs in tissue-specific manner and affects the daily production of T3.

After being released into circulation, thyroid hormones must pass a series of checkpoint to act in various tissues: the iodothyronines circulate in the blood bound to transport proteins, they need to interact with membrane channels to penetrate in the cells and, after reaching the interior of the cell, they become the target of seleno-deiodinase, from which they can be activated or deactivated. Finally, the proportion of hormone biologically active can enter the nucleus and modulate the transcriptional activity of the nuclear receptor. Alteration of any of these metabolic steps can modify the intracellular thyroid hormone balance.

However, there is a very powerful homeostatic system, regulated by the hypothala-

• **Figure 1.** Mechanism of action of thyroid hormones



Source: Dayan, Panicker, 2009 [1], adapted.

mus-pituitary-thyroid, which, in normal conditions, allows to keep constant the plasma concentrations of T3 and T4.

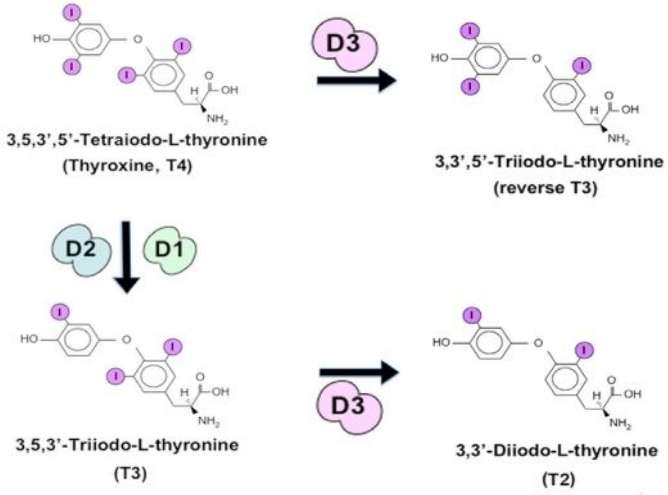
The response of the cell to the levels of T4 depends on the intracellular metabolism. Cells who do not possess the deiodinase use only the T3 from the plasma then the plasma triiodothyronine is responsible for the entire amount of T3 present in the nucleus of these cells. Instead, in privileged tissues, such as the central nervous system, with a rich deiodinase activity, the plasma T3 contributes only in small part to the amount of intranuclear T3. Therefore, in cells with D2 the saturation of the T3 receptor is very high, whereas in cells with D3 the saturation of T3 receptor is very low.

The deiodinase, therefore, are a powerful tool to change the thyroid status of a single cell without disrupting the plasma concentration of the hormone.

A very clear example of the power of deiodinase is in the brown adipose tissue where the adrenergic stimulation causes an induction of D2 and an increase of the intracellular concentration of T3, responsible for the thermogenesis. Experiments on murine models have shown that mice lacking D2 are not able to react to heat stress and die of hypothermia.

In muscle tissue, however, the local conversion of T4 in T3 is critical to maintain the muscle homeostasis. Mice lacking D2 fail to repair the muscle fibrocells. D3 also

• **Figure 2.** Peripheric metabolism of T4



Source: Bianco *et al.*, 2002 [2].

plays a role: in the placenta protects the foetus from maternal hyperthyroidism inactivating T3, while in the skin the D3, expressed by keratinocytes, and in the dermis preserving the euthyroidism as, for example, in women who use cosmetics based on thyroid hormones. In the absence of diodinase, the ability to repair the wounds is delayed and altered.

The deiodinase have a fundamental role in the regulation of peripheral effects of thyroid hormones. In euthyroidism the contribution of deiodinase D1 and D2 is equivalent, while in hyperthyroid subjects prevails the enzymatic action of D1, the main target of propylthiouracil.

It is important not to confuse the homeostasis of plasma T3 with the homeostasis of the tissue T3. The finding of normal circulating levels of triiodothyronine does not mean that all tissues have the proportion of T3 they need. Experiments conducted on D2-depleted mice have shown that, even in presence of normal levels of plasma T3, the central nervous system is in hypothyroidism.

In all those conditions in which the 5'-deiodinase activity is lacking, for example for a genetic alteration or polymorphisms, we will have normal levels of plasma T3, but some tissues will be hypothyroid because the inefficiency of deiodinase could not be able to normalize the amount of tissue T3, despite the presence of a good plasma homeostasis.

Finally, note that many functional alterations of the thyroid status that occur in case of neoplastic diseases may be due to the expression of paraneoplastic deiodinase. It has been documented an increased expression of D3 in some liver hemangiomas,

childhood cancers that usually tend to be resolved in the first 2 years of age. These tumors over-express the D3 causing a severe form of hypothyroidism from consumption since the D3 degrades all the hormone present in the circulation. In contrast, over-expression of D2 is responsible of thyrotoxicosis for excessive production of T3 in some neoplasms of thyroid origin.

In summary, we can say that the deiodinase represent a powerful homeostatic system able to guarantee the plasma and tissue balance of thyroid hormones. The tissue-specific metabolism of iodothyronines is critical to ensure to the single cell the availability of thyroid hormones appropriate to its functional condition and represents a new interpretation of the mechanism of action of thyroid hormones.

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Cardiovascular risk in subclinical hypothyroidism

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Alterations in thyroid function may have an impact on many organs and tissues, including the cardiovascular system [1].

The clinical significance of the subclinical thyroid dysfunction is much debated and the management and treatment of subclinical hypothyroidism is controversial [2-4].

For many years, the evidence on the cardiac effects of subclinical hypothyroidism were insufficient, as well as the benefits of thyroxine treatment. Numerous studies have been published in recent years to shed light on the need for treatment of subclinical hypothyroidism.

The clinical significance of subclinical hypothyroidism can be found at cardiovascular level [4-9]. In the cardiac muscle the T_3 has effects on the cardiovascular function. T_3 regulates many functions, including the activity of the calcium-ATPase of the sarcoplasmic reticulum, the activity of the Na+/K+-ATPase and the activity of the voltage channels of potassium [5,6]. The increase in the reuptake of calcium from the sarcoplasmic reticulum is translated into an improvement of the diastolic function of the heart, an increase of the availability of calcium ions and an improvement of the systolic function [10].

In hypothyroid subject, even subclinical deficiency of tissue T_3 determines an alteration of the reuptake of calcium and thus an altered diastolic filling [6,10]. The interesting thing, though, is that in the hypothyroid patient, the diastolic dysfunction is reversible through treatment with levothyroxine [10].

Another important effect of thyroid hormone is on the peripheral vascular resistance (total peripheral resistance-TPR) [6]. Hypothyroidism is associated with an increase in TPR and a reduced availability of nitric oxide [11]. The increase in TPR can be improved from thyroxine therapy [10].

The diastolic dysfunction and impaired vasodilation leads to a stress systolic dysfunction that is reversible with correction of the hormonal dysfunction [5].

Hypothyroidism also affects the plasma levels of cholesterol [7]. Levels of TSH> 10 mU/L are most frequently associated with hypercholesterolemia, especially if the patient is a smoker and has insulin resistance [2,4,7].

An increased risk of heart failure has been reported in the presence of values of TSH>10 mU/L [2].

An endothelial dysfunction was assessed at the level of the coronary circulation in a group of middle-aged and young patients with a persistent subclinical hypothyroidism not yet associated with cardiovascular risk factors [11]. The results showed the presence of impaired coronary flow reserve, indicating a predisposition to coronary events [11]. It has been reported an increased mortality for coronary events in patients with TSH> 10 mU/L [2].

Therefore, there is now evidence for the treatment of subclinical hypothyroidism in presence of a TSH>10 mU/L, mainly in order to reduce the cardiovascular risk.

In patients with TSH between 4.5 and 10 mU/L, although some studies have shown an improvement of the cardiovascular parameters, the literature data are still scarce to draw conclusions [2,4].

It would therefore be desirable a personalized treatment in subclinical mild hypothyroidism (TSH from 4.5 to 10 mU/L). The therapy should be considered especially in young people if there are cardiovascular risk factors, while it is useful monitoring asymptomatic patients with no risk factors [2,4].

Subclinical hypothyroidism is a risk factor for coronary mortality in the young, but not in the very old. The risk of coronary heart disease is present especially among young people and tends to flatten at around 60 years. The increase in TSH in people aged> 85 years seems to be associated with reduced cardiovascular mortality. In the elderly, therefore, the treatment of subclinical hypothyroidism is controversial [2].

In conclusion, subclinical hypothyroidism (TSH>10 mU/L) is associated with a high risk of coronary heart disease and heart failure. Randomized clinical trials are needed to evaluate the effects of L-thyroxine on cardiovascular end points [12].

The best therapeutic approach for this disease remains, therefore, individualized therapy [2].

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Evaluation of replacement therapy of hypothyroidism with T4 alone or in association T4/T3

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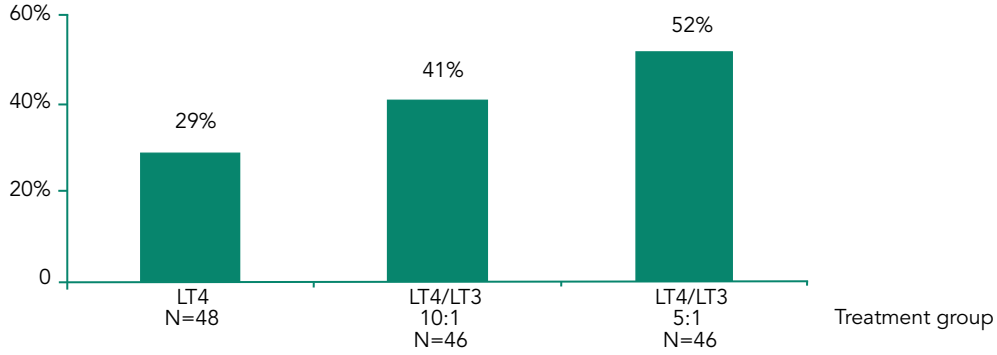
Replacement therapy with thyroxine is traditionally the treatment of choice in hypothyroid patients. In most cases it is fully effective and, thanks to dosage of TSH and peripheral hormones, its monitoring is simple and precise.

However, in a minority of treated patients, quality of life does not seem satisfactory, even when hormone levels indicate a good compensation of hypothyroidism. In the main cases, the percentage of patients receiving replacement therapy with single thyroxine which presents subjective complaints is 5-10%. This figure is clearly in excess than the prevalence of feeling of unsatisfactory well-being detected in the not thyreopatic adult population. Some of these cases can be traced to comorbidity or psychological factors, such as the knowledge that they had undergone a thyroidectomy, of having to perform a chronic therapy for life or the necessity of having to make periodic checks over time. However, sometimes it seems doubtful whether monotherapy with levothyroxine is adequate and is able to mimic in all subjects the physiological trend of the production of thyroid hormones, or if the absence of the administration of triiodothyronine may have an unfavourable role in at least a part of hypothyroid.

According to some studies, the non-administration of T3 is a real problem for these patients, because it correlates to an actual diminution of quality of life. The study of Bunevicius *et al*. [1] seems to demonstrate that the quality of life is most frequently altered in patients on monotherapy replacement compared to those in T4/T3 combination therapy. The study, however, is characterized by significant bias that do not allow considering the results as final. In a randomized clinical trial in double-blind, [2], part of the therapy with T4 has been replaced with a dose of T3 so as to obtain a ratio of 5:1 and T4/T3, respectively, of 10:1. The results were then compared with monotherapy with LT4. Although there was not a significant

• **Figure 1.** Replacement therapy of hypothyroidism with T4 alone vs. T4/T3 combination. Distribution of preferences for the type of therapy by patients at the end of the study



Source: Appelhof *et al.*, 2005 [2].

modification of the main physiological variables, most of the patients reported a preference for the combination therapy (• **Figure 1**).

In literature there are several randomized clinical trials designed to investigate this aspect of the substitution therapy, but they are very heterogeneous for the modalities of recruitment, duration, study design, aetiology and severity of hypothyroidism, doses given and T4/T3 ratio and the diversity of the questionnaires used to assess the quality of life. Most of these data seems to support that the LT4 monotherapy is adequate for a complete replacement of hypothyroidism (• **Figures 2a and 2b**) and that there are no significant clinical differences compared to the treatment with combined T4/T3.

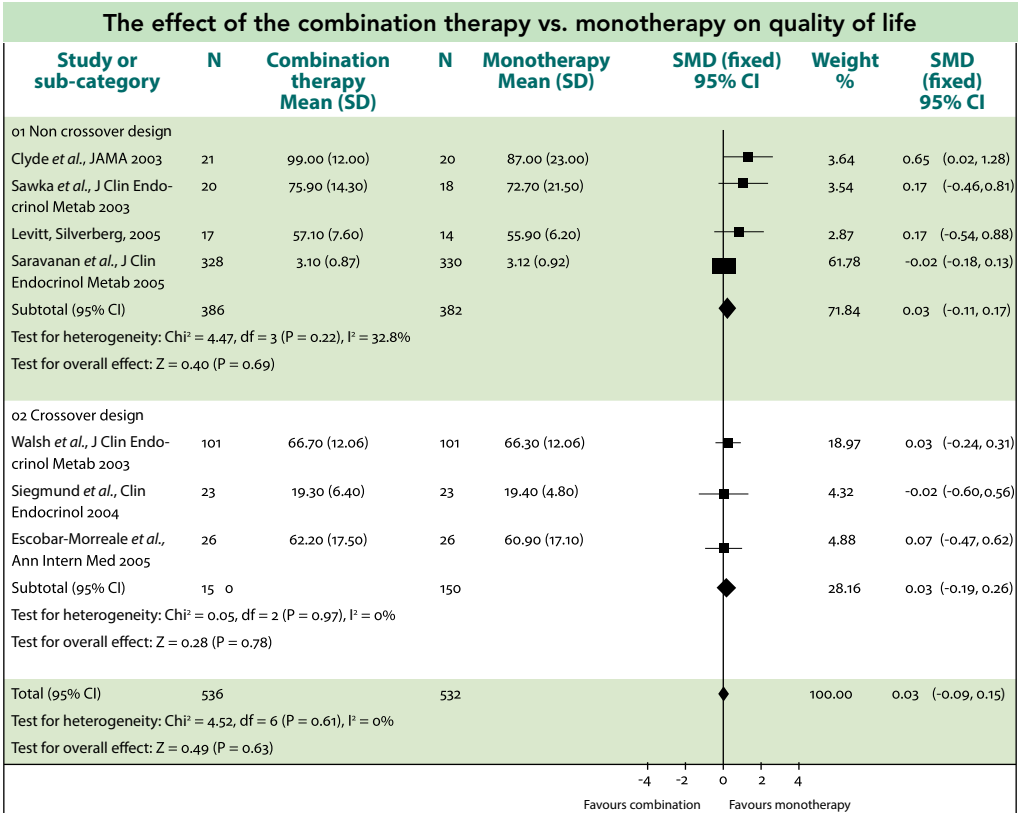
In 2006, the publication of a meta-analysis [3] has marked, for a certain period of Time, the tombstone of the association T4/T3 since all parameters examined were found to be not significant in terms of advantages with the addition of T3 to the therapy (• **Figure 3**). The authors concluded with an opinion of full negativity respect to the combination therapy and confirmed monotherapy as a standard treatment of hypothyroidism.

In experimental models, however, it has been shown that the plasma and tissue concentrations of thyroid hormones may be different due to the variable peripheral action of deiodinase. Fundamental, in this regard, is the work of Escobar-Morreale *et al.* [4] on thyroidectomized rats that showed the marked heterogeneity of T3 levels in different tissues by administering replacement therapy with LT4 alone.

A confirmation of these experimental data in humans comes from an elegant randomized study with cross-over conducted by Celi *et al.* of 14 patients [5] in order to assess the metabolic effects induced by the therapy. The treatment with LT4 was replaced from that with T3, administered 3 times a day to reproduce the physiological rhythm.

After maintaining similar levels of TSH in patients subjected to two different ther-

• **Figure 2a.** Replacement therapy of hypothyroidism with T4 alone vs combination T4/T3. Meta-analysis of published randomized controlled trials: effects of the two treatment modalities on quality of life and mood tone



Source: Grozinsky-Glasberg *et al.*, 2006 [3].

apies was assessed the quality of life with validated questionnaires and were analyzed the main metabolic variables. Although the quality of life was not found significantly modified in the two groups, it was found that treatment with T3 induces an improvement in the levels of total and LDL cholesterol, an increase in plasma SHBG (index of euthyroidism in the liver) and, especially, a significant reduction of body weight, even in the short time period of the study (• **Figure 4**). The results of this study confirm that the mode of administration of T3 and the T4/T3 ratio adopted in most of the previous studies do not mimic adequately the characteristics of the physiological thyroid secretion, since a single daily intake of T3 causes a high peak but short of the concentration of plasma T3 and inserts it late compared to healthy subjects.

To achieve the thyroid homeostasis at the tissue level contribute variables only

• **Figure 2b.** Replacement therapy of hypothyroidism with T4 alone vs combination T4/T3. Meta-analysis of published randomized controlled trials: effects of the two treatment modalities on quality of life and mood tone

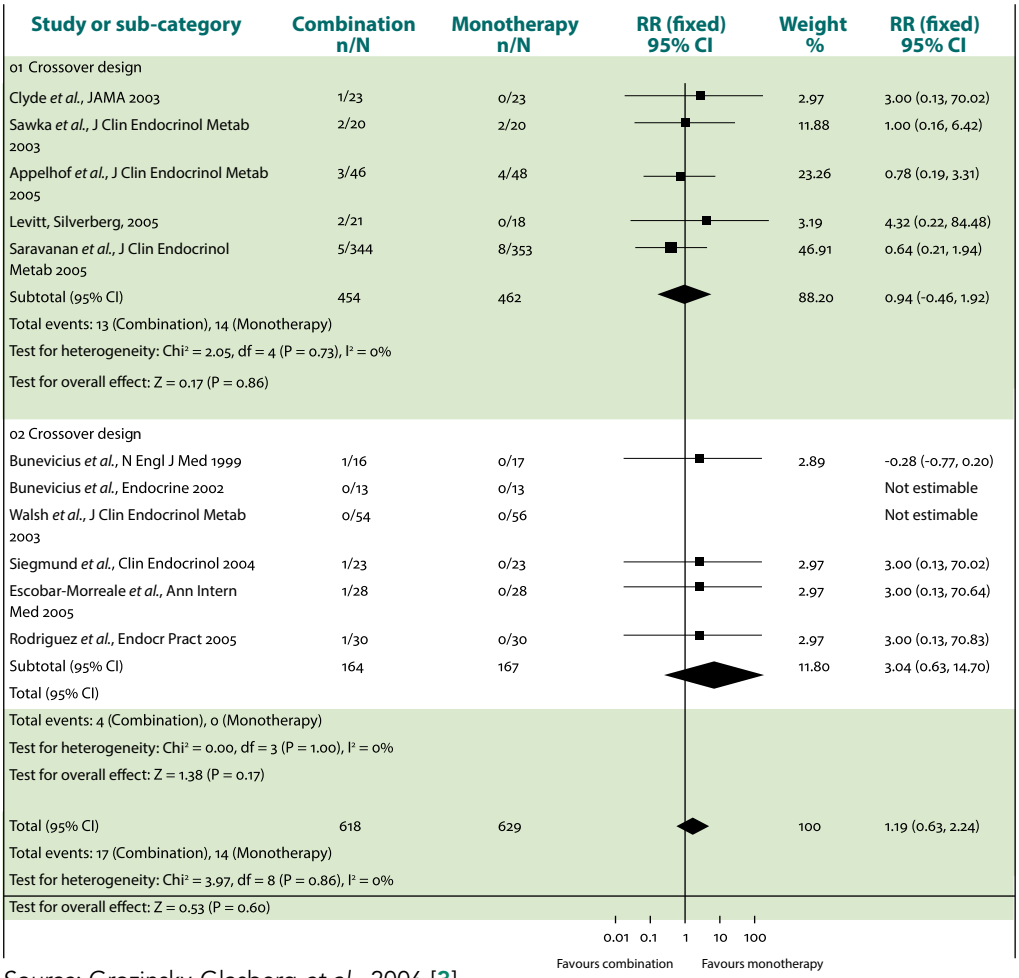
The effect of monotherapy and combination therapy on depression

Study or sub-category	N	Combination therapy Mean (SD)	N	Monotherapy Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Quality
01 Non crossover design								
Appelhof *et al.*, J Clin Endocrinol Metab 2005	45	24.00 (9.10)	45	25.20 (10.00)		10.31	-0.12 (-0.54, 0.29)	A
Clyde *et al.*, JAMA 2003	17	4.65 (5.61)	17	3.82 (4.10)		7.32	0.16 (-0.51, 0.84)	A
Sawka *et al.*, J Clin Endocrinol Metab 2003	20	0.69 (0.64)	19	0.56 (0.58)		7.77	0.21 (-0.42, 0.84)	A
Levitt, Silverberg, 2005	17	5.40 (3.10)	14	5.20 (2.70)		6.98	0.07 (-0.64, 0.77)	D
Saravanan *et al.*, J Clin Endocrinol Metab 2005	324	4.26 (2.41)	328	4.54 (2.39)		13.10	-0.12 (-0.27, 0.04)	D
Subtotal (95% CI)	423		423			45.49	0.08(-0.22, 0.05)	
Test for heterogeneity: $Chi^2 = 1.73$, df = 4 (P = 0.78), $I^2 = 0\%$								
Test for overall effect: Z = 1.23 (P = 0.22)								
02 Crossover design								
Bunevicius *et al.*, N Engl J Med 1999	33	7.90 (5.30)	33	9.80 (7.70)		9.43	-0.28 (-0.77, 0.20)	
Bunevicius *et al.*, Endocrine 2002	10	3.30 (3.50)	10	5.20 (5.10)		5.45	-0.42 (-1.30, 0.47)	
Escobar-Morreale *et al.*, Ann Intern Med 2005	26	23.90 (29.40)	26	23.80 (28.80)		8.74	0.00(-0.54, 0.55)	
Walsh *et al.*, J Clin Endocrinol Metab 2003	101	37.60 (1.70)	101	36.10 (1.70)		11.80	0.88(0.59, 1.17)	
Siegmund *et al.*, Clin Endocrinol 2004	23	5.50 (5.70)	23	6.90 (6.70)		8.32	-0.22 (-0.80, 0.36)	
Rodriguez *et al.*, Endocr Pract 2005	301	10.40 (7.50)	30	8.40 (7.60)		10.77	0.27 (-0.11, 0.64)	
Subtotal (95% CI)	494		223			54.51	0.09(-0.37, 0.55)	
Test for heterogeneity: $Chi^2 = 27.69$, df = 5 (P = 0.0001), $I^2 = 81.9\%$								
Test for overall effect: Z = 0.39 (P = 0.70)								
Total (95% CI)	917		646			100.00	0.07 (-0.20, 0.34)	
Test for heterogeneity: $Chi^2 = 42.11$, df = 10 (P < 0.00001), $I^2 = 76.3\%$								
Test for overall effect: Z = 0.51 (P = 0.61)								

Source: Grozinsky-Glasberg *et al.*, 2006 [3].

partially known, varying from species to species, and from individual to individual, and that we are not able to modulate. Among them, the mode of transport of hormones in the plasma and from this in the cells and the peripheral conversion of T4 to T3. We know that there are genetic polymorphisms for these mechanisms, which may alter in a poorly predictable manner the hormonal tissue-specific availability and the response to therapy in different subjects [6].

• **Figure 3.** Replacement therapy of hypothyroidism with T4 alone vs. T4/T3 combination. Meta-analysis of published randomized controlled trials: adverse events recorded by the two therapeutic modalities

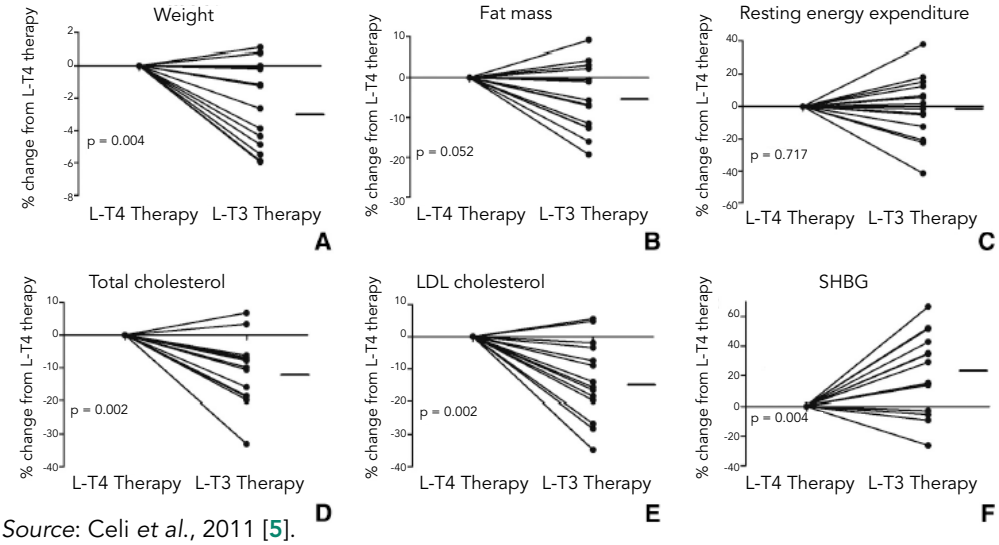


Source: Grozinsky-Glasberg *et al.*, 2006 [3].

In conclusion, the available evidence does not suggest that combined treatment in humans is used as the replacement therapy of choice. The animal models, however, showed a superiority of the combination therapy in ensuring hormonal homeostasis in the tissues, even if the animal metabolism not perfectly reflects the human one.

The LT4 monotherapy, therefore, remains the standard treatment for hypothyroidism. In a minority of patients who, despite the evidence of appropriate therapy compliance, have symptoms that disturb the quality of life or show an unjustified upward trend in weight, it is appropriate to test for a limited period of time the combined

• **Figure 4.** Metabolic effects of replacement therapy with T3 (in three divided daily doses) compared to substitution treatment with T4 alone



Source: Celi *et al.*, 2011 [5].

therapy. The combination therapy should be undertaken only after the exclusion of comorbidities (especially autoimmune), which may affect these disorders, and the presence of cardiovascular risk factors. The combined treatment should be started with small doses of T3 such as to enable a T4/T3 ratio of about 13:1, similar to that of the physiological secretion. No attempt should be performed in pregnant women, elderly patients, and in subjects with cardiovascular risk factors.

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Subclinical hypothyroidism: literature data

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The guidelines AACE/ATA (American Association of Clinical Endocrinologists/ American Thyroid Association) [1] recommend to treat subclinical hypothyroidism (TSH <10 mU/L) in symptomatic patients with thyroid antibody positivity or cardiovascular risk factors, evidence of atherosclerotic disease or heart failure. The data on quality of life, mortality and morbidity did not show significant differences between subclinical hypothyroid patients treated and untreated, for which, in these cases, personalized therapy remains the best strategy of conduct [2,3].

The iodothyronines regulate numerous functions in the body, reason why the alteration of their levels can determine the appearance of a wide range of clinical manifestations. Controversial is the role of thyroid hormones at psychoneurological level: type and severity of mood disorders correlated to subclinical hypothyroidism have not been fully delineated, although depressive symptoms seem to be more frequent in this condition [4]; it is also not well elucidated the possible correlation between cognitive disorders and subclinical hypofunction, as the opinion result of the recent meta-analysis of Joffe *et al.* [4] does not favour either of the two hypotheses, reporting a comparable number of studies supporting one or the other argument. To tip the balance towards a participation of thyroid hormones in causing deleterious effects at this level contributes the work of Aghili *et al.* [5], where the authors claim to have detected an improvement in cognitive function of patients with subclinical hypothyroidism compared to those treated with placebo (• **Table 1**). Negatives remain, however, the results reported by Wijsman *et al.* [6], in which the follow-up of a large sample of elderly subjects with subclinical hypothyroidism did not show associations with reduced cognitive performance.

Extremely important is the role that is increasingly emerging for thyroid hormones with respect to the renal function: in chronic renal failure an untreated subclinical

• **Table 1.** Baseline and final scores for the intervention and control groups divided for subtest of the Wechsler Memory Scale

WMS Subtests	Intervention group			Control group		
	Baseline score*	Final score*	Value of *p*	Baseline score*	Final score*	Value of *p*
Information	5.88 ±0.34	5.78 ±0.49	0.26	5.7 ±0.54	5.7 ±0.54	1.00
Orientation	4.53 ±0.67	4.66 ±0.6	0.25	4.4 ±0.7	4.3 ±0.73	0.62
Mental control	8.03 ±0.99	7.35 ±1.33	0.002	6.4 ±0.97	7.04 ±1.2	0.024
Logical memory	10.83 ±2.94	12.31 ±2.32	< 0.001	9.5 ±1.9	10.2 ±2.6	0.14
Digits forward and backward	8.9 ±1.44	8.48 ±1.6	0.11	8.18 ±1.7	8.18 ±1.5	1.00
Associate learning	7.1 ±2.47	12.9 ±1.53	0.014	16.8 ±2.1	16.7 ±2.5	0.76
Visual reproduction	12.9 ±1.53	12.37 ±1.62	0.13	13.3 ±1.3	12.03 ±1.6	0.003
Age-corrected score	105 ±2.8	115 ±2.6	0.002	101.27 ±6.9	100.6 ±6.6	0.4
Memory quotient	101.45 ±7.34	107.03 ±7.44	< 0.001	106.4 ±12.1	105.4 ±12.06	0.5

*Data are shown as mean ± SD.

Source: Aghili *et al.*, 2012 [5].

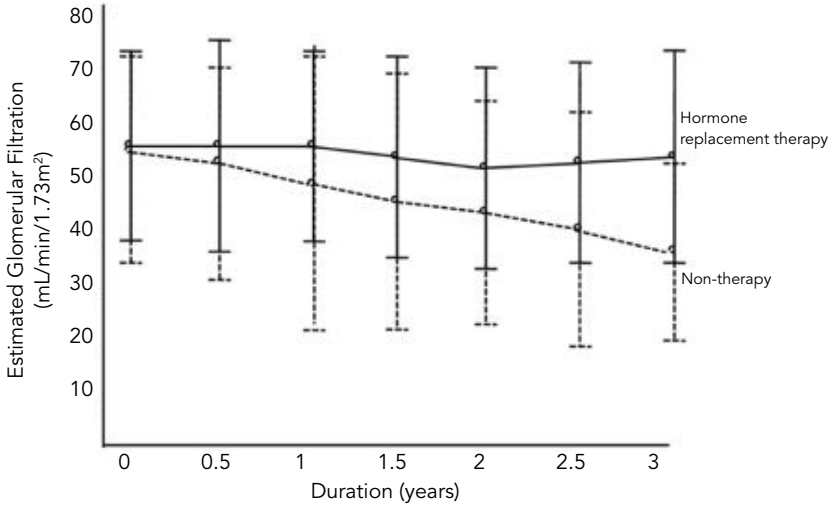
hypothyroidism may favour the evolution of the renal disease. In recent studies it has been shown that the glomerular filtration of subclinical hypothyroid subjects with impaired renal function is preserved by the replacement therapy with levothyroxine [7, 8], laying the foundations for the correction of thyroid dysfunction in these patients (• **Figure 1**, • **Table 2**). It has also been highlighted by Ng *et al*. the need of an increase of the dose of erythropoietin in diabetic patients on haemodialysis and with associated hypothyroidism both clinical and subclinical, if it is not correct [9].

Also interesting is the role of subclinical hypothyroidism and its interactions with martial therapy required by iron deficiency anemia: in an innovative study from Ravanbod *et al*. and published in *The American Journal of Medicine* in 2013 [10], in fact, the treatment of any concomitant subclinical hypothyroidism, in addition to iron integration, is able to greatly improve the outcome.

Currently there are no unambiguous and conclusive data on the relationship between thyroid dysfunction and disorders of male sexual function. Some scientific papers show a higher prevalence of hypoactive sexual desire, delayed ejaculation and erectile dysfunction in the presence of hypothyroidism [11,12] (• **Figures 2 and 3**); others, however, do not show significant changes compared to the control group neither for the clinical nor for the subclinical hypothyroidism [9] (• **Figure 4**).

The thyroid hypofunction, however, seems to have repercussions on the reproductive hormonal status: it has been related to the reduction of testosterone, SHBG, estrogens, LH, and FSH, to alteration of sperm morphology, to an increase of erectile

• **Figure 1.** Variation of the values of the estimated glomerular filtration rate in patients with chronic renal failure and subclinical hypothyroidism: continuous line for the treated group and dotted line for the untreated group



Source: Shin, 2012 [7].

• **Table 2.** Comparison of changes in glomerular filtration rate among patients treated with replacement therapy and not

	Treated patients[a]	Nontreated patients[b]	*P* value
n	180	129	
eGFR (ml/min/1.73 m²)			
At baseline	57.8 ± 17.0	56.1 ± 19.0	0.43
At 6 months	57.8 ± 19.3	52.8 ± 19.6	0.21
At 12 months	57.6 ± 17.0	50.3 ± 25.4	0.04
At 18 months	56.5 ± 18.5	47.7 ± 23.1	<0.01
At 24 months	54.4 ± 18.8	45.8 ± 20.1	<0.01
At 30 months	55.8 ± 18.9	41.9 ± 21.5	<0.01
At 36 months	57.8 ± 19.3	38.9 ± 16.1	<0.01
The slope of decline in eGFR (ml/min/yr/1.73 m²)	-2.11 ± 1.12	-5.93 ± 1.65	0.04

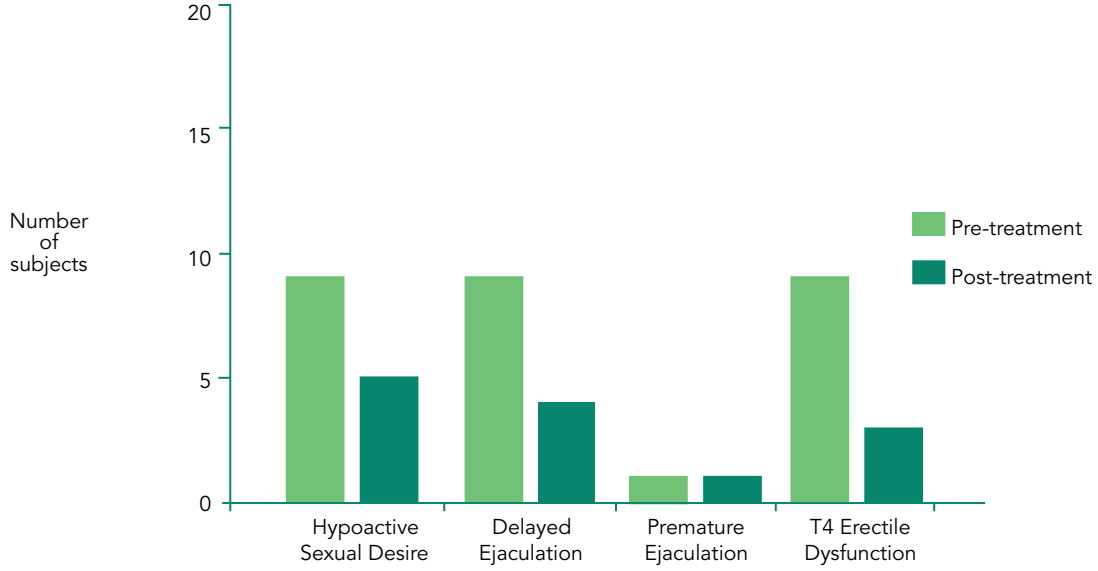
Values are expressed as mean ± SD; eGFR is calculated by the MDRD-4 equation.

[a] Patients who were treated with thyroid hormone for subclinical hypothyroidism.

[b] Patients who were not treated with thyroid hormone for subclinical hypothyroidism.

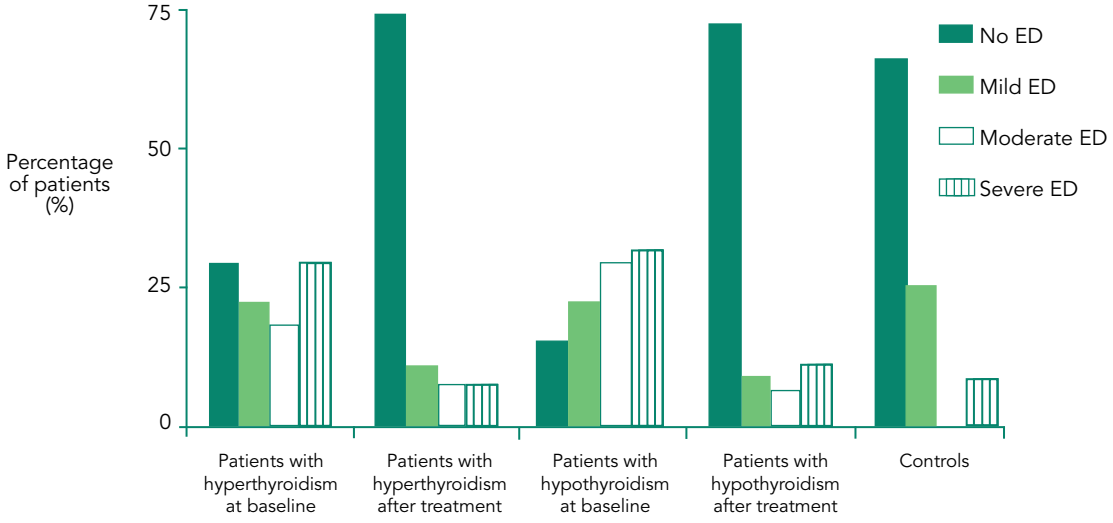
Source: Shin *et al.*, 2012 [7].

• **Figure 2.** Prevalence of sexual dysfunction before and after treatment of hypothyroidism



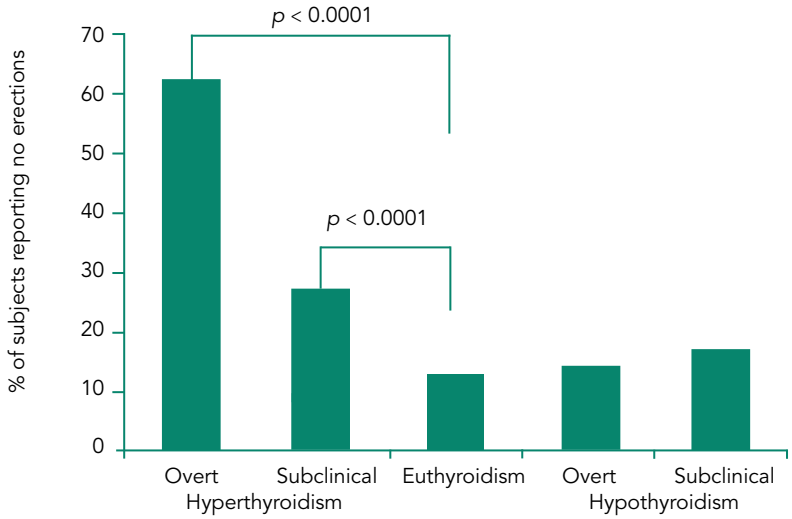
Source: Carani *et al.*, 2005 [11].

• **Figure 3.** Distribution of the subjects in each study depending on the degree of erectile dysfunction at baseline and after treatment of the thyroid dysfunction



Source: Krassas *et al.*, 2008 [12].

• **Figure 4.** Percentage of subjects referring no erection divided by thyroid disease



Source: Corona *et al.*, 2012 [13].

dysfunction and delayed ejaculation. Furthermore, a higher prevalence of peroxidase antibodies was found in infertile men with impaired motility and sperm morphology.

The assessment of thyroid function should therefore be investigated in patients with fertility problems, or erectile dysfunction.

The subclinical hypothyroidism, unlike the clinical, has a limited negative influence on the female sexual function. A significant percentage of women with hypothyroidism, both clinical and subclinical, complains a reduction in sexual satisfaction assessed in studies using questionnaires [14,15].

Even the beneficial effects obtained by regular physical exercise may be influenced by subclinical deficiency of thyroid function: it is, in fact, able to reduce the positive effects achieved by regular physical activity, reducing the influence on insulin sensitivity [16]; Furthermore, the correction with replacement therapy is able to improve the submaximal cardiopulmonary performance of patients [17].

Finally, also at gastroenteric level the subclinical hypothyroidism is perhaps able to produce deleterious effects: it, in fact, emerged from the analysis of data reported by Laukkarinen *et al*. in *The Journal of Clinical Endocrinology & Metabolism* [18] a higher prevalence of subclinical hypothyroidism in patients with cholelithiasis. Of course, the data have to be confirmed with further investigations to evaluate if the hormone therapy may prevent the appearance of these lithiasic formations.

In view of the possible clinical implications, recently emerged from a subclinical

thyroid dysfunction, it must be increasingly delineating the real possibility of obtaining benefits from replacement therapy not only in patients with clinical evident disease, but also in those in which the classic symptoms of hypothyroidism are not manifest, and in which the negative consequences of a minor deficiency of thyroid hormone may be more subtle, but not for this not deleterious.

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Replacement therapy in adults: problems and solutions

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TSH is a peripheral marker through which we evaluate the adequacy of thyroxine therapy. Many things can interfere with thyroid homeostasis and require an adjustment of the dose.

Among the factors most involved emerge patients' poor compliance, timing of administration, diseases of the gastrointestinal system, assumption of concomitant medications.

In the presence of high levels of TSH in patients on therapy with LT4 it is important, first of all, to be sure that the patient is actually taking the medication and that understands the correct mode of assumption.

A normal gastric acidity allows the intestinal absorption of about 80% of levothyroxine sodium administered per os, with a plasma peak in the first hour followed then by a plateau. It has been shown that the reduction of gastric acidity is associated with an increase of the daily LT4 [1]. The levothyroxine must be administered on an empty stomach and away from drugs that reduce the acidity of the stomach or which can interact with it in the intestinal lumen.

Many substances interfere with the intestinal absorption of LT4, between which calcium [2], iron [3], soybean [4], the phosphate binders used in chronic kidney failure [5, 6] and cholestyramine [7].

It has been documented that in subjects taking radiolabelled thyroxin with cholestyramine, there is not peak of the urinary radioactivity, but it appears a late and exaggerated peak of marked thyroxine in the faeces [7].

Often these medications must be taken several times during the day, so it is important to help the patient find a suitable time window for the assumption of LT4 and corresponding to his lifestyle, in order to increase the patient compliance.

After making sure of the proper administration of the drug, if high levels of TSH

persist, it is necessary to investigate the possible presence of pathologies of the gastrointestinal tract which can interfere with the absorption of thyroid hormone.

An interesting study [8] demonstrated the increased needs of levothyroxine in patients diagnosed with celiac disease who had a free diet. The gluten-free diet, however, was able to restore the normal absorption in these patients (• **Figure 1**).

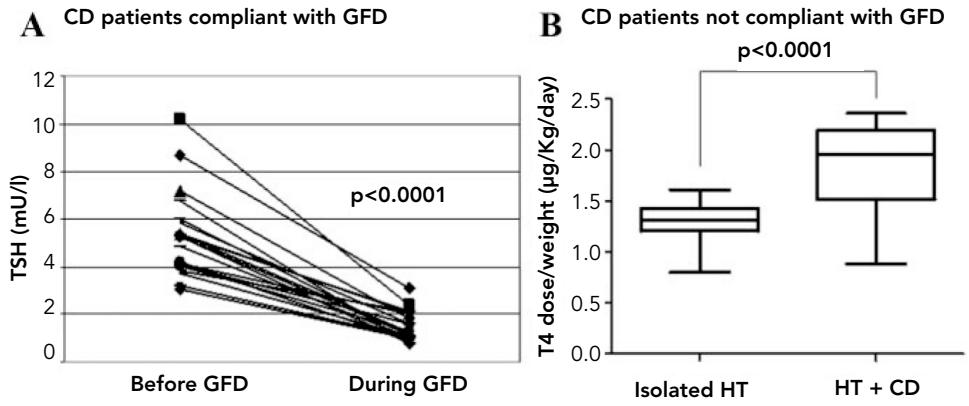
Contrary to what one might expect, bariatric surgery increases the absorption of LT4, causing a problem in some cases of overdose (• **Figure 2**). After excluding all these possible pharmacological and pathological causes of malabsorption, if we are unable to restore the hormonal balance of the thyroid we must use the absorption test of thyroxine. There are different protocols, some provide for the administration of 250μg of LT4, others provide for the administration of the highest dose that has proved inefficient in the patient under examination.

At this point, if the test shows that the levothyroxine is absorbed, it must again seriously consider a problem of compliance. A careful but serene medical history often allows us to clarify the presence of psychological problems interfering with proper adherence to the prescription. In the case problems of compliance are excluded, the only alternative that remains to be taken into consideration is the possibility that the patient consumes very quickly the thyroxine administered.

In addition to the deiodinase conversion, inactivated thyroid hormones may be further metabolized and eliminated via the bile by the hepatic cytochromes. Their activity is fairly stable over time, although there are some substances that can alter it. Drugs such as rifampicin, phenytoin, carbamazepine, phenobarbital and some antiretroviral drugs are enzyme inducers, capable of accelerating the metabolism of thyroid hormones.

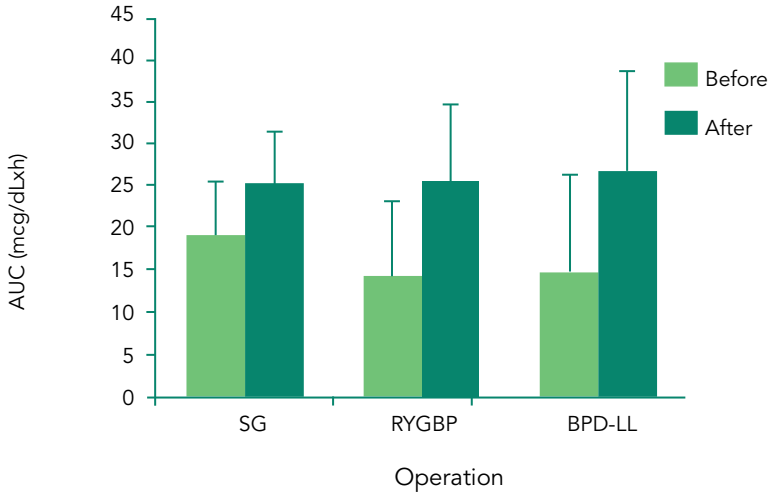
Rifampicin has been studied in 67 euthyroid patients [10] stratified on the basis of antibody positivity. In none of those with negative TPOAb there was an alteration of

• **Figure 1.** Celiac disease and absorption of thyroxin



Source: Virili *et al.*, 2012 [8].

• **Figure 2.** Bariatric Surgery and absorption of thyroxine



Source: Gktosina *et al.*, 2013 [9].

the thyroid function, indicating that probably, in the absence of thyroid disease, the hormonal system has great flexibility that the drug cannot disturb. Unlike the case of euthyroid patients with chronic thyroiditis: most of them remain euthyroid but some show an evolution towards hypothyroidism, probably due to a lower functional reserve (• **Figure 3**).

Other drugs with similar effects are tyrosine-kinase inhibitors, such as Imatinib, that are able to increase the TSH in some hypothyroid patients. The mechanism of action is still not entirely clear: it could be due to a hepatic effect but also to the alteration of the intestinal vascularization and then of the absorption of the drug.

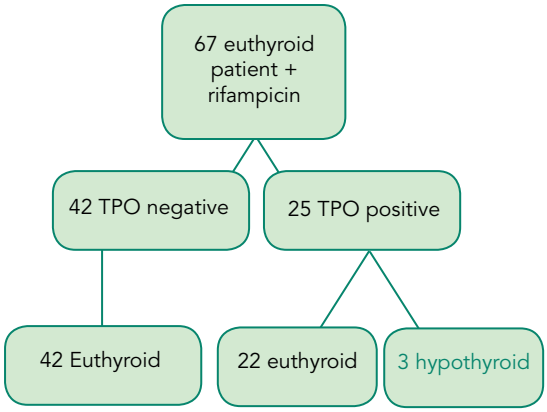
In last hypothesis, we must consider the consumptive hypothyroidism, such as in case of hepatic hemangioma, tumor associated to an over-expression of deiodinase 3 and therefore to inactivation of thyroid hormones.

In the patient with nephrotic syndrome there is an increase in renal excretion of T4 linked to proteinuria, more evident in patients treated with LT4 compared to euthyroid patients (• **Figure 4**).

Finally, a physiological cause of increased need for LT4 is represented by pregnancy (• **Figure 5**).

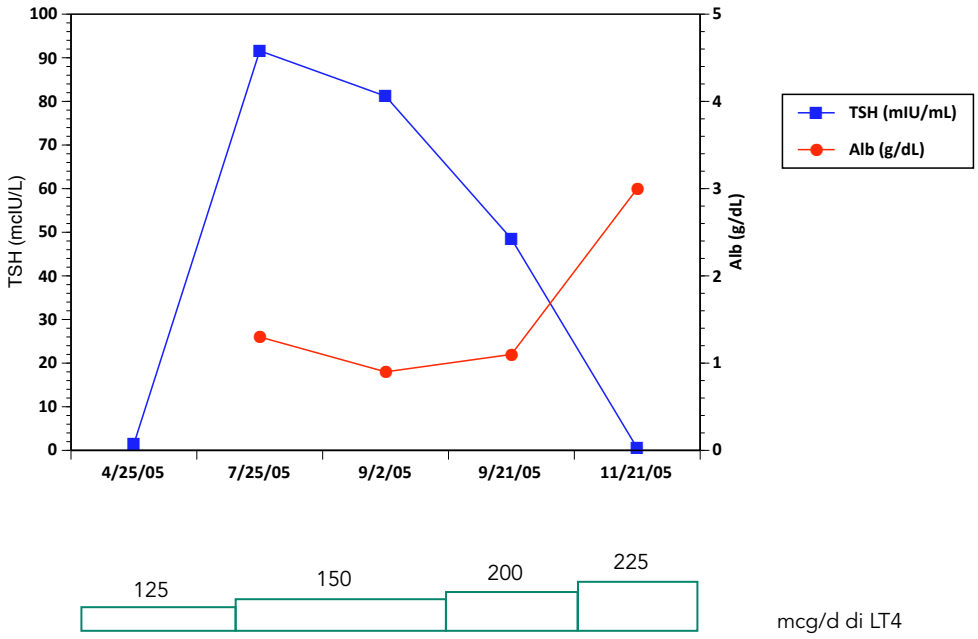
In summary, in the presence of high values of TSH in patients taking an appropriate dose compared to their weight and their age, we first need to assess adherence to therapy. It is essential to perform an accurate drug history and also investigate assumption

• **Figure 3.** Rifampicin and thyroid function



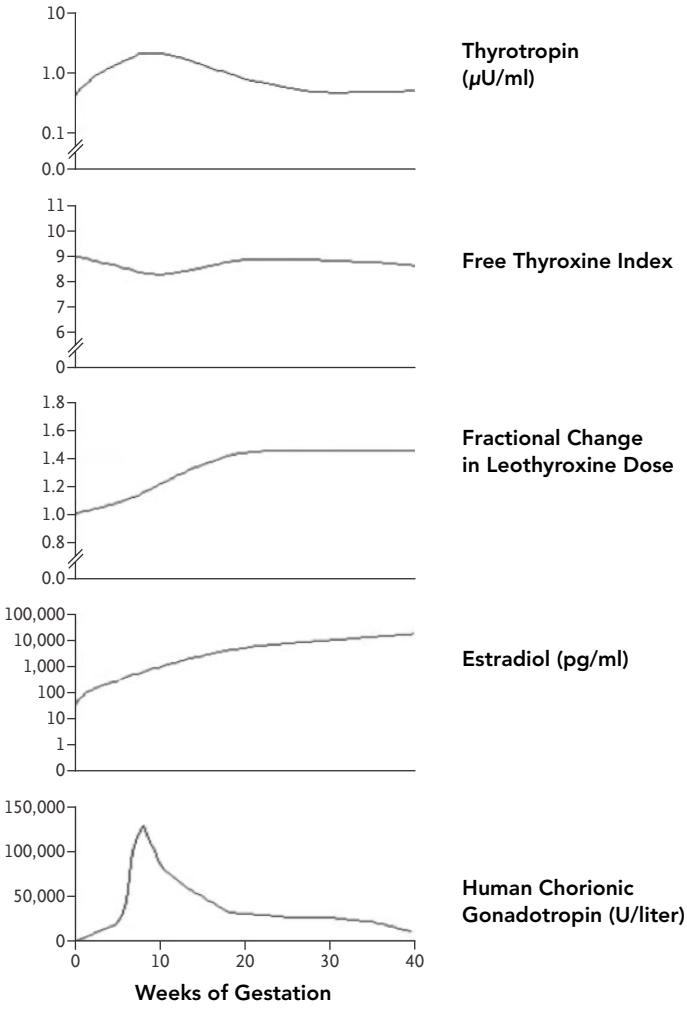
Source: graphical representation of data extrapolated from Takasu *et al.*, 2006 [10].

• **Figure 4.** Nephrotic syndrome and replacement therapy



Source: graphical representation of data extrapolated from Chandurkar *et al.*, 2008 [11].

• **Figure 5.** Hypothyroidism and pregnancy: increased need for T4



Source: Alexander *et al.*, 2004 [12].

of supplements, soy and any other substance that may interfere with the absorption of levothyroxine. It is important to space the drugs from the assumption of thyroid hormone, bearing in mind that thyroxin may be taken at any time as long as fasting and away from other medications. It is the responsibility of the physician to inform the patient about the mode of administration and adjust the treatment on the lifestyle of his patients in order to increase the compliance.

It is also necessary to exclude pathological causes of malabsorption. Today there are new formulations of levothyroxine with better dissolubility and a more rapid absorption which can be considered as an alternative in patients with malabsorption.

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Conclusions

Indications for therapy with LT4 in subclinical hypothyroidism in developmental age

The hot topic of this first forum of Endocrinology, organized by the IBSA Foundation, was the appropriateness of thyroxine treatment at different stages of life.

In paediatric age the issue is further complicated by the scarcity of studies on healthy children that allow us to identify with certainty the true reference range of TSH.

Today it is widely acknowledged that the TSH range is wider in the first years of life and shrinks gradually with the attainment of adulthood.

Even at an early age are fundamental the etiological diagnosis of thyroid dysfunction and the investigation of the morphological appearance of the gland, since subclinical hypothyroidism in developmental age is often transient, especially if not due to an alteration of the immune system. We must, then, think about the possibility of being in front of transitional forms of subclinical hypothyroidism that do not require an immediate therapy, but a simple monitoring in order not to be mistaken for a pathological situation that could be physiological for the age.

Subclinical hypothyroidism in asymptomatic patients with negative thyroid autoantibodies and without a clear aetiology, requires a check over time because they often show an evolution towards euthyroidism.

On the other hand, there are those who are in favour of early treatment of children with thyroid dysfunction, even subclinical, given the correlation with alterations of physical and mental development. Therapy, in fact, has no particular side effects if administered at the appropriate dose.

We know that the tissues have compensatory mechanisms to mitigate a slight hypothyroidism, so we should not be surprised that, with minor hormonal alterations, we are unable to demonstrate clinically that the hypothyroidism can be harmful.

During a mean follow-up period of 3 years, as the study by Wasniewska et al. [1], the biochemical and laboratory alterations may not become obvious, while in the body there may still be significant changes with implications for the development of the child. So, why we should try these compensatory mechanisms in children deciding not to treat?

There are many data showing that the thyroxin therapy improves the clinical condition in patients with subclinical hypothyroidism, but we have hundreds of studies on its effectiveness on congenital hypothyroidism. At present, in developmental age we should then treat until proven otherwise, that is, until the next clinical trial do not show that the decision not to adopt a therapy is really harmless. Transient hypothyroidism is as congenital hypothyroidism because the damage is done in the first months of life and the etiological diagnosis is often delayed, especially if we are looking for a genetic cause.

Ultimately, then, it seems that in case of doubt it is better to treat the forms that may be transient. Today, however, we begin to have some data on isolated hyperthyrotropinemia with normal growth and neuropsychological development; we have to be, therefore, more flexible in deciding whether treatment is required at the time of the diagnosis and if it is for a lifetime. It should not be denied treatment in children aged <3 years because it is difficult to discriminate the cause of hypothyroidism; however, it may be more favourable a transient treatment in hyperthyrotropinemia in adolescence. In few words, the specialist should be guided by laboratory data, but also from the clinic, in taking his decisions and cannot stop only at TSH dosage.

Thyroid hormones for fertility and in pregnancy

In women of childbearing age thyroid hormones regulate many functions of the reproductive life.

The iodothyronines together with oestrogen and progesterone induce follicular maturation, regulate endometrial thickness and stimulate the production of progesterone by luteal cells. Alterations in thyroid function are reflected, therefore, in all phases of the reproductive cycle of a woman.

The existence of a correlation between pregnancy and thyroid is known to all for some time now. It is most likely an association with multifactorial aetiology, not only due to thyroid dysfunction, but especially to a primary alteration of the immune system.

The positivity of the antiperoxidase antibodies is correlated with a higher incidence of abortions even in euthyroid women, often probably explainable with the contemporary presence of other autoimmune diseases such as antiphospholipid syndrome.

Women with chronic lymphocytic thyroiditis also feature a higher risk of disease progression during pregnancy; they must, therefore, be monitored frequently to timely diagnose and treat the appearance of thyroid hypofunction.

Hypothyroidism, even in subclinical form, has a negative impact on the gestational outcome, for which it should be correct pharmacologically, bearing in mind that an increase of approximately 30% of the requirements of LT4 is usually necessary during the gestational period.

These data were confirmed also in women who have resorted to techniques of medically assisted fertilization; further studies are planned to assess the effects of therapy in euthyroid women with antibody positivity who are preparing to make a MAP.

Ovarian stimulation may represent an event triggering thyroid imbalance in women with autoimmune thyroiditis, reason why it is important to ensure the presence of a good thyroid hormonal compensation and evaluate the signs of abnormal immune system.

The presence of thyroid autoantibodies should always be sought in women with recurrent fetal loss. However it is not recommended to perform a universal screening in all women planning a pregnancy, but only in selected cases through accurate medical history and physical examination.

Selenium supplementation in pregnant women with positive TPOAb reduces antibody values and the incidence of postpartum thyroiditis. Selenium has therefore also immune-modulatory functions and the finding of an appropriate level in follicular fluid is a good predictor for the gestational outcome.

It is important to get to the pregnancy in optimal conditions, and with adequate reserves of iodine and selenium and a good functional thyroid balance. Given the higher probability of progression of autoimmune thyroid disease during the gestational period there is need for a close follow-up. Therapy should be initiated in the presence of levels of TSH>2.5 mU/L. necessary to maintain adequate thyroxine values because it is the hormone that crosses the placental barrier and reaches the foetal nervous system. Conditions of hypothyroxinemia, in presence of normal TSH values, are probably due to iodine deficiency, a condition in which it is preferred the synthesis of T3.

Replacement therapy with thyroid hormones in the adult

There is a group of patients treated with LT4 that, despite a good functional compensation, is not satisfied with their quality of life and complains of a variety of symptoms and signs that leads to thyroid dysfunction, such as the tendency to gain weight, the feeling of reduced physical performance and alteration of mood tone.

The recent study by Celi et al. [2] showed that indeed, in patients in therapy with T3 after 5 weeks there is a reduction of cholesterol and body weight (1.7 kg) and differences in the calorimetery compared to the group treated with LT4. Already in other works emerged a preference for combination therapy in a subclass of patients and, more importantly, it seemed that the combination therapy had a beneficial role against the tendency to gain weight.

Of course, the weight and quality of life are not reliable parameters on which to base ourselves to start the T4/T3 combination therapy. However, one cannot avoid reflecting on the fact that there can be actually pathophysiology reasons able to clarify why a minority of hypothyroid patients is not satisfied with monotherapy with levothyroxine. One possible explanation could be given to the presence of polymorphisms in the genes of deiodinase that become clinically evident in patients with thyroidectomy in LT4 replacement therapy. After total thyroidectomy, in fact, the thyroid deiodinase activity is lost and, therefore, the production of T3 is reduced.

Perhaps the LT4 alone, if the deiodinase system is deficient, is not able to guarantee perfectly a hormonal balance and some patients then need a higher dose to normalize TSH. However, by increasing the dosage of LT4 we cannot be sure of getting euthyroidism in all tissues, as well as we reach it in the blood. In the literature, there are few works that have tested in thyroidectomised humans the impact of the lack of thyroid deiodinase on the functional homeostasis.

In terms of the evidence we do not have definitive answers; instead, at clinical practice level, it is up to the specialist to identify that 5-10% of patients who show symptoms that are not solved by monotherapy. They may represent ideal candidates to be submitted for a short period, to combined T4/T3 treatment in order to assess the possible benefit.

While, admittedly, the combination therapy may not be the initial approach in all hypothyroid subjects. The current therapy with once daily dosing of T3 does not mimic the physiological hormone secretion and determines the appearance of peak plasma levels of triiodothyronine.

The quality of life, the weight and all the other parameters analyzed so far are not suited to objectively compare the two therapies as affected by several factors. It would be more appropriate to assess the basal metabolic rate, the bioempedance and effects on body composition, i.e. the fat-to-fat-free mass ratio.

So far, only animal models have demonstrated benefits on body mass and then on the obesity trend, showing a severe weight gain in mice lacking deiodinase type 2.

The use of T3 in the treatment of obesity in humans is a very interesting hypothesis from the therapeutic point of view, but needs further investigation.

At present, the data emerging from various clinical trials must therefore always be taken with caution, because the therapy does not mimic the physiological production of T3 and treatment targets are not accurate and comparable in an appropriate manner.

In all patients in treatment and, in particular, those dissatisfied with the therapy, it is of paramount importance to ensure that it is respected the individually tailored dose. Since this is a chronic therapy must try to cut it out on the lifestyle of the patient, in order to increase compliance and achieve the therapeutic target.

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"The treatment of subclinical hypothyroidism in children, women and adults" is the theme of the I Forum organized by the Fondazione IBSA, whose primary purpose is to promote, support and contribute to the development of scientific research and become a point of reference and a meeting point for researchers, students, doctors and patients.

With the publishing project "Papers of Fondazione IBSA", of which this volume is the first act, Fondazione IBSA intends to share the contents of the Forum with a wide audience, with the aim to raise awareness about issues and pathologies with a strong health and socio-economic impact.

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