Five-year prospective evaluation of thyroid function in girls with subclinical mild hypothyroidism of different etiology

Malgorzata Wasniewska, Tommaso Aversa, Mariacarolina Salerno¹,
Andrea Corrias², Maria Francesca Messina, Alessandro Mussa², Donatella Capalbo¹,
Filippo De Luca and Mariella Valenzise

Department of Pediatric, Gynecological, Microbiological and Biomedical Sciences, University of Messina, Via Consolare Valeria, 98125 Messina, Italy, ¹Pediatric Endocrinology Unit, Department of Translational Medical Sciences, University 'Federico II', Naples, Italy and ²Department of Pediatrics, University of Turin, Turin, Italy

Correspondence
should be addressed
to F De Luca
Email
filippo.deluca@unime.it

Abstract

Aim: To follow-up for 5 years thyroid status evolution in 127 girls with mild (TSH 5–10 mU/l) subclinical hypothyroidism (SH) of different etiologies.

Patients: The population was divided into two age-matched groups of 42 and 85 girls with either idiopathic (group A) or Hashimoto's thyroiditis (HT)-related SH (group B). Group B was in turn divided into three subgroups, according to whether SH was either isolated or associated with Turner syndrome (TS) or Down syndrome (DS).

Results: At the end of follow-up the rate of girls who became euthyroid was higher in group A (61.9% vs 10.6%), whereas the rates of patients who remained SH (55.3% vs 26.2%), became overtly hypothyroid (30.6% vs 11.9%) or required levothyroxine (L-T₄) therapy (63.5% vs 23.8%) were higher in group B. Among the girls of group B, the risk of remaining SH or developing overt hypothyroidism was higher in the subgroups with TS or DS than in those with isolated HT.

Conclusions: Long-term prognosis of mild and idiopathic SH is frequently benign, even though a L-T₄ treatment may be needed throughout follow-up in almost a quarter of cases; long-term prognosis is different in the girls with either idiopathic or HT-related SH; and the association with either TS or DS impairs the outcome of HT-related SH.

European Journal of
Endocrinology
(2015) 173, 801–808

Introduction

Subclinical hypothyroidism (SH) is a biochemical condition characterized by serum thyrotropin (TSH) concentrations above the upper limit of the reference range and serum free thyroxine (FT₄) levels within the reference range (1). In pediatric age, SH is detected with increasing frequency, as thyroid function tests are routinely performed in children with very different clinical problems (2, 3). SH may be possibly caused by the same thyroid disorders that result in overt thyroid function impairment, in particular, Hashimoto's thyroiditis (HT) (4). In many cases, however, no definite etiology can be found (idiopathic SH).

The main clinical problem in the patients with SH is whether they should be treated or not, a problem that is still controversial due to the lack, even in adulthood, of randomized trials revealing significant benefits of levothyroxine (L-T₄) treatment on hypothyroid symptoms, life quality, serum lipid levels, and/or heart function (5).

In childhood, this is an even more controversial issue (6, 7, 8, 9, 10) and the only available study comparing the effects of L-T₄ treatment vs no therapy in idiopathic SH suggests that therapy is unable to modify post-therapy outcome of hyperthyrotropinemia and to prevent the risks

of a subsequent TSH increase after treatment withdrawal (11). In the children with HT-related mild SH, it has been just recently reported that the evolution of thyroid function tests seems to be frequently characterized by a deterioration over time, whereas such risk is very low in the children with idiopathic SH (12). However, the available prospective studies on the natural history and prognosis of SH in children are very few and based on 2–3 years follow-up investigations (12, 13, 14, 15, 16), which hampers the ability of drawing firm conclusions about the relevance of those findings.

In the present study, we have prospectively investigated the evolution of thyroid hormonal status, throughout a 5-year period, in a selected population consisting of only girls with either idiopathic or HT-related mild SH. In a limited number of cases, HT was associated with either Turner syndrome (TS) or Down syndrome (DS), i.e., two chromosomopathies that are known to be linked with an increased risk of autoimmune diseases (17, 18, 19, 20, 21, 22, 23, 24, 25) and especially thyroid diseases (26, 27, 28, 29, 30, 31).

The aims of our study were to establish, through a prolonged follow-up, whether long-term thyroid status prognosis may differ in the girls with either idiopathic or HT-related mild SH and whether the association with either TS or DS may modify the outcome of HT-related SH.

Patients and methods

Study population

The study population consisted, overall, of 127 girls aged between 2.5 and 18.0 years at the time of SH diagnosis

(median 9.7 years), who were identified in our clinics, during the period 2000–2008, as having a mild and either idiopathic or HT-related SH and fulfilled the following inclusion criteria: age ≤ 18.0 years at the time of SH diagnosis; TSH serum levels ranging between 5 and 10 mU/l; and no concomitant chronic treatment with pharmacological agents that might interfere with SH progression, such as antiepileptics, glucocorticoids, or iodinated drugs.

The entire series was divided into two groups, according to whether SH in the different cases was idiopathic (group A) or HT-related (group B). Patients of group A fulfilled the following criteria: negativity for both thyroglobulin and thyroid peroxidase serum autoantibodies (TGAb and TPOAb respectively) and no thyroid enlargement and no hypoechogenic gland pattern at ultrasonography. Patients of group B fulfilled the following criteria for diagnosis of HT: positivity for serum TGAb or TPOAb and a hypoechogenic thyroid pattern, consistent with autoimmune thyroid disease.

In both groups the patients were in good clinical status and clinically euthyroid at the time of recruitment. All of them had been referred to our pediatric endocrine centers by their pediatricians, due to the incidental finding of high TSH levels at their annual check-up, based on a diagnostic protocol that also included TSH measurement.

Group A consisted of 42 girls who were younger than 15 years at recruitment. Of these, 27 were prepubertal and 15 pubertal. Group B consisted of 85 girls, who were not older than 18 years at recruitment. Of these, 57 were prepubertal and 28 pubertal (Table 1).

Table 1 Ages (years) and prevalences (%) of pubertal patients, TSH (mIU/l), FT₄ (pmol/l), thyroid peroxidase and thyroglobulin autoantibody (TPOAb and TgAb) serum levels (mIU/l) at the start of follow-up in the two groups with either idiopathic subclinical hypothyroidism (SH; group A) or Hashimoto's thyroiditis (HT)-related SH and in three subgroups of patients with HT-related SH.

	Age	Pubertal patients	TSH	FT ₄	TPOAbs	TGAb
Group A (n=42)	7.4 (2.5–14.0)	35.7	6.0 (5.0–9.9)	14.3 $\pm$ 3.4	–	–
Group B (n=85)	9.0 (2.5–18)	32.9	6.4 (5.0–9.9)	13.3 $\pm$ 3.0	100 (34–6400)	96 (28–2500)
P	0.2000	0.7550	0.0420	0.1160	–	–
Subgroup B1 ^a (n=22)	10.5 (4.0–15.9)	50.0	5.6 (5.0–7.8)	14.3 $\pm$ 3.4	305.5 (40–2042)	172.5 (35–2002)
Subgroup B2 ^b (n=21)	13.3 (6.3–18.0)	42.9	7.3 (5.0–9.4)	13.9 $\pm$ 2.5	347.0 (40–6400)	100.0 (35–2500)
Subgroup B3 ^c (n=42)	4.5 (2.5–18.0)	19.0	7.0 (5.0–9.9)	12.1 $\pm$ 3.5	66.4 (34–2400)	50 (29–1926)
P B1 vs B2	0.0070	0.6400	0.0008	0.6440	0.0420	0.5780
P B1 vs B3	0.0004	0.0100	0.0020	0.0240	0.4420	0.0007
P B2 vs B3	0.0001	0.0450	0.7970	0.0530	0.0030	0.0450

^aNo association with either Turner or Down syndrome.

^bAssociation with Turner syndrome.

^cAssociation with Down syndrome.

Clinical Study	M Wasniewska and others	Long-term outcome of subclinical hypothyroidism	173:6	803
----------------	-------------------------	---	-------	-----

Patients of group B were in their turn divided into three subgroups, according to whether HT-related SH was either isolated (subgroup B1), associated with TS (subgroup B2), or DS (subgroup B3). These subgroups consisted, respectively, of 22, 21, and 42 girls.

Median ages (and ranges) at the start of follow-up and prevalences of the girls who had entered puberty at that time, in the different groups and subgroups, are detailed in Table 1.

Study design

All of the girls who were diagnosed in our clinics, during the period 2000–2008, as having a mild and either idiopathic or HT-related SH and fulfilled the above reported inclusion criteria were consecutively recruited for this prospective study.

From the time of recruitment all of them were followed-up as outpatients every 12 months for a pre-established period of 5 years and only those who completed the entire follow-up period were considered for this study.

At each examination TSH, FT₄, TPOAb, and TGAb serum levels were investigated. In the patients who exhibited, at the annual investigations, a further increase in TSH levels to >10 mIU/l and/or a pathological decrease of FT₄ levels to <10.3 pmol/l, L-T₄ treatment was begun immediately, according to our guidelines (4) and other recommendations (32, 33). In the patients who, during follow-up, exhibited a dramatic fall in TSH serum levels to <0.3 mIU/l and/or a concomitant increase of FT₄ to >24.4 pmol/l, methimazole treatment was begun immediately.

With regard to thyroid function at the end of the 5-year observation period, patients of both groups were evaluated according to FT₄ and TSH serum levels and classified into the following biochemical patterns: euthyroidism (both TSH and FT₄ within normal limits); SH (normal FT₄, as opposed to elevated TSH); overt hypothyroidism (elevated TSH with low FT₄); and hyperthyroidism (suppressed TSH, as opposed to either normal or elevated FT₄).

The prevalence rates of the patients who, in the two groups, either normalized or maintained TSH within the initial limits, exhibited an overt hypothyroidism biochemical picture at the end of follow-up or required L-T₄ therapy during the 5-year follow-up period were compared between them. The same comparisons were performed, in the context of group B patients, among those belonging to the subgroups B1, B2, and B3.

The girls who were under L-T₄ therapy at the end of 5-year follow-up were analyzed 6 weeks after treatment withdrawal. Those who were under methimazole treatment at the end of observation period were considered as patients who shifted over time from HT to Graves' disease (GD), provided that TSH receptor autoantibodies (TRABs) were positive.

Methods

Serum levels of TSH (normal range 0.3–4.5 mIU/l) and FT₄ (normal range 10.3–24.4 pmol/l) were measured by RIA methods. TPOAbs (reference range 0–20 IU/ml) and TGABs (reference range 0–30 IU/ml) were measured by chemiluminescent immunometric assays (34).

TRAB serum levels were measured by a second generation radioreceptor assay using the human recombinant TSH receptor only in the patients who, during follow-up, developed a hyperthyroid biochemical picture and underwent methimazole therapy. According to this method, values above 1.5 IU/ml are considered as positive (35).

Statistical analysis

Results are expressed as mean $\pm$ s.d. or median and range values, as appropriate. Comparisons between groups were performed by Student's unpaired and paired *t*-test (normally distributed data) or Mann-Whitney and Wilcoxon test (non-normally distributed data), as appropriate. Frequency rates were compared by the χ^2 test. Correlations between quantitative variables were assessed using Pearson's correlation analysis. The level of significance was set at 0.05 for all of the statistical analyses. The study design was approved by the ethical committees of the hospitals participating in our study and the children's parents gave informed consent. Appropriate consent was also obtained earlier from the study group for thyroid diseases of the Italian Society for Pediatric Endocrinology and Diabetology.

Results

Main data at the start of follow-up

Median age at follow-up onset was not significantly different in the girls of group A than in those of group B (Table 1). Even though expressed as mean $\pm$ s.d., patients' age at entry was similar in these two groups (7.5 ± 3.8 years vs 8.9 ± 4.9 years, $P=0.200$). Furthermore, the prevalence rates of patients who had entered puberty at follow-up initiation did not significantly differ in these two groups.

Clinical Study	M Wasniewska and others	Long-term outcome of subclinical hypothyroidism	173:6	804
----------------	-------------------------	---	-------	-----

Among the girls of group B, the oldest ones belonged to subgroup B2, while the youngest ones belonged to subgroup B3. Consequently, the prevalence of girls who had entered puberty at the time of SH diagnosis was significantly lower in subgroup B3 than in the other two subgroups.

TSH values were initially slightly higher in group B than in group A, whereas no differences were detected between these groups in terms of FT₄ values.

In the context of girls with HT-related SH, those with DS (subgroup B3) exhibited both higher TSH and lower FT₄ values with respect to those of subgroup B1, whereas the girls with TS (subgroup B2) exhibited higher TSH but very similar FT₄ levels when compared with subgroup B1 patients. Both TSH and FT₄ values were not different in subgroups B2 and B3.

The lowest autoantibody serum levels were initially found in the subgroup of girls with DS, whereas no differences were detected between subgroups B1 and B2.

Main data at the end of follow-up

Median age at the end of follow-up was very similar in the girls of groups A and B and no significant differences between these cohorts were detected even though age was expressed as mean $\pm$ s.d. (12.3 ± 4.0 years vs 13.8 ± 4.9 years, $P=0.0941$; Table 2). Furthermore, the prevalence rates of patients who had entered puberty at the time of study withdrawal did not significantly differ in these groups.

Among the girls of group B, the oldest ones belonged to subgroup B2, whereas the youngest ones belonged to subgroup B3. Consequently, the prevalence of girls who had entered puberty at the end of follow-up period was

significantly lower in subgroup B3 than in the other two subgroups.

During follow-up median TSH serum levels significantly decreased in the patients of group A, while they significantly increased in group B girls. Therefore, at the end of follow-up, median TSH values became significantly higher in group B patients than in those of group A. By contrast, during the same observation period, mean FT₄ serum levels significantly decreased in group B girls, whereas they remained unchanged in those of group A. Nevertheless, mean FT₄ levels, at the end of follow-up, did not significantly differ in these two groups.

In the context of patients with HT-related SH, during follow-up, those with TS (subgroup B2) as well as the girls with no chromosomopathies (subgroup B1) exhibited both a significant increase of TSH values and a significant decrease of FT₄ values. By contrast, during the follow-up period, the girls of subgroup B3 maintained substantially unchanged baseline TSH and FT₄ serum levels.

As a consequence of these time-related changes, at the end of follow-up, the girls of subgroup B2 showed the highest TSH values and the lowest FT₄ values, with respect to the patients of the other two subgroups. By contrast, at the end of follow-up, the girls with DS exhibited TSH and FT₄ serum levels that were not significantly different than those detected in subgroup B1 patients.

Thyroid function patterns at the end of 5-year follow-up

At the end of follow-up, the majority of girls with idiopathic SH (26/42) became biochemically euthyroid,

Table 2 Age (years) and prevalence (%) of pubertal patients and TSH (mIU/l) and FT₄ (pmol/l) serum levels at the end of follow-up in the two groups with either idiopathic subclinical hypothyroidism (SH; group A) or Hashimoto's thyroiditis (HT)-related SH and in three subgroups of patients with HT-related SH.

	Age	Pubertal patients	TSH	P*	FT ₄	P*
Group A (n=42)	12.1 (7.5–19.0)	66.7	2.4 (1.2–13.8)	0.0196	14.5 $\pm$ 2.3	0.9284
Group B (n=85)	14.4 (7.5–23.0)	71.8	7.6 (1.1–15.0)	0.0005	12.1 $\pm$ 2.7	0.0064
P	0.0941	0.5550	0.0023		0.0821	
Subgroup B1 ^a (n=22)	15.7 (9.0–20.9)	95.5	8.0 (1.1–14.2)	0.0390	13.1 $\pm$ 3.9	0.0017
Subgroup B2 ^b (n=21)	18.3 (11.3–23.0)	95.2	12.7 (6.9–15.0)	0.0017	9.0 $\pm$ 2.5	0.0120
Subgroup B3 ^c (n=42)	9.0 (7.5–23.0)	47.6	7.1 (2.2–14.2)	0.5790	12.5 $\pm$ 1.4	0.9585
P B1 vs B2	0.0092	0.9731	0.0176		0.0076	
P B1 vs B3	0.0004	0.0002	0.2279		0.3141	
P B2 vs B3	0.0001	0.0002	0.0121		0.0092	

*Vs the corresponding levels measured at the start of follow-up.

^aNo association with either Turner or Down syndrome.

^bAssociation with Turner syndrome.

^cAssociation with Down syndrome.

Clinical Study	M Wasniewska and others	Long-term outcome of subclinical hypothyroidism	173:6	805
----------------	-------------------------	---	-------	-----

whereas such an evolutive pattern was observed in a very low number of girls with HT-related SH (9/85) (Table 3).

Among the 16 patients of group A who did not become over time biochemically euthyroid, 10 (62.5%) required L-T₄ treatment during follow-up. Over time, five of them had developed an overt hypothyroidism and the remaining five had increased their TSH values to > 10 mU/L.

In the context of group B, most girls maintained, over time, a condition of SH or deteriorated their thyroid function picture to overt hypothyroidism. The prevalence of patients who needed L-T₄ therapy during follow-up was, therefore, significantly higher in the patients of group B than in those of group A.

In group B, the poorest scores in terms of TSH normalization during follow-up were observed in both the subgroups with chromosomopathies. Nevertheless, while most girls with TS worsened their initial thyroid function pattern from SH to overt hypothyroidism over time, the majority of those with DS remained SH.

If subgroup B1 girls were compared with those of group A, the risk of developing an overt hypothyroidism over time was significantly higher (45.4% vs 11.9%, $P=0.003$). Furthermore, the percentage of subgroup B1 girls who required L-T₄ therapy during follow-up was significantly higher (63.6% vs 23.8%, $P=0.002$).

A shifting from HT to GD (with increased FT₄, suppressed TSH and positive TRABs) was recorded during follow-up in 3/85 girls of group B (but in none of group A). All of these girls belonged to the subgroup B3.

Discussion

To the best of our knowledge, this is the first prospective study aiming to compare the outcome of thyroid function tests, after a 5-year follow-up, in two sex- and age-matched pediatric populations with either idiopathic or HT-related mild SH.

The first consideration, which emerges from the analysis of the results of our longitudinal study, is that the natural history of idiopathic SH in pediatric age seems to be characterized by a benign long-term evolution. In fact, the majority of these patients (61.9%) spontaneously normalized over time their TSH values, and only a small minority (11.9%) became overtly hypothyroid. Nevertheless, it has to be pointed out that almost a quarter of group A girls required L-T₄ treatment during the observation period, which underlines the importance of a biochemical follow-up, even in the children with idiopathic and mild SH (33, 36). According to the recent guidelines of the European Thyroid Association, in these children monitoring can be performed every 12 months due to the low risk of progression (33).

Furthermore, the results of the present study confirm, on the basis of a more prolonged prospective evaluation, the recent inference that underlying HT negatively affects the natural course of SH in children, irrespective of other concomitant risk factors (12). In fact, when compared with group A girls, those belonging to group B exhibited both decreased probabilities of TSH normalization and an increased risk of thyroid function deterioration over time, irrespective of whether HT-related SH was or was not

Table 3 Prevalences (%) of the different biochemical patterns of thyroid function detected, at the end of a 5-year follow-up, in the two groups with either idiopathic subclinical hypothyroidism (SH; group A) or Hashimoto's thyroiditis (HT)-related SH (group B) and in three subgroups of patients with HT-related SH and a percentage of those who, in the different groups and subgroups, required L-T₄ treatment during follow-up.

	Euthyroidism	SH	Overt hypothyroidism	Hyperthyroidism	Overall dysfunctions	L-T ₄ therapy
Group A (n=42)	61.9	26.2	11.9	0	38.1	23.8
Group B (n=85)	10.6	55.3	30.6	3.5	89.4	63.5
<i>P</i>	0.0001	0.0020	0.0200	0.2180	0.0001	0.0001
Subgroup B1 (n=22) ^a	36.4	18.2	45.4	0	63.6	63.6
Subgroup B2 (n=21) ^b	0	33.3	66.7	0	100	80.9
Subgroup B3 (n=42) ^c	2.4	85.7	4.8	7.1	97.6	54.8
<i>P</i> A vs B1	0.0520	0.4730	0.0030	–	0.0520	0.0020
<i>P</i> B1 vs B2	0.0020	0.2550	0.1610	–	0.0020	0.2060
<i>P</i> B1 vs B3	0.0002	0.0001	0.0001	0.1990	0.0002	0.4950
<i>P</i> B2 vs B3	0.4760	0.0001	0.0001	0.2090	0.4760	0.0420

^aNo association with either Turner or Down syndrome.

^bAssociation with Turner syndrome.

^cAssociation with Down syndrome.

associated with TS or DS. In fact, even in the subgroup with HT and no chromosomopathies, L-T₄ therapy was needed more often than in the group with idiopathic SH.

The different SH outcome in groups A and B cannot be explained by a different age or a different distribution of prepubertal and pubertal patients, because such parameters were very similar in the two groups.

Another peculiar aspect of the present study is that the patient series with HT-related SH was in turn divided in three subcohorts of girls with or without chromosomopathies. This study design gave us the opportunity to evaluate whether the association with either TS or DS may modify the natural history of mild SH in the girls with HT.

Our results confirm, throughout a prospective 5-year study, the sporadic reports that the association with either TS (26, 37) or DS (38) seems to be able to affect the course of HT by increasing the risk of a thyroid function deterioration over time. In particular, it is noteworthy that the almost totality of our patients with HT-related SH and associated TS or DS exhibited, at the end of the observation period, a biochemical picture of thyroid dysfunction: either SH, overt hypothyroidism or hyperthyroidism.

In the present study, both TGAb and TPOAb serum levels were distinctly lower in DS girls than in those with TS, which seems to support the hypothesis that, in the pathogenesis of HT-related SH, other factors apart from autoimmunity might be involved in DS patients (39, 40, 41). However, it has to be emphasized that, in the present study, all the DS girls with SH exhibited an underlying HT.

A further finding that deserves to be emphasized in this study is that, in 7.1% of DS girls, HT switched over time toward GD. This is not surprising considering that such a conversion is known to be detectable in the natural history of patients with HT (42, 43, 44, 45, 46) and has also been specifically described in children with either TS (29, 30, 31) or DS (38, 47). Moreover, the shifting HT→GD has been, just recently, found to be more common in GD children with these chromosomal aberrations than in those without them (48).

Finally, from a methodological point of view, it is known that age-specific reference ranges should be used when measuring TSH and FT₄ in children. During very early life, in fact, the values of these hormones may range widely, making it challenging to interpret measurements in infants and, especially, newborns (49). In the present study, however, median ages of the girls included in the two study groups with either idiopathic or HT-related SH were very similar and no patients <2.5 or >18 years were initially included in the overall study population.

Nevertheless, we are well aware of the fact that, in the context of group B, median ages were significantly different in the subgroups, particularly between subgroups B2 and B3. Therefore, TSH and FT₄ values in these subgroups might be hard to compare among them. In fact, it is known that TSH values are greatest during the first months of life and subsequently tend to decrease with age (50).

Surprisingly, in the present study, the highest TSH values were detected, both at entry and at the end of follow-up, in the subgroup of TS patients, i.e., those with the most advanced median age. These findings suggest that, if compared with the other patient subgroups, the TS girls with HT-related SH are *per se* more inclined to deteriorate their thyroid status over time, irrespective of age.

Conclusion

Long-term prognosis of mild and idiopathic SH is frequently benign, even though a L-T₄ treatment may be needed throughout follow-up in almost a quarter of cases. Long-term prognosis is different in the girls with either idiopathic or HT-related SH. The association with either TS or DS impairs the outcome of HT-related SH.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- Cooper DS & Biondi B. Subclinical thyroid disease. *Lancet* 2012 **379** 1142–1154. (doi:10.1016/S0140-6736(11)60276-6)
- Lazar L, Frumkin RB, Battat E, Lebenthal Y, Phillip M & Meyerovitch J. Natural history of thyroid function tests over 5 years in a large pediatric cohort. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1678–1682. (doi:10.1210/jc.2008-2615)
- Zadik Z. Overuse or misuse of thyroid function tests in pediatrics. *Journal of Pediatric Endocrinology & Metabolism* 2009 **22** 875–876. (doi:10.1515/JPEM.2009.22.10.875)
- Arrigo T, Wasniewska M, Crisafulli G, Lombardo F, Messina MF, Rulli I, Salzano G, Valenzise M, Zirilli G & De Luca F. Subclinical hypothyroidism: the state of the art. *Journal of Endocrinological Investigation* 2008 **31** 79–84. (doi:10.1007/BF03345571)
- Villar HC, Saconato H, Valente O & Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database of Systematic Reviews* 2007 **3** CD003419. (doi:10.1002/14651858.CD003419.pub2)

Clinical Study	M Wasniewska and others	Long-term outcome of subclinical hypothyroidism	173:6	807
----------------	-------------------------	---	-------	-----

- 6 Niedziela M. Subclinical hypothyroidism: dilemmas in the treatment of children. *Journal of Endocrinological Investigation* 2007 **30** 529–531. (doi:10.1007/BF03346340)
- 7 Monzani A, Prodam F, Rapa A, Moia S, Agarla V, Bellone S & Bona G. Endocrine disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. *European Journal of Endocrinology* 2012 **168** R1–R11. (doi:10.1530/EJE-12-0656)
- 8 Bona G, Prodam F & Monzani A. Subclinical hypothyroidism in children: natural history and when to treat. *Journal of Clinical Research in Pediatric Endocrinology* 2013 **5** (Suppl 1) 23–28. (doi:10.4274/jcrpe.851)
- 9 De Luca F, Corica D, Pitrolo E, Santucci S & Romeo M. Idiopathic and mild subclinical hypothyroidism in childhood: clinical management. *Minerva Pediatrica* 2014 **66** 63–68.
- 10 O'Grady MJ & Cody D. Subclinical hypothyroidism in childhood. *Archives of Disease in Childhood* 2011 **96** 280–284. (doi:10.1136/adc.2009.181800)
- 11 Wasniewska M, Corrias A, Aversa T, Valenzise M, Mussa A, De Martino L, Lombardo F, De Luca F & Salerno M. Comparative evaluation of therapy with L-thyroxine versus no treatment in children with idiopathic and mild subclinical hypothyroidism. *Hormone Research in Paediatrics* 2012 **77** 376–381. (doi:10.1159/000339156)
- 12 Aversa T, Valenzise M, Corrias A, Salerno M, De Luca F, Mussa A, Rezzuto M, Lombardo F & Wasniewska M. Underlying Hashimoto's thyroiditis negatively affects the evolution of subclinical hypothyroidism in children irrespective of other concomitant risk factors. *Thyroid* 2015 **25** 183–187. (doi:10.1089/thy.2014.0235)
- 13 Wasniewska M, Salerno M, Cassio A, Corrias A, Aversa T, Zirilli G, Capalbo D, Bal M, Mussa A & De Luca F. Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. *European Journal of Endocrinology* 2009 **160** 417–421. (doi:10.1530/EJE-08-0625)
- 14 De Luca F, Wasniewska M, Zirilli G, Aversa T & Arrigo T. At the end of a two-year follow-up elevated TSH levels normalize or remain unchanged in most the children with subclinical hypothyroidism. *Italian Journal of Pediatrics* 2010 **36** 11. (doi:10.1186/1824-7288-36-11)
- 15 Cerbone M, Bravaccio C, Capalbo D, Polizzi M, Wasniewska M, Cioffi D, Improda N, Valenzise M, Bruzzese D, De Luca F *et al.* Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. *European Journal of Endocrinology* 2011 **164** 591–597. (doi:10.1530/EJE-10-0979)
- 16 Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, Salerno M, Cappa M, Baiocchi M, Gastaldi R *et al.* The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. *Clinical Endocrinology* 2012 **76** 394–398. (doi:10.1111/j.1365-2265.2011.04251.x)
- 17 Elsheikh M, Dunger DB, Conway GS & Wass JA. Turner's syndrome in adulthood. *Endocrine Reviews* 2002 **23** 120–140. (doi:10.1210/edrv.23.1.0457)
- 18 Roizen NJ & Patterson D. Down's syndrome. *Lancet* 2003 **361** 1281–1289. (doi:10.1016/S0140-6736(03)12987-X)
- 19 Goldacre MJ, Wotton CJ, Seagroatt V & Yeates D. Cancers and immune related diseases associated with Down's syndrome: a record linkage study. *Archives of Disease in Childhood* 2004 **89** 1014–1017. (doi:10.1136/adc.2003.046219)
- 20 Bakalov VK, Gutin L, Cheng CM, Zhou J, Sheth P, Shah K, Arepalli S, Vanderhoof V, Nelson LM & Bondy CA. Autoimmune disorders in women with Turner syndrome and women with karyotypically normal primary ovarian insufficiency. *Journal of Autoimmunity* 2012 **38** 315–321. (doi:10.1016/j.jaut.2012.01.015)
- 21 Larizza D, Calcaterra V & Martinetti M. Autoimmune stigmata in Turner syndrome: when lacks an X chromosome. *Journal of Autoimmunity* 2009 **33** 25–30. (doi:10.1016/j.jaut.2009.03.002)
- 22 Jørgensen KT, Rostgaard K, Bache I, Biggar RJ, Nielsen NM, Tommerup N & Frisch M. Autoimmune diseases in women with Turner's syndrome. *Arthritis and Rheumatism* 2010 **62** 658–666. (doi:10.1002/art.27270)
- 23 Salzano G, Lombardo F, Arrigo T, Sferlazzas C, Wasniewska M, Valenzise M & De Luca F. Association of five autoimmune diseases in a young woman with Down's syndrome. *Journal of Endocrinological Investigation* 2010 **33** 202–203. (doi:10.1007/BF03346582)
- 24 Lleo A, Moroni L, Calia L & Invernizzi P. Autoimmunity and Turner's syndrome. *Autoimmunity Reviews* 2012 **11** A538–A543. (doi:10.1016/j.jautrev.2011.11.015)
- 25 Grossi A, Crinò A, Luciano R, Lombardo A, Cappa M & Fierabracci A. Endocrine autoimmunity in Turner syndrome. *Italian Journal of Pediatrics* 2013 **39** 79. (doi:10.1186/1824-7288-39-79)
- 26 Livadas S, Xekouki P, Fouka F, Kanaka-Gantenbein C, Kaloumenou I, Mavrou A, Constantinidou N & Dacou-Voutetakis C. Prevalence of thyroid dysfunction in Turner's syndrome: a long-term follow-up study and brief literature review. *Thyroid* 2005 **15** 1061–1066. (doi:10.1089/thy.2005.15.1061)
- 27 Fukuda I, Hizuka N, Kurimoto M, Morita J, Tanaka S, Yamakado Y & Takano K. Autoimmune thyroid diseases in 65 Japanese women with Turner syndrome. *Endocrine Journal* 2009 **56** 983–986. (doi:10.1507/endocrj.K09E-141)
- 28 Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA, Chillaron-Jordan JJ, Corretger JM & Cano-Pérez JF. Hyperthyroidism in a population with Down syndrome (DS). *Clinical Endocrinology* 2009 **71** 110–114. (doi:10.1111/j.1365-2265.2008.03419.x)
- 29 Wasniewska M, Corrias A, Messina MF, Crisafulli G, Salzano G, Valenzise M, Mussa A & De Luca F. Graves' disease prevalence in a young population with Turner syndrome. *Journal of Endocrinological Investigation* 2010 **33** 69–70. (doi:10.1007/BF03346552)
- 30 Gawlik A, Gawlik T, Januszek-Trzciakowska A, Patel H & Malecka-Tendera E. Incidence and dynamics of thyroid dysfunction and thyroid autoimmunity in girls with Turner's syndrome: a long-term follow-up study. *Hormone Research in Paediatrics* 2011 **76** 314–320. (doi:10.1159/000331050)
- 31 Valenzise M, Aversa T, Corrias A, Mazzanti L, Cappa M, Ubertini G, Scarano E, Mussa A, Messina MF, De Luca F *et al.* Epidemiology, presentation and long-term evolution of Graves' disease in children, adolescents and young adults with Turner syndrome. *Hormone Research in Paediatrics* 2014 **81** 245–250. (doi:10.1159/000357130)
- 32 Cooper DS. Clinical practice. Subclinical hypothyroidism. *New England Journal of Medicine* 2001 **345** 260–265. (doi:10.1056/NEJM200107263450406)
- 33 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R & Vaidya B. European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *European Thyroid Journal* 2014 **3** 76–94. (doi:10.1159/000362597)
- 34 Wasniewska M, Corrias A, Salerno M, Mussa A, Capalbo D, Messina MF, Aversa T, Bombaci S, De Luca F & Valenzise M. Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. *Hormone Research in Paediatrics* 2012 **78** 232–236. (doi:10.1159/000343815)
- 35 Wasniewska M, Corrias A, Salerno M, Lombardo F, Aversa T, Mussa A, Capalbo D, De Luca F & Valenzise M. Outcomes of children with hashitoxicosis. *Hormone Research in Paediatrics* 2012 **77** 36–40. (doi:10.1159/000334640)
- 36 Gawlik A, Such K, Dejner A, Zachurzk A, Antosz A & Malecka-Tendera E. Subclinical hypothyroidism in children and adolescents: is it clinically relevant? *International Journal of Endocrinology* 2015 **2015** 691071. (doi:10.1155/2015/691071)
- 37 Aversa T, Messina MF, Mazzanti L, Salerno M, Mussa A, Faienza MF, Scarano E, De Luca F & Wasniewska M. The association with Turner syndrome significantly affects the course of Hashimoto's thyroiditis in children, irrespective of karyotype. *Endocrine* 2015. In press. (doi:10.1159/000357130)
- 38 Aversa T, Salerno M, Radetti G, Faienza MF, Iughetti L, Corrias A, Predieri B, Mussa A, Mirabelli M, De Luca F *et al.* Peculiarities of

Clinical Study	M Wasniewska and others	Long-term outcome of subclinical hypothyroidism	173:6	808
----------------	-------------------------	---	-------	-----

- presentation and evolution over time of Hashimoto's thyroiditis in children and adolescents with Down's syndrome. *Hormones* 2015 **14** 410–416. (doi:10.14310/horm.2002.1574)
- 39 van Trotsenburg AS, Vulsma T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, Tijssen JG & de Vijlder JJ. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 3304–3311. (doi:10.1210/jc.2005-0130)
 - 40 Meyerovitch J, Antebi F, Greenberg-Dotan S, Bar-Tal O & Hochberg Z. Hyperthyrotropinaemia in untreated subjects with Down's syndrome aged 6 months to 64 years: a comparative analysis. *Archives of Disease in Childhood* 2012 **97** 595–598. (doi:10.1136/archdischild-2011-300806)
 - 41 Claret C, Goday A, Benaiges D, Chillarón JJ, Flores JA, Hernandez E, Corretger JM & Cano JF. Subclinical hypothyroidism in the first years of life in patients with Down syndrome. *Pediatric Research* 2013 **73** 674–678. (doi:10.1038/pr.2013.26)
 - 42 Ludgate M & Emerson CH. Metamorphic thyroid autoimmunity. *Thyroid* 2008 **18** 1035–1037. (doi:10.1089/thy.2008.1551)
 - 43 Wasniewska M, Corrias A, Arrigo T, Lombardo F, Salerno M, Mussa A, Vigone MC & De Luca F. Frequency of Hashimoto's thyroiditis antecedents in the history of children and adolescents with Graves' disease. *Hormone Research in Paediatrics* 2010 **73** 473–476. (doi:10.1159/000313395)
 - 44 Kamath C, Young S, Kabelis K, Sanders J, Adlan MA, Furmaniak J, Rees Smith B & Premawardhana LD. Thyrotrophin receptor antibody characteristics in a woman with long-standing Hashimoto's who developed Graves' disease and pretibial myxoedema. *Clinical Endocrinology* 2012 **77** 465–470. (doi:10.1111/j.1365-2265.2012.04397.x)
 - 45 Troisi A, Novati P, Sali L, Colzani M, Monti G, Cardillo C & Tesaro M. Graves' thyrotoxicosis following Hashimoto's thyroiditis. *Research and Reports in Endocrine Disorders* 2013 **3** 13–15. (doi:10.2147/RRED.S38053)
 - 46 Champion B, Gopinath B, Ma G, El-Kaissi S & Wall JR. Conversion to Graves' hyperthyroidism in a patient with hypothyroidism due to Hashimoto's thyroiditis documented by real-time thyroid ultrasonography. *Thyroid* 2008 **18** 1135–1137. (doi:10.1089/thy.2008.0142)
 - 47 De Luca F, Corrias A, Salerno M, Wasniewska M, Gastaldi R, Cassio A, Mussa A, Aversa T, Radetti G & Arrigo T. Peculiarities of Graves' disease in children and adolescents with Down's syndrome. *European Journal of Endocrinology* 2010 **162** 591–595. (doi:10.1530/EJE-09-0751)
 - 48 Aversa T, Lombardo F, Corrias A, Salerno M, De Luca F & Wasniewska M. In young patients with Turner or Down syndrome, Graves' disease presentation is often preceded by Hashimoto's thyroiditis. *Thyroid* 2014 **24** 744–747. (doi:10.1089/thy.2013.0452)
 - 49 Verburg FA, Kirchgässner C, Hebestreit H, Steigerwald U, Lentjes EG, Ergezinger K, Grelle I, Reiners C & Luster M. Reference ranges for analytes of thyroid function in children. *Hormone and Metabolic Research* 2011 **43** 422–426. (doi:10.1055/s-0031-1275326)
 - 50 Kapelari K, Kirchlechner C, Högl W, Schweitzer K, Virgolini I & Moncayo R. Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. *BMC Endocrine Disorders* 2008 **8** 15. (doi:10.1186/1472-6823-8-15)

Received 11 May 2015

Revised version received 27 July 2015

Accepted 15 September 2015