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**Title : Subclinical Hypothyroidism in Perimenopausal women- a study of 648 women in Maitreyi Health Care Programme**

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## **Subclinical Hypothyroidism in Perimenopausal women- a study of 648 women in Maitreyi Health Care Programme**

### **ABSTRACT**

**Introduction:** Many age related chronic diseases, including thyroid dysfunction, are expressed in the perimenopausal period. Maitreyi's Health Care Screening Programme (HCP) for women in this age and for older women includes estimation of S.TSH for detection and management of hypothyroidism.

**Objective :** The aim of the study was to determine the prevalence of hypothyroidism in community based Health Care Programme (HCP) for perimenopausal women.

**Methods:** Six hundred forty eight consecutive women who availed of Maitreyi HCP between April 1999 to March 2004 were included. Maitreyi's HCP includes comprehensive health questionnaires, gynecological and physician's check up, biochemical investigations of CBC (Complete Blood Count), GTT (glucose tolerance test), lipid profile, S. creatinine and S.TSH (Thyroid stimulating hormone). Pap smear and pelvic sonography, urine stool examination for occult blood are also included. A multidisciplinary trans-system team offers this community oriented programme. Serum TSH in all 648 women, and Serum T3 and T4 in retrospective analysis , were measured by Radioimmunoassays.

**Result s:** During this screening of 648 women, 31 cases were known hypothyroid cases. Out of the remaining 617 women 9.8% of women had S.TSH levels between 5 and 5.9  $\mu$ IU/ml and 10.6% of women had levels between 6 and 9.9  $\mu$ IU/ml. Serum TSH levels  $>10$   $\mu$ IU/ml were observed in 7.9% of women. Symptoms such as myalgia, arthralgia, fatigue, forgetfulness depression and menorrhagia (common for menopause, hypothyroidism or aging) were observed in upto 40% of women in this group. Total cholesterol and BMI were elevated in more than 50% of cases.

**Discussion:** SH is a diagnostic possibility to be considered when STSH levels are observed between 5 and 10 uIU/ml. In our series in screening of 648 cases 21. 4 % of cases had mildly raised STSH and were advised further evaluation.. In view of the possible benefits for neuropsychiatric symptoms and quality of life, guidelines for management are suggested in an algorithm which is being followed at Bhavan's SPARC. Recent literature on initiation of Thyroid Replacement Therapy in Sub-clinical Hypothyroidism is reviewed and discussed.

**INTRODUCTION:** Sub-clinical hypothyroidism is common in adult population. Its prevalence may increase up to 20% in women older than 60 years of age<sup>1,2</sup>. Sub-clinical Hypothyroidism (SH) is defined as a stage showing elevated serum thyroid stimulating hormone (TSH) and normal serum levels of thyroxin (T4) and triiodothyronine (T3)<sup>3</sup>. It has various synonyms like (1) Mild thyroid failure (2) Early/Latent thyroid failure (3) Compensated thyroid state (4) Pre-clinical hypothyroidism (5) Biochemical hypothyroidism. Subjects may be asymptomatic at the time of screening or mild symptoms may be present. Symptoms of myalgia, diminished memory, arthritis, fatigue, emotional instability, premenstrual tension syndrome (PMTS) and menorrhagia etc can be confused with other conditions like menopausal syndrome, ageing, anemia and Diabetes mellitus. SH therefore is detected either through screening programmes or through health check ups<sup>3</sup>. Availability of ultra sensitive assays for estimation of serum TSH has made it possible to detect these cases much earlier than actual clinical appearance of goiter, or classical hypothyroidism or myxedoema which is rarely seen in urban settings. Adverse effects of overt hypothyroidism on metabolic function eg hypercholesterolemia and on target tissues like neuromuscular systems, myocardium, haemopoetic system are well known<sup>3,4</sup>. Subclinical hypothyroidism is currently under intense investigation including at Bhavan's SPARC in its Maitreyi Health Care Programme for women at, and above 40 years of age.

**OBJECTIVE :** The aim of the study was to determine the prevalence of hypothyroidism in community based Health Care Programme (HCP) for perimenopausal women.

**MATERIAL & METHODS:** Six hundred forty eight consecutive women who availed of Maitreyi HCP between April 1999 to March 2004 were included in this analysis. Maitreyi's HCP includes comprehensive health questionnaires, gynecological and physician's check up, biochemical investigations of CBC (Complete Blood Count), GTT (glucose tolerance test), lipid profile, S. creatinine and S.TSH (Thyroid stimulating hormone). Pap smear, pelvic sonography, and routine urine and stool examination for occult blood are also included. A multi-disciplinary and trans-system team offers this community oriented programme..

**Hormone assays:** S. TSH was measured in fasting blood sample with an ultra sensitive assay (RIA). All sample aliquots were preserved at - 80° C for any further analysis. As this was a screening programme, S.T3 and T4 were not measured as a routine but only in those who had S.TSH values

between  $\geq 5$  and  $< 10$   $\mu\text{IU/ml}$  (n=127) and only when adequate serum aliquots were available (n=53).

Serum TSH, T3 and T4 were measured using radioimmunoassay (DSL). The sensitivity of S.TSH is  $<0.1$   $\mu\text{IU/ml}$ . The cross reactivity is  $< 0.01\%$  for other hormones like PRL, FSH, LH, hCG and GH. The normal range in our laboratory is 0.5 to 6  $\mu\text{IU/ml}$ . The sensitivity for Serum T3 was  $<0.3$  ng/dl and cross reactivity with T2 and T4 is less than 0.5%. The normal range for ST3 in our laboratory is 70 to 100 ng/dl. The sensitivity of T4 assay was 0.6  $\mu\text{g}$ . The cross reactivity with T3 was  $<2\%$ . The normal range for ST4 in our laboratory is 5 – 13  $\mu\text{g/dl}$ . Low, medium and high level Quality Control samples were run in all assays and the assays were maintained within the Quality Control limit throughout the study period.

## **RESULTS :**

**Serum TSH levels :** Out of 648 women 31 cases were known hypothyroids and were excluded from the present analysis. The remaining 617 cases were further grouped according to S.TSH levels as given in Table 1.

**Table 1.**

Out of the 31 known cases of hypothyroidism 16 cases had STSH  $> 6$   $\mu\text{IU/ml}$  and 2 had levels between 5 & 5.9  $\mu\text{IU/ml}$ .

A large number of women i.e. 441 ( 71.7%), had S.TSH level below 5  $\mu\text{IU/ml}$ . (Group I). Sixty one women belonging to Group II had serum TSH level between 5 and 5.9  $\mu\text{IU/ml}$ . Group III, a potential SH group had values between 6 and 9.9  $\mu\text{IU/ml}$ . The remaining 49 women in group IV had values at or above 10  $\mu\text{IU/ml}$ .

**Symptom Evaluation in SH:** Symptoms related to hypothyroidism were analysed in relation to S.TSH levels as shown in Table 2.

**Table2.**

The most commonly observed symptoms were fatigue/weakness, forgetfulness and depression. Almost 40% of women in both groups (II and III) of SH complained of fatigue and weakness. Whilst 1/3<sup>rd</sup> women in groups II, III and IV reported increased forgetfulness in recent times. Depression was more common in groups II and III and least seen in group IV; menorrhagia was reported by 8 to 10% of cases in group II, III and IV. Premenstrual Tension Syndrome (PMTS) and arthralgia were reported by 4.9 to 13.6% of women in groups II and III and were less frequent in group IV. Weight gain was most common in group II (16.6%). Symptoms of frank hypothyroidism like lethargy, sleepiness, mood swings, constipation, muscle cramps, swelling of feet, headache and dizziness were reported by very few cases (<3%) in all these groups.

**Body Mass Index (BMI) , hemoglobin status and serum cholesterol in SH :** The distribution of body mass index (BMI), hemoglobin (Hb) and S. cholesterol levels were analysed in those with raised TSH levels above 5  $\mu$ IU/ml.(Gr. II, III, IV-Table 3).

When all women were analysed irrespective of STSH levels the BMI was raised in 69.9% of women indicating that this whole group of women seeking the screening programme were from a relatively rich socio economic group.

### **Table 3.**

BMI was raised in > 55% of women in all 3 groups and was maximum in group III.

Anemia i.e. Hb <11 gm% , was observed in around 30% of cases in all 3 groups. Similarly S. cholesterol was raised (>200 mg%) in 42 to 50% of cases in above groups.

When all perimenopausal women are considered as a whole (first consecutive 250 cases) S. cholesterol was elevated more than 200 mg% in 24% of women. BMI was raised in 65% of total group.

### **Serum T3 and T4 in SH**

As estimation of S.T3 and S.T4 was carried out subsequently in preserved aliquots and it was obtained in out of 53/127 cases belonging to groups II and III . S.T3 levels were within normal limits in all 53

cases. S. T4 was subnormal in 3 women in group II (3.9, 4.3 and 4.7 $\mu$ g/100ml) , and in 3 women from Group III ( 2.7, 3.4, 3.7  $\mu$ g/ml/100ml respectively).

### **Thyroid Replacement Therapy (TRT) in SH**

Two illustrative case histories with S. TSH level below 7  $\mu$ IU/ml when screening was done, and who came for long term follow up to our center are given below in Table 4.

**Table 4.**

Both women had symptoms suggestive of SH for 2-8 years. However these were attributed to menopause and aging. S. TSH was found to be elevated after the screening programme., second time in one woman. TRT produced symptomatic relief in both however both discontinued the treatment after 3 months and 3 years respectively. Reassessment confirmed elevated S.TSH and antibody positivity. Restarting of TRT produced symptomatic relief in both as assessed by follow up visits.

There were other women who did not have symptoms or antibody measurement but who could not be followed up as this is a screening programme.

**DISCUSSION:** The diagnosis of SH is important in women in peri and postmenopausal period. The percentage of women with S.TSH levels between 6 and 9.9  $\mu$ IU/ml (Group III) was 10.6% and between 5 and 5.9 mIU/ml (Group II) was 9.8% in the present series. Some of the larger series such as Wickham<sup>1</sup> study and the Colorado study<sup>2</sup> have reported prevalence of SH from 1 to 10%. In a recent study by Akbar et al<sup>3</sup> the prevalence in elderly women above 50 years of age was as high as 35%.

Women with SH can remain asymptomatic if their thyroid function is well compensated. However some of them may have symptoms like menorrhagia, Pmts, fatigues, myalgia, arthralgia, tingling and numbness, neuropsychiatric effects like impaired cognition, forgetfulness, emotional liability and depression. These symptoms can also be part of the menopausal syndrome or aging process. The common symptoms in this study from Group II and III were fatigue, weakness, forgetfulness, depression,, arthralgia, weight gain, menorrhagia and PMTS and were similar to those reported by other authors like Cooper<sup>4</sup> and Zulewski<sup>5</sup>.

Significant association of hypercholesterolemia leading to atherosclerosis and hypothyroidism has been recognized for a long time <sup>6</sup>. Cross sectional studies of SH patients have shown higher total cholesterol and LDL cholesterol levels than seen in euthyroid controls<sup>7</sup> (Elder J et al – 13 No). In our study raised cholesterol levels (>200 mg%) were observed in more than 42% of cases.

Significantly raised BMI in SH has been reported by Zulewski et al<sup>5</sup>. Though we observed raised BMI in more than 50% of cases from Group II and Group III, obesity is as such common in this age group as observed in the first consecutive 250 women in Maitreyi HCP.

SH is considered to be a phase of compensated thyroid deficiency. In our series retrospective measurement of thyroid hormone showed normal T3 level in all cases of SH, but slightly lower T4 level in 3 cases from Groups II and III.

There is a dilemma for initiating Thyroid Replacement Therapy (TRT) in women with SH. It is controversial issue and medical opinion regarding the treatment of SH is divided since there are no large scale multicentric placebo-controlled randomized trials to settle this issue. Several studies in the literature have shown higher prevalence of mild symptoms of thyroid deficiency in patients with SH as compared with age-matched controls <sup>2,5</sup>. Significant improvement in suggestive of symptoms hypothyroidism has been observed by Cooper et al <sup>4</sup> and Meir et al <sup>8</sup>. In their randomized placebo controlled trials with TRT in sub clinical hypothyroidism, mean S. TSH value was 11.7 and 12.7  $\mu$ IU/ml respectively. Nystrom et al observed symptomatic response even at mean S. TSH of 7.7  $\mu$ IU/ml. On the other hand Kong et al <sup>10</sup> did not observe symptomatic relief with similar mean S.TSH value of 7.5  $\mu$ IU/ml. Even Jaeschke et al <sup>11</sup> reported no relief of symptoms in their series with a mean S.TSH of 10.7  $\mu$ IU/ml. Measurement of free T4 has been advised but cases may have symptoms despite normal T4 levels.

The main reason for advocating TRT in SH are the possibility of relief of neuropsychiatric symptoms and the possible prevention of long term cardiovascular complications if treatment is given. Some studies have not shown any clear cut benefits of TRT in SH <sup>12,13, 14</sup>. However others have observed relief in neuropsychiatric symptoms and reduced lipid levels as well as reduced intima-media thickness in SH after TRT <sup>15,16,4,8,17</sup>. Our two illustrative cases indicate the possible benefits of initiating TRT in SH. Quality of life which was affected for 2 and 8 years was improved after TRT in both. Some investigators have recommended initiation of TRT if thyroid antibody titres are positive<sup>18</sup>,

however since the positivity is not observed in all cases of hypothyroidism others do not depend on antibody titres.

It is important to initiate and/or monitor optimal dose of TRT at menopause. In the present series these were 31 known cases of primary hypothyroidism and 49 were newly detected. Out of 31 known cases 18 had STSH > 5  $\mu$ IU/ml and were therefore undertreated. They required an increment in TRT. On the other hand menopausal osteoporosis / penia can get aggravated by excessive dose of TRT<sup>19</sup>. One may also have to consider adjusting TRT – dose in women who have started Estrogen Replacement Therapy (ERT) The demand for TRT is increased in women taking HRT probably because of the increase in thyroid binding globulin protein which may occur in response to estrogen therapy<sup>20</sup>.

The question of relationship of thyroid dysfunction at menopause is complex. Whether this is related to declining ovarian function has been explored in a study by Viceconti et al<sup>21</sup>. They attempted to determine the correlation of menopausal estrogen deficiency with thyroid dysfunction. They measured serum inhibin B and FSH, both being sensitive markers of ovarian failure, and correlated these hypo and hypothyroidism in 51 premenopausal and 40 postmenopausal women. They observed no association in the premenopausal group. However in postmenopausal women with thyroid dysfunction they observed increased levels of serum inhibin and decreased levels of S.FSH This indicates an effect of thyroid dysfunction in these women.

Lastly it is important to realize that overt hypothyroidism may be a continuum of SH as reported by others and in our earlier studies<sup>6,14, 22,23</sup>. In view of the above discussion, Maitreyi HCP identifies 3 factors for initiation of TRT in Subclinical Hypothyroidism i.e clinical cues, abnormal cholesterol profile and positive thyroid antibody titre. TRT should be initiated in presence of any 2 associations. An algorithm has been evolved by us for the management of SH in women as given in Fig 1.

### **Figure 1.**

**CONCLUSION::** Maitreyi's Health Screening for women at and above 40 years has shown that more than 10% of women were detected to have elevated STSH, suggestive of SH. The presence of 2 or 3 important associations like mild symptomatology (however vague), hypercholesterolaemia, and presence of thyroid antibodies dictate initiation of TRT.

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**Table 1 S.TSH levels in 617 cases Maitreyi**

S.TSH $\mu$ IU/ml	Group	No	%
< 5	I	441	71.7%
5 – 5.9	II	61	9.8%
6 – 9.9	III	66	10.6%
10 +	IV	49	7.9%

**Table – 2 : Common symptoms observed in woman with S.TSH (raised)**

	Group II	Group III	Group IV
Fatigue/weakness	24 – (39.3%)	27 (40.9)	12 (24.5%)
Forgetfulness	19 (31.1%)	23(34.81%)	18 (36.7%)
Depression	11 (18%)	14 (21.2%)	2 (4%)
Menorrhagia	5 (8.2%)	7 (10.6%)	4 (8.2%)
PMTS	3 (4.9%)	9 (13.6%)	1 (2%)
Weight gain	4 (6.5%)	11 (16.6%)	3 (6.1%)
Athralgia	6 (9.8%)	7 (10.6%)	1 (2%)

**Table 3. Percentage of cases with raised BMI, anaemia and raised cholesterol in women with elevated S TSH**

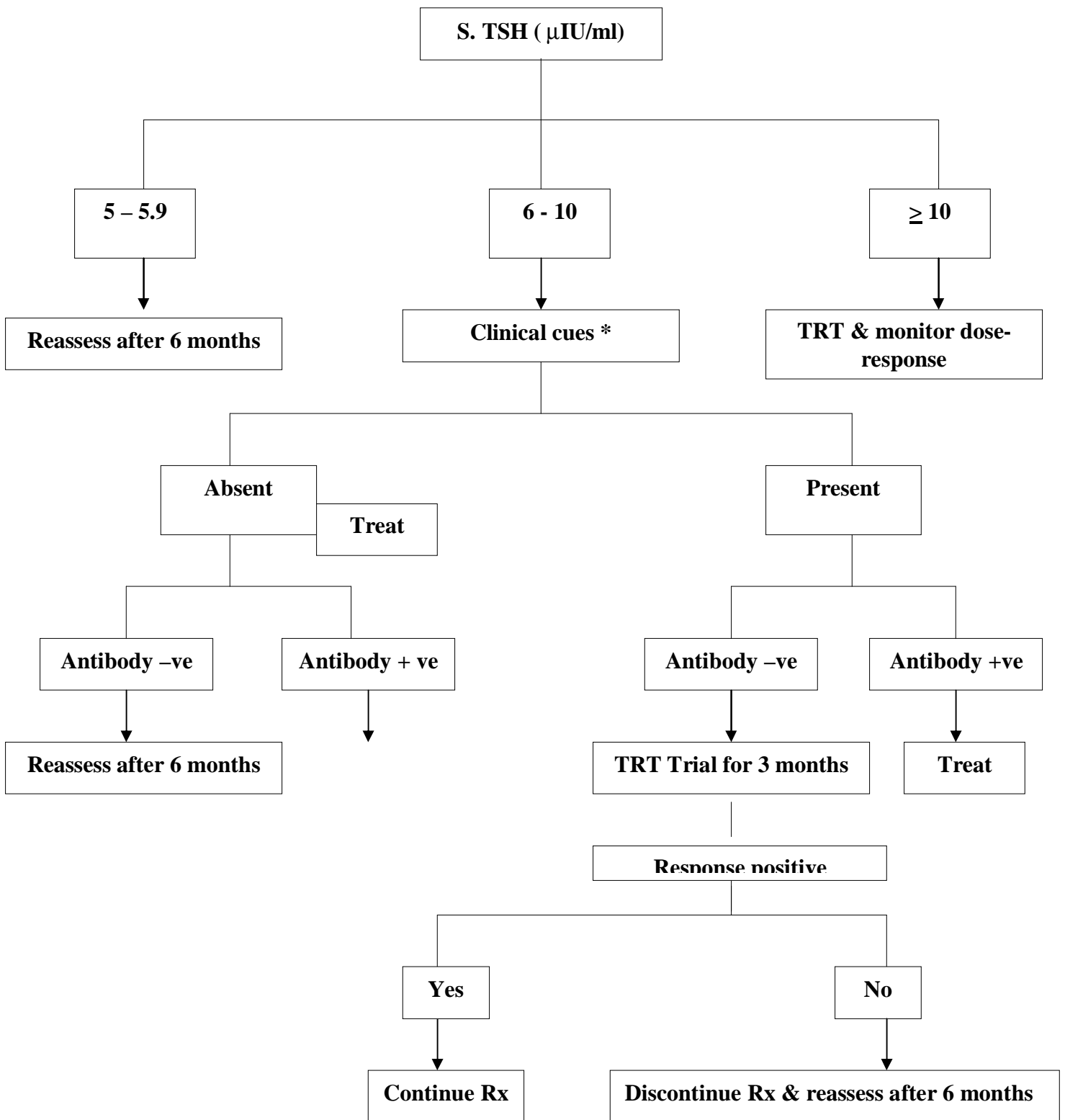
Group	TSH( $\mu$ IU/ml)	Number	BMI ( $>25\text{kg/m}^2$ )	Hb $< 11\text{gm}\%$	Cholesterol $> 200$ mg%
II	5 – 5.9	61	35 (57.4%)	19 (31.2%)	26 (42.6%)
III	6 – 9.9	66	47 (71.2%)	13 (19.7%)	33 (50%)
IV	$\geq 10$	49	28 (57.%)	14 (28.6%)	25 (51%)

BMI = Body mass index, Hb = Hemoglobin.

**Table 4: Two Illustrative Cases of SH**

Case I	Age Yrs	M history	Wt.Kg	BM Kg/m <sup>2</sup>	Presenting	TSH $\mu$ IU/ml	Other invest	Remarks
BB  (Date 17/12/2000       Date Feb 2002	56	10 yrs Menopause	58	24.02	Fatigue, weakness, Forgetfulness, Myalgia – 8yrs	6.8      6.6	S.Chol-204 S.LDL-143 AMA +ve T3 – 175ng/dl T4 8.8 $\mu$ IU/ml T3-92 T4-9.6	TRT for 3 months dl Symptomatic Relief TRT stopped   Recurrence Of symptoms TRT restarted. Symptom relief
Case No. II HK Date:25/6/2000      29/2/2004	55	10 yrs Menopause	70.5	30.0	Puffiness of face, body constipation, emotional lability Depression myalgia, Jt. Pains 2 yrs. Recurrence of Symptoms Hoarsness of voice	10      12	S.Chol. 227 mg%      AMA + ve	1998- TSH-5.7 TRT started In 2000      TRT stopped On 4/4/2003 TRT restarted. Symptom relief

TRT= Thyroid Replacement Therapy



\* Free T4 – optional TSH = Thyroid Stimulating Hormone TRT = Thyroid Replacement Therapy

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