



## Editorial

# Misery of TSH

### Introduction

Over the past 15 to 20 yrs there has been a rapid expansion of knowledge regarding Thyroid diseases in obstetrics and gynecology. A remarkable downgrading of the clinical aspects of hypothyroidism and hyperthyroidism has resulted into tremendous increase in the number of Thyroid Function Tests and has also led to the confusion in the diagnosis of Thyroid diseases. In 1997, Weetman AP reported that a diagnosis of clinical hypothyroidism can be made on the basis of biochemical values only and that signs and symptoms are not necessary<sup>1</sup>. While in the same year Skinner GRB et al disagreed and reported that biochemical tests can be misleading and the diagnosis should be done on clinical ground only.<sup>2</sup> Recently, low level of Thyroid Stimulating Hormone (TSH) is considered to be the most important biochemical diagnostic test of hyperthyroidism but exact numerical value has not been assigned to the serum concentration of TSH below which suppression of TSH is considered to occur. TSH value varies from centre to centre depending upon the sensitivity of the local assay. Hence, depending upon the serum TSH concentration alone the diagnosis of Thyroid disease has led to become confusion.

### Thyroid Stimulating Hormone (TSH)

TSH is also known as thyrotropin, an anterior pituitary hormone which is controlled by hypothalamic hormone TRH. It has been reported that increased thyroid hormone inhibits anterior pituitary secretion of TSH mainly by direct effect on the anterior pituitary itself and by much weaker effects acting through the hypothalamus<sup>3</sup>. Regardless of the mechanism of the feedback, its effect is to maintain an almost constant

concentration of free thyroid hormones in the circulating body fluids. The whole basis of TSH as a biological marker is as follows, a high value indicates an underactive gland and a low TSH value indicates an overactive gland. Hence elevated level of TSH indicates primary hypothyroidism and low TSH level indicates hyperthyroidism. The serum TSH is a preferred test since TSH only can detect mild i.e. subclinical degrees of excess or deficient thyroid hormones. But less sensitive TSH assays are prone to produce false negative results on sample with subnormal TSH concentrations. With improved sensitivity (functional sensitivity  $\leq 0.02$  mIU/L) in TSH assay, it is now considered that TSH measurement is a more sensitive test than FT4 for detecting hypo and hyperthyroidism. Hence, some countries now promote TSH as first strategy for diagnosing thyroid dysfunction. Other countries still favor the TSH+FT4 combined approach as diagnosis only by TSH strategy can miss patients with Central hypothyroidism or TSH secreting pituitary tumor<sup>4</sup>. One has to also keep in mind that TSH/FT4 relationship can be discordant in conditions like sick euthyroid states, pregnancy related increased thyroxine binding globulin and hCG mediated thyroid stimulations. In one of the population surveys, the prevalence of subclinical hypo- and hyperthyroidism with abnormal TSH and normal FT4 has been reported to be about 10% and 2% respectively<sup>5</sup>. Despite the clinical sensitivity of TSH, a TSH central strategy has two primary limitations. First, it assumes that hypothalamic-pituitary function is intact and normal. Secondly, it assumes patient's thyroid status is stable<sup>4</sup>. If above criteria are not met, serum TSH results can give misleading diagnosis. TSH is a labile hormone and subject to non-thyroidal pituitary influences i.e.

glucocorticoids, somatostatin, dopamine etc that can disrupt the TSH/FT4 relationship <sup>6</sup>. When investigating the cause of an abnormal TSH with normal FT3 and FT4, it is important to repeat TSH level after 3 weeks to confirm the abnormal TSH level. After confirming a high TSH abnormality, a TPOAb measurement is a necessary for establishing the presence of thyroid autoimmunity as the cause of mild (subclinical) hypothyroidism. The development of thyroid failure is considered when higher concentration of TPOAb is present. After confirming a low TSH abnormality it can be difficult to establish a diagnosis of mild (subclinical) hyperthyroidism <sup>7</sup>. If a multinodular goiter is present then thyroid autonomy is the likely cause of mild (subclinical) hyperthyroidism.

Further, there are no data available on the relative importance of biochemical thyroid stimulating hormone test and clinical symptoms and signs in assessing thyroid dysfunction. Secretion of thyroid stimulating hormone is influenced by many factors other than the negative feedback inhibition by thyroxine or triiodothyronine. Changes in thyroid stimulating hormone, thyroxine, and triiodothyronine concentrations during systemic illness are not understood properly. Thyroid stimulating hormone cannot be interpreted in patients with systemic illness. Because of the above factors possibility of false positive and false negative results should be considered while interpreting thyroid stimulating hormone concentrations <sup>8</sup>.

### **TSH and Pregnancy**

Serum TSH value during pregnancy is influenced by the thyrotropic activity of elevated circulating hCG concentration. Thus by using classical reference range for serum TSH, one may misdiagnose hypothyroidism in normal women who have high TSH level and hyperthyroidism in normal women who have low serum TSH value <sup>9</sup>. To overcome this problem the clinical picture should go hand in hand with TSH interpretation. One should also consider that pregnancy related volume increase with sympathetic activation complicates the clinical interpretation. Therefore if clinical suspicion is high, serial TSH estimations in weekly or twice weekly intervals initially are important in reaching the correct diagnosis.

### **Hypothyroidism and pregnancy**

The prevalence of clinical and sub-clinical hypothyroidism during pregnancy is estimated to be 0.3 to 0.5% and 2.3% respectively. Chronic autoimmune thyroiditis is the main cause of hypothyroidism during pregnancy <sup>10</sup>.

**Maternal Aspects:** There is known association between hypothyroidism and decreased fertility. Many years ago hyperprolactinaemia due to increased hypothalamus TRH secretion was believed to be cause of infertility. Recent epidemiological and clinical observations of a large number of patients demonstrated that hypothyroidism is associated with only minor menstrual disturbances and minimal change in serum prolactin concentration <sup>11</sup>. Thyroid hormones modulate the LH and FSH mediated control of granulosa cell function. Thus hypothyroidism interferes with ovulation and therefore results into low conception rate. Patient with basal TSH less than 2.5 mIU/l or TRH stimulated TSH less than 20mIU/l treated with T4 therapy had increased conception rate<sup>12</sup>. Hypothyroidism in pregnant women carry an increased risk for early and late obstetric complications like abortion, gestational hypertension, placental abruption and PPH. These complications are more frequent with overt hypothyroidism (OH) than sub clinical hypothyroidism (SCH). When they were adequately treated with thyroxine, the risk of obstetric complications is significantly reduced<sup>13</sup>. Glinor D et al reported that abortion rate is higher with higher basal TSH and not with elevated thyroid antibodies <sup>14</sup> while others reported that there is significant abortion rate in presence of antibodies to thyroid peroxidase or thyroglobin <sup>15</sup>.

**Fetal Aspects:** Untreated maternal OH & SCH are associated with adverse neonatal outcomes including premature birth, LBW, RDS and perinatal deaths <sup>13</sup>. Thyroid hormone is necessary for normal fetal brain development. There was significant increased risk of impairment in neuropsychological indices including IQ scores and school learning ability in the offspring of hypothyroid mothers <sup>16</sup>.

### Hyperthyroidism and pregnancy

The prevalence of hyperthyroidism in the United States is approximately 1% (0.4% clinical and 0.6% subclinical) and during pregnancy it is 0.1 to 0.4% (12). Grave's disease contributes to about 85% of hyperthyroidism<sup>17</sup>. When subnormal TSH concentration is detected during pregnancy hyperthyroidism must be ruled out due to normal physiological changes during pregnancy and hyperemesis gravidarum. Overt hyperthyroidism has adverse effect on the mother and fetus. In the normal pregnant woman, TSH level typically falls in the mid to late first trimester coincident with rising hCG levels. Therefore, subnormal serum TSH level in the first half of pregnancy should not be interpreted as hyperthyroidism<sup>18</sup>.

**Maternal Aspects:** Improper treatment of thyrotoxicosis can increase the risk of medically indicated preterm delivery. In retrospective studies of 450 patients by Millar L K et al<sup>19</sup>, the rates of complications of preeclampsia 7% vs. 22%, congestive heart failure 3% vs. 60% and thyroid storm 2% vs. 21% in treated v/s untreated patients respectively. Even in those hyperthyroid women in whom control was achieved before delivery, the incidences of preeclampsia (11.1%) and preterm delivery (8.4%) were more than control<sup>20</sup>. Poorly controlled hyperthyroidism is also associated with increased risk of IUGR, LBW and perinatal mortality<sup>21</sup>.

**Fetal Aspects :** It is associated with significant risk of fetal and neonatal thyroid disease which presents as fetal tachycardia, IUGR, fetal cardiac failure and fetal goiter<sup>22</sup>.

**Clinical Utility of TSH Assays :** (Functional Sensitivity < 0.02 mIU/L) Serum TSH measurements are an important pre-natal and first trimester screening test to detect mild (subclinical) hypothyroidism in the mother and is the sensitive test for detecting mild (subclinical), as well as overt, primary hypo-or hyperthyroidism. It has been observed that majority of healthy euthyroid subjects have a serum TSH concentration below 2.5 mIU/L. Patients with a serum TSH above 2.5 mIU/L when confirmed by a repeat TSH measurement made after 3 weeks, indicates the early stages of thyroid failure with positive TPOAb test. With serial serum TSH measurement

the L-T4 replacement dose for primary hypothyroidism and for monitoring L-T4 suppression therapy is done. Only TSH cannot be used to diagnose central hypothyroidism. When the serum FT4 is low and yet the serum TSH is only minimally elevated (<10 mIU/L), a diagnosis of central hypothyroidism should be done.

### Conclusion

Thyroid dyfunctions are commonly seen in obstetrics & gynaecology and are associated with poor outcome. With Functional Sensitivity of  $\leq 0.02$  mIU / Serum TSH measurement is a reliable test for detecting mild (subclinical), as well as overt primary hypo-or hyperthyroidism. But secretion of thyroid stimulating hormone is influenced by many factors other than the negative feedback inhibition by thyroxine or tri-iodothyronine. Thyroid stimulating hormone cannot be interpreted in patients with systemic illness and other dysfunctions like central hypothyroidism. Serum TSH value during pregnancy is influenced by the thyrotropic activity of elevated circulating hCG concentration particularly near the end of first trimester. Therefore by using classical values of reference range for serum TSH, one may misdiagnose thyroid dysfunction. All above factors can reduce the diagnostic accuracy of serum TSH resulting into mismanagement of Thyroid Dysfunctions, particularly during pregnancy and put TSH in a miserable state.

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