# The Effect of Thyroxine Treatment in Infertile Subclinical Hypothyroid Patients

**Hanan L. Sudek.*** **MBChB, MSc, PhD Reproductive Physiology.**

**Summary:**

**Background:** Sub-clinical hypothyroidism (SCTD) is most commonly an early stage of hypothyroidism. Although the condition may resolve or remain unchanged, within a few years in some patients, overt hypothyroidism may develop, with low free $T_4$ levels as well as a raised thyroid stimulating hormone(TSH) level. In general thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome. As screening for thyroid disease becomes more common, SCTD is being diagnosed more frequently in clinical practice. The aim of the study is to find out the effect of treating SCTD with thyroxin on the fertility status of the female patient.

**Patients and methods:** Forty three infertile patients attending the infertility clinic at Baghdad teaching hospital were compared to 32 control un explained infertility women. After exact history and examination, hormonal analysis (T3 and T4, TSH, Prolactin and Progesterone) and ultrasound were done for patients and control, then the patients were randomly divided into 2 groups one group was given thyroxine treatment, the other group was given parlodel, and after 3 months the hormonal analysis and ultrasound were repeated and compared to the previous results.

**Results:** Comparing the patient group to the control showed a significant increase in the TSH and prolactin level in patients group but the progesterone concentration was not significantly different between the groups. After giving thyroxine the group who received it showed significant reduction in prolactin and improvement in the dominant follicle size and progesterone level while the group who was given parlodel showed only significant reduction in prolactin with no significant increase in the other 2 parameters.

**Conclusion**: TSH in subclinical hypothyroidisim is correlated positively with age and with the prolactin concentration. Treatment with thyroxine induces a significant improvement in the fertility statues including the significant decrease in prolacttin concentration and increase in the dominant follicle size and increase in the progesterone level compared to those given parlodel only. This makes it obvious that treating patients with SCTD have a significant reflection on their fertility and ability for future pregnancy.

**Key words:** thyroid dysfunction, sub- clinical hypothyroidism, infertility.

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## Introduction:

The term subclinical hypothyroidism (SCTD) is used for patients who have mildly increased levels of serum thyrotropin hormone (TSH) but normal thyroid hormone (thyroxine and triiodiothyronine) levels.

An increase in serum TSH concentration is an early and sensitive indicator of decreased thyroid reserve (1), and the prevalence of SCTD has been reported to be between (4 and 10%) of adult population samples (2).

The clinical signs and symptoms of hypothyroidism are manifest when the disease is fully developed. But even in the earliest (subclinical stage), one or more of these findings may occur. In one study, symptoms of subclinical hypothyroidism in a group of patients were shown to be Dry skin, cold intolerance and easy fatigability were significantly more common in the patients with raised TSH levels, and these symptoms improved after treatment with thyroid hormone (3). In another study in female patients with subclinical hypothyroidism, a clinical index based on symptoms and physical signs were shown to be more abnormal in patients with higher TSH levels, even though all patients had normal serum levels of $T_4$ and free $T_4$. These studies suggest that some patients with subclinical hypothyroidism do indeed have clinical manifestations of mild thyroid failure (4).

Subclinical hypothyroidism is caused by the same disorders of the thyroid gland as those that cause overt hypothyroidism, Chief among these is chronic autoimmune thyroiditis (Hashimoto's disease), which is commonly associated with increased titers of antithyroid antibodies (5).

Persistent TSH increase is noticed in subacute thyroiditis, postpartum thyroiditis, and painless thyroiditis. Other causes include thyroid injury: partial thyroidectomy or other neck surgery, radioactive iodine therapy, and external radiotherapy of the head and neck. Less common causes of hypothyroidism include the use of drugs impairing thyroid function: iodine and iodine-containing medications, inadequate replacement therapy for overt hypothyroidism, and

**Department of Physiology /College of Medicine, Baghdad University*

thyroid infiltration (6, 7, 8, 9). Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility (10). It is a cause of infertility and habitual abortion (11).

Mild hypothyroidism may also contribute to disturbing reproductive function, which was found in many researches including a study in Vienna, where abortions appeared to be associated with higher TSH, but not with elevated thyroid antibodies (12)

A panel of experts recently divided patients with SCTD into two categories: patients with mildly increased serum TSH levels (4.5–10 mIU/liter), and patients with more severely increased serum TSH levels (>10 mIU/liter) (13).

At the beginning of this century thyroid preparations were already being administered to women with clinical signs of hypothyroidism to improve ovarian function for fertility reasons and to treat menorrhagia (14). Later, after endocrine thyroid tests had been established many euthyroid women were also treated with thyroid hormones on a routine basis merely because they were anovulatory (15).

The aim of this study was to find out the effect of treating those patients with subclinical hypothyroidism with thyroxin on their fertility status.

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**Patients and methods:**

Forty three infertile patients attending the infertility clinic at Baghdad teaching hospital were compared to 32 control unexplained infertility women.

Full history and examination was done to patients and control including obstetrical and gynecological history, examination of the thyroid gland, and semen analysis for the husband to exclude male factor of infertility.

The patients and control also were free of any drug during the last 3 months before the beginning of the study.

All patients were told about the research study. Related history and physical examination data were recorded in a pre-designed data collection sheet.

Inclusion criteria for patients were age 20 to 45 years, and a normal thyroid ultrasound with no morphological lesions, TSH level more than 5.0 mIU/liter on 2 consecutive blood tests. Exclusion criteria were defined as history of thyroid disease, goiter, or other morphological thyroid anomalies, including nodules or very high levels of basal prolactin.

The patients and control were examined for ovarian function in an untreated menstrual cycle by a commonly used endocrinological screening protocol (including doing hormonal analysis (LH, FSH, Prolactin, TSH, T4 and T3) in cycle day 3 and progesterone in cycle day 21. Serum samples were stored at –20°C for later analysis.

The control group are women having unexplained infertility with normal T3,T4 and TSH concentration i.e euthyroid.

Ultrasound in cycle day 12 was done for the determination of the dominant follicle size and to exclude any pathology.

Patients are described as having subclinical hypothyroidism when their serum concentrations of T4 and triiodothyronine (T3) are normal; the serum TSH concentration is raised. and because SCTD is only detected as a TSH abnormality, the definition of the TSH reference range is critical (16).Over the last three decades, the upper reference limit for TSH has declined from about 10 mIU/liter with the first-generation TSH RIAs to about 4.0–4.5 mIU/liter with subsequent TSH assays and the use of thyroid antibody tests to prescreen subjects (17, 18). But this study depended on the reference range of 0.5-5 mU/L (19).

The patients were divided into 2 groups, were randomly assigned to receive low dose levothyroxine tablets, 50 mcg orally once a day (levothyroxine, 50 mcg/tablet, Glasxo, UK) for 3 months. TSH evaluation was done each month to avoid decreasing TSH below normal range. The other group received only bromocriptine myslate tablets (2.5 mg/tablet, parlodel, Novartis, once per day).

In the following cycle the hormonal analysis and ultrasound which were done in the first cycle before treatment were repeated and the results were recorded.

Enzyme immunoassay for the quantitative determination of Thyroid Stimulating Hormone (TSH) T3 .T4 (Thyroid hormone) and prolactin in human serum was used (BioCheck Enzyme Immunoassay).

All data are expressed as the mean ± SEM. t test (two-sided) used to show the difference between 2 groups**.** Correlation coefficient between continuous variables was also determined. Significance was defined as $P \leq 0.05$, using SPSS for Windows (version 10.0, SPSS)

**Results:**

The mean of age ,TSH ,prolactin and progesterone for patients and control groups are shown in table 1,where there is no significant difference in age between patients (32.256 ± 6.188**)** and control (31.438 ± 6.064**),**while it is obvious that there is a significant difference in TSH level between the patients and the control euthyroid group.

The patients group were shown also to have a significantly higher prolactin level than the control group, while progesterone concentration was higher in control groups but with no significant difference from the patients group.

**Table (1): Age, TSH, prolactin and progesterone in patients and control groups before treatment.**

| | Range | Patients | Control | Range | P |
|---|---|---|---|---|---|
| Age | 20-42 (Years ) | 32.256 ± 6.188 n= 43 | 31.438 ± 6.064 n=32 | 21-43 (Years ) | >0.1 |
| TSH | 5.2-15 mIU/liter | 8.319 ± 2.440 | 1.366 ± 0.474 | 0.7- 2.4 mIU/liter | <0.005 |
| Prolactin | 30-66 µg/l | 36.954 ± 3.854 | 10.313 ± 3.906 | 8-20 µg/l | <0. 005 |
| Progesterone | 0.5-2.3 ng/ml | 1.244 ± 0.439 | 3.134 ± 0.531 | 2.4-4.2 ng/ml | >0.1 |

After correlating the TSH with the age of the patients, it is found to be correlated positively i.e. with increasing age, there is increase in the TSH level in the blood but the correlation was not statistically significant (table 2).

**Table (2): Correlation between TSH level and age in patients group.**

| | TSH | |
|---|---|---|
| | r | p |
| Age | 0.182 | > 0.05 |

Table 3 showed that prolactin level in patients group is correlating positively and significantly with the TSH level, so by increasing TSH there is increase in the prolactin level.

**Table (3): Correlation between TSH level and prolactin level in patients group.**

| | TSH | |
|---|---|---|
| | r | p |
| Prolactin | 0.4102 | <0.005 |

After giving thyroxin treatment to the first group of patients, it is obvious that prolactin level decreased significantly after treatment and there is significant improvement in the dominant follicle size. The progesterone level gained a significant increase after the treatment as demonstrated in table 4**.**

**Table (4): Comparison between prolactin, dominant follicle, and progesterone before and after treatment with thyroxin in first group of patients.**

| | Before treatment | After treatment | p |
|---|---|---|---|
| Prolactin | 36.88 ± 3.598 n= 25 | 21.44 ±7.343 n= 25 | <0.005 |
| Dominant follicle | 11.4 ± 2.723 | 17± 1.443 | <0.005 |
| Progesterone | 1.232± 0.439 | 2.56± 0.676 | <0.005 |

The other group of patients who received parlodel only showed significant reduction in prolactin but the improvement in the dominant follicle size and progesterone level are not significant (table 5).

**Table (5): Comparison between prolactin, dominant follicle, and progesterone before and after treatment with parlodel in second group of patients.**

| | Before treatment | After treatment | p |
|---|---|---|---|
| Prolactin | 37.056 ± 4.290 n=18 | 22.556 ±7.213 n=18 | <0.05 |
| Dominant follicle | 12.056± 2.182 | 14.222± 1.396 | >0.1 |
| Progesterone | 1.261± 0.453 | 1.556± 0.440 | >0.1 |

**Discussion:**

Measuring TSH level in patients and control groups demonstrate that it is significantly higher in patients (8.319 ± 2.440) than control group (1.366 ± 0.474).

This goes with a study in Belgium, which showed that the mean serum TSH levels were significantly higher in women of infertile couples compared to an age-matched control population of women (10). And 80% of these patients with SCTD have a serum TSH of less than 10 mIU/L (20).

Prolactin level in patients group was also significantly higher than control, this agrees with a study done by Lunenfeld et al, who suspected that patients with increased prolactin values are often hypothyroid women (21), Maj Kenneth etal reported also that Hyperprolactinemia is common in suclinical hypothyroid patients hypothyroid patients (22), and when correlating the TSH with the prolactin level there was a significant positive correlation, which was found also by Cramer and co-workers., who states that TSH and prolactin were positively correlated in subclinical hypothyroid women undergoing In Vitro Fertilization (IVF) (23). This correlation was also documented in a study done in India in 2009 (24). However, this cannot be observed regularly because some studies found that no correlation was observed between TSH and PRL levels, but they recommend

further studies with a large sample size and long follow-up that are necessary to validate the variation in TSH and prolactin levels (25, 26).

It is found also in this study that TSH is correlated positively with age, which means that with increasing age there are more chances to experience subclinical hypothyroid state. This goes with the results of other researchers who found that spontaneous subclinical hypothyroidism is more common in women and the incidence increases with age. In community surveys, around 10% of women over 55-60 years of age have been found to have a serum TSH concentration over 5 or 6 mU/L ( 27, 20), but some researchers said that it is more found in young and middle aged women( 28).

After treatment with thyroxin, the level of prolactin decreased significantly. This was reported also by another study which states that, serum prolactin concentrations fell to normal during T4 therapy in more than a half of the patient treated. And some of the rest of the patients in whom the concentration remained high a brain MRI had a pituitary abnormality (29). , and this was reflected also on the dominant follicle size where it is observed that there is a significant increment in the size of the dominant follicle, in addition to that there is significant increment in the progesterone level, and this is important since preliminary data have suggested that female infertility due to corpus luteum insufficiency may be caused by subclinical hypothyroidism (15). Thus, thyroxine therapy has generally been recommended for all subclinical hypothyroid infertile patients to improve luteal function (30).On the other hand treating the other group of patients with parlodel only results in significant decrease in prolactin level but there was no significant improvement in dominant follicle size or progesterone level. These findings clarify that treatment with thyroxine probably correct any biochemical abnormality in order to provide as normal a hormonal environment for pregnancy as possible (31).

It is clear that thyroxine therapy is indicated in overt hypothyroidism and uniform agreement exists that it is also indicated for patients whose TSH levels are permanently increased above 10 mIU/L. The grey zone to treat or not to treat considers patients with TSH levels between 5 – 10 mIU/L. Therapy for these milder forms is controversial. In clinical practice some doctors treat all such patients while others choose to reassess the thyroid function in 3-6 months to find out if the thyroid abnormality is transient (32).

So one can notice from the results of the study that treating those with subclinical hypothyroisdisim with thyroxin seems to affect the fertility status positively, which agrees with the result of other researchers who found that L-Thyroxine supplementation has been recommended to achieve pregnancies in subclinical hypothyroid patients (30).

**Conclusion:**

Subclinical hypothyroidism is a cause of infertility that can be missed as noticed from its effect on prolactin level in patients having this condition and a consequent effect on the dominant follicle size and the progesterone concentration which indicates the ovulatory status of these patients. TSH level as a guid for diagnosing subclinical hypothyroidisim increased with increasing age as indicated by the significant positive correlation between them and it correlated positively and significantly also with the prolactin level. Treatment with thyroxin is found to be very effective in infertile SCTD since it causes a significant decrease in the prolactin level and a significant increase in the dominant follicle size and progesterone concentration,which will potentiate the ability of the female to get pregnant in the future .

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