Original Article

# Thyroxine Therapy for Recurrent Pregnancy Loss in Hypothyroid Women



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## ABSTRACT

**Objective:** To estimate the optimal TSH level for starting T4 treatment in subclinical hypothyroidism.
**Study Design:** Non-randomized clinical trial study
**Place and Duration of Study:** This study was conducted at the Tertiary Obstetric Hospital at Al-Kindy College of Medicine, Iraq from March 2022 to May 2023.
**Methods:** It comprised 77 cases. The participants were women with TSH levels above 2.5 mU/L and with RPL. The study had two groups based on thyroid-stimulating hormone (TSH) levels (TSH level 2.5-4 mU/L and TSH ≥4 mU/L groups). Participants received T4 therapy and were followed for 6 months. The primary outcome was the rate of successful pregnancy, followed until delivery and the gestational age and birth weight of the newborn.
**Results:** The rate of successful pregnancy, gestational age, and birth weight were not different between the two groups. The titer of thyroid peroxidase antibodies was significantly reduced after 6 months of T4 therapy, but the starting threshold of the treatment did not influence the amount of reduction of the titer. Regression analysis showed, the titer of thyroid peroxidase antibodies after 6 months of treatment was significantly associated with increased rate of successful pregnancy.
**Conclusion:** Reducing the thyroid-stimulating hormone treatment threshold alone may not guarantee improved pregnancy outcomes. The study suggests that T4 therapy's benefits may be more closely linked to antibody titer changes.


**Key Words:** Levothyroxine, Thyroid-stimulating hormone (TSH), Thyroid peroxidase antibodies, Recurrent miscarriage, Pregnancy outcomes

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## INTRODUCTION

Recurrent pregnancy loss has been linked to subclinical hypothyroidism. Debates regarding levothyroxine (T4) starting thresholds as the American Thyroid Association suggested to decreases the threshold of starting the treatment of subclinical hypothyroidism from 4 mU/L to 2.5 mU/L.

According to the European Society for Human Reproduction and Embryology (ESHRE) guidelines, recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies.[1] Thyroid autoimmunity affects about fifth the cases of RPL women.[2] Subclinical hypothyroidism (SCH) and thyroid peroxidase antibodies (TPOAb) positivity are associated with adverse pregnancy outcome.[3]

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Levothyroxine medication reduced the risk of miscarriage and increased fertility in women with thyroid disease, according to research by Dal Lago et al.[4] Recently, American Thyroid Association[5] suggested to decrease the threshold of starting the treatment of SCH from 4mU/L to 2.5 mU/L, based on a study conducted by Negro et al[6] that found increased RPL at a thyroid-stimulating hormone (TSH) level 2.5 mU/L. This reduction in the threshold is associated with increased prescription rates of levothyroxine treatment, with possible increased maternal concern. Given these changes in guidelines it is crucial to examine the optimal threshold for starting levothyroxine therapy.

## METHODS

This is a prospective non-randomized clinical trial conducted in tertiary obstetric hospital from 1st March t2022 to 30th May 2023. The participants were all women with RPL who visits the fertility clinic during the period of the study. The inclusion criteria were childbearing aged women (18-40 years), had recurrent pregnancy loss, with TSH level is equal or higher than 2.5 mU/L and normal T3 and T4 levels. women with known cause of RPL (examples of conditions include antiphospholipid syndrome, uterine anomalies, genetic/chromosomal problems, and so forth), women had chronic medical illnesses, those with allergy or

intolerance to levothyroxine therapy, or those already receiving levothyroxine treatment were excluded.

According to TSH level, the participants divided into two groups, those with TSH level 2.5-4 mU/L and those with TSH ≥4 mU/L. Data collected included demographics of the participants, the number of pregnancy losses, and the number of live births, alone with measurement of baseline level of TPOAb level. All participants receive levothyroxine therapy (eEuthyrox 50 Mcg Tablet, Merck) in a dose of 1.6 µg/kg/day early in the morning on an empty stomach. Follow up of the participants for the first six months and measuring the new TPOAb level and reporting the primary outcome which was the rate of SP (defined as pregnancy that continued beyond first trimester), the pregnant women were followed till time of delivery and the secondary outcomes were reported which were the gestational age at which delivery happened and the birth weight of the neonate.

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study received approval from the hospital's ethical and scientific authorities. This study was registered at clinical trials.gov website (identification number: NCT06036576), consent was obtained from all the participants after thoroughly discussing the study and patient's options.

The data entered and analyzed through SPSS-26 for statistical analysis. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were analysed for significance using the student t-test and reported as mean and standard deviation (SD). Skewed variables were evaluated for significance using the Mann-Whitney U test and reported as median and minimum to maximum range. The significance level was assessed using either the Chi-square test or the Fisher exact test, depending on appropriateness. A p value of ≤0.05 is regarded to be statistically significant.

# RESULTS

The total number of women presented was 136 cases, 59 cases were excluded from the study (35 women had chronic medical condition (diabetes or hypertension), 17 cases had antiphospholipid syndrome, and 7 cases smokers), and the total number of SCH cases was 77 cases. Based on TSH level at which levothyroxine treatment started, the data divided into two groups: group A women with TSH ranged from 2.5 to 4 mU/L which was 39 cases (50.6%) and group B with TSH ≥4mU/L which was 38 cases (49.4%). The women age, BMI, the number of previous pregnancy loss and live births were not different between the two groups. The presence of TPOAb is not different regarding the level of TSH at which treatment started. The rate of successful pregnancy was not different between the two groups. Women that get pregnant were not different in regard to the gestational age at delivery or neonatal birth weight (Table 1). Based on the presence of TPOAb the data divided into two groups TPOAb+ group represent 57 cases, and TPOAb- in 20 cases, the outcome of pregnancy further examined and no difference in the pregnancy outcome, gestational age at time of delivery, nor birth weight were found (Table 2). The titer of TPO antibodies was significantly reduced after six months of levothyroxine therapy, yet the starting threshold of the treatment did not influence the amount of reduction of TPO Ab titer (Table 3). After application of regression analysis, we found that the titer of TPO Ab after six months of treatment was significantly associated with increased rate of successful pregnancy. No influence on the starting level of levothyroxine therapy (Table 4).

**Table No.1: Distribution of data according to TSH level threshold**

| **Variables** | | **TSH 2.5-4mU/L (n=39)** | **TSH ≥ 4mU/L (n=38)** | **P value** |
|---|---|---|---|---|
| Age (years)* | | 34 (17-38) | 28 (16-40) | 0.084 |
| BMI (kg/m$^2$)† | | 27.11 ±2.23 | 27.32 ±2.26 | 0.685 |
| No. of pregnancy loss* | | 4 (3-6) | 5 (3-6) | 0.156 |
| No. of live birth* | | 1 (0-3) | 1 (0-3) | 0.233 |
| TSH (mU/L)* | | 3.34 (2.5-3.98) | 6.41 (4.05-7.96) | <0.0001 |
| TPO antibodies (UI/ml)‡ | Positive | 32 (82.1%) | 25 (65.8%) | 0.104 |
| | Negative | 7 (17.9%) | 13 (34.2%) | |
| Pregnancy outcome‡ | Successful pregnancy | 11 (28.25) | 9 (23.75) | 0.796 |
| | Miscarriage | 28 (71.8%) | 29 (76.3%) | |
| GA at time of delivery (weeks)* | | 36 (32-39) [n=11] | 35.29 (28.29-38)[n=9] | 0.331 |
| Birth weight (grams)† | | 2364.64 ±406.98 [n=11] | 2167 ±699.49 [n=9] | 0.467 |

*Data presented in the form Median (minimum-maximum);p-value calculated using Mann Whitney u test

†Data presented in the form of mean ±SD; p value calculated using student t test

‡Data presented in the form of number (percent); p value calculated using fishier exact test

**Table No.2: Study outcomes according to presence of TPO antibodies and threshold of starting levothyroxine therapy**

| Variable | | TPOAb+ | | | TPOAb- | | |
|---|---|---|---|---|---|---|---|
| | | TSH 2.5-4 mU/L (n=32) | TSH ≥ 4 mU/L (n=25) | P value | TSH 2.5-4 mU/L (n=7) | TSH ≥ 4 mU/L (n=13) | P value |
| Pregnancy outcome‡ | Successful pregnancy | 9 (28.1%) | 5 (20%) | 0.479 | 2 (28.6%) | 4 (30.8%) | 0.919 |
| | Miscarriage | 23 (71.9%) | 20 (80%) | | 5 (71.4%) | 9 (69.2%) | |
| GA at time of delivery (weeks)* | | 36 (33-39) [n=9] | 35.29 (28.43-38) [n=5] | 0.190 | 33.5 (32-35) [n=2] | 34.29 (28.29-38) [n=4] | 1.000 |
| Birth weight (grams)† | | 2368.44 ±454.85 [n=9] | 2310.6 ±899.73 [n=5] | 0.898 | 2347.5 ±21.92 [n=2] | 1987.5 ±384.81 [n=4] | 0.158 |

**Table No.3: TPO antibody titer before and after six months of treatment and comparison of the level of reduction of antibody level based on threshold of treatment**

| TPOAb titer | | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|
| Baseline level | | 586 | 380 | 751 | <0.0001 |
| After6 months | | 430 | 244 | 577 | |
| Difference in Ab level* | TSH 2.5-4 | 120.5 | -113 | 474 | 0.822 |
| | TSH ≥ 4 | 156 | -154 | 413 | |

*The difference calculated as follows: baseline TPO Ab level- TPO Ab level after 6 months of treatment. Negative value was found as some cases had elevated TPO Ab titer on treatment.

**Table No.4: Logistic regression analysis (successful pregnancy as dependent variable)**

| Independent variables | B | S.E. | Wald | P value | Exp(B) |
|---|---|---|---|---|---|
| Threshold 2.5-4 | 0.057 | 1.006 | 0.003 | 0.955 | 1.059 |
| Age | 0.016 | 0.038 | 0.185 | 0.667 | 1.017 |
| BMI | -0.07 | 0.125 | 0.316 | 0.574 | 0.932 |
| No. of pregnancy loss | 0.099 | 0.264 | 0.14 | 0.708 | 1.104 |
| No. of live birth | 0.115 | 0.26 | 0.196 | 0.658 | 1.122 |
| TSH | 0.175 | 0.301 | 0.34 | 0.56 | 1.192 |
| Baseline TPO AB titer | -0.003 | 0.002 | 1.954 | 0.162 | 0.997 |
| after 6 months | 0.006 | 0.003 | 3.913 | 0.048 | 1.006 |
| Constant | 0.458 | 4.263 | 0.012 | 0.914 | 1.581 |

# DISCUSSION

According to the American Thyroid Association, greater maternal TSH levels have been linked to a higher likelihood of miscarriage.[5] The therapeutic starting thresholds for SCH patients have been discussed as a result of this finding. According to Negro et al[6], a TSH level above 2.5mIU/L in the first trimester may be associated with a greater probability of miscarriage. In order to avoid selection biases, our study tried to choose a sample with the least amount of age and BMI variation. Every participant in our study fell into the category of recurrent miscarriage since they had all experienced a minimum of three pregnancies lost.

Our findings differ noticeably from a number of recent researches. While Liu et al[7] supported the possible dangers of increased TSH during early pregnancy, our investigation was unable to detect a statistically significant difference in successful pregnancy outcomes based on TSH therapy initiation thresholds. In a different context, Maraka et al[8] emphasized the advantages of levothyroxine therapy for SCH patients with thyroid autoimmunity in preventing pregnancy problems.

The outcome of pregnancy was not influenced by threshold of treatment in cases of neither SCH with TPOAb+ nor SCH with TPOAb- groups. the trial conducted by van Dijk et al[9] found that the levothyroxine treatment had no effect on the outcome of pregnancy in SCH either positive or negative TPO titer.

The presence of TPO Ab was uniformly distributed according to the threshold of treatment. Levothyroxine supplementation is associated with significant reduction of TPO Ab titer after six months of treatment. The threshold of treatment was not influencing the level of titer reduction, in other words just starting treatment of levothyroxine could improve the titer of antibody. Similarly suggested by Mosaddegh et al.[10]

The single independent predictor of successful pregnancy in this study was found to be level of TPO

ab titer after six months of levothyroxine treatment. In other words, the increase in the pregnancy rate found by previous studies may be attributable to the effect of levothyroxine treatment on antibody titer rather than a direct relationship. Similarly, Dong et al[11] found that cases of RPL associated with thyroid autoimmunity rather than levothyroxine therapy.

This study indicates that just lowering the treatment threshold might not always result in better results. The interaction between SCH and the results of pregnancies may be influenced by other latent factors. For instance, Salazar et al[12] mentioned how thyroid function and pregnancy outcomes are influenced by environmental contaminants and nutritional shortages.

The current study is constrained by the absence of a control group, which would have offered a more thorough analysis of levothyroxine's effectiveness. Larger, multi-center randomized controlled trials may be required in the future.

# CONCLUSION

Reducing the TSH treatment threshold alone may not be sufficient to ensure improved pregnancy outcomes. There could be more unidentified factors affecting how SCH and pregnancy outcomes interact. After six months of treatment with levothyroxine, TPO antibody titers significantly decreased. The TSH threshold at which treatment was started had no effect on the size of this decline. The only indicator of a successful pregnancy after six months of levothyroxine treatment was the titer of TPO antibodies. This implies that rather than directly interacting with TSH levels, the possible advantages of levothyroxine therapy in reducing pregnancy problems may be more closely linked to its effect on antibody titers.

**Author's Contribution:**

| | |
|---|---|
| Concept & Design or acquisition of analysis or interpretation of data: | Sarah Al-Musawi, Kamal Al-Jawdah |
| Drafting or Revising Critically: | Sarah Al-Musawi, Kamal Al-Jawdah |
| Final Approval of version: | All the above authors |
| Agreement to accountable for all aspects of work: | All the above authors |

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