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Original Article

# Effect of extra-low dose levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism undergoing in vitro fertilization and embryo transfer

Yi-Ting Chen [a], Chung-Han Ho [b], Ming-Ting Chung [a], Jen-Yu Wen [a], Yi-Lun Lin [a], Tsun-Wen Hsiao [a], Yung-Chieh Tsai [a, c, *]

[a] Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Chi Mei Medical Center, Tainan, Taiwan
[b] Department of Medicine Research, Chi Mei Medical Center, Tainan, Taiwan
[c] Department of Sport Management, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

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ABSTRACT

*Objective:* This study was undertaken to test the therapeutic effect of extra-low dose of levothyroxine (LT4; 25 mcg/day) to preconception and pregnant women with subclinical hypothyroidism (SCH).
*Materials and methods:* This is a retrospective study, SCH women who succeeded in their first in vitro fertilization (IVF) cycle between January 1, 2018, to December 31, 2020 were included. SCH is defined as normal serum free thyroxine (T4) level and an elevated serum thyroid stimulating hormone (TSH) level >4 mIU/L. Extra-low dose of levothyroxine (LT4; 25 mcg/day) was prescribed to the SCH women from the establish of diagnosis of SCH to the end of pregnancy. The pregnancy outcomes (miscarriage, live birth, preterm birth, and small for gestational age baby) were compared to the euthyroid pregnant women.
*Results:* Totally, 589 women were screened, and 317 cases received their first time IVF treatment. 167 women were clinically pregnant after IVF treatment, 155 of them were euthyroid and 12 of these women were diagnosed to have SCH. The average age of the participants was 35 years old. There were no significant differences in age, body mass index (BMI), anti-müllerian hormone (AMH), types of embryo transfer, number of embryos to transfer, or embryo stage during transfer between two groups. The live birth rate, miscarriage rate, and preterm birth rate in women with SCH supplemented with extra-low dose of LT4 were non-inferior to euthyroid patients (miscarriage rate: $P = 0.7112$; live birth rate: $P = 0.7028$; preterm delivery: $P = 0.2419$; small for gestational age: $P = 0.2419$).
*Conclusion:* Our result demonstrated that supplementation with extra-low dose of levothyroxine at 25 mcg/day to SCH women can produce the comparable obstetrical and neonatal outcome as that in euthyroid pregnant women. Accordingly, we suggest extra-low-dose of levothyroxine may be considered as a safe and effective alternative for those SCH pregnant women who were not tolerated to the standard dose of levothyroxine.


## Introduction

Subclinical hypothyroidism (SCH) is defined as normal serum levels of free thyroxine (T4) with elevated thyroid stimulating hormone (TSH) without obvious clinical symptoms [1]. The prevalence of SCH in the reproductive-age population is approximately 4–8% [2], while in infertile women, the incidence of SCH can reach 13.9% [3]. Previous studies have demonstrated that women with subclinical thyroid disease before conception or during pregnancy were associated with adverse outcomes such as pregnancy loss, premature delivery, hypertensive disorders, and adverse neurocognitive outcomes (IQ) in their offspring [4–7].

The diagnosis of SCH is based on thyroid function testing. Since different upper limits and the cutoff value of normal TSH reference range have been used in previous publications, the benefits of levothyroxine (LT4) supplementation for SCH have always been controversial. For example, Rao et al., have confirmed the beneficial effects of LT4 supplementation in reducing the risk of pregnancy loss and preterm birth in women with SCH [8,9]. Bein et al. also demonstrated that LT4 supplementation could reduce the risk of

* Corresponding author. Center for Reproductive Medicine, Depart of Obstetrics and Gynecology, Chi Mei Medical Center, No. 901, Zhong Hua Rd., Yongkang Dist., Tainan City 710402, Taiwan.
*E-mail address:* yung0613@ms2.hinet.net (Y.-C. Tsai).

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adverse pregnancy outcomes in women with SCH in their systematic review and meta-analysis [10]. Ding et al. confirmed LT4 treatment could reduce the risk of pregnancy loss, preterm delivery and gestational hypertension in their report [11]. Currently, the American Society for Reproductive Medicine (ASRM) and the European Thyroid Association (ETA) have suggested LT4 treatment in women with SCH (TSH >4.0 mIU/L) to reduce miscarriage rates and improve pregnancy outcome when receiving assisted reproduction technology (ART) [12]. The American Thyroid Association (ATA) also recommends the supplementation of LT4 for infertile women with SCH to improve the fertilization rate of oocytes and clinical pregnancy outcome when receiving ART [4].

However, despite LT4 supplement for preconception and pregnant SCH women has been suggested, the optimal dosage of LT4 supplementation is still undetermined. The dose of LT4 for preconception and pregnant SCH women in previous studies was around 50–100 mcg/day [13–15]. Still, some patients have experienced different degrees of adverse effects, such as increased heart rate, sweating, and anxiety. According to the American Association of Clinical Endocrinologists (AACE) and American Thyroid Association (ATA) guidelines, a low dose of 25–75 mcg/day is usually sufficient for achieving euthyroid levels in SCH patients. Since it carries the potential risk of overtreating the patients with SCH than overt hypothyroidism [16], the ideal dosage of LT4 should be as low as possible while maintaining the therapeutic effect. In this study, we gave our SCH patients an extra-low dose of LT4 (25 mcg/day) and reported the obstetrical and perinatal outcomes as compared to euthyroid pregnant women.

## Materials and methods

This is a retrospective, single-center study. Women who underwent their first in vitro fertilization (IVF) retrieval cycle between January 2018 and December 2020 were recruited. Patients over 42 years old with known thyroid dysfunction, newly diagnosed overt hypothyroidism, hyperthyroidism, thyroid autoimmunity, donor eggs, or missing data were excluded. Data were collected from electronic and paper-based medical records.

All patients received a TSH examination before starting their IVF treatment. Patients with normal serum-free T4 but elevated TSH (>4 mIU/L) level were diagnosed to have SCH. SCH patients would receive LT4 supplement at 25 mcg/day for at least one month before ovarian stimulation and continuously during pregnancy. In all the patients, a GnRH antagonist protocol or progestin-primed ovarian stimulation (PPOS) protocol was used for controlled ovarian stimulation. Recombinant human FSH (rhFSH) with or without human menopausal gonadotropin (HMG) or recombinant human LH was administered from the third day of the menstrual cycle. Dual trigger with hCG and GnRH agonist or GnRH agonist alone were given for final oocyte maturation when one or more follicles reached a mean diameter of ≥18 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 34–36 h after rhCG or GnRH agonist injection. The harvested oocytes were fertilized either by traditional insemination or intracytoplasmic sperm injection (ICSI). Either fresh or frozen embryo transfer was performed according to the patient's clinical condition. The embryos were transferred at 3 days or 5 days after oocyte retrieval. Luteal phase support was provided by either micronized progesterone 200 mg (Utrogestan) three times daily or 90 mg of vaginal P gel (Crinone gel 8%) with or without 50 mg intramuscular progesterone or 125 mg hydroxyprogesterone caproate. All patients returned approximately 14 days after embryo transfer for a quantitative serum human chorionic gonadotropin (hCG) evaluation to confirm pregnancy. A visible intrauterine sac at 5–6th weeks by transvaginal ultrasound was defined as clinical pregnancy. The miscarriage rate was defined as the ratio of fetal loss before the 20th week of gestation in all pregnant women. The live birth rate was calculated as the percentage of deliveries with at least one infant among all pregnant women. Preterm delivery was defined as babies born alive before 37 weeks of gestation. Small for gestational age (SGA) was defined as weight less than the 10th percentile for gestational age using Hadlock's proportionality formula. The primary outcomes included miscarriage rate, live birth rate, preterm birth, and SGA baby in this study.

The Chi–Square test, or Fisher exact test, and Wilcoxon rank sum test were used to compare the distributions of categorical and continuous variables between subjects with TSH levels of ≤4 and >4 mU/L with LT4 treatment, respectively, and expressed as frequency (%) and median. Logistic regression analysis was conducted to estimate the odds ratio (OR) of TSH levels and reproductive outcomes. First, a univariate analysis was conducted to estimate the crude OR of the outcome. Second, age, body mass index (BMI) and anti-müllerian hormone (AMH) were included in the multivariate regression model to adjust for potential confounding factors. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

## Ethical approval

The study protocol has been reviewed and approved by the Institutional Review Board of Chi Mei Medical Center (11107–007), Tainan, Taiwan.

## Results

A total of 589 women were screened, and 317 women were enrolled after excluding patients who did not meet our inclusion criteria. Of the 167 women with clinical pregnancy, the average age was 35 years, among which 92 (55.09%) women were older than 35 years. 92.8% (155/167) of patients had TSH concentrations ≤4 mIU/L and 7.2% (12/167) of patients were newly diagnosed with SCH with TSH concentrations >4 mIU/L. There were no statistically significant differences in age, BMI, AMH, types of embryo transfer, number of embryos to transfer, embryo stage during transfer and clinical outcomes between two groups (Tables 1 and 2).

Nine of 12 (75%) women in group I and 124 of 155 (80%) women in group II had live births (P = 0.7028). The miscarriage rate was 20% (31/155) in the euthyroid group and 25% (3/12) in the SCH group (P = 0.7112). Seventeen (13.7%) euthyroid women and none of the SCH women had preterm delivery (P = 0.6031). Thirty-one (25%) euthyroid women and four (44%) women with SCH had small for gestational age baby (P = 0.2419). The results were also not statistically significantly different between two groups. Logistic regression was used to estimate the odds ratio (OR) for TSH levels and reproductive outcomes. After adjusting for age, BMI, and AMH level, there was still no statistically significant difference between group I and II (Table 3). The 44% of SGA babies in the SCH group was mainly due to the small sample size. Further analysis of these women revealed some of them had a history of medical problems such as chronic epilepsy in one mother and severe uterine adenomyosis in two.

## Discussion

Thyroid hormone (TH) has been shown not only to influence the endometrial and placental physiology but also to be essential for fetal brain development in the embryonic phase. TH receptors (THR) and TSH receptors (TSHR) are widely expressed in the feto-maternal unit during implantation, and both the endometrium

**Table 1**
Characteristics of 167 pregnant women between TSH level of ≤4 and TSH >4 mIU/L with LT4 treatment.

| | Total | TSH ≤4 | TSH >4 (LT4 treatment) | p-value |
|---|---|---|---|---|
| | N[a] = 167 | N = 155 | N = 12 | |
| Age (y/o) | 35.00 (33.00–38.00) | 35.00 (33.00–38.00) | 34.00 (32.50–36.50) | 0.2394 |
| <35 | 75 (44.91) | 67 (42.23) | 8 (66.67) | |
| ≥35 | 92 (55.09) | 88 (56.77) | 4 (33.33) | |
| BMI (kg/m$^2$) | 24.44 (21.48–27.41) | 24.46 (21.64–27.51) | 21.52 (20.04–25.16) | 0.1289 |
| BMI subgroup; N (%) | | | | 0.1178 |
| <18.5 | 8 (4.79) | 6 (3.87) | 2 (16.67) | |
| 18.5 ≤ BMI<24 | 66 (39.52) | 61 (39.35) | 5 (41.67) | |
| ≥24 | 93 (55.69) | 88 (56.77) | 5 (41.67) | |
| AMH (ng/ml); N (%) | | | | 1.0000 |
| ≥2.5 1 | 89 (53.29) | 83 (53.55) | 6 (50.00) | |
| <2.5 0 | 78 (46.71) | 72 (46.45) | 6 (50.00) | |
| Embryo transfer | | | | 0.4804 |
| Fresh | 40 (23.64) | 35 (22.88) | 4 (33.33) | |
| Frozen | 127 (76.36) | 118 (77.12) | 8 (66.67) | |
| No. of embryos to transfer | | | | 0.7256 |
| N = 1 | 40 (23.95) | 37 (23.87) | 3 (25.00) | |
| N = 2 | 110 (65.87) | 101 (65.16) | 9 (75.00) | |
| N = 3 | 17 (10.18) | 17 (10.97) | 0 | |
| Embryo stage | | | | 0.5458 |
| Day 3 | 57 (34.13) | 52 (33.55) | 5 (41.67) | |
| Day 5 | 110 (65.87) | 103 (66.45) | 7 (58.33) | |

[a] N: case number.

**Table 2**
Pregnancy and neonatal outcomes of 167 pregnant women and 133 women who have live birth between TSH level of ≤4 and TSH >4 mIU/L with LT4 treatment.

| | Total | TSH ≤4 | TSH >4 (LT4 treatment) | p-value |
|---|---|---|---|---|
| | N = 167 | N = 155 | N = 12 | |
| Miscarriage; N (%) | 34 (20.24) | 31 (20.00) | 3 (25.00) | 0.7112 |
| Live birth; N (%) | 133 (79.64) | 124 (80.00) | 9 (75.00) | 0.7028 |
| | Total | TSH ≤4 | TSH >4 (LT4 treatment) | |
| | N = 133 | N = 124 | N = 9 | |
| Neonatal birth weight (grams); N (%) | | | | 0.2419 |
| ≥10% | 98 (73.68) | 93 (75.00) | 5 (55.56) | |
| <10% (SGA[a]) | 35 (26.32) | 31 (25.00) | 4 (44.44) | |
| Gestational age (weeks); N (%) | | | | 0.6031 |
| ≥37 | 116 (87.22) | 107 (86.29) | 9 (100) | |
| <37(Preterm) | 17 (12.78) | 17 (13.71) | 0 (0) | |

[a] SGA: Small for gestational age, defined as below 10th percentile by Hadlock calculator.

**Table 3**
The odds ratios of selected characteristics between TSH levels of ≤4 and >4 mIU/L with LT4 treatment.

| | TSH≤4 vs. TSH>4 (LT4 treatment) | | | |
|---|---|---|---|---|
| | Crude OR | p-value | Adjusted ORs[c] | p-value |
| Miscarriage[a] | 0.90 (0.26–3.17) | 0.8747 | 0.81 (0.22–2.94) | 0.7502 |
| Live birth[a] | 0.75 (0.19–2.94) | 0.6793 | 0.79 (0.19–3.25) | 0.7410 |
| Neonatal birth weight (grams)[b] (N = 133) | | | | |
| ≥10% | 1.00 (ref.) | | 1.00 (ref) | |
| <10% (SGA) | 2.40 (0.61–9.51) | 0.2121 | 2.30 (0.57–9.27) | 0.2400 |
| Gestational age (weeks)[b] (N = 133) | | | | |
| ≥37 | 1.00 (ref.) | | 1.00 (ref) | |
| <37(Preterm) | 0.32 (0.02–6.76) | 0.4666 | 0.35 (0.02–7.13) | 0.4973 |

[a] Only calculated pregnant women (N = 167).
[b] Only calculated women who had live birth (N = 133).
[c] Adjusted ORs were adjusted with age, BMI, and AMH.

and the trophoblast might be influenced by TH either directly or through TH effects on the synthesis and activity of implantation-mediating molecules [17]. Previous reports have indicated that the local action of TH on the endometrium and embryo during the implantation period is crucial for a successful pregnancy [8–11]. Abnormal TH levels in placental trophoblasts followed by diminished trophoblast endocrine function may result in a direct consequence of pregnancy loss. Furthermore, trophoblasts dysfunction also impairs the placental vascular formation and may induce many obstetric complications, such as preterm birth, SGA babies, and preeclampsia [18].

SCH is defined as an elevated TSH level with normal levels of free thyroxine. Previous research has found that it affects 0.25–2.5% of all pregnancies, depending on the definitions used and the populations studied. SCH during pregnancy has been associated with early pregnancy loss, gestational diabetes, hypertension and pre-eclampsia, placental abruption, premature rupture of membranes and neonatal death. LT4 treatment has been used in SCH women who are trying to conceive or already pregnant. LT4 is a synthetic medicine of thyroxine (T4) that mimics its physiologic effects. ATA guidelines suggest TSH levels should be kept at ≤2.5 mIU/mL throughout the pregnancy [4]. Guideline from European Thyroid Association suggests TSH should be maintained below 2.5

mIU/mL in the first trimester and 3 mIU/mL in the second and third trimesters [12]. Rahman et al. declared that LT4 at 50–100 mcg/day might decrease miscarriage and increase live birth rate [15]. Kim et al. reported that 50 mcg/day of LT4 could improve embryo quality, decrease miscarriage and increase the live birth rate [14]. Nazarpour et al. also suggested that a dose of 1 mcg/kg/day reduced preterm delivery and newborn admissions to the neonatal unit [9]. Despite the agreement of supplementation of LT4 for SCH pregnant women has been reached, the optimal dosage of T4 for SCH mother has never been concluded [19,20]. For the majority of studies, 50 mcg/day was suggested [2,14], but AACE/ATA guidelines and previous report have declared a potential overtreatment in these women. Indeed, it is prone to overtreat SCH women than women with overt hypothyroidism, since free T4 concentrations were normal before medication in SCH women [16,21].

Despite rare, iatrogenic hyperthyroidism, defined as overtreatment with LT4, has been reported during pregnancy [24]. The first study published in 1998 reported the prevalence of iatrogenic hyperthyroidism [23]; 2.5% was overtly thyrotoxic [22]. Lage et al. reported recently, among hypothyroidism pregnant women treated with levothyroxine, 1.03% were overtreated [24]. Indeed, in the first few weeks of pregnancy, there are physiological changes that might induce gestational transient thyrotoxicosis (GTT). The GTT might originate from the increased thyroid stimulation by endogenous hCG production from the placenta and become deteriorated by an inappropriate exogenous thyroid supplementation [25]. Therefore, the dosage of LT4 for SCH mother should keep effective but remain as low as possible to prevent the potential over-treatment from exogenous T4 supplementation [26]. Korevaar et al. reported abnormal maternal freeT4 concentrations during pregnancy was associated with lower child IQ and lower gray matter and cortex volume [27]. Maraka and Lemieux et al. analyzed 5405 women with SCH and detected overtreatment of thyroid hormones with an increased risk of adverse pregnancy outcomes such as preterm delivery, gestational diabetes, and preeclampsia [28]. Lemieux et al. found the overtreatment with LT4 in pregnant women at any time during pregnancy might be associated with a twice high risk of preterm delivery [29]. Dash et al. suggested while LT4 supplementation has potential beneficial effects but also carries a higher risk of gestational diabetes [30].

In our study, all pregnant women with SCH were prescribed with an extra-low dose of LT4 before conception and during pregnancy, and we found live birth rate is non-inferior to the euthyroid pregnant women. The miscarriage rate, preterm birth rate, and small for gestational age rate were also comparable between the two groups by the analysis of odd ratio under logistic regression. There were some limitations in our study. First, the major pitfall in this retrospective study was the lack of post-treatment TSH level data. Although we administered an extra-low dose of LT4 supplementation and there is no evidence in the published literature that such a dosage can cause iatrogenic hyperthyroidism, the absence of post-treatment TSH level assessment is a notable limitation. Therefore, we recommend measuring TSH levels as a critical criterion for evaluating treatment efficacy, which should be performed six to eight weeks after the initiation of therapy, with subsequent testing every two or three months [4]. It is noteworthy that none of the patients in our study complained of palpitations, tremors, or anxiety while undergoing treatment with 25 mcg/day of LT4. Nevertheless, symptoms alone are not enough for evaluating TSH levels since SCH patients are typically asymptomatic, and mild hyperthyroidism may not result in noticeable symptoms. Therefore, we encourage SCH patients taking LT4 supplements to routinely check their post-treatment TSH levels. In the futures, further extensive studies may be necessary to investigate the changes in TSH levels under extra-low dose of LT4 treatment. Though it is a pity that the post-treatment serum TSH level was not available, the therapeutic effect of extra-low dose of T4 on the SCH pregnant women has been justified by the final obstetrical and neonatal outcomes in this study. To our knowledge, only a limited studies have ever reported the pregnancy outcomes after treatment with an extra-low dose of LT4. We hope to remind clinician that if the patients were not tolerated the standard dose of LT4, then 25 mcg/day of LT4 might be an alternative to avoid overdose effects. The second pitfall in this study is the relatively small size of sample. Despite this, different statistical analysis methods have been conducted to justify our result. Third, the original study design failed to compare the efficacy of LT4 and placebo in SCH patients. Since established guidelines from professional societies strongly recommend LT4 supplements to improve ART and pregnancy outcomes in SCH patients, it might induce some ethical challenges if we refused to give the SCH women purposely.

In conclusion, we found supplementation with an extra-low dose of levothyroxine at 25 mcg/day for SCH women might produce the same clinical outcome as that in euthyroid patients. Extra-low dose levothyroxine may be administered as a safe and effective alternative for patients who were not tolerated the standard dose of levothyroxine.

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## Author contribution

Dr. YC Tsai designed this study, provided data and revised this article. Dr. YT Chen collected data and wrote this article; Mr. CH Ho conducted statistics analysis; the other authors provided their opinions and joined the discussion.

## Declaration of competing interest

The authors declare no conflicts of interest relevant to this article.

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