Outcome of in vitro fertilization in women with subclinical hypothyroidism

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Abstract

Background: Previous studies examining associations between subclinical hypothyroidism (SCH) with in vitro fertilization (IVF) outcome indicate some benefits of levothyroxine (LT4) treatment. But IVF outcomes in treated SCH women whose serum Thyroid Stimulating Hormone (TSH) concentration did and did not exceed 2.5 mIU/L before the IVF cycle has not been studied thoroughly.

Methods: In this study, we performed a prospective cohort study with 270 treated subclinical hypothyroidism patients undergoing their first IVF retrieval cycle at a single site.

Results: SCH in women receiving LT4 replacement with a basal TSH level between 0.2-2.5 mIU/L displayed a similar rate of clinical pregnancy (47.4% vs 38.7%, $P = .436$), miscarriage (7.4% vs 16.7%, $P = .379$) and live birth (43.9% vs 32.3%, $P = .288$) compared to women with a basal TSH level between 2.5-4.2 mIU/L.

Conclusion: Strictly controlled TSH (less than 2.5 mIU/L) before IVF may have no effect on the pregnancy rate in LT4 treated SCH women.

Keywords: Thyroid function, in vitro fertilization, Controlled ovarian stimulation, Subclinical hypothyroidism, Infertility

Background

Subclinical hypothyroidism (SCH) is a common mild thyroid disorder in women of childbearing age and may contribute to increased risk of infertility and adverse obstetric outcome of pregnancy. Observational studies examined the effect of SCH on pregnancy related outcomes, and it has been associated with multiple adverse outcomes in many, but not all, studies [1]. A recent multicenter, randomized, placebo-controlled trial found that pregnant women with treated SCH whose median TSH was 4.2 mIU/l are at the same frequencies for pregnancy loss, placental abruption, premature rupture of membranes, and neonatal death compared with untreated women [2]. Although unsound evidence exists, several professional organizations have maintained to recommend routine prenatal screening for and treatment of SCH during pregnancy [3, 4].

The alteration of serum estrogen level during pregnancy has a profound physiological impact on thyroid function. Production of thyroid hormone increases by approximately 50% during pregnancy as a normal physiological response [5]. The functional reserve of thyroid is poor in hypothyroid women substituted with levothyroxine (L-T4) and they need to increase dose of medication to maintain normal thyroid function during pregnancy. Controlled ovarian stimulation (COH) is a standard component of in vitro fertilization (IVF), which is able to induce a supra-physiological maternal serum estradiol level and may have a greater effect on thyroid function than natural conception [6, 7]. Several investigations showed that IVF had an effect on serum TSH level in L-T4 treated hypothyroid women [8]. Moreover, the majority of evidence shows that SCH has a negative effect on outcome of IVF [9]. However, whether this negative influence may be attenuated with L-T4 treatment, the benefits of strictly controlled TSH level before IVF are still unknown [3, 9]. Our aim was to investigate the rate of pregnancies of IVF in SCH women substituted with L-T4 and evaluate whether TSH less than 2.5 mIU/l is the optimal cut-off point before IVF cycle. We performed a prospective cohort study with patients...
undergoing their first IVF retrieval cycle at a single cite from January 2015 to March 2016 (15 months).

Methods

Patients

Four thousand and seven hundred twenty subfertile women who underwent either classical IVF or IVF-Intracytoplasmic Sperm Injection (ICSI) were enrolled between January 2015 and March 2016 at the first people's hospital of Yunnan Province PR China. The level of TSH was screened and the subjects with TSH level above 4.2 mIU/L were selected, serum levels of TSH, free triiodothyronine (FT3), free thyroxine (FT4) were measured. SCH is defined as an elevated TSH concentration (TSH 4.2-20 mIU/L) with normal serum levels of FT4. When SCH was confirmed, treatment with L-T4 was started and the target TSH level is within 0.2-4.2 mIU/L. After the approval of Institutional Review Board, we selected women aged 37 years or less who underwent their first fresh IVF retrieval cycle, using their own oocytes. Two hundred and seventy SCH women substituted with LT4 were considered for further study. They were eligible if serum TSH level was within 0.2-4.2mIU/L one month proceeding the IVF cycle. Age-matched euthyroid women who underwent either classical IVF or ICSI were selected as control group in the same period. This analysis exclusively refers to the first treatment cycle.

During COH, participants were monitored closely with transvaginal ultrasound and serum hormone levels. When a lead follicle R18 mm in size was identified, intramuscular hCG was administered with oocyte retrieval 36 hours later. Three to 5 days after retrieval, embryo transfer (ET) was performed, and participants returned 14 days later for measuring serum hCG levels. Positive pregnancy test was defined as positive serum hCG, and participants were followed to determine pregnancy outcome (10 months). Samples were processed and serum stored at -20 °C for batched analysis. Exclusion criteria included those patients with ovarian hyperstimulation (E2 > 4000 pg/ml, the number of follicles over 20), poor ovarian response (less than three follicles after ovarian stimulating drugs), poor compliance. Clinical endpoints were rates of clinical pregnancy (gestational sac on ultrasound), miscarriage (loss after gestation). Overall rates of clinical pregnancy (44.31% vs 42.64%, P = .251) and miscarriage (10.3% vs 10.7%, P = .39) were not significantly different between the two study groups (Table 1). Eighty-two of 176 (46.6%) L-T4 treated SCH women who underwent ET had positive pregnancy tests. Seventy-eight of 176 (44.31%) became clinically pregnant. Eight pregnancies (10.3%) resulted in miscarriages (before 12 weeks of gestation). Overall rates of clinical pregnancy (44.31% vs 38.36%, P = .379) and live birth (32.3%) had a live birth, 4 (16.7%) resulting in miscarriage. Of the remaining 62 participants with a TSH level within 2.5-4.2mIU/L before the IVF cycle, 28 (45.2%) of them had positive pregnancy tests but only 24 (38.7%) became clinically pregnant, 20 (32.3%) had a live birth, 4 (16.7%) resulting in miscarriages. The rates of clinical pregnancy (P = .379) and live birth (P = .288) were similar between two groups. In addition, total number of oocytes

Laboratory Analysis

The levels of serum TSH, FT4, FT3 and thyroid peroxidase antibody (TPOAb) were measured with electrochemiluminescence (ECL) immunoassays (CobasElesys 601, Roche). The TSH assay had a reference range of 0.27–4.2mIU/L with intra-assay coefficient of variation (CV) of 1.57–4.12%. For FT4, the reference range was 12.2–22pmol/L with intra-assay CV of 2.24%-6.33%. The FT3 reference range was 3.1-6.8pmol/L with intra-assay CV of 2.42%-5.63%. The TPOAb assay range was 5.0-1,000 IU/mL with intra-assay CV of 6.7%. Positive TPOAb status was >35 IU/mL. Positive pregnancy test was defined by serumβ-hCG more than 25mIU/ml, typically on day 12–14 after oocyte retrieval.

Statistical analysis
Quantitative values were expressed as mean ± SD or as median and interquartile range, as appropriate. Wilcoxon Rank-Sum test (nonparametric analysis) was used for continuous data without a normal distribution; Chi-Square analysis was used for categorical data with large cell counts, the Fisher-Exact test analysis for categorical data with small cell counts, a p-value <0.05 was considered statistically significant.

Results
We found in a cohort of 4720 subfertile women undergoing IVF that 5.8% of them had SCH. Two hundred and seventy SCH women were enrolled and substituted with L-T4. Ninety-four SCH women were excluded because their IVF cycle were cancelled, one hundred and seventy-six of 270 women (66.2%) completed all pregnancy study visits and included in the final analysis. Of the 4407 women (93.3%) with normal thyroid screen results, 200 were eligible and participated in the study.

Baseline characteristics of the levothyroxine treated SCH group and the euthyroid group were similar. The frequencies of adverse pregnancy outcomes did not differ significantly between the two study groups (Table 1). Eighty-two of 176 (46.6%) L-T4 treated SCH women who underwent ET had positive pregnancy tests. Seventy-eight of 176 (44.31%) became clinically pregnant. Eight pregnancies (10.3%) resulted in miscarriages (before 12 weeks of gestation). Overall rates of clinical pregnancy (44.31% vs 38.36%, P = .251) and miscarriage (10.3% vs 10.7%, P = .39) were not significantly different between L-T4 treated SCH women and euthyroid women who underwent IVF in the same period.

One hundred and fourteen of 176 L-T4 treated SCH women (64.8%) had a TSH level within 0.2-2.5mIU/L before the IVF cycle. Fifty-four (47.4%) of them had positive pregnancy tests and all of them had clinical pregnancies. Fifty (43.9%) had a live birth and four (7.4%) pregnancy resulted in miscarriage. Of the remaining 62 participants with a TSH level within 2.5–4.2mIU/L before the IVF cycle, 28 (45.2%) of them had positive pregnancy tests but only 24 (38.7%) became clinically pregnant, 20 (32.3%) had a live birth, 4 (16.7%) resulting in miscarriages. The rates of clinical pregnancy (P = .379) and live birth (P = .288) were similar between two groups. In addition, total number of oocytes
In this study, we enrolled 4720 subfertile women who underwent IVF for thyroid function examination. The incidence of SCH was 5.8%, using an upper cutoff TSH level of 4.2 mIU/L, which is consistent with previous investigations [12, 13].

Multiple studies have reported an association of SCH with an increased risk of adverse pregnancy outcomes including placental abruption, preterm birth, fetal death, and preterm premature rupture of membranes (PPROM) [3, 14], but not all. There is fair evidence that SCH, defined as TSH outside of the normal reference range in pregnancy, is associated with miscarriage [3, 15]. Untreated SCH affected the pregnancy outcomes in women requiring IVF, such as decreased pregnancy rate, implantation rate and delivery rate. Current data have demonstrated some benefits of L-T4 treatment in reducing these events [9]. In 2007, investigators performed a randomized trial on a population of 70 infertile patients with SCH who had undergone IVF. Patients were randomly assigned to either the L-T4 treatment group (50–100 mcg L-T4 starting at one month before the assisted reproduction technology procedure) or the placebo group. They found that compared with untreated group, the miscarriage rate was significantly lower (9% vs 13%, respectively) and the clinical pregnancy rate and delivery rate were significantly higher (35% and 10% vs 26% and 3%, respectively) in L-T4 treatment group[16]. Another study randomized 64 women with SCH to the L-T4 treatment group (50 mcg L-T4 starting at day 1 of ovarian stimulation) or the control group [17]. They observed a significant increase in the number of grade I or II embryos (P = .007) and in the implantation rate (26.9% vs 14.9%, P = .044). The miscarriage rate was significantly lower in the L-T4 treatment group (0 vs 33.3%; P = .021) and as a result, the live-birth rate was significantly higher in the L-T4 treatment group (53.1% vs 25%, P = .039). In our study, 176 SCH women were substituted with L-T4 and their TSH levels were maintained within 0.2-4.2 mIU/L one month before the IVF cycle. We found that the rate of positive pregnancy test, clinical pregnancies and miscarriage were similar between treated SCH women and euthyroid women who underwent IVF, which is consistent with previous investigations. The investigation found that IVF outcome was not significantly hampered in women with adequately treated hypothyroidism [18].

Using the definition of TSH level greater than the upper limit of normal range (4-5 mIU/L) with normal FT4 levels, the incidence of SCH has been reported approximately 4–8% in reproductive age population [10, 11]. Similarly, the incidence of SCH during pregnancy ranged from 2 to 2.5% [3]. Some investigators reported that SCH is more prevalent in infertile women [12, 13]. In a retrospective study, an elevated serum TSH was found in 4% of 335 infertile Finnish women with unknown history of thyroid dysfunction [8]. The incidence was highest in those with ovulatory dysfunction (6%) and unexplained infertility [5]. In this study, we enrolled

| Table 1 Baseline characteristics and IVF outcomes in Treated SCH and Euthyroid Patients |
|------------------------------------------|
| Number of patients | Sub-Hypo women | Euthyroid women | P |
|------------------------------------------|
| Age (yrs) | 29.89 ± 4.07 | 30.45 ± 4.21 | 0.056 |
| BMl(kg/m2) | 22.76 ± 3.54 | 22.41 ± 2.89 | 0.099 |
| TSH range(mIU/L) | 0.32,4.21 | 0.57,4.21 | 0.420 |
| Indication to IVF | | | 0.439 |
| Tubal factor infertility | 50% | 54.3% | |
| Ovulatory dysfunction | 7.95% | 5.9% | 0.059 |
| Endometriosis | 2.2% | 1.4% | |
| Male | 15.9% | 16.2% | |
| Mixed | 21.6% | 20% | |
| Unexplained infertility | 6.5% | 6.7% | |
| Clinical pregnancies | 44.31% | 38.36% | 0.251 |
| Miscarriages | 10.3% | 10.7% | 0.39 |

retrieved (P = .752), good quality embryos (P = .752) were similar between these two groups. The baseline characteristics and cycle outcome of women whose serum TSH did and did not exceed the threshold of 2.5 mIU/L before the IVF cycle are shown in Table 2. No statistically significant differences were observed. An intragroup analysis according to thyroid autoimmunity detected also failed to document any significant result (data not shown).

Subgroup analyses were performed within the group of women with treated SCH. We compared women with (n = 102) and without (n = 74) thyroid autoimmunity. The median serum TSH before the IVF cycle was 1.81 (0.95–3.69) and 1.71 (0.95–2.69) mIU/L, respectively (p = 0.22). Baseline characteristics of the two study groups were similar with the exception of total amount of recombinant FSH, which was slightly higher in women without thyroid autoimmunity (1950.0 ± 1650.0 vs. 2400.0 ± 1950.0 IU, p = 0.031). The main findings of the IVF outcomes are summarized in Table 3. No statistically significant differences emerged.

Discussion

Using the definition of TSH level greater than the upper limit of normal range (4-5 mIU/L) with normal FT4 levels, the incidence of SCH has been reported approximately 4–8% in reproductive age population [10, 11]. Similarly, the incidence of SCH during pregnancy ranged from 2 to 2.5% [3]. Some investigators reported that SCH is more prevalent in infertile women [12, 13]. In a retrospective study, an elevated serum TSH was found in 4% of 335 infertile Finnish women with unknown history of thyroid dysfunction [8]. The incidence was highest in those with ovulatory dysfunction (6%) and unexplained infertility [5]. In this study, we enrolled
are increased with a TSH level higher than 2.5 mIU/L but less than the upper range of normal at the time of conception in IVF. Although unsound evidence exists, recent Clinical Practice Guideline by The Endocrine Society suggests TSH levels in subclinical women should be less than 2.5 mIU/L before pregnancy, particularly in women requiring IVF [4]. One study measured 1231 women pursuing assisted reproductive technologies (ART). In this study, investigators found no evidence of an elevated pregnancy loss rate in women with preconception elevated TSH (2.5–4.0 mIU/L) [22]. The observation is in agreement with a recent study by Reh et al. who found no difference in clinical pregnancy, delivery, or miscarriage in patients with mildly elevated basal TSH (>2.5 and <4.0 mIU/L) compared to patients with a normal TSH (>0.4 to <2.5 mIU/L) [20]. Other studies suggest that there is a trend toward increasing risk of miscarriage with increasing TSH level, although this trend did not reach statistical significance [21]. These controversial results raise questions about the current guideline recommended threshold of 2.5 mIU/L for treating SCH when thyroid antibody was positive. In our study, no differences in the rates of positive pregnancy test, clinical pregnancies, miscarriage or live birth were observed in treated SCH women with different TSH level. There was no significant difference between the two groups with the number of oocytes

| Table 2 Baseline characteristics and IVF outcomes in women serum TSH concentration did and did not exceed 2.5 mIU/L before the IVF cycle |
|---------------------------------|-----------------|-----------------|---|
| Characteristics                 | TSH ≥ 2.5 mIU/L | TSH < 2.5 mIU/L | P  |
| Age (yrs)                       | 30.48 ± 4.07    | 29.56 ± 4.37    | 0.336 |
| BMI(kg/m²)                      | 23.60 ± 4.05    | 22.29 ± 3.18    | 0.099 |
| Previous pregnancies            | 48.4%           | 54.4%           | 0.972 |
| AFC                             | 12.00 ± 5.00    | 12.00 ± 8.00    | 0.0  |
| TSH(mIU/L)                      | 2.60,4.21       | 0.32,1.88       | 0.005 |
| FT3(pmol/L)                     | 4.73 ± 0.76     | 5.10 ± 0.99     | 0.001 |
| FT4(pmol/L)                     | 17.29 ± 2.29    | 20.10 ± 3.99    | 0.439 |
| Indication to IVF               |                |                | 0.8  |
| Tubal factor infertility        | 45.2%           | 52.6%           | 6.4% |
| Ovulatory dysfunction           |                |                | 8.8% |
| Endometriosis                   | 3.2%            |                | 0%   |
| Male                            | 12.9%           |                | 17.5%|
| Mixed                           | 25.8%           |                | 19.3%|
| Unexplained infertility         | 6.5%            |                | 1.8% |
| Protocol of stimulation         |                |                | 0.436|
| Long protocol                   | 77.4%           | 89.5%           | 0.106|
| Short protocol                  | 6.5%            | 3.5%            | 0.128|
| GnRH antagonists                | 3.2%            |                | 0.752|
| ART procedure                   |                |                | 0.001|
| IVF                             | 75.8%           | 70.2%           | 0.767|
| ICSI                            | 24.2%           | 29.8%           | 0.436|
| Duration of stimulation(Days)   | 11.23 ± 1.82    | 11.98 ± 2.09    | 0.288|
| Total amount of recombinant FSH administration | 2025 ± 825 | 2475.00 ± 1350.00 | 0.108|
| Serum estradiol at HCG Administration(pg/ml) | 1983.50 ± 2079 | 2529.00 ± 2005.00 | 0.752|
| Total number of oocytes retrieved | 10.00 ± 8.00   | 11.00 ± 8.00    | 0.767|
| Total number of good quality embryos | 2.00 ± 3.00    | 4.00 ± 6.00     | 0.379|
| Clinical pregnancies            | 38.7%           | 47.4%           | 0.288|
| Miscarriages                    | 16.7%           | 7.4%            | 0.288|
| Live birth rate                 | 32.3%           | 43.9%           | 0.288|

Data are reported as %, mean ± standard deviation or quartile, as appropriate

AFC = antral follicle, BMI = body mass index, FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone
retrieved and in the implantation rate. In addition, we also use TSH values greater than 2.5 mIU/L on HCG administra-
day as a cut-off point. There were no differences in the rates of positive pregnancy test, clinical pregnancies, mis-
carriage or live birth in different groups (data not shown).

However, due to the small sample size, the statistical power of this study was limited. In addition, since we didn't adjust the levothyroxine dose during COH, we cannot determine whether there is an association between TSH alteration during ART and IVF outcome. We didn't measure urinary iodine in this study that was also a flaw. Finally, according to ATA guideline, we arbitrarily chose 2.5 mIU/L as a strictly controlled TSH threshold. It would have been more appropriate to refer to a local threshold since reference range may vary among different ethnics and is not always correct to use the same threshold for all ethnics.

Conclusion
In conclusion, our results suggest that L-T4 treatment in women with SCH requiring IVF had similar rates of pregnancy and adverse pregnancy outcomes compared to euthyroid women. Strictly controlled TSH (less than 2.5 mIU/L) before IVF may have no effect on the pregnancy rate and maternal adverse pregnancy results. Whether the risk of other adverse outcomes could be attenuated calls for further studies to evaluate the effectiveness of thyroid hormone treatment in this population.

Abbreviations
ART: Assisted Reproductive Technology; COH: Controlled ovarian stimulation; ET: Embryo Transfer; FT3: Free Triiodothyronine; FT4: Free Thyroxine; ICSI: Intracytoplasmic Sperm Injection; IVF: in vitro fertilization; L-T4: Levothyroxine; SCH: Subclinical hypothyroidism

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors’ contributions
YC and HS wrote the manuscript. YC, LZ and HS designed the experiments; YC, LZ, RG and BN performed the experiments; BN, LZ,YP and JG participated in the analysis and discussion of the results. All authors read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
All experiments were performed in strict accordance with the Ethics Committee at The First People's Hospital of Yunnan P.R. China. Informed consent was obtained from all subjects. The Institutional Committee of the First People's Hospital of Yunnan P.R. China approved the experimental protocols (registration number: 2015092003).

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Table 3 Baseline characteristics and IVF outcomes in women with treated subclinical hypothyroidism with or without thyroid antibodies

| Characteristics                        | AB POS | AB NEG | P   |
|----------------------------------------|--------|--------|-----|
| Protocol of stimulation                |        |        |     |
| Long protocol                          | 88.3%  | 97.3%  | 0.241 |
| Short protocol                         | 3.9%   | 2.7%   |     |
| GnRH antagonists                       | 7.8%   | 0%     |     |
| ART procedure                          |        |        |     |
| IVF                                    | 70.6%  | 81.1%  |     |
| ICSI                                   | 29.4%  | 18.9%  |     |
| Duration of stimulation (Days)         | 11.0 ± 10.0 | 12.0 ± 10.25 | 0.204 |
| Total amount of recombinant FSH administra- | 1950.0 ± 1650.0 | 2400.0 ± 1950.0 | 0.031 |
| Serum estradiol at HCG Administration (pg/ml) | 2566.36 ± 1162.43 | 2269.04 ± 1239.37 | 0.34 |
| Total number of oocytes retrieved      | 10.00 ± 6.00 | 11.00 ± 7.25 | 0.922 |
| Total number of good quality embryos   | 2.00 ± 1.00 | 3.00 ± 1.00 | 0.965 |
| Clinical pregnancies                   | 47.1%  | 40.6%  | 0.566 |
| Miscarriages                           | 9.0%   | 18.2%  | 0.602 |
| Live birth rate                        | 43.1%  | 34.4%  | 0.291 |
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