Association between TSH Level and Pregnancy Outcomes in Euthyroid Women Undergoing IVF/ICSI: A Retrospective Study and Meta-analysis*

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Summary: The aim of this study was to determine the association between thyroid-stimulating hormone (TSH) level and pregnancy outcomes in euthyroid women undergoing *in vitro* fertilization (IVF)/intra-cytoplasmic sperm injection (ICSI). A total of 1185 women were enrolled in the retrospective study, and 12 studies with a total of 6624 women were included in the meta-analysis (including the data of the present retrospective study). Participants in the retrospective study were divided into two groups in terms of their serum TSH levels: TSH ≤2.5 mIU/L group (*n*=830) and TSH >2.5 mIU/L group (*n*=355). They were monitored for the status of clinical pregnancy or miscarriage. In the TSH ≤2.5 mIU/L group, 441 (53.1%) women achieved clinical pregnancy, while 48 (5.8%) had early pregnancy loss and 12 (1.4%) had ectopic pregnancy. In the TSH >2.5 mIU/L group, 175 (49.3%) women achieved clinical pregnancy, while 21 (5.9%) had early pregnancy loss and 3 (0.8%) had ectopic pregnancy. No significant differences were observed between the two groups in pregnancy outcomes (*P*=0.126, *P*=0.512, *P*=0.297). The meta-analysis also revealed no significant difference in the clinical pregnancy rate and the miscarriage rate between women with serum TSH ≤2.5 mIU/L and those with serum TSH >2.5 mIU/L. In conclusion, high TSH levels (TSH level >2.5 mIU/L) did not affect clinical pregnancy rate or increase miscarriage rate in euthyroid women undergoing IVF/ICSI.
Key words: euthyroid; pregnancy outcomes; *in vitro* fertilization; intra-cytoplasmic sperm injection

The thyroid gland is crucial for female fertility. Thyroid dysfunction may induce ovulatory disorders, menstrual irregularities, infertility, and increase the morbidity during pregnancy[1]. Detecting the levels of thyroid-stimulating hormone (TSH) is a cheap and simple method to ascertain thyroid function[2]. TSH is a critical hormone for women who try to get pregnant. Currently, assisted reproductive technology (ART) has benefited a significant number of women to become pregnant. Several studies have indicated that serum TSH levels are associated with controlled ovarian stimulation (COH), which is a standard component of ART[3, 4]. The change in TSH levels has been associated with a sub-optimal environment for the implantation and development of the embryo[5]. Moreover, thyroid-related receptors are present in human granulosa cells and in the endometrium, and are variably distributed in these cells during folliculogenesis[6]. Hence, optimal TSH levels are crucial for women trying to become pregnant, especially in euthyroid women undergoing ART.

It is generally believed that women with thyroid disorders should receive therapy before COH. However, there is controversy regarding the upper limit of normal TSH levels. Some studies indicated that 2.5 mIU/L is the upper limit of normal TSH levels[7]. This level has been endorsed in the guidelines published by the American Society for Reproductive Medicine (ASRM) and American Thyroid Association (ATA)[8]. Nevertheless, some studies reported that women with TSH levels above 2.5 mIU/L were still within normal levels, and similar rates of clinical pregnancy and early pregnancy loss were found in these women[9]. Hence, the cut-off of TSH concentrations remains inconsistent. Although several studies have demonstrated the effect of TSH on the clinical pregnancy rate of women undergoing ART[10], there is a scanty of data with respect to the effect of TSH levels on Chinese women undergoing ART.

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In the present study, we retrospectively analyzed the association between TSH levels and pregnancy outcomes in euthyroid Chinese women undergoing *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI). A meta-analysis of the literature was also performed to further validate the findings.

1 MATERIALS AND METHODS

1.1 Study Participants in the Retrospective Study

This retrospective study was performed in the Reproductive Medicine Center of Tongji Hospital in Hubei Province, China, between September 2016 and February 2017. It was approved by the Ethics Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology, China. All the study participants were undergoing either IVF or ICSI. A thorough history of all participants was obtained, with general and gynaecologic examinations performed. The inclusion criteria for this study were as follows: study participants had fresh embryos for the procedure; the levels of serum TSH, free triiodothyronine (FT3), free thyroxine (FT4) and thyroid peroxidase antibody (TPOAb) were detected using electro-chemiluminescence immunoassays before COH for IVF/ICSI; normal thyroid function was defined as elevated serum TSH levels (0.35–4.94 mIU/L) with normal serum levels of FT3 and FT4; TPOAb of the participants was negative. Patients who received hormone drugs including levothyroxine sodium tablets (L-T4) in the past six months were excluded from the study.

1.2 Study Procedure

During COH, study participants were monitored closely using transvaginal ultrasound and serum hormone levels measured. When the diameter of the dominant follicle reached 18 mm or over, intramuscular human chorionic gonadotropin (HCG) 6500 IU (HCG for injection, Livzon Pharmaceutical Group Inc., Guangzhou, China) was administered. Oocytes were then retrieved 36 h later. Three to five days after retrieval, embryo transfer (ET) was performed. At the same time, 90 mg progesterone sustained-release vaginal gel (Snow Ketone, Fleet laboratories Limited, United Kingdom) and 40 mg dyhrogesterone tablets (Duphaston, Abbott Biologicals B.V., Netherlands) were administered daily for luteal support. Twelve to 14 days after transfer, quantitative serum HCG measurements were performed. All study participants were monitored to determine pregnancy outcomes. The main outcome was clinical pregnancy rate, and was defined by observing fetal cardiac activity in the uterus by transvaginal ultrasound about 4 weeks after embryo transfer. The secondary outcomes were miscarriage rate and ectopic pregnancy rate. Miscarriage was defined as loss of the gestational sac or fetal heart activity within 20 weeks after confirming clinical pregnancy. Ectopic pregnancy was defined by observing pregnancy outside of the uterus on transvaginal ultrasound at 4 weeks post embryo transfer.

1.3 Grouping

Euthyroid subjects who underwent IVF/ICSI were divided into two groups in terms of their serum TSH levels: TSH ≤2.5 mIU/L group and TSH >2.5 mIU/L group. TPOAb of all the subjects was negative.

1.4 Statistical Analysis of the Retrospective Study

The Statistical Package for Social Science Version 21.0 (SPSS, USA) was used for statistical analysis. All hypothesis tests were two-sided. Categorical data were presented as numbers and percentages. As all the continuous variables were normally distributed, they were presented as mean±standard deviation. To compare clinical characteristics and parameters between the two groups, Student's *t*-test was used for continuous variables and chi-square test for nominal variables. Pregnancy rate was compared using Pearson's chi-squared or Fisher's exact test. Binary logistic regression was used for multivariate analysis of the probability of pregnancy. P value <0.05 was considered statistically significant.

1.5 Meta-analysis

A comprehensive review of the literature was performed for the meta-analysis, using the search terms "thyroid gland," "thyroid," "thyroid-stimulating hormone," or "TSH," and "*in vitro* fertilization," "IVF," "intra-cytoplasmic sperm injection," "ICSI," "intraoperative," "assisted reproductive technology," or "ART," in PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (the last search was performed on June 30, 2017). The references of the retrieved articles were examined for further identification of relevant publications. The studies, which used a case-control design, were published in English, contained sufficient data to calculate hazard ratio and 95% confidence interval, and were included in the meta-analysis. If a case-control design was not used or no extractable data were available, the articles were excluded from the aggregated meta-analysis. These studies were only briefly described in this meta-analysis. No attempt was made to identify unpublished studies. Stata 14.0 software was used to perform the meta-analysis.

2 RESULTS

2.1 Results of Retrospective Study

Totally, 1498 women undergoing either classical IVF or ICSI with fresh embryos transfer were screened. After detection of serum levels of TSH, FT3, and FT4, 71 women were found to need further endocrine therapy before IVF/ICSI. Two hundred and thirty-nine women were excluded from the study for their TPOAb

was positive on the tests. Three women were excluded for they had taken prescribed hormone drugs. In total, 1185 women were enrolled in our study. Based on their serum TSH levels, the participants were divided into two groups, with 830 in the TSH ≤2.5 mIU/L group and 355 in the TSH >2.5 mIU/L group.

Characteristics of the euthyroid participants who underwent IVF/ICSI are presented in table 1. The baseline variables between the two groups were similar. The mean TSH levels were significantly different between the two groups (1.61±0.50 *vs.* 3.22±0.57 mIU/L, *P*=0.035). The mean age (*P*=0.811), body mass index (*P*=0.870), anti-Müllerian hormone (AMH) level (*P*=0.241), endometrial thickness on day of HCG administration (*P*=0.937), progesterone (P) level on day of HCG administration (*P*=0.140), number of retrieved oocytes (*P*=0.332), time of infertility (*P*=0.217) and number of different infertility types (*P*=0.228) were similar between the two groups. However, there were significant differences in the baseline FSH levels (*P*=0.038), the number of antral follicle count (AFC) (*P*=0.000) and estradiol (E2) levels on the day of HCG administration (*P*=0.000) between the two groups.

During follow-up by telephone or e-mail, we compared the clinical pregnancy rate, miscarriage rate and ectopic pregnancy rate between the two groups. The results are shown in table 2. In the TSH ≤2.5 mIU/L group, 441 (53.1%) women were clinically pregnant, 48 (5.8%) women had early pregnancy loss and 12 (1.4%) had ectopic pregnancy. In the TSH >2.5 mIU/L group, 175 (49.3%) women were clinically pregnant, 21 (5.9%) women had early pregnancy loss and 3 (0.8%) women had ectopic pregnancy. No significant differences were observed between the two groups in the clinical pregnancy rate, miscarriage rate and ectopic pregnancy rate (*P*=0.126, *P*=0.512, *P*=0.297).

Table 1 Baseline characteristics in euthyroid women undergoing IVF/ICSI

Characteristics	TSH ≤2.5 mIU/L	TSH >2.5 mIU/L	*P* value
Total (*n*)	830	355	
Age (year)	31.48±4.62	31.01±4.86	0.811
BMI (kg/cm^2)	21.68±2.79	21.89±2.84	0.870
Baseline FSH level (mIU/mL)	7.87±2.66	7.73±2.13	0.038*
AMH (ng/mL)	4.53±3.61	4.95±3.80	0.241
TSH (mIU/L)	1.61±0.50	3.22±0.57	0.035*
AFC (*n*)	13.77±6.69	17.53±7.81	0.000*
Endometrial thickness (mm)#	11.66±2.58	11.89±2.56	0.937
E2 (pg/mL)#	2805.41±1355.14	2831.90±1519.95	0.000*
P (ng/mL)#	0.87±0.26	0.88±0.30	0.140
Retrieved oocytes (*n*)	10.43±4.50	10.68±4.63	0.332
Time of infertility (year)	3.44±2.63	3.38±2.41	0.217
Infertility (*n*)			
Primary	477	213	0.228
Secondary	353	142	

#On day of HCG administration; BMI: body mass index; FSH: follicle-stimulating hormone; AMH: anti-Müllerian hormone; TSH: thyroid-stimulating hormone; AFC: antral follicle count; E2: estradiol; P: progesterone; *P<0.05

Table 2 Comparison of pregnancy outcomes in euthyroid women undergoing IVF/ICSI

Parameters	TSH ≤2.5 mIU/L	TSH >2.5 mIU/L	*P* value
Clinical pregnancy rate (%)	441 (53.1)	175 (49.3)	0.126
Miscarriage rate (%)	48 (5.8)	21 (5.9)	0.512
Ectopic pregnancy rate (%)	12 (1.4)	3 (0.8)	0.297

Furthermore, binary logistic regression analysis of this cohort showed that baseline FSH levels had a significant effect on clinical pregnant rate with a parameter estimate of 0.940 (*P*=0.041) (table 3). TSH levels had no significant effect on the clinical pregnancy rate with a parameter estimate of 1.089 (*P*=0.556).

Table 3 Binary logistic regression analysis of factors for clinical pregnancy rate in euthyroid women undergoing IVF/ICSI

Characteristics	OR	95% CI	*P* value
Age	0.969	(0.938–1.002)	0.062
Baseline FSH level	0.940	(0.030–4.162)	0.041*
AFC	1.020	(0.997–1.045)	0.094
Serum E2 level#	1.000	(1.000–1.000)	0.684
Serum P level#	0.844	(0.490–1.454)	0.542
Time of infertility	1.001	(0.948–1.057)	0.971
Serum TSH level	1.089	(0.821–1.444)	0.556

#On day of HCG administration; *P<0.05

2.2 Results of Meta-analysis

To further pinpoint the association between TSH level and pregnancy outcomes in euthyroid women undergoing IVF/ICSI, a systematic meta-analysis was launched. The titles and abstracts of the literatures

were reviewed, and 15 studies were identified for further analysis. All the 15 studies were examined in detail to ascertain which articles to be included in the meta-analysis. Two independent researchers evaluated each publication. Only 11 articles met the inclusion criteria (fig. 1). Our present data were also included in the meta-analysis. These 12 articles provided sufficient data to calculate the pooled hazard ratio[11–21] (table 4).

For euthyroid women undergoing IVF/ICSI, the meta-analysis (fig. 2 and 3) showed that there was no significant difference in the clinical pregnancy rate between women with serum TSH ≤2.5 mIU/L and those with serum TSH >2.5 mIU/L (RR 1.03, 95% CI 0.96–1.11, *P*=0.289). No significant difference was noted in

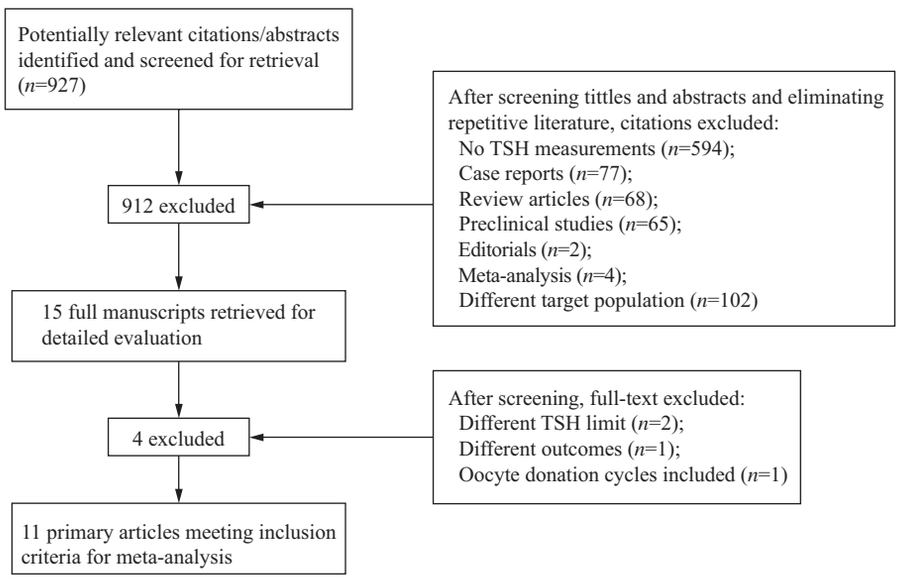

Fig. 1 Flowchart of the meta-analysis

Table 4 Characteristics of the twelve studies included in the meta-analysis (including our study)

No.	Authors	Year	Study design	TSH limit	ART protocol	Number of women with TSH ≤2.5 mIU/L	Number of women with TSH >2.5 mIU/L	ART outcomes
1	Reh A *et al*[11]	2010	Retrospective cohort study	TSH <2.5 mIU/L; TSH ≥2.5mIU/L	IVF	807	248	CP; miscarriage
2	Michalakis KG *et al*[12]	2011	Retrospective cohort study	TSH (0.4–2.5mIU/L) TSH (2.5–4.0 mIU/L)	IVF; ICSI	842	278	CP; miscarriage
3	Fumarola A *et al*[13]	2013	Retrospective cohort study	TSH ≤2.5 mIU/L; TSH >2.5 mIU/L	ICSI	206	57	CP
4	Benaglia L *et al*[14]	2013	Prospective cohort study	TSH ≤2.5 mIU/L; TSH >2.5 mIU/L	IVF	114	61	CP
5	Mintziori G *et al*[15]	2014	Retrospective cohort study	TSH ≤2.5 mIU/L; TSH >2.5 mIU/L	IVF; ICSI	120	38	CP; miscarriage
6	Chai J *et al*[16]	2014	Retrospective cohort study	TSH <2.5 mIU/L; TSH ≥2.5 mIU/L	IVF; ICSI	508	119	CP; miscarriage
7	Sordia-Hernandez LH *et al*[17]	2014	Retrospective cohort study	TSH <2.49 mIU/L TSH (2.5–4.2 mIU/L)	IVF	173	60	CP
8	Aghahosseini M *et al*[18]	2014	Retrospective cohort study	TSH <2.5 mIU/L; TSH ≥2.5 mIU/L	IVF	484	327	CP
9	Zeng X *et al*[19]	2014	Prospective cohort study	TSH <1.7 mIU/L TSH (1.7–2.5 mIU/L) TSH (2.5–3.5 mIU/L) TSH >3.5 mIU/L	IVF; ICSI	138	144	CP; miscarriage
10	Weghofer A *et al*[20]	2015	Retrospective cohort study	TSH ≤2.5 mIU/L; TSH >2.5 mIU/L	IVF; ICSI	77	21	CP
11	Coelho Neto MA *et al*[21]	2016	Retrospective cohort study	TSH <2.5 mIU/L; TSH (2.5–4.0 mIU/L)	IVF; ICSI	455	162	CP; miscarriage
12	Ours	2017	Retrospective cohort study	TSH ≤2.5 mIU/L; TSH >2.5 mIU/L	IVF; ICSI	830	355	CP; miscarriage

CP: clinical pregnancy

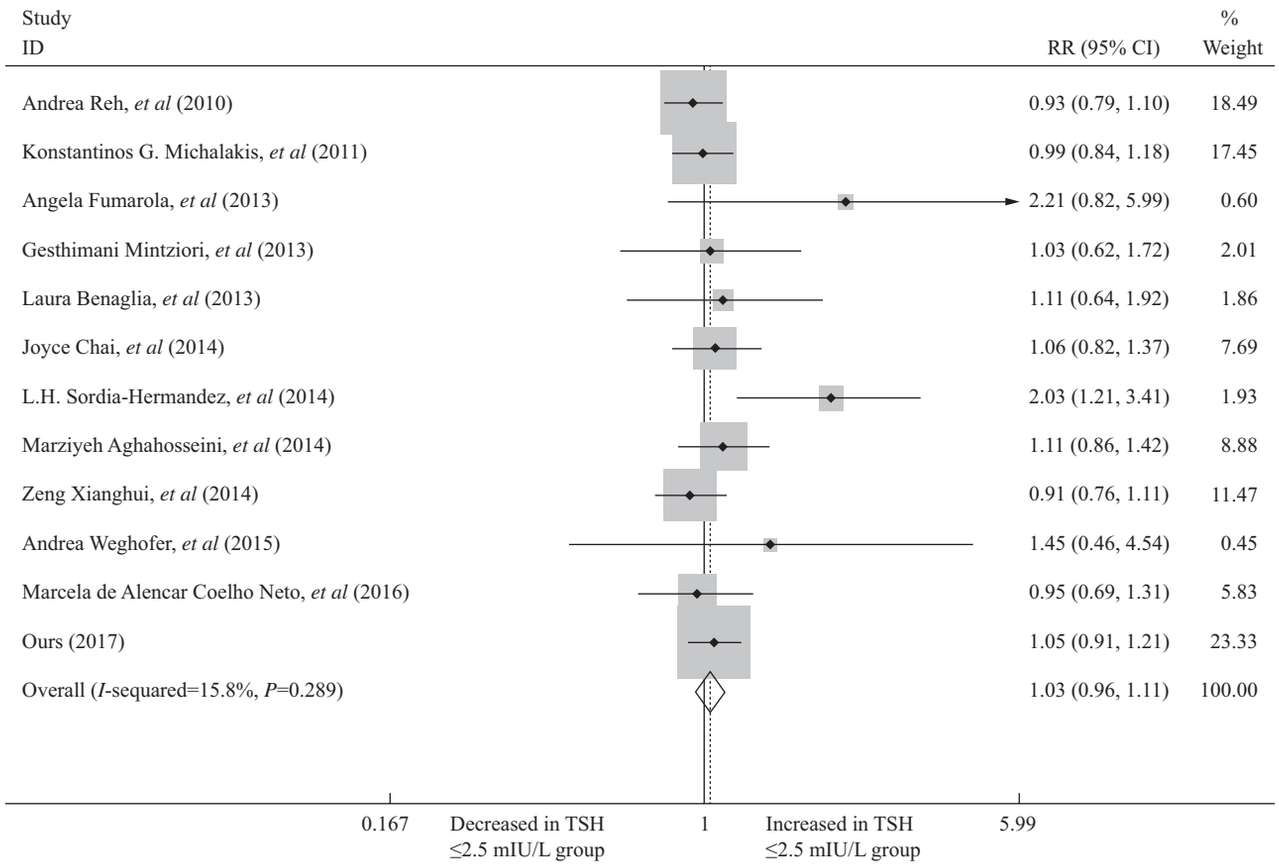

Fig. 2 Comparison of clinical pregnancy rate between euthyroid women with TSH ≤2.5 mIU/L and those TSH >2.5 mIU/L

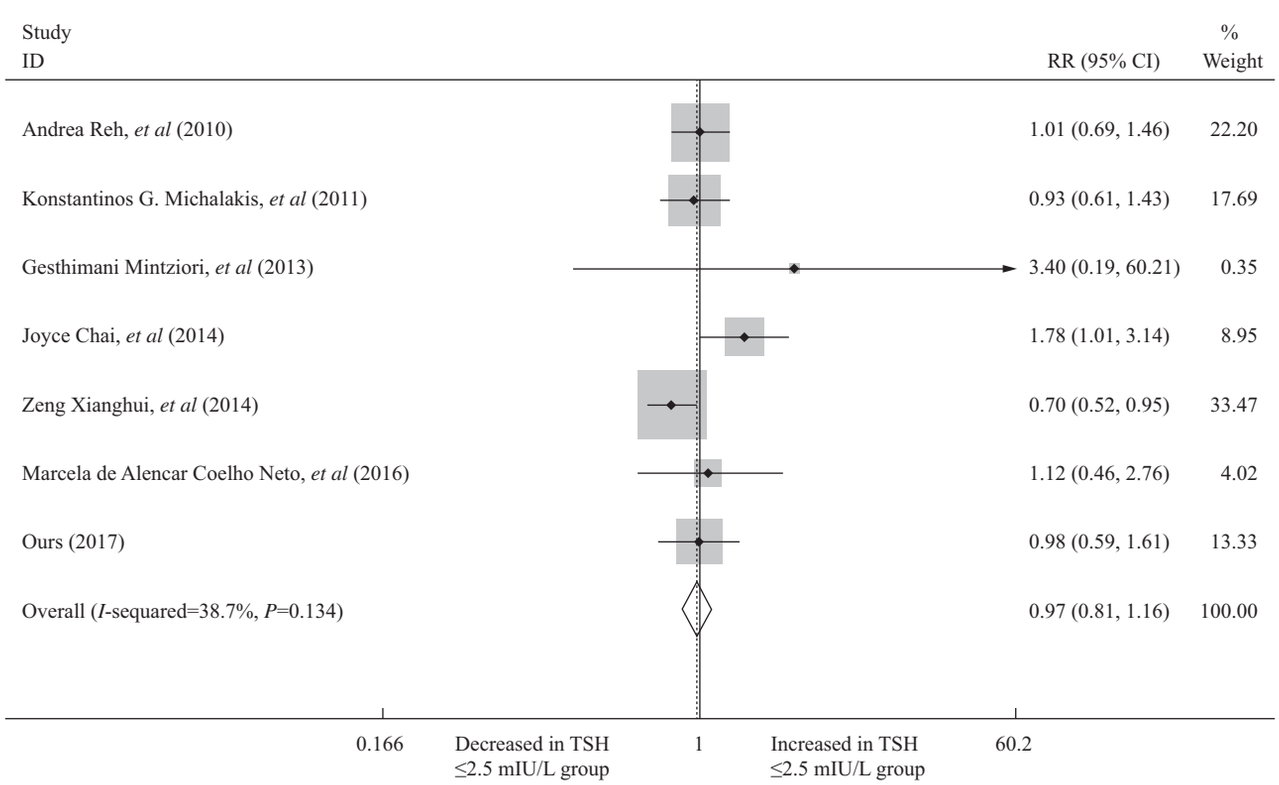

Fig. 3 Comparison of miscarriage risk between TSH ≤2.5 mIU/L and TSH >2.5 mIU/L groups in euthyroid women undergoing IVF/ICSI

the miscarriage rate between the two groups either (RR 0.97, 95% CI 0.81–1.16, *P*=0.134). The Begg's funnel plot was performed to assess the publication bias of the trials. The shapes of the funnel plot of the pregnancy outcome data did not reveal any evidence of obvious asymmetry.

3 DISCUSSION

Our study demonstrated that maintaining serum TSH levels ≤2.5 mIU/L had no benefit for clinical pregnancy rate or miscarriage rate in euthyroid women undergoing IVF/ICSI. Although the clinical pregnant rate and the miscarriage rate were lower in euthyroid women with serum TSH level >2.5 mIU/L, the difference was not statistically significant.

Currently, thyroid function screening by serum TSH levels is required for infertile women who attempt to get pregnant. Based on TSH levels, infertile women are classified as hyperthyroid, euthyroid or hypothyroid. For patients with thyroid disorders, administration of LT4 is necessary for improving pregnancy outcomes and has been supported by several studies[22]. However, for euthyroid women, especially those undergoing IVF/ICSI, the requirement for maintaining TSH levels less than 2.5 mIU/L has been controversial. Based on ASRM guidelines, for TSH levels between 2.5 mIU/L and 4.5 mIU/L, recommendations are equivocal. The guideline provides two options for the management: either monitor TSH levels and intervene when TSH is greater than 4 mIU/L or administer LT4 to maintain TSH that is less than 2.5 mIU/L. In previous studies, the level of TSH was raised for at least one month during COH[23], which resulted in a sub-optimal environment for the implantation and development of the embryo. Our present study demonstrated that serum TSH levels increased after COH, and exceeded the normal threshold of TSH levels 2.5 mIU/L before COH[24]. In other words, COH could expose women undergoing IVF/ICSI to a higher risk of significant hypothyroidism. Nevertheless, our results indicated that even with TSH levels >2.5 mIU/L before COH, the pregnancy outcomes after ART were not affected. This suggests that transient high TSH levels (greater than the upper limit of TSH normal threshold) had no untoward effect on pregnancy outcomes. However, some study reported that continual high TSH levels could reduce the rate of pregnancy[10], which was accepted by most researchers. Possibly the duration of high TSH levels is another key factor affecting pregnant outcomes, besides the level of TSH concentration. Mechanisms behind this phenomenon have yet to be elucidated in further study.

In our retrospective study, we used a TSH level of 2.5 mIU/L as our cut-off point to divide euthyroid women undergoing IVF/ICSI into two groups. Their mean age, BMI, AMH level, endometrium thickness and P level on the day of HCG administration, number of retrieved oocytes, time of infertility and number of different infertility types were not significantly different. However, baseline FSH levels were significantly higher, the number of AFC was significantly fewer and the E2 levels on the day of HCG administration were significantly lower in the serum TSH ≤2.5mIU/L group. We speculate that this may be due to the presence of TSH receptors in the human ovary. TSH is a key mediator in folliculogenesis and endometrium receptivity. In contrast, the clinical pregnancy rate and miscarriage rate were slightly higher in the TSH ≤2.5 mIU/L group. Interestingly, in this group, women seemed to have slightly weaker ovarian function. However, the pregnancy outcomes were similar between the two groups. The benefit of maintaining serum TSH levels ≤2.5 mIU/L needs to be demonstrated in further follow-up studies. In addition, the binary logistic regression analysis in the overall group indicated that baseline FSH levels had a significant effect on clinical pregnancy rates, which was demonstrated in previous studies[25]. TSH levels had no association with clinical pregnancy rates for euthyroid women undergoing IVF/ICSI.

Our retrospective study was an observational study and measurements for serum TSH before ART were limited. Furthermore, several studies have suggested that TSH levels fluctuate during COH, and serum TSH levels before ART may not fully represent thyroid function during fertility treatment[22].

In conclusion, our findings suggested that normal 'high' levels of TSH (TSH level >2.5 mIU/L) did not affect clinical pregnancy rates or miscarriage rates in euthyroid women undergoing IVF/ICSI. Hence, taking LT4 before IVF/ICSI to keep TSH levels ≤2.5 mIU/L may have no benefit to pregnancy outcome. Further multi-center studies with larger cohorts are necessary to confirm our findings.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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