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Effects of controlled ovarian stimulation on thyroid stimulating hormone in infertile women

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ABSTRACT

Objective: To study the effects of long-acting gonadotropin-releasing hormone agonist (GnRH-a) on thyroid function in euthyroid patients of in vitro fertilization (IVF)/ intracytoplasmic sperm injection of embryo transfer (ICSI-ET) and to investigate the timing and alteration of thyroid stimulating hormone (TSH) during controlled ovarian stimulation(COS).

Materials and methods: Euthyroid patients scheduled for IVF/ICSI were enrolled. Euthyroidism was defined as having no history of hypothyroidism with normal TSH before IVF. Long GnRH-a protocol was chosen as COS protocol. 207 patients were divided into two groups based on basal serum TSH level: group A with 0.35mIU/LTSH2.5mIU/L (n = 137) and group B with 2.5mIU/L ≤ TSH4.5mIU/L (n = 70). Serum TSH was tested on 6 time points: before COS (2–5days in menstrual cycle, before GnRH-a injection), Gn injection day 1, Gn injection day 5, human chorionic gonadotropin (HCG) day, 14 and 28 days after transplantation. The serum TSH, clinical pregnancy and abortion rate were investigated.

Result: The serum TSH value was significantly ($P < 0.05$) increased after injection of long-acting GnRH-a in all patients. Both groups had significant ($P < 0.05$) increases in serum TSH level after long-acting GnRH-a injection. The TSH level was increased in 131(63.3%) patients after GnRH-a injection, of which twenty (9.7%) had subclinical hypothyroidism with TSH level over 4.5 mIU/L. The other 76 (36.7%) patients had decreased TSH. In group A, 79 (57.7%) patients showed an increase of TSH, including three patients (2.2%) with simultaneous rise of TPOAb and four (2.9%) diagnosed of subclinical hypothyroidism with TSH level over 4.5 mIU/L, and the rest fifty-eight (42.3%) patients had decreased TSH with one patient with elevated TPOAb who was diagnosed with subclinical hyperthyroidism. In group B, fifty-two (74.3%) patients showed an increase of TSH, including thirteen (18.6%) patients with elevated TPOAb and sixteen (22.9%) patients diagnosed of subclinical hypothyroidism with TSH level over 4.5 mIU/L, and the rest eighteen (25.7%) patients had decreased TSH with one patient diagnosed with subclinical hyperthyroidism. Group B had a significant higher proportion of patients with elevated serum TSH than group A (P 0.05). Compared to the baseline level, serum TSH ascended distinctly and reached peak level on HCG day in all patients. Group A and B had similar trends of alteration. Patients in group A had significantly (P0.05) higher clinical pregnancy rate than in group B. No significant (P0.05) difference in abortion rate were observed between the two groups.

Conclusion: GnRH-a can significantly increase serum TSH levels with possible development of subclinical thyroid dysfunction. Infertile patients with serum TSH > 2.5 mIU/L are more susceptible to GnRH-a while patients with basal TSH less than 2.5 mIU/L may get a higher clinical pregnancy rate when receiving IVF/ICSI.

Introduction

Normal thyroid function plays an important role for pregnancy and fetal development. Infertility and menstrual disorders are possibly caused by thyroid disorders [1]. Adverse pregnancy outcomes, including miscarriage, preterm delivery, early abortion and fetal development abnormalities, have been associated with

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inadequately or untreated maternal thyroid disorders [1]. Thyroid dysfunction may affect the treatment outcome in infertile patients receiving assisted reproductive technology. At the same time, assisted reproductive technology may affect thyroid function [2]. Studies have shown that serum thyroid stimulating hormone (TSH) levels are the most sensitive, accurate and diagnostic indicator of thyroid function [3]. Some evidence suggests that elevated TSH in controlled ovarian stimulation (COS) may be associated with overdose of ovulation drugs, but the specific trends and pathophysiological mechanisms of thyroid-associated hormones are not clear [4]. Gonadotropin-releasing hormone agonist (GnRH-a) is a common agent for pituitary descending regulation because it is an analogue of gonadotropin-releasing hormone (GnRH) with several site-specific substitutions but has a higher receptor affinity than GnRH. It competes with GnRH in binding GnRH receptor and increases release of follicle hormone (FSH) and Luteiruzing hormone (LH). Sustained administration can down-regulate GnRH receptor and inhibit synthesis and release of LH and FSH, thereby inhibiting ovarian function, estrogen and progesterone synthesis. It can eliminate the endogenous LH peak release to achieve an effect of pituitary down-regulation. Some evidence suggests that drugs inhibiting hypothalamic function in the in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) process also affect the function of the hypothalamic-pituitary-thyroid regulatory axis, but reported cases are minimal [5]. A large number of studies have involved changes in thyroid function in the COS process, but the trends in these changes, the pathophysiological mechanisms, and whether different ovulation programs may have different effects on them are still controversial. We recognize that there is currently no routine testing of thyroid function in the IVF/ICSI prenatal and COS procedures, and there is controversy over control of thyroid-associated hormone levels in patients receiving IVF/ICSI and insufficient thyroid function monitoring for patients with hypothyroidism who receive thyroid supplementation. These conditions may be part of the reasons for a decreased success rate of IVF/ICSI but an increased incidence of adverse pregnancy outcomes [6].

Currently, the relationship between basal TSH and IVF/ICSI outcomes in infertile patients is still controversial. Because different races of people may have different levels of thyroid hormones and receptors, there are different views regarding whether TSH level of infertility women should be reduced to below 2.5 mIU/L before initiating pregnancy [7]. Most scholars believe that the defined normal upper limit of subclinical hypothyroidism TSH should be 4.5 mIU/L, but some scholars suggest a more reasonable upper limit of 2.5 mIU/L, because women suffering from the disease have a TSH level above 2.5 mIU/L in early pregnancy stage and need to receive thyroxine replacement therapy [6]. Some research observed that in infertile women who received IVF/ICSI treatment, the probability of premature birth and low birth weight infants with TSH > 2.5mIU/L was significantly greater than that of TSH < 2.5 mIU/L [8]. They suggested that in regions with sufficient iodine supplement, a proper serum TSH normal upper limit should be at 2.5mIU/L, and this value should be defined higher in iodine deficient regions [9]. In this study, the subjects were randomly divided into two groups according to the TSH threshold to explore the effect of different TSH thresholds on IVF outcomes. This study monitored the levels of thyroid-associated hormones in the COS process before and after GnRH-a administration, during ovulation and at multiple time points after transplantation to investigate changes of thyroid function in infertility patients with normal thyroid function who received IVF/ICSI treatment. The change of TSH level in the COS process was also monitored to analyze the effect of basal TSH on IVF/ICSI clinical pregnancy rate and abortion rate.

Materials and methods

This was a prospective cohort study conducted in 286 patients who received IVF/ICSI treatment from January 2016 to December 2016. This study was approved by the ethics committee of our hospital with signed informed consent obtained from all patients. The inclusion criteria were age range 20–35 years, body mass index (BMI) 18 kg/m^2 – 24 kg/m^2, normal thyroid function (0.35mIU/L < TSH < 4.5mIU/L, thyroid peroxidase antibody (TPOAb) <35IU/ml, 2.76 pmol/L < FT3 < 6.45 pmol/L and 8.75 pmol/L < FT4 < 22 pmol/L), no history of thyroid diseases, normal menstrual cycle basic hormone levels (on menstrual day 2), and normal ovarian reserve function. The exclusion criteria were patients with diabetes, immune system diseases including systemic lupus erythematosus, history of chemotherapy, smoking, narcotic drug dependence in recent half year, endometriosis, intrauterine adhesions, endometrial polyps and other gynecological diseases.

After passing screening of basic serum hormone and B-ultrasound, every patient was administered long-acting GnRH-a leuprolide acetate microspheres of 3.75 mg (Baye, Leuprorelin Acetate Microspheres for Injection, Livzon Pharmaceutical Co., Ltd.) on the second day of menstruation. Twenty-eight to thirty days later, basic serum hormone and B-ultrasound examination were performed. For patients who had reached the pituitary down-regulation standard, subcutaneous injection of recombinant follicle stimulating hormone (rFSH, Gonal-F, Switzerland Merck Serono) was administered with 150IU – 225IU/day for COS. Drug doses were adjusted based on the patients' follicle size and hormone levels.

Patients with over 3 follicles with a diameter over 18 mm were given choriogon adotropin alfa (recombinant human Chorionic Gonadotropin, r-hCG, Ovidrel® EMD Serono, Inc.) 250 ug to trigger ovulation. Thirty-six hours after triggering, oocyte retrieval was performed by vaginal ultrasound guided puncture. IVF/ICSI was then performed. Embryo culture was conducted, and ultrasound-aided embryo transfer was performed on day 3 after oocyte retrieval. Whole embryo cryopreservation was conducted for patients with ovarian hyperstimulation syndrome and patients with suboptimal endometrium.

Biochemical pregnancy was indicated by positive blood human chorionic gonadotropin (HCG) 14 days after transplantation. Clinical pregnancy was indicated by B-ultrasound detectable gestational sac 28–30 days after transplantation, including ectopic pregnancy. Patients were administered through vagina corpus luteum gel for luteal support until 11–12 weeks of pregnancy. Follow-up observations were performed on patients' pregnancy outcome.

All patients were divided into two groups based on the basal serum TSH levels: group A with 0.35 mIU/L < TSH < 2.5 mIU/L and group B with 2.5 mIU/L ≤ TSH <4.5 mIU/L. The outcome was measured for changes of serum TSH before and after GnRH-a injection and changes of serum TSH during IVF/ICSI. The serum TSH was measured at 6 time points: (1) before COS (menstruation 2–5 days), (2) Gn Day 1 (after injection of GnRH-a), (3) Gn Day 5, (4) HCG day, (5) 14 days after transplantation and (6) 28 days after transplantation. The clinical pregnancy rate (P) was calculated by the following equation: P = number of clinical pregnancy per 100 embryo transfers. The miscarriage rate (M) was calculated with M = number of cycles of miscarriage per 100 clinical pregnancies.

Patient serum levels of TSH, FT3, FT4 and TPOAb were measured with the Siemens immulite 2000xpi Automatic Electroluminescence Immunoassay System (Siemens, Germany) and matching kits, whereas the serum FSH, LH, E2, P and β-HCG were measured with the Beckman UniCel DxI800 Analyzer (Beckman Coulter, USA) and matching kits in 4 ml venous blood samples obtained at 7: 30–9:30 am.

Statistical analysis

Clinical and laboratory continuous data were presented as mean ± standard deviation for normal distribution, and non-normal distribution data are presented as medians (interquartile range). For non-continuous or non-normal distribution data, non-parametric Wilcoxon rank sum test was used. Variables between groups were compared by chi-square test or the Fisher exact test. Serum TSH levels at six time points were analyzed using repeated-measure ANOVA. Since the data didn't meet sphericity assumption, Greenhouse-Geisser was used for adjustment ($F = 1.366$, $p = 0.260$). The SPSS19.0 statistical software package (IBM, Chicago, IL, USA) was used for data analysis. The statistical significance was defined as $P < 0.05$.

Results

A total of 207 patients fulfilled all the requirements and were eventually included for last analysis. They were divided into group A with 137 patients and group B with 70 patients based on the basal TSH level. There was no significant ($P > 0.05$) difference between the two groups in age, year of infertility, BMI, basal FSH level, basal LH level, basal E2 level and basal polyp follicle number (AFC) (Table 1).

The serum TSH value was significantly ($P < 0.05$) increased after injection of long-acting GnRH-a in all patients (Fig. 1). The levels of serum TSH in groups A and B were significantly higher than those before injection ($P < 0.05$) (Fig. 2). An increasing tendency of TSH was also demonstrated in both groups during the use of gonadotropin hormone (Gn). The geometric mean of the serum FSH at different time points was shown in Fig. 1. Compared with basal TSH (1), the serum TSH level was elevated during the whole process of COS and reached the peak after HCG administration (4). After that, the TSH level was slightly decreased but still higher than the basal TSH value.

Among all 207 patients, 131 (63.3%) had elevated serum TSH, 20 (9.7%) had TSH > 4.5 mIU/L, and 16 (7.7%) had TPOAb higher than the normal value (Table 2). On the other hand, 76 (36.7%) patients had decreased serum TSH, of which two (1.0%) had TSH < 0.35 mIU/L, and one (0.5%) had TPOAb higher than the normal value.

In group A with 137 patients, 79 (57.7%) had elevated serum TSH, of which three (2.2%) were accompanied with increased TPOAb. Four (2.9%) patients had TSH > 4.5 mIU/L, with normal FT3 and FT4, but no reduced metabolic symptoms like chills or fatigue, and one of the four patients (0.7%) was diagnosed as subclinical hypothyroidism accompanied by elevated TPOAb. On the other hand, 58 patients (42.3%) in group A had decreased serum TSH, including one (0.7%) patient with subclinical thyroid hyperthyroidism accompanied with increased TPOAb. This patient had TSH < 0.35mIU/L, elevated FT3 and FT4, without palpitations, sweating or goiter.

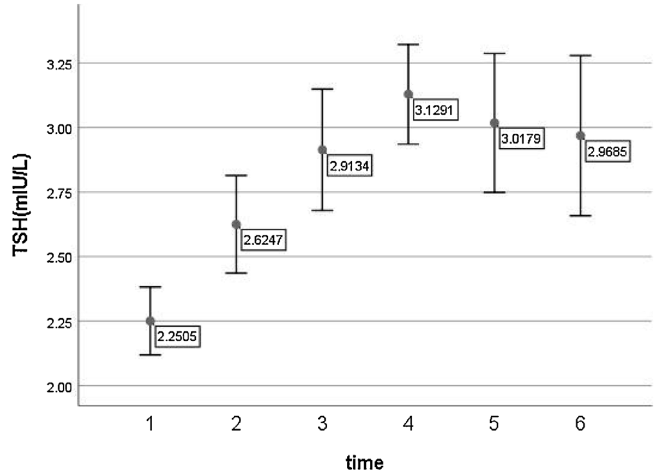

Fig. 1. Thyroid stimulating hormone (TSH) changes over time during controlled ovarian stimulation (COS) in all patients. Geometric mean values with standard error bars were shown. Time points: 1. baseline status before gonadotropin-releasing hormone agonist (GnRH-a) injection, 2. After GnRH-a injection before stimulation, 3. Five days after initiating stimulation, 4. At administration of human chorionic gonadotropin, 5. Two weeks after embryo transfer and 6. Four weeks after embryo transfer.

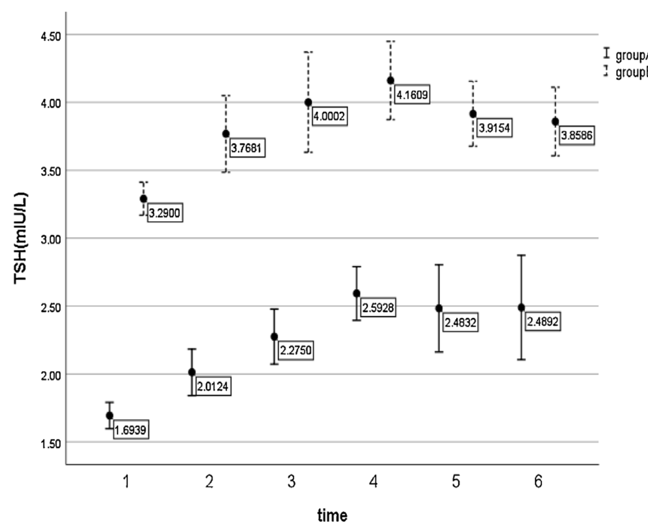

Fig. 2. Thyroid stimulating hormone (TSH) changes over time during controlled ovarian stimulation (COS) in groups A and B. A: TSH2.5 mIU/L and B: 2.5mIU/L ≤ TSH 4.5 mIU/L. Geometric mean values with standard error bars were shown. Time points: 1. basal status before gonadotropin-releasing hormone agonist (GnRH-a) injection, 2. After GnRH-a injection before stimulation, 3. Five days after initiating stimulation, 4. At administration of human chorionic gonadotropin, 5. Two weeks after embryo transfer and 6. Four weeks after embryo transfer.

Table 1
Demography of the patients.

	A(n = 137)	B(n = 70)	*P*
Age (years)	28.85 ± 3.03	29.04 ± 2.75	0.65
Duration of infertility (years)	3.24 ± 1.98	3.60 ± 2.21	0.237
BMI (Kg/)	22.64 ± 3.30	22.41 ± 4.88	0.688
bFSH (mIU/ml)	6.59 ± 1.93	6.74 ± 2.00	0.614
bLH (mIU/ml)	4.96 ± 2.46	5.78 ± 3.75	0.1
bE_2 (pg/ml)	41.71 ± 20.35	42.77 ± 21.85	0.736
AFC	10.93 ± 2.59	10.50 ± 2.38	0.242

Note: BMI, body mass index; bFSH, baseline follicle-stimulating hormone; bLH, baseline luteinizing hormone; bE_2, baseline estradiol; AFC, antral follicle count. * $P < 0.05$.

Table 2
TSH increase and decrease after injection of GnRH-a in the groups.

No.	Total (n = 207)	Group A (n = 137)	Group B (n = 70)	*P*
TSH increase	131(63.3%)	79 (57.7%)	52 (74.3%)	0.019*
TSH decrease	76 (36.7%)	58 (42.3%)	18 (25.7%)	0.019*
Total	207 (100%)	137 (100%)	70 (100%)	

Note: No., number; TSH, thyroid stimulating hormone; gonadotropin-releasing hormone agonist.
* $P < 0.05$.

In group B with 70 patients, 52 (74.3%) had elevated serum TSH, of which thirteen (18.6%) were accompanied with increased TPOAb. Sixteen (22.9%) patients had subclinical hypothyroidism with the TSH > 4.5 mIU/L, normal FT3 and FT4, but no reduced metabolic symptoms (Table 2). Six (8.6%) patients were accompanied by elevated TPOAb. However, 18 (25.7%) had decreased serum TSH, of which one (1.4%) was diagnosed as subclinical thyroid hyperthyroidism with the TSH < 0.35mIU/L, increased FT3 and FT4, but no palpitations, no sweating nor goiter.

Both groups displayed a higher proportion of increased TSH rather than decreased TSH (Table 2). The proportion of increased TSH in group B was significantly ($P < 0.05$) higher than in group A.

The TSH levels changed significantly over time ($P = 0.000$ for each).For all patients as a whole group, the overall trend of serum TSH in the COS process showed a gradual increase to reach the peak on the HCG day, followed by a slight fall (Fig. 1).Patients with serum TSH less than 2.5 mIU/L and ranging 2.5–4.5 mIU/L in our study displayed the same pattern of change (Fig. 2).

The clinical pregnancy rate in group A was significantly ($P < 0.05$) higher than in group B (Table 3). The abortion rate of group B was higher than that of group A, but the difference was not significant ($P > 0.05$) due to insufficient sample size.

Discussion

It is well known that thyroid dysfunction results in frequent occurrences of menstrual disturbances, impaired fertility, and adverse outcome both for mother and fetus. IVF/ICSI is one of the most important means of treating infertility, and some research found that thyroid function may vary during IVF/ICSI [2].

Our study found that injection of long-acting sustained-release GnRH-a (3.75 mg) induced an overall increasing trend in the serum TSH level, with more patients presenting increased rather than decreased TSH levels. Patients with normal thyroid function may display subclinical hypothyroidism, subclinical hyperthyroidism, autoimmune thyroid disease and other symptoms of thyroid dysfunction if they had continuous GnRH-a pituitary down regulation treatment. This is consistent with results reported in previous clinical cases [10–14]. A brief hyperthyroidism or hypothyroidism symptom may develop after application of GnRH-a in patients [10]. Patients with hypothyroidism might display a brief hyperthyroidism after application of long-acting GnRH-a [11]. Moreover, the application of long-acting GnRH-a may induce subclinical hypothyroidism with increased TPOAb, Grave's disease or Hashimoto's thyroiditis in patients with normal thyroid function [12,11–14]. Considering that GnRH receptors are present in the thyroid gland cells of the pituitary gland and ovarian granulosa cells, it is possible that GnRH may influence thyroid-associated hormones in the circulation through both central and peripheral effects [15].

After administering long-acting GnRH-a in our study, more patients had increased serum TSH level than those with decreased TSH level, including patients with serum TSH > 4.5mIU/L, who were diagnosed as subclinical hypothyroidism. Subclinical hypothyroidism may decrease the IVF/ICSI success rate but increase the abortion rate, leading to fetal mental retardation [1,16]. Currently, the most widely accepted diagnostic indicator of serum TSH for subclinical hypothyroidism is a normal upper limit of 4.5 mIU/L [15]. But some scholars believe that an upper limit of 2.5mIU/L in the serum TSH level would be more reasonable, because for women of childbearing age, a suitable TSH range should be less than 2.5mIU/L at the early stage of pregnancy, and thyroxine supplement therapy is needed if the serum TSH exceeds 2.5 mIU/L. According to the American Thyroid Association (ATA), for patients with subclinical hypothyroidism, the serum TSH should be controlled below 2.5 mIU/L. Close monitoring of thyroid-associated hormone levels and increased monitoring frequency should be conducted especially for patients with increased TPOAb [17]. The American Society for Reproductive Medicine (ASRM) believes that women preparing for pregnancy should receive Levothyroxine (LT4) treatment and control TSH below 2.5 mIU/L if the serum TSH is over 4 mIU/L. For women with a TSH concentration of 2.5–4 mU/L, close monitoring of thyroid-related hormone levels is recommended; the thyroxine therapy may also be used to reduce the TSH level to 2.5 mIU/L or less. For infertile patients with the TSH above 2.5 mIU/L combined with autoimmune thyroid diseases (AITD), LT4 supplement therapy is recommended to improve the pregnancy rate and get a better pregnancy outcome [18]. GnRH-a-induced TSH increase can be monitored according to the above guidelines, and for patients undergoing IVF / ICSI treatment with the TSH over 4mIU/L, appropriate thyroid drug replacement therapy may be applied. Currently, no large-scale clinical research is available to support this treatment for improved pregnancy outcome.

Table 3
Clinical pregnancy and abortion rates in the groups.

IVF outcome	Group A (n = 137)	Group B (n = 70)	*P*
Clinical pregnancy rate (%)	66.0% (58/88)	36.8% (14/38)	0.002*
Abortion rate (%)	10.3%(6/58)	14.3%(2/14)	0.648

Note: IVF, in vitro fertilization.
* $P < 0.05$.

In the application of GnRH-a to induce pituitary down-regulation, we observed cases of TPOAb turnover in TPOAb negative patients. Some of these patients were diagnosed as subclinical hypothyroidism. AITD may cause thyroid dysfunction in infertile patients. On one hand, TPOAb inhibits enzyme activity by binding to TPO, thus reducing thyroid hormone synthesis. On the other hand, it can induce complement effects by activating lymphocyte-mediated cell lysis and destroying thyroid cells, resulting in abnormal thyroid function [19,20]. Among the subjects receiving IVF/ICSI, no significant differences existed in the transfer success rate and clinical pregnancy rate between TPOAb positive and normal groups, with a higher fertility rate in the TPOAb positive patients. However positive TPOAb could cause higher abortion rates and reduce live births, leading to adverse effects on pregnancy outcomes [21]. Therefore, for patients displaying increased TPOAb after injection of long-acting GnRH-a, close monitoring of thyroid-related hormone levels, including serum TSH levels, should be performed. For patients manifesting subclinical hypothyroidism, timely thyroid hormone supplement therapy should be administered, and thyroid-associated hormone levels should be determined before undergoing embryo transfer.

In our study, two patients with normal thyroid function showed subclinical hyperthyroidism after GnRH-a hypopituitarism. The mechanism behind this phenomenon is not clear. Pregnancy with hyperthyroidism increased the possibility of fetal growth retardation, still birth, abortion, premature birth and other adverse pregnancy outcomes [22]. A systematic review shows that thiouracil and methimazole treatment can significantly reduce the risk of preterm birth and the risk of low birth weight in women with hyperthyroidism [23]. We aborted fresh embryo transfer in these two patients and treated them with anti-thyroid drug propylthiouracil immediately after oocyte retrieval. One patient returned to normal thyroid function in a short time, and the other had subclinical hypothyroidism. This result showed that GnRH-a induced-hyperthyroidism may be easily corrected and that hypothyroidism could be avoided by drug dose adjustment. This is consistent with the conclusion that patients with hyperthyroidism can return to normal performance in a relatively short period of time [10,11].

By comparing the difference of TSH increase after GnRH-a hypopituitarism between groups A and B, we found that patients with basal TSH concentrations of 2.5–4.5 mIU/L were more prone to serum TSH increase. This suggests that patients with higher TSH may be more susceptible to GnRH-a. Therefore, close monitoring of thyroid function should be performed in patients with serum TSH of 2.5–4.5 mIU/L, and drug treatment is needed in case of abnormalities.

We also found that patients with TSH < 2.5 mU/L had higher rates of clinical pregnancy when receiving IVF/ICSI ($P < 0.05$). It is suggested that controlling serum TSH below 2.5 mU/L before entering the IVF/ICSI cycle may be helpful in increasing the pregnancy rate. Although the abortion rate was lower in patients with the TSH below 2.5 mU/L than in patients with TSH ranging 2.5–4.5 mIU/L, no statistically significant difference ($P > 0.05$) was shown due to the small sample size. A retrospective study found that the basal TSH level was positively correlated with the abortion rate but negatively correlated with the pregnancy rate [24]. Patients with TSH greater than 2.5 mU/L before IVF treatment may have adverse outcomes such as premature birth and low birth weight infants [24]. A study randomly divided infertile women who received IVF into the treatment group receiving levothyroxine tablets and the control group with placebos [25]. The abortion rate in the treatment group was significantly lower than in the control group [25]. The clinical pregnancy rate and the live birth rate of the treatment group were significantly higher than in the placebo group [25]. This suggests that thyroid hormone replacement therapy may have a positive effect on the pregnancy outcomes. Although the clinical pregnancy rate has been reported higher in patients receiving IVF / ICSI with the serum TSH less than 2.5 mU/L than in patients with the TSH ranging 2.5–4.5mIU/L, there is no statistical significance ($P > 0.05$), indicating no significant ($P > 0.05$) difference in the IVF / ICSI outcomes between patients with TSH ranging 0.5–4.5 mIU/L [26]. There is still a great deal of controversy on setting the threshold of TSH at 2.5 mU/L or less before IVF/ICSI treatment, and more research is needed for this.

For all patients, the overall trend of serum TSH in the COS process showed a gradual increase to reach the peak at the HCG day, followed by a slight fall. Patients with serum TSH less than 2.5 mIU/L and of 2.5–4.5 mIU/L in our study showed a similar trend. A number of studies have shown that changes in thyroid function in the COS process vary widely [5,27,28]. It has been reported that approximately 30% to 40% of patients with normal thyroid function develop abnormal during the course of COS treatment [28]. Most reports suggest that serum TSH levels have increased during the COS, which is consistent with our findings. However, there are also studies reporting that the serum TSH levels did not change in the treatment of IVF / ICSI [29,30]. A systematic review suggests that the serum TSH is increased in the process of ovulation induction, often exceeding the reference TSH threshold of 2.5 mIU/L in early pregnancy, but this trend still requires a large number of prospective clinical studies to confirm [27]. The rise in E2 in the COS process may be a crucial factor in the above changes [31,32]. Firstly, it may lead to an increase in thyroxine-binding globulin (TBG) expression, which in turn reduces serum FT4 concentration and increases TSH synthesis by hypothalamic-pituitary-thyroid axis negative feedback [31]. Secondly, it may increase the level of anti-thyroid antibodies by inhibiting T helper cell-mediated immune responses [32]. It has been found that TSH has a tendency to rise in COS while FT4 has a tendency to decrease in this process, which is more pronounced in patients with increased TSH after HCG and treatment for hypothyroidism [33]. Another study showed that serum TSH, TBG and T4 levels were gradually increased from day 1 after Gn until the day before oocyte retrieval, which was higher than the baseline value before ovulation [34]. The baseline TSH value determines the level at which the TSH value can be achieved in the COS process. Most of the TSH values that are over 2.5 mIU/L are due to the higher baseline TSH values in the patients. Researchers believe that there is no need for special treatment and intervention when the TSH level does not reach subclinical hypothyroidism or in patients with AITD [28]. However, a recent review concluded that thyroid function should be closely monitored during the COS process, and when the TSH value exceeds 2.5 mIU/L, L-thyroxine tablets should be given for replacement therapy [35].

In summary, the application of GnRH-a to induce pituitary down regulation may increase serum TSH levels with possible development of subclinical thyroid dysfunction and may necessitate close monitoring of the thyroid function. Infertile patients with serum TSH > 2.5mIU/L are more susceptible to GnRH-a while patients with basal TSH less than 2.5mIU/L may get a higher clinical pregnancy rate when receiving IVF/ICSI.

Declaration

The data can be provided on requirement.

None of the authors have any competing interests in the manuscript.

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