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Original Article

Influence of hypothyroidism on in vitro fertilization outcomes

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Abstract: Purpose: To analyze whether the thyroid status is affecting *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) outcomes. Methods: In this retrospective cohort study, we reviewed the medical records of 426 infertile women who underwent IVF/ICSI cycles. Included were hypothyroid (HypoT-LT4) patients with serum thyroid-stimulating hormone (TSH) concentrations > 4.0 μIU/mL, which were treated with levothyroxine (LT4) (n = 28), untreated subclinical hypothyroid (scHypoT) (n = 128), as well as euthyroid (euT) patients (n = 270). Measured parameters were total gonadotropin (Gn) dosage, luteinizing hormone (LH), estradiol and progesterone (P) serum concentrations on human chorionic gonadotropin (hCG) trigger day, number of retrieved oocytes, mature (metaphase II) oocytes, fertilization rate, the number of two pronuclei (2PN) embryos, top quality embryos on day 3 of development, number of embryos transferred, endometrial thickness as well as implantation, clinical pregnancy, miscarriage and ongoing pregnancy rates. Results: HypoT-LT4 women had significantly decreased implantation (P = 0.046) and ongoing pregnancy (P = 0.034) rates as well as increased pregnancy loss (P = 0.042) and chemical pregnancy rates (P = 0.035) compared to euT and scHypoT women. scHypoT patients had significantly decreased single clinical pregnancy (P = 0.038) and increased twin pregnancy (P = 0.034) rates compared to euT and HypoT-LT4 women. The percentages of transfer per retrieval cycles and βhCG positive transfer cycles, clinical pregnancy rates per transfer cycles, as well as ectopic pregnancy rates and the occurrence of ovarian hyperstimulation syndromes (OHSS) were similar among the 3 groups. Conclusions: HypoT-LT4 patients had low implantation and high pregnancy loss rates. There was no evidence that IVF/ICSI outcomes were impaired among scHypoT and euT patients.

Keywords: IVF-ET, hypothyroidism, subclinical hypothyroidism, pregnancy, levothyroxine, infertility, TSH

Introduction

Thyroid disease is one of the most common endocrine disorders of reproductive-aged women [1]. The prevalence of overt hypothyroidism in the general population ranges from 2% to 4%, while the prevalence of subclinical hypothyroidism, defined as an elevated serum thyroid-stimulating hormone (TSH) level associated with a normal free thyroxine (FT4) level and without frank symptoms of hypothyroidism [2], ranges from 0.4% to 0.5% [3]. Overt hypothyroidism may result in reproductive disturbances including menstrual irregularities due to ovulatory dysfunction, miscarriage, and obstetrical complications as well as impaired fetal brain development [4, 5]. Like overt hypothyroidism, subclinical hypothyroidism has also been linked with poor obstetric outcomes [6].

It has been proposed that ovary stimulation induces a rapid increase in serum estradiol concentrations, resulting in excess thyroxine-binding globulin (TBG) production and sialylation by the liver [7]. This increase in TBG increases the number of circulating thyroxine-binding sites and tends to reduce free thyroxine (FT4) concentrations; the latter can induce TSH production from the pituitary gland. Thus, estradiol induces an additional strain on the hypothalamic-pituitary-thyroid axis and might therefore impair thyroid hormone distribution and kinetics [8]. In fact, an underlying thyroid abnormality was found in 46% of women who experiencing IVF failure [9] and TSH levels were inversely proportional to the fertilization rates at IVFs [10]. Although it is well accepted that infertile women with overt hypothyroidism should be treated with an adequate dose of LT4 during

pregnancy [11], it is not yet clear that what TSH level is appropriate in patients treated with levothyroxine before IVF or ICSI treatments. In a recent systematic review, that included 11 studies, it was suggested that for subclinical hypothyroidism and thyroid autoimmunity evidence is insufficient to recommend treatment with LT4 before conception and in early pregnancy [12]. On the other hand, other researchers have recommended that pregnant women with subclinical hyperthyroidism or those planning pregnancy should be treated with LT4 to reduce the risks of a miscarriage and fetal developmental impairments [13].

This retrospective study was performed to compare IVF/ICSI outcomes of LT4 treated hypothyroid patients with untreated subclinical hypothyroid and euthyroid women, to obtain clinical information about hypothyroidism and IVF interventions.

Patients and methods

The research was approved by the institutional review board of the Peking University First Hospital and written informed consent was obtained from all participants. In a retrospective cohort study, we reviewed the medical records of 426 infertile women aged 40 years or less who underwent IVF/ICSI treatments between January 2007 and June 2012 in the academic IVF center of the Peking University First Hospital, using their own oocytes and their husbands' sperm.

Basic demographic and infertility data (tubal factor, endometriosis, anovulation, uterine factor, diminished ovarian reserve, male factor, unexplained) were collected before the interventions. All patients had their baseline serum concentrations of triiodothyronine 3 (TT3), TT4, free triiodothyronine 3 (FT3), FT4 and TSH serum concentrations measured prior to commencing IVF or ICSI, and according to the levels they were categorized into three groups: euthyroid (euT) (TSH: 0.4-2.5 μIU/mL), subclinical hypothyroid (scHypoT) (TSH: 2.5-4.0 μIU/mL, FT4 normal) and hypothyroid with LT4 medication (HypoT-LT4) (TSH > 4.0 μIU/mL, or TSH 0.25-4.0 μIU/mL with FT4 reduced), in accordance with the 2011 guidelines of the American Thyroid Association (ATA) [14]. HypoT-LT4 patients were medicated for at least 3 months with 25-150 μg levothyroxine per day to adjust and maintain their TSH serum concentrations to 0.4-4.0 μIU/mL. scHypoT patients were not treated following the recommendations of their endocrinologists.

All patients underwent controlled ovarian hyperstimulation (COH), with standard gonadotropin-releasing hormone agonist or antagonist protocols and received daily recombinant follicle-stimulating hormone (rFSH) 150-300 IU, with or without human menopausal gonadotropin (HMG) 75-150 IU. When 3 follicles ≥ 18 mm were present, 10,000 IU hCG was injected. Oocytes were retrieved 36-38 hours later and the oocytes/embryos were cultured in Sydney IVF Medium (COOK IVF, Queensland, Australia). Two or three embryos were transferred into the uterine cavity on cleavage day 3. Luteal support with daily 60 mg intramuscular progesterone injections was continued until 10 weeks of gestation.

IVF cycle results, including Gn dosage, LH, estradiol and P serum concentrations on HCG trigger day, the number of retrieved oocytes, mature (metaphase II) oocytes, the number of 2PN and top quality embryos on day 3 of development (≥ 6 cells and < 25% fragmentation), the number of embryos transferred as well as endometrial thickness and implantation, clinical pregnancy, fertilization, miscarriage and ongoing pregnancy rates during and after the treatments, were analyzed.

Statistical analyses

All analyses were performed using SPSS for Windows (version 16.0. Chicago, SPSS Inc.). When the quantitative data were normally distributed, a variance test followed by the SNK method was used for evaluating intergroup differences. In case of non-parametric distribution, Mann-Whitney or Wilcoxon tests were performed and for intergroup comparisons the Bonferroni method was applied. The qualitative data (the frequencies of various infertility factors and categorical variables) were compared using Chi-squares of Fisher exact tests among 3 groups, whereas intergroup differences were evaluated using a Kruskal-Wallis test. All *P* values are two-sided and *P* values < 0.05 were considered to be statistically significant.

Results

A total of 426 IVF cycles of 28 (6.6%) HypoT-LT4, 270 (63.4%) euT and 128 (30.0%) scHypoT patients were analyzed. The 3 groups were sim-

Table 1. Pre-IVF characteristics of euT, scHypoT and HypoT-LT4 patients

	EuT (n = 270)	Hypo-LT4 (n = 28)	ScHypoT (n = 128)	*P* value[#]
Number of patients (%)	270 (63.4%)	28 (6.6%)[a]	128 (30.0%)[b,c]	**< 0.0001**
Age (years)	31.5 ± 4.5	30.2 ± 4.42	31.32 ± 4.56	0.3474
Infertility time (years)	3.2 ± 1.3	2.8 ± 1.7	3.4 ± 1.1	0.0614
TT3 (nmol/L)	1.67 ± 0.29	1.60 ± 0.27	1.71 ± 0.35	0.1880
TT4 (nmol/L)	105.76 ± 17.81	110.83 ± 20.25	104.02 ± 18.88	0.1971
FT3 (pmol/L)	4.29 ± 0.45	4.05 ± 0.83[a]	4.27 ± 0.42	**0.0402**
FT4 (pmol/L)	14.25 ± 1.91	13.73 ± 4.08	13.77 ± 3.24	0.1668
TSH (μIU/L)	1.65 ± 0.57	3.32 ± 1.59[a]	3.34 ± 0.72[c]	**< 0.0001**
Basic FSH (μIU/mL)	6.63 ± 2.17	7.47 ± 2.46	7.00 ± 2.21	0.0733
Basic LH (μIU/mL)	3.97 ± 1.90	4.5 ± 2.79	4.26 ± 2.04	0.2198
Basic E2 (pg/mL)	32.72 ± 15.76	34.94 ± 10.26	35.32 ± 18.5	0.3049

[#]*P* values of comparisons (Mann-Whitney or Chi-square) among all 3 groups; the bold numbers are significant. TT, triiodothyronine; FT, free triiodothyronine; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; TSH, thyroid-stimulating hormone. [a]euT group compared with the Hypo-LT4 group ($P < 0.05$), [b]Hypo-LT4 group compared with the scHypoT group ($P < 0.05$), [c]euT group compared with the scHypoT group ($P < 0.05$).

Table 2. Infertility factor diagnoses of euT, HypoT-LT4 and scHypoT patients

Infertility Diagnosis	euT (n = 270, %)	HYPOT-LT4 (n = 28, %)	scHypoT (n = 128, %)	*P* value[#]
Tubal factor	63 (23.3)	5 (17.8)	29 (22.7)	0.8681
Endometriosis	25 (9.3)	2 (7.1)	12 (9.4)	0.9396
Anovulation	27 (10.0)	3 (10.7)	12 (9.4)	0.9746
Uterine factor	9 (3.3)	1 (3.6)	3 (2.3)	0.8619
Unexplained	3 (1.1)	1 (3.6)	0 (0)	0.1938
Male factor	102 (37.8)	11 (39.3)	52 (40.6)	0.9362
Diminished ovarian reserve	14 (5.2)	2 (7.1)	11 (8.6)	0.4697
Combined factors	27 (10.0)	3 (10.7)	9 (7.0)	0.6545

[#]*P* values are for comparisons (chi-square or fisher exact test) among all 3 groups.

ilar regarding the age distribution, infertility time, TT3, TT4, FT4 and basic serum FSH, LH and estradiol serum concentrations measured before the IVF interventions. The mean pre-IVF treatment serum FT3 concentration of the euT and scHypoT groups were not significant different, but significantly higher in the euT compared to the Hypo-LT4 group; TSH concentrations of both the HypoT-LT4 and scHypoT groups were 3.32-3.34 μIU/mL and were significantly higher than in euT women (**Table 1**).

Chi-square comparisons indicated that tubal factor, endometriosis, anovulation, uterine factor, unexplained, male factors and diminished ovarian reserve (DOR) as well as combined infertility factors were similar among the 3 groups (**Table 2**).

Responses to COH treatments of the 3 groups are shown in **Table 3**. There was no significant difference between the 3 groups regarding the stimulation protocols used (data not shown) or total dosage of gonadotropins administered, LH concentration on hCG trigger day, number of top quality embryos, transferred embryos and embryos cryopreserved as well as the number of IVF/ICSI.

On the other hand days of Gn, estradiol and progesterone concentration on hCG trigger day, numbers of oocytes retrieved, MII oocytes, 2PN as well as the number of fertilizations were significant different among the 3 groups. Endometrial thickness prior to embryo transfer was > 10 mm in all 3 groups (**Table 3**).

HypoT-LT4 women had significantly decreased implantation and ongoing pregnancy rates in addition to enhanced pregnancy losses and chemical pregnancy rates. Single clinical pregnancies occurred more frequently among HypoT-LT4 patients compared to euT and particularly scHypoT women, who developed significantly decreased single and increased clinical twin pregnancies. The percentages of transfer per retrieval cycles and βhCG positive transfer cycles, clinical pregnancy rates per transfer cycles, as well as ectopic pregnancy rates and occurrence of ovarian hyperstimulation syndromes were similar among the 3 groups (**Table 4**).

Table 3. COH outcomes of IVF/ICSI cycles performed in euT, HypoT-LT4 and scHypoT patients

	EuT (n = 270)	HypoT-LT4 (n = 28)	ScHypoT (n = 128)	*P*-Value[#]
Total dosage of Gn (IU)	2815 ± 885	2942 ± 1140	2915 ± 982	0.5310
Day of Gn	10.2 ± 1.2	11.1 ± 0.3[a]	10.5 ± 0.8[b,c]	**< 0.0001**
LH (HCG DAY) (μIU/mL)	1.24 ± 1.02	1.22 ± 0.75	1.43 ± 1.31	0.2569
E2 (HCG DAY) (pg/mL)	2941.42 ± 140.15	2167.71 ± 302.83[a]	2870.22 ± 115.96[b,c]	**< 0.0001**
P (HCG DAY) (ng/mL)	1.17 ± 0.16	0.73 ± 0.32[a]	1.04 ± 0.15[b,c]	**< 0.0001**
Number of oocytes	13.5 ± 7.28	9.57 ± 6.45[a]	12.92 ± 7.03	**0.0217**
Number of MII oocytes	11.1 ± 6.25	7.5 ± 5.27[a]	10 ± 5.85	**0.0061**
Number of fertilizations	9.5 ± 2.3	6.43 ± 4.6[a]	8.25 ± 5.88[c]	**< 0.0001**
IVF/ICSI	176/94	20/8	90/38	0.5260
Number of 2PN	7.82 ± 5.07	4.5 ± 3.71[a]	7.0 ± 5.24	**0.0028**
Number of top quality embryos	3.22 ± 2.73	2.07 ± 2.33	3.17 ± 3.08	0.1197
Number of transferred embryos	1.94 ± 0.89	1.71 ± .061	1.78 ± 0.93	0.1447
Number of cryopreserved embryos	5.16 ± 4.28	4.00 ± 3.61	4.23 ± 4.5	0.0796
Endometrial thickness	10.3 ± 2.1	10.5 ± 2.8	10.1 ± 3.1	0.6520

[#]*P* values for comparisons (Mann-Whitney or Chi-square) among all 3 groups. Top-quality embryos: ≥ 6 cells and < 25% fragmentation. The bold numbers are significant. [a]euT group compared with the Hypo-LT4 group ($P < 0.05$), [b]Hypo-LT4 group compared with the scHypoT group ($P < 0.05$), [c]euT group compared with the scHypoT group ($P < 0.05$).

Table 4. IVF/ICSI Outcomes of euT, HypoT-LT4 and scHypoT patients

	euT (%)	HypoT-LT4 (%)	scHypoT (%)	*P* value[#]
Number of transfer cycle/retrieval cycle	234/270 (86.7)	26/28 (92.9)	108/128 (84.4)	0.837
Implantation embryos/transfer embryos	194/524 (37.0)	14/48 (29.2)	82/228 (36.0)	**0.046**
Positive-βhCG/transfer cycle	144/234 (61.5)	16/26 (61.5)	58/108 (53.7)	0.278
Clinical pregnancy/transfer cycle	126/234 (53.8)	12/26 (46.2)	50/108 (46.3)	0.20
Single/clinical pregnancy	70/126 (55.9)	10/12 (83.3)	18/50 (36.0)	**0.038**
Twins/clinical pregnancy	44/126 (34.9)	4/12 (33.3)	32/50 (64.0)	**0.034**
Triplet/clinical pregnancy	12/126 (9.5)	0/12 (0)	0/50 (0)	
Chemical pregnancy/transfer	18/234 (7.7)	4/26 (15.4)	8/108 (7.4)	**0.035**
Pregnancy loss/pregnancy	18/126 (14.3)	4/12 (33.3)	12/50 (24.0)	**0.042**
Ectopic/pregnancy	2/126 (1.6)	0/12 (0)	2/50 (4.0)	0.145
Ongoing pregnancy/clinical pregnancy	106/126 (84.1)	8/12 (66.7)	36/50 (72.0)	**0.034**
OHSS	36 (13.2)	0 (0)	16 (12.5)	0.322

[#]*P* values for comparisons (chi-square of fisher exact text) among all 3 groups. The bold numbers indicate significance. OHSS: ovarian hyperstimulation syndrome.

Discussion

It is commonly accepted that overt hypothyroidism results in frequent occurrences of menstrual irregularities, infertility and an unfavorable outcome both for the mother and fetus, while these complications can be alleviated by adequate medication [10, 11]. Our data show that in LT4 treated hypothyroid patients, top quality embryos, endometrial thickness and clinical pregnancy rates did not differ from euthyroid and subclinical hypothyroid women, whereas implantation and ongoing pregnancy rates were significantly decreased while pregnancy losses, chemical pregnancy and single clinical pregnancy occurrences were significantly increased. Actually, in our study, only 2 patients in the euthyroid group showed poor fertilization, defined as having fewer than 50% of inseminated oocytes successfully fertilized, but the reduced implantation and elevated pregnancy loss rates in the medicated hypothyroid group illustrated that application of LT4 to control TSH in the range of 2.5-4.0 μIU/mL before IVF treatments did not completely eliminate the adverse effects of pregnancy outcomes in women with

overt hypothyroidism. The ATA [14] and Endocrine Society Clinical Practice Guideline (ESCPG) [15] guidelines recommend the treatment of clinical hypothyroidism in pregnancy with LT4 to maintain upper TSH serum concentration limits of 2.5 μIU/mL in the first trimester and 3.0 μIU/L in the second and third trimester, but there were no guidelines for hypothyroidism treatment before Assisted Reproductive Technology (ART). Our study suggests, that pre-IVF TSH serum concentrations might be controlled to an upper range of 2.5 μIU/mL, which might improve IVF/ICSI results, because serum TSH levels in the range of 2.5-4.0 μIU/mL did not have deleterious effects on oocyte quality but rather on implantation failure and pregnancy rates as well as fertiliztion. More clinical trials are necessary to validate unequivocally this hypothesis.

Opinions about the treatment and management of subclinical hypothyroidism are still controversial. Some scholars recommended, that LT4 should be administered to subclinical hypothyroid patients [13, 16, 17]. However, the ATA indicated that a recent Cochrane review of randomized controlled trials could not find an effect of levothyroxine treatment on pregnancy outcomes for women with subclinical hypothyroidism. It is advised in the guidelines to treat subclinical hypothyroid women only when thyroid antibodies are also detected [14]. The ESCPG guidelines recommend that there is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcomes and furthermore that treatment could potentially adversely affect the fetus [15]. Also other studies have reported that 2.5-4.0 μIU/mL elevated TSH serum concentrations in subclinical hypothyroidism patients were not associated with adverse ART events or pregnancy outcomes [18, 19]. Our data confirmed that oocyte number, embryo quality, implantation and clinical pregnancy rates as well as pregnancy loss rates were similar in untreated subclinical hypothyroid and euthyroid patients.

It is unclear why the IVF/ICSI results were significantly different between untreated subclinical hypothyroid patients and treated hypothyroidism patients, although their TSH serum concentrations were in the same range. It might reflect the effects of overt hypothyroidism itself, effects of levothyroxine use or as yet unknown factors. These findings deserve further attention as risk factors for IVF/ICSI outcomes.

Our study is limited by its retrospective design and lack of data regarding pregnancy and fetal neurodevelopmental outcomes. Prospective randomized controlled trial is needed to address these points.

In conclusion, hypothyroid patients with LT4 treatment and TSH serum concentrations of 2.5-4.0 μIU/mL had significantly lower implantation and significantly higher pregnancy loss rates compared to euthyroid and unmedicated subclinical hypothyroid IVF patients. There is no evidence that IVF/ICSI outcomes were impaired among untreated subclinical hypothyroid patients compared with euthyroid patients.

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Disclosure of conflict of interest

None.

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