Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection

Chung-Hoon Kim, M.D., Ph.D., Jun-Woo Ahn, M.D., Sunjung Park Kang, M.D., Sung-Hoon Kim, M.D., Hee-Dong Chae, M.D., and Byung-Moon Kang, M.D., Ph.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, South Korea

Objective: To investigate whether levothyroxine (LT4) treatment has beneficial effects on IVF results and pregnancy outcome in infertile patients with subclinical hypothyroidism undergoing IVF/intracytoplasmic sperm injection (ICSI).
Design: Prospective, randomized trial.
Setting: University-affiliated infertility clinic.
Patient(s): A total of 64 infertile patients with subclinical hypothyroidism, defined as an elevated serum TSH level associated with a normal free T4 level and without frank symptoms of hypothyroidism.
Intervention(s): Patients were randomized into an LT4 treatment group or control group. For the LT4 treatment group, 50 μg LT4 was administered from the first day of controlled ovarian stimulation for IVF/ICSI.
Main Outcome Measure(s): Results of IVF and pregnancy outcome.
Result(s): There were no differences in patient characteristics between the two groups. Total dose and days of recombinant human FSH used for controlled ovarian stimulation were also similar. The number of grade I or II embryos was significantly higher in the LT4 treatment group than in the control group. There was no significant difference in the clinical pregnancy rate per cycle between the two groups. However, the miscarriage rate was significantly lower in the LT4 treatment group than in the control group. Embryo implantation rate and live birth rate were significantly higher in the LT4 treatment group. In the control group, both thyroid peroxidase antibody and thyroglobulin antibody levels were significantly higher in the miscarried subgroup than in the delivered subgroup.
Conclusion(s): LT4 treatment can improve embryo quality and pregnancy outcome in subclinical hypothyroid women undergoing IVF/ICSI. (Fertil Steril® 2011;95:1650–4. ©2011 by American Society for Reproductive Medicine.)

Key Words: Levothyroxine, subclinical hypothyroidism, IVF, pregnancy

Hypothyroidism may affect the hypothalamic–pituitary–gonadal axis and the peripheral metabolism of sex steroids (1–3). Therefore, hypothyroidism may cause menstrual abnormalities, infertility, increased risk of miscarriage, obstetric complications, and adverse outcomes in offspring (3, 4). The clinical symptoms of hypothyroidism result from low levels of free thyroxine (FT4). Most cases of hypothyroidism are immune-related, and the prevalence of thyroid autoimmunity among infertility patients was higher than that of a similar age group (5). Women with antithyroid antibodies (ATAs) might be at an increased risk of miscarriage and obstetric complications, even in a subclinical hypothyroid and euthyroid state (3, 6).

Received September 30, 2010; revised November 26, 2010; accepted December 1, 2010; published online December 30, 2010.
C-H.K. has nothing to disclose. J-W.A. has nothing to disclose. S.P.K. has nothing to disclose. S-H.K. has nothing to disclose. H-D.C. has nothing to disclose. B-M.K. has nothing to disclose.
Reprint requests: Chung-Hoon Kim, M.D., Ph.D., Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, College of Medicine, University of Ulsan, Asan Medical Center, 388-1, Poognap-dong, Songpa-gu, Seoul, South Korea (E-mail: chnkim@amc.seoul.kr).

Subclinical hypothyroidism is usually defined as an abnormally elevated serum TSH level with a normal FT4 level and without frank symptoms of hypothyroidism (7). The prevalence of subclinical hypothyroidism is approximately 4% to 8.5% in the general population (8) and significantly higher in patients with infertility (9). Subclinical hypothyroidism in pregnancy may be associated with maternal and fetal repercussions (10). The increased need for thyroid hormones during pregnancy can lead to an aggravation of subclinical hypothyroidism in pregnant women. Benefits of treatment in infertile women with subclinical hypothyroidism have not been clearly proven. Nevertheless, it is recommended that pregnant women or those planning pregnancy are treated to reduce risks of miscarriage and fetal developmental impairment (8).

Infertile women with overt hypothyroidism should be treated with an adequate dose of levothyroxine (LT4), especially before infertility treatment (3). However, in infertile women with subclinical hypothyroidism, the effect of LT4 supplementation in infertility treatment including IVF remains unclear. Therefore, this study was performed to investigate whether LT4 treatment has a beneficial effect on IVF results and pregnancy outcomes in infertile women with subclinical hypothyroidism undergoing IVF/intracytoplasmic sperm injection (ICSI).

0015-0282/$36.00
doi:10.1016/j.fertnstert.2010.12.004

MATERIALS AND METHODS

Patients

Our prospective, randomized study was performed at a university-based infertility clinic at the Asan Medical Center, Seoul, South Korea. The study population consisted of 64 infertile patients with subclinical hypothyroidism who had undergone 64 IVF/ICSI cycles between March 2006 and September 2009. Subclinical hypothyroidism was defined as an elevated serum TSH level >4.5 mIU/L with a normal FT4 level and without frank symptoms of hypothyroidism (7).

The institutional review board of the University of Ulsan College of Medicine, Asan Medical Center, approved the study, and all patients provided written informed consent. The subjects, aged 27–41 years, were randomized into either the LT4 treatment group (n = 32) or control group (n = 32) by the use of sealed envelopes and a computer-generated list. The sequence of allocation to the two groups was provided to the investigating physicians, and randomization was performed as planned according to the randomization list order.

All subjects had regular ovulatory cycles (duration, 21–35 days). They were in good health with normal cardiac, hepatic, and renal functions, and they had experienced spontaneous onset of puberty and normal sexual development. None of subjects had a previous medical history of subclinical and clinical hypothyroidism, and they had not taken any infertility medications (clomiphene and/or gonadotropins) within the preceding 3 months.

Ovarian Stimulation Protocols

For the LT4 treatment group, 50 μg LT4 (Synthyroxine; Dalim BioTec, Seoul, Korea) was administered every morning from the first day of controlled ovarian stimulation (COS) and continued up to the day of serum β-hCG measurement. Serum TSH and FT4 were also measured at the same time as serum β-hCG was measured. If pregnancy was confirmed, an adequate dose of LT4 was given continuously throughout the pregnancy. Even in pregnant women included in the control group, an adequate dose of LT4 was supplemented when overt hypothyroidism was detected during pregnancy. The LT4 dosage was titrated to reach and thereafter maintain serum TSH concentrations of <2.5 mIU/L in the first trimester. Serum TSH and FT4 levels were remeasured every 4–6 weeks, and symptoms of clinical hypothyroidism were investigated on every visit for routine prenatal examination throughout the pregnancy.

In all subjects, a GnRH antagonist multiple-dose protocol was used for COS. Recombinant human FSH (rhFSH) (Gonal-F; Merck Serono, Geneva, Switzerland) at a dose of 150–225 IU/d was administered from the third day of the menstrual cycle. The starting dose of rhFSH was determined according to age, basal FSH level, body mass index (BMI), and antral follicle count (AFC). The dose of rhFSH was adjusted according to ovarian response, every 3 to 4 days. When the mean diameter of the lead follicle reached 13 to 14 mm, the GnRH antagonist cetrorelix (Cetrotide, Merck Serono) at a dose of 0.25 mg/d was started and continued daily up to the day of hCG injection. A recombinant hCG (rhCG) (Ovidrel, Merck Serono) dose of 250 μg was administered subcutaneously to induce follicular maturation when one or more follicles reached a mean diameter of ≥18 mm. Blood samples were drawn for serologic tests for TSH, FT4, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb) on the day of hCG injection.

In both groups, transvaginal ultrasound-guided oocyte retrieval was performed 36 hours after rhCG injection, and one to four embryos, after IVF or ICSI, were transferred into the uterus on the third day after oocyte retrieval. Luteal support was provided by administering 90 mg of vaginal P gel (Crinone gel 8%, Merck Serono) once daily from the day of oocyte retrieval.

Pregnancies were confirmed by rising serum β-hCG concentrations and transvaginal ultrasonographic evidence of a gestational sac. The serum level of β-hCG was measured 11 days after ET.

Measurement of β-hCG was performed by radioimmunoassay using an hCG MAIAclone kit (Serono Diagnostics, Woking, United Kingdom).

TABLE 1

Patient characteristics.

Characteristic	LT4 treatment	Control	*P* value
Patients, n	32	32	
Age of patients (y)	36.0 ± 2.4	36.1 ± 2.2	NS[a]
Age of husbands (y)	40.8 ± 3.5	40.3 ± 3.3	NS[a]
Infertility duration (mo)	48.0 ± 24.3	44.2 ± 23.6	NS[a]
BMI (kg/m^2)	21.5 ± 1.9	21.7 ± 2.1	NS[a]
Nullipara, n (%)	19 (59.4)	18 (56.3)	NS[b]
AFC	9.7 ± 3.8	9.8 ± 3.3	NS[a]
Basal FSH (IU/L)	6.6 ± 1.7	6.8 ± 1.7	NS[a]
Basal LH (IU/L)	5.4 ± 1.2	5.2 ± 1.1	NS[a]
Basal T (ng/mL)	0.2 ± 0.1	0.3 ± 0.1	NS[a]
Basal free T (pg/mL)	0.6 ± 0.2	0.7 ± 0.2	NS[a]
PRL (ng/mL)	16.2 ± 3.4	15.8 ± 3.3	NS[a]
TSH (mIU/L)	6.6 ± 1.7 (4.6–9.8)	6.7 ± 1.8 (4.6–9.6)	NS[a]
FT4 (ng/dL)	1.2 ± 0.2	1.2 ± 0.2	NS[a]
TPOAb (IU/mL)	256.9 ± 256.5	221.5 ± 167.0	NS[a]
Patients with TPOAb(+), n (%)	26 (81.3)	25 (78.1)	NS[b]
TGAb (IU/ml)	39.6 ± 27.3	43.2 ± 34.6	NS[a]
Patients with TGAb(+), n (%)	7 (21.9)	8 (25.0)	NS[b]
Indications, n (%)			
Tubal factor	10 (31.3)	9 (28.1)	NS[b]
Endometriosis III or IV	6 (18.7)	7 (21.9)	NS[b]
Male factor	13 (40.6)	13 (40.6)	NS[b]
Unexplained	3 (9.4)	3 (9.4)	NS[b]

Note: Values are mean ± SD (range of TSH levels) unless otherwise noted. NS = not significant.

[a] Student's *t* test.

[b] Fisher's exact test or χ^2 test.

Kim. LT4 for subclinical hypothyroidism. Fertil Steril 2011.