PRECONCEPTION L-T_4 TREATMENT IS BENEFICIAL IN SUBFERTILE WOMEN WITH SUBCLINICAL HYPOTHYROIDISM UNDERGOING IN VITRO FERTILIZATION TREATMENT

Kim C-H, Ahn J-W, Kang S P, Kim S-H, Chae H-D, Kang B. **Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection.** Fertil Steril 2011; 95:1650-4. Epub December 30, 2010.

SUMMARY

BACKGROUND

Pregnant women with hypothyroidism are at increased risk of antepartum obstetric complications, mainly miscarriages and premature deliveries. Whether therapy of fertility is affected by autoimmune thyroid disease (ATD) is debatable. The incidence of miscarriages after in vitro fertilization (IVF) in women with ATD appears to be increased. The objective of the authors was to investigate whether levothyroxine (L-T_4) treatment has beneficial effects on the results of IVF and the outcome of pregnancy in infertile patients with subclinical hypothyroidism who are undergoing IVF/intracytoplasmic sperm injection (ICSI).

METHODS

This is a prospective, randomized trial at a university-affiliated infertility clinic in Seoul, South Korea. All subjects had regular ovulatory cycles (duration, 21 to 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 had a history of subclinical or clinical hypothyroidism, and they had not taken any infertility medications (clomiphene and/or gonadotropins) within the preceding 3 months.

A total of 64 infertile patients with subclinical hypothyroidism (serum thyrotropin [TSH] level, >4.5 mIU/L, with a normal serum free thyroxine [T_4]) were recruited. Patients were randomly assigned to an L-T_4 treatment group (mean TSH [±SD], 6.6±1.7; 95% confidence interval [CI], 4.6 to 9.8]; free T_4, 1.2±0.2) or a control group (TSH, 6.7±1.8; 95% CI, 4.6 to 9.6; T_4, 1.2±0.2) (P not significant). There were no differences in patient characteristics between the two groups; the mean age was 36.0±2.4 years in the L-T_4 treated women, as compared with 36.1±2.2 in the controls (P not significant). The indications for IVF were not significantly different among the two groups: tubal factor, 31.1% versus 28.1%; endometriosis, 18.7% versus 21.9%; male factor, 40.6% versus 40.6%; and unexplained, 9.4% versus 9.4%. For the L-T_4 treatment group, 50 µg of L-T_4 was administered from the first day of controlled ovarian stimulation for IVF/ICSI, and it was continued up to the day of serum b-human chorionic gonadotropin measurement, at which time, serum TSH, free T_4, thyroid peroxidase autoantibody (TPOAb) and thyroglobulin antibody (TGAb) were also measured (L-$T_4$4 treatment group TSH, 2.3±0.4, vs. control group TSH 6.9±2.0; P<0.001; free T_4, 1.4±0.3 vs. 1.0±0.2; P<0.001). If pregnancy was confirmed, an adequate dose of L-T_4 was given continuously throughout the pregnancy. Even in pregnant women included in the control group, an adequate dose of L-T_4 was supplemented when overt hypothyroidism was detected during pregnancy. The L-T_4 dosage was titrated to reach and thereafter maintain serum TSH concentrations of <2.5 mIU/L in the first trimester. Serum TSH and free T_4 levels were remeasured every 4 to 6 weeks.

RESULTS

Total dose and days of recombinant human FSH used for controlled ovarian stimulation were similar among the two groups. The number of grade I or II embryos was significantly higher in the L-T_4 treatment group than in the control group. There was no significant difference in the clinical pregnancy rate per cycle between the two groups (17 of 32 [53.1%] in the treatment groups vs. 12 of 32 [37.5%] in the controls; P not significant). However, the miscarriage rate was significantly lower in the L-T_4 treatment group than in the control group (P = 0.021), as well as the live birth

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rate per cycle initiated (53.1% vs. 25%; P = 0.039). In the control group, both TPOAb and TGAb levels were significantly higher in the subgroup with miscarriages than in the subgroup with deliveries. One women in the control group had overt hypothyroidism at 24 weeks of gestation. Prematurity at 31 weeks of gestation occurred in one woman in the control group; no prematurity occurred in the treated group.

CONCLUSIONS

$L\text{-}T_4$ treatment can improve embryo quality, implantation rate, and live birth rate in infertile women with subclinical hypothyroidism undergoing IVF/ICSI. The dose of $L\text{-}T_4$ should be adjusted as the pregnancy progresses.

COMMENTARY

Abnormal obstetrical outcomes, mainly miscarriages and preterm delivery in women with autoimmune thyroid disease, have recently been established in two meta-analysis publications (1, 2). In some, but not all, of the studies, serum TSH values were above the accepted normal range for the first trimester of pregnancy (3), implying the possibility of subclinical hypothyroidism as an additional risk factor for obstetrical complications. In one of the meta-analyses (2), the incidence of miscarriages in subfertile women with chronic thyroiditis (eight publications with a total of 233 TPOAb-positive women) was significantly higher as compared with women with negative thyroid autoantibodies (1758 women; odds ratio, 3.15; 95% CI, 2.23 to 4.44. In the only previous prospective study of 24 euthyroid TPOAb-positive women who were undergoing assisted fertility treatment and given $L\text{-}T_4$, the miscarriage rate was not statistically different from that in the control group (4). One important unique feature of the protocol in the study under discussion is that $L\text{-}T_4$ treatment of subclinical hypothyroidism was started at the beginning of IVF treatment, with normalization of serum TSH in the majority of patients at the time of implantation and the adjustment of $L\text{-}T_4$ dosage with progression of pregnancy. Whether the beneficial effect of $L\text{-}T_4$ treatment is due to embryo quality, implantation, or both is unclear at present. The importance of assessing thyroid function in women undergoing fertility treatment appears reasonable in view of this study. Contrary to the authors' statement that "thyroid evaluation has become a routine workup for infertile women," it is my experience in clinical practice that thyroid tests are not performed routinely before IVF treatment, even on women who are receiving $L\text{-}T_4$ treatment.

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