

# In Vitro Fertilization Outcomes Do Not Differ between Women with Adequately Treated Hypothyroidism and Women without Thyroid Disease

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Busnelli A, Somigliana E, Benaglia L, Leonardi M, Ragni G, Fedele L. In vitro fertilization outcomes in treated hypothyroidism. *Thyroid*. April 2, 2013 [Epub ahead of print].

## SUMMARY ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●

### Background

The risk of infertility is increased among women with autoimmune thyroid disease (1). Three previous studies have examined the effects of levothyroxine (L-T<sub>4</sub>) treatment for hypothyroidism on the outcomes of in vitro fertilization (IVF), with conflicting results (2-4).

### Methods

This was a case–control study. Cases were 137 women treated with L-T<sub>4</sub> for overt or subclinical hypothyroidism who underwent IVF with intracytoplasmic sperm injection (IVF-ICSI) from 2009 to 2011 at the infertility unit of a single Italian institution. Controls were 274 age-matched euthyroid women with no history of L-T<sub>4</sub> treatment who underwent IVF-ICSI at the same institution. Women were excluded if they were 40 years of age or older or if they had a history of previous IVF-ICSI cycles; women were also excluded if they had free T<sub>4</sub> or free T<sub>3</sub> values outside the reference ranges or serum TSH  $\geq 2.5$  mIU/L. IVF-ICSI was performed according to a standard clinical protocol. Pregnancy was diagnosed by ultrasonography at 4 to 5 weeks after embryo transfer. Pregnancy outcomes were ascertained by telephone calls after delivery. The primary outcome was live birth rate per IVF cycle. Differences between cases and controls were assessed using independent-sample paired t-tests, Wilcoxon rank-sum tests, or Fisher's exact tests.

### Results

Among the cases, 51% initially had overt hypothyroidism and 49% had subclinical hypothyroidism, with a median TSH before initiation of L-T<sub>4</sub> therapy of 4.8 mIU/L. A total of 58% of cases were anti-thyroid antibody–positive. The median L-T<sub>4</sub> dose was 75  $\mu$ g daily. Smoking history, menstrual regularity and cycle length, number of previous deliveries, day 3 serum follicle-stimulating hormone, indications for IVF-ICSI, and baseline TSH (1.6 mIU/L vs. 1.5 mIU/L) did not differ between the cases and controls. The cases did have a higher body-mass index (the weight in kilograms divided by the square of the height in meters; 22.9 vs. 21.9;  $P = 0.013$ ). Baseline characteristics of the antithyroid antibody–positive and antithyroid antibody–negative cases did not differ.

Among the cases, there was a higher rate of cancelled cycles for poor response (3.6% vs. 0.7%,  $P = 0.04$ ); the mean duration of ovarian stimulation was longer (10.9 days vs. 10.1 days,  $P = 0.001$ ); and the proportion of women who did not undergo embryo transfer was higher (17% vs. 7%,  $P = 0.006$ ). Pregnancies resulted in 36% of cases and 34% of controls; there were no differences in pregnancy rates per started cycle, per oocyte retrieval, or per embryo transfer. Sixteen percent of cases and 22% of controls suffered a miscarriage ( $P = 0.5$ ). Live births resulted in 30% of cases and 27% of controls; live birth rates did not

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differ per started cycle, per oocyte retrieval, or per embryo transfer. Among the cases, outcomes did not differ by antithyroid antibody status. Outcomes among the patients treated for subclinical and overt hypothyroidism did not differ except that the women with a history of overt hypothyroidism had more embryos transferred (mean, 2.1 vs. 1.9;  $P = 0.03$ ).

## Conclusions

Although the women with hypothyroidism were more likely to have IVF cycle cancellation for poor response and had lower rates of embryo transfer, pregnancy rates resulting from IVF-ICSI did not differ between women with adequately treated hypothyroidism (TSH <2.5 mIU/L) and euthyroid women.

## ANALYSIS AND COMMENTARY ● ● ● ● ●

These findings are discordant with those of Kilic et al. (3) and of Scoccia et al. (4), which reported reduced implantation and pregnancy rates in women with treated hypothyroidism as compared with women without thyroid dysfunction. However, mean serum TSH values of 2.2 mIU/L and 2.5 mIU/L in these previous studies suggest that treatment was not adequate in all participants. Kim and colleagues (2) previously randomly assigned 64 women with subclinical hypothyroidism who were undergoing IVF-ICSI to L-T<sub>4</sub> versus placebo and found lower miscarriage rates and higher live birth rates in treated women (mean TSH at the time of IVF initiation, 2.3 mIU/L) as compared with controls (mean TSH, 6.9 mIU/L). These results suggest a benefit of L-T<sub>4</sub> treatment for IVF outcomes in women with hypothyroidism, an outcome that could not be directly demonstrated by

Busnelli and colleagues, since all of the women with hypothyroidism in their study received L-T<sub>4</sub>.

An important limitation of this study is the lack of data regarding adequacy of thyroid hormone-replacement throughout pregnancy in the studied women. Although there were no differences in outcomes of the antithyroid antibody-positive and negative L-T<sub>4</sub>-treated women, the antithyroid antibody status of the control women was not ascertained.

Studies to date provide suggestive, although not unequivocal, evidence that L-T<sub>4</sub> treatment improves IVF outcomes in women with hypothyroidism. Given the average \$12,400 cost per IVF cycle in the United States (5), it seems prudent to ensure that serum TSH is <2.5 mIU/L in all women with hypothyroidism prior to IVF cycle initiation.

## References

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