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In Vitro Fertilization Pregnancy Rates in Levothyroxine-Treated Women With Hypothyroidism Compared to Women Without Thyroid Dysfunction Disorders

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Background: Untreated hypothyroidism can lead to ovulatory dysfunction resulting in oligo-amenorrhea. Treatment with levothyroxine can reverse such dysfunction and thus should improve fertility. The purpose of this retrospective study was to assess whether *in vitro* fertilization (IVF) pregnancy rates differ in levothyroxine-treated women with hypothyroidism compared to women without thyroid dysfunction/disorders.
Methods: Treated hypothyroid and euthyroid women undergoing IVF at an academic IVF center were studied after Institutional Review Board approval. Women with hypothyroidism were treated with levothyroxine 0.025–0.15 mg/day for at least 3 months to maintain baseline thyrotropin (TSH) levels of 0.35–4.0 μU/mL prior to commencing IVF treatment (HYPO-Rx group). Causes of infertility were similar in both groups with the exception of male factor, which was more common in the HYPO-Rx group. The main outcomes studied were implantation rate, clinical pregnancy rate, clinical miscarriage rate, and live birth rate.
Results: We reviewed the first IVF retrieval cycle performed on 240 women aged 37 years or less during the period January 2003 to December 2007. Women with treated hypothyroidism ($n = 21$) had significantly less implantation, clinical pregnancy, and live birth rates than euthyroid women ($n = 219$).
Conclusions: We conclude that, despite levothyroxine treatment, women with hypothyroidism have a significantly decreased chance of achieving a pregnancy following IVF compared to euthyroid patients. A larger prospective study is necessary to assess confounding variables, confirm these findings, and determine the optimal level of TSH prior to and during controlled ovarian hyperstimulation for IVF.

Introduction

Thyroid disease is one of the most common endocrine disorders of reproductive-aged women (1). Overt hypothyroidism is seen in about 0.3%–0.7% of this population, with an additional 2%–7% of women presenting with subclinical hypothyroidism, defined as an elevated serum thyrotropin (TSH) level associated with a normal free thyroxine (fT4) level and without frank symptoms of hypothyroidism (2–5).

Hypothyroidism has long been associated with menstrual disorders and infertility (6–9). The percentage of women seen for *in vitro* fertilization (IVF) with increased TSH levels is thought to be higher than that in the general population, although the exact proportion remains unclear due to differences in study design, patient selection, and demographic variations (10–12). Women with subclinical hypothyroidism, undergoing IVF, were found to have lower implantation and live birth rates, and an increased miscarriage rate compared to women with the same diagnosis who were treated with empiric levothyroxine during IVF (13). Overt hypothyroidism has also been associated with negative pregnancy outcomes and ovulatory dysfunction, although the mechanisms leading to menstrual disruption remain unclear (14).

Treatment of hypothyroidism with levothyroxine usually restores a normal menstrual pattern, reverses hormonal alterations, and improves fertility (7,8,10). However, some women with treated hypothyroidism still fail to conceive and seek infertility treatment, including controlled ovarian hyperstimulation (COH) and/or IVF. The impact of ovarian stimulation on thyroid function was first investigated by Muller and co-workers (15), who found decreased fT_4 levels in women undergoing COH, whereas estradiol (E_2), TSH, thyroxine-binding globulin (TBG), total triiodotyronine (T_3), and total T_4 levels increased. Similar effects of COH on

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thyroid function in IVF have been documented in women without thyroid disease (16,17). To date, detailed information regarding the effect of treated hypothyroidism on COH and IVF outcomes is limited.

In this retrospective study, our goal was to compare the IVF outcomes in treated hypothyroid women (HYPO-Rx) with the women without thyroid dysfunction disorders.

Methods

Patients and procedures

This was a retrospective cohort study in an academic IVF center. After Institutional Review Board approval, we reviewed the medical records of women aged 37 years or less who underwent their first IVF retrieval cycle between January 2003 and December 2007, using their own oocytes. Demographic and infertility information was collected, as well as IVF cycle results, including peak E2, the number of mature (metaphase II) oocytes, fertilization rate, the number of top quality embryos on day 3 of development (≥ 6 cells and $< 25\%$ fragmentation), number of embryos transferred, endometrial thickness, implantation rate, clinical pregnancy rate, live birth rate, and clinical miscarriage rate.

All patients had their TSH level measured at our institution's laboratory prior to commencing IVF treatment. HYPO-Rx women had been diagnosed previously by their primary care physician and had been treated for 3 months or longer with a prescribed dose of levothyroxine 0.025–0.15 mg/day, with the dose adjusted to maintain a TSH level of 0.35–4.0 μU/mL (normal range in use by our institution's laboratory). Women categorized as euthyroid had TSH levels that fell within our laboratory's normal range. None of the patients included in the study were diagnosed as hyperthyroid based on the TSH level measurement and they did not have a visible goiter or palpable thyroid nodules.

All women underwent COH with standard gonadotropin-releasing hormone agonist or antagonist protocols. Patients received daily recombinant follicle-stimulating hormone (rFSH) 150–450 IU, with or without human menopausal gonadotropin 75–150 IU; when 3 follicles ≥ 18 mm were present, human chorionic gonadotropin (hCG) 5000 or 10,000 IU was given intramuscularly (IM). Oocytes were retrieved 35 hours later and embryos were transferred on cleavage day 3. Luteal support with daily progesterone IM was continued until 10 weeks of gestation.

Endocrine assays

Baseline cycle day 3 FSH, E2, and TSH were determined prior to IVF with a chemiluminescence immunoassay (Beckman Coulter, Fullerton, CA). For FSH, the reference range was 3.4–10.0 mIU/mL (conversion factor to standard international (SI) units = 1.0); intra- and interassay coefficients of variation (CV) were 3.5% and 5.6%, respectively. For TSH, the reference range was 0.35–4.0 μU/mL (conversion factor to SI units = 1.0); intra- and interassay CVs were 3.12% and 3.86%, respectively. Baseline and stimulated E2 could be accurately measured within the range 20–4800 pg/mL (conversion factor to SI units = 3.67), and the intra- and interassay CV were $\leq 12\%$ for concentrations > 120pg/mL. When E2 results were > 4800 pg/mL, samples were diluted 1/5 with Estradiol S0 Calibrator (Beckman Coulter).

Statistical analysis

Statistical analysis with the two-sample Student *t*-test (parametric analysis) was used for continuous data with a normal distribution and a Wilcoxon Rank-Sum test (non-parametric analysis) for continuous data without a normal distribution; Chi-square analysis was used for categorical data with large cell counts, the Fisher-Exact test analysis for categorical data with small cell counts, and the Cochran-Mantel-Haenszel test for data with rare outcomes (SAS Statistical Software Version 9.1; SAS Institute, Inc., Cary, North Carolina). A *p*-value of < 0.05 was considered significant.

Results

A total of 240 IVF retrieval cycles were reviewed, of which 8.8% ($n = 21$) were performed on treated hypothyroid (HYPO-Rx) women and 219 cycles on euthyroid women. Both groups were similar in age distribution and pretreatment serum day 3 FSH level (Table 1). The mean pre-IVF treatment serum TSH level for both the euthyroid and HYPO-Rx patient groups was ≤ 2.5 μU/mL. However, the distribution of pre-IVF treatment serum TSH levels in HYPO-Rx women was significantly higher than that in euthyroid women (Table 1).

The etiology of infertility was distributed similarly for the two treatment groups among tubal factor, endometriosis, anovulation, uterine factor, combined factors, and unexplained infertility. However, the incidence of male factor infertility was found to be significantly higher in the HYPO-Rx group than in the euthyroid group (Table 2).

Response to COH for HYPO-Rx and euthyroid women is given in Table 3. There was no significant difference between the two groups in the stimulation protocols used (data not shown) or the amount of gonadotropins administered, the number of days of stimulation, or peak E2 level. Endometrial thickness measurements prior to embryo transfer were available for 6 of 21 HYPO-Rx and 70 of 219 euthyroid women. The mean endometrial thickness in both groups was > 10 mm (data not shown). There were no significant differences in the number of mature oocytes retrieved, number of top quality embryos, or the number of embryos transferred, although there was a significantly lower fertilization rate in the HYPO-Rx group (Table 3). The laboratory procedures

Table 1. Characteristics of Treated Hypothyroid and Euthyroid Patients Included in the Analysis

	HYPO-Rx women	*Euthyroid women*	p-*Value*[a]
Number of patients	21	219	–
Age (years)[b]	33 ± 3	32 ± 4	0.156
Day 3 FSH (mIU/mL)[b,c]	7.0 ± 2.2	7.0 ± 2.6	0.958
TSH (μU/mL)[b,d]	2.5 ± 1.3	1.8 ± 0.9	0.021
TSH range	(0.53–4.0)	(0.39–4.0)	

[a] *p*-Value obtained by two-way Student *t*-test.
[b] Values represent mean ± SD.
[c] FSH reference values: 3.4–10.0 mIU/mL.
[d] TSH reference values: 0.35–4.0 μU/mL.
HYPO-Rx, treated hypothyroid; FSH, follicle-stimulating hormone; TSH, thyrotropin; SD, standard deviation.

Table 2. Etiologies of Infertility in Treated Hypothyroid and Euthyroid Patients

Etiology	*HYPO-Rx women*	*Euthyroid women*	*p-Value*[a]
Tubal factor	14.3%	19.2%	0.773
Endometriosis	9.5%	6.8%	0.650
Anovulation	9.5%	11.0%	1.000
Uterine factor	4.8%	0.5%	0.168
Unexplained	0%	11.4%	0.141
Male factor	52.4%	27.8%	0.019
Combined factors	9.5%	23.3%	0.178

[a]*p*-Value obtained by Chi-square test.

Table 4. *In Vitro* Fertilization Outcome in Treated Hypothyroid and Euthyroid Patients

	HYPO-Rx women	*Euthyroid women*	p-Value
Transfer rate	85.7%	90.0%	0.467[a]
Implantation rate	8.1%	33.1%	0.001[b]
Clinical pregnancy rate/retrieval	14.3%	46.6%	0.004[c]
Live birth rate/retrieval	14.3%	37.3%	0.035[c]
Clinical miscarriage rate	0%	19.6%	< 0.001[d]

[a]*p*-Value obtained by Fisher-Exact test.
[b]*p*-Value obtained by Wilcoxon Rank-Sum test.
[c]*p*-Value obtained by Chi-square test.
[d]*p*-Value obtained by Cochran-Mantel-Haenszel test.

used were consistent for both study groups throughout the study period.

HYPO-Rx women had a significantly decreased implantation rate, clinical pregnancy rate, and live birth rate compared to euthyroid women, as shown in Table 4. The three HYPO-Rx women who achieved a clinical pregnancy had a live birth (100%), compared to 80.4% (82/102) in the euthyroid group ($p < 0.001$).

Discussion

In this retrospective study, we have focused, for the first time, on the impact of treated hypothyroidism on IVF treatment outcomes. This study compared first cycle IVF outcomes in HYPO-Rx women to euthyroid women treated concurrently at our center. We found that HYPO-Rx women comprised 8.8% of our IVF cohort, which is higher than the prevalence of overt hypothyroidism in the general reproductive-age women (0.3%–0.7%) (2,3,5). This may be due to the selection bias inherent in a retrospective study, or the possibility that despite treatment with levothyroxine, these women still have an increased risk of infertility.

Table 3. Controlled Ovarian Hyperstimulation Outcome Measures from *In Vitro* Fertilization Cycles Performed in Treated Hypothyroid and Euthyroid Patients

	HYPO-Rx women	*Euthyroid women*	*p-Value*[a]
FSH/hMG (IU)[b,c]	3825 (1350, 7500)	3225 (675, 9150)	0.312
Day of hCG[b]	11.0 (8.0, 13.0)	11.0 (6.0, 17.0)	0.199
Peak estradiol (pg/mL)[b]	2202.0 (1033, 5096)	2372.0 (318, 8412)	0.865
Number of mature oocytes[b]	7.0 (3.0, 23.0)	10.0 (0, 38.0)	0.094
Fertilization rate[b]	60.0% (30.0, 100.0)	71.4% (0, 120.0[d])	0.045
Number of top quality embryos[b,e]	2.0 (0, 10.0)	3.0 (0, 25.0)	0.089
Number of embryos transferred[b]	2.0 (0, 3.0)	2.0 (0, 5.0)	0.275

[a]*p*-Value obtained by Wilcoxon Rank-Sum test.
[b]Values represent median (minimum, maximum).
[c]Dose of gonadotropins used; FSH and/or hMG.
[d]Number of oocytes fertilized also included oocytes in metaphase I at the time of insemination.
[e]Top-quality embryos: ≥6 cells and ≤25% fragmentation.
hMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin.

Decreased implantation, clinical pregnancy, and live birth rates in HYPO-Rx women may be a direct consequence of the use of gonadotropins for COH. During COH, the E2 concentrations are much higher than normal and are comparable to those found in the second trimester of pregnancy (400–600 pg/mL) (18). These supraphysiological estrogen levels lead to elevated thyroid-binding globulin levels, which consequently may bind more T_4, resulting in a decrease of free thyroid hormone (15,18). As serum fT_4 levels decrease, serum TSH levels increase through the classical hypothalamo-pituitary-thyroid feedback mechanism (19,20). While lower serum fT_4 levels lead to TSH stimulation of the thyroid gland in euthyroid women, compromised thyroid gland function and the administration of a fixed dose of levothyroxine in HYPO-Rx women will likely affect the recovery of fT_4 levels.

Thyroid function may also be affected by the administration of hCG to trigger ovulation. TSH and hCG are both glycoproteins with a common α-subunit and hormone-specific β-subunits that share 85% sequence homology in the first 114 amino acids and contain 12 cysteine residues at highly conserved positions. Therefore, it is likely that hCG can cross-react with the TSH receptor (21,22). Free T_4 levels have been reported to be increased during the first trimester in spontaneous conception and in pregnancies conceived through IVF, consistent with a thyrotropic role for hCG (16,23). As a result, thyroid hormone production increases by a direct effect of hCG on the thyroid gland in euthyroid women, bypassing the hypothalamo-pituitary-thyroid pathway. This mechanism may counteract the lowering of serum fT_4 due to high TBG production during COH in euthyroid women; however, its efficacy may be altered in HYPO-Rx women. Furthermore, hCG remains active for several days after ovulation and may continue to have a stimulatory effect on the thyroid gland during peri-implantation in euthyroid women (24).

The increased thyroid hormone demand imposed by COH and early pregnancy may therefore require increased dosing of levothyroxine in the HYPO-Rx women who undergo IVF to maintain their TSH levels within the acceptable range

(24,25). Indeed, the data from this study support the need for carefully controlled TSH levels prior to, during, and after COH for IVF treatment and during early pregnancy in HYPO-Rx women in an effort to minimize an apparent negative impact of altered TSH and thyroid hormone levels on maturing follicles and oocytes and their subsequent ability to fertilize and support embryo viability. No miscarriages occurred in the group of HYPO-Rx women who conceived, although this is based on very limited data. We did detect one biochemical pregnancy and one ectopic pregnancy in the HYPO-Rx group of patients (data not shown). Abolovich and co-workers reported a significant increase in the miscarriage rate when hypothyroid patients were undertreated (26). Maruo and co-workers also reported a significant association between lower thyroid hormone levels and increased miscarried rates (27).

We found a significantly lower oocyte fertilization rate in HYPO-Rx women compared to euthyroid women. This may be due to the higher frequency of male factor in the HYPO-Rx group, which required intracytoplasmic sperm injection (data not shown). However, the number of top-quality embryos available for transfer, the number of embryos transferred, and the number of patients undergoing a transfer did not differ significantly between the two study groups. Therefore, the differences in pregnancy rates in these patients were not related to the etiology of infertility in these couples. A negative association between raised serum TSH levels and fertilization outcome in women undergoing IVF has been reported by Cramer and co-workers (28). A lower fertilization rate was also reported by Kilic and co-workers (29) in HYPO-Rx compared to euthyroid patients. Indeed, TSH and thyroid hormone receptors have been reported in human granulosa cells and both T_3 and T_4 have been found in the follicular fluid (30–32). Alterations in TSH levels may therefore negatively influence oocyte quality and function in HYPO-Rx patients.

We found no significant difference in the endometrial thickness between the two study groups. Kilic and co-workers reported no significant difference in the endometrial volume in HYPO-Rx compared to euthyroid patients (29). However, morphometric studies examining endometrial changes in rats showed a decrease in epithelial cell volume, height of the luminal epithelium, and absolute endometrial volume in hypothyroid rats (33,34). While these changes were less pronounced in levothyroxine-treated hypothyroid rats, hypothyroidism may cause structural changes in the epithelium that do not impact endometrial thickness but may affect implantation and clinical pregnancy rates.

We did not examine the effect of thyroid autoimmunity, prevalent in 5% to 20% of women of childbearing age (35), on IVF outcome. However, similar pregnancy rates in IVF have been reported for euthyroid women with or without thyroid antibodies, while HYPO-Rx women with thyroid antibodies were observed to have a lower clinical pregnancy rate than euthyroid women with thyroid antibodies (29,36,37). Taken together, these results indicate that it is treated hypothyroidism rather than the presence of thyroid auto-antibodies that impacts pregnancy rates and support our observations that despite undergoing treatment for hypothyroidism, these women still have lower implantation, clinical pregnancy, and live birth rates following IVF than euthyroid women.

TSH levels prior to and during IVF in HYPO-Rx women have been studied on a limited basis. Stuckey *et al.* reported the development of overt hypothyroidism during IVF treatment in two patients taking levothyroxine (38). Preconception TSH levels of $>2.5\,\mu$U/mL have been associated with lower gestational age at delivery and lower birth weight in women undergoing IVF (39). Indeed, a maximum TSH level of $2.5\,\mu$U/mL before pregnancy in HYPO-Rx women has been recommended recently by the Endocrine Society in a Clinical Practice Guideline (40). Patients included in our study undergoing IVF treatment had a mean baseline TSH level of $\leq 2.5\,\mu$U/mL. Clinical recommendations regarding the optimal TSH level await further study and could be addressed by a randomized trial in an IVF cohort with treated hypothyroidism.

There are some limitations to our study. Our observations were made from data collected retrospectively from all women <37 years of age who underwent IVF treatment during the study period. Our single center is small, leading to a small number of patients in the HYPO-Rx group. Furthermore, their hypothyroidism was diagnosed and treatment commenced prior to their presenting at our clinic for IVF, and information regarding thyroid antibodies was not obtained. Differences were noted in the patient populations and their IVF treatment outcomes between the two study groups; however, the evidence presented points toward a negative impact of altered TSH levels on IVF treatment outcome in women with thyroid dysfuntion. Nevertheless, our findings represent the largest study to date on the impact of treated hypothyroidism in an IVF population and are the first to show that treated hypothyroidism can negatively affect implantation, clinical pregnancy, and live birth rates.

We conclude that treated hypothyroidism is associated with significantly decreased implantation, clinical pregnancy, and live birth rates compared to euthyroid women. These differences may be related to changes in thyroid hormone levels during COH that may exert a detrimental influence on the oocyte and/or the endometrium. A larger prospective study is necessary to assess confounding variables, confirm these findings, and determine the optimal level of TSH prior to and during COH for IVF.

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