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Subclinical elevations of TSH and assisted reproductive technology outcomes

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Abstract

The prevalence of moderately elevated TSH levels consistent with subclinical hypothyroidism (2.5–4.0 μIU/mL) was 23% in a cohort of 1231 women pursuing assisted reproductive technologies. Preconception elevated levels of TSH were associated with diminished ovarian reserve, but were not associated with adverse ART or pregnancy outcomes.

Keywords

TSH; autoimmunity; ART; subclinical hypothyroidism; diminished ovarian reserve

In women of reproductive age the prevalence of overt hypothyroidism ranges from 0.4% to 0.5%, while the prevalence of subclinical hypothyroidism ranges from 2% to 4% (1,2). 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 (3,4,5). Like overt hypothyroidism, subclinical hypothyroidism has also been linked with infertility and poor obstetrical outcomes (3,6). Benhadi et al. (7) studied a cohort of 2,497 Dutch women with spontaneous pregnancies at an average of 13 weeks gestation and found that mildly elevated TSH levels in early pregnancy were associated with an increased risk of miscarriage, fetal demise and neonatal death. In addition, Casey et al. (6) studied over 17,000 women with subclinical hypothyroidism and observed a higher incidence of preterm birth and placental abruption. Of further concern, pregnant women with subclinical hypothyroidism may have a reduced functional thyroid reserve, so hypothyroidism can develop or worsen as the gestation progresses (8). Collectively, these data suggest that subtle increases of TSH in pregnancy may have significant reproductive consequences for women.

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TSH is the most accurate, sensitive indicator of subtle thyroid dysfunction (9). Even small changes in free T4 concentrations result in large alterations in TSH (10). While thyroid autoimmunity (TAI) is the number one cause of thyroid dysfunction (1), thyroid abnormalities can appear before the presence of antithyroid antibodies (11). Therefore TSH is a better standardized measurement for detection of thyroid dysfunction in infertility patients. A recent Clinical Practice Guideline by The Endocrine Society suggests TSH levels should be <2.5 μIU/mL in the first trimester of pregnancy (12). TSH measurement during pregnancy is complicated by pregnancy-induced changes in binding globulins and has led to trimester-specific reference ranges for TSH (13).

Since pregnancy is associated with poor outcomes if complicated by overt hypothyroidism (3), TSH levels are routinely assayed prior to assisted reproductive technologies (ART) (14,15). In fact, an underlying thyroid abnormality was found in 46% for women experiencing ART failure (11) and TSH levels were inversely proportional to the fertilization rate at ART (16). While it is clear that *pregnancies* complicated by subclinical hypothyroidism in the fertile population have poor outcomes, the relevance of *preconception* subclinical hypothyroidism in infertile patients undergoing ART has not been thoroughly examined. The aim of this study was to examine the possible relationship between subclinical elevations in TSH prior to ART with ART outcomes.

Fifteen hundred first-time autologous ART cycles performed at Shady Grove Fertility Center from January 1, 2007 to December 31, 2007 comprised the study cohort. All patients with a baseline TSH measurement prior to treatment were included in this retrospective analysis. The study was IRB-approved. For patients with more than one basal TSH measurement prior to ART treatment, the most recent measurement before the ART cycle was used. Baseline serum concentrations of TSH were typically measured on day 3 of a non-treatment cycle, but most often within 6 weeks of beginning ovarian stimulation, and categorized as: Low (<0.4 μIU/mL); Normal (0.4–2.5 μIU/mL); Moderately (subclinical) elevated (2.5–4.0 μIU/mL); or High (>4.0 μIU/mL). Medical endocrine evaluations and treatment were initiated in patients with a basal values of TSH >4.0 μIU/mL in accordance with guidelines of The Endocrine Society. Following an appropriate interval of replacement therapy, attempts were made to normalize T3, T4 and TSH levels prior to stimulation in such women. For asymptomatic patients with a TSH >2.5 μIU/mL and <4.0 μIU/mL a T4 level was not routinely measured.

Patient age and quantitative treatment outcomes (including total medication dosage, peak serum estradiol concentration, number of oocytes retrieved, fertilization rate, number of embryos transferred, gestational age and weight of singletons at birth) were compared among TSH groups by Analysis of Variance (ANOVA). Frequencies of various infertility diagnoses, as well as categorical treatment outcomes (including the proportions of initiated cycles undergoing oocyte retrieval and embryo transfer, frequency of embryo cryopreservation, ovarian hyperstimulation syndrome (OHSS), pregnancy, pregnancy loss after identified clinical pregnancy and live birth rates) were compared among TSH groups by χ^2 analysis.

Diminished ovarian reserve (DOR) was defined as an elevated cycle day 3 FSH (typically>14 IU/L), or baseline antral follicle count <5, and/or poor response to previous ovarian stimulation. Total medication dosage was calculated as the sum of all FSH and hMG medications taken during stimulation. Fertilization rate was calculated as the percentage of 2pn oocytes obtained divided by oocytes retrieved. All embryo cryopreservation occurred at the blastocyst stage on day 5 or 6 after oocyte retrieval and fertilization, only if morphologically high quality blastocysts were available. A positive pregnancy test was defined as a serum βhCG concentration >5 IU/L, typically on day 12–14 after oocyte

retrieval. Clinical pregnancy was defined by visualization of a gestational sac on ultrasound four to five weeks after oocyte retrieval.

Of the 1500 possible subjects, 269 women were excluded for unrecorded basal TSH levels. A total of 1231 patients met inclusion criteria. While TSH values fell within the normal range for the majority of patients, 23% of women had moderately elevated TSH values in the range of 2.5–4.0 μIU/mL, consistent with subclinical hypothyroidism.

Patient age was similar among TSH groups (Table 1). Infertility diagnoses were similar among TSH groups, except for diminished ovarian reserve. Chi-square comparisons indicated that, compared to the normal TSH group, the diagnosis of DOR was significantly higher in the high TSH group ($p=0.020$) and marginally higher in the moderate TSH group, although statistical significance was not observed ($p=0.090$). Logistic regression indicated a statistically significant increase in the frequency of diminished ovarian reserve with increasing TSH levels across all groups ($p=0.023$). None of the patients with low TSH (<0.4 μIU/mL) were diagnosed with diminished ovarian reserve, while 18% of the patients with high TSH (>4.0 μIU/mL) were diagnosed with diminished ovarian reserve.

Total medication dosage, peak serum estradiol concentration, rates of oocyte retrieval and embryo transfer, numbers of oocytes retrieved and embryos transferred, fertilization rate, rates of embryo cryopreservation, positive pregnancy test, clinical pregnancy, pregnancy loss and live birth were all similar with no statistically significant differences among TSH groups (Table 1). There were 223 and 73 singleton births in the normal and moderately elevated TSH groups respectively. Gestational age and birth weight for these singleton births did not differ significantly (Table 1).

This study is one of the largest analyses to relate basal TSH levels with outcome in ART patients. The prevalence of a moderately elevated TSH was 23% in this cohort. Poppe et al. (3) reported subclinical hypothyroidism in infertility patients to occur in only 1% to 4% of subjects. However, in agreement with our findings, Raber et al. (17) prospectively investigated a group of 283 infertile women and reported that 34% had subclinical hypothyroidism.

Of note, elevated TSH levels were significantly associated with DOR independent of age. Many cases of hypothyroidism are associated with anti-TPO antibodies, an autoimmune process; it is possible that a similar autoimmune process could be coupled with non-age-related DOR in this population, but the reasons for the association of DOR and elevated TSH are unclear at this time. Consistent with the finding of DOR, there was a trend (statistically insignificant) toward increased medication usage in women with moderately elevated TSH. Elevated basal TSH levels were also associated with a trend toward decreased number of oocytes retrieved ($p=0.19$). Interestingly, we found no evidence of an elevated pregnancy loss rate in women with elevated TSH. The observation that subclinical hypothyroidism does not impact pregnancy rate is in agreement with a recent study by Reh et al. (18) who found no difference in clinical pregnancy, delivery, or miscarriage in 248 patients with mildly elevated basal TSH (>2.5 and <4.0 μIU/mL) compared to 807 patients with a normal TSH (>0.4 to <2.5 μIU/mL).

DOR is unquestionably associated with reductions in oocytes and pregnancy, and increased ART medication usage and miscarriage. While we did observe reduced oocytes and increased medication usage in women with DOR, the differences were not significant. The percentage of women with DOR was <20% of the total number of subjects with elevated TSH levels; therefore we suspect the subgroup of DOR and elevated TSH was likely too small to reach statistically significant differences for these outcomes. While not statistically

significant, these trends are consistent with a prior report that ovarian hyperstimulation was altered in women with thyroid autoimmunity (15).

We observed that increased TSH levels tended to be related to slightly earlier deliveries (normal TSH 258 days, moderate TSH 256 days, high TSH 254 days), and slightly lower birth weights (normal 3215 g, moderate 3134 g, high 3059 g), but none of these outcomes reached statistical significance ($p>0.05$). A recent Cochrane review (19) of 3 randomized controlled trials comparing pharmacological intervention for hypothyroidism and subclinical hypothyroidism noted a 72% reduction of preterm delivery (RR 0.28; 95% CI 0.10 to 0.80). However, the authors concluded the evidence examined was insufficient to recommend treatment for subclinical hypothyroidism, but emphasized the need for further research (19). In two recent randomized prospective trials not considered in the Cochrane review, improved clinical pregnancy rates were observed in ART patients treated with levothyroxine compared to untreated patients if TSH values were >4.5 μIU/mL (20) or >4.0 μIU/mL at screening (21). Both studies (20, 21) included patients with TSH levels above the moderately elevated range 2.5–4.0 μIU/mL, which was the focus of our analysis.

This study is limited by its retrospective design. Prospective analysis of a larger cohort is needed to assess the association of DOR with subclinical hypothyroidism. Thyroxin levels were not routinely measured in this cohort because of the low yield of the test in an asymptomatic patient with a mildly elevated TSH level, but a normal T4 would have helped to exclude the rare case of hypothyroidism.

In conclusion, moderately elevated TSH levels were common among women pursuing ART. We found no evidence that ART outcomes were impaired among patients with preconception elevations in TSH consistent with a diagnosis of subclinical hypothyroidism compared to women with a normal TSH level prior to ovarian stimulation.

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Table 1

Patient characteristics and ART outcomes according to basal TSH categorization.

Baseline TSH (μIU/mL)	Low (<0.4)	Normal (0.4–2.5)	Moderate (2.5–4.0)	High (>4.0)	P-value[a]
Patient No (% of total)	15 (1%)	842 (68%)	278 (23%)	96 (8%)	N/A
Age (years)	34.7 ± 4.4	34.9 ± 4.3	35.1 ± 4.5	35.0 ± 4.3	0.97
Infertility Diagnosis					
DOR	0%	10%	14%	18%	0.023
Endometriosis	13%	8%	9%	8%	0.90
Male factor	27%	33%	36%	39%	0.54
Ovulatory	7%	14%	13%	17%	0.61
Tubal	20%	19%	16%	10%	0.15
Uterine	0%	4%	4%	4%	0.72
Unexplained	33%	25%	25%	17%	0.30
ART Treatments					
Stimulation medications (IU)	3636 ± 2267	3747 ± 1763	3956 ± 1736	4070 ± 1906	0.16
Peak estradiol (pg/mL)	1769 ± 1284	1839 ± 1203	1881 ± 1207	1816 ± 1257	0.94
Retrieval	11 (73%)	722 (86%)	247 (89%)	87 (91%)	0.16
Oocytes	11.3 ± 6.4	14.1 ± 7.5	13.3 ± 7.2	12.9 ± 7.6	0.19
Fertilization	61%	65%	64%	66%	0.88
Transfer	11 (73%)	697 (83%)	238 (86%)	86 (90%)	0.17
Embryos Transferred	1.9 ± 0.5	2.0 ± 0.7	2.0 ± 0.7	2.0 ± 0.7	0.96
ART Outcomes					
Embryo cryo	3 (20%)	301 (36%)	97 (35%)	29 (30%)	0.42
OHSS	0 (0%)	22 (3%)	15 (5%)	2 (2%)	0.11
Positive β-hCG	8 (53%)	437 (52%)	140 (50%)	48 (50%)	0.96
Clinical Pregnancy	5 (33%)	368 (44%)	123 (44%)	38 (40%)	0.72
Pregnancy Loss	1 (20%)	73 (20%)	26 (21%)	8 (21%)	0.99
Live Birth	4 (27%)	295 (35%)	97 (35%)	30 (31%)	0.80
Singleton GA (days)	255 ± 4	258 ± 16	256 ± 11	254 ± 11	0.44
Singleton BW (grams)	3133 ± 581	3215 ± 576	3134 ± 543	3059 ± 496	0.47

[a] P-values are for comparisons (ANOVA or chi-square) among all four TSH groups.

DOR=Decreased ovarian reserve, Transfer=Number of patients who underwent embryo transfer, Embryo cryo=Number of patients with embryos that were cryopreserved, GA=Gestational age, BW=Birth weight.

Note: The sum of diagnosis percentages is greater than 100% because patients with multiple infertility diagnoses are included for each applicable diagnosis.