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Original Research Article

Association between Subclinical Hypothyroidism and Infertility in Women of Reproductive Age: A Prospective Observational Study

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Abstract

Background: Subclinical hypothyroidism (SCH) is characterized by elevated TSH and normal free T4, and may have an impact on ovulation, ovarian reserve and conception, but the connection between SCH and female infertility is not clear.

Objective: To estimate the prevalence of confirmed SCH in infertile women and its relationship to infertility and 12-month pregnancy outcomes.

Methods: A prospective observational study of 200 women with a mean age of 26.3 years (range 20-38 years) who were infertile and 100 fertile controls with a mean age of 27.8 years (range 20-38 years) were recruited. Thyrotin and free thyroxine were determined twice with a 6-8 week interval between measurements, and the thyroid peroxidase antibody, prolactin, anti-Mullerian hormone and reproductive characteristics were evaluated. The infertile participants were provided with regular individual treatment and followed for 12 months.

Results: Confirmed SCH occurred in 37/200 infertile women (18.5%) and 7/100 controls (7.0%; p=0.009). Mean thyrotropin was higher among infertile women (3.12 +/- 1.61 vs 2.28 +/- 1.18 mIU/L; p<0.001), while free thyroxine was similar. SCH was most common in the group of ovulatory infertility (30.0%) and unexplained infertility (20.7%) (p=0.006 overall). When age, BMI, PCOS, thyroid autoimmunity, prolactin and ovarian reserve were controlled for, the association between SCH and infertility persisted (adjusted OR 2.54; 95% CI 1.05-6.15; p=0.039). The rate of clinical pregnancy was higher in women with SCH (48.6%) and euthyroid infertile women (65.0%) (p=0.060) and the median time to pregnancy was longer in women with SCH (7.8 vs 5.4 months; p=0.018). SCH was independently associated with decreased likelihood of conception (adjusted HR 0.64; 95% CI 0.41-0.99; p=0.047).

Conclusions: Infertile women had a higher prevalence of confirmed SCH, which was correlated with delayed conception. Thyroid testing may be repeated to enhance endocrine evaluation in the evaluation of infertility.

Keywords: Subclinical Hypothyroidism; Female Infertility; Thyrotropin; Time To Pregnancy; Thyroid Autoimmunity; Reproductive Age.

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Introduction

Infertility is a significant reproductive health problem and is traditionally defined as the failure to conceive after a period of regular unprotected sex. It can have various causes, including ovulatory dysfunction, tubal disease, endometriosis, decreased ovarian reserve, uterine causes, male causes or an unexplained cause after routine investigation [1].

Thyroid hormones regulate the hypothalamic-pituitary-ovarian axis, follicular development, steroidogenesis, ovulation, endometrial receptivity, implantation and early placentation. A physiological basis for the relationship of thyroid status and female reproduction has been established, as thyrotropin and thyroid hormone receptors have been found in ovarian and endometrial tissue [2].

Hypothyroidism is known to cause menstrual irregularity and poor fertility. It can affect gonadotropin secretion, stimulate thyrotropin-releasing hormone and prolactin, decrease sex hormone-binding globulin, and cause anovulation

or luteal dysfunction. The general association of mild thyroid dysfunction and human reproduction has been extensively reviewed, but there are important uncertainties at the subclinical end of the spectrum [3].

Subclinical hypothyroidism is characterized by biochemically elevated thyrotropin levels and normal free thyroxine levels. Preconception and pregnancy guidelines highlight the importance of taking into account laboratory methodology, population characteristics, thyroid autoimmunity and pregnancy status when determining diagnostic thresholds. In women who are seeking treatment for infertility, thyroid testing is recommended as overt thyroid disease should not be overlooked [4].

It is not clear if the elevated level of thyrotropin by itself is responsible for infertility. The 2024 American Society for Reproductive Medicine guideline found conflicting evidence regarding the association between SCH and infertility and evidence for routine low thyrotropin levothyroxine use. It also highlighted the need to not treat women who are otherwise euthyroid with a thyrotropin level of < 2.5 mIU/L [5].

Previously, clinical studies showed a greater incidence of SCH and thyroid autoimmunity in women with infertility, especially in women with ovulatory disorders. Abalovich et al. noted that there were subtle thyroid abnormalities that were clinically significant in certain groups of infertile patients, but that the definitions of thyroid abnormalities and treatment varied from current standards [6].

The large preconception cohorts have confirmed that thyrotropin levels outside the reference range are correlated with decreased fecundability and increased time to pregnancy. Preconception TSH levels were correlated with delayed conception in a population-based study in China, with the lowest reproductive risk in the mid-normal range of TSH [7]. Thyroid status also may be associated with ovarian reserve in older reproductive-age women. However, Rao et al. found that ovarian-reserve markers were lower in women with SCH who were 35 years or older, suggesting that age and ovarian biology may influence the relationship between thyroid function and fertility [8].

Published studies are retrospective, limited to assisted reproductive technology, and/or employ different thresholds for thyrotropin or lack a fertile comparison group. In addition, there have been fewer studies that have compared pregnancy outcomes at baseline with follow-up in the future under routine clinical care. The present study was thus designed to investigate the relationship of SCH to female infertility and to explore time to pregnancy and clinical pregnancy within 12 months of follow-up in infertile women based on the initial thyroid status.

Materials and Methods

This was an observational study of prospective design that was carried out in reproductive medicine, gynecology and endocrinology services of a tertiary teaching hospital. At the first study visit, women were enrolled and standardized baseline evaluation was done before or at the beginning of fertility treatment.

Study Groups: The women in the infertility group were 200 women aged 20-38 years who had not become pregnant after 12 months of regular unprotected sexual activity, or 6 months if they were 35 years or older. The fertile control group consisted of 100 women with spontaneous pregnancy within the past 2 years within the same age group as the infertile group, who had at least one live birth or an ongoing pregnancy beyond 12 weeks and who had no history of infertility or recurrent pregnancy loss.

Inclusion and exclusion criteria will be followed.

All participants who were eligible had a normal uterus and one or more ovary. Exclusion criteria included known overt thyroid disease, thyroid surgery or radioiodine treatment in the past, thyroid medication prior to baseline sampling, hyperthyroidism, premature ovarian insufficiency, uncontrolled diabetes, chronic renal or hepatic disease, systemic corticosteroid use, pregnancy at the time of laboratory assessment, and incomplete thyroid testing. Women with bilateral tubal agenesis and couples who underwent azoospermia surgery and were told that they would not have been able to conceive spontaneously or through conventional treatment were excluded as they would not have been comparable.

Baseline Fertility Evaluation: A detailed history was recorded to include duration and nature of infertility, regularity of periods, dysmenorrhea, previous pregnancies, pelvic surgery, medication history, and family history of thyroid disease. Blood pressure, height and weight were measured. Uterine morphology, antral follicle count and ovarian appearance were assessed using transvaginal ultrasonography. Semen analysis was done based on the laboratory protocols, and tubal patency was assessed when indicated. To analyze, the primary factor identified at multidisciplinary review was used for classification of infertility, which included the following categories: ovulatory, tubal, male factor, unexplained, and mixed.

Lab assessment and thyroid definitions: Fasting venous blood was obtained on cycle days 2-5, if possible. Measures of thyrotropin, free thyroxine, TPOAb, prolactin, follicle-stimulating hormone,

luteinizing hormone, estradiol, and anti-Mullerian hormone were obtained by validated automated assays. Patients with SCH were those who had a thyrotropin level of 4.0-9.9 mIU/L and free thyroxine level in the reference range, with repeat tests performed after 6 weeks. Euthyroidism was considered to be thyrotropin 0.40-3.99 mIU/L and normal free thyroxine. A TPOAb concentration of >34 IU/mL was taken as positive. Women who had thyrotropin levels ≥ 10 mIU/L or had low levels of free thyroxine were considered to have overt hypothyroidism and were not included in the analysis.

The clinical management and follow-up: The study protocol did not specify treatment. Individual fertility management was provided based on the cause of the infertility and current clinical recommendations. Women with confirmed SCH were referred to endocrinology and levothyroxine initiation and dose were based on the treating clinician's judgement. The participants who were infertile were contacted monthly for 12 months or until a clinical pregnancy was achieved. The following data was collected: conception date, treatment modality, biochemical pregnancy, ultrasound confirmed clinical pregnancy, pregnancy loss, and ongoing pregnancy. Clinical pregnancy was determined by the presence of an intrauterine gestational sac or fetal pole or cardiac activity by ultrasonography.

Outcome Measures: The main result was the incidence of SCH in infertile women vs fertile controls. Secondary outcomes were: mean thyrotropin, thyroid autoimmunity, prevalence of SCH by category of infertility, association between SCH and infertility after adjustment, clinical pregnancy within 12 months, time to pregnancy, and early pregnancy loss among women who conceived.

Sample Size: At least 188 infertile women and 94 fertile controls were needed to achieve 80% power, a 2:1 allocation, a two-sided alpha of 0.05, and assuming a prevalence of 18% for SCH in infertile women and 6% in fertile controls. In order to accommodate for incomplete repeat testing, the targets were raised to 200 and 100, respectively.

Statistical Analysis: Data analysis was done with SPSS version 29.0 and R version 4.3. Continuous variables are reported as mean +/- SD or median (IQR). As appropriate, the independent-samples t test, Mann-Whitney U test, chi-square test, and Fisher exact test were used. The adjusted odds ratios for infertility were estimated using logistic regression. A priori selected variables were age, BMI, positivity of TPOAb, polycystic ovary syndrome, prolactin and AMH. Time to clinical pregnancy was estimated using Kaplan-Meier analysis and adjusted hazard ratios were estimated using Cox proportional-hazards regression. Women who started levothyroxine were included in the primary pragmatic analysis and treatment initiation was treated as a time-varying covariate; a sensitivity analysis was conducted excluding follow-up after treatment initiation. The results were considered to be statistically significant when $p<0.05$.

Results

Among 336 women screened, 22 did not meet eligibility criteria, eight declined participation, and six did not complete repeat thyroid testing. The final cohort included 200 infertile women and 100 fertile controls.

Baseline age, residence, and smoking exposure were comparable. Infertile women had a modestly higher mean body mass index, a greater frequency of irregular cycles, and higher median prolactin. Anti-Mullerian hormone was lower in the infertility group, although the difference was small. Baseline characteristics are presented in Table 1.

Confirmed SCH was identified in 18.5% of infertile women and 7.0% of controls (p=0.009). Mean thyrotropin was 3.12 +/- 1.61 mIU/L in the infertility group and 2.28 +/- 1.18 mIU/L in controls (p<0.001); free thyroxine did not differ. TPOAb positivity was more frequent among infertile women (20.0% vs 10.0%; p=0.029). Within the infertility group, 60 women had a principal ovulatory factor, 36 a tubal factor, 46 a male factor, and 58 unexplained infertility. SCH prevalence was highest with ovulatory infertility (30.0%) and lowest with male-factor infertility (8.7%; p=0.006) (Table 2).

After adjustment for age, body mass index, TPOAb status, polycystic ovary syndrome, prolactin, and anti-Mullerian hormone, SCH remained associated with infertility (adjusted OR 2.54; 95% CI 1.05-6.15; p=0.039). Each 1 mIU/L increase in thyrotropin was associated with a 22% increase in the adjusted odds of infertility.

During 12 months, clinical pregnancy occurred in 18/37 women with SCH (48.6%) and 106/163 euthyroid infertile women (65.0%; p=0.060). Median time to pregnancy among those who conceived was 7.8 months in the SCH group and 5.4 months in the euthyroid group (p=0.018).

The adjusted hazard ratio for clinical pregnancy with SCH was 0.64 (95% CI 0.41-0.99; p=0.047). Early pregnancy loss was numerically more frequent with SCH but did not reach statistical significance (16.7% vs 9.4%; p=0.39) (Table 3).

Table 1: Baseline characteristics of infertile women and fertile controls

Characteristic	Infertile women (n=200)	Fertile controls (n=100)	p-value
Age, years	30.6 +/- 4.2	30.0 +/- 4.0	0.24
Body mass index, kg/m2	25.3 +/- 4.1	24.2 +/- 3.6	0.025
Irregular menstrual cycles, n (%)	58 (29.0)	13 (13.0)	0.002
Primary infertility, n (%)	137 (68.5)	Not applicable	-
Duration of infertility, years	3.2 +/- 1.8	Not applicable	-
Anti-Mullerian hormone, ng/mL	2.54 +/- 1.41	2.91 +/- 1.36	0.031
Prolactin, ng/mL, median (IQR)	15.8 (11.9-21.7)	13.7 (10.8-18.2)	0.018
Family history of thyroid disease, n (%)	31 (15.5)	9 (9.0)	0.12
Polycystic ovary syndrome, n (%)	44 (22.0)	8 (8.0)	0.003

IQR, interquartile range. Values are mean +/- SD unless otherwise indicated.

Table 2: Thyroid findings and distribution of subclinical hypothyroidism

Measure/category	Infertile women	Fertile controls or comparator	p-value
Thyrotropin, mIU/L	3.12 +/- 1.61	2.28 +/- 1.18	<0.001
Free thyroxine, ng/dL	1.14 +/- 0.15	1.17 +/- 0.14	0.10
TPOAb positive, n (%)	40/200 (20.0)	10/100 (10.0)	0.029
Confirmed SCH, n (%)	37/200 (18.5)	7/100 (7.0)	0.009
SCH in ovulatory infertility	18/60 (30.0)	Other infertility categories	0.006
SCH in unexplained infertility	12/58 (20.7)	Other infertility categories	
SCH in tubal-factor infertility	4/36 (11.1)	Other infertility categories	
SCH in male-factor infertility	4/46 (8.7)	Other infertility categories	

TPOAb, thyroid peroxidase antibody; SCH, subclinical hypothyroidism. The p-value of 0.006 compares SCH prevalence across the four principal infertility categories.

Table 3: Adjusted associations and 12-month pregnancy outcomes

Outcome/predictor	Effect or frequency	95% CI	p-value
SCH and infertility	Adjusted OR=2.54	1.05 to 6.15	0.039
Thyrotropin per 1 mIU/L and infertility	Adjusted OR=1.22	1.04 to 1.43	0.014
TPOAb positivity and infertility	Adjusted OR=1.58	0.72 to 3.47	0.25
Clinical pregnancy: SCH	18/37 (48.6%)	-	0.060
Clinical pregnancy: euthyroid	106/163 (65.0%)	-	
Time to clinical pregnancy with SCH	Adjusted HR=0.64	0.41 to 0.99	0.047
Median time to pregnancy, months	7.8 vs 5.4	-	0.018
Early loss among pregnancies	16.7% vs 9.4%	-	0.39

Logistic regression adjusted for age, body mass index, TPOAb, polycystic ovary syndrome, prolactin, and anti-Mullerian hormone. The Cox model additionally included infertility category, treatment modality, and levothyroxine initiation. OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Discussion

The present prospective study revealed that subclinical hypothyroidism was more than twice as common in the infertile women as in the fertile controls. This association remained after controlling for adiposity, thyroid autoimmunity, polycystic ovary syndrome, prolactin and ovarian reserve. SCH was more common in the group of women with ovulatory infertility and was linked to a longer time to clinical pregnancy over 12 months of routine care. The results are biologically plausible as thyroid hormones have a role in the hypothalamic-pituitary-ovarian axis and in the granulosa cells, oocytes, endometrium and placenta of the ovary [2,3]. Even when free thyroxine is in the reference range, mild thyroid dysfunction can have an impact on gonadotropin responsiveness, steroidogenesis, prolactin, luteal function, and implantation.

The SCH prevalence found here was similar to those reported in some infertility clinics, but the prevalence of SCH depends on the population, iodine status, type of assay and diagnostic criteria used [6]. Endocrine evaluation is indicated in the concentration of cases in the groups of ovulatory and unexplained infertility, but cannot be used to exclude other reproductive disorders as they may occur together.

Women with SCH had delayed conception, which is consistent with the preconception cohort evidence showing a relationship between thyrotropin outside the reference range and reduced fecundability [7]. The difference in clinical-pregnancy proportion was not quite statistically significant, while the time-to-pregnancy model was

still significant after adjustment. This pattern indicates a slight decrease in reproductive ability, not a total loss of reproductive function.

There is mixed evidence from populations of women seeking fertility treatment. High-normal TSH levels were not consistently correlated with adverse outcomes in women with normal thyroid function who were undergoing IUI [9]. SCH has also been associated with decreased ovarian reserve in women 35 years of age or older [8] but the association remained after adjustment for anti-Mullerian hormone, indicating that ovarian reserve alone was not responsible for the association.

Today, the upper reference limit for thyrotropin prior to conception is recommended and a value above 2.5 mIU/L is a warning sign of disease [5]. Uncertainty is also highlighted in reviews about the threshold for biochemical changes, the treatment and the benefit of live birth [10,11]. A recent extensive review agrees with the recommendation for thyroid testing during infertility evaluation and emphasizes the importance of the individual interpretation [12].

The study was enhanced by the prospective enrollment, repeated thyroid testing, standard thyroid hormone assays, and follow-up of infertile study participants. The limitations are that it was a single centre study, there may have been referral bias and it was not a randomized treatment. Complete infertility investigation was not performed on fertile controls, residual confounding may have occurred and treatment initiation during follow-up may have affected the outcome of conception. So, the findings are correlative and not causal.

Thyrotropin and free thyroxine should be considered as part of the infertility evaluation and an isolated mild elevation of thyrotropin should be confirmed prior to diagnosis. Management should be guided by antibody status, symptoms, category of infertility, treatment plan and biochemical abnormality. Randomized trials of women with confirmed preconception SCH are warranted to assess the effect of levothyroxine on time to pregnancy or live birth.

The treatment threshold still has clinical significance. There is clear evidence that levothyroxine benefits women planning for conception when preconception or gestational thyrotropin is above about 4.0 mIU/L, and less for lower levels [13]. A systematic review of preconception and early-pregnancy cohorts also found subclinical thyroid dysfunction to be correlated with poor reproductive outcomes, with heterogeneity in definitions of subclinical thyroid dysfunction [14]. Thyroid autoimmunity can also affect fertility and the outcome of assisted-reproduction procedures without causing a thyroid hormone deficiency [15].

There is some uncertainty about the need for routine thyroxine replacement in women with subfertility [16]. The clinical and obstetric outcomes in treated cohorts with high-normal and low-normal thyrotropin have not been consistently different [17]. A recent synthesis also failed to support the use of preconception levothyroxine therapy for mild subclinical hypothyroidism to improve fertility or prevent miscarriage, and confirmed the need to assess for persistent biochemical abnormality and individualize therapy [18].

Conclusion

Infertile women were significantly more likely than fertile controls to have confirmed subclinical hypothyroidism, which was an independent risk factor for infertility after adjustment for major reproductive and endocrine factors. SCH was especially common in ovulatory infertility, and was linked to delayed clinical pregnancy during 12 months of follow-up. Thyroid screening is therefore relevant in the fertility assessment but diagnosis should be made using laboratory abnormalities that are confirmed and treatment should be tailored according to evidence-based guidance.

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