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DO ELEVATED TSH LEVELS PREDICT EARLY PREGNANCY LOSS IN ART PATIENTS?

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Abstract

Introduction—The upper limit of normal TSH has been revised from 5 mIU/L to 2.5 mIU/L. We sought to evaluate IVF patients and the association between abnormal TSH and early pregnancy loss.

Methods—A retrospective study of patients who had TSH levels measured within the 2 weeks prior to their fresh autologous IVF cycles (2002–2014). Cohorts were stratified by oocyte age (<35, [35–38), [38–41), [41–43) and ≥43 years), and TSH level ((0–0.5], (0.5–2.5], (2.5–5], and (5–23) mIU/L). Patients were followed until pregnancy loss or delivery. Model was assessed by chi-square of ANOVA with significance at $p<0.05$.

Results—TSH was abnormally elevated (>5 mIU/L), mildly elevated ((2.5–5] mIU/L) or suppressed (≤0.5 mIU/L) in 46, 317 and 65 of the 1201 total cycles, respectively. Treatment resulted in 630 pregnancies, 524 clinical pregnancies and 409 deliveries. Pregnancy loss rates were increased in patients ≥38 yo ($p<0.001$) but not [35–38) yo ($p=0.40$) compared with those <35 yo. Early pregnancy loss rate was not associated with TSH level ($p>0.30$) compared with euthyroid patients after adjusting for oocyte age.

Conclusion—Early pregnancy loss rate in IVF patients appears to have no relation to recent TSH levels.

Keywords

Thyroid stimulating hormone; early pregnancy loss; subclinical hypothyroidism; euthyroid; in vitro fertilization

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Declaration of Interest Statement

The authors report no declarations of interest

Introduction

Affecting between 2–5% of all pregnant women in the United States, subclinical hypothyroidism (SCH) is a disorder characterized by an abnormality in the hypothalamic-pituitary-thyroid axis that results in a normal serum thyroxine (T_4) and high serum thyroid-stimulating hormone (TSH)[1]. While guidelines for the management of women with SCH undergoing assisted reproductive technology (ART) treatment exist[2], the optimal treatment of these patients is in part limited by insufficient outcome data on early pregnancy loss.

Thyroid disorders have been associated with adverse pregnancy outcomes[3–6], although the mechanism of action is unknown[7]. It is clear, though, that T_4 is a critical hormone for proper placental and fetal development[8]. Since the fetal thyroid gland does not begin to produce appreciable quantities of thyroid hormone until about 16 weeks of gestational age, the fetus is dependent on maternal thyroid function in the first trimester[8]. Throughout the pregnancy, maternal free T_4 must rise by about 50% above preconception levels to support the needs of the fetus[9]. Consequently, ART patients with overt thyroid disease, particularly hypothyroidism, must be closely monitored and levothyroxine medications must be titrated throughout pregnancy to ensure proper hormonal balance[10].

Overt hypothyroidism (OH), diagnosed by a high TSH and low T_4, is associated with infertility as well as poor pregnancy outcomes[11], including early pregnancy loss, stillbirth, and preterm delivery[3, 4, 12–14]. The potential consequences of SCH (i.e. a state in which only TSH but not T_4 is abnormal) have been suggested by some to be similarly dire, including an increased risk of placental abruption and preterm birth[15], although other studies failed to identify any significant differences in early pregnancy loss rate among women with SCH compared with those without[16, 17]. However, most studies on the effects of SCH on early pregnancy loss rates[15, 16, 18] have been limited by questions of population heterogeneity and applicability of results to the ART population[2] and have failed to demonstrate a link between SCH and early pregnancy loss [16, 17].

Discrepancies in the normal range of TSH have also left an unclear definition for SCH, which may complicate the management of pregnant patients[16]. While lower serum limits have remained consistent, the upper limit has undergone a dramatic shift over the past several years[23]. The National Association of Clinical Biochemistry (NACB)[24] and the American Thyroid Association (ATA) reduced the upper limit of TSH from 4.5 mIU/L to 2.5 mIU/L during the first trimester of pregnancy[2]. Other clinical institutions, such as the American Association for Clinical Chemistry (AACC) have traditionally defined 5.0 mIU/L as the upper limit of normal [25]. This new definition is estimated to increase the prevalence of SCH in pregnant American women from 2–3% to 15%, labeling approximately 600,000 women annually with a potentially clinically inconsequential diagnosis[23]. The Task Force recommends that all women with SCH who are positive for anti-thyroperoxidase antibodies (TPOAb+) be treated with levothyroxine[2], based on evidence from a single prospective randomized trial in Italy [26]. A follow-up study by the same authors found an increased pregnancy loss rate in TPOAb- SCH patients[27], although the guidelines do not currently recommend levothyroxine treatment for TPOAb- SCH patients or universal thyroid hormone screening during pregnancy[28, 29].

Given the substantial barriers to achieving pregnancy in the ART population, identification of optimal preconception TSH levels is particularly important. Moreover, the superovulation of ART produces rapid increases in E_2[19] that induce hepatic synthesis of thyroid binding globulin and result in decreased free, unbound T_4[20–22], potentially exacerbating underlying SCH. The potential for adverse reproductive consequences from iatrogenically induced SCH therefore mandates particular focus on this ART population.

By examining the outcomes of a large cohort of ART patients, this study seeks to determine whether elevated TSH levels are predictive of early pregnancy loss in ART. It attempts to address whether the new TSH criteria for pregnancy in ART patients are likely to produce any clinical benefit as well as help the reproductive medical community more accurately identify, counsel, and treat women who are at risk of early pregnancy loss based on their TSH status.

Methods

Study design

A single-center retrospective cohort analysis was performed on patients who completed an in vitro fertilization (IVF) cycle and had a TSH measurement within 2 weeks of the IVF cycle start date from July 1st, 2002 to May 1, 2014. Study groups were identified from an electronic medical records database. Patients with a known history of overt thyroid disease, i.e. a diagnosis of Graves' disease, subacute thyroiditis, Hashimoto thyroiditis, or thyroid malignancy, were excluded. Patients were stratified by oocyte age, binned as <35, [35–38), [38–41), [41–43) and ≥43 years old (yo), and TSH level, binned as (0–0.5], (0.5–2.5], (2.5–5] and (5–23) mIU/L. Patients with TSH (0.5–2.5] were classified as the "euthyroid" group.

Participants

Stimulation protocol—Patients underwent standard COH for IVF either with a down-regulation protocol with leuprolide acetate (Lupron®, AbbVie Inc., North Chicago, IL), an antagonist protocol (Ganirelix Acetate®, Organon USA Inc., Roseland, NJ or Cetrotide®, EMD Serono, Rockland, MA) or a Microflare protocol (Lupron®, AbbVie Inc., North Chicago, IL). Final oocyte maturation was induced with r-hCG alone (Ovidrel®, EMD Serono, Rockland, MA) or, in patients with high ovarian response and/or at risk for ovarian hyperstimulation syndrome (OHSS) undergoing an antagonist protocol, with 40 IU of leuprolide acetate (Lupron®, AbbVie Laboratories, Chicago, IL) concomitant with 1000–1500 IU of hCG (Novarel®, Ferring Pharmaceuticals, Parsippany, NJ). Vaginal oocyte retrieval (VOR) was performed by using transvaginal ultrasound guidance 36 hours later.

Outcome variables

The primary outcome variable was early pregnancy loss rate. Early pregnancy losses were defined as a positive pregnancy test that was followed by loss of a gestational sac (GS) or fetal heart (FH) activity within 20 weeks of gestation. Early pregnancy loss rate was calculated as the ratio of early pregnancy losses to the number of patients with a positive pregnancy. A clinical pregnancy was defined as the detection of a GS on an ultrasound (US) examination 22–25 days after retrieval. Monozygotic twins were considered as one sac in

this analysis. A pregnancy was defined as the detection of serum β-hCG ≥5 mUI/mL within 14 days following VOR. Pregnancy rate (PR) and clinical PR were calculated as the ratio of total pregnancies and ongoing clinical pregnancies, respectively, to the number of ART cycles entailing an embryo transfer (ET).

Statistical analysis

Statistical analysis was performed using R (R project) [30]. Descriptive data are represented as mean ± standard deviation. After a positive pregnancy test, early pregnancy losses were modeled by oocyte age and TSH level bin with a binomial regression using a log link function. A generalized linear model was employed so that cycles performed using embryos from the same couple in the context of a different preconception TSH level were counted as separate events. Model was assessed by chi-square of ANOVA with significance at $p<0.05$.

This research was approved by the Western Institutional Review Board (WIRB). Because of its retrospective nature, a formal consent was not required.

Results

In patients (n=1134) aged 22.4–47.1 years, IVF cycles (n=1201) were completed according to different protocols. 804/1201 (66.9%) Antagonist, 270/1201 (22.4%) MicroFlare, and 127/1201 (10.6%) Down Reg. 704/1201 (58.6%) of the total cycles were inseminated with ICSI, 458/1201 (38.1%) were inseminated conventionally, and the remainder 39/1201 (3.2%) were split.

In the total IVF cyles (n=1201), TSH was abnormally elevated (>5 mIU/L) or suppressed (≤0.5 mIU/L) in 46/1201 (3.83%) and 65/1201 (5.41%) cycles, respectively (Table 1). When evaluated according to stricter TSH criteria for identifying SCH (>2.5 mIU/L), TSH was elevated in 363/1201 (30.2%) cycles. Treatment resulted in 630 pregnancies, 524 clinical pregnancies and 409 deliveries.

Increasing oocyte age was associated with significantly increased early pregnancy loss rates in patients ≥38 yo ($p<0.001$) but not [35–38] yo ($p=0.40$) compared with those <35 yo, with increasing effect strength with age. We observed no significant differences in the early pregnancy loss rate across all TSH bins compared with euthyroid patients ($p>0.30$ for all groups) after adjusting for oocyte age.

Discussion

Given the substantial prevalence of SCH in the IVF population, a better understanding of the clinical consequences of hypothyroidism in women intending conception is critical, particularly in those who would have formerly been classified as euthyroid. In this large analysis of patients undergoing IVF, women with elevated TSH measurements were found to have comparable early pregnancy loss rates to those whose TSH levels were within normal limits when adjusted for age.

By evaluating the TSH level of IVF patients, we found that 3.83% of women had a TSH>5mIU/L and 26.4% of women had a TSH between 2.5 and 5 mIU/L, indicating that

the TSH upper limit captured an additional 317 women out of the total 1140 women. The rate of SCH within this IVF study population is significantly greater than the rate predicted among women in the United States, which is 2–5%[23]. However, a strong selection bias likely drives this disparity, as the patients being closely monitored with a TSH level close to their cycle date are the most likely to have some underlying thyroid dysfunction.

Prior studies that have aimed to demonstrate the risks of SCH defined by a TSH >2.5 mIU/L have produced contradictory and often negative results[2, 16], although a decrease in pregnancy complications was observed in women who were TPOAb+ and had a TSH >2.5 mIU/L and treated with levothyroxine early in pregnancy[2]. These findings may be compatible with those from our study given the overall low prevalence of TPOAb in the IVF population[31].

Importantly, this study design differs from previous investigations in several critical ways. By evaluating TSH measurements within two weeks of IVF cycle initiation, we are able to best approximate the true preconception TSH level. This methodology substantially limits the effects of variation in intraindividual TSH levels. This study is additionally strengthened by its large sample size (n=1140 couples), which allowed many IVF cycles to be analyzed. Finally, by controlling for age, we were able to decrease the effects of confounding from a known predictor of early pregnancy loss.

There are, however, limitations in this study. It is limited primarily by its retrospective design. Second, because data was not uniformly collected on subjects' medications or medication history, we were not able to exclude women who were taking levothyroxine or any other thyroid medication. It is unknown whether SCH was an incidental finding or if this may have been related to the initial infertility diagnosis. Because T4 levels were not consistently collected, we are also unable to assess whether patients with mildly elevated TSH still maintained normal T4 levels and hence met technical criteria for SCH. Presence of antithyroid antibodies was not routinely measured either, precluding systematic exclusion of such patients. We were, however, able to exclude women with current or previously diagnosed overt thyroid disease, making it less likely that women taking levothyroxine were a part of the study group. Despite drawing from an extensive database of patients from over a decade, OH patients undergoing IVF without documented resolution of their TSH levels were uncommon (<5% of the chemical pregnancies studied) and patients with SCH remained in the minority (<30% of chemical pregnancies studied).

The limited statistical power of this study prohibits drawing definite conclusions despite the lack of observed effects. These challenges are likely to become more acute as clinicians in our center and elsewhere consistently treat TSH to <2.5 mU/L prior to attempting conception by IVF, including in those who are TPOAb-, despite the lack of randomized controlled trials addressing the potential benefits of levothyroxine[2]. Until such studies are performed, clinicians seeking guidance for management will be forced to scour the literature for similar cohort studies.

While our findings suggest that the TSH cutoffs below 5mIU/L are not clinically significant from the standpoint of early pregnancy loss rates by 12 weeks of pregnancy, future research

may focus on the effects of TSH on other outcomes for IVF patients, including the success rate of different IVF protocols and folliculogenesis, as well as the long-term health outcomes for children born to SCH mothers. Although limited statistical power prevents this study from generating clear conclusions, the lack of a significant trend suggests that TSH levels may not necessarily pose a barrier to successful ART treatment.

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Table 1

Cycles are binned by TSH level and descriptive statistics calculated for all bins. Numerical data are represented as mean with standard deviation in parentheses.

TSH Level (mlU/L)	(0,0.5]	(0.5,2.5]	(2.5,5]	(5,23]
Cycles	65	773	317	46
Age (years)	37.4(4.5)	37.0 (4.6)	37.4(4.4)	36.6 (5.1)
Day 3 FSH (mlU/mL)	6.8 (4.0)	6.4(3.6)	6.3 (3.6)	5.8 (3.9)
BMI (kg/m2)	24.1 (4.5)	24.0 (4.7)	25.4(5.3)	25.3 (4.8)
Peak E2 (pg/mL)	2147.9 (1062.1)	2064.0(1062.3)	2011.4(1033.6)	1841.7 (975.5)
AMH (ng/mL)	1.9 (2.7)	2.3 (3.1)	2.0 (2.3)	1.2 (.6)
BAFC	10.1 (5.1)	10.2 (6.3)	9.7 (6.5)	8.6 (5.2)
Follicles ≥l4mm	12.4(6.2)	11.3 (6.6)	11.1 (6.5)	10.1 (7.0)
Starting Gnd Dose (IU)	229.0(100.7)	240.3 (81.2)	239.0(85.2)	225.4(89.7)
Cumulative Gnd Dose (IU)	2109.9 (1122.2)	2366.7 (989.5)	2437.4(1018.4)	2210.9 (1053.8)
Pregnancies	33	399	173	25
Clinical Pregnancies	36	461	224	27
Live Births	19	256	118	16

FSH: Follicle stimulating hormone
BMI: body mass index
AMH: Anti-Müllerian hormone
BAFC: basal antral follicle count
Gnd: gonadotropin