Controlled ovarian hyperstimulation as a stress test for the thyroid

Thyroid hormone plays a relevant role in female reproduction. Thyroid hormone receptors are abundantly present throughout the female reproductive tract, and thyroid hormone regulates key processes in reproductive physiology, particularly through the downstream effects of follicle-stimulating hormone and luteinizing hormone (LH). From a clinical point of view, the role of thyroid hormone is reflected by the consequence of thyroid disease. Hypothyroidism and hyperthyroidism are well-established modifiable risk factors for subfertility through the direct effects mentioned above but also through indirect effects, such as hyperprolactinemia, and alterations in gonadotropin-releasing hormone sensitivity and estradiol concentrations. The treatment indication for overt thyroid disease has been ubiquitously recognized, and recent studies have shown no benefit of levothyroxine treatment for euthyroid thyroid autoimmunity (1). However, the benefit of levothyroxine treatment for milder forms of thyroid disease, in particular subclinical hypothyroidism, remains unknown. This knowledge gap is frequently exploited by fertility specialists to treat women with a normal thyroid function (i.e., a thyroid-stimulating hormone [TSH] concentration of >2.5 mU/L or even lower). Such nonevidence-based practices cause unnecessary psychosocial and biologic harm due to overdiagnosis and overtreatment.

In the current issue, Busnelli et al. (2) report the results of their systematic review and meta-analysis assessing thyroid function test changes throughout controlled ovarian hyperstimulation (COH). Studying these changes is especially relevant because in this field, high-quality clinical evidence is scarce and low-quality clinical data are often overinterpreted. Therefore, future clinical studies or interventions should be based on thyroid physiology rather than having a non-hypothesis-based approach. Experimental studies and studies on human physiology provide a good basis for the current study. Low thyroid hormone availability is associated with suboptimal local ovarian stimulatory effects of follicle-stimulating hormone and LH because thyroid hormone regulates 3,β-hydroxysteroid dehydrogenase (the final step in progesterone formation), aromatase (the final step in estradiol formation), and LH/human chorionic gonadotropin receptor expression (3). Considering that COH is a state of supraphysiologic ovarian stimulation, this indicates that the identification of women with abnormal thyroid function test results that arise during COH may ultimately improve their outcomes. At the same time, COH is a state of an increased demand for thyroid hormone production. Although the thyroid function test results remain stable throughout a normal menstrual cycle, a rapid increase in the estradiol concentration during COH increases thyroxine-binding globulin concentrations and type-3 deiodinase gene transcription (deactivating thyroid hormone), leading to lower thyroid hormone availability and a subsequent increase in TSH concentration (3).

After extracting data from 11 studies, the investigators showed that in euthyroid women undergoing in vitro fertilization/intracytoplasmic sperm injection, the mean TSH concentration increased by 0.69 mU/L (95% confidence interval [CI], 0.30–1.08) during COH, and this effect persisted until a positive pregnancy test result, whereas there was practically no change in the mean free thyroxine (FT4) concentration (−0.34 pmol/L [95% CI, −0.91 to 0.23]) (2). Subanalyses investigating women with thyroid autoimmunity revealed highly heterogeneous results (effect estimates ranged between −0.1 to 2.86 mU/L), probably owing to the small number of women (n = 7–24), suboptimal statistical modeling in the original studies, and combining thyroperoxidase antibody-positive women with thyroglobulin antibody-positive women (the latter are unlikely to present a reduced thyroid functional capacity). Women with hypothyroidism treated with a fixed dose of levothyroxine were also studied, which is relevant because in this group, thyroid function cannot be increased because of an increase in TSH concentrations, making it a better controlled experiment. In these women, the mean TSH concentration increased by 1.50 mU/L (95% CI, 1.10–1.89), which persisted for at least 3 months after COH.

This study provides the best quantitative data on the effects of COH on thyroid function using a rigorous methodology and considers a longitudinal aspect with a baseline measurement that practically excludes reverse causality (2). It was not determined whether clinicians could have based the type of COH on the thyroid function test outcome, which makes the results of analyses after stratification for the different regimens difficult to interpret. The extent of thyroid function changes, especially in hypothyroid women treated with levothyroxine, indicates that COH is a state of an increased demand for thyroid hormone production. The 1.50 mU/L increase in the mean TSH concentration in this group strengthens the recommendations of international guidelines to aim for a TSH treatment target of <2.5 mU/L in women treated with levothyroxine before pregnancy because this decreases the risk that relevant undertreatment will remain unidentified in between thyroid function assessments (4). Moreover, the minor increase in the TSH concentration among euthyroid women re-emphasizes that there is no basis at all for levothyroxine treatment in euthyroid women.

This study also clearly exhibits that the quantity and quality of the currently available data is inadequate to identify women at high risk of developing clinically meaningful thyroid function test abnormalities during COH that would require levothyroxine treatment (2). We certainly agree with the investigators that future prospective studies are required to identify subgroups with clinically meaningful thyroid function changes. An important limitation of this study is its design. An aggregate data meta-analysis cannot adequately deal with between-study differences in statistical methods, TSH/FT4 assays, and definitions of (ab)normal TSH, FT4, or thyroid antibody concentrations. This should be considered as a form of measurement error that can reduce the effect estimates toward the null.

Therefore, in parallel to new prospective studies, an individual participant data meta-analysis could provide relevant insights and can serve as a basis for the design of future studies (5).

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https://doi.org/10.1016/j.fertnstert.2021.04.025

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REFERENCES

1. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med 2019;380:1316–25.
2. Busnelli A, Cirillo F, Levi-Setti PE. Thyroid function modifications in women undergoing controlled ovarian hyperstimulation for IVF: a systematic review and meta-analysis. Fertil Steril 2021;116:218–31.
3. Korevaar TI. Thyroid disorders during preconception, pregnancy, and the postpartum period. In: Werner and Ingbar's. The thyroid, 11. Philadelphia, PA: Wolters Kluwer; 2020.
4. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315–89.
5. Korevaar TI, Derakhshan A, Taylor PN, Meima M, Chen L, Bliddal S, et al. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: a systematic review and meta-analysis. JAMA 2019; 322:632–41.