Thyroid function during ovarian stimulation: a systematic review

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Objective: To review the evidence regarding thyroid function and thyroid autoimmunity (TAI) changes in women undergoing ovarian stimulation (OS).
Design: Studies eligible for the systematic review were those that reported data on thyroid function or TAI both before and during OS or within 1 month after OS.
Setting: Academic hospital.
Patient(s): Women with abnormal thyroid function or TAI (n = 419) and controls (n = 425).
Intervention(s): Ovarian stimulation.
Main Outcome Measure(s): Serum TSH, free thyroxine, free tri-iodothyronine and thyroid antibodies.
Result(s): Seven studies, between 2000 and 2011, were included. Serum TSH concentrations were significantly increased in three studies and were not changed in two studies. Serum free thyroxine concentrations were increased in two studies, were not changed in one, and were decreased in another. Serum free tri-iodothyronine concentrations were not changed in the only study in which they were measured. Thyroid antibody concentrations were decreased in one study and were not changed in two studies, even in the presence of changes in thyroid function.
Conclusion(s): The current evidence is inconclusive regarding OS effect on thyroid function or TAI. Serum TSH concentrations may be increased during or within 1 month after OS, exceeding the threshold of 2.5 mU/L suggested for the first trimester of pregnancy, but further prospective studies are needed to provide conclusive evidence for or against universal evaluation of thyroid function and TAI in women undergoing OS. (Fertil Steril® 2011;96:780–5. ©2011 by American Society for Reproductive Medicine.)

Key Words: Thyroid gland, thyroid-stimulating hormone, thyroid autoimmunity, ovarian stimulation, assisted reproduction

Ovarian stimulation (OS) is an integral part of many assisted reproduction technology (ART) procedures. These also include down-regulation of the pituitary–gonadal axis (e.g., GnRH agonists or -antagonists) and triggering of final oocyte maturation (e.g., hCG). Although there is some evidence that OS can impair thyroid function (1, 2), the relevant pathophysiology has not been fully elucidated.

It has been proposed (2) that OS induces a rapid increase in serum E_2 concentrations, resulting in excess thyroxine-binding globulin (TBG) production and sialylation by the liver. This increase in TBG increases the number of circulating thyroxine-binding sites and tends to reduce free thyroxine (fT_4) concentrations; the latter can induce TSH production from the pituitary gland. Thus, E_2 induces an additional strain on the hypothalamic–pituitary–thyroid axis and can, therefore, considerably impair thyroid hormone distribution and kinetics (3).

In addition, it is well known that TSH and hCG, as well as their respective receptors, share structural homologies; as a result, endogenous hCG has thyrotropic effects (4). High hCG concentrations that are achieved during OS, either by triggering final oocyte maturation or by using hCG-containing gonadotropins, may be associated with thyroid stimulation, both functionally (lower serum TSH concentrations) and anatomically (increased thyroid volume).

Moreover, E_2, whose concentrations are profoundly increased during OS (2), can suppress the T-helper cell responses type 1 (Th1) and stimulate the T-helper cell responses type 2 (5). Because thyroid autoimmunity (TAI) (i.e., increased serum concentrations of antithyroid peroxidase [anti-TPO] and/or antithyroglobulin [anti-Tg] antibodies) is a Th1-mediated process (6), it is expected to be improved after OS.

The rapidly increasing E_2 concentrations during OS might also have a central action on thyrotropin-releasing hormone, because there is evidence from animal models that E_2 can down-regulate the thyrotropin-releasing hormone messenger RNA concentrations in the paraventricular nucleus in vivo (7).

The evidence concerning the effect of OS on thyroid function is conflicting. Stuckey et al. (8) have shown that OS can result in subclinical hypothyroidism (high TSH concentrations) in women being euthyroid on thyroid hormone replacement. Poppe et al. (9) reported overt hypothyroidism (high TSH and low T_4 concentrations) after OS. On the other hand, Reh et al. (10) found no evidence of diminished thyroid reserve as a result of peak serum E_2 concentrations of 2,000–3,000 pg/mL on the day of hCG administration in women with TAI.

The research question of this study was, "Does OS result in changes of thyroid function or TAI?" To answer this question, we systematically reviewed the evidence regarding thyroid function changes in women undergoing OS.

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MATERIALS AND METHODS

Search Strategy

We performed a search in PubMed and EMBASE using the string [("controlled ovarian hyperstimulation" OR "OS" OR "ovarian stimulation" OR "in vitro fertilization" OR "IVF" OR "intra-cytoplasmic sperm injection" OR "ICSI" OR "assisted reproduction" OR "ART") AND "thyroid"] from inception to March 2011.

Eligibility of Relevant Studies

For a study to be included it had to report data on thyroid function (i.e., TSH, fT_4, free tri-iodothyronine [fT_3], TBG) or TAI (i.e., anti-TPO and/or anti-Tg antibodies) before and during OS or within 1 month after OS. There were no exclusion criteria regarding study design (i.e., prospective or retrospective) or OS protocol.

Data Extraction

Information from each study was extracted independently by two reviewers (G.M. and K.A.T.) using a standardized data extraction form. General characteristics of each study (first author, year of publication, setting), characteristics of study groups, OS protocol, thyroid function, and/or TAI assessment before and after OS, as well as reproductive outcomes (the latter, where available), were recorded.

RESULTS

Study Identification

Of 211 studies that were initially identified, 155 were not relevant to the systematic review aim and 33 were reviews, case reports, case series, or animal studies. Of the remaining 23 studies, 16 did not include thyroid function or TAI assessment both before and during/after OS. Seven studies were included in the systematic review.

Study Characteristics and OS Protocols

Table 1 presents the seven studies that have reported on thyroid function or TAI changes in women undergoing OS (1, 2, 11). These studies were published from 2000 to 2011. The OS protocols used involved GnRH agonists and -antagonists, human recombinant FSH, or hMG and hCG. The study by Kim et al. (12, 13) was the only one in which women with hypothyroidism were included; all other studies investigated euthyroid women with or without TAI.

Thyroid Function

Serum TSH concentrations were significantly increased in three studies (1, 2, 11) (one during OS [1] and two within 1 month after OS [2, 11]) and were not changed in two studies (12, 13) (Tables 2 and 3). In the former three studies (1, 2, 11), TSH concentrations equaled or exceeded the threshold of 2.5 mU/L suggested for the first trimester of pregnancy. In one study, TSH concentrations were increased only in cycles in which pregnancy was not achieved (10). Serum fT_4 concentrations were increased in two studies (2, 11) (both within 1 month after OS), were not changed in one (13), and were decreased in another (1) (during OS).

Concentrations of anti-Tg and/or anti-TPO antibodies were measured both before and after OS in two studies (1, 14) (Table 2). Thyroid-stimulating hormone and/or fT_4 concentrations after OS were not different in women with or without TAI (2, 10, 13). Serum fT_3 concentrations were not changed in the only study in which they were measured (13), whereas serum TBG concentrations were increased after OS in the only study in which they were measured (1) (during OS).

Thyroid Autoimmunity

Anti-TPO and/or anti-Tg antibody concentrations were decreased in one study (1) (during OS) and were not changed in two studies (11, 14) (Tables 2 and 3), even in the presence of changes in thyroid function.

Meta-analysis

The limited number of the studies, the diversity of the studied groups of women, and the wide range of the primary outcomes prevented the conduct of a meta-analysis.

TABLE 1

Studies of thyroid function during assisted reproduction techniques.

ID	First author, year (reference)	Setting, country	Study characteristic	OS protocol
1.	Muller, 2000 (1)	Academic center, the Netherlands	Retrospective study	GnRH analog and hMG
2.	Poppe, 2004 (2)	Academic center, Belgium	Prospective study First ART cycle	GnRH agonist and hMG or hrFSH
3.	Poppe, 2005 (11)	Academic center, Belgium	Prospective study First ART cycle	GnRH agonist and hMG or hrFSH
4.	Haller, 2006 (14)	Private center, Estonia	Prospective study	GnRH agonist (n = 7, 5.4%) or GnRH antagonist (n = 122, 94.6%) and hrFSH
5.	Reh, 2011 (10)	Academic center, United States	Retrospective study First IVF cycle	GnRH antagonist (long luteal), GnRH agonist, or follicular microdose GnRH agonist
6.	Kim, 2011 (12)	Academic center, South Korea	Prospective study	GnRH antagonist multiple-dose protocol and rhFSH
7.	Monteleone, in press (13)	Academic center, Italy	Prospective study	GnRH-antagonist and hrFSH

Note: hrFSH = human recombinant FSH.

Mintziori. Thyroid function during ovarian stimulation. Fertil Steril 2011.