Almost all infertility patients will have a thyroid-stimulating hormone (TSH) level obtained because thyroid disease frequently occurs in patients who are asymptomatic. The United States National Health and Nutrition Examination Survey (NHANES III) found the prevalence in people without symptoms is 4.6% for hypothyroidism and 1.3% for hyperthyroidism. Thyroid disease has been associated with altered ovarian function, subfertility and increased spontaneous abortion rates. Therefore, thyroid screening for infertile women is suggested.

**Thyroid regulation**

The regulation of the thyroid gland is analogous to the regulation of the reproductive cycle. The thyroid gland produces thyroid hormone and the ovary produces estrogen, both of which exert negative feedback control on the hypothalamic-pituitary axis. The pituitary releases stimulating hormones which are thyroid-stimulating hormone for the thyroid gland and follicle-stimulating hormones for the ovary. The thyroid gland produces two forms of thyroid hormone, T3 and T4. T4 is the primary hormone released by the thyroid, but this is in fact a prohormone since it is the T3 which has the highest affinity for the thyroid hormone receptor in target tissues. T4 is roughly 80% of the daily thyroid hormone production by the thyroid gland. T4 is metabolized primarily by the liver and kidneys to T3. T3 interacts with the receptor on target tissue cell membranes, and once inside the target cell moves to the nucleus where it binds to DNA receptors.

Thyroid hormone acts on virtually every tissue with various actions, depending upon the tissue involved. In general, thyroid hormone regulates metabolic rate, affects production of certain proteins and influences the action of hormones.

The production of thyroid hormone is limited by the amount of iodine in the diet, but with normal availability of iodine, thyroid hormone production is regulated as a negative feedback system. T4 inhibits the release of thyroid-releasing hormone from centers in the hypothalamus (much like E2 inhibits GnRH). Reduced secretion of TRH results in less TSH being released and thus a reduction in the production of thyroid hormone. Clinically, an elevated TSH is a sign of an underperforming thyroid gland, just like a failing ovary can be seen when FSH levels rise. Low TSH levels are a sign of overproduction of thyroid hormone. Disease of the thyroid can be hypothyroidism, hyperthyroidism or subclinical disease. TSH is used to alert the healthcare provider to the presence of these pathologies.

**Hypothyroidism**

Hypothyroidism primarily results from either inadequate iodine in the diet (infrequent in the U.S. for patients on a normal diet) or an autoimmune cause and is termed Hashimoto’s thyroiditis (with or without a goiter present). Hypothyroidism can cause a number of symptoms, including tiredness, intolerance to cold, weight gain and cognitive alterations. The diagnosis is suspected when the screening TSH is elevated and confirmed by consistently elevated TSH levels and low T4 levels. Patients with Hashimoto’s thyroiditis frequently have antithyroid antibodies, especially antithyroid peroxidase antibodies. Thyroid antibodies can be anti-peroxidase, anti-thyroglobulin or anti-thyrotropin receptor antibodies (TRAbs), which can be either blocking or neutral depending upon their effects on the TSH receptor. Postpartum 5% of women will develop hypothyroidism, of which 20% will remain hypothyroid. The treatment of choice is levothyroxine, and the adequacy of therapy is monitored using TSH.
Hyperthyroidism

Hyperthyroidism commonly consists of two forms, which are Grave’s disease (toxic diffuse goiter) or Plummer’s disease (toxic nodular goiter). Plummer’s disease is most frequently encountered in postmenopausal women and thus is an infrequent concern for infertility patients. The diagnosis is suspected when the TSH levels are low. The diagnosis is confirmed by consistently low TSH levels and elevated T4 or T3 levels. Radioactive iodine uptake studies will confirm the diagnosis and anti-thyroid antibodies may be present. Thyroid antibodies directed to the TSH receptor can be stimulating, leading to Grave’s disease; blocking, which can lead to Hashimoto’s thyroiditis; or neutral. The TPO antibody is frequently used as a surrogate for the TRAbs. Stimulating TRAbs bind to the TSH receptor and cause release of TSH, thus resulting in increased T4/T3 production by the thyroid gland.

There are three main treatment options—radioactive iodine, surgery or medications. Beta-blockers (propranolol) or methimazole are medication options for immediate or short-term management. Radioactive iodine renders the patient hypothyroid and thus requires thyroid replacement. Surgery is less frequently used because other forms of treatment are effective and surgery runs the risk of removing the parathyroid glands with the removal of the thyroid gland.

Subclinical hypothyroidism

Subclinical hypothyroidism is diagnosed by an elevated TSH and a normal T4. For infertility purposes, the goal is to treat anyone with a TSH of > 2.5 µIU/ mL. Top-normal TSH values are in general considered to be 4.5 µIU/ mL. The presence of antithyroid antibodies can help predict which patients are at an increased risk of developing overt thyroid disease. Treatment for subclinical hypothyroidism has been suggested to reduce the subfertility rate and the spontaneous abortion rate.

The ACOG practice guidelines report there is insufficient evidence to support the recommendation for treatment of subclinical hypothyroidism in pregnant patients. However, a recent review by Vissenberg et al. (2015) suggests there exists a relationship between subclinical hypothyroidism, subfertility and spontaneous abortion. The authors emphasize that more research is needed to clarify the relationship between antithyroid antibodies and reduced reproductive success. Until then, infertility patients will probably continue to be treated for subclinical hypothyroidism.
About the author:
For the past 35 years, Dr. John S. Rinehart has maintained an exclusive practice in infertility and reproductive endocrinology in the Chicago area. He completed his residency in obstetrics and gynecology at Johns Hopkins Hospital and his fellowship in reproductive endocrinology at Harvard Medical School and Brigham and Women’s Hospital. Since 1985, Dr. Rinehart has been board certified in obstetrics/gynecology, and since 1988 in reproductive endocrinology and recertified in his subspecialty in 1999. In addition, Dr. Rinehart completed his law degree with a concentration in health law at DePaul University College of Law, Chicago, in 2002. Dr. Rinehart maintains his academic connection as senior educator at Pritzker School of Medicine at the University of Chicago through frequent lecturing, input to hospital-based ethics committees and IRB-approved research studies. Dr. Rinehart is the director of the Division of Reproductive Endocrinology/Infertility at St. Francis Hospital, Evanston, Illinois. He regularly works with residents and medical students in clinical settings and classroom lecturing, and is sought after for his expertise in both medical and legal perspectives of fertility management. Dr. Rinehart is also a member of the Society of Reproductive Surgeons, the Society for Reproductive Endocrinology and the Society for the Study of Reproduction.

References
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