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HYPOTHYROIDISM IN WOMEN



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Thyroid disorders in general and hypothyroidism in particular is extremely common and especially in women. Menarche, pubertal growth and development, menstrual cycles, fertility, fetal development, post partum period, reproductive years and the post menopausal years are profoundly influenced by the thyroid status of the woman. The high prevalence of thyroid disorders in women is possibly due to autoimmune nature of the thyroid disorders.

Thyroid Physiology

Circulating T_4 is exclusively secreted by the thyroid gland while only about 20% of the circulating T_3 is produced by the gland, the rest coming from peripheral conversion of T_4 to T_3 . Intrapituitary conversion of T_4 to T_3 regulates TSH secretion. Hypothalamic TRH stimulates TSH production which in turn stimulates the thyroid to secrete T_4 and T_3 . 99.97% of the circulating T_4 is bound, mostly to thyroid binding globulin and partly to thyroid binding prealbumin and albumin. The half life of T_4 is one week. 99.5% of the circulating T_3 is bound, more weakly than T_4 , has a shorter half life of one day but is metabolically the active compound. The clinical significance of this in women is the fact that oral contraceptives, pregnancy and hormone replacement therapy profoundly affect thyroid binding globulin. It is therefore necessary to do Free T_4 and Free T_3 levels in women.

Hypothyroidism – Etiology

- Thyroid failure (high TSH level)
- Autoimmune (Hashimoto's) thyroiditis
- Treated Graves' disease (radioiodine, surgery, antithyroid drugs)
- Inadequate thyroid hormone replacement
- Iodine and iodine-containing medication
- Lithium

Less common causes

- Hypopituitarism (low TSH level)
- Hypothalamic (low TSH level)
- Serum TSH elevations unrelated to hypothyroidism
- Nonthyroidal illness
- Adrenal insufficiency (Addison's disease)
- Drugs (metoclopramide and domperidone)
- TSH-producing pituitary tumors
- Thyroid hormone resistance syndromes

Hypothyroidism and Puberty

Prepubertal girls could present with growth retardation, premature thelarche or other signs of precocious puberty including early menarche. This phenomenon is explained by excessive secretion of the α subunit which may activate gonadotropin receptors and by hyperprolactinemia caused by elevated TRH. Therapy with thyroxine causes prompt regression of pubertal signs. Delayed puberty with growth retardation (with delayed bone age) is the more common presentation. Therapy with thyroxine induces catch up growth and progression of puberty.

Menstrual Cycles

Anovulatory cycles presenting as oligomenorrhea, amenorrhea or menorrhagia have all been reported. Hyperprolactinemia that accompanies long standing primary hypothyroidism may cause galactorrhea and amenorrhea. Acquired coagulation defects of hypothyroidism, like the pseudo Von Willebrand syndrome may further aggravate the menorrhagia. Central hypothyroidism (Pituitary or hypothalamic) may be accompanied by deficiencies of gonadotropins causing amenorrhea. Thyroxine therapy normalises thyroxine, TSH and prolactin levels and restores the normal, hormonal milieu.

Fertility

Untreated hypothyroidism may cause anovulatory cycles and luteal phase defects and lead to subfertility. About 10% of recurrent miscarriages have been reported due to the presence of antithyroid antibodies (in the euthyroid state). Evaluation of thyroid function with Free T_4 and TSH is recommended in all women presenting with ovulatory dysfunction, galactorrhea and luteal phase defects. In addition to thyroid function tests, antithyroid antibodies (antithyroid peroxidase and antithyroglobulin) are recommended in women with recurrent miscarriages.

Pregnancy

Maternal thyroid hormone metabolism undergoes profound changes during pregnancy:

- a) Increased glomerular filtration rate causing increased iodine clearance causing a state of iodine deficiency. This is clinically significant only in iodine deficient areas.
- b) Small increase in maternal thyroid volume, which does not cause significant clinical enlargement of the thyroid.

- c) Increase in thyroid binding globulin due to maternal estrogen causing significant rise in Total T_4 and Total T_3 . Free hormones are generally within the normal range making Free T_4 and TSH, the tests of choice in pregnant women.

Fetal Thyroid Function

The fetus begins to synthesize T_4 and T_3 around 10 weeks of gestation and is under pituitary control by 20 weeks. The thyroxine need of the fetus before 10 weeks of gestation is met by maternal thyroid hormones. Iodine in any form (oral, topical, intravenous) crosses the placenta and may cause hypothyroidism and goiter in the fetus.

Fetal hypothyroidism is suggested by a fetal goiter on ultrasound or delayed femoral epiphyses and can be confirmed by measuring serum thyroxine and TSH on Cord blood. Hypothyroidism can be treated with intra-amniotic injection of thyroxine. We have treated six babies in utero with intra-amniotic thyroxine with euthyroid status at birth and uneventful course during follow up thus far. All babies born to parents with a thyroid disorder should undergo neonatal screening (Free T_4 , TSH) or Cord blood within 30 minutes or 5 days after birth.

Maternal Hypothyroidism during Pregnancy

Thyroxine requirements increase by about 50 mg in over 50% of women during pregnancy. This has been our experience as well. The recommendations are:

- a) Measuring serum Free T_4 and TSH as soon as pregnancy is confirmed.
- b) Repeat Free T_4 , TSH once every trimester.
- c) Increase dose of thyroxine to keep TSH level within the normal range.
- d) Recheck Free T_4 , TSH, 6 weeks after delivery and readjust the dose as needed.

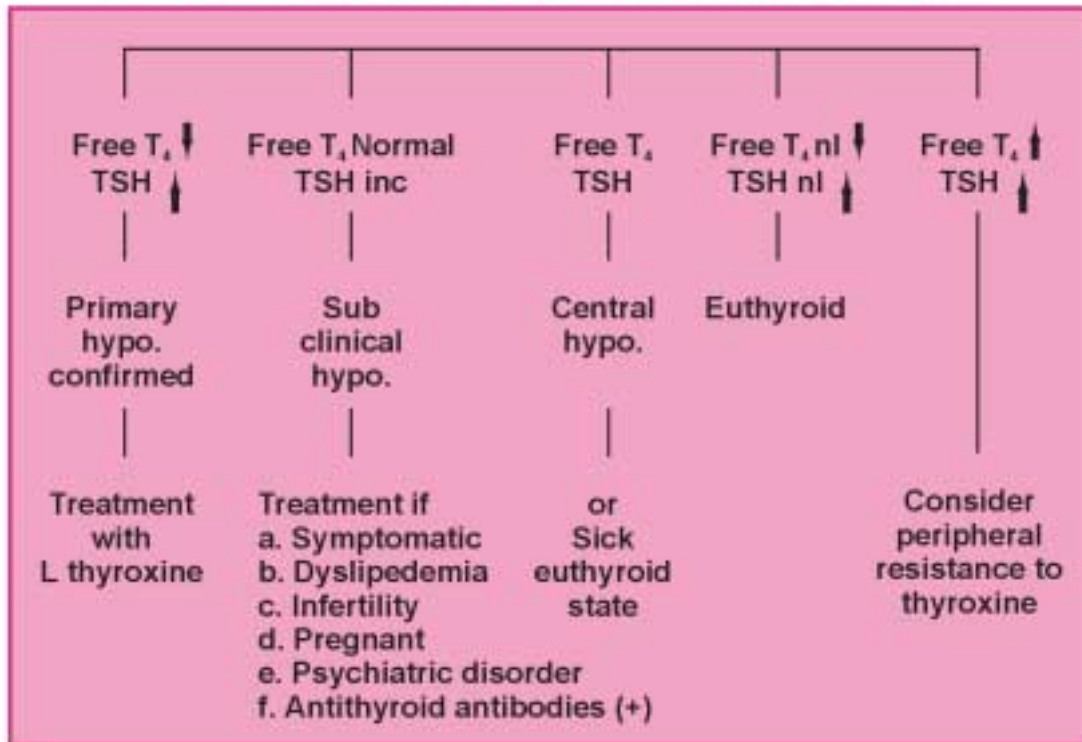
Untreated or underreplaced women with hypothyroidism are more prone to hypertension and pre-eclampsia and poor mental development in the offspring. Medications commonly used during pregnancy like iron, antacids and fiber laxatives interferes with the absorption of thyroxine and they should be administered several hours after thyroxine. It is our recommendation to give thyroxine, in the fasted state, (early morning) and iron supplements after dinner. Breast feeding is safe and the small amount of thyroxine that is secreted into the breast milk does not significantly influence the baby's thyroid status.

Hypothyroidism in nonpregnant Women

Symptoms may be non specific and mild like fatigue, weight gain, lethargy or quite profound with hoarse, slow speech, depression, cold intolerance,

constipation, menstrual irregularities, galactorrhea and extreme fatigue. Physical finding such as puffiness of face, goiter, dryness of skin and delayed deep tendon reflexes are present in many. Diagnosis is confirmed by measuring Free T₄ and TSH. Mild elevation of TSH with normal free T₄ is termed subclinical hypothyroidism and seems to be more common in women, especially over age 65 years.

CLINICAL SUSPICION OF HYPOTHYROIDISM



Post Menopausal Women

Hypothyroidism is extremely common in older women. Subclinical hypothyroidism is reported to occur in women over 65 years with 5% of them progressing to frank thyroid failure yearly if they were antibody positive and 2.6% per year, if they were antibody negative.

Postmenopausal women should be screened for thyroid dysfunction even when mildly symptomatic. Therapy with thyroxine should be initiated at a lower dose and gradually raised to avoid over replacement. Atrial fibrillation, worsening of ischemic heart disease and accelerated bone turnover have all been reported with over replacement, especially in post menopausal women.

Post Partum Thyroiditis

A transient form of autoimmune thyroiditis affects about 3.5% of women (higher percentage in some population). These women go through a hyperthyroid phase and then a hypothyroid phase usually presenting about 3-6 months after delivery. Postpartum, depression could be associated with this condition. Symptomatic hypothyroid women should be treated with thyroxine and reassessed about a year later to confirm return to euthyroid state. Presence of antithyroid antibodies, goiter and prior postpartum thyroiditis predisposes the woman to recurrence of thyroiditis.

Summary

1. Hypothyroidism is extremely common in women, most likely due to the autoimmune nature of many of the thyroid disorders.
2. Hypothyroidism has profound effects on the reproductive system causing varied clinical presentations during the different stages of a woman's life.
3. Prepubertal and pubertal girls may present with growth or pubertal delay or rarely precocious puberty.
4. Oligomenorrhea, menorrhagia, galactorrhea and amenorrhea are frequent 'menstrual' disorders.
5. Subfertility may be caused by ovulatory dysfunction and luteal phase defects in untreated hypothyroid women.
6. Recurrent miscarriages may happen in women who are antithyroid antibody positive.
7. All women with thyromegaly during pregnancy need evaluation with thyroid function tests. Free T_4 and TSH are the ideal tests and should be done each trimester and dosage of thyroxine adjusted. Majority of women need a higher dose of thyroxine during pregnancy.
8. Subclinical and overt hypothyroidism are common in postmenopausal women. Over replacement should be avoided for fear of accelerated bone turnover and worsening of underlying cardiac diseases.
9. Levothyroxine is the preferred agent. Simultaneous administration of Iron, Sucralfate, Cholestyramine, Antacids, Calcium, Fiberlaxatives, Lovastatin should be avoided.
10. Empirical use of thyroxine (without biochemical confirmation) for the management of obesity, infertility, menstrual irregularities and non specific symptoms is to be avoided.

Selected Reading

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