Chapter

51 Maternal Hypothyroidism: A Clinical Perspective

AG UNNIKRISHNAN

INTRODUCTION

Maternal hypothyroidism, in simple terms, refers to low thyroid hormone levels during pregnancy. The diagnosis is made by a TSH that is greater than normal, and this situation deserves therapy. Many studies have shown that maternal thyroid hormones are very important in pregnancy[1-3]. Most importantly, emerging data seems to suggest that thyroid hormones are especially important for fetal brain development, especially during early pregnancy[4]. This article will discuss the importance, diagnosis and management of maternal hypothyroidism, from a clinician's perspective.

Thyroid Physiology in Pregnancy

Pregnancy may be associated with several physiological changes in laboratory tests of thyroid function (Table 1)[5-9]. During pregnancy, there is an increased requirement of thyroid hormones, and this is achieved by an increased thyroid gland function. However, in subjects with pre-existing hypothyroidism, where the gland lacks the functional reserve to increase thyroxine secretion appropriately, there is an approximately 25-47% increase in dosage requirement during pregnancy[5]. Also, iodine deficiency can compromise thyroid function in pregnancy[6,7]. In addition, as HCG levels increase in pregnancy, there is a transient suppression of TSH in the first trimester[8]. Finally, the estrogenic milieu of pregnancy results in increased sialic acid content of thyroxine-binding globulin (TBG); this reduces the clearance of TBG and prolongs its circulation time[9]. This increase in TBG (which binds to thyroid hormones) can result in a falsely high thyroid hormone (especially T4) levels during pregnancy; however adaptation mechanisms ensure that the free or active thyroid hormone levels are kept normal. Though these changes affect both the thyroid hormones (T3 and T4), T4 is the more appropriate hormone to measure, and it has been suggested that *free* T4 hormones be measured in pregnancy. In case total T4 is being used as a measuring tool, recent reports suggest that a different cut-off be used: It has been reported that the normal upper limit of total T4 level in pregnancy is 1.5 times the upper limit in non-pregnant adults[5]. Also, autoimmune thyroid disorders remit during pregnancy as a part of the immunosuppressive effects of pregnancy. Classically, there is a post-partum period of exacerbation. Patients who are euthyroid but positive for antithyroid antibodies have an increased rate of miscarriage[10]. The reason for this is not well understood.

Table 1: Some physiological thyroid alterations in pregnancy

Phenomenon	*Explanation*
High thyroxine-binding globulin (TBG)	Increased serum estrogen
First trimester TSH suppression	HCG
Slight increase in FT4	HCG
Goiter in iodine deficiency areas	Increased iodide clearance
Goiter in iodine sufficient areas	Increased demand
Increased T4 and T3 demand	High type III deiodinases
High total T4 and T3	Increase in TBG
Increased thyroglobulin	Increased demand for thyroid hormones

Maternal Hypothyroidism: Clinical Importance

The prevalence of maternal hypothyroidism, as defined by a raised TSH level, is about 2.5% of all pregnancies[11]. This means that about 40 patients need to be screened to detect one case. In iodine-sufficient areas, the most common cause is Hashimoto's thyroiditis.

Table 2: Adverse outcomes associated with maternal hypothyroidism

Maternal disorders
Gestational hypertension
Increased use of cesarean section
Anemia
Placental abruption
Preterm labor
Postpartum hemorrhage
Fetal disorders
Fetal loss
Disorders of brain development
Low IQ scores
Fetal distress
Low birth weight
Cretinism

The diagnosis of maternal hypothyroidism is important because of its implications on both maternal and fetal outcomes (Table 2)[2,12]. This is even true with subclinical hypothyroidism[13]. In addition to these issues is the important etiologic association between hypothyroidism and infertility[14].

In the last few decades, emerging evidence has linked thyroid hormones with fetal brain development. This issue of recent interest deserves a special focus. Classic studies on neurological cretinism had earlier shown that iodine deficiency caused fetal brain damage[15]. This occurs presumably by reducing thyroid hormone synthesis, as iodine is an integral component of both T3 and T4. However, in addition to iodine deficiency, any cause of maternal hypothyroidism in early pregnancy can cause fetal brain damage.

The fetus develops a thyroid gland only after 3 weeks, and this thyroid gland can trap iodine and synthesize thyroid hormones only after about 3 months. Till this time, it is the mother who gives thyroid hormones to her fetus through placental diffusion. Even after 3 months, maternal T4 transfer continues to occur[12]. Is the quantity of thyroxine transferred substantial? In order to answer this question, Vulsma et al studied 25 neonates with complete inability to produce thyroid hormones[16]. T4 levels in the cord serum of affected neonates ranged from 35 to 70 nmol per liter. The authors concluded that this level purely accrued from maternal thyroxine (T4) transfer, and that this indicated substantial maternal-fetal thyroxine transfer during the first trimester. What could these thyroid hormones do in this period? In animal studies, thyroid hormones regulate neuronal proliferation, migration of neurons, synapse formation and myelination[17-19]. It has been hypothesized that T4 gets converted to tri-iodothyronine (T3) in the cerebral cortex, which binds to specific nuclear receptor isoforms to serve these functions. Hypothyroidism as a result low maternal T4 may be overt, or can even present with very subtle neurological defects, like learning disabilities or a low intelligence quotient.[17-19]

Overall data seems to suggest that maternal hypothyroidism is of crucial significance during both early and late phases of pregnancy. Thus, maternal hypothyroidism is a common and serious problem, which needs early diagnosis and therapy. The issue of universal screening during pregnancy for this common, serious and easily treatable disease definitely merits consideration, but is a hotly debated controversy.

Diagnosing Maternal Hypothyroidism

It is difficult to make a diagnosis of hypothyroidism based on symptoms and signs alone. Even when there are subtle symptoms, like weight gain and constipation, they may be attributed to pregnancy itself. Thus the diagnosis is made by serum TSH estimation. Ideally, trimester-specific normative TSH data is essential, though not available. There is an urgent need for developing normative trimester specific TSH levels from longitudinal studies[20]. A TSH value that is more than the upper limit of normal (i.e. > 4mU/L) should alert the clinician to the diagnosis. Recent studies have suggested that free T4 must also be simultaneously tested during screening[21]. This is because a low free T4, even with a normal TSH, is now considered abnormal (especially in iodine deficient zones), and this deserves therapy Thus the focus seems to be shifting towards maternal hypothyroxinemia rather than hypothyroidism[21].

Wherever free T4 testing is not available or cannot be relied upon, the total T4 may be used: normal levels of total T4 in pregnancy may be decided by multiplying non-pregnant levels by a factor of 1.5 for pregnant women[5]. Antithyroid antibody testing is not mandatory, but may serve two purposes: firstly, it identifies underlying autoimmunity and secondly, high antibody titers are associated with pregnancy losses[22].

Treatment

The drug of choice is levothyroxine (LT4). In subjects with florid, overt hypothyroidism, the dose required is 2 μg/kg/day[5]. The increased dose is important to cover for higher thyroxine demand during pregnancy. In

subjects with subclinical hypothyroidism / in subjects with a slightly high TSH (4-10 mU / L), the dose of LT4 is 100 µg / day.

Considerations are slightly different in subjects with pre-gestational hypothyroidism i.e. in subjects who have become pregnant while already taking LT4 for hypothyroidism. These subjects require a 25-47% increase in dosage. Indeed, it has been recommended that when a hypothyroid woman taking LT4 becomes pregnant, the dose should be increased by about 25-50 µg as soon as pregnancy is diagnosed[23]. Usually, the dosage required is stable and plateaus beyond the 20th week; after this time, very frequent monitoring is not needed[23,24]. Women taking iron or calcium tablets should not take them with LT4. These tablets may be taken about 4 hours after taking LT4. Iodine intake is important in pregnancy, an important consideration in iodine-deficient zones[25].

Follow-up and Targets of Therapy

During the first half of pregnancy, it is best to do monitoring with free T4 and TSH every 3-4 weeks. But later on, the monitoring may be done every 6 weeks. The target TSH level in pregnancy is <2.5 mU / L[5]. In subclinical hypothyroidism, the dose may be increased by about 50 µg at a time. However, in cases where the TSH is still very high (>10 mU / L), the dosage may need to be increased by 75 to100 µg[5]. Soon after delivery, the dose must be reduced to the pre-pregnancy dosage, and then thyroid functions checked after 6 weeks.

Controversy: Levothyroxine in Euthyroid Antibody-Positive Subjects

Thyroid autoimmunity is a risk factor for pregnancy loss[26]. Three explanations have been proposed: firstly, antithyroid antibodies may only be a marker of generalized autoimmunity, which could explain the high occurrence of miscarriages[22]. Secondly anti-TPO (anti-thyroid peroxidase) antibodies, a marker of autoimmune thyroid disease (AITD) could pick out groups of subjects with subtle damage to the thyroid gland. These subjects might be at risk of developing hypothyroidism because the thyroid gland that is damaged via autoimmune mechanisms is unable to adjust to the physiological loads that are imposed on it during pregnancy[22]. The third hypotheses questions the role of these antibodies, suggesting that both anti-TPO positivity as well as miscarriages are common in older women: Thus this hypothesis suggests that the link between thyroid autoimmunity and pregnancy loss is a statistical aberration that is borne out of the confounding effect of age[22]. None of these hypotheses have been proved or disproved, despite several studies on the issue.

A recent study attempted to answer this fascinating question[27]. In a prospective study of euthyroid pregnant women, subjects with anti-TPO positivity were either treated with LT4 (n = 57) or not treated (n = 58). The authors reported that LT4 therapy in euthyroid TPO+ve pregnancies could improve miscarriage rate by 75% and premature deliveries by 69%[27]. Antibody positive subjects had a higher TSH at baseline (though within the euthyroid range) as compared with antibody negative group. The results of this study suggest that subjects with the autoimmune thyroid disease may have a subtle deficiency of thyroid hormones due to impaired adaptability, and also implies that the judicious use of levothyroxine, at least in subjects with a high-normal TSH, could improve outcomes. More studies are needed before these findings can change clinical practice.

REFERENCES

1. Leung A, Millar L, Koonings P, Montoro M, Mestman J. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993; 81:349-53.
2. Davis L, Leveno K, Cunningham F. Hypothyroidism complicating pregnancy. Obstet Gynecol 1988;72:108-12.
3. Blazer S, Moreh-Waterman Y, Miller-Lotan R, Tamir A, Hochberg Ze. Maternal Hypothyroidism May Affect Fetal Growth and Neonatal Thyroid Function. Obstet Gynecol 2003;102:232-41.
4. Morreale de Escobar G, Obregon M, Escobar del Rey F. Role of thyroid hormone during early brain development. Eur J Endocrinol 2004;151:U25-37.
5. LeBeau S, Mandel S. Thyroid disorders during pregnancy. Endocrinol Metab Clin North Am 2006;35:117-36,vii.
6. Dunn JT, Delange F. Damaged Reproduction: The Most Important Consequence of Iodine Deficiency. J Clin Endocrinol Metab 2001;86:2360-3.
7. Berghout A, Wiersinga W. Thyroid size and thyroid function during pregnancy: An analysis. Eur J Endocrinol 1998;138:536-542.
8. Ballabio M, Poshychinda M, Ekins R. Pregnancy-induced changes in thyroid function: Role of human chorionic gonadotropin as putative regulator of maternal thyroid. J Clin Endocrinol Metab 1991;73:824-31.
9. Fantz CR, Dagogo-Jack S, Ladenson JH, Gronowski AM. Thyroid Function during Pregnancy. Clin Chem 1999;45:2250-8.
10. Iijima T, Tada H, Hidaka Y, Mitsuda N, Murata Y, Amino N. Effects of autoantibodies on the course of pregnancy and fetal growth. Obstet Gynecol 1997;90:364-9.
11. Klein R, Haddow J, Faix J, et al. Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 1991;35:41-6.
12. Utiger RD. Maternal Hypothyroidism and Fetal Development. N Engl J Med 1999;341:601-2.

13. Casey BM, Dashe JS, Wells CE, et al. Subclinical Hypothyroidism and Pregnancy Outcomes. Obstet Gynecol 2005;105:239-45.
14. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Hum Reprod Update 2003;9:149-61.
15. Cao X-Y, Jiang X-M, Dou Z-H, et al. Timing of Vulnerability of the Brain to Iodine Deficiency in Endemic Cretinism. N Engl J Med 1994;331:1739-44.
16. Vulsma T, Gons M, de Vijlder J. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med 1989;321:13-6.
17. Auso E, Lavado-Autric R, Cuevas E, del Rey FE, Morreale de Escobar G, Berbel P. A Moderate and Transient Deficiency of Maternal Thyroid Function at the Beginning of Fetal Neocorticogenesis Alters Neuronal Migration. Endocrinology 2004;145:4037-47.
18. de Escobar G, Obregon M, del Rey F. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pract Res Clin Endocrinol Metab 2004;18:225-48.
19. Kester MHA, Martinez de Mena R, Jesus Obregon M, et al. Iodothyronine Levels in the Human Developing Brain: Major Regulatory Roles of Iodothyronine Deiodinases in Different Areas. J Clin Endocrinol Metab 2004;89:3117-3128.
20. Mandel S, Spencer C, Hollowell J. Are detection and treatment of thyroid insufficiency in pregnancy feasible? Thyroid 2005;15:44-53.
21. Morreale de Escobar G, Jesus Obregon M, Escobar del Rey F. Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia? J Clin Endocrinol Metab 2000;85:3975-87.
22. Glinoer D. Miscarriage in Women with Positive Anti-TPO Antibodies: Is Thyroxine the Answer? J Clin Endocrinol Metab 2006;91:2500-02.
23. Toft A. Increased Levothyroxine Requirements in Pregnancy—Why, When, and How Much? N Engl J Med 2004;351:292-4.
24. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and Magnitude of Increases in Levothyroxine Requirements during Pregnancy in Women with Hypothyroidism. N Engl J Med 2004;351:241-9.
25. Delange F. Iodine deficiency as a cause of brain damage. Postgrad Med J 2001; 77:217-20.
26. Negro R, Mangieri T, Coppola L, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: A prospective study. Hum. Reprod 2005;20:1529-33.
27. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications. J Clin Endocrinol Metab 2006;91:2587-91.