CHAPTER

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Burden of Thyroid Diseases in India. Need for Aggressive Diagnosis

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Introduction

The burden of thyroid disease in the general population is enormous. Thyroid disorders are the most common among all the endocrine diseases in India.[1] In studies from western literature as many as 50% of people in the community have microscopic nodules, 3.5% have occult papillary carcinoma, 15% have palpable goitres, 10% demonstrate an abnormal thyroid-stimulating hormone level, and 5% of women have overt hypothyroidism or hyperthyroidism.[2] Despite the coverage of National iodine deficiency diseases control programme (NIDDCP) in India, iodine deficiency is still prevalent in many parts of India.[3] In this update article, an attempt is made to describe the epidemiology of thyroid diseases in India from the limited available data and recommendations are made for thyroid disease screening.

Spectrum of thyroid diseases in the community

The burden of thyroid diseases in the community is formed by both the benign and the malignant diseases. In general, the diseases of the thyroid can be classified as given in Table 1.

A major burden of thyroid diseases in the community comprises of iodine deficiency diseases, congenital hypothyroidism, nodular goitres (toxic, non toxic), Graves' thyotoxicosis, and Hashimoto's thyroiditis with hypothyroidism, thyroid malignancies and thyroid diseases associated with pregnancy.

Table I : Classification of thyroid diseases

I. Diseases associated with thyrotoxicosis

1. Graves' disease
2. Toxic nodular goitre a) Toxic adenoma b) Toxic multinodular goitre
3. Thyroiditis
4. TSH secreting pituitary tumors
5. hCG induced hyperthyroidism e.g. gestational, trophoblastic disease associated
6. Iodine induced hyperthyroidism e.g. iodine, Amiadarone
7. Thyrotoxicosis factita

II. Diseases associated with hypothyroidism

1. Goitrous hypothyroidism e.g. Hashimoto's thyroiditis, iodine deficiency, lithium
2. Congenital hypothyroidism
3. Atrophic hypothyroidism: e.g. Hashimoto's thyroiditis, post ablative
4. Central hypothyroidism

III. Euthyroid

1. Diffuse nontoxic (simple) goitre
2. Nodular thyroid disease e.g. solitary nodule, multinodular
3. Thyroid neoplasia: e.g. follicular adenoma, thyroid malignancy

Table 2 : Spectrum of Iodine Deficiency Diseases

Fetus	Abortions, Still births, Congenital anomalies, Neurologic cretinism, Myxedematous cretinism Psychomotor defects
Neonate	Increased perinatal mortality, Neonatal hypothyroidism, Retarded mental and physical development
Child and Adolescent	Increased infant mortality, Retarded mental and physical development
Adult	Goitre and its complications, Iodine induced hyperthyroidism
All Ages	Goitre, Hypothyroidism, Impaired mental function, Increased susceptibility to nuclear radiation

Congenital hypothyroidism

Congenital hypothyroidism (CH) is the commonest metabolic disorder in the newborn and is one of the major causes of preventable mental retardation. Maldevelopment (aplasia, hypoplasia) and maldescent (ectopia) commonly grouped together as thyroid dysgenesis are the usual causes of primary congenital hypothyroidism.[4] Worldwide, neonatal screening program for CH have significantly reduced the intellectual deficits in the hypothyroid children treated early. Newborn screening and thyroid therapy started within 2 weeks of age can normalize cognitive development.[5] Growth rate and adult height are normal in children with CH in whom thyroxine therapy is consistently maintained. There are only minor differences in intelligence, school achievement, and neuropsychological tests in adults with CH that was treated early with thyroxine compared with control groups of classmates and siblings.[5]

The worldwide incidence is 1:4000.[4,5] The exact incidence of congenital hypothyroidism in India is unknown. Studies by Desai et al based on a neonatal screening program in Mumbai places the incidence at 1: 2500 –1: 2800.[6] Higher incidence was described from Hyderabad, and preliminary data from Kerala.[7,8] Currently there are no national programs for CH screening. Since only 5-10 % of children detected with a screening program can be diagnosed clinically, instituting a screening program is very essential.[4] Such programs have to be supported with standardized procedures for collection and processing of samples, centralized laboratories, quality control measures and effective methods for recalling patients with abnormal values for retesting and initiating treatment. Although the AAP recommends a heel prick sample after 48 hours of life, umbilical cord sampling is a practical and effective way to diagnose CH and has been recommended by the Indian Academy of Pediatrics (IAP) as an alternative[9,10]

In the absence of a national program, organizations like IAP should bring out guidelines for CH screening and institutions should develop local guidelines for screening all new borns with umbilical or heel prick sampling.

Iodine deficiency diseases

Iodine deficiency diseases (IDD) refers to all the clinical and subclinical effects of iodine deficiency and can be prevented by adequate intake of iodine.[11] The effects of iodine deficiency are related to the adaptations of the thyroid gland to reduction in the iodine in the diet and the neurological and developmental defects related to the reduced thyroid hormone synthesis by the thyroid gland. Iodine deficiency is claimed to be world's single most common cause of preventable brain damage and mental retardation.[12] IDD has a wide spectrum affecting pregnant women, new born, children and adolescents.[12]

IDD is a global health problem despite the efforts by most countries to combat it.[13] In India no state is free from iodine deficiency and 200 million people are affected by it. Following the successful Kangra experiment, the government of India introduced the National Goitre Control Programme in 1962 and National IDD control programme (NIDDCP) in 1998.[3] Under the National Iodine Deficiency Disorders Control Programme in India, iodization of salt is the recommended strategy, with the level of iodization fixed at a minimum of 15 parts per million (ppm) at the consumer level and 30 ppm at the production level. (Salt Dept) Most Indian states have introduced mandatory salt iodization through legislation. The salt department and the state governments are responsible for monitoring the salt iodine content at both the production and consumption levels.[3] This has lead to significant reduction in the prevalence of IDD in India.[16] Revaluation of the iodine status in different parts of the country has reveled that there is still pockets of iodine deficiency. In a study from Bihar, there was a 60% reduction in goitre prevalence from 1979 to 1993-94. The median urinary iodine concentration was found to be 85.6 µg/L. Urinary iodine concentration was less than 50 µg/L in 31.5% of the subjects suggesting iodine insufficiency.[17] Serial studies from Delhi from 1980 to 1996 have shown a reduction in goitre prevalence but as many as 59.9% of children surveyed in 1996 had UIE less than 10 µg/dl.[18,19] Even in 1997, 119 cases of neurological cretinism were reported from Sikkim proving that IDD is still a major public health problem in the Himalayan belt.[20]

Thus, despite the gains achieved by the national program of salt iodisation, pockets of iodine deficiency exist in India. Measures should be taken to identify these areas and increase the penetration of iodized salt.

Hypothyroidism and Hyperthyroidism

There is limited data on the prevalence of hypothyroidism and hyperthyroidism in India. Most of the studies from India have concentrated on the effectiveness of the iodisation program and have looked at the prevalence of residual thyroid disease in school children and adolescents.[21,22,23] A study of 6283 healthy schoolgirls from various parts of the country showed that 28% of the girls had goitre. FNAC carried out successfully in 764 goitrous girls revealed juvenile autoimmune thyroiditis (JAT) in 58 (7.5%), which included Hashimoto's thyroiditis in 43 (5.6%) and focal lymphocytic thyroiditis in 15 (1.9%). In subjects with FNAC-proven JAT, overt clinical and biochemical hypothyroidism was seen in 3 (6.5%) and subclinical hypothyroidism in 7 (15%). Subclinical hyperthyroidism was detected in 5.1% cases of JAT, and none had overt hyperthyroidism.[21]

Another study looked at familial clustering of autoimmune thyroiditis among first degree relatives of patients diagnosed as juvenile autoimmune thyroid disease and among those diagnosed as colloid goitre. This study found a high prevalence of autoimmune thyroid disease (Anti TPO +, FNAC proven autoimmunity) among first-degree relatives of patients with lymphocytic thyroiditis (78%). Of the 222 first-degree relatives studied, 8 new cases of overt hypothyroidism and 45 new cases of subclinical hypothyroidism were diagnosed. The study recommended screening of all first-degree relatives of patients with autoimmune thyroiditis with TSH measurements.[22]

A hospital-based study from Mumbai in 800 children referred for thyroid problems showed that 79% had hypothyroidism (goitrous as well as nongoitrous), 19% had euthyroid goitres and 2% had hyperthyroidism. The authors have highlighted the high prevalence of dyshormonogenesis and congenital hypothyroidism in the patients screened.[8] The low degree of awareness of thyroid disease leading on to severe manifestations has resulted in reports of rare presentations like multicystic ovaries in girls with hypothyroidism.[24,25]

Patients with Graves' disease can occasionally have thyroid nodules. In regions of iodine deficiency, thyroid nodules are more likely. The etiology of thyroid nodules in Graves' thyrotoxicosis managed by surgery was described in a series from Lucknow. Thirty-five (26.9%) of patients with Graves' disease managed surgically had thyroid nodules. The incidence of thyroid carcinoma, in cases having nodule with Graves' disease was 17.1%. (6/35 cases) The authors concluded that the incidence of thyroid nodules in Graves' disease is similar to iodine sufficient region and recommended early thyroidectomy in these cases.[26]

In hyperthyroidism, patients with toxic multinodular goitre and Graves' disease have an option of surgical management for permanent remission. Considering the high cost and limited availability of radioactive iodine, thyroidectomies are common in India. A retrospective study of 325 cases of hyperthyroidism managed by surgery showed that the predominant etiology was Graves' disease (185) followed by toxic MNG (105), and autonomously functioning thyroid nodules (AFTN) (n = 35). The complications included temporary hypocalcemia (24%), permanent hypocalcemia (3%), and permanent vocal-cord palsy (1%). Cost effectiveness of thyroid surgery with low complication rates should encourage this modality of treatment in Indian population.[27]

Thus data from India shows a high prevalence of hypothyroidism and autoimmune thyroiditis in first-degree relatives of patients with JAT. Evaluating the cost effectiveness of surgical management in patients with Graves' thyrotoxicosis is needed before it can be recommended.

Thyroid nodules

Thyroid nodules may be benign (simple nontoxic or multinodular goitre, follicular adenomas and cysts) or malignant (papillary carcinoma, follicular carcinomas and medullary carcinoma). They are more common in females and prevalence mainly depends on age, sex, iodine intake, diet (goitrogens), therapeutic and environmental radiation exposure. Although the vast majority are benign lesions, about 5% may actually represent thyroid cancer.[28] Palpation of the thyroid gland during routine physical examination is the easiest and least expensive method for detection, albeit the least sensitive. Findings from palpation alone suggest that the prevalence of thyroid nodules in the general population ranges from 4% to 7% in the United States. In the Framingham Study, 6.4% of women and 1.5% of men had palpable thyroid nodules.[29] Using a 7.5-MHz transducer, a non-biased population-based study in Hyvinkaa, Finland, detected nodules in 27% of women and 15% of men.[30] Autopsy studies have shown that 50 % of consequent autopsies had thyroid nodules.[31]

Evaluation of a thyroid nodule includes a good clinical history focusing on symptoms of hypothyroidism and thyrotoxicosis, symptoms suggestive of obstruction including hoarseness of voice and family history of malignant or benign thyroid disease. Palpation of the thyroid to determine the size of the nodule, cervical lymphandenopathy and its relation to trachea and retrosternal extension is important in diagnosis. Laboratory testing will include T4, TSH, thyroid antibodies, fine needle cytology and imaging.

There are limited studies from India on the epidemiology of thyroid nodules. In a study involving 14,762 schoolchildren (56.0% girls and 44.0% boys), aged 6-18 years, with a countrywide representation, the overall prevalence of goitre was 23.0% with a higher frequency in girls. FNB was successful in 75.6% of subjects without any significant complications. The cytologic diagnoses in 1,312 successful cases were colloid goitre (92.8%), Hashimoto's thyroiditis (4.6%), focal lymphocytic thyroiditis (1.7%) and hyperplastic goitre (0.9%). The authors concluded that there is possibility of significant role of environmental goitrogens in the causation of goitre in the postiodisation period.[23]

Majority of the thyroid nodules in the post iodisation phase are thyroid nodules. Because of the high prevalence of thyroid nodules even in non-endemic areas, clinical examination should remain the first tool in evaluation with rational use of imaging and FNAC.

Thyroid malignancies

Thyroid tumors are the most common endocrine neoplasms. 5-10% of all thyroid nodules coming to medical attention are carcinomas. The diagnosis can be established by a thorough medical history, clinical examination, imaging and FNAC of the nodule. In areas of iodine sufficiency, papillary carcinomas are the predominant variety. Different studies from India show a predominance of papillary malignancy followed by follicular malignancies. The overall prognosis for thyroid carcinoma is worse in endemic goitre regions, in comparison with regions with an adequate dietary iodine intake, perhaps because of the higher incidence of un-differentiated thyroid malignancies in iodine deficiency areas.[32] Even in regions with endemic goitres (and iodine deficiency), papillary neoplasms predominate over follicular cancers.[33,34] Two large series of medullar carcinomas of the thyroid was reported from India.[35,36] Male predominance was reported in MTC in contrast to differentiated thyroid malignancies.[35]

A study by Bal et al addressed the prevalence of thyroid malignancies in children. 85% of the 122 patients had papillary carcinoma of thyroid. The disease was found to be more aggressive and widespread in younger age groups (< or =10 years), with male preponderance and high mortality. Cervical lymph node involvement was seen in 66% of patients, and distant metastasis, mainly pulmonary, in 29%. In children less than 10 years of age, 75% of patients had distant metastasis at the time of presentation.[37] Although the distribution of malignancy according to the types is similar to world literature, the incidence of distant metastasis is significantly more that that reported from iodine sufficient areas of the world.[38] Whether these differences is due to iodine deficiency per se or is contributed by a referral bias and late presentation in India is not clear. Epidemiological studies of cancer in India show an increased incidence of thyroid cancers in females in southwest coastal districts and also in Kerala.[39,40]

Studies from India show that thyroid malignancy presents at an advanced stage compared to western literature. Proactively profiling the cytology of thyroid nodules at first detection will lead to detection of thyroid malignancies at an earlier stage.

Thyroid diseases in pregnancy

Thyroid disorders are the second most common endocrinopathies found in pregnancy.[41] In regions endemic for IDD, the fetus and pregnant mothers are exposed to the deleterious consequences of iodine deficiency. Hyperthyroidism affects 1-4 in 1000 pregnancies. Graves' disease accounts for 90-95% of these cases. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3– 0.5% for overt hypothyroidism and 2–3% for subclinical hypothyroidism. Thyroid autoantibodies are found in 5–15% of women in the childbearing age and are a risk factor for hypothyroidism during pregnancy and post partum period. Hashimoto thyroiditis is the most common cause. Atrophic thyroiditis is less common. Postpartum thyroiditis (PPT) affects 1 in 20 women in the postpartum period.[41] Since hypothyroidism and hyperthyroidism are common endocrine disorders in women, the burden of undetected thyroid diseases in the antenatal mother is significant.

Uncontrolled hyperthyroidism in pregnancy can lead to various maternal complications include miscarriage, infection, preeclampsia, preterm delivery, congestive heart failure, thyroid storm, and placental abruption. Fetal and neonatal complications include prematurity, small for gestational age babies, intrauterine fetal death, toxemia, and fetal or neonatal thyrotoxicosis.[42] Maternal complications of untreated hypothyroidism include anemia, preeclampsia, placental abruption, postpartum hemorrhage, cardiac dysfunction, and miscarriage. Fetal or neonatal complications include prematurity, low birth weight, congenital anomalies, stillbirths, and poor neuropsychological development. 30 % of patients with PPT can progress to permanent hypothyroidism. PPT can present as postpartum depression and there is a high risk for recurrence in the subsequent pregnancies.[42]

Dietary iodine deficiency occurring during pregnancy (even when considered mild or moderate) leads to maternal hypothyroxinemia enhanced thyroidal stimulation via the pituitary (TSH) feedback mechanisms, and ultimately goitre formation in mother and fetus.[41] When such women are given iodine supplements started early during gestation, goitre formation can be prevented. Women in the childbearing age should have an average iodine intake of 150 mcg/d. During pregnancy and breastfeeding, women should increase their daily iodine intake to 250 mcg on average.[41]

There are limited studies from India on thyroid diseases in pregnancy. In a hospital based cross sectional study from West Bengal focusing on iodine sufficiency status in pregnant women, 78.3 per cent had urine iodide excretion (UIE) > 10 mg/dl and was similar to the control population.[43] Other studies from India quote a higher degree of iodine insufficiency in pregnant women from Himachal Pradesh and Uttaranchal.[44,45] A study from Mumbai highlighted on the optimization of thyroid management in pregnancy and the improved neonatal outcomes associated with it.[46] Another hospital-based study highlighted the increased incidence of maternal and perinatal complications associated with hypothyroidism in pregnancy recommending universal screening.[47]

In the absence of any convincing evidence for or against routine screening of thyroid diseases in pregnancy, the Endocrine Society Clinical Practice guidelines recommend case finding among the following groups of women at high risk for thyroid dysfunction.[41]

- Women with a history of hyperthyroid or hypothyroid disease, PPT, or thyroid lobectomy
- Women with a family history of thyroid disease
- Women with a goitre
- Women with thyroid antibodies (when known).
- Women with symptoms or clinical signs suggestive of thyroid underfunction or over function, including anemia, elevated cholesterol, and hyponatremia
- Women with type I diabetes
- Women with other autoimmune disorders
- Women with infertility should have screening with TSH as part of their infertility work-up.
- Women with prior therapeutic head or neck irradiation.
- Women with a prior history of miscarriage or preterm delivery

Conclusion

In summary, there is a high burden of thyroid diseases in India. There is a paucity of data on the epidemiology of thyroid diseases. Due to lack of resources, screening for thyroid diseases in the general population is not cost effective. However, ensuring adequate iodine nutrition of pregnant women and children and screening for congenital hypothyroidism are interventions that require a priority in the Indian population.

- Iodine nutrition should be ensured in all women of reproductive age group especially in areas identified to be endemic for IDD
- Aggressive case finding in pregnant women at risk for thyroid disease
- Targeted screening for thyroid diseases in high risk population in all age groups
- Investigating thyroid nodules with FNAC to identify malignancy. In view of the low incidence of thyroid cancers, community screening for thyroid cancer is not warranted.
- Congenital hypothyroidism screening for all new borns and establishment of a national screening programme
- Family screening for first degree relatives in all patients with juvenile autoimmune thyroiditis

The above suggestions are based on evidence from Indian and Western literature and clinical guidelines of various organizations. Implementing these measures would go a long way in improving the thyroid health of our population.

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