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PREVALENCE OF HYPOTHYROIDISM AMONGST PREGNANT WOMEN

Gynecology

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ABSTRACT

BACKGROUND: Thyroid disorders are the commomest endocrine disorders in women of reproductive age group.The most common thyroid disorder in pregnancy is hypothyroidism.During early pregnancy foetus is totally dependant on maternal thyroid hormone supply.Thyroid hormone is critical for intellectual development of foetus.

MATERIALS AND METHODS: History of all pregnant women in study was taken.Clinical examination of all pregnant women in study was done.Serum TSH(Thyroid Stimulating Hormone) level of all women was measured in first trimester between 6-10 weeks of gestation.

RESULTS: Prevalence of hypothyroidism was 9.2 %.Prebalence of subclinical hypothyroidism was 8.5 % and that of overt hypothyroidism was 0.7 %.Risk factors are advanced maternal age and increased BMI(Body Mass Index).

CONCLUSIONS: Prevalence of hypothyroidism is increased in pregnancy.So screening of hypothyroidsn is required in first trimester in all pregnant women.

KEYWORDS

Hypothyroidism,Prevalence,Screening

INTRODUCTION

Hypothyroidism has adverse effects on pregnant woman and her foetus.Prevalence of hypothyroidism in pregnancy is around 2.5 %. Hypithyroidism in pregnancy causes postpartum haemorrhage, preeclampsia, premature birth,low birth weight, abruptio placentae, anaemia, neonatal respiratory distress, mental retardation, miscarriage, etc. Hypothyroidism in pregnancy is treated by levothyroxine. Thyroid dysfunction in pregnancy is caused by human chorionic gonadotropin and estrogen.Thyroid dysfunction in pregnancy is often overlooked by nonspecific symptoms and hypermetabolic state of pregnancy.Serum TSH is the initial and most reliable test for assessing thyroid dysfunction during pregnancy.Use of trimester specific normal values of serum TSH is recommended due to dynemic changes during pregnancy.Normal upper limit of serum TSH during first trimester is 2.5 mIU/L.Concentration and half life of TBG are increased during pregnancy due to estrogen.So values of total T4 and T3 hormones are increased during pregnancy but values of free or unbound T4 and T3 remain largely unchanged.Overt hypothyroidism is characterised by increase in serum TSH above 10 mIU/L and decrease in thyroxine.Subclinical hypothyroidism is defined as serum TSH level of 4-10 mIU/L.Levels of T3 and T4 are not changed in subclinical hypothyroidism.

Current guidelines for screening of thyroid dysfunction during pregnancy differ between agressive case finding approach versus universal screening.Due to uncertainity of universal iodine sufficiency and higher incidence of thyroid antibody positivity in India,Indian Thyroid Society recommends universal screening approach.

North Indian women have highest prevalence of hypothyroidism during pregnancy.Majority of women in study had anti thyroid peroxidase antibody suggesting autoimmune aetiology.Incidence of thyroid dysfunction increases with advancing age.Hypothyroidism is associated with positive family history for autoimmune diseases such as autoimmune thyroiditis.BMI is positively related to serum TSH and negatively related to serum free T4 level in women with overt hypothyroidism.

With the proposed study we intend to emphasize the need for universal screening for hypothyroidism during pregnancy.

MATERIALS AND METHODS

This study was conducted in LG Hospital of Ahmedabad.Consents of all subjects were taken.

INCLUSION CRITERIA

- Primi and multigravida belonging to any age group
- Singleton pregnancy
- Pregnant women in first trimester

EXCLUSION CRITERIA

- Women with pregestational hypothyroidism
- Women with gestational trophoblastic disease
- Women with multiple pregnancy

Normal value of serum TSH in first trimester is 0.1-2.5 mIU/L.All women with level more than upper limit were subjected to measurement if free T4 level to classify as overt or subclinical hypothyroidism.

STATISTICAL ANALYSIS

Prevalence was calculated using descriptive method.Outcome variables of age and BMI were compared according to thyroid status using t test and TSH and free T4 were analysed using chi square test.p value of less than 0.05 was considered statistically significant.

RESULTS

Total number of subjects was 1000.

TABLE-1 Distribution Of Study Population According To Thyroid Status

Thyroid status	Number	Percentage
Euthyroid	892	89.2
Thyroid dysfunction	108	10.8

TABLE-2 Distribution Of Study Population According To Sybtypes If Thyroid Dysfunction

Subtype of thyroid dysfunction	Number	Percentage
Euthyroid	892	89.2
Overt Hypothyroid	7	0.7
Subclinical Hypothyroid	85	8.5
Subclinical hyperthyroid	16	1.6
Overt hyperthyroid	0	0

TABLE-3 AGE WISE DISTRIBUTION OF SCREENED POPULATION

Age	Euthyroid	Thyroid dysfunction
<20	60	12
20-25	345	29

25-30	327	41
30-35	123	14
>35	37	12

TABLE-4 DISTRIBUTION OF THYROID DYSFUNCTION ACCORDING TO BMI

BMI	EUTHYROID	THYROID DYSFUNCTION
<18.5	28	5
18.5-25	677	70
25-30	156	29
>30	31	4

DISCUSSION

Taken in aggregate,thyroid disorders are common in young women so they are frequently managed during pregnancy.There is an intimate relation between maternal and fetal thyroid function,and drugs that affect maternal thyroid gland also affect fetal gland.

THYYROID PHYSIOLOGY AND PREGNANCY-

Maternal thyroid changes are substantial,and normally altered gland structure and function arr sometimes confused with thyroid abnormalities.First,maternal serum concentrations of thyroid binding globulin are increased concomitantly with total or bound thyroid hormone levels.Second,thyrotropin,also known as thyroid stimulating hormone(TSH),currently plays central role in screening and diagnosis of thyroid disorders in pregnancy.Human chorionic gonadotropin (hCG) secreted by placental trophoblast causes decrease in serum TSH due to weak TSH receptor stimulation in early pregnancy.TSH does not have direct effect on fetus because TSH cannot cross placenta.During the first 12 weeks of gestation,when serum hCG levels are maximal,thyroid hormone secretion is stimilated.Increased level of serum free T4 causes inhibition of secretion of thyrotropin releasing hormone (TRH) from hypothalamus.This causes inhibition of TSH secretion from pituitary gland.Accordingly,TRH is undetectable in maternal serum.Conversely,beginning at midpregnancy, TRH becomes detectable in fetal serum,but levels are static and do not increase with advancing geatation.Throughout pregnancy,maternal thyroxine is transferred to fetus.Maternal thyroxine is required for development of fetal brain especially before development of fetal thyroid gland function.Maternal contribution of thyroid hormone to fetus continues even after development of fetal thyroid gland at 12 week of gestation.Maternal sources contribute 30 % thyroxine to fetus at full term.

HYPOTHYROIDISM-

Overt or symptomatic hypothyroidism has been reported to complicate between 2 and 10 pregnancies per 1000.It is characterised by insidious nonspecific clinical findings like fatigue,cold intolerance,weight gain,muscle cramps,constipation,etc.Pathologic enlargement of thyroid gland is seen in women of area with endemic iodine deficiency and in cases of Hashimoto's thyroiditis.Other findings include edema,hair loss,prolonged relaxation phase of deep tendon reflexes,dry skin,etc.Cases of subclinical hypothyroidism include asymptomstic individuals with measurable antithyroid peroxidase or antithyroglobulin antibodies.Euthyroid autoimmune thyroid disease represents a new investigative frontier in screening and treatment of thyroid dysfunction during pregnancy.

OVERT HYPOTHYROIDISM AND PREGNANCY-

Most common cause of hypothyroidism in pregnancy is Hashimoto's thyroiditis.It is characterised by destruction of thyroid gland by autoantibodies especially anti thyroid peroxidase antibodies.Clinical identification of hypothyroidism is difficult in pregnancy because signs and symptoms are nonspecific.Thyroid analyte testing should be done in women with symptoms and women with history of thyroid disease.Severe hypothyroidism is uncommon during pregnancy because it is associated with infertility and spontaneous abortion.Even women with treated hypothyroidism undergoing in vitro fertilisation have a significantly decreased chance of achieving pregnancy.

TREATMENT-Hypothyroidism is treated by replacement therapy.It is treated by levothyroxine.Dose is 1-2 microgram/kg/day or approximately 100 microgram daily.Women who are athyreotic after thyroidectomy or radioiodine therapy may require higher doses.Surveillance is with TSH levels measured at 4 to 6 week intervals,and the thyroxine doses are adjusted by 25 to 50 microgram increments until TSH values become normal.Pregnancy is associated with an increased thyroxine requirement in approximately a third of supplemented women.Because a similar increased requirement of thyroxine is seen in postmenopausal hypothyroidism after estrogen replacement,the increased demand in pregnancy is believed to be related to increased estrogen production.

Increased thyroxine requirements begin as early as 5 weeks.Increase in T4 causes suppression of TSH in more than a third of women.

Pregnancy Outcome With Overt Hypothyroidism-

Hypothyroidism is associated with following complications:

- Preeclampsia
- Placental abruption
- Low birth weight(< 2 kg)
- Stillbirth
- Cardiac dysfunction,etc.

FETAL AND NEONATAL EFFECTS-

There is no doubt that maternal and fetal abnormalities are related.In both,thyroid function is dependent on adequate iodine intake and its deficiency early in pregnancy can cause maternal and fetal hypothyroidism.Maternal TSH receptor blocking antibodies can cross placenta and cause fetal thyroid dysfunction.

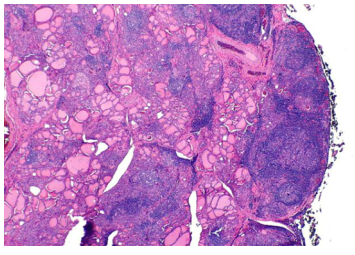
SUBCLINICAL HYPOTHYROIDISM-

This thyroid condition is common in women,but its incidence can be variable depending on age,race,dietary intake of iodine and serum TSH thresholds used to establish diagnosis.Progression of subclinical hypothyroidism to overt hypothyroidism is affected by TSH level,age,other disorders such as diabetes and presence and concentration of antithyroid antibodies.

HASHIMOTO's THYROIDITIS-

It is the most common cause of hypothyroidism in pregnancy.It is autoimmune disorder. It is also known as Hashimoto's disease, chronic lymphocytic thyroiditis, autoimmune thyroiditis and struma lymphomatosa.

FIGURE-1 Microscopic Appearance Of Thyroid Gland In Hashimoto's Thyroiditis



There is gradual destruction of thyroid gland in this disease.Early on there may be no symptoms.Over time the thyroid may enlarge forming a painless goiter.Potential complications include thyroid lymphoma.

It is caused by genetic and environmental factors.Risk factors include family history and presence of another autoimmune disease.Diagnosis is confirmed by blood tests for T4,TSH and antithyroid antibodies.It was first described by Japanese physician Hakaru Hashimoto in 1912.In 1957 it was recognised as autoimmune disease.

Symptoms of Hashimoto's thyroiditis are fatigue,weight gain,pale or puffy face,feeling cold,joint and muscle pain,constipation,dry and thin hair,depression,panic disorder,slowed heart rate,etc.This disease is 7 times more common in women than in men.The thyroid gland may become firm,large and lobulated,but changes in thyroid gland can also be nonpalpable.Enlargement of thyroid gland is due to lymphocytic infiltration and fibrosis rather than tissue hypertrophy. Physiologically, antibodies against thyroid peroxidase(TPOAb) and/or thyroglobulin cause gradual destruction of follicles of thyroid gland.Accordingly,the disease can be detected by looking for these antibodies in blood.It is also characterised by invasion of thyroid gland by leukocytes, especially T lymphocytes.A rare but serious complication is thyroid lymphoma, generally the B cell type,non Hodgkin's lymphoma.

The strong genetic component is borne out in studies on monozygotic twins,with a concordance of 38-55 %,with an even higher concordance of circulating thyroid antibodies not in relation to clinical presentation(up to 80 % in monozygotic twins).Neither result was seen

to a similar degree in dizygotic twins,offering strong favour for high genetic aetiology.

Hashimoto's thyroiditis is associated with *CTLA-4*(Cytotoxic T Lymphocyte Antigen-4) gene polymorphisms.It downregulates T lymphocytes i.e,decreases functioning of T lymphocytes.So polymorphism of this gene causes increase in activity of T lymphocytes.Family history of thyroid disorder is common,with the *HLA-DR5* gene most commonly implicated conferring a relative risk of 3 in UK.

Having other autoimmune diseases is a risk factor for autoimmune thyroiditis and the opposite is also true.Autoimmune diseases associated to autoimmune thyroiditis are as below:

- Celiac disease
- Diabetes mellitus type 1
- Alopecia
- Vitiligo

Preventable environmental factors,including high iodine intake, selenium deficiency, as well as infectious diseases and certain drugs,have been implicated in development of autoimmune thyroiditis in genetically predisposed individuals.

Autoimmune thyroiditis is characterised by antibodies against following targets:

- Thyroid peroxidase
- Thyroglobulin and
- TSH receptors

Few patients have none of the above autoantibodies.

Some people have these antibodies without developing autoimmune thyroiditis.Nevertheless,antibody dependent cell mediated cytotoxicity is a aubstantial factor behind the apoptotic fall out of autoimmune thyroiditis.Activation of vytotoxic T lymphocytes(CD8+ T lymphocytes) in response to cell mediated immune response affected by helper T lymphocytes(CD4+ T lymphocytes) is central to thyrocyte destruction.As is characteristic of other type 4 hypersensitivities, recruitment of macrophages is another effect of helper T lymphocyte activation,Th1 axis lymphocytes producing inflammatory cytokines within thyroid tissue to further macrophage activation and migration in to the thyroid gland for direct effect.There us enlargement of thyroid gland.Capsule is intact and gland is still distinct from surrounding tissue.Gland is infiltrated by plasma B cells which can often be seen as secondary lymphoid follicles(germinal centers,not to be confused with normally present colloid filled follicles that constitute the thyroid).Severe thyroid atrophy presents often with denser fibrotic bands within the confines of the capsule.

Diagnosis is made by detection of TPOAb in serum.Few cases are seronegative.Autoimmune thyroiditis is often misdiagnosed as depression,anxiety,chronic fatigue syndrome, fibromyalgia, cyclothymia, etc. Goiter of autoimmune thyroiditis is not painful to touch. Periorbital myxoedema is seen. Measurement of serum free T3, free T4, TSH, TPOAb, anti thyroglobulin antibodies and antimicroaomal antibodies help in accurate diagnosis.

Hashimoto's disease presenting as mania is known as Prasad's syndrome,after Ashok Prasad who first described it.

Complications of Hashimoto's disease associated with oregnancy are neonatal hydrocephalus,hyposoadiasis,respiratoery distress and preterm delivery.

LEVOTHYROXINE-

It is manufactured form of thyroid hormone,thyroxine(T4).Its bioavailability is 40-80 %.Its elimination half life is around 7 days.It is excreted in feces and urine.Its side effects are weight loss,anxiety, trouble tolerating heat, fast heart rate, trouble sleeping, tremor, sweating, etc. It is not recommended in women with recent history of heart attack. Its dose should be adjusted according to serum levels of TSH and T4. Much of the effect of levothyroxine is following its conversion to triiodothyronine(T3).It was first made in 1927.It is on the World Health Organisation's list of essential medicines,the most effective and safe medicines needed in health system.

THYROID LYMPHOMA-It is malignant tumour of thyroid gland.It is complication of Hashimoto's disease.It is usually B cell type non Hodgkin's lymphoma.It is characterised by rapidly enlarging painless neck mass,dyspnoea,dysphagia,hoarseness of voice,etc.It is similar to anaplastic thyroid cancer.It is differentiated from anaplastic cancer by fine needle aspiration cytology.Staging of thyroid lymphoma is as below:

TABLE-5 STAGING OF THYROID LYMPHOMA

Stage	Characteristics
1E	Tumour limited to thyroid gland
2E	Tumour in thyroid gland and regional lymph nodes
3E	Tumour on both sides of diaphragm
4E	Disseminated tumour

Factors associated with poor prognosis in thyroid lymphoma are advanced stage,large size(10 cm) and spread to mediastinum.

TABLE-6 Prevalence Of Hypothyroidism In Pregnant Women Of Different States Of India

State	Prevalence
Uttar Pradesh	15.7
Karnataka	7.8
Haryana	19.4
Tamil Nadu	8.7
West Bengal	11.8
Telangana	8.6
Maharashtra	14
Delhi	16.2
Kashmir	39
Andhra Pradesh	8.9
Total	13.1

ANTITHYROID AUTOANTIBODIES-

They are autoantibodies against one or more components of thyroid.They are as below:

1-Anti-TPO antibodies-They are specific for autoantigen called TPO.It is 105 kDa glycoprotein.It catalyses iodine oxidation and thyroglobulin tyrosyl iodination in thyroid gland.Most antibodies are directed against conformational epitopes of immunogenic carboxyl terminal region of TPO protein.Some antibodies are durected against linear epitopes.They are seen in 90 % cases of Hashimoto's thyroiditis.10-15 % normal people can have high titres of these autoantibodies.They are produced by infiltrating lymphocytes with minor contributions from lymph nodes and bone marrow.They damage thyroid by complement activation and antibody dependent cell cytotoxicity.

2-Anti-TSH receptor antibodies-They can be activating,blocking or neutral.Blocking antibodies are associated with thyroiditis.

Other autoantibodies are antithyroglobulin antibodies and anti sodium/iodine symporter antibodies.

CONCLUSION

Thyroid dysfunction is often associated with maternal and fetal complications in pregnancy.1000 women were included in the present study.The level of TSH was measured in first trimester.The prevalence of thyroid dysfunction was 10.8 %.Prevalence of hypothyroidism was 9.2 %.Prevalence of subclinical hypothyroidism was 8.5 % and prevalence of overt hypothyroidism was 0.7 %.Risk of hypothyroidism increases with advanced maternal age and increased BMI. Maternal age above 30 years is considered risk factor for hypothyroidism in pregnancy.There is positive association between BMI and serum TSH.There is negative association between BMI and serum free T4 level.Most cases of hypothyroidism in pregnancy are cases of sunbclinical hypothyroidism.A few cases are cases of overt hypothyroidism.

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