Review Article

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Pregnancy with Subclinical Hypothyroidism: Obstetric and Neonatal Effects

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Abstract

Thyroid disorders are common for the Obstetrician as well as neonatologist and paediatrician in their day to day practice. While there are universal consensus, clear guidelines and treatment protocols for treating overt hypothyroidism with pregnancy, and infancy, subclinical hypothyroidism has remained a cause for concern to the general physician, paediatrician and the Obstetrician equally. Poor obstetric outcomewith subclinical hypothyroidism has been reported (recurrent abortions, low birth weight etc) but the long term neonatal neuro-development outcome does not seem to be altered much. Altered physiological status and different lower cut-off values during pregnancy for treating hypothyroidism has led to increased complexity of this scenario. Though many treatment options are available for non-pregnant women, levothyroxine (LT4) is considered standard of care for the pregnant women and neonates with subclinical hypothyroidism.

In view of all this newer updates there is a need to have a relook at the present scenario and plan the best treatment with evidence based medicine for these pregnant females.

Keywords: Subclinical Hypothyroidism; Pregnancy; Neonatal; Thyroid Dysfunction.

Introduction

Thyroid hormone dysfunctions are the second most commonly encountered endocrinal problem in pregnancy [1]. Altered thyroid function can have significant impact on the obstetric and the neonatal outcome of pregnancy. While hypo-function of the hormone is a common occurrence, hyper-function is also sometimes encountered. This abnormal levels of thyroid hormone, specially hypothyroidism can have significant impact on the pregnancy outcome in the form of abortion, preterm labour, gestational hypertension, GDM, poor APGAR scores at birth, poor neonatal outcome, neurodevelopmental delay, low IQ and many more. While overt hypothyroidism requires treatment with replacement therapy to prevent all these adverse events, subclinical hypothyroidism may not warrant so much concern. Doubt exist over the effects of subclinical hypothyroidism and its adverse obstetric and neonatal outcome, and hence also the need for replacement in pregnancy. Many new studies have come up in recent years which throw light on our understanding of these issues, which will be reviewed here.

Pregnancy and the Physiological Changes

Mild thyroid gland enlargement is commonly seen during pregnancy- this enlargement is usually diffuse and mild, though sometimes may be moderate. Both hyperplasia and hypertrophy play a role in this change and is also contributed by increased vascularity. This enlargement takes care of increased demands of foetus and mother during pregnancy. While mild thyromegaly is considered physiological, gross enlargement should warrantneed for further investigation.

Thyroid function test are altered in pregnancy owing to numerous other changes which occur in

blood and transport mechanisms; so thyroid function tests must be interpreted with caution. Increased oestrogen of pregnancy leads to increase in Thyroid binding globulin (TBG) synthesis in liver along with many other transport proteins, and decreased hepatic clearance [2]. TBG has more affinity for T4 than T3; more of binding leads to less of free T4 in circulation causing more secretion of TSH from pituitary. Also the alpha subunit of hCG which is similar to alpha subunit of TSH stimulate the thyroid epithelial cells for release of T3 & T4; and consequently decrease in TSH. This new equilibrium between increased TBG &T4, leads to increase in total T4 levels but the free T4 generally remains the same or may be slightly lowered; and TSH values also decrease in pregnancy.

Production and supply of Thyroid hormones from the thyroid gland, is dependent on supply of Iodine. Requirement of Iodine increases by almost 50% in pregnancy as there is more demand at thyroid gland and increase in renal clearance as glomerular filtration rate has increased. Iodine intake during pregnancy should be atleast 250mcg/d [3], but should not exceed 500mcg/d; which can be achieved by diet or supplements. Though it has been seen that daily iodine intake in few countries eg Japan is much more than the standard recommendations as their diet is rich in seafood, without any significant adverse effect. It is important to have adequate Iodine intake preferably starting before conception. Indian diet at most places, is usually sufficient to meet iodine requirements, and can be reasonably ensured after fortification in salt and some other food. Tarai region / Himalaya valley region, which are generally deficient in Iodine [14], supplementation before conception in form of Potassium Iodide as vitamin supplements might be helpful.

Subclinical Hypothyroidism (SCH) - Effect on Pregnancy

The estimated prevalence of hypothyroidism in pregnancy is 2-3%. Of these, 0.3-0.5% is OH and 2-2.5% is SCH [9]. Prevalence of hypothyroidism across different studies have also varied significantly; probably different cut-off values,dietary iodine intake , method of estimation and many more factors account for this differences. Manystudies have shown adverse pregnancy events with increasing thyrotropin levels; it can be in form of abortions, preterm labour, gestational hypertension, and gestational diabetes to name a few. In a study by Chen et al in 2014 in Chinese population, incidence of gestational hypertension was 1.8% in normal and 3.5% in SCH mothers, PROM 4.97% and 8.6%, GDM 3.74% and 2.15%, preterm delivery 3.5% and 3.504% among normal and SCH mothers respectively [4]. Many Indian studies also have similar observations; Mohanty et al [5] observed significant increased rate of pre-ecclampsia in SCH pregnant mothers.

Increased still birth rate was also seen in some studies [4,6]. The chances of progression of subclinical hypothyroidism to overt hypothyroidism also increases for these women.

Many prospective and retrospective studies have demonstrated an increased risk of pregnancy complications associated with mildly elevated maternal TSH concentrations, especially in TPOAb-positive women, however the benefit of treating SCH has been addressed very few of them [7].

Subclinical Hypothyroidism (SCH) - Effect on Neonate

Adverse early and late neonatal events were noticed by many studies with hypothyroidism. Liang-Miao Chen et al in their study found increased rate of foetal distress, low birth rate and growth restriction in SCH pregnancies as compared to normal mothers [4].

Thyroid hormones have great impact on foetal development and growth. Human foetal acquires the ability to synthesize thyroid hormone at approximately 7- 12 weeks of gestation. Neuro development delays were found to be associated with iodine deficient areas [7,8].

Neurodevelopment delay and low IQ was found in some studies but later many other studies failed to show such association [7]. Presently studies are being conducted in United Kingdom and Netherlands which may throw light on these issues. Probably complex effect of prematurity and impaired growth also has an important role to play in neuro-psychological development and IQ status. So the effect of SCH on neuro development delay is inconclusive presently.

Screening in Pregnancy for Hypothyroidism

Despite of the known effects of subclinical hypothyroidism on pregnancy, and availability of a safe and reliable test (TSH) routine screening is not yet recommended by American College Obstetrics Gynaecology (ACOG), American Thyroid Association (ATA) and many other associations. Most of these associations/ societies are from Iodine sufficient areas. Instead of routine screening aggressive case finding is recommended in the antenatal period. Recommendations from ministry of health and family welfare, maternal health

division, Government of India is also the same [9], but to proactively find the cases of suspected SCH in an busy and overloaded antenatal OPDs in India, as is the situation in most of the government hospitals is a challenge which should also be taken into consideration. Indian Thyroid Society and few more societies in world recommends routine screening of all pregnant ladies. One needs to balance the cost effectiveness of routine screening in a resource constrained country, with chances of missed cases and cost spent on management of the affected pregnancy and the neonate.

TSH measurement must be asked for in following clinical scenario- clinical suspicion of hypo/ hyperthyroidism, history of thyroid nodule, goitre, thyroid surgery, autoimmune diseases, BOH, previous preterm delivery/ abortion, age >30years, history of cancers especially for head and neck irradiation, drugs eg lithium, amiodorone etc.

While the debate for universal screening is going on, those favouring universal screening cite that easy availability of screening test, increased prevalence of thyroid problems during pregnancy, low cost and easily available treatment should favour universal screening. Also targeted screening may miss a large number of SCH cases, as high as >33% [10].

Till we clear the clouds of confusion about universal vs selective screening, individualisation of cases and offering them information about benefits vs harms and helping the women decide and choose to go ahead with TSH test or not may be adapted.

Diagnosis of SCH

TSH values > 10 milieq/L, symptoms and signs suggestive of hypothyroidism qualifies for overt hypothyroidism and require treatment. If no symptoms outside pregnancy and TSH< 10 milieq/L does not warrant therapy if pregnancy is not being planned. SCH can only be diagnosed by lab tests as there are very few and vague symptoms, often mimicking normal pregnancy.

What should be the cut-off value for TSH beyond which replacement will benefit pregnant women needs to be well established. Earlier ACOG, ATA ,ETA have recommended a TSH cut-off 2.5, 3, and 3 miliEq/ L for the first, second and third trimesters respectively [11]. These reference ranges are probably not valid all over the world due to differences in geographic, ethnic variance as has been shown in various studies [11,12]. ATA in their recent guideline published in 2017, state that trimester specific cut-off values to be established ideally for each regions for pregnancy with adequate Iodine intake. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPOAb status [7]. Cut-off value of TSH in this recent guideline has been raised from 2.5 to 4 miliEq/L in the first trimester as many studies from different part of the world, including India [13], China and other countries have found the physiologic variation of this hormone may be a little more for the upper limit [7]. Mankar et al have also published a reference range forthyroid function test in Indian women [14], and similarly many other studies, in different countries have published their reference ranges.

Using different cut-off values may further cloud this problem in managing this situation for the general obstetricians; so presently using the trimester specific values given and updated by American Thyroid association taking into considerations latest development in this field seems appropriate.

The accuracy of serum FT4 measurement by different immunoassays is inûenced by pregnancy and also varies signiûcantly between manufacturers. In lieu of measuring FT4, TT4 measurement (with a pregnancy-adjusted reference range) is a highly reliable means of estimating hormone concentration during the last part of pregnancy [7].

The causes for hypothyroidism in developing and developed countries is also different; while iodine deficiency is thecommon cause for hypothyroidism in developing nations, autoimmune thyroiditis is the commonest cause in developed countries. Thyroid autoantibodies are found in more than half cases of SCH and > 80% in overt hypothyroidism; therefore circulating antibodies against TPO and TG should be measured along with T4. Elevated TSH with TPO antibodies is the gold standard for diagnosis of chronic hypothyroidism (Hashimoto's thyroiditis). The immune system is suppressed during pregnancy, so thyroid antibody titre also decrease by approximate 60% in mid pregnancy. In many of these women rebound thyroid antibody increase may occur in post-partum period up to 6 months, which earlier had negative anti thyroid antibody and raised TSH.

Treatment

Should SCH be treated or not? The beneficial effects of treating SCH in pregnancy has an impact on improving obstetric and neonatal outcomes; this has cleared the doubt of whether to treat on not in pregnancy. ATA in its 2017 guidelines recommends treating women with SCH should be treated by levothyroxine specially if TPO-Ab is also positive. In women where TPO-Ab is negative and TSH value is more than the trimester specific cut-offs, treatment

should be considered.

Hypothyroidism in pregnancy is treated by oral Levothyroxine therapy; other thyroid preparation eg T3 or Desiccated thyroid should not be used during pregnancy. Levothyroxine is given in early morning, empty stomach. Night time administration may be an option in those pregnant women where morning sickness precludes its intake.

Women already on replacement therapy need to increase their dose by 30-50% depending on the aetiology of hypothyroidism and pre-pregnancy TSH levels. Alternatively they may be advised to take extra 2 tablets per week of the same dose. TSH levels should be checked after 4-6 weeks in first trimester and once during second and third trimester. The dose need to be adjusted so that TSH comes in that trimester specific reference range.

After delivery pre -pregnancy dose to be resumed. If SCH is diagnosed during pregnancy treatment may be stopped after delivery.

With negative TPO antibody should discontinue levothyroxine after pregnancy, and TSH values to be checked at 6weeks and 6 months and at 1 year. Women with positive TPO antibody are at high risk for developing overt hypothyroidism later and will require periodic monitoring of their thyroid function. Adequately treated women with SCH usually have good obstetric outcome and any additional maternal or foetal surveillance tests are generally not needed, unless indicated for other obstetric reasons.

New Born Screening

Congenital hypothyroidism is one of the most important and a treatable cause of intellectual impairment in paediatric age group [15]; many countries have introduced routine screening of neonates for this reason which is usually done after 48 hrs of birth to avoid physiological surge at birth. Routine new-born screening and treatment can virtually eliminate intellectual impairment due to thyroid problems [15, 16,18].

Countries with resource constrains can at least adopt screening of newborns where mother was on treatment for thyroid dysfunction. Obstetrician must communicate about the thyroid abnormality treatment of mother to the neonatologist / paediatrician at birth of baby. New-borns are also treated with levothyroxine if hypothyroidism is detected. Neonatal screening for congenital hypothyroidism needs to be introduced in this country which has significantly high incidence of CH to prevent future morbidity from mental and physical handicaps [17].

Timely detection and treatment of thyroid problems in pregnancy not only improves the obstetric outcome but also influences the neonatal outcome, and has the potential to influence long term intellectual outcome. While the debate of universal screening versus selective screening continues, every country can adopt their preferred method according to the prevalence of this condition, economic constraints, burden of this condition and other health conditions and health budget. A treating general practitioner and general obstetrician needs to be aware about this condition and its implication- potential benefits and costs for testing and treatment.

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