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HYPOTHYROIDISM AND PREGNANCY : EFFECTS ON PREGNANCY OUTCOMES; DIAGNOSIS AND MANAGEMENT

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ABSTRACT Hypothyroidism is quite a common hormonal disorder complicating pregnancy and its outcomes. Maternal thyroid hormone plays pivotal role in neurodevelopment of fetus and thus proper screening and effective management of hypothyroid during pregnancy is of utmost importance. Hypothyroidism during pregnancy is associated with increased risk of a number of adverse maternal and fetal outcomes like miscarriage, low birth weight baby, perinatal mortality and impaired neuropsychological development of baby. While targeted case finding is generally practised, recent evidence seems to indicate that universal screening might be a better option. Trimester specific cut-offs for TSH during pregnancy has made the targets for management quite specific and precise. Drug of choice for treating hypothyroidism is Levothyroxine (LT4) and must be started as soon as the mother is diagnosed with hypothyroidism and if already on LT4, then dose increment should be considered. Regular monitoring of thyroid functions and appropriate interpretation of thyroid function tests is needed in pregnancy. After pregnancy dose of LT4 can be reduced to the pre-pregnancy level.

KEYWORDS : Hypothyroidism, Pregnancy, Subclinical Hypothyroidism

INTRODUCTION

Over the past several years it has been proved that maternal thyroid disorder influence the outcome of mother and fetus, during and also after pregnancy. The most frequent thyroid disorder in pregnancy is maternal hypothyroidism. Hypothyroidism is one of the commonest endocrine disorders in women of reproductive age group[1] and poses an important clinical challenge.

It is well established fact that thyroid hormones play a critical role in the fetal neurological development. However, as the fetal thyroid gland starts functioning only after 12-14 weeks of gestation, the fetus relies solely n the transplacental passage of maternal thyroid hormones during early pregnancy for its development. Furthermore, maternal thyroid hormones continue to contribute to the fetal thyroid hormone pool till late gestation. Therefore, it is biologically plausible that maternal hypothyroidism, particularly in early pregnancy, may impair neurological development of the fetus.[1] This was observed four decades ago by Evelyn Man et al, who reported reduced intelligence quotients (IQ) in children born to hypothyroid mothers. A large prospective study published in 1999 reported that such children had an IQ 7 points below mean IQ of children of euthyroid women.[2] Progeny of hypothyroid women were three times as likely to have learning disabilities than children of euthyroid mothers.[3] Similar results have been reported from USA and the Netherlands.[4,5]

Both overt and subclinical maternal hypothyroidism has also been found to be associated with several obstetric complications, including miscarriages, premature births and gestational hypertension[6], and adequate thyroid hormone replacement may reduce the risk of these complications. Taken together, these observations underscore the importance of timely detection and optimal treatment of hypothyroidism in pregnancy. [1]

Epidemiology: In pregnancy, overt hypothyroidism is seen in 0.2% cases[7] and sub clinical hypothyroidism in 2.3% cases[8]. Fetal loss, fetal growth restriction, pre-eclampsia and preterm delivery are the usual complications of overt hyperthyroidism (low TSH and high T3, T4) seen in 2 of 1000 pregnancies whereas mild or sub clinical hyperthyroidism (suppressed TSH alone) is seen in 1.7% of pregnancies and not associated with adverse outcomes[9]. Autoimmune positive euthyroid pregnancy shows doubling of incidence of miscarriage and preterm delivery.

Between 2.2 % to 2.5 % women have been found to have serum TSH levels of 6 mU/L or greater at 15 to 18 weeks' gestation.[10] A recent observational study amongst 100 pregnant women in (first trimester) North India reported a prevalence of 14.3 % subjects to have TSH levels >4.5 mIU/L which was the cutoff used for definition of hypothyroidism(in first trimester). [11]

Pathophysiology of Thyroid during Pregnancy: Pregnancy influences thyroid function in multiple ways. Not only does the maternal HPT(Hypothalamus Pituitary thyroid) axis undergoes a series of adjustments, the fetus develops its own HPT axis and the placenta plays an active role in iodide and T4 transport and metabolism. Thus, an integrated three- compartment thyroid model exists during gestation[12]

From 12th week, placental changes resist T4 passage to fetus and fetal pituitary thyroid axis start functioning like adult.[13]

In pregnancy, half life of Thyroxin Binding Globulin (TBG) increases from 15min to 3days and concentration becomes 3 times by 20 weeks due to the effect of oestrogen driven glycosylation, which increases the level of T3 and T4 making its estimation non reliable. But fT3 and fT4 remain unaffected, and are of choice for estimating the thyroid function during pregnancy.

HCG and TSH due to structural similarity produce hormone spillover syndrome in 1st trimester, manifested as stimulation of TSH receptors by HCG and biochemical hyperthyroidism. This is common in multiple pregnancy, hyperemesis gravidarum and trophoblastic diseases. Diagnosis of false hyperthyroidism should be avoided in these cases.

Depletion of iodine can occur due to increased glomerular filtration and greater thyroidal uptake due to higher T4 concentration. In several maternal iodine deficiency, compensation if fails can lead to cretinism in the offspring.

Concentration of the enzyme deiodinase III (which converts T4 to T3 and further breakdown) is increased in placenta and reduces thyroxin transfer.[13]

Because of physiological changes values of thyroid hormones during pregnancy differ from non-pregnant values. Values in pregnancy also vary from trimester to trimester. “Trimester-specific” ranges in vogue for TSH are 0.1- 2.5 µIU/ml in the first trimester (due to the stimulatory effects of hCG) 0.2-3 µIU/ml in the second and 0.3-3 µIU/ml in third trimester.[14]

Obstetrical Complications of maternal hypothyroidism: Maternal hypothyroidism may place the mother at an increased risk of adverse obstetrical outcomes. Untreated hypothyroidism is associated with increased risk for [10] :

- Pregnancy induced hypertension (PIH)
- Low birth weight baby
- Placental abruption
- Miscarriage, and
- Perinatal mortality

A study by Idris et al[15] , found that in addition to an increased risk of

low birth weight, hypothyroidism early and late in pregnancy may also increase the rate of Caesarean section.

Neonatal and long term complications of maternal hypothyroidism: In addition to adverse obstetrical outcomes, maternal hypothyroidism is associated with adverse neonatal outcomes. Neuropsychological deficits in the offspring from as early as 3 weeks to 9 years of age have been observed.[10] Multiple studies have shown that neonates born to mothers with hypothyroidism, had impaired neuropsychological development.[16-18]

Treatment of maternal hypothyroidism decreases the risk of neurodevelopmental deficits in the offspring. The stage of development during which the lack of T4 in the fetus is most detrimental for neurodevelopment is thought to be the first trimester.[10,19] However, another study showed that maternal treatment at a later stage in pregnancy is also beneficial for neonatal outcome.[10,20]

Anti –thyroid antibodies have been suggested to be independent markers of 'at risk' pregnancy. Euthyroid women with recurrent miscarriage have increased levels of autoantibodies either against TG(thyroglobulin) or TPO while the probability of abortion in women with anti thyroid antibodies has been shown to be greater than in controls. There are animal models in which active immunisation of mice with TG has raised antibodies to TG, and leading to increased fetal wastage and lower fetal and placental weights.

The prevalence of antithyroid antibodies has been reported to be 15-20 % in normal pregnant women, compared with 20 -25 % in women with recurrent miscarriages.

Screening for hypothyroidism: Screening for pregnancy and thyroid dysfunction is currently a subject of debate in the fraternity. While the joint statement by the American Thyroid Association and American Association of Clinical Endocrinologists' 2013 favors targeted high – risk case finding, it does not recommend universal screening for patients who are pregnant or are planning pregnancy, including assisted reproduction.[21]

Yet on the other hand, experts suggest that over half (55 %) of pregnant women with abnormalities suggestive of autoimmune thyroiditis and/or hypothyroidism would be missed if only those with high – risk criteria were examined; thus warranting a more extensive screening of thyroid autoimmunity and dysfunction.[22,23]

Probably at present moment we would only screen the high risk group women who fulfil any of the following criteria[24]

1. History of hypo / hyperthyroidism or thyroid lobectomy or post partum thyroiditis
2. Family history of thyroiditis
3. Goitre
4. Thyroid auto-antibodies
5. Symptoms, signs or biochemical markers suggestive of thyroid disease
6. Type 1 diabetes
7. Other autoimmune disorders
8. Infertility
9. Previous head or neck irradiation
10. History of miscarriage or preterm delivery

Management: Timely treatment of maternal hypothyroidism is of utmost importance, because adverse outcomes for both mother and baby are greatly reduced, if not eliminated, when patients are treated timely. Even when treatment is initiated later in pregnancy or is insufficient to restore a euthyroid state, the babies of treated mothers will show normal neurodevelopment than the babies of non- treated mothers.[10]

Thus, given the increased risk for adverse obstetrical and neonatal outcomes in untreated patients, it is prudent to treat all pregnant women who have hypothyroidism. Levothyroxine (LT4) is the treatment drug of choice. It is found to be well tolerated during pregnancy.[10]

The changes in thyroid physiology during pregnancy have two important implications in the management of gestational hypothyroidism [1] : firstly, HCG secretion in pregnancy stimulates thyroid hormones with associated suppression of TSH. Therefore, the reference range of serum TSH in pregnancy is trimester specific and is lower than the non pregnant population.[1] And secondly, the increased renal clearance of iodine, transplacental passage of thyroid hormones and metabolism of thyroid hormones by placental deiodinases in pregnancy mean that most hypothyroid women need to increase the dose of LT4 by 30-40 % to maintain euthyroidism during pregnancy, and this need for an increased dose of LT4 starts as early as 4-6 weeks of gestation.[1]

The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum released in 2017, recommend the following practices for hypothyroid women planning conception, are pregnant and are postpartum:[24]

Guidelines for treatment of Hypothyroidism during pregnancy

1. Both maternal and fetal hypothyroidism exert serious adverse effects on the fetus, so maternal hypothyroidism should be avoided by early diagnosis at the first prenatal visit or at diagnosis of pregnancy
2. In cases of hypothyroidism diagnosed before pregnancy, adjust the preconception T4 dose to reach a TSH level not higher than 2.5m/ml before pregnancy.
3. By 4-6 weeks of gestation, the T4 dosage needs to be increased by about 30-50%.
4. If overt hypothyroidism is diagnosed during pregnancy, thyroid function should be normalized as rapidly as possible. The target is to achieve and maintain TSH concentrations below 2.5mU/ml in first trimester (or 3 mU/ml in second and third trimesters) or to trimester specific normal TSH ranges. This can be achieved by rapidly titrating the T4 dosage to reach and maintain the target TSH levels. A reassessment of the thyroid function should be carried out within 30 to 40 days.
5. Women who have thyroid antibodies in the early stages of their pregnancy but are otherwise euthyroid, should be monitored for elevations of TSH above the normal range because they are risk of developing hypothyroidism.
6. Sub clinical hypothyroidism: Recommend T4 replacement as T4 treatment has been shown to improve obstetrical outcome, though do not modify long-term neurological development in the offspring.
7. After delivery, dose of T4 need to be decreased in most hypothyroid women.[25]

Clinicians should also bear in mind that some medications, including iodine, lithium, carbamazepine, phenytoin, rifampin, amiodarone, aluminium hydroxide, cholestyramine, sucralfate, glucocorticoids and propranolol have the potential to interfere with LT4 requirements. As many pregnant women take vitamin supplementation , it is also important to note that ferrous sulphate and calcium carbonate can each reduce the absorption of LT4 if taken concurrently. [10]

Management of Subclinical Hypothyroidism: The joint statement of ATA and AACE does not support treating patients with subclinical hypothyroidism. The possible exception to this statement is pregnancy, where the rate of pregnancy loss, including spontaneous miscarriage before 20 weeks gestation and stillbirth after 20 weeks, have been reported to be increased in thyroid antibody negative women with TSH values between 2.5 and 5.0 μIU/mL[21]

It is further understood that the presence of elevated anti TPO antibody titres in patients with subclinical hypothyroidism helps to predict progression to overt hypothyroidism – 4.3 % per year with anti TPO antibody vs. 2.6 % per year without elevated anti TPO antibody titres. The higher risk of developing overt hypothyroidism in anti TPO antibody positive patients is the reason that several professional societies and many clinical endocrinologists endorse its measurement in those with subclinical hypothyroidism.[21]

The Endocrine Society Clinical Practice Guideline as well as ATA guideline considering recommends T4 replacement in women with SCH who are anti TPO antibody positive (level B) because the potential benefits outweigh the potential risks. ESC practice guideline recommends serial TSH measurement without treatment and treating only when SCH evolves into overt hypothyroidism.[24,26]

Monitoring: Clinicians must follow hypothyroid women closely during pregnancy and increase the dose of LT4 as required as per serial TSH recording.[10]

Several investigators have suggested that TSH levels should be monitored to assess the adequacy of thyroid hormone replacement during pregnancy. However, others have argued that serum fT4 levels should be monitored, because these more closely reflect the hormone available to cross the placenta[10]

Neurodevelopment follow up of the babies of hypothyroid mothers is also important in order to identify cognitive deficiencies as early as possible and provide appropriate management[10]

DISCUSSION AND CONCLUSION

- Hypothyroidism during pregnancy is associated with adverse neonatal and obstetrical outcomes.
- Screening for thyroid dysfunction is recommended at first antenatal visit or in women who are planning pregnancy in near future.[27]
- It is must to treat all pregnant women who have hypothyroidism even if diagnosed later in pregnancy.[10]
- Levothyroxine (LT4) is the treatment drug of choice.
- LT4 replacement is recommended in women with Subclinical hypothyroidism who are anti TPO antibody positive (Level B-USPSTF). [28,29] T4 replacement can be considered in women with SCH who are anti TPO antibody negative but the evidence of benefit is still lacking.
- In a known hypothyroid woman on LT4 replacement prior to pregnancy, the dose of LT4 needs to be increased by 30-50 % to maintain euthyroid state during pregnancy.[1]
- Physicians must monitor the thyroid functions every four weeks during pregnancy and increase the dose of LT4 as required.[1,24]
- Neurodevelopment follow-up of the babies of hypothyroid mothers is also recommended for early detection of cognitive deficits.[10]
- Post partum, dose of LT4 should be lowered back to pre-pregnancy level, with monitoring the TSH level. [25]

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