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Gynaecology

MANAGEMENT OF SUBCLINICAL HYPOTHYROID PREGNANT PATIENTS – REVEIW OF LITERATURE

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ABSTRACT Hypothyroidism is a common medical condition that occurs more often in pregnant women. Thyroid dysfunction during pregnancy has been an important research area in clinical endocrinology due to the fact that thyroid dysfunction has immense impact on maternal and fetal outcomes.Thyroid gland in hypothyroid women are not able to respond either to thyrotropin or to chorionic gonadotropin, so the incremented requirement for thyroxine is not achieved and the serum thyrotropin concentration increases Thus, pregnancy creates a challenge for the thyroid, particularly where thyroid reserve is limited, or iodine deficiency is present.he levothyroxine dose required to attain the TSH target levels varied significantly, depending on the baseline TSH levels.It is well-established that overt hypothyroidism in pregnancy should be treated, the recommended levothyroxine doses but when it comes to the subject of subclinical hypothyroidism,there is no clear guidelines about dose of levothyroxine.This review of literature gives us a vision about the intial and trimester specific mean levothyroxine doses in Subclinical hypothyroidism in pregnancy

KEYWORDS : Subclinical hypothyroidism , levothyroxine ,pregnancy

1. INTRODUCTION

Thyroid gland is one of the largest endocrine gland in body. The name "Thyroid" derived from Greek word – means Sheild Gland. It is highly vascular organ brownish red in colour butterfly shaped gland, located in front of neck below larynx , 2 inches long with 2 lobes, weight 15 to 20 grams in adults. Thyroid gland makes two hormones – Levothyroxine (T4) and Triidothyronine (T3), which plays important role during pregnancy.

During normal gestation, thyroid hormone production is augmented in order to meet the increased physiologic demands of growing fetal placental unit. There is increase in total serum T4 T3 concentrations and Estrogen mediated thyroid binding globulin (TBG) but decrease in free T3, T4 in pregnancy [1][2][3]**.** Serum TSH decreases in first trimester due to HCG hormone which has thyrotropin like activity between 8 to 14 weeks of pregnancy. TSH levels during pregnancy are lower as compared to TSH levels in a non-pregnant state.

The production of thyroid hormones and iodine requirement each increases by approximately 50% during pregnancy the fetus relies on maternal T4 exclusively before 12 weeks and partially thereafter for normal fetal neurologic development. (FIGURE 2)

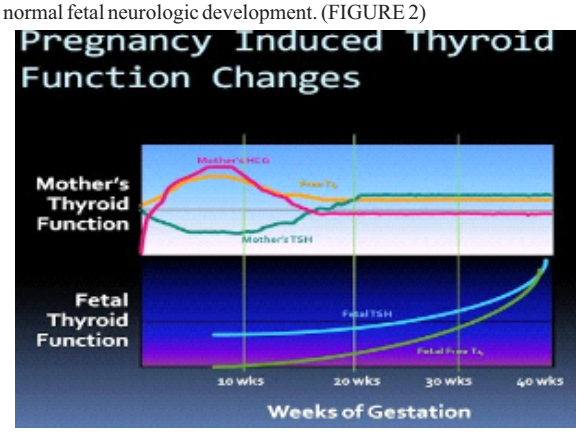


Figure 2

Pregnancy is considered as a relative state of iodine deficiency due to deficiency of iodine in deit, increased iodine excretion in urine, placental deiodination of T4 and active transport of iodine to fetoplacental unit [4][5]. therefore recommended average iodine intake during peregnancy is between 250 and 500 ug/day [6][7]. The infant can develop intense neurologic impairement and mental retardation as a result of severe iodine deficiency**.**

There are varities of disorders associated with thyroid gland. Most common thyroid disorder associated with pregnancy is hypothyroidism. Hypothyroidism is defined as a decrease production of thyroid hormones from thyroid gland in body. It is most common endocrine disorder in pregnancy. It can be overt hypothyroidism or subclinical hypothyroidism. SCH is defined as serum TSH level between 2.5 to 10 mIU/l with normal free T4 levels, women with TSH > 10 mIU/l irrespective of the free T4 levels are considered as overt hypothyroid.[8] [9][10]In overt hypothyroidism Serum TSH level increased with decrease in free T4 level but in Subclinical hypothyroidism Serum TSH level increases with freeT4 levels remain normal.

The early recognition of abnormality in thyroid function tests during pregnancy is important for the well being of both the mother as well as the fetus as thyroid dysfunction has been associated with pregnancy complications such as preterm birth, hypertension, low birth weight, placental abruption and fetal death**.**[11],[12]

In most of the cases SCH is a laboratory diagnos. Serum TSH is the best indicator of insufficient thyroid hormone due to primary hypo thyroidism[7]. American thyroid association (ATA) recommended a TSH normal refrence range of 0.1 to 2.5 mIU/L for the first trimester, 0.2 to 3.0 mIU/L for second trimester and 0.3 to 3.0 mIU/L for the third trimester[7] but till date no authority has given any clear cut guidelines about intial dose of levothyroxine to be started for patients with subclinical hypothyroidism during pregnancy. so we have reviewed literature to understand dosage regime of levothyroxine which is optimal for urgent correction of hypothyroid state in pregnancy.

DATA COLLECTION AND MANAGEMENT

Reviewers working independently and in duplicate using a standardized web-based form collected the following information from each eligible study: (i) baseline clinical features: gestational age at screening, race/ethnicity, body mass index (BMI), history of smoking, previous pregnancy, pregnancy loss, and preterm delivery, family history of thyroid disease, use of in vitro fertilization/assisted reproduction to achieve the index pregnancy, and educational level; (ii) TSH, T4, and thyroid peroxidase (TPO) antibody levels; (iii) main and other outcomes. The definition of SCH used in each study was also extracted. Disagreements were resolved by discussion and consensus. Unclear data were confirmed with the study author when possible.

REVIEW OF LITERATURE

Thyroid dysfunction during pregnancy has been an important research area in clinical endocrinology due to the fact that thyroid dysfunction has immense impact on maternal and fetal outcomes.[17] [18] Thyroid dysfunction is associated with pregnancy complications such as preterm birth, hypertension, low birth weight, placental abruption and fetal death**.**[19] The production of thyroid hormones and iodine requirement each increases by approximately 50% during pregnancy**.**[20]

Maternal thyroxine specifically have been found to play and important role, particularly in early pregnancy because the fetal thyroid gland is unable to synthesize thyroxine until after 10 weeks of gestation.[21]

Subclinical hypothyroidism is a mild form of hypothyroidism in which serum TSH concentration is elevated with normal free T4 levels.[22] Word "Subclinical" suggests that the disease is in its early stage with changes in TSH already apparent but decreases in thyroid hormone

levels yet to come.

American thyroid association (ATA) recommends screening of hypothyroidism for high risk population only, that will miss out as many as 30% of subclinical hytpothyroid cases [(23) (24)]. Indian Thyroid Society (ITS) recommends screening of TSH levels in all pregnant women at the time of their first visit, ideally during pre-pregnancy evaluation or as soon as pregnancy is confirmed (26) Risk factors for developing hypothyroidism include personal or family history of thyroid dysfunction, advanced maternal age, diabetes, other autoimmune disorders, and morbid obesity[(26)]

A recent meta-analysis including 11 observational studies showed that compared with normal thyroid function, maternal SCH was associated with indicators of intellectual disability in offspring.[(26)]

In India due to deficiency of iodine in deit, prevalence rate of subclinical hypothyroidism is high as compare to other countries.

Dhanwal DK, Prasad S et al. study concludes that there is a high prevalence of hypothyroidism (14.3%), majority being subclinical in pregnant women during first trimester from India and universal screening of hypothyroidism may be desirable in our country

Chen LM, **Du WJ et al.** study was performed to gain insight into the impacts of SCH on maternal and perinatal outcomes. 4.63% of pregnant women were diagnosed with SCH. Pregnant women with SCH had increased risks of developing GH and PROM. Fetuses and infants of women with SCH had significantly higher risks of IUGR and LBW compared with those born to euthyroid mothers. There are prospective and retrospective studies have demonstrated an increased risk of pregnancy complications associated with mildly elevated maternal TSH concentrations.

Taylor PN, **Minassian C et al.** study included Forty-six percent of levothyroxine-treated women aged 18–45 years had a TSH level greater than 2.5mU/L (recommended upper level in the first trimester). Among pregnant women who had their TSH measured in the first trimester, 62.8% had a TSH level greater than 2.5 mU/L, with 7.4% greater than 10 mU/L. Women with TSH greater than 2.5 mU/L in the first trimester had an increased risk of miscarriage compared with women with TSH 0.2–2.5 mU/L after adjusting for age, year of pregnancy, diabetes, and social class (P = .008). The risk of miscarriage was increased in women with TSH 4.51–10 mU/L [odds ratio (OR) 1.80, 95% confidence interval (CI) 1.03, 3.14)] and TSH greater than 10 mU/L (OR 3.95, 95% CI 1.87, 8.37) but not with TSH 2.51–4.5 mU/L (OR 1.09, 95% CI 0.61, 1.93).Which concludes that majority of levothyroxine-treated women have early gestational TSH levels above the recommended targets (>2.5 mU/L) with a strong risk of miscarriage at levels exceeding 4.5 mU/L. There is an urgent need to improve the adequacy of thyroid hormone replacement in early pregnancy.

Vermiglio F, **Lopresti VP et al.** study has been showed that even mild iodine deficiency may be associated with attention deficit and hyperactivity disorders in off spring.Over a period of almost 10 years, they carried out a prospective study of the neuropsychological development of the offspring of 16 women from a moderately iodine-deficient area (area A) and of 11 control women from a marginally iodine-sufficient area (area B) whose thyroid function had been monitored during early gestation[(28)(29)].

Neurodevelopment outcomes were improved in children who received iodine supplementation early in pregnancy and were lost if supplementation was started after 10 week of pregnancy. [(32)(33)]

Stagnaro G, Chen X et al. found increase incidence of early preterm delivery before 32 weeks in subclinical hypothyroid pregnant patients.[(34)]

Similar observation was found in Chinese population indicating that children of women with SCH, mean intelligence and motor scores significantly lower than controls.[(35)]

Haddow J, Palomaki G et al in 1999 conducted the first large scale prospective study on subclinical hypothyroidism was reported by which revealed that children born to untreated SH women had low average IQ level than that of treated women.[(36)]

A higher rate of spontaneous pregnancy loss was observed in a study of 642 women with serum TSH ranging between 2.5 to 5 mIU/L in the first trimester than in 3481 women with TSH below 2.5.[(37)]

Negro R etal. reported a significantly higher pregnancy loss rate in TPOAb-negative women with TSH concentrations between 2.5 and 5.0 mU/L compared to those with TSH concentrations below 2.5 mU/L (6.1% vs. 3.6%).[(37)]

Subclinical hypothyroidism being specifically associated with very early embryo loss at 6.5 weeks[(38)], preterm birth, abruptio placentae and postpartum thyroiditis.[(39)(40)]

In a large prospective study of more than 16000 pregnant women, those with SCH were at higher risk for placental abruption and preterm delivery compared with euthyroid women.[(41)]

Studies have shown that children of women whose TSH values elevated during pregnancy have significant reduction in intelligent quotient scores and have poor intellectual function during later part of life [(42)]

Drug of choice for treatment of Hypothyroidism in pregnancy is levothyroxine. There are observational studies suggesting a beneficial effect of levothyroxine treatment in pregnant women with SCH [(43) (44) (45)].Sodium thyroxine (levothyroxine) is more stable and effective thyroid hormone compound[(46)]

Levothyroxine Sodium belongs to category A for use during pregnancy and can be used safely during pregnancy and lactation without any adverse effect on mother or fetus.

Side effects

Adverse events are generally caused by incorrect dosing. Long-term suppression of TSH values below normal values will frequently cause cardiac side-effects and contribute to decreases in bone mineral density (low TSH levels are also well known to contribute to osteoporosis)

Too high a dose of levothyroxine causes hyperthyroidism. Overdose can result in heart palpitations, abdominal pain, nausea, anxiousness, confusion, agitation, insomnia, weight loss, and increased appetite. Allergic reactions to the drug are characterized by symptoms such as difficulty breathing, shortness of breath, or swelling of the face and tongue. Acute overdose may cause fever, hypoglycemia, heart failure, coma, and unrecognized adrenal insufficiency.

Acute massive overdose may be life-threatening; treatment should be symptomatic and supportive. Massive overdose can be associated with increased sympathetic activity and thus require treatment with beta-blockers.

Levothyroxine (Figure 5) is to be taken orally, in the morning empty stomach, The patient should be asked not to take anything orally for at least half an hour after intake of the medicine. There should be a 4 to 5 hours of gap before taking medicines such as vitamins, calcium and iron tablets as interactions in gastrointestinal tract can reduce thyroxine absorption

The starting dose of thyroxine will depend on the degree of hypothyroidism, weight of patient and other medical problems.

(47) According to European thyroid association guidelines weight, associated medical disorders and serum TSH play a role in deciding the required LT4 dosage.

(48) Levothyroxine is available in market in different doses from 12.5 ug to 300 ug.It is a white pill which has long half life of 7 days so once daily administration is enough. It acts by activation of nuclear receptors. Average dose used is 1.6ug/kg.

The Amercian thyroid association updated guidelines in 2017 recommends that thyroxine should be given if there are antibodies present with intial TSH is 2.5 to 4 mIU/l and if the intial TSH is 4 mIU/l or more start thyroxine irrespective of antibody status but as india is developing country with high iodine deficient areas even if TSH is between 2.5 to 4, thyroxine should be started irrespective of TPO antibody status.[(48)(49)(50).(51)]

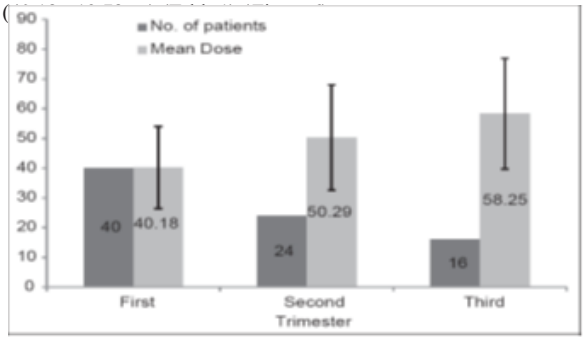
Thyroid function to be checked soon after starting therapy between 4 to

6 weeks and uptitrate the dose aiming to achieve a TSH below 2.5 mIU/L in first trimester as quickly as possible [52]

With regard to the safety of LT4, overtreatment resulting in exogenous hyperthyroidism during pregnancy. HCG stimulates the maternal thyroid as previously discussed, but in contrast to TSH, HCG production is not regulated via negative feedback from FT4. Therefore high dose LT4 treatment during pregnancy may lead to high FT4 levels, particularly when treatment starts before the HCG peak at 10 weeks. High thyroid hormone levels has also been associated with preeclampsia and decreased birth weight [53]

Based upon this review of the literature, it is clear that for women who are diagnosed with SCH during pregnancy, there is no official recommendation regarding the starting LT4 dose and there is a necessity to both update and promulgate novel guidelines in regard to levothyroxine treatment during pregnancy because early treatment with levothyroxine may reduce associated risks[54].

Study done by **chakaraborty S**[55] showing mean dose of levothyroxine used in SCH is less than dose of overt hypothyroidism.The mean levothyroxine dose used in the first trimester was 40.18 ± 13.78 µg. The mean levothyroxine dose used in the third trimester was 58.25 ± 18.57 µg. Significant increase in the mean dose of levothyroxine required in the third trimester (58.25 ± 18.57 µg) as compared to the first trimester (



Trimester	No. of patients	Mean Dose	Std. Dev.	Minimum Dose	Maximum Dose
First	40	40.18	13.78	25	75
Second	24	50.29	17.69	25	75
Third	16	58.25	18.57	25	100

Figure 6

DISCUSSION

Hypothyroidism is a common medical condition that occurs more often in pregnant women. Thyroid dysfunction during pregnancy has been an important research area in clinical endocrinology due to the fact that thyroid dysfunction has immense impact on maternal and fetal outcomes[53].

Thyroid hormone for the growing embryo is essential during pregnancy for normal brain development and also to prevent complications during delivery and the postpartum period. In the first trimester, the baby gets its' thyroid hormone exclusively from the mother.

Thyroid gland in hypothyroid women are not able to respond either to thyrotropin or to chorionic gonadotropin, so the incremented requirement for thyroxine is not achieved and the serum thyrotropin concentration increases Thus, pregnancy creates a challenge for the thyroid, particularly where thyroid reserve is limited, or iodine deficiency is present.

In subclinical hypothyroidism serum TSH levels incresaed but free T4 levels remain with in normal limit. Impact of Subclinical Hypothyroidism on pregnancy is a matter of debate. Many studies have shown that he children of the subclinical hypothyroid subjects did statistically less well on developmental tests. The children of women whose TSH levels were elevated during the mid trimester of pregnancy had a slight but significant reduction in intelligence quotient scores between 7 to 9 years of age when compared with infants of euthyroid women.[33]

There are observational studies suggesting neurodevelopment outcomes were improved in children who received iodine supplementation early in pregnancy and were lost if supplementation was started after 10 week of pregnancy [32] [33] This signifies beneficial effect of levothyroxine treatment in pregnant women with SCH and If optimal initial doses of levothyroxine (LT_4) given to pregnant women with newly discovered hypothyroidism, leads to prompt attainment of normal thyrotropin (TSH) levels and help in minimizing pregnancy complications. [43][44][45]

For adjustment of levothyroxine dose in hypothyroid pregnant women, there are various controversies surrounding the amount of this dosage adjustment. Initial dosing of levothyroxine can vary greatly and based on the amount of residual thyroid function retained by the patient, the body weight or lean body mass of the patient, and thyroid-stimulating hormone levels.

The Amercian thyroid association updated guidelines in 2017 recommends that thyroxine should be given if there are antibodies present with intial TSH is 2.5 to 4 mIU/l and if the intial TSH is 4 mIU/l or more start thyroxine irrespective of antibody status but as India is developing country with high iodine deficient areas even if TSH is between 2.5 to 4, Levothyroxine should be started irresepective of antibodies status.[43]

National Guidelines for Screening of Hypothyroidism during Pregnancy, India. 2014 Dec. recommends to start thyroxine for all hypothyroid pateints in pregnancy. [24] [51]. Thyroid function should be checked soon after starting therapy between 4 to 6 weeks and uptitrate the dose to achieve TSH below 2.5 mIU/L as quickly as possible in first trimester [52].

Chakaraborty S Chakaraborty J[55] **et al** has done similar study with following results- The mean levothyroxine dose used in the first trimester was 40.18 ± 13.78 µg and in the third trimester was 58.25 ± 18.57 µg. Significant increase in the mean dose of levothyroxine required in the third trimester (58.25 ± 18.57 µg) as compared to the first trimester (40.18 ± 13.78 µg, $P = 0.0012$).

Abalovich et al. study suggested Levothyroxine doses in Pregnant Women With Newly Diagnosed Hypothyroidism as follows.

For subclinical mean LT_4 dose is 77.98 (µg/day) and 1.26 (µg/kg/day) and for overt hypothyroidism it is 147.08 (µg/day) and 2.33 (µg/kg/day).[56]

Duntas, L.H. et al study shows when commencing levothyroxine therapy, initial dose requirements can vary greatly from small doses such as 25–50 µg in an individual with mild or subclinical disease, where the therapy may be supplementing endogenous function, to larger doses of 88–175 µg in cases of patients with negligible endogenous thyroid function

The levothyroxine dose required to attain the TSH target levels varied significantly, depending on the baseline TSH levels.[57][56]

It is well-established that overt hypothyroidism in pregnancy should be treated, the recommended levothyroxine doses ranging from 1.20-2.33 mcg/kg/day during pregnancy, depending on the severity of hypothyroidism but when it comes to the subject of subclinical hypothyroidism, there is no clear guidelines about dose of levothyroxine.

Amercian thyroid guidelines tells about Target TSH levels in pregnancy, but the doses of levothyroxine needed to attain these levels are not specified.

With regard to the safety of LT4, overtreatment resulting in Iatrogenic hyperthyroidism which occurs more often during pregnancy. HCG stimulates the maternal thyroid as previously discussed, but in contrast to TSH, HCG production is not regulated via negative feedback from FT4. Therefore high doses of LT4 during pregnancy may lead to high FT4 levels, particularly when treatment starts before the HCG peak at 10 weeks. High thyroid function has also been associated with preeclampsia and decreased birth weight of newborn[52].

Overzealously treated patients are at high risk for accelerated bone loss as well as the risk of osteoporosis and vertebral fractures[58].

For women who are diagnosed with SCH during pregnancy, there is no

official recommendation regarding the starting dose of levothyroxine and there is a necessity to both update and promulgate novel guidelines in regard to levothyroxine treatmen during pregnancy because early treatment with levothyroxine may reduce associated risks[53].

Based upon this discussion, it is clear that in hypothyroid pateints treatment should be started as soon as possible with appropriate dose of levothyroxine to prevent maternal morbity as well as mental retardation in newborns.

A systematic review was therefore conducted, summarizing the evidence for the adverse clinical impact of SCH during pregnancy and for the value of levothyroxine therapy in mitigating that impact.In overt hypothyroidism pateint is a diagnosed case of hypothyroidism before conception. They need high dose of levothyroxine. In subclinical hypothyroidism first diagnosed in pregnancy need less dose of thyroxine as compare to overt hypothyroidpateints.

In our review of literature mean dose of thyroxine and Trimester specific doses are less as compare to dose of overt hypothyroid pateints.So as per observations, Subclinical hypothyroid pateints can be treated with low dose thyroxine without any associated side effects and also there is significant change in mean dose of levothyroxine when pateint shift from one trimester to another.

CONCLUSION

Untreated maternal hypothyroidism have adverse effects on both the mother and fetus, but it can potentially be prevented by adequate levothyroxine replacement. Subclinical hypothyroidism in pregnancy manifests due to less reserve of thyroid hormones in mother. During pregnancy, hypothyroidism should be treated aggressively, to normalize thyroid levels as soon as possible to have less side effect on maternal or developing fetus.

Significant improvement in the thyroid function as indicated by higher proportion of patients achieving normal TSH values with significant increase in the mean levothyroxine dose used during the course of treatment gives us guideline about the initial starting doses of levothyroxine.

High dose of thyroxine has its own side effects like IUGR babies, preeclampsia, osteoporosis and weight loss in mother.It is clear that when pateint move from first to second trimester than there is significant change in levothyroxine dose.This also happens when pateint move from second to third trimester. Hence we have to keep pateint on regular follow up for TSH level in every trimester.

Mean levothyroxine doses in Subclinical hypothyroidism in pregnancy quite low as compared to non pregnant and overt hypothyroid patients.This signifies that subclinical hypothyroid pateints can be treated with low dose thyroxine without any risk of associated side effects.

There is significant increased in dosage of thyroid hormone in third trimester of pregnancy which is due to increased demand by fetus. This implies that serum TSH should be repeated in third trimester for every pregnant hypothyroid pateint to optimize the dose of thyroxine.

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