Original article

Subclinical Hypothyroidism in Pregnancy - A Case Series

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Abstract

Background: Effects of overt hypothyroidism on pregnancy outcomes and foetal development are well established and treatment protocol is reputable. ***Method and material:*** The prevalence and effects of subclinical hypothyroidism (SCH) on pregnancy are not yet clear. Hence, universal screening of all pregnant women is still debatable and treatment of detected sub clinical hypothyroidism is yet to have general consensus as data regarding beneficial effects of treatment to mother and foetus in SCH cases is inadequate. ***Result:*** Odisha is a known endemic area of Iodine deficiency and reports of occurrences of SCH in Odisha are very limited. This study is a case series, done to detect the prevalence of SCH in pregnancy in the ante-natal unit of a medical college and hospital catering to a large population of Odisha. ***Conclusion:*** This prospective study included screening of the pregnant women for thyroid function and follow – up of the cases with SCH till confinement to record any adverse effects of the thyroid dysfunction on obstetric outcome.

Key words :– Sub-clinical hypothyroidism; pregnancy; preterm delivery; preeclampsia obstetric outcome; small for gestational age; Gestational diabetes

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Introduction

Thyroid hormones T4 and T3 have an eclectic role in body affecting almost every organ and metabolic process. Pregnancy is a state of altered metabolism as the female body tries to adapt to the needs of the growing foetus. In order to meet the increased demand, the thyroid hormone level also change in pregnancy through the hypothalamic pituitary thyroid (HPT) axis regulation[1]. There is increased secretion of Thyroxin and TBG (Thyroid binding globulins) in pregnancy with a decrease in TSH (Thyroid stimulating hormone) level[2]. Production of a deiodinase from the placenta also leads to increased thyroid hormone synthesis in pregnancy[3]. The thyrotrophic effect of hCG is also responsible for this effect on the thyroid status in pregnancy[4].

The growing foetus exclusively depends upon the maternal thyroid hormones for the first 12 weeks[5]. Lack of thyroid hormone in mother hence can adversely affect the foetal development. Thyroid adequacy also is essential for proper placental development[6]. Literatures document that anomalous thyroid status; hyper and hypothyroidism are associated with adverse obstetric outcomes like abortions, abruption placenta, preeclampsia of pregnancy, low birth weight (LBW), IUGR (intra-uterine growth retardation) and even foetal death[7-10]. On long term follow up, the children born to hypo/hyper thyroid mothers' depicted intellectual slothfulness[11-13].

Subclinical hypothyroidism is defined as the condition where TSH level is high but Thyroxin T4 level is normal. SCH is very commonly observed in pregnancy, more so in endemic areas with Iodine deficiency[14, 15].Association of anti-TPO antibodies are also more commonly observed in SCH in pregnancy[16].

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Consensus regarding reference range of TSH in pregnancy is contentious as various bodies recommend various reference limits.

Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum recommends a trimester specific range of TSH in pregnancy which is lower than in normal adult i.e. first trimester: 0.1-2.5 mIU/L, second trimester: 0.2-3.0 mIU/L, third trimester: 0.3-3.0 mIU/L[17]

This is also approved by USPSTF which states that in absence of a reference range specific for each trimester the above mentioned range should be considered[18] However data from studies on Indian women differ by depicting very minimal difference between reference range in normal adult and pregnancy[19]

Effects of overt hypothyroidism on pregnancy and foetal development are well established and treatment protocol is reputable .Insufficient data about the prevalence, repercussions and treatment benefits of subclinical hypothyroidism in pregnancy has made universal screening of all pregnant women and initiation of therapy to the diagnosed SCH cases still arguable [17, 20].

Odisha is a known endemic area of Iodine deficiency and there are limited documentations of occurrences of SCH in Odisha [21, 22].

This study was thus done to detect the prevalence of SCH in pregnancy in first trimester in the ante-natal unit of a medical college and hospital catering to a large population of Odisha. This prospective study included screening of the pregnant women for thyroid function and follow – up of the cases with SCH having TSH in the range 2.5-4.2mIU/L, lowering the upper limit of TSH to 2.5mIU/L, till confinement to record any adverse effects of the thyroid dysfunction on obstetric outcome.

Materials and Methods

This study was done in the department of Biochemistry, IMS and SUM Hospital, Bhubaneswar. 200 pregnant women with singleton pregnancy, apparently healthy in their first trimester attending the Obstetrics and Gynaecology OPD were randomly selected for the study.

Women with h/o thyroid disease, family h/o thyroid abnormalities, suffering from any other endocrine abnormalities or acute/chronic diseases, on steroid and hormone medications, subjected to neck radiation, were excluded from the study.

The study was approved by the institutional ethical committee.

After obtaining informed consent, the study group was screened for TSH and T4.

Blood samples were collected and analysed for TSH and T4 by chemiluminescence in an autoanalyzer with commercially available kits.

Considering the disparity in the reference range of thyroid parameters in pregnancy and recommendations of various bodies and data documented in several literatures in this context,

We divided the SCH cases into two groups – Group 1 with TSH >4.2mIU/L with normal T4 and Group 2 with TSH between 2.5- 4.2mIU/L, T4 level normal. Overt hypothyroidism cases with TSH >2.5mIU/L and low T4 and Group 1 SCH cases with TSH >4.2mIU/L and T4 normal were excluded from follow-up and referred for further evaluation. Women with TSH in the range 2.5-4.2mIU/L with T4 normal (Group 2) were followed up till confinement and their pregnancy outcomes were recorded and analyzed. Statistical analysis was done in Microsoft Excel sheet with student's t test. P value <0.05 was taken as statistically significant.

Observations

Table 1- The Study Population

Groups	TSH	T4	n	Percentage
Euthyroid	< 2.5mIU/L	N	154	77%
Overt Hypothyroidism	>2.5mIU/L	Low	10	5%
Subclinical hypothyroidism Group 1	4.2mIU/L -10 mIU/L	N	9	4.5%
Sub clinical hypothyroidism Group 2	2.5-4.2 mIU/L	N	27	13.5%

Table 2 – Analysis of Age, BMI and Thyroid Status between Euthyroid and SCH Group of the Study Population

	Euthyroid n=163	Hypothyroidism n= 10	SCH Group 1 n=9	SCH Group 2 n=27
Age	25± 5.4	26± 4.6	24± 4.0	25± 5.7
BMI	21± 2.2	25± 2.7*	23± 1.8	22± 2.5
TSH (mIU/L)	1.3± 0.8	11.2± 3.2**	7.6± 1.4*	3.4± 0.6*
T4 (nmol/L)	123± 26.7	45 ± 8.4**	85± 8.2*	87± 10.4*

*p<0.05, ** p<0.01, Student's t test

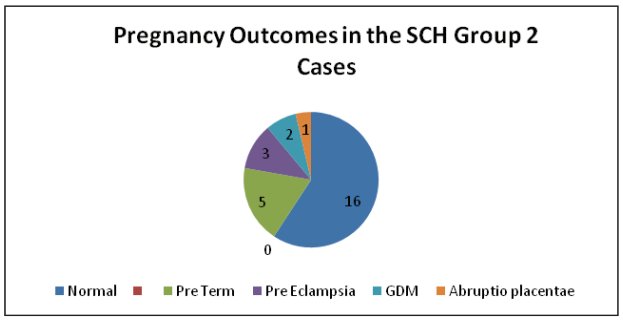

Figure 1 : Pregnancy outcomes in the SCH group 2 cases

This Case Series showed an occurrence of 13.5% (n=27) of SCH in pregnancy screened in 1st trimester in first ante natal visit with TSH level between 2.5-4.2mIU/L,T4 within normal range .9 cases (4.5%) were having TSH >4.2mIU/L, T4 normal, 77% (n=154) were euthyroid (TSH<2.5mIU/L,T4 normal) and 5% (n=10) were having overt hypothyroidism(TSH >2.5mIU/L, T4 low) (Table 1). Altogether 18% of the study population were found to be having SCH if the upper limit is taken to be 2.5mIU/L whereas with a upper limit of 4.2mIU/L, the incidence of SCH reduced to 4.5%.

The mean age and BMI of the euthyroid cases was 25± 5.4 and 21± 2.2 respectively. The mean age of the SCH Group 1 was 24± 4.0 and their BMI was calculated to be 23± 1.8. The mean age of the SCH Group 2 was 25± 5.7 and their BMI was calculated to be 22± 2.5. The age and BMI of the overt hypothyroidism cases were 26 ± 4.6 and 25± 2.7 respectively. The difference in BMI of the overt hypothyroidism cases showed a statistically significant difference compared to the euthyroid cases while other groups registered no significant difference in the age and BMI compared to the euthyroid study population (Table 2).

Serum TSH level in the euthyroid cases was 1.3± 0.8 mIU/L and it was found to be 11.2± 3.2 mIU/L in the overt hypothyroidism cases. Serum T4 level was 123± 26.7 nmol/L and 45± 8.4 nmol/L in the euthyroid and overt hypothyroidism cases respectively (Table 2). On analysis the difference was found to be statistically significant (p<0.01)

The measured values of TSH and T4 in SCH group 1 and group 2 were 7.6± 1.4 and 85± 8.2 and 3.4± 0.6 and 87± 10.4 respectively. The observed value were significantly different from the euthyroid cases (p<0.05) .The difference in TSH values in group 1 and group 2 of the SCH cases were also statistically significant (p<0.05) though their T4 levels showed no significant difference.

The overt hypothyroidism cases and Group 1 SCH cases were referred for further evaluation and intervention.

TSH estimation repeated in each trimester in the group 2 SCH cases didn't show any significant rise and remained below 4.2mIU/L.

On follow-up of the SCH Group 2 cases till delivery, it was observed that 5 cases had a preterm delivery within 32-34 weeks of gestation with SGA (small for gestational age) babies. Apart from this, the other complications noted were pre-eclampsia in 3 cases, GDM in 2 cases, and abruptio placentae in one case figure1.

Discussion

Subclinical hypothyroidism is a very common endocrine abnormality associated with pregnancy. The growing foetus is solely dependent upon maternal thyroid hormones in the first three months of intra uterine life .The thyrotrophic action of beta hCG and regulation of HPT axis usually tries to meet the extra demand for thyroxin in pregnancy. The need for Iodine also increases leading to an Iodine deficient status if not adequately supplemented. Literatures show that overt hypothyroidism adversely affects the pregnancy and foetal outcome (9, 10, 23). Similar observations have also been made in cases of subclinical hypothyroidism (24-26). In long term follow-up children born to SCH mothers

show intellectual slowness [11, 12]. Apart from Iodine deficiency, the other most common factor for thyroid hormone deficiency has been attributed to anti-TPO antibodies [16].

In spite of literatures accumulating for adverse effects of SCH on pregnancy and foetal outcomes, still there has been no consensus regarding routine screening of ante-natal cases for thyroid profile.

Prevalence of hypothyroidism during pregnancy is found to be different in diverse geographic areas with it being higher in Asian countries than in the West[26-32]. Broadly, it is observed that prevalence of clinical and subclinical hypothyroidism is higher in Indian population the reason of which may be attributable to increased anti-TPO Ab positivity leading to autoimmune thyroiditis, presence of goitrogens in Indian diet as well as various micronutrient deficiencies like Selenium and Iron[11, 24, 33]. Ramprasad et al documented a prevalence of 6.47% (31), Parham et al registered a prevalence of 11.9% [29], Dhanwal et al [30] documented a prevalence of 13.5% of SCH in pregnancy. In our study 18% of the study population were found to be having SCH if the upper limit for TSH is taken to be 2.5mIU/L whereas with a upper limit of 4.2mIU/L, the incidence of SCH reduced to 4.5%.Considering the adverse effects of subclinical hypothyroidism in pregnancy and recent guidelines by various professional bodies, it seems logical to reduce the cut-off of TSH to 2.5mIU/L in order to diagnose SCH early in pregnancy and prevent its atrocious effects.

Banovac et al [34] have registered in their findings that placenta has strong affinity for T3 and is dependent on thyroid hormones for its growth. Maruo et al [35] have documented a probable role of T3 in trophoblast growth and development in human placenta by stimulating production of 17β estradiol and epidermal growth factor. Repercussions of maternal thyroid hormone abnormality on placental growth and their influence on the villous and extravillous trophoblast proliferation, incursion and viability has been documented in various studies [36,37]. Imperfect trophoblast growth is supposedly responsible for IUGR (intra uterine growth retardation) which in turn leads to SGA babies [38]. In our study, 5 cases had pre-term delivery with SGA babies within 32-34 weeks. Faulty placental development due to SCH may be attributed for these complications as accumulating facts have pointed towards the role of thyroid hormones on villous development and apposite placental growth [36,37]. Studies have also revealed that circulating thyroid hormones are less in IUGR foetal serum compared to gestation matched normal foetal serum [39, 40, 41]

Development of pre-eclampsia in 3 cases and abruption placenta in 1 case reflects the role of thyroid hormones in development and normal functioning of placenta as many studies has established placental deficits as an etiological factor in pre-eclampsia.

Past studies have shown that pre-eclampsia happen due to deficient uteroplacental circulation resulting in oxidative stress, hypoxia and infarction in placenta [42,43]while recent evidences register an inflammatory component in the development of this serious disorder [44-47]. Hence accumulating literatures now give more importance to inflammation as a major cause of pre-eclampsia and pre term labour in pregnancy.

Thyroid hormones belong to Group I hormones having intracellular receptors and response elements in DNA affecting expression of various genes [48-51] including many genes linked with inflammation.[52]. Thyroid hormones play a role in inflammation which in turn is a vital cellular process in pre eclampsia.

Maternal serum and cord blood analysis has documented low thyroxine level with high TSH in preeclampsia cases linked with placental insufficiency.[53, 54]

2 cases (7.4 %) in our study group with SCH developed gestational Diabetes mellitus (GDM). Feely et al documented that SCH coexisted in 30% cases of GDM [55]. Many other literatures have also documented an association of thyroid abnormalities, notably overt and subclinical hypothyroidism as well as autoimmune thyroiditis with GDM [56-60]. This correlation has been substantiated by depiction of an inverse association between Metforfin and TSH level [61, 62, 63]. Hence, screening for thyroid dysfunction in diabetes patients, ät-risk" patients for GDM, with anti-TPO antibody positivity, or with TSH concentrations in the upper limits of normal range has been advised by many studies.

Hence, from many accumulating data it is more or less evident that thyroid abnormalities and diabetes mellitus are very frequently associated and coexists in pregnancy which has multiple adverse effects on the pregnancy outcome. Moreover, hypothyroidism both overt and sub-clinical is proven to be adversely affecting pregnancy with complication like pre term delivery, abruption placenta, pre-eclampsia,

IUGR and increased foetal loss. Children born to untreated hypothyroid mothers on long term follow – up has also shown signs of mental slowness and low intellectual development. Universal screening of pregnant women for thyroid status and initiation of treatment in SCH cases is yet to have universal consensus as data regarding beneficial effects of treatment to mother and foetus in SCH cases is inadequate. Determination of a specific cut-off limit for TSH for diagnosis of SCH in pregnancy in India is also essential as in our study it was observed that reducing the upper limit to 2.5mIU/L resulted in detection of 27 more cases of asymptomatic SCH which on follow-up depicted some complications in their pregnancy outcome.

Limitations of our study

Our study was a case series where we have not followed up the euthyroid, the overt hypothyroidism and Group 1 SCH cases till their confinement to compare with the Group 2 SCH cases. The prevalence of SCH in the screened population was as high as 18 % when the cut-off for TSH was reduced to 2.5mIU/L that was randomly selected and were not "at risk" group and 40.7% (11 out 0f 27 cases) of the SCH cases developed some complications in their pregnancy tenure resulting in adverse outcomes. Hence, multicentre intervention trials with larger cohorts involving universal screening and initiation of treatment to all SCH cases in pregnancy with careful follow-up to record the beneficial effects on mother and child is needed to reach a general consensus on mandatory thyroid status screening in all pregnant women.

Conclusion

Hypothyroidism and Diabetes mellitus are the two most frequent endocrine disorders associated with pregnancy. Both affect the pregnancy and foetal status unfavourably. Moreover apart from Iodine deficiency, anti-TPO antibody positivity is also frequently detected in clinical and subclinical hypothyroidism in pregnancy. It is also observed in various studies that late detection and treatment of hypothyroidism in pregnancy has failed to improve the obstetric outcome. This study was done on a small cohort taking only the SCH cases till confinement yet it was noticeable that hypothyroidism was detected in women who were not "at risk" population and many of them developed some complications associated with pregnancy. Hence, mandatory screening of all pregnant women should be strongly advocated in first trimester in their first ante natal visit for early detection and timely intervention of hypothyroidism including SCH and reduce its detrimental effects on maternal and foetal well being.

Conflict of interest: None

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