Maternal Serum TSH Value in Early Pregnancy and its Relation with Pregnancy Outcome

Swet Nisha[1], Rekha Kumari[2], Uday Kumar[3]

ABSTRACT

Introduction: Thyroid disorders in pregnancy are among the common endocrine disorders. During pregnancy several physiological changes occur in maternal thyroid function and failure to adapt to these changes result in thyroid dysfunction. Thyroid dysfunctions have many adverse effects on mother and fetus, like miscarriages, preeclampsia, eclampsia, placental abruption, preterm delivery, low birth weight, post partum haemorrhage, neonatal hypothyroidism and impaired neurological and intellectual development of fetus. Study aimed to find out the prevalence of thyroid dysfunction in pregnancy and to know maternal and foetal outcome.

Material and methods: This cross sectional clinical study was carried out at Obstetrics and Gynecology department in collaboration with Biochemistry Department, IGIMS, Patna, Bihar from August 2018 to August 2019 including 100 pregnant women with single intrauterine pregnancy in first trimester between 6-14th weeks of gestation. TSH level was estimated in all the pregnant women along with FT3, FT4, and Anti TPO Ab. According to the thyroid profile, patients were divided into 4 groups- Normal/ Subclinical/ Overt hypothyroidism and hyperthyroidism and followed till delivery for maternal and perinatal outcome.

Results: In our study of 100 patients, 87 were found to have normal thyroid function and 13 cases were having subclinical hypothyroidism, using a cut off TSH level of 2.5-10uIU/ml in AntiTPO Ab positive and 4-10uIU/ml in AntiTPO Ab negative cases. No case of hyperthyroidism or overt hypothyroidism was found. These 100 patients were divided into two groups. Patients having normal thyroid function were included in Group 1 and patients with subclinical hypothyroidism were included in group 2. In subclinical hypothyroidism group 5(38.46%) cases were AntiTPO Ab positive and 8 cases were AntiTPO Ab negative.

Conclusion: Our study concludes that there is high prevalence of subclinical hypothyroidism (13%) in pregnant women during 1st trimester. No significant difference was seen in maternal and foetal outcome between euthyroid patients and treated subclinical hypothyroid patients.

Keywords: Hypothyroidism, Pre eclampsia, Thyroid Dysfunction

INTRODUCTION

Pregnancy has a profound but reversible effect on the thyroid gland and its function. These physiological changes include increased concentrations of thyroid hormone-binding globulin, thyroid hormones and thyroglobulin, enhanced iodine clearance by the kidneys and a mild thyrotropic effect of rising human chorionic gonadotropin on TSH secretion.[1] In developing countries, women living in iodine deficient area do not cope up with the changes, resulting in hypothyroidism during pregnancy. In iodine replete areas, the prevalence of spontaneous hypothyroidism has been found to be 1-2%, and it is more common in older women.[2] Hypothyroidism in women causes subfertility and even if they conceive, there is increased risk of abortion, gestational hypertension, abruption placenta, preterm labour, anaemia and post-partum haemorrhage.[3] Hypothyroidism causes irreversible brain damage of fetus leading to neurological abnormalities, neonatal jaundice, delayed milestone and decreased intelligent quotient level.[4,5,6,7] In developed countries, the commonest cause of hypothyroidism in pregnancy is autoimmune thyroiditis.[8] Thyroid auto-immunity appears to be a risk factor for abortions and preterm birth.[9] In the women of reproductive age group the presence of thyroid antibodies is relatively common.[9,10,11] During pregnancy the presence of anti-thyroid peroxidase (anti-TPO) antibodies alerts to the risk of the development of post-partum thyroiditis, reported to be developed in approximately 50% of the women.[12,13] The present study was carried out to know the prevalence of thyroid disorders in pregnancy and its maternal and foetal outcome.

MATERIAL AND METHODS

This Longitudinal prospective clinical study was carried out at Obstetrics and Gynaecology department in collaboration with Biochemistry department, IGIMS, Patna, Bihar after clearance from institutional ethics committee. 100 OPD patients visiting obstetrics and gynaecology department of IGIMS, Patna were taken into the study.

Inclusion Criteria

Singleton pregnancy between 6-12 weeks
Primigravida /Multigravida

Exclusion Criteria

Documented history of Thyroid Dysfunction on treatment
Multiple pregnancy

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Gestational Trophoblastic diseases
Any medical co-morbidities
Bad obstetric history
Informed consent was taken from all the patients and along with the routine investigations, TSH, FT3, FT4 and Anti TPO Ab were done in all the patients. The patients were divided into two groups according to TSH levels Group 1 (Euthyroid) and Group2 (Subclinical hypothyroid). Levothyroxine was supplemented to all the subclinical hypothyroid patients. The patients were followed till delivery for maternal and perinatal outcome. Cord blood TSH were collected at the time of delivery.

Group 1:	(Control group): TSH levels 0.3-4 uIU/ml with normal FT3 and FT4 and AntiTPO Ab negative(n = 87)
Group 2:	(Test group): TSH levels >2.5 uIU/ml and AntiTPO Ab positive OR TSH>4uIU/ml with normal FT3 and FT4 (n = 13)

The patients with TSH values more than 2.5 uIU/ml and Anti TPO Ab positive or TSH > 4uIU/ml irrespective of Anti TPO Ab were given treatment with levothyroxine as per their TSH levels.[14,15] All these hypothyroid patients were followed after 1 month of treatment, and then every 3 monthly till delivery for TSH levels, clinical condition and pregnancy outcome. None of the patients were found overt hypothyroid or hyperthyroid.
Baseline data: A detailed information with respect to age, parity, educational status, method of conception, menstrual history, obstetrical history, (abortion or preterm delivery) present pregnancy, medical, surgical, personal and family history of every patient was taken. General physical, systemic and obstetric examination was done. If required, period of gestation was confirmed by ultrasonography (USG). Routine investigations (Hb, ABO Rh, HIV, HBsAg,75mg GCT, Serum TSH, FT3, FT4, Anti TPO Ab and urine R/E) were done in all the patients. Patients with Serum TSH 0.3-4uIU/ml and Anti TPO Ab negative (0-9.0 IU/ml) were categorised as control group (Group-1) whereas patients with Serum TSH>2.5 uIU/ml and Anti TPO Ab positive(>9.0 IU/ml) or Serum TSH>4-10 uIU/ml irrespective of Anti TPO Ab were categorised as subclinical hypothyroid and supplemented with thyroxin according to Serum TSH value (Group-2). None of the patients were overt hypothyroid (serum TSH> 10uIU/ml irrespective of Anti TPO Ab status) or hyperthyroid (serum TSH<2.5th percentile or <0.3 uIU/ml).
Maternal outcomes were assessed in respect to:
Abortion
Pre eclampsia
Anemia
Oligohydramnios
Preterm delivery
PPH
Foetal outcomes were assessed by
Birth weight
NICU admission
Hyperbilirubinemia
Neonatal hyper/hypothyroidism

STATISTICAL ANALYSIS

The data was analysed for mean, proportion. Chi square was calculated for association. The P value =< 0.05 was considered as significant. Analysis was done using EPIDATA analysis software V2.

RESULTS

The baseline characteristics of the study population are given in table 1.
Majority of patients in both the groups were primigravida (59.77% in Group 1, euthyroid and 53.85% in Group 2, subclinical hypothyroid).

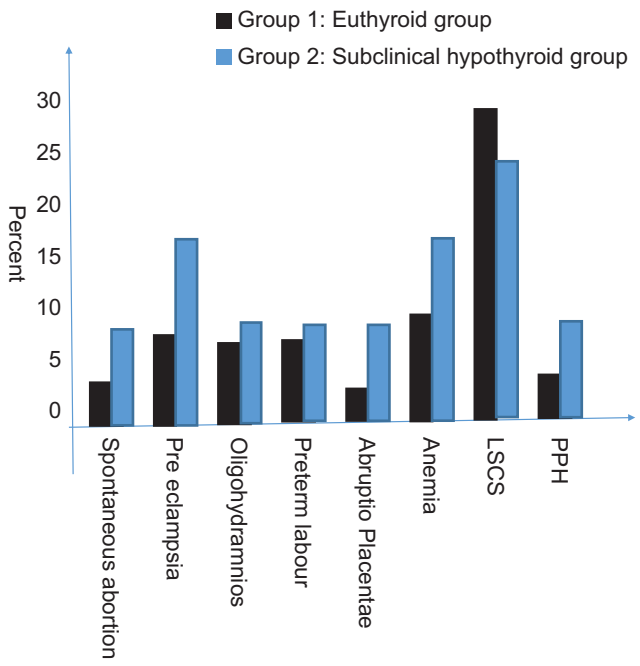

Figure-1: Maternal Outcome

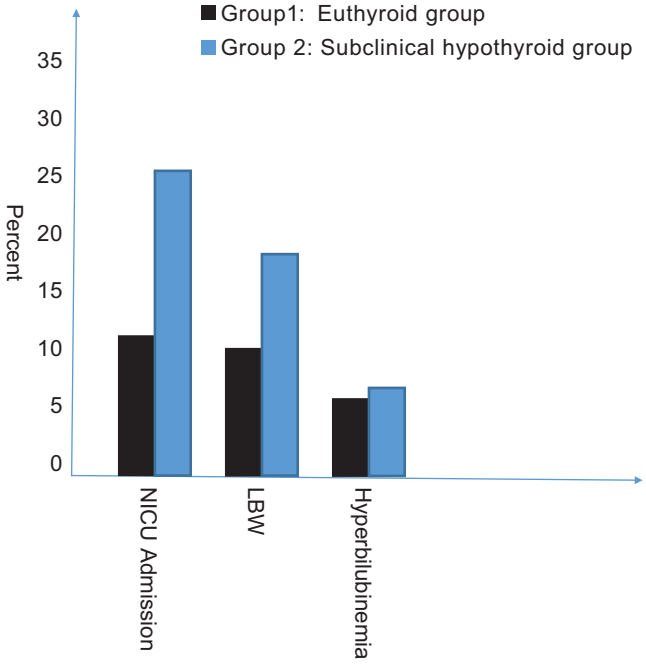

Figure-2: Fetal Outcome

	Group 1	Group 2
Mean age	23.58±1.87 years	24.6±1.45 years
Mean Hb	10.343±1.152 gm/dl	10.445±1.284 g dL-1,
Mean BMI	23.8±6.0Kg/m2	22.3±7.0Kg/m2
Primigravida	59.77%	53.85%

Table-1: Baseline characteristics

	Booking visit	1 month	2nd trimester	3rd trimester
Group 1	1.42±0.97uIU/ml			
Group 2	5.16±1.67uIU/ml	2.21±1.54	1.79±1.17	1.63±0.67

Table-2: Mean TSH Level in Group 1(Euthyroid) and Group 2 (Subclinical hypothyroid)

	Group 1(n=87)	Group 2(n=13)	p value
Spontaneous abortion	3 (3.45%)	1 (7.69%)	0.4664
Mean POG	38.65 weeks	37.39 weeks	0.6141
Pre eclampsia	6 (6.90%)	2 (15.38%)	0.7830
Oligohydramnios	5 (5.75%)	1 (7.69%)	0.6102
Abruption Placentae	1 (1.15%)	1 (7.69%)	0.7830
Preterm delivery	5 (5.75%)	1 (7.69%)	0.7317
Anemia	7 (8.05%)	2 (15.38%)	0.7967
LSCS	23 (26.44%)	3 (23.08%)	0.4664
PPH	3 (3.45%)	1 (7.69%)	0.4664

Table-3: Maternal outcome

	Group 1	Group 2	P value
NICU Admission	11 (12.64%)	4 (30.77%)	0.1968
LBW	10 (11.49%)	3 (23.08%)	0.4739
Hyperbilirubinemia	6 (6.90%)	1 (7.69%)	0.9165

Table-4: Fetal outcome

The reference range for normal TSH was 0.3-2.5uIU/ml if AntiTPO Ab positive and 0.3-4uIU/ml in AntiTPO Ab negative patients in all the trimesters. Total 13% patients were found to be subclinical hypothyroid. Mean maternal TSH level was significantly higher in group 2 (subclinical hypothyroid) as compared to group 1 (euthyroid) at booking visit. All these subclinical hypothyroid patients were given treatment with levothyroxine as per their TSH levels. All the patients were followed till delivery with Serum TSH level. The mean TSH level at the time of delivery in group 2 patients was significantly lower as compared to the mean TSH levels in 1st trimester and was comparable to euthyroid patients. Mean TSH levels of both the groups are shown in table 2.

Mean FT3 level in group 1 was 2.24±0.431pg/ml and in group 2 was 2.42±0.38 pg/ml and the difference was not statistically significant. Mean FT4 level in group 1 was 1.025±0.151 ng/dl and in group 2 was 1.043±0.131 ng/dl and the difference was not statistically significant.

Anti TPO Ab (TPO Ab) testing was done in all the patients. The TPO Ab levels less than 9 IU/ml were taken as negative. In Group 2, 38.46% patients were Anti TPO Ab positive i.e out of 13 subclinical hypothyroid patients, 5 were Anti TPO Ab positive; three patients had TSH levels between 2.5 and 4uIU/ml and two patients had TSH levels above 6 uIU/ml. All patients in Group 1 were Anti TPO Ab negative. In both the groups, majority of deliveries were vaginal i.e 73.56% in euthyroid group (group 1) and 76.92% in subclinical hypothyroid group (group 2). None of the maternal outcome was found to be statistically significant($p > 0.05$). Maternal outcomes of both the groups are shown in table 3 and fig-1.

Eleven babies (12.64%) in group 1 and four babies (30.77%) in group 2 had NICU admission. There was no intrauterine death in either of the group. Foetal outcomes were also not statistically significant ($p>0.05$) between the two groups (Table 4, fig-2).

Cord blood TSH values were 3.17±2.1 uIU/ml and 4.47_+ 2.4 uIU/ml in group 1 (euthyroid) and group 2 (subclinical hypothyroid) respectively. Positive correlation was observed between maternal TSH at first trimester and cord blood TSH ($r = +0.225$, $p<0.05$). Negative correlation was observed between the TSH levels in first trimester and mean birth weight of neonates ($r = -0.037$, $p<0.05$). A negative correlation between cord blood TSH and birth weight of babies ($r = -0.16$, $p<0.05$) was observed.

DISCUSSION

Foetal and placental growth seems to be affected by thyroid dysfunction in early pregnancy. Mean maternal TSH level was significantly higher in group 2 as compared with group 1 at booking visit. Subclinical hypothyroid patients were given treatment with levothyroxine as per their TSH

levels. The mean TSH level at the time of delivery in group 2 (subclinical hypothyriod) patients was significantly lower as compared with the mean TSH levels in 1st trimester and was comparable to euthyroid patients. Springer et al. (2009)reported that in normal pregnant women mean TSH levels in first trimester to be 1.213 uIU/ml excluding those with history of thyroid disease and autoimmunity. Human chorionic gonadotropin has thyrotropic activity and thus its elevated concentration is responsible for lower serum TSH levels, mainly in the first trimester.[16]

Springer et al., 2009 have also shown an inverse correlation between TSH and FT4 levels due to the thyrotropic properties of human chorionic gonadotropin.[16] Human chorionic gonadotropin levels increase in the first 10 weeks of pregnancy, and then subsequently decrease leading to a decrease in FT4 and an increase in TSH levels. In addition, there is rise in thyroxine-binding globulin levels because of high estrogen levels, thereby increasing total T4 levels.[17]

Antithyroid antibodies may serve as a marker of autoimmune condition that causes risk for foetal death i.e exert a direct adverse effect on the pregnancy. Women with thyroid autoimmunity may be euthyroid and suffer subfertility, and used to develop subclinical or overt hypothyroidism during the first trimester.[18,19] Anti thyroperoxidase (TPO) antibodies have diagnostic and prognostic significance.

In the present study, TPO Ab positivity was found to be 38.46% in subclinical hypothyroid group (Group 2). It was observed that all patients in euthyroid group (Group 1) were thyroid auto-antibody negative. The incidence of TPO positivity in pregnant women was reported to be 19.6% by Stagnaro-Green and Glinoer (2004) and 11.7% by Negro et al. (2006) & Springer et al. (2009).[10,16,18] In different studies, TPO Ab positivity has been found to be associated with higher maternal TSH levels and lower FT4 level, and risk of subclinical hypothyroidism increases by 8 fold and risk of overt hypothyroidism increases by 26 fold.[18,20,21,22,23]

Majority of patients were able to carry their pregnancy to term gestation. Mean gestational age at delivery was 38.65 weeks in Group 1 (euthyroid) and 37.39 weeks in Group 2 (subclinical hypothyroid) in the present study. The result was similar to the studies Allan et al., 2000; Mannisto et al., 2009; Casey et al., 2005.[22,24,25] Thyroid autoimmunity is an important risk factor for abortion and preterm birth.[8] In women with subclinical hypothyroidism, preterm deliveries were significantly increased, which accounted for increased admissions to the NICU and respiratory distress syndrome in the offspring compared with the offspring of euthyroid women.[25] Seventy two percent (72%) relative reduction in preterm delivery has been shown in euthyroid women with autoantibodies when given treatment with levothyroxine.[18] In our study, 5.75% pre-term deliveries were found in euthyroid group (Group 1) and 7.69% in subclinical hypothyroid group on levothyroxine supplementation (Group 2). Similar to our study, Sharma et al. 2007 showed that there was no significant difference in preterm deliveries among treated hypothyroid and euthyroid patients.[26] In the present study, the incidence of pre-eclampsia was found to be 6.90% in euthyroid group (Group 1) and 15.38% in subclinical hypothyroid group (Group 2) i.e no significant difference was found in treated hypothyroid and euthyroid pregnant women when compared for development of pre eclampsia, which is similar to Sharma et al. (2007).[26] In the present study, 3 infants (23.08%) in subclinical hypothyroid group (Group 2) and 10 infants (11.49%) in euthyroid group (Group 1) were LBW whereas five infants (5.75%) in euthyroid group (Group 1) and 1 (7.69%) infant in subclinical hypothyroid group (Group 2) were delivered prematurely. For the maturation of tissues of brain, lungs, skeleton, intestine and heart, as well as for the non-shivering thermogenesis in the neonates, thyroid hormone is essential. Thyroid hormone-dependent tissue maturation occurs in a highly regulated, temporal sequence in which the ontogeny of the hypothalamic pituitary-thyroid axis is tightly linked to the tissue-specific expression of the thyroid hormone receptor and the local maturation of the deiodinase system that generates T3 from T4. An association between overt maternal hypothyroidism and low birth weight has been shown by Sardana et al., 2009.[27] Many studies have shown association of thyroid function and autoimmunity in early pregnancy with adverse pregnancy and birth outcomes.[28] An increased rate of preterm delivery has been seen among women with subclinical hypothyroidism.[25]

Cord blood TSH values were 3.17±2.1 uIU/ml and 4.47_+ 2.4 uIU/ml in euthyroid group (group 1) and subclinical hypothyroid group (group 2) respectively. Positive correlation was observed between maternal TSH at first trimester and cord blood TSH ($r = +0.225$, $p<0.05$). Similar positive correlation between maternal and cord blood TSH, with r-value of +0.08, $p<0.05$ have been shown by Medici et al. (2011).[23] The association was found to be similar even after exclusion of TPO Ab positive patients and additional correction of ethinicity, smoking and socioeconomic status. It has been shown that pregnant women with inadequate dietary iodine intake in the third trimester had lower birth weight infants than the pregnant women with adequate dietary iodine intake.[29] In the present study, negative correlation was observed between the TSH levels in first trimester and mean birth weight of neonates ($r = -0.037$, $p<0.05$). A negative correlation between cord blood TSH and birth weight of babies ($r = -0.16$, $p<0.05$) was also observed.

Abalowich et al. (2002) concluded that the outcome of pregnancies was based mainly on the treatment received in both overt or subclinical hypothyroidism.[3] Sharma et al. in 2007 showed that there was no significant difference in the complications between euthyroid patients and hypothyroid patients under treatment.[26] Negro et al. (2006) showed that levothyroxine (LT4) administration in thyroid autoimmunity positive pregnant women, during the early stages of pregnancy, reduces the risk of abortions and the rate of premature deliveries.[18] A recent meta-analysis of 18 cohort studies found that pregnant women with untreated subclinical hypothyroidism are at higher risk for pregnancy loss, placental abruption, premature rupture of membranes, and neonatal death compared with euthyroid women.[30] Current guidelines recommend levothyroxine treatment in

pregnant women with subclinical hypothyroidism.[31,32]

CONCLUSION

Thyroid profile is a must at first booking visit as fetus needs thyroxine for brain development, growth and lung maturation.

In our study, subclinical hypothyroidism in pregnancy has been found to be the commonest thyroid dysfunction. TSH levels were found to be higher in first trimester in subclinical hypothyroid women as compared to euthyroid pregnant women. Thus, adequate replacement therapy should be done to keep TSH within the specific reference range (ATA). Normal thyroid function is necessary to avoid abortions, to maintain normal placental development and function throughout gestation to avoid preterm deliveries and for proper foetal neurodevelopment. Thus, in the present study, it has been shown that in pregnancy, subclinical hypothyroidism is the commonest thyroid disorder and optimum thyroxine replacement in time results in maternal and perinatal outcome similar to euthyroid patients.

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