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

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ABSTRACT

The present prospective clinical study was carried out in 200 pregnant women with single intrauterine pregnancy of gestational age between 6-14th weeks. Thyroid function tests namely TSH, FT_3, FT_4, TPO Ab and TG Ab were done. The patients were followed till delivery for perinatal outcome. Maternal and cord blood for TSH were collected at the time of delivery. The role of levothyroxine on maternal and fetal outcome in these patients was also studied. Mean FT_3 and FT_4 levels in Group 1 were comparable. Mean TSH levels at first trimester in Group 2 were significantly higher than those in Group 1 ($p = 0.04$). The patients with raised TSH levels were given treatment with levothyroxine as per their TSH levels. The mean TSH levels at the time of delivery in Group 2 patients were significantly lower as compared to the mean TSH levels in the first trimester and they were comparable to euthyroid patients ($p = 0.32$). The TPOAb positivity was found to be 14%. The TGAb positivity was found to be 7%. It was observed that all patients in Group 1 were thyroid auto-antibody negative. Cord blood TSH values were 4.47±2.1 mIU L^{-1} and 6.88±2.3 mIU L^{-1} in Group 1 and Group 2, respectively, $p<0.01$. The correlation between maternal TSH at first trimester and cord blood TSH was positive ($r = +0.227$, $p<0.01$). Negative correlation was observed between the TSH values in first trimester and average birth weight of neonates ($r = -0.038$, $p<0.05$). Negative correlation was observed between cord blood TSH and birth weight of babies ($r = -0.15$, $p<0.05$). Subclinical hypothyroidism and thyroid antibody positivity were associated with increased incidence of low birth weight babies. However, biochemical parameters and perinatal outcomes were better after thyroxine replacement therapy. It can be inferred that optimum thyroxine replacement in early gestation results in good perinatal outcome.

Key words: Maternal, cord blood, TSH, TGAb, TPO Ab, thyroid hormone

INTRODUCTION

Data from human and animal studies suggest that pregnancy alters normal thyroid function. Indicative 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 (Glinoer *et al*., 1990).

Women with hypothyroidism have decreased fertility, even if they conceive, risk of abortion is increased, along with the risk of gestational hypertension, anaemia, abruption placenta and post-partum haemorrhage (Abalovich *et al*., 2002). The adverse foetal outcomes include irreversible brain damage leading to neurological abnormalities, decreased intelligent quotient levels, malformations and neonatal jaundice (Fantz *et al*., 1999; Walker *et al*., 2005; Haddow *et al*., 1999; Smallridge and Ladenson, 2001).

Autoimmune thyroiditis is the commonest cause of hypothyroidism in pregnancy in developed counties (Klein *et al*., 1991). Thyroid autoimmunity appears to be one of the determining factors in pregnancy loss. Thyroid auto-immunity represents a risk factor for infertility. The presence of thyroid antibodies is relatively common in women of reproductive age (Stagnaro-Green and Glinoer, 2004; Bussen and Steck, 1995; Thangaratinam *et al*., 2011). There is evidence that thyroid autoimmunity is an important risk factor for abortions and pre-term birth (Thangaratinam *et al*., 2011).

Free Thyroxin (FT_4) is not affected by the concentration of the binding proteins and its concentration during pregnancy is partly affected by both the inflow of iodine and the duration of the pregnancy. Presence of anti-thyroid peroxidase (anti-TPO) antibodies during pregnancy also alerts to the danger of the development of post-partum thyroiditis, about 50% of anti TPO positive women have some thyroid dysfunction after delivery (Premawardhana *et al*., 2004; Nicholson *et al*., 2006).

In the present study, maternal thyroid functions were studied in early gestation. The role of levothyroxine on maternal and foetal outcome in these patients was also studied.

MATERIALS AND METHODS

This prospective clinical study was carried out in 200 pregnant women with single intrauterine pregnancy (gestational age: 6-14 weeks) attending the antenatal clinic at Outpatient Department of Obstetrics and Gynaecology in Pt. B.D. Sharma P GIMS, Rohtak. Informed consent was taken from all the patients. Thyroid function tests namely TSH, FT_3, FT_4 TPO Ab and TG (thyroxine binding globulin) Ab were done (Walker *et al*., 2005). The patients were followed till delivery for perinatal outcome. Maternal and cord blood TSH were collected at the time of delivery. The patients were divided into two groups according to TSH levels:

Group 1: (Control group): TSH levels between 0-2.5 mIU L^{-1} with normal FT_3 and FT_4 (n = 100)
Group 2: (Test group): TSH levels >2.5 mIU L^{-1} with normal FT_3 and FT_4 (n = 100)

The patients with positive TPO Abs and TG Abs antibodies and those with TSH values more than 2.5 mIU L^{-1} were given treatment with levothyroxine as per their TSH levels (Biondi, 2007). These patients were followed every 3 monthly till delivery for TSH levels, clinical condition and pregnancy outcome.

Exclusion criteria: The patients already on treatment for thyroid disorder, those with overt hyperthyroid and overt hypothyroid on screening and those suffering from medical disorders like hypertension, diabetes mellitus and heart diseases were excluded from the study.

Baseline data: A detailed history with respect to present, past, obstetrical, medical, surgical and personal history of every patient was taken. Data regarding maternal age, weight, parity and educational status, method of conception, history of fever, any radiation exposure and any medical disorder like diabetes mellitus, hypertension, previous preterm delivery or miscarriage was collected. A detailed general physical, systemic, obstetric and pelvic examination was carried out. Period of gestation was confirmed by ultrasonography (USG), if required. Routine investigations (Hb, ABORh, STS, HIV, HBsAg, urine C/E, 75 mg GCT) were carried out at the first visit. Data was tabulated as Mean±S.D. Student's t-test was applied. Differences in the proportions between different categorical variables were tested through Chi square test of significance.

RESULTS

Mean age of patients in Group 1 and Group 2 was 22.58±1.89 years and 23.6±2.449 years, respectively. Mean Hb in Group 1 and Group 2 was 10.214±1.162 and 10.334±1.294 g dL^{-1}, respectively. Majority of patients in both the groups were primigravida (60% in Group 1 and 51% in Group 2).

Mean FT_3 levels in Group 1 were 5.33±0.631 pmol L^{-1} and in Group 2 was 5.38±0.72 pmol L^{-1} and the difference was not statistically significant. Mean FT_4 levels in Group 1 were 13.15±1.561 pmol L^{-1} and in Group 2 was 12.34±1.634 pmol L^{-1}) and the difference was not statistically significant.

The reference range for normal TSH was 0.1-2.5 mIU mL^{-1} in first trimester and 0.3-3.0 mIU mL^{-1} in second and third trimester (Glinoer, 2011). Mean TSH levels at first trimester in Group 2 were significantly higher than those in Group 1 ($p = 0.04$). The patients with raised TSH levels were given treatment with levothyroxine as per their TSH levels. The mean TSH levels at the time of delivery in Group 2 patients were significantly lower as compared to the mean TSH levels in the first trimester and they were comparable to euthyroid patients ($p = 0.32$).

All the patients were subjected to thyroid auto-antibody testing (TPOAb and TGAb). The TPO Ab levels less than 70 IU mL^{-1} were judged as negative. The TG Ab levels less than 110 IU mL^{-1} were considered negative. Overall, TPOAb positivity was found to be 14%. The TGAb positivity was found to be 7%. Six percent of patients were both TPOAb and TGAb positive. It was observed that all patients in Group 1 were thyroid auto-antibody negative.

Out of 14 patients who were TPOAb positive, eight patients had TSH levels between 2.5 and 5 mIU L^{-1} and 6 patients had TSH levels above 5 mIU L^{-1}. Out of 7 patients who were TGAb positive, 2 patients had TSH levels between 2.5 and 5 mIU L^{-1} and 5 patients had TSH levels above 5 mIU L^{-1}. It was observed that out of 6 patients who were both TPOAb and TGAb positive, 4 patients had TSH values above 5 mIU L^{-1} (Table 1).

Mean period of gestation (POG) at delivery was found to be 38.36 weeks in Group 1 and 37.93 weeks in Group 2 in the present study. Majority of deliveries were vaginal in both the groups. Lower Segment Caesarean Section (LSCS) were performed in 29 cases out of 94 patients in Group 2 which was higher than in Group 1 (13 out of 97). Majority of new borns were appropriate for gestational age in both the groups (86% in Group 1 and 68% in Group 2). Twenty nine patients in Group 1 and eleven patients in Group 2 delivered low birth weight babies (i.e., <2500 grams). Three patients in Group 1 and six patients in Group 2 had spontaneous abortions. Out of 97 patients followed till delivery in Group 1, 10 patients had preterm delivery. Out of 94 patients followed till delivery in Group 2, 16 had preterm delivery.

In Group 1, there was no intrauterine death. In Group 2, 1 (1.06%) patient had intrauterine death at 31 weeks of gestation, this patient was also TPOAb positive.

Table 1: Thyroid hormone parameters in both the groups (Mean±SD)

	Groups		
Parameters	1	2	p-value
FT_3 (pmol L^{-1})	5.330.631	5.38±0.72	0.24
FT4 (pmol L^{-1})	13.15±1.561	12.34±1.634	0.12
Maternal TSH in first trimester (mIU L^{-1})	1.54±0.641	5.29±1.64	0.04
Maternal TSH at delivery (mIU L^{-1})	1.90±0.684	3.29±0.872	0.32

Seven patients in Group 1 and twelve patients in Group 2 developed preeclampsia. The difference was not statistically significant in two groups (p = 0.34). Four patients had antepartum haemorrhage in Group 1, out of which 2 had abruptio placenta and 2 (2.06%) had placenta praevia. In Group 2, there were 5 patients of antepartum haemorrhage, all were having abruptio placenta.

TPOAb positivity was found in 14% of patients in Group 2. All the patients in Group 1 were TPOAb negative. The TGAb positivity was found in 7% cases. Significant association was found between LBW babies and TG Ab positivity.

Mean maternal TSH was higher in Group 2 as compared with Group 1 (p-value = 0.04). Cord blood TSH values were higher in Group 2 as compared to Group 1 (p = 0.0001). Positive correlation was observed between maternal TSH at first trimester and cord blood TSH (r = +0.227, $p<0.05$). Negative correlation was observed between the TSH levels in first trimester and mean birth weight of neonates (r = -0.038, $p<0.05$). A negative correlation between cord blood TSH and birth weight of babies (r = -0.15, $p<0.05$).

DISCUSSION

Thyroid dysfunction early in pregnancy seems to affect fetal and placental growth. Mean FT_3 in Group 1 and Group 2 were not statistically significant. There was no significant association seen between rate of abortions and FT_3 levels in the present study in either of the group. Ashoor *et al.* (2010) observed that there was no significant association between the gestation at foetal loss and FT^3 (p = 0.917). Mean FT_4 was not statistically significant in both the groups. These findings are comparable with various studies in literature. The maternal FT_4 was not found to be associated with abortions and rate of pre-term deliveries. Allan *et al.* (2000) reported that mean T_4, free T_4, T_4/TBG became progressively lower as TSH measurements increased though the difference was not significant. Benhadi *et al.* (2009) also reported insignificant difference between FT_4 levels and abortions.

Mean TSH levels at first trimester in Group 2 were higher than those in Group 1 which was statistically significant (p = 0.04). The patients with raised TSH levels were given treatment with levothyroxine as per their TSH levels. The mean TSH levels at the time of delivery in Group 2 patients were lower as compared to the mean TSH levels in the first trimester and they were comparable to euthyroid patients (p = 0.32). Thus providing an indirect evidence that treatment with levothyroxine was efficacious in bringing down mean TSH levels in Group 2. Springer *et al.* (2009) reported mean TSH levels in first trimester to be 1.213 mIU L^{-1} in a study in pregnant women excluding those with history of thyroid disease and autoimmunity. The thyrotropic activity of elevated circulating human chorionic gonadotrophin concentration is responsible for lower serum TSH levels, mainly in the first trimester.

In Group 2, mean TSH levels in first trimester were negatively correlated with FT_4 (r = -0.231, $p<0.05$). Studies have shown an inverse correlation between TSH and FT_4 levels due to the thyrotropic properties of human chorionic gonadotropin (Springer *et al.*, 2009). After an initial increase in the first 10 weeks of pregnancy, human chorionic gonadotropin levels subsequently decrease leading to a decrease in FT_4 and an increase in TSH levels. In addition, the high estrogen levels lead to a rise in thyroxine-binding globulin levels, thereby increasing total T_4 levels (Alexander, 2011). Benhadi *et al.* (2009) described inverse relationship between TSH and FT_4. Ashoor *et al.* (2010) have reported the correlation coefficient of -0.697 between TSH and FT_4.

Antithyroid antibodies may exert a direct adverse effect on the pregnancy, they may serve as a marker of other autoimmune conditions that cause foetal death. Women with thyroid autoimmunity may be euthyroid before pregnancy but develop subclinical or overt hypothyroidism during the first trimester, or such women suffer subfertility and become pregnant at an older age which itself is associated with increased risk of foetal loss (Negro *et al*., 2006; Idris *et al*., 2005). Anti thyroperoxidase (TPO) antibodies are markers of autoimmune process in the thyroid gland and have diagnostic and prognostic significance.

In the present study, TPOAb positivity was found to be 14% and TGAb positivity was found to be 7%. Six percent of patients were both TPOAb and TGAb positive. It was observed that all patients in Group 1 were thyroid auto-antibody negative. Stagnaro-Green and Glinoer (2004) had reported 19.6% incidence of TPO positivity in their study (Thangaratinam *et al*., 2011). Negro *et al*. (2006) had reported 11.7% patents were TPOAb positive in pregnant women. Study by Springer *et al*. (2009) found that 11.7% of pregnant women were TPOAb positive.

TSH levels were found to be positively correlated with TPOAb positivity in 14% cases in the present study. Our findings are in agreement with those reported in literature (Ashoor *et al*., 2010; Benhadi *et al*., 2009; Negro *et al*., 2006; Mannisto *et al*., 2009). Medici *et al*. (2011) have reported that TPOAb positivity was associated with higher maternal TSH levels, lower FT_4 levels and an 8 fold increased risk of subclinical hypothyroidism and 26 fold higher risk of overt hypothyroidism.

Majority of patients were able to carry their pregnancy to term gestation. Mean gestational age at delivery was found to be 38.36 weeks in Group 1 and 37.93 weeks in Group 2 in the present study. These findings are similar to those reported in literature (Allan *et al*., 2000; Mannisto *et al*., 2009; Casey *et al*., 2005).

There is evidence that thyroid autoimmunity is an important risk factor for abortion and preterm birth (Klein *et al*., 1991). The course of pregnancy was uneventful in majority of patients. In the present study, pre-term deliveries were seen in 10% cases in Group 1 and in 16% cases in Group 2. In the present study, 5 out of 16 cases with pre-term delivery were TPO Ab positive. Significant association of preterm deliveries was observed in TG Ab positive as compared to TG Ab negative women.

Negro *et al*. (2006) reported 72% relative reduction in preterm delivery with levothyroxine treatment in euthyroid women with autoantibodies. TPOAb positive women were demonstrated to have a high incidence of preterm birth (22.4%) if they were not treated with levothyroxine, whereas TPOAb positive women treated with levothyroxine experienced a preterm birth rate of 7.2% which was in keeping with the generally accepted incidence.

The prevalence of thyroid autoantibodies and the severe impact of preterm birth on the mother, child and community. There is compelling evidence that levothyroxine intervention that may be of great benefit. Casey *et al*. (2005) had reported that preterm deliveries were significantly increased in women with subclinical hypothyroidism compared with controls which accounted to significant increase in admissions to the intensive care unit and diagnosis of respiratory distress syndrome compared with the offspring of women who were euthyroid. Sharma *et al*. (2007) reported no significant difference in preterm deliveries between treated hypothyroid and euthyroid patients ($p<0.01$).

The incidence of pre-eclampsia was observed in 7% patients, in Group 1 and 12% patients, in Group 2 in the present study. The difference was not statistically significant ($p>0.05$).

Sharma *et al.* (2007) had reported no significant difference in the development of pre-eclampsia in treated hypothyroid and euthyroid pregnant women. Likewise, Casey *et al.* (2005) have reported no significant difference between the incidence of pre-eclampsia in hypothyroid and euthyroid group.

Thyroid hormone is essential for the maturation of many tissues, including the brain, skeleton, lungs, heart and intestine, as well as for the development of nonshivering thermogenesis in the neonatal period. 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 T_3 from T_4.

Most common complication observed was low birth weight. There were 29 LBW (30.9%) neonate in Group 2 which was significantly higher than in Group 1, in which 11 LBW (11.3%) neonate were born ($p<0.01$). There were 15(16%) premature infants in Group 2 and 10 (10.3%) in Group 1. Our findings are in agreement with those reported in literature (Sharma *et al.*, 2007).

In the present study, TPOAb positivity was 14% and TGAb positivity was 7%. Six percent of patients were both TPOAb and TGAb positive. All patients in Group 1 were thyroid auto-antibody negative. In the TPOAb positive patients, the incidence of various complications was pre-term delivery (35%), spontaneous abortion (21%), pre-eclampsia (21%), intrauterine growth restriction (7%) and oligohydramnios (7%) in present study. TGAb positivity was found in 7% cases. In TGAb positive patients, the incidence of various complications was p reterm delivery (42%), pre-eclampsia (28%), oligohydramnios (14%), breech (14%) and low birth May 31, 2014 weight (42%). Pre-term delivery rate was statistically significant between TGAb positive ($n = 3$) and negative patients ($n = 13$) in Group 2 ($p = 0.003$). Significant association was found between LBW babies and TG Ab positivity. Karakosta *et al.* (2012) observed association of thyroid function and autoimmunity in early pregnancy with adverse pregnancy and birth outcomes. Casey *et al.* (2005) observed an increased rate of preterm delivery among women with subclinical hypothyroidism, suggested that an increase rate of preterm delivery among TPO-Ab-positive women may be related to impaired thyroid function. In contrast, did not report any significant relation between TPOAb and child loss but TPOAb positivity was associated with lower FT_4 and higher TSH values.

Presence of thyroid peroxidase antibodies during the time of increasing thyroid hormone demand such as pregnancy implies that the mother may become hypothyroid during gestation. Maternal hypothyroidism, therefore, may ultimately be responsible for the adverse outcome. Also, thyroid autoantibodies represent a broader signal of immune activation. Thyroid peroxidase antibodies are not directly causing the complications per se but rather imply the presence of a heightened autoimmune state in the mother and the presence of a separate, albeit undetected, immune process that is directly pathologic to the pregnancy.

Mean maternal TSH was lower in Group 1 as compared to Group 2 ($p = 0.04$), Cord blood TSH values were lower in Group 1 as compared to Group 2. The correlation between maternal TSH at first trimester and cord blood TSH was positive ($r = +0.227$, $p<0.05$). Medici *et al.* (2011) have reported a positive correlation between maternal and cord blood TSH, with r-value of +0.08, $p<0.05$. Association remained similar after exclusion of TPOAb positive mothers and additional correction of smoking, socioeconomic status and ethinicity.

In normal pregnancy, the role of thyroid hormone in foetal growth is indirectly supported by previous work showing that babies born to women with inadequate dietary iodine intake in the

third trimester had lower birth weights than those born to women with adequate dietary iodine intake (Alvarez-Pedrerol *et al*., 2009). In the present study, a negative correlation between cord blood TSH and birth weight of babies was observed ($r = -0.15$, $p<0.05$). This association between thyroid hormone and measures of foetal growth is consistent with previous studies showing an association between overt maternal hypothyroidism and low birth weight (Sardana *et al*., 2009).

No significant difference was seen in majority of complications between hypothyroid women under treatment and euthyroid women in present study. Abalowich *et al*. (2002) concluded in their clinical study that the evolution of pregnancies did not depend on whether the hypothyroidism was overt or subclinical but mainly on the treatment received. Sharma *et al*. (2007) also stated that no significant differences were seen in complications between hypothyroid women under treatment and euthyroid women. Negro *et al*. (2006) studied the benefits of levothyroxine (LT_4) administration to thyroid autoimmunity positive pregnant women. The LT_4 treatment turned out to be extremely effective in reducing the number of abortions when given during the early stages of pregnancy. Also, the rate of premature deliveries was also significantly reduced in women whose LT_4 treatment was started after the first trimester. Pop *et al*. (2003) have concluded that levothyroxine therapy beginning after 10 weeks of gestation would not eliminate any already established fetal neurodevelopmental impairment from hypothyroxinemia and concluded that treatment may be ineffective only if given after this time.

TSH levels were significantly higher in first trimester in subclinical hypothyroid women as compared to euthyroid pregnant women. The FT_3 and FT_4 levels in subclinical hypothyroid women were comparable to euthyroid pregnant women. No significant differences were seen in majority of complications between subclinical hypothyroid women on thyroxine replacement therapy and euthyroid women. Subclinical hypothyroidism and thyroid antibody positivity were associated with increased incidence of low birth weight babies. However, biochemical parameters and perinatal outcomes were better after thyroxine replacement therapy. It can be inferred that euthyroxinemia is primarily important in early pregnancy to avoid abortions, to maintain normal placental development and function throughout gestation to avoid preterm deliveries and for proper fetal neurodevelopment. It can be concluded that optimum thyroxine replacement in early gestation results in good perinatal outcome.

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