

Prepregnancy Hypothyroidism versus Gestational Hypothyroidism: A Comparative Study

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Abstract

Introduction: Hypothyroidism managed inadequately in pregnancy may have grave outcomes for both mother and baby. Understanding pregnancy outcomes in our country with low awareness about thyroid diseases is important. **Objectives:** The objectives of the study were to evaluate demographic features and biochemical parameters in patients with prepregnancy hypothyroidism versus patients diagnosed to have primary hypothyroidism during pregnancy and to assess pregnancy outcomes. **Study Design:** Prospective design **Materials and Methods:** The study was conducted in a tertiary care center in Bengaluru for 2 years. The patients were divided into two groups - Group I: Prepregnancy hypothyroidism and Group II: Hypothyroid during pregnancy. They were further staged according to ESI guidelines as subclinical or overt hypothyroidism. **Statistical Analysis:** Chi-square and Mann-Whitney test. **Results:** A total of 452 pregnant women with hypothyroidism were analyzed. The data of 371 delivered pregnancies were available. Group I and II had 196 (43.36%) and 256 (56.64%) patients, respectively. Age at presentation (years) was 27.09 ± 4.19 in Group I versus 25.74 ± 4.29 in Group II ($P = 0.003$); gestational age (weeks) was 9.04 ± 5.41 in Group I versus 13.81 ± 9.12 in Group II ($P = 0.000$). There was one case of congenital hypothyroidism in baby in each group. Mean birth weight was 2.90 ± 0.39 kg in Group I versus 2.88 ± 0.36 kg in Group II; $P = 0.608$. There were four abortions in Group I versus ten in Group II ($P = 0.231$), 104 cesarean sections in Group I compared to 133 in Group II; ($P = 0.382$). There was no difference in number of cesarean sections, abortions and low birth weight babies between overt and subclinical hypothyroidism subgroups. **Conclusions:** Group I patients presented earlier for testing suggesting awareness was good in this group. There was no difference in pregnancy outcome between the two groups. Overt versus subclinical status did not have any different effects on pregnancy outcomes in any group.

Keywords: Adverse pregnancy outcomes, ESI guidelines, gestational hypothyroidism, prepregnancy hypothyroidism

INTRODUCTION

Untreated maternal hypothyroidism has several adverse maternal and fetal outcomes. The maternal effects are decreased fertility, anemia, preeclampsia, miscarriage, abruptio placenta, and postpartum hemorrhage.^[1] Patients carry an estimated 60% risk of fetal loss when overt hypothyroidism was not adequately detected and treated.^[2] Leung *et al.* demonstrated a 22% risk of gestational hypertension in pregnant women with overt hypothyroidism; untreated maternal hypothyroidism has many undesired consequences such as premature birth and low birth weight. It also causes increased neonatal respiratory distress syndrome.^[3] There is also increased the risk of fetal death in pregnant women with overt hypothyroidism.^[4]

There is limited data on characteristics of hypothyroidism during pregnancy from India. There is no study to compare differences in patients having hypothyroidism before pregnancy

and hypothyroidism diagnosed during pregnancy. The aim of this study was to evaluate phenotypic features and biochemical parameters in patients with prepregnancy hypothyroidism versus gestational hypothyroidism (hypothyroid diagnosed during pregnancy) and to assess pregnancy outcomes in Indian population.

MATERIALS AND METHODS

This was a prospective study conducted in a tertiary care center in Bengaluru over a period of 2 years from January 2013 to December 2014. Ethical Review Committee approval

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was taken. Consecutive pregnant patients with either known hypothyroidism or hypothyroidism diagnosed during pregnancy according to endocrine society guideline^[5] and who signed written informed consent were recruited in the study.

Patient population and data collection

A total of 452 pregnant patients with hypothyroidism were enrolled in the study. A detailed medical history was recorded and physical examination was done. Patients presenting in all trimesters were followed up till delivery. Records such as weight, goiter, thyroxin dose, and biochemical tests were maintained. For pregnancy outcome, data were taken from the hospital registry if patient delivered in our institute and were telephonically contacted if delivered outside.

Biochemical tests

Thyroid stimulating hormone (TSH), free T4, and random blood sugar were done at baseline, and free T4 and TSH were repeated in each trimester. Total T4, T3, HbA1c, and free T3 were recorded if available. All the tests were done with an automated analyzer (Siemens Dimension, RxL Max. United States of America). All the hormonal assays were done by chemiluminescence method. Blood glucose was measured by glucose oxidase method.

Group division

The patients were divided into two groups. Group I was women having prepregnancy hypothyroidism. Group II was women diagnosed as gestational hypothyroidism. The patients in both groups were further staged according to endocrine society guideline^[5] as subclinical (a) or overt (b) hypothyroidism.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 20.0 software. Continuous variables are expressed as median and categorical variables are expressed as numbers and percentages. After calculating descriptive statistics, differences between groups were assessed with χ^2 and Fisher's exact tests for categorical variables and Student's *t* or Wilcoxon tests for continuous variables. Missing data were not taken into consideration. The statistical significance was considered as probability <5% ($P < 0.05$).

RESULTS

Clinical and biochemical characteristics

A total of 452 pregnant women with hypothyroidism were enrolled in the study. Out of 452 patients data for 383 pregnant ladies was available. Since 12 of them had first trimester abortion 371 ladies who completed 9 months pregnancy could be analyzed. Figure 1 explains the number of patients enrolled in study. Descriptive analysis of all patients was performed. Their baseline characteristics are in Table 1.

In Group I, out of 196 patients, 166 presented in first, 28 in second, and 2 in third trimester. Six patients had hypertension. Their mean systolic and diastolic blood pressure (BP) values

were 145.6 ± 4.80 mmHg and 92.20 ± 1.90 mmHg. Eleven patients had diabetes.

In Group II, out of 256 patients, 129 were diagnosed in first, 101 in second, and 26 in third trimester. Ten patients had hypertension. One patient was hypertensive before pregnancy, whereas nine had gestational hypertension. Their mean systolic and diastolic BP values were 147.0 ± 5.20 mmHg and 94.62 ± 2.65 mmHg. Twenty-five patients had diabetes. The dose of thyroxin was more in the prepregnancy hypothyroid indicating some were overt hypothyroid. The mean thyroxin dose required 62.20 ± 30.05 and 1.02 ± 0.37 ug/kg/day.

Pregnancy outcomes

Rate of cesarean section was higher in patients with hypothyroidism during pregnancy compared to normal population [Table 2].

The rate of cesarean section, premature delivery, and low birth weight was comparable between Group I and II [Table 3].

The mean birth weight was comparable in two groups (2.90 ± 0.39 kg in Group I vs. 2.88 ± 0.36 kg in Group II, $P = 0.608$). There were two babies who had congenital hypothyroidism. Their TSH values were 69 and 49.16 uIU/ml.

Table 1: Baseline characteristics of Group I and II patients

Parameter	Group I (n=196)	Group II (n=256)	P
Age (years)	27.09±04.17	25.74±04.29	0.001
Gestation at presentation (weeks)	9.04±05.41	13.81±09.12	<0.01
Thyroxin dose	89.93±41.37	62.20±30.05	0.000
Family history of hypothyroidism (%)	27 (13.77)	23 (8.98)	0.130
Initial TSH (uIU/ml)	12.65 (7.54-24.79)	5.54 (4.29-7.78)	0.024

TSH: Thyroid stimulating hormone

Table 2: Comparative pregnancy outcome data of study population and normal population

Parameter	Hypothyroid pregnancies (n=383), n (%)	Normal pregnancies (n=5000), n (%)	P
Cesarean section	237/371 (63.89)	1957/5000 (39.14)	0.001

Table 3: Group-wise pregnancy outcome data

Parameter	Group I (n=156), n (%)	Group II (n=215), n (%)	P
Normal delivery	52 (33.33)	82 (38.13)	0.382
Cesarean section	104 (66.67)	133 (61.87)	
Premature delivery	8 (5.12)	7 (3.25)	0.259
Low birth weight	13 (8.33)	19 (7.42)	0.519

Table 4: Group-wise pregnancy outcome data for abortion and fetal loss

Parameter	Group I (n=159), n (%)	Group II (n=224), n (%)	P
	155 live births, 1 still birth during cesarean and 3 first trimester losses	214 live births, 1 third trimester loss delivered normally and 9 first trimester abortions	
Miscarriage/fetal loss	4/159 (2.51)	10/224 (4.46)	0.231

The number of miscarriages and fetal loss were comparable between Group I and II

There was no difference in number of miscarriages/fetal loss between the two groups [Table 4].

Correlation of autoimmunity and pregnancy outcomes

Two hundred and fifty-four patients with anti-thyroid peroxidase (TPO) antibody values were analyzed. One hundred and sixty-six patients were anti-TPO positive (65.35%) and 88 patients (34.65%) were anti-TPO negative. Anti-TPO positivity correlated with miscarriage/pregnancy loss, low birth weight and premature delivery. In multivariate logistic regression analysis, anti-TPO antibody was associated with increased risk of pregnancy losses ($P = 0.001$). The risk of low birth weight was more in both anti-TPO positive patients ($P = 0.001$) and patients with diabetes ($P = 0.001$). The risk of cesarean was associated with history of diabetes ($P=0.001$) but not with anti-TPO antibody ($P=0.604$). Anti-TPO positivity ($P=0.001$) and diabetes ($P=0.015$) both were associated with risk of premature delivery.

Out of 254 anti-TPO positive patients, outcome data of 148 patients were available. Out of 88 anti-TPO negative patients, outcome data of 84 patients were available. The analysis of same is presented in Table 5.

Out of total 14 miscarriages/pregnancy loss, six patients who were anti-TPO positive had TSH which was above trimester-specific range at the time of abortion. The four patients had first trimester abortion, whereas two had third trimester fetal loss and still birth. Eight patients had TSH which was within trimester-specific range and seven had anti-TPO positive value. Elevated TSH level did not correlate significantly with early pregnancy losses ($P = 0.178$). Diabetes ($P = 0.67$) and hypertension ($P = 0.434$) did not correlate with pregnancy loss.

DISCUSSION

This is the first comparative study in India of prepregnancy versus hypothyroid during pregnancy women and their pregnancy outcomes. TSH measurement is not a part of routine screening guidelines in pregnancy.^[5] In our center, TSH is measured routinely in all pregnant women. Haddow JE *et al.* have found that routine TSH testing is performed in 48% of all prenatal care practices and 76% of urban obstetric practices.^[6] Furthermore, percentage of number of hypothyroid women at our center was higher (9.04%) compared to that reported in literature.^[7]

As patients were divided into two groups: prepregnancy and hypothyroid diagnosed during pregnancy, this enabled us to

Table 5: Anti-thyroid peroxidase positivity and pregnancy outcomes

Parameter	Anti-TPO positivity, n (%)	Anti-TPO negativity, n (%)	P
Miscarriage/pregnancy loss	13/148 (8.78)	1/84 (1.19)	0.014
Low birth weight	22/135 (16.29)	2/83 (2.40)	< 0.01
Cesarean section	89/135 (65.92)	50/83 (60.24)	0.287
Premature delivery	13/135 (9.62)	0/83 (0.00)	0.002

TPO: Thyroid peroxidase

assess the effect of hypothyroidism on various pregnancy clinical, biochemical, and outcome parameters. Prepregnancy hypothyroid women presented at an earlier gestational age thus indicating good awareness about the disorder. This group had 51% patients with elevated TSH levels at time of conception in spite of being on treatment. Our findings are similar to a study in Sweden in which 50.9% patients with known hypothyroidism on treatment had an elevated TSH at the time of conception.^[8]

Thyroxin dose requirement was higher in prepregnancy hypothyroid group as this group had more number of overt hypothyroid cases. Anti-TPO antibody positivity has been shown to have several adverse effects on pregnancy outcomes independent of thyroid dysfunction. Autoimmunity increases risk of preeclampsia, preterm delivery, intrauterine growth retardation, and low 1st min Apgar score.^[9,10] In euthyroid women increased the risk of miscarriage has been associated with anti-TPO positivity in some^[14] but not all studies.^[11,12] Negro *et al.* showed that anti-TPO positivity increases risk of first trimester miscarriage independent of thyroid function.^[13] In our study, anti-TPO was strongly associated with premature delivery, rate of abortion/fetal loss, and low birth weight. However, there was no significant association between anti-TPO positivity and rate of cesarean section.

Hypothyroidism is known to be associated with increased rate of cesarean sections.^[14] In our study, the rate of cesarean section was more compared to normal deliveries ($P = 0.001$). However, there was no difference between the two groups. Hypothyroidism also is shown to increase risk of lower birth weight, fetal death, and premature labor.^[11,12,13,15] However, we did not have comparative data of low birth weight, fetal loss/abortion, and premature labor from normal population.

There were no significant differences between two groups (Group I and II) in incidences of premature delivery, abortion and low birth weight babies. Thus, timing of diagnosis

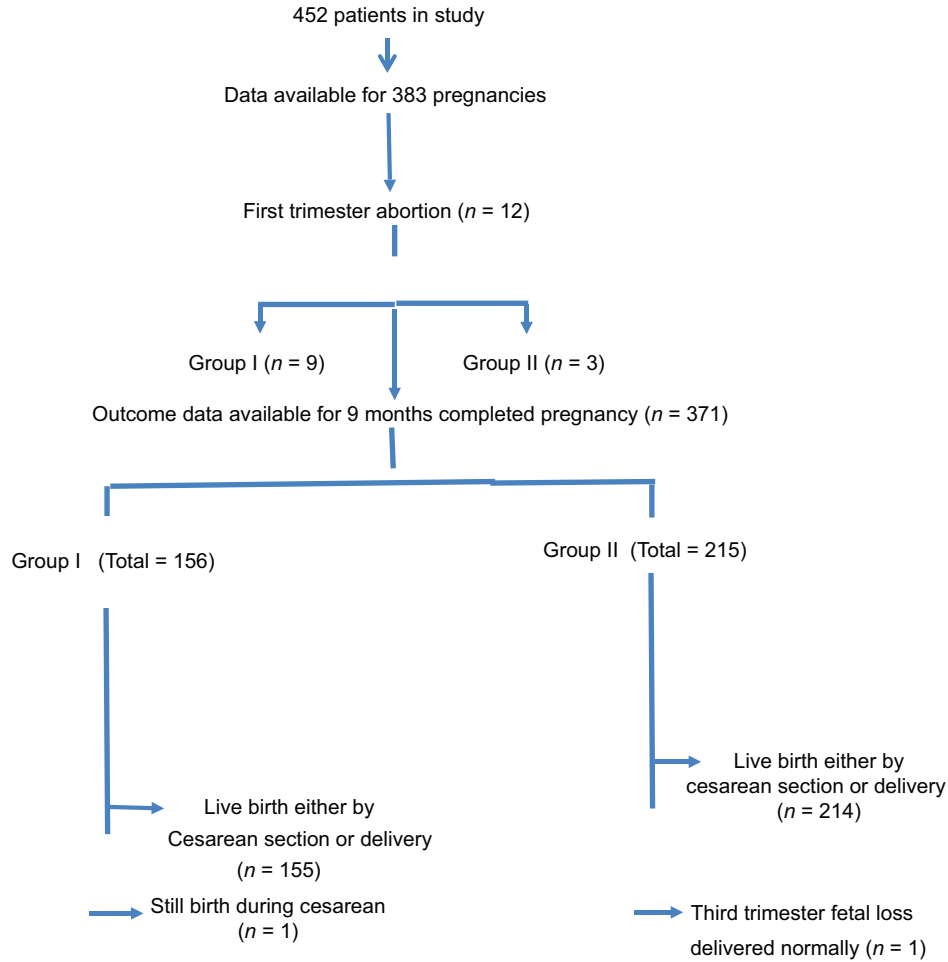


Figure 1: Group-wise analysis of pregnancy outcome data

of hypothyroidism did not have any bearing on pregnancy outcomes. In each group, there was no difference in pregnancy outcomes between subclinical and overt hypothyroidism.

The combination of diabetes and hypothyroidism is associated with higher rate of infertility, cesarean sections, preterm deliveries, hypertensive disorders of pregnancy, and adverse pregnancy outcomes.^[16] Similarly, pregnancy induced hypertension are independently associated with increased risk of adverse maternal and fetal pregnancy outcomes.^[17-20] However, in our study, diabetes with hypothyroidism was associated with risk of low birth weight and cesarean section but not with premature delivery and miscarriage and fetal loss. Preeclampsia was not associated with any of the adverse pregnancy outcomes. This could probably be due to very small numbers with diabetes and hypertension and also that those were well controlled.

Significant proportions (15.48%) of patients in our study were treatment noncompliant as suggested by raised trimester-specific TSH levels in spite of treatment. In one

study, 54% primary hypothyroid nonpregnant patients had out of range TSH even on treatment.^[21] This underscores the importance of reinforcement of adherence to treatment. 7.07% rate of overtreatment in our study highlights the fact that patient education regarding regular TSH monitoring is required.

There are many strengths of our study such as prospective design and large sample size. The data were collected by questionnaire and patients were followed up for long term with a large number of events. Confounders were adjusted while assessing the effect of anti-TPO antibodies on pregnancy outcomes.

The novelties of this study are its structural design comparing prepregnancy hypothyroid women characteristics with those of hypothyroidism diagnosed during pregnancy and comparison of many parameters in two different groups.

The limitations to study, all patients did not deliver at our center. Patients who delivered at other places were telephonically contacted and data collected. Anti-TPO was not done for all patients.

CONCLUSIONS

Prepregnancy hypothyroid patients presented earlier indicating better awareness about the disorder. The levothyroxine dose requirement is higher in this group due to large number of cases being overt hypothyroid. Anti-TPO positivity is strongly associated with all pregnancy losses and premature delivery. The pregnancy outcomes were not different between the prepregnancy hypothyroid patients and those who were diagnosed during pregnancy. Overt or subclinical hypothyroid subgroups did not have different pregnancy outcomes. The mean levothyroxine dose in subclinical gestational hypothyroidism was 1.02 ± 0.37 ug/kg/day.

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Conflicts of interest

There are no conflicts of interest.

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