ORIGINAL RESEARCH

A prospective observational study of thyroid dysfunctions during pregnancy and its effect on maternal and fetal outcome in a tertiary care

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ABSTRACT

Background: Thyroid disorders are frequent in women of reproductive age, with a major influence on both female reproductive function and fetal development. Pregnancy is associated with profound modifications in the regulation of thyroid function. Women with thyroid dysfunction both overt and subclinical are at increased risk of pregnancy-related complications such as threatened abortion, preeclampsia, preterm labour, placental abruption, and postpartum haemorrhage. Fetal complications include low birth weight, IUGR, neonatal hyperthyroidism, still birth and perinatal mortality. As Assam lies on the foot hills of Himalayas, the prevalence of thyroid dysfunction, as expected, is high in general population including pregnant ladies hence this study is an effort to throw some light in this direction. **Methods:** This prospective study was conducted enrolling 132(both primipara & multipara), irrespective of the gestational age, attending the antenatal OPD of Gauhati Medical College was enrolled for the study. TSH, free T4, and anti TPO antibody values were assessed. TSH and free T4 was planned to be repeated at necessary intervals according to the results of thyroid function tests in the first visit. At the end, obstetric and perinatal outcome of the pregnancy was noted. **Results:** In the study, 59.84% had normal thyroid function, 32.57% had hypothyroidism (subclinical in 25% andovert in 7.57%), 6.06% had gestational thyrotoxicosis and 1.51% had Grave's disease. 28.78%had TPO positivity.In the group with subclinical hypothyroidism, PIH, GDM, preterm delivery, APH, abortion and LSCS were higher compared to the group with normal TSH though not significant. In the group with overt hypothyroidism, IUGR and neonatal jaundice requiring phototherapy were significantly higher compared to the group with normal TSH. **Conclusions:** Thyroid dysfunction among reproductive age group females is associated with significant adverse effects on maternal and fetal outcome spotlighting the essence of routine antenatal thyroid screening in first trimester.

Key Words: Hypothyroidism, Hyperthyroidism, anti TPO, subclinical hypothyrsoidism

INTRODUCTION

Thyroid disorders are frequent in women of reproductive age, with a major influence on both female reproductive function and fetal development. Pregnancy affects virtually all aspects of thyroid hormone economy.[1]

Hashimoto's thyroiditis is the most common cause of hypothyroidism. Overt hypothyroidism is estimated to occur in 0.3-0.5% of pregnancies and subclinical hypothyroidism appears to occur in 2-3%.[2] Both obstetrical and fetal complications occur with an increased frequency in pregnant women with hypothyroidism[3]. These complications are more frequent and more severe in women with overt hypothyroidism than subclinical hypothyroidism (SCH). Most importantly, adequate treatment with thyroid hormone greatly reduces risks of a poorer obstetrical outcome[3].Maternal complications of untreated hypothyroidism include anaemia, preeclampsia, placental abruption, postpartum haemorrhage, cardiac dysfunction, and miscarriage. Fetal or neonatal complications include prematurity,

low birth weight, congenital anomalies, and stillbirth. Overt maternal hypothyroidism has also been associated with damage to fetal intellectual development, presumably because of inadequate transplacental supply of hormone during early pregnancy.[4]

Hyperthyroidism affects 0.1-0.4% of pregnancies. Grave's disease accounts for 85% of these cases.[5] Uncontrolled hyperthyroidism, especially in the second half of pregnancy, can lead to numerous complications. The most common complication of uncontrolled hyperthyroidism in pregnant women is gestational hypertension, with a risk of preeclampsia that is ~5-fold greater.[6] Other obstetrical complications include miscarriage, infection, preterm delivery, congestive heart failure (CHF), thyroid storm, and placental abruption.[7]Fetal and neonatal complications include prematurity, small size for gestational age, intrauterine fetal death, and fetal or neonatal goiter and/or thyrotoxicosis. Overtreatment may also cause iatrogenic fetal hypothyroidism.[8]

Another cause of hyperthyroidism results directly from the stimulatory action of human chorionic gonadotropin (hCG) on the thyroid and this etiology is associated with transient hyperthyroidism in the first half of gestation. This syndrome is referred to as gestational transient thyrotoxicosis (GTT) and differs fundamentally from Grave's disease in that it is not of autoimmune origin, is usually mild and seldom requires treatment.[9]

As Assam lies on the foot hills of Himalayas, the prevalence of thyroid dysfunction, as expected, is high in general population including pregnant ladies. A study by Kharkongor et al in 1998 in Meghalaya found a prevalence of hypothyroidism in 1.11% and 1.43% in the non-pregnant and the pregnant women, respectively.[10] This is very high as compared to that of the non-endemic goitre belt of India (0.071%).[10] No large-scale study has been conducted in recent time from Assam on thyroid dysfunction during pregnancy with particular emphasis on the effect of thyroid dysfunction on maternal obstetric and fetal outcome. With a back ground of high prevalence of hypothyroidism in Assam and a strong association of adverse pregnancy outcome with thyroid dysfunction during pregnancy we intend to do this present study with a view to emphasize the need of routine screening for thyroid dysfunction in pregnancy to reduce maternal and fetal mortality and morbidity.

Materials and methods:

This prospective study was conducted enrolling 132 (both primipara & multipara), irrespective of the gestational age, attending the antenatal OPD of Gauhati Medical College was enrolled for the study. Five milliliter (ml) of blood was collected in red capped plain vacutainers for TSH, free T4, and anti TPO antibody in their first visit. The serum was separated and stored in minus 20 degree Celsius prior to analysis. TSH and free T4 was planned to be repeated at necessary intervals according to the results of thyroid function tests in the first visit. TSH and free T4 was done by Radioimmunoassay and anti TPO antibody was done by Chemiluminescence method (Immulite 1000).

INCLUSION CRITERIA

A total of 132 consecutive pregnant subjects (both primipara & multipara), irrespective of the gestational age, attending the antenatal OPD of Gauhati Medical College was enrolled for the study. Patients with multiple pregnancies were also included.

EXCLUSION CRITERIA

1. Subjects with known thyroid disorders who were on medications for their thyroid related disease.
2. Subjects with history of diabetes mellitus.
3. Subjects with hypertension and other known medical disorders likely to affect pregnancy outcome.
4. Patients on chronic medications like amiodarone, propanolol,steroidsetc which are known to affect thyroid status.

Informed consent was taken from the patients and thorough clinical evaluation was done according to the proforma, to look for features of thyroid dysfunction if any, including presence of goitre. The gestational age and expected date of delivery was noted.

Patients were followed up till the end of their pregnancy and maternal as well as fetal outcomes were recorded. Serum TSH, free T4 and anti TPO antibody were done as initial hormonal investigations, and the subjects were grouped based on their thyroid function tests according to the American Thyroid Association (ATA) guidelines 2011.[11] The division into different groups is as follows: -

Group 1(control group): Normal thyroid function without thyroid autoimmunity (TSH 0.4 – 2.5 μIU/mL, TPO Ab negative)

Group 2: Normal thyroid function with thyroid autoimmunity (TSH 0.4–2.5 μIU/mL, TPO Ab positive)

Group 3: Subclinical hypothyroidism without thyroid autoimmunity (TSH 2.5–10μIU/mL, Free T4: normal 0.9 – 2.32 pmol/dl, TPO Ab negative)

Group 4: Subclinical hypothyroidism with thyroid autoimmunity (TSH 2.5–10 μIU/mL, Free T4: normal 0.9 – 2.32 pmol/dl, TPO Ab positive)

Group 5: Overt hypothyroidism without thyroid autoimmunity (TSH 2.5–10 μIU/mL with Free T4 <0.9 pmol/dl or TSH > 10 μIU/mL irrespective of free T4, TPO Ab negative)

Group 6: Overt hypothyroidism (TSH 2.5–10 μIU/mL with Free T4<0.9 pmol/dl or TSH> 10 μIU/mL irrespective of free T4, TPO Ab positive)

Group 7: Gestational thyrotoxicosis (TSH<0.4 μIU/mL, TPO Ab negative)

Group 8: Graves' disease (TSH<0.4 μIU/mL, FT4>2.32 pmol/dl, TPO Ab positive)

Statistical analyses were performed using SPSS software, version 16 (SPSS, Chicago, IL, USA).

Student's t- test was done to find the significance of difference between means whenever applicable. The $\chi 2$ statistic with Yates' correction, Mann-Whitney U test, Fisher's exact test and Pearson's correlation test were applied whenever appropriate. A p value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

One hundred and thirty-two consecutive pregnant subjects of various gestational ages attending the antenatal OPD were recruited for the study. Of these, 65 subjects were primiparous and 67 were multiparous. We had one twin pregnancy and the remaining were singleton. The mean age of the subjects was 25.19 (± 4.17) years. Out of 132 patients at screening, 33 patients were in first trimester, 52 were in second trimester and the rest 47 were in third trimester. The mean gestational age at presentation was 25.03 (±14.12) weeks. The patients were divided into different groups as shown in table 1.

Table 1: Distribution of patients according to their thyroid function status

	Patient groups	Number (Percentage)
Normal (n=79; 59.84%)	Group 1 (normal TSH,without TAI)	64 (81.01%)
	Group 2 (normal TSH,with TAI)	15 (18.98%)
Subclinical hypo (n=33; 25%)	Group 3 (subclin hypo without TAI)	19 (57.57%)
	Group 4 (subclin hypo with TAI)	14 (42.42%)
Overt hypo (n=10; 7.57%)	Group 5 (overt hypo without TAI)	3 (30%)
	Group 6 (overt hypo with TAI)	7 (70%)
Gestational thyrotoxicosis (n=8; 6.06%)	Group 7 (GTT)	8*
Grave's disease (n=2; 1.51%)	Group 8 (GD)	2

TAI: Thyroid autoimmunity, ***** One subject in this group had molar pregnancy.

In our study, group 1 with normal TSH and negative anti TPO antibody was considered as controls. The prevalence of hypothyroidism was 32.57% (SCH: 25%; OH: 7.57%) and that of GD was 1.51%. Goiter was present in 11 subjects (8.33%). Thyroid autoimmunity in the form of TPO Ab positivity was seen in 38 subjects (28.78%). Of the 132 subjects, follow-up data is available for 120 while the rest 12 (9.09%) were lost to follow up. Among the pregnant women lost to follow up, 9 were from the group with normal thyroid function, 1 from subclinical hypothyroidism, 1 from overt hypothyroidism and 1 from the group with gestational thyrotoxicosis. We had one subject presenting with symptoms of thyrotoxicosis in whom an ultrasound done revealed molar pregnancy.She subsequently underwent dilatation and evacuation (D&E).

Table 2: Baseline biochemical characteristics in different groups (n=132)

	Group 1 n = 64	Group 2 n = 15	Group 3 n = 19	Group 4 n = 14	Group 5 n = 3	Group 6 n = 7	Group 7 n = 8	Group 8 n = 2
TSH mIU/L (Mean±SD)	1.66±0.44	1.47±0.64	5.26±1.94	4.71±1.91	8.03±1.46	22.2±18.6	0.038±0.03	0.002±0.02
FreeT4 (Mean±SD)	1.48±0.38	1.47±0.44	1.47±0.36	1.29±0.31	0.72±0.75	0.84±0.13	1.96±0.16	6.37±0.81
TPO IU/ml (Mean±SD)	82.8±21.03	393.8±422.2	104.6±24.5	542.85±45	77.16±2.51	417±391.4	60.57±17.02	337±77.07

PIH, abortion, preterm delivery and APH were seen in 18.3%, 6.66%, 5% and 1.66% respectively while GDM and maternal death were each observed in 0.83% of the subjects.

- LSCS was done in 33.3% of the subjects, most common indication being fetal distress.

Table 3: Maternal outcome in various groups irrespective of thyroid autoimmunity (n=120)

Outcome	Normal TSH (n=70)	Subclinical hypo(n=32)	P	Overt hypo(n=9)	p	GTT (n=7)	p	Graves (n=2)	P	Total events
PIH	10(14.2%)	6 (18.7%)	0.412	4 (44.4%)	0.026	1(14.2%)	0.889	1(50%)	0.243	22(18.3%)
GDM	0	1(3.12%)	0.315	0		0		0		1(.83%)
Preterm delivery	3 (4.28%)	3(9.37%)	0.276	0	0.114	0	0.33	0		6 (5%)
APH	1(4.2%)	1(3.12)	0.265	0	0.312	0	0.21	0		2(1.66%)
Maternal death	0	0		0		0		1(50%)	0.004	1(0.83%)

Abortion	2 (2.85%)	3(9.37%)	0.454	2(22.2%)	0.031	0		1(50%)	0.012	8(6.66%)
NVD	46 (65.71%)	16 (50%)	0.465	3(33.3%)	0.549	6(85.7%)	0.612	0	0.089	71 (59.1%)
LSCS	22 (31.42%)	13(40.6%)	0.769	4 (44.4%)	0.588	0	0.078	1 (50%)	0.629	40(33.3%)
D& E	-	-	-	-	-	1(14.2%)	-	-	-	1 (0.83%)

P value <0.05 is significant

PIH, GDM, preterm delivery, APH, abortion and LSCS were higher among subclinical hypothyroid compared to the group with normal TSH though not significant (p>0.05).

In the group with overt hypothyroidism, PIH and miscarriage was significantly higher compared to the group with normal TSH (p=0.026 & p=0.031 respectively).

Maternal outcome in group with GTT did not differ significantly from the group with normal TSH (p>0.05).

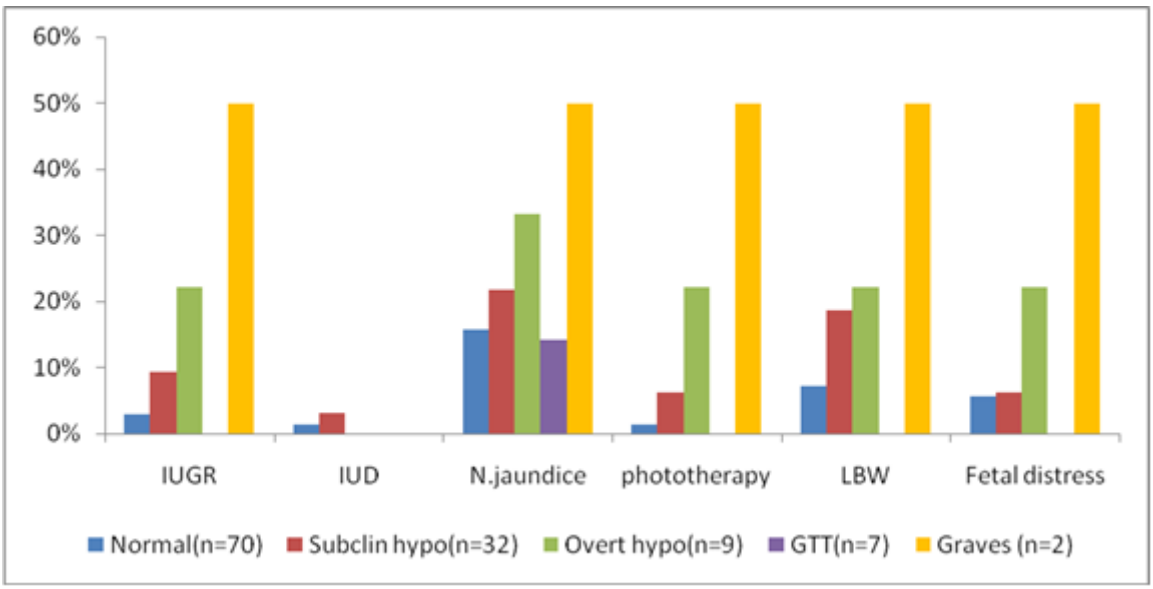
We had 2 patients with Grave's disease presenting in early 2nd trimester. One of them expired 3 days following delivery due to cardiac failure.

Miscarriage and maternal death were significantly higher in the group with GD compared to group with normal TSH (p<0.05).

No case of PPH was observed in our study subjects

Table 4: Fetal and neonatal outcomes in various groups irrespective of thyroid autoimmunity

	Normal (n=70)	Subclinical hypo (n=32)	p	Overt hypo (n=9)	p	GTT (n=7)	p	Graves (n=2)	p	Total events
IUGR	2 (2.85%)	3 (9.37%)	0.15	2 (22.2%)	0.013	0		1 (50%)	0.001	8 (6.6%)
Neonatal Jaundice	11 (15.71%)	7 (21.8%)	0.38	3 (33.3%)	0.193	1 (14.2%)	0.92	1 (50%)	0.023	23 (19.1%)
Photo therapy	1 (1.42%)	2 (6.25%)	0.45	2 (22.2%)	0.003	0		1 (50%)	0.0001	6 (5%)
Low birth weight	5 (7.14%)	6 (18.7%)	0.073	2 (22.2%)	0.134	0		1 (50%)	.031	14 (11.6%)
IUD	1 (1.42%)	1 (3.12%)	0.53	0	0.747	0		0	---	2 (1.6%)
Fetal distress	4 (5.71%)	2 (6.25%)	0.044	2 (22.22%)	0.078	0		1 (50%)	.015	9 (7.5%)



- In the group with subclinical hypothyroidism, fetal distress was significantly higher compared to the group with normal TSH (p=0.044). Other outcomes did not differ significantly between the two groups.
- In the group with overt hypothyroidism, IUGR (p= 0.013) and neonatal jaundice (0.003) requiring phototherapy were significantly higher compared to the group with normal TSH while other outcomes did not differ significantly.

- Fetal and neonatal outcomes did not differ significantly between the groups with GTT and normal TSH.

In the group with Grave's disease, IUGR, neonatal jaundice, phototherapy, LBW, and fetal distress were significantly higher ($p < 0.05$) compared to group with normal TSH.

Table 5: Maternal, Fetal and neonatal outcome in treated and untreated subclinical hypothyroidism with or without thyroid autoimmunity

Subclinical Hypothyroidism (n=32)						
	TPO NEGATIVE (N=19)			TPO POSITIVE (N=13)		
	Treated	Untreated	p	Treated	Untreated	p
	(n=11)	(n=8)		(n=8)	(n=5)	
Maternal Outcome						
PIH	1(9%)	2(25%)	0.0348	1(12.5%)	2(40%)	0.0252
GDM	1(9%)	0	0.381	0	0	-
Preterm	1(9%)	0	0.381	1(12.5%)	1(20%)	0.715
APH	0	0	-	0	1(20%)	0.188
Abortion	1(9%)	0	0.381	0	2(40%)	0.042
NVD	7(63.6%)	3(37.5%)	0.125	4(50%)	2(40%)	0.725
LSCS	3(27.2%)	5(62.5%)	0.125	4(50%)	1(20%)	0.279
Fetal Outcome						
IUGR	1(9%)	1(12.5%)	0.811	0	1(20%)	0.14
Neonatal jaundice	2(18.1%)	2(25%)	0.829	1(12.5%)	2(40%)	0.071
Photo therapy	0	1(12.5%)	0.242	0	1(20%)	0.14
LBW	1(9%)	2(25%)	0.348	1(12.5%)	2(40%)	0.071
IUD	0	0	-	0	1(20%)	0.14
FD	0	1(12.5%)	0.228	0	1(20%)	0.14

In thegroup with TPO negative SCH, we found PIH to be significantly higher ($p=0.034$) in the untreated compared to the treated group while other outcomes did not differ significantly. In the group with TPO positive SCH, PIH and miscarriage was significantly higher in the untreated compared to the treated group while preterm delivery, APH and mode of delivery did not differ significantly between the two groups. In thegroups with TPO negative and positive subclinical hypothyroidism, IUGR, neonatal jaundice, phototherapy, LBW, and fetal distress were not significantly different between treated and untreated groups.

DISCUSSION

The present study was done in Gauhati Medical College attached to OBG department. A total of 132 pregnant women (both primipara & multipara), irrespective of the gestational age were included in the study. It was a prospective study. The main aim of the study was to know the impact of maternal thyroid dysfunction on maternal and fetal outcome.

The maternal physiological changes that occur in normal pregnancy induce complex endocrine and immune responses. Thyroid diseases, especially those of autoimmune origin, are common in women of childbearing age. A few studies have been published addressing the special circumstances of thyroid physiology and pathophysiology in the gravid woman.[12,13]

Although thyroid disorders are an important barrier to pregnancy, significant thyroid dysfunction is still found in 1%–2% of gravid women, and subclinical forms of thyroid disease are even more prevalent.[14,15]

In our study, subclinical hypothyroidism was associated with complications like PIH (18.7%), anaemia (12.5%), AB (4.8%), APH (3.12%), preterm delivery (9.37%), IUGR(13.46%), Abortion (9.37%), respiratory distress(6.25%), IUD(3.12%), neonatal jaundice (21.8%), LBW (low birth weight, 18.7%). Our results were like the incidence of complications of subclinical hypothyroidism done by few studies[16,17,18]

In our study, overt hypothyroidism was associated with complications like PIH (44.4%), AP (0%), abortion (22.2%), IUGR (22.2%), fetal distress (22.2%) and IUD (0%), neonatal jaundice (33.3%), LBW (22.2%). In a study done by Ajmani et al,[19] the complications like PE (16.6%), AP (16.6%), anaemia (8.3%),abortion(16.6%), PPH(8.3%), PTD(33.3%), IUGR(25%), RD (25%)and IUD(16.6%) were seen in cases of overt hypothyroidism. In a study done by Leung et al.[20] the incidence of complications in overt hypothyroidism were like PE(22%) and IUD(4%). In a study done by Sahu M T et al.[21] the complications like PE(20.7%), PTD(4.7%), IUGR(13.8%) and IUD(2.9%) were seen in overt hypothyroidism. In a study done by Thanuja et al.[22] the incidence of complications like AP(33.4%) and abortion(66.7%) seen in overt hypothyroidism. In a study done by Ablovich et al.[23]the complications like APH (19%) and IUD(3%) were seen in cases of overt hypothyroidism. The incidence of complications varied in different studies but some studies are

comparable. In our study the incidence of PIH, Neonatal jaundice and respiratory distress were high compared to other studies.

In our study, prevalence of hyperthyroidism was 7.57% (10/132), out of which we had 2 cases of Grave's disease (1.51%), 7 cases of gestational thyrotoxicosis (5.30%) and 1 case with molar pregnancy (0.75%). In the group with Grave's disease, one patient had abortion soon after starting treatment while the other patient who was non-compliant with therapy, expired 3 days following delivery due to cardiac failure. Grave's disease was significantly ($p<0.05$) associated with miscarriage (50%), maternal death (50%), IUGR (50%), neonatal jaundice requiring phototherapy (50%), LBW (50%) and fetal distress (50%) compared to patients with normal thyroid function. In the group with GTT, pregnancy outcomes were same as those with normal thyroid function.In a study done by Nambiar et al[24]found prevalence of GD to be 0.6% and that of GTT to be 6.4%. In patients with GTT thyroid functions normalized in majority of the patients (70%) by an average gestational age of 14.4 weeks.

The prevalence of PIH in hypothyroidism, in our study is comparable to that of other studies. Our study is also comparable to the study by Negro et al[25]which has shown that treatment of maternal hypothyroidism leads to a significantly decreased PIH. Mukhopadhyay A et al found PIH in 37.5% of the pregnant subjects with hypothyroidism out of which 60% of the subjects were anti TPO antibody positive and 31.5% anti TPO antibody negative and 3.69% study subjects found to have APH and GDM in 5.26% and 12.5% of the hypothyroid pregnant subjects respectively. APH was seen in the TPO negative hypothyroid group while GDM was observed in 10.52% and 20% of the TPO negative and positive hypothyroid subjects respectively. [26] In this study,[26]pre-eclampsia was seen in 16.6% of the hypothyroid subjects, out of which 15.7% were TPO negative and 20% were TPO positive. Sharma Partha P et al[27] found that most common maternal complication in hypothyroid women was preeclampsia (21.95% vs. 14.89% in controls, $p=0.99$). they also found that APH and GDM in 2.44% and 7.31% of the hypothyroid pregnant subjects compared to 4.25% ($z=0.79$) and 2.12% ($z=1.22$) of the controls respectively. Sahu M T et al[21] found PIH in 20.7% of overt hypothyroidism which was significantly higher compared to controls ($p=0.04$). In this study PIH was found in 9.8% of subclinical hypothyroidism which however did not differ significantly from the controls (7.8%).[21]Sejekan Prema et al[28] found PIH to be significantly higher in hypothyroid pregnant women ($p<0.01$).

In our study, out of 132 subjects screened, clinical high-risk characteristics as per Endocrine society guidelines 2012,[29] were present in 24.24% of the subclinical and 50% of the overt hypothyroid groups. Thus, by targeted case finding as recommended by these current guidelines we would have missed around 75.76% and 50% of the subclinical and overt hypothyroid subjects respectively.

CONCLUSION

Maternal thyroid dysfunction is associated with significant adverse effects on maternal and fetal outcome like PE(25%),Abruptio placenta(1.5%),anaemia(11%),PTD(18.8%),PPH(2%), and NICU admission(42.5%) etc emphasizing the importance of routine antenatal thyroid screening in first trimester. Our study accentuates the need to prevent and control thyroid dysfunction during pregnancy, by maintaining thyroxine levels among mothers in the high normal range. This will help to reduce complications like PPH, abortion, preterm labour, anemia, Preeclampsia, and low birth weight etc. Even in the group with normal thyroid function, thyroid autoimmunity was associated with significantly higher prevalence of antepartum haemorrhage due to placental abruption, neonatal jaundice requiring phototherapy and intra uterine fetal death.

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