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Thyroid Dysfunction and Maternal and Fetal Complications in Pregnancy: A study in a tertiary care hospital, Dhaka, Bangladesh.

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Abstract:
Background: *Thyroid dysfunction is not uncommonly observed during pregnancy which may affect pregnancy outcome.*
Aim and objectives*: The study was aimed to evaluate the pregnancy outcome in thyroid dysfunction among pregnant mother in a tertiary level hospital setting.*
Materials and methods: *This observational and longitudinal study encompassed 300 pregnant mothers who were recruited on consecutive basis in their first trimester from the Department of Obstetrics and Gynecology, BSMMU and antenatal clinic of a maternity hospital after fulfillment of inclusion criteria. Assay for anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies as well as free thyroxin (FT4) and thyroid stimulating hormone (TSH) were done by automated chemiluminescent method. Study subjects were categorized into normal and disorder groups on the basis of American Thyroid Association (ATA) defined criteria and all pregnant women were followed throughout the pregnancy till delivery, to note any adverse feto-maternal outcome.*
Results: *Age (mean ± SD) of subjects was 25.68 ± 4.50 years and median gestational age: 11.0 weeks. More than 50% mothers had either grade I or grade II goiter. By stratification of thyroid function on the basis of ATA criteria, 54.3% were euthyroid, 34% subclinical hypothyroid (SCH), 6.3% overt hypothyroid, 3% subclinical sperthyroid and 2.3% overt hyperthyroid. The prevalence of goiter was more frequent among the dysfunctional group than that of euthyroid (/2=10.571,p=0.032). Comparison among functional groups categorized by ATA criteria and conventional criteria for thyroid stimulating hormone (TSH) revealed gross disparity between the two criteria, whereupon ATA criteria was stringent (□[2]= 610.024 p<0.001). Through most of the mothers were negative for antithyroid antibodies, positive antibody was more prevalent among dysfunctional subgroups (p<0.001). Abortion rate was not statistically different between the positive and negative groups (9.1% vs 4.1%, p=0.843) and overall frequency of abortion was less than 10%. Maternal complications (hypertension-preeclampsia, spontaneous abortion, placental abruption,caesarean section and postpartum hemorrhage; p=NS for all) were not statistically different between euthyroid and dysfunctional group. Similarly, fetal complication was relatively more in dysfunctional group but without any statistically significant difference between euthyroid and dysfunction group (Preterm delivery, low birth weight, perinatal morbidity, congenital anomaly and intra uterinedeath; p=NS for all). Overall Caesarean section was more with euthyroid group (□ 2= 8.270,p=0.004). Stratification of birth weight did not reveal any significant difference between the dysfunctional and the euthyroid groups. The anti TPO correlates strongly (r=0.374, p<0.001) with antiTG and inversely with TSH (r=-0.260, p<0.001) in the euthyroid group.*
Conclusions*: Thyroid function should be evaluated early in pregnancy for better pregnancy outcome. The findings of thisobservational and longitudinal study may be helpful in farther researches and in treatment arena.*
Key Words: *Thyroid Dysfunction, Pregnancy, First Trimester, Antithyroid Antibodies, Maternal Complications.*

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I. Introduction

Thyroid disorders is one of the most common endocrine disorders seen in pregnancy in Bangladesh.[1,2] These disorders are the second most common endocrinopathies found in pregnancy after diabetes mellitus[3], Several changes are observed in maternal thyroid function during pregnancy, and failure to adapt these physiological changes result in thyroid dysfunction, especially if complicated by the presence of thyroid antibodies[4]. The excess or deficiency of maternal thyroid hormones, mostly during early pregnancy, can influence pregnancy outcome and fetal development.[5] Pregnancy may affect the course of thyroid disorders and conversely thyroid diseases may affect the course of pregnancy.[6] About 2%-5% of pregnant women suffer from any variety of thyroid disorders and timely intervention can be done if detected early.[7] Pregnancy has a profound impact on thyroid gland and thyroid function. The gland increases 10% in size in iodine-replete countries and by 20%- 40% in areas of iodine deficiency. Production of thyroxin (T4) and tri-iodothyronine (T3) increases by 50%, along with 50% increases in the daily iodine requirement in response to several factors.[8] Human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH), due to structural similarity produce hormone spillover syndrome in first trimester, manifested as stimulation of TSH receptor by hCG. As a result, serum thyroxine (T4) and tri-iodothyronine (T3) levels are elevated, whereas TSH levels are reduced. This is common in multiple pregnancies, hyperemesis gravidarum and trophoblastic diseases. Pregnancy related hyperestrogenism induces a 100% rise in serum thyroxine-binding globulin (TBG), as a result of changes in (TBG) half-life. Therefore, diagnosis of false hyperthyroidism should be avoided in these cases as the TSH level shows relatively low level.[9]Over the last two decades, there have been major advances in understanding the deleterious impact that thyroid disease has on pregnancy outcome.[10] Abnormal thyroid function during pregnancy is clinically significant for the mother and fetus and has crucial influence on multiple aspects of maternal obstetric outcome. SCH is associated with gestational hypertension, gestational diabetes, pre-eclampsia, preterm delivery and pregnancy loss.[8] Thyroid diseases in pregnancy are not uncommon or less frequent. It has been proved that maternal thyroid disorders influence the outcome of mother and fetus during and also after pregnancy.[11] Poorly controlled disease during pregnancy can cause serious complications for both mother and fetus.[12] Sufficient data on pregnancy outcome in patients with thyroid disorders are lacking in our country. Hence, this study is undertaken to observe the frequency of thyroid dysfunction and maternal ae well as fetal complications in pregnancy.

II. Objectives

a) General objective:

- To observe the frequency of thyroid dysfunction and maternal as well as fetal complications in pregnancy.

b) Specific Objectives:

- To evaluate the frequency of thyroid dysfunction in early pregnancy.
- To compare the frequencies of complication, listen euthyroid and treated dysfunctional groups.
- To compare the frequencies of complications in antibody positive and antibody negative groups with thyroid dysfunction.

III. Methodology And Materials

This is a cohort study which was carried out during December 2012 to June 2014 at the department of Endocrinology, BSMMU, Dhaka, Bangladesh. This observational and longitudinal study encompassed 300 pregnant mothers who were recruited on consecutive basis in their first trimester from the department of Obstetrics and Gynecology. BSMMU and antenatal clinic of a maternity hospital after fulfillment of inclusion criteria. Assay for anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies as well as free thyroxin (FT4) and thyroid stimulating hormone (TSH) were done by automated chemiluminescent method. Study subjects were categorized into normal and disorder groups on the basis of American thyroid association (ATA) defined criteria and all pregnant women were followed throughout the pregnancy till delivery, to note any adverse feto-maternal outcome.

- **Inclusion Criteria**
  - Pregnant women with biochemically proved thyroid dysfunction in the 1st trimester (normal function considered as control).
  - Female, aged 20 to 35 years.
  - Mothers not taking any thyroxine supplement.
- **Exclusion Criteria**
  - Patients with already known thyroid disease.
  - Patients with other co-morbid disease assessed clinically or biochemically
  - Pregnant women not willing to participate or give consent.

IV. Results

Characteristics of the participants are shown in Table-I. Mean maternal age (±SD) was 25.68±4.50 years. Median gestational age on recruitment in the first trimester was 11.0 weeks. Most of the mothers were housewife (74.0%) followed by service holder (19.3%) and students (6.7%). About one third mother (29%) had history of previous abortion; 37% were primigravida and 46% were nulliparous indicating abortion or miscarriage in some mothers. There was no goiter in 47% mothers whereas 43% had grade I and 10% had grade II goiter (fig-I). As shown in Tables and Figures according to ATA criteria more than half of the mothers (54.3%) fell into euthyroid group followed by subclinical hypothyroid (34%), overt hypothyroid, (6.3%), subclinical hyperthyroid (3.0%), clinical hyperthyroid (2.6%). As observed in this study, most of the mothers having thyroid dysfunction of any form had associated goiter (OH:78.9%, SCH:56.9%, subclinical hyperthyroidism: 66.7%, hyperthyroidism: 71.4%) while it was 46% in mothers in normal thyroid function (χ^2= 10.571, p=0.032.For the convenience of further analysis all mothers were grouped into two: euthyroid, who had normal thyroid function according to ATA criteria and all the rest into thyroid dysfunctional group. Maternal age (24.99±4.35 vs 26.50±0.57, mean ±SD, P=0.004) was different but mean (±SD) gestational age (10.38±1.76 vs 10.50±1.92, p=0.563) was not statistically different between euthyroid and thyroid dysfunctional groups. There was no statistically difference for history of previous pregnancy (χ^2=2.380, p=0.304). However, goiter was significantly more in the dysfunctional group (χ^2=6.997, p=0.008)In this study, the frequencies of positive and negative status of antithyroid antibodies among the ATA defined functional classes. Out of 300 pregnant mothers more than 200 were negative for both antibodies, 28 were positive for both antibodies, while 50 were positive for only anti-TPO and 12 were positive for only anti-TG ($p<0.001$, by McNemar's test). These frequencies for euthyroid (n=19): 6,8,4 and 1 (p=0.375), for hypothyroid (n=7): 2,0,4 and 1 (p=0.375), for SCH (n=102): 69, 10, 18 and 5 (p=0.011) and for subclinical hyper (n=9): 5,2,2 and 0(p=0.500) respectively. When antibody status was considered combined 90 subjects were positive and 210 were negative. Frequencies of positive and negative antithyroid antibodies status among various subclasses were found to be disturbed differently. OH (68.4%), Overt hyper (71.4%) and Subclinical hyper (44.4%) were found to be more positive for antithyroid antibodies than that for euthyroid (1.5%) and SCH (32.4%) subclasses of subjects which were statistically different (χ^2= 25.885, p<0001). There was no statistically significant difference for the frequency of abortion between the positive and negative status of antithyroid antibody (χ^2=0.089, p=0.843). Also, the frequency of abortion in both positive (9.8%) and negative (8.4%) subjects were less than 10%. Frequency of maternal complications during and after pregnancy is displayed in here. Hypertension-preeclampsia was found in 24, spontaneous abortion 24, placental abruption 2, Caesarean section in the dysfunction group (Euthyroid vs. dysfunction: hypertension-preeclampsia 45.8% vs. 54.2%, p= 0.505, placental abruption 0% vs. 100%, p=0.137, caesarean section 48.6% vs. 51.4%, p= 0.094). As shown in Tables and Figures frequency of caesarean section was the most frequent complication in all subjects of SCH, OH, subclinical hyperthyroidism and clinical hyperthyroidism (71.1%, 61.1%, 57.1%, 85.7%, 12.5% and 28.6% respectively) followed by hypertension-preeclampsia (8.1%, 10.5% respectively), Spontaneous abortion (7.1%, 21.1%, 25.0% and 0% respectively).

Table-I: Characteristics of the studied pregnant women (N=300)

Characteristics	Value
Numbers	**300**
Maternal age (Yrs. M+SD)	25.64 ± 4.504
Profession	
Housewife	222(74.0%)
Service	58 (19.3%)
Students	20 (6.7%)
Median gestetional age (wks.)	11
Gravita	
1	110 (36.7%)
2	96 (32.0%)
≥3	94 (31.3%)
Parity	
o	138 (46%)
1	105 (35%)
2	42 (14%)
≥3	15(5%)
History of previous abortion	141(47%)
Thyromegaly	
Grade 0	129(43%)
Grade1	129(43%)
Grade2	30(10%)

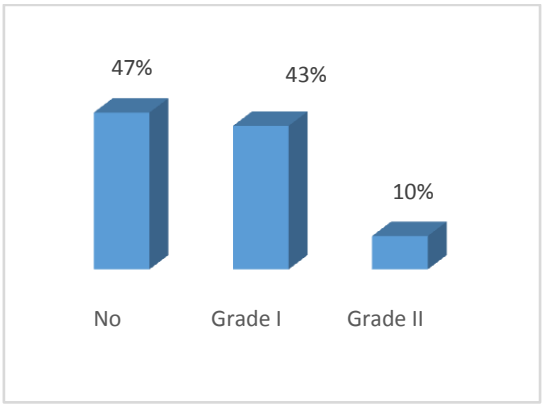

Figure I: Frequency of various grades of goiter (N=300)

Table-II: ATA defined thyroid function in studied pregnant women. (n=300)

Parameter	n	%
Euthyroid	163	54.3
Overt Hypothyroidism	19	6.3
Subclinical Hypothyroidism	102	34
Overt Hyperthyroidism	7	2.3
Subclincal Hyperthyroidism	9	3
Total	300	100

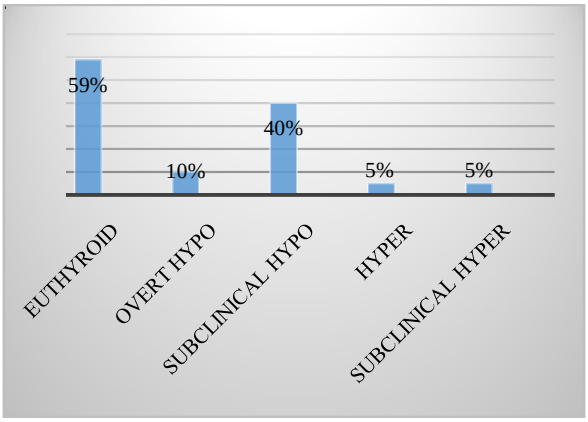

Figure II: Functional Categories of the subjects. (n=300)

Table-III: Relationship between ATA defined functional status and goiter (N=300)

Goiter Status	ATA defined functionl groups						χ^2, p
	Euthyroid	Overt Hypo	Overt hyper	Subcl. Hypo	Subcl. Hyper	Total	χ^2=10571 p=0.032
Goiter	75(46.0)	15(78.9)	05 (71.4)	58(56.9)	6(66.7)	159(53)	
No Goiter	88(54.0)	04(21.1)	02(28.6)	44(43.1)	03(33.3)	141(47)	
Total	163	19	7	102	9	300	

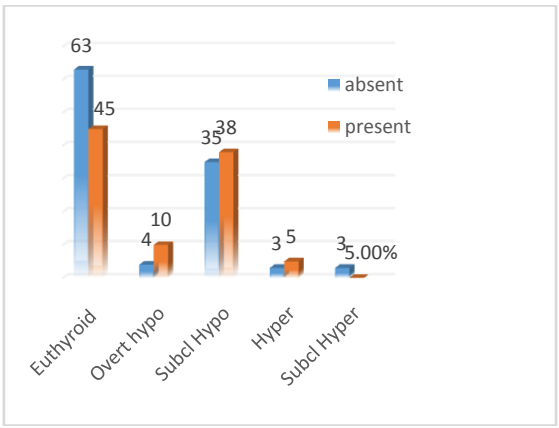

Figure III: Frequency of goiter among the functional groups

Table-V: Anti-thyroid antibody status among the studied subjects (n=300)

Antibody Status	ATA defined functional groups					Total
	Euthyroid	Hypo thyroid	Hyper thyroid	Subclin. Hypo	Subclin Hyper	
Only anti-TPO ab positive	22	4	4	18	2	50
Onli anti-TG ab positive	5	1	1	5	0	12
Both anti-TPO and anti-TG positive	8	8	0	10	2	28
Both anti-TPO and anti-TG negative	128	6	2	69	5	210
Total	163	19	7	102	9	300
P value	0.002	0.375	0.375	0.011	0.5	<0.001

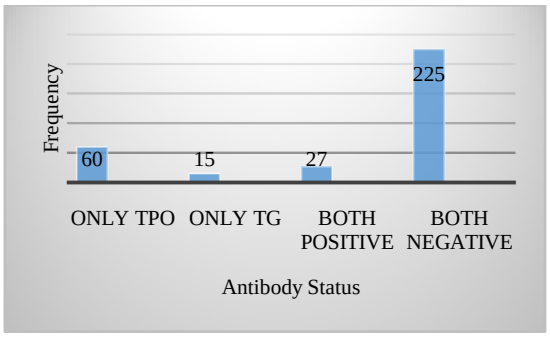

Figure IV: Status of anti-thyroid antibody the functional groups.

Table VI: Antibody status among ATA defined functional groups (n=300)

Functional Status	Antibody Status		Total	□ ² and p
	Positive(%)	Negative (%)		
Euthyroid	35(21.5)	128(78.5)	163	□ ² = 25.885, p<0.001
Overt Hypothyroidism	13(68.4)	6(31.6)	19	
Subclinical Hypothyroidism	33(32.4)	69(67.6)	102	
Overt Hyperthyroidism	5(71.4)	2(28.6)	7	
Subclinical Hyperthyroidism	4(44.4)	5(55.6)	9	
Total	90	210	300	

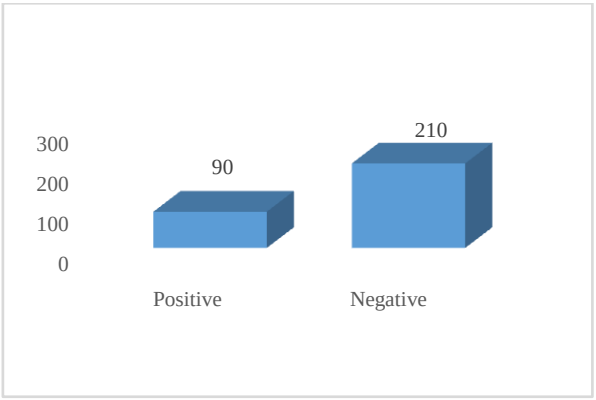

Figure V: Combined antibody status in the functional subgroups (N=300)

Table VII: Association between history of abortion and thyroid antibody positivity (n=279)

Abortion	Antibody status		Total	□ ², p
	Positive	Negative		
Yes	8(9.1)	168.4)	24	□ ²= 0.039 P=0.843
No	80 (90.9)	175(91.6)	255	
Total	88	191	279	

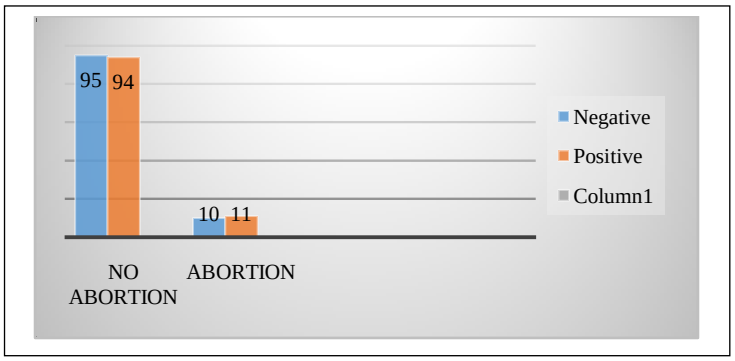

Figure VI: Frequency of abortion and its relevance to antibody status.

Table VIII: Maternal complications in euthyroid and thyroid dysfunction patients

Complications	Euthyroid	Dysfunction	Total	□ ²	P
Hypertention/Preeclampsia	11(45.8)	13(54.2)	24	0.444	0.505
Spontaneous abortion	11(45.8)	13(54.2)	24	0.444	0.505
Placental abruption	0(0)	2(100)	2	2.211	0.137
Caesarean section	90(48.6)	95(51.4)	185	2.809	0.094
Postpartum haemorrhage	0(0)	0(0)	0	-	-

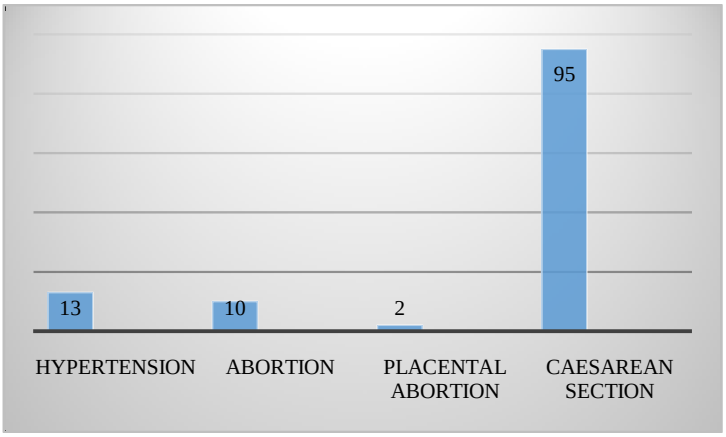

Figure-VII: Frequency of maternal complications in functional subgroups (Thyroid dysfunction)

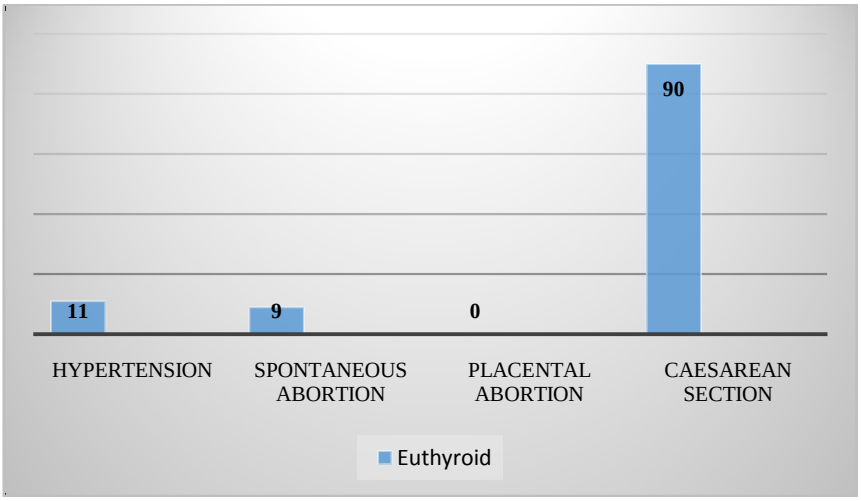

Figure-VIII: Frequency of maternal complications in functional subgroups

Table-IX: Frequency of maternal complications in functional subgroups.

Complications	Subclinical hypo (n=96-99)	Overt hypo (n=18-19)	Subclinial hyper (n=7-8)	Cilinical hyper (n=7)
Hypertention/Preeclampsia	08(8.1)	02(10.5)	0.1(12.5)	02(28.6)
Spontaneous abortion	07(7.10)	04(21.1)	02(25.0)	00(0.0)
Placental abruption	02(2.0)	00(0.0)	00(0.0)	00(0.0)
Caesarean section	74(77.1)	11(61.1)	04(57.1)	0.6(85.7)

V. Discussion

This study was performed to detect the adverse pregnancy outcome in patients with thyroid disorders according to trimester specific reference range defined by ATA, who has no story of detectable thyroid abnormality of risk factors prior to pregnancy. In this study, overall dysfunction group was higher among the subjects having positive antibody status. However, case of euthyroid, frequency of positive antibody was less. According to ATA defined TSH level, out of 300 studied subject 163(54.3%) were euthyroid, 102(34%) subclinical hypothyroid, 19 (6.3%) overt hypothyroid, 9 (3%) subclinical hyperthyroid and 7(2.3%) clinical hyperthyroid. Similar study conducted by Begum et al[1] in BSMMU using the conventional non-pregnant referencerange for TSH in 200 pregnant women (up to 20 wks. of gestation) showedsubclinicalhypothyroid 5%, overt hypothyroid 3%, subclinical hyperthyroid 4% and overt hyperthyroid 3.5%. Another study by Shah et al[3] in India involving 2000 pregnant women attending antenatal clinic using the conventional nonpregnant TSH reference range shows, 94% were euthyroid, 3.5% had subclinical hypothyroidism, had overt hypothyroidism and 0.6% had overt hyperthyroidism. The higher percentage in our study could be due to higher autoimmunity in our population or gradual increment of autoimmunity worldwide and iodine deficiency may be a contributory cause but this information cannot be generated from our study as urinary iodine estimation was not done. Subclinical hypothyroidism was 34% which does not correspond with other previous reports. Thehigher percentage may be due to TSH values were measured according to ATA criteria[8] where upper limit of cut off value for TSH was 2.5 mIU/L. Hasanat et al[13] had studied status of antithyroid antibody in Bangladesh among male and nonpregnant female and observed higher frequency of autoimmune thyroid disease (48.36%) with antibody positivity in Hashimotos thyroiditis (63.0%), atrophic thyroiditis (44.7%) and Graves' disease (36.4%). Others have observed prevalence of hyperthyroidism significantly higher in anti TPO antibody positive pregnant women than anti-TPO antibody positive pregnant women than anti-TPO antibody negative pregnant women.[5] These findings were consistent with this study. Prevalence of subclinical hypothyroidism among pregnant women was found fairly high among Indians and they have high rates of TPO antibody positivity.[5] This study supports similar findings in Bangladeshi pregnant women.Antibody positivity (21.5%) among euthyroid subject in this study is also consistent with data from the third National Health and Nutrition Examination Survey (NHANES-III), where anti-TPO positivity and anti-TG antibody positivity was found in 12.6% and 13.6% of euthyroid women respectively.[9] Women in euthyroid state but with thyroid autoimmunity are twice likely to experience spontaneous miscarriage as it probably represents a generalized activation of immune system or there is an increased risk of progression to subclinical hypothyroidism or probably due to transplacental transfer of thyroid receptor blocking antibodies.[14,4,10] Significant statistical difference was found among the subgroups for status of antibody, when two antibodies were considered separately for relation with ATA defined thyroid dysfunction. Apropos with this, there was observed significant difference for frequency of antibody positivity between euthyroid and dysfunction groups in the present study. However, this study showed that anti-TPO and anti-TG antibody strongly correlated in euthyroid group and anti-TPO titer inversely corelated with weeks of gestation in dysfunction group. In this context, Mannisto et al[15] describes that both anti-TPO antibody and anti-TG antibodies are independent risk factors for subsequent thyroid disease.In observing frequency of maternal complications during and after pregnancy, hypertension-preeclampsia was found in 24, spontaneous abortion 24, placental abruption 2, caesarean section 185 and PPH in none among the studied mothers. When compared between euthyroid and dysfunction groups, these complications were not statistically different except a higher frequency for caesarean section in the dysfunction group (Uthyroid vs. dysfunction: hypertension-preeclampsia 45.8% vs. 54.2%, p=0.505, spontaneous abortion 45.8% vs. 54.3%, p=0.505, placental abruption 0% vs. 100%, p=0.137, caesarean section 48.6% vs. 51.4%, p=0.094). Higher frequency for caesarean section may be attributed to the fact that electively mothers with thyroid dysfunction might have preferred caesarean section. Perinatal morbidity like birth asphyxia, jaundice is in higher frequencies in both groups and mostly seen in preterm delivery patients. The association of thyroid disease and adverse perinatal morbidity was not solely due to preterm delivery.[15]Maternal and fetal complications in antibody positive subjects were not significantly higher in our study in any functional group. When birth weight of the babies was compared between euthyroid and dysfunction groups after stratification of the birth weight into three categories, the very LBW was found only in dysfunctional group. This may be due to the fact that all mothers were under treatment if found dysfunction in first trimester.

LIMITATIONS OF THE STUDY

This study was carried out at a tertiary level hospital, subjects represented mostly urban and semi-urban population, so true prevalence in our country as a whole might not have been reflected. Some participants were not in regular follow up schedule and 21 subjects were dropped and it may be due to some factors like lack of awareness, superstition and other antenatal visits in their nearby antenatal or private clinics. TT4 was not estimated which might have caused some masking of true function. The optimal method to assess serum FT4 during pregnancy is measurement of T4 in the dialysate or ultra-filtrate of serum samples employing on-line extraction/ liquid chromatography/ tandem mass spectrometry (LC/MS/MS), is not used in this study.

VI. Conclusion And Recommendations

Thyroid function should preferably be checked during pregnancy otherwise subclinical thyroid dysfunction which attributes to maternal and fetal complications may be missed. In the present study using the ATA defined reference ranges for defining thyroid disorders in pregnancy, overall frequency of thyroid dysfunction was found higher in asymptomatic pregnant women in their first trimester than that as it conventionally believed. It indicates the necessity of carrying out screening test in all pregnant women regardless of the risk factors. Early diagnosis and treatment of thyroid disorders can prevent the adverse pregnancy outcome and thereby more attention to thyroid disorders is needed in pregnant patients.

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