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Overt and subclinical hypothyroidism among Bangladeshi pregnant women and its effect on fetomaternal outcome

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Abstract

Objectives: Thyroid disorders are among the common endocrine problems in pregnant women. It is now well established that not only overt but subclinical thyroid dysfunction also has adverse effects on maternal and fetal outcome. There are few data from Bangladesh about the prevalence of thyroid dysfunction in pregnancy. With this background, this study aims to find out thyroid dysfunction (both overt and subclinical hypothyroidism) in pregnancy and its impact on obstetrical outcome. Methods: We studied the evaluation of 50 admitted pregnancies corresponding to 29 women with subclinical hypothyroidism and rest 21 was overt hypothyroidism. Detailed history and examination were performed. Apart from routine obstetrical investigations, Thyroid Stimulating Hormone (TSH) estimation was done. Their obstetrical and perinatal outcomes were noted. Results: Overt hypothyroidism was significantly ($p<0.05$) higher in 25 to 44 years age group. However two and three abortions were significantly ($p<0.05$) higher in overt hypothyroidism patients. In sub clinical hypothyroidism 86.2% conceived firstly within 2 years and 66.7% in overt hypothyroidism patients conceived firstly in between 3 to 5 years after marriage. Overt hypothyroids were prone to have pregnancy-induced hypertension 42.9%, intrauterine growth restriction ($P=0.001$) and gestational diabetes (38.1%) as compared to subclinical cases. Neonatal complications were significantly more in overt hypothyroidism group. Mean TSH level was significantly ($p<0.05$) higher in overt hypothyroidism patients but mean FT_4 level was almost similar in both groups. Majority of the patient underwent caesarean section in both groups due to associated medical and obstetrical complications. None of the babies showed hypothyroidism by cord blood tests. In this analysis our results showed that overt hypothyroidism among Bangladeshi pregnant women are associated with more maternal complication & adverse parental outcome than subclinical hypothyroidism. The adequate treatment of hypothyroidism during gestation minimizes risks and generally, makes it possible for pregnancies to be carried to term without complications. Significant adverse effects on maternal and fetal outcome were seen emphasizing the importance of routine antenatal thyroid screening.

Introduction

Thyroid gland disease is most common endocrine disease in Bangladesh.[1] Thyroid disorders constitute one of the most common endocrine disorders seen in pregnancy. In one study, overt hypothyroid disorder was found in 1.3 per 1,000 and subclinical disease in 23 per 1,000.[1] Some studies[2] reported prevalence of overt hypothyroidism between 1 and 2% and subclinical hypothyroidism in 8% of women. Women with hypothyroidism have relatively increased infertility, miscarriage rates and carry an increased risk for obstetric and fetal complications.[3] The main obstetric complications are anemia, preeclampsia, placental abruption and postpartum hemorrhage. Fetal complications include prematurity, low-birth weight (LBW), fetal distress in labor, fetal death and perinatal death.[4]

Many hypothyroid women (>70%) have anovulatory cycles and when they conceive have high rates of fetal loss in the first trimester (more than twice as many spontaneous abortions as normal woman). Studies have shown that the fetuses of hypothyroid woman have 10% - 20% more congenital anomalies, 20% more perinatal mortality and 50% - 60% higher rates of impaired mental and somatic development.[5]

Overt hypothyroidism complicates 0.2% of all pregnancies, subclinical hypothyroidism is found in 0.4% pregnancies.[6] There is now increasing understanding of the association between not only overt, but also subclinical thyroid disorders and dysfunctions with adverse consequences on both obstetric outcome and long-term neurological development of the offspring.

It is generally accepted that a proportion of women with hypothyroidism need to increase their dose of thyroxine during pregnancy, but it is unclear how these dose changes should be decided. While some studies suggest that decisions should be based on thyroid function tests at the booking visit and during pregnancy and have reported that many women would not need an increment, others have proposed a global increase in the thyroxin dose as soon as pregnancy in confirmed. There are concerns about this as not only may it be unnecessary for many women but also fetal exposure to excess T_4 and T_3 may be associated with miscarriage and low birth weight.[7]

All these data have been collected from studies in the developed countries. In developing countries, such as Bangladesh, there is a paucity of available data in relation to thyroid dysfunction, especially subclinical thyroid dysfunction. With this in mind, this prospective study was undertaken to determine thyroid disorders, both clinical and subclinical among pregnant Bangladeshi women attending antenatal clinic of a tertiary care teaching hospital to see the effect of thyroid disorders on pregnancy outcome. It also aims to identify the importance of thyroid screening among pregnant women in our population.

Materials and Methods

This study was a prospective evaluation of 50 women with singleton pregnancies carried out at Bangabandhu Sheikh Mujib Medical University, Dhaka, a tertiary care teaching hospital that caters predominantly to low and middle socioeconomic group. This study was done over a period of 1 year from January 2012 to December 2012. Approval from the institutional ethics committee was obtained. We followed 50 pregnancies corresponding to 29 women with subclinical hypothyroidism and 21 with overt hypothyroidism at the time of diagnosis. Pregnant women classified into 2 groups. Group I- subclinical hypothyroid, Group II- overt hypothyroid patients. 5 ml cord blood from neonate was taken to see the level of TSH & FT_4; it is repeated on day 5.

Recently diagnosed hypothyroid pregnant women (either during the study period, or within the 6 previous months of study period) for whom, data related to the diagnosis is available, admitted patients who were diagnosed as overt & subclinical hypothyroidism during antenatal check up are included. Women were excluded if they had multi-fetal gestation, known chronic disorders, such as diabetes, hypertension or had previous bad obstetric history with known cause, subject presenting a major and objectifiable risk of not being able to follow-up until the next TSH level, all contraindications to levothyrox or thyroxin intolerable patients.

Detailed history and examination were performed with special regard to maternal age, parity, gestational age, prior obstetric, medical, surgical history and clinical features suggestive of thyroid dysfunction. Informed consent to participate in this study was taken. Serum samples were collected in plain vial for TSH estimation. Serum FT_4 and TSH was measured by Abbott Axsym System from the laboratory. The normal range for TSH is 0.5–5.5 mIU/L for this laboratory. Women with overt (clinical) hypothyroidism defined as high TSH with low-free T_4. Subclinical hypothyroidism also known as mild hypothyroidism was defined as TSH that is elevated in the presence of normal blood levels of thyroid hormone.

Women diagnosed with abnormal hormone values were referred to endocrinology clinic of respective institution for a simultaneous treatment and follow-up. Routine ante partum management was done and women were followed till delivery. Maternal outcome variables included were the occurrence of anemia, preeclampsia, gestational diabetes, overall rate of cesarean section, cesarean section for fetal distress, and postpartum hemorrhage. Measured neonatal outcomes included the incidence of low birth weight, prematurity, intrauterine growth restriction (IUGR), Apgar score at 1 min, neonatal intensive care unit admission and fetal demise.

Analyses were performed using the statistical package of SPSS, version 20.0. The effects of thyroid dysfunctions were analyzed by comparing the frequencies of various outcomes in the above mentioned groups. Continuous data were presented as mean±SD and analyzed using unpaired, two-tailed student's t-test. Proportional data were compared using Chi-square test where appropriate. The results from the logistic regression are expressed as relative risk (RR) and the corresponding 95% confidence interval and 'P' values. $P<0.05$ was considered statistically significant.

Results

Out of 50 women studied over a year time span, 29 were subclinical hypothyroid- group I and 21 were overtly hypothyroid- group II.

Maternal demographic characteristics are shown in Table I. There was significant difference in baseline demographics of pregnant women from the clinical center. Maternal age was high in pregnant women with overt hypothyroidism. In group 1-62.1% of the

patients were in the age group 15-24 years, where as in group II (66.7%) were in the age group 25-44 years, this difference in age between the groups was significant –Table I.

The number of abortion/miscarriages was more common in group II patients than that of group I patients. Significant ($p<0.05$) difference was observed in Table II between the groups, comparing the number of abortions. 72.4% patients in group I had hypothyroidism for <1 year but in group II (42.9%) had hypothyroidism for more than 5 years. Statistically significant ($p<0.05$) difference was observed between groups regarding duration of hypothyroidism Table III.

Table IV illustrates the medical complications assessed in antenatal period. The overt hypothyroid women were more prone to have pregnancy-induced hypertension (23.8%), diabetes mellitus (38.1%) and anemia (42.9%). Other medical disorders like chronic hypertension, anemia with GDM, GDM with pre-eclampsia and thalassaemia with GDM were observed only in group II patients.

Mean gestational period was 36±2.5 weeks in group I and 35.8±1.4 weeks in group II patients. Mean gestational weeks was not statistically significant ($p>0.05$) in unpaired t-test (Table V).

Maternal and fetal complications were observed more in group II than that of group I. Prolonged 2nd stage was more common in group II, which was observed in 13.8% in group I and 42.9% in group II. Similarly, fetal distress was more common in group II (80.9%) compared to group I (41.4%). Statistically significant ($P<0.05$) difference between groups was observed in all complications (Table VI).

The overall rate of cesarean section was high in all groups and cesarean section for fetal distress was carried out in significantly higher number of women due to associated medical and obstetrical complications.

Table VII shows the thyroid supplements/thyroxin (50µg) of the study patients and it was found that in group I (55.2%) of the study patients received one tablet of thyroxine per day. However, majority (71.4%) of the group II patients received three tablets (150µg) per day. Statistically significant ($p<0.05$) difference was observed in chi-square test regarding thyroid supplements.

Mean TSH level at 2nd and 3rd trimester of pregnancy shows statistically significant ($p<0.05$) in unpaired t-test (Table VIII).

Birth weight and APGAR score at 1st minute showed statistically significant ($p<0.05$), difference between groups but others were not significant ($p>0.05$). Perinatal death occurred in 1 baby after 5 days admission in NICU due to respiratory distress and complications of prematurity (Table IX).

Cord TSH and neonatal day-5 TSH screening was performed and no significant association was found between them and maternal TSH.

Table I: Demographic data

Variables	Group I (n=29)		Group II (n=21)		P value
	No.	%	No.	%	
Age (years):					
15-24	18	62.1	7	33.3	0.044
25-44	11	37.9	14	66.7	
Parity :					
Primi gravid	8	27.6	5	23.8	0.763
Multi gravid	21	72.4	16	76.2	

Table II: Obstetrical variables

Parameters	Group I (n=29)		Group II (n=21)		P value
	No.	%	No.	%	
Previous abortions:					
One abortion	5	17.2	6	28.6	0.339
Two abortions	4	13.8	11	52.4	0.003
Three abortions	0	0.0	3	14.3	0.035
1st conception after marriage:					
≤ 2 years	25	86.2	7	33.3	0.001
3 – 5 years	4	13.8	14	66.7	

Table III: Duration of hypothyroidism (in years)

Parameters	Group I (n=29)		Group II (n=21)		P value
	No.	%	No.	%	
< 1 year	21	72.4	0	0.0	0.001
1 – 3 years	8	27.6	6	19.0	
4 – 5 years	0	0.0	8	38.1	
> 5 years	0	0.0	9	42.9	

Table IV: Maternal medical complications assessed in antenatal period.

Variables	Group I (n= 29)		Group II (n= 21)	
	No.	%	No.	%
Anemia	5	17.2	9	42.9
Preeclampsia	1	3.4	5	23.8
Diabetics mellitus	3	10.3	8	38.1
Chronic hypertension	0	0.0	3	14.3
GDM with medical disorder:				
Anemia with GDM	0	0.0	3	14.3
GDM with preeclampsia	0	0.0	3	14.3
Thalassaemia with GDM	0	0.0	3	14.3

Table V: Gestational period of Study population

Gestational period	Group I (n=29)		Group II (n=21)		P value
	No.	%	No.	%	
24 – 31	0	0.0	3	14.3	
32 – 34	10	34.5	0	0.0	
35 – 37	7	24.1	13	61.9	
>37	12	41.4	5	23.5	
Mean±SD	36±2.5		(35.8 ± 1.4)		0.752

Table VI: Obstetrical outcome

Variables	Group I (n= 29)		Group II (n= 21)		P value
	No.	%	No.	%	
Mode of delivery:					
Normal vaginal delivery	5	17.2	3	16.7	0.959
Caesarean section	24	82.8	15	83.3	
Complications during delivery:					
Maternal Complication:	1	3.4	4	19.0	0.069
Impending eclampsia	0	0.0	3	14.3	0.035
PPH	4	13.8	9	42.9	0.020
Prolonged 2nd stage					
Fetal Complication:					
Fetal distress	12	41.4	17	80.9	0.005
IUD	0	0.0	3	14.3	0.035

Table VII: Distribution of the study patients according to thyroxin supplement (50 µgm)

Thyroid supplements/Thyroxin	Group I (n= 29)		Group II (n= 21)		P value
	No.	%	No.	%	
Not received supplement	3	10.3	0	0.0	0.001
One tab (50 µg) per day	16	55.2	1	4.8	
Two tab (100 µg) per day	10	34.5	5	23.8	
Three tab (150 µg) per day	0	0.0	15	71.4	

Table VIII: Distribution of the study patients according to TSH level and FT_4 level (n= 50)

Variables	Group I (n= 29)		Group II (n= 21)		P value
	Mean±SD	Range	Mean±SD	Range	
TSH level (µIU/ml)					
1st trimester of preg.	12.6±19	(0.6-27.7)	13.9±10.4	(6.1-49.2)	0.847
2nd trimester of preg.	0.41±0.7	(0.3-0.5)	0.93±0.23	(0.7-1.3)	0.043
3rd trimester of preg	2.0±1.1	(0.7-3.3)	2.9±1.3	(2.0-4.3)	0.039
FT_4 level (µg/dl)					
1st trimester of preg.	1.5±1.1	(0.8-2.5)	1.1±0.9	(0.3-2.1)	0.583
2nd trimester of preg.	1.7±1.2	(0.9-2.7)	0.9±0.7	(0.2-1.9)	0.173
3rd trimester of preg	1.6±1.3	(0.8-2.6)	1.8±0.6	(0.2-2.7)	0.287

Table IX: Neonatal Outcome

Variables	Group I (n= 29)		Group II (n= 21)		P value
	No.	%	No.	%	
Birth weight (kg)					
<2.5 kg	8	2.76	12	80.0	0.001
>2.5 kg	21	72.4	3	20.0	
APGAR score at 1 min					
≤6	11	37.9	11	73.3	0.026
≥7	18	62.1	4	26.7	
Admission in NICU					
Yes	4	13.8	3	20.0	0.593
No	25	86.2	12	80.0	
Cord blood					
Hypothyroidism present	0	0.0	0	0.0	-
Hypothyroidism absent	29	100.0	15	100.0	

Discussion

Thyroid gland disease is most common endocrine disease in Bangladesh.[1] Congenital hypothyroidism is a common preventable cause of mental retardation. Hypothyroid women who become pregnant carry an increased risk of obstetrical complications. Overtly hypothyroid women experienced a 20% - 40% incidence of maternal complications, including anemia preeclampsia, placental abruption and postpartum hemorrhage.[4]

The maternal age of clinical hypothyroid group was high which may be due to the difficulty associated with fertility. One study[8] observed that the age range of the patients was 15 to 45 years with mean±SD age was 33.3±12.3 years and most of the patients were between 20-30 years, which are closely resembled with the current study.

Conversely, in hypothyroid women with adequate treatment, the frequency of abortions was minimal and pregnancies were in general carried to term without complications.

The number of abortion/miscarriages was more common in overt hypothyroidism patients than that of subclinical hypothyroidism patients in this current study. Two and three abortions were significantly ($p>0.05$) higher in overt hypothyroidism patients. More recently, however it has been published that 8.9% abortion in the whole study patients, out that 14.3% and 6.5% in sub clinical hypothyroidism and overt hypothyroidism respectively.[8] Many hypothyroid women have anovulatory cycles and when they conceive have high rates of fetal loss in the first trimester (more than twice as many spontaneous abortion as normal woman).[9]

Most (72.4%) patients had <1 year and 42.9% had more than 5 years of hypothyroidism in sub clinical hypothyroidism patients and overt hypothyroidism patients respectively. The difference in duration of the diseases was found to be statistically significant ($p<0.05$). Regarding duration of hypothyroidism Wier FA et al[10] showed the median duration of hypothyroidism was 3.0 years with range form 1.4 to 5 years in sub clinical hypothyroidism patients and 3.0 years with range from 1.5 to 5 years in overt hypothyroidism patients ($p=0.806$). Similarly, Miah et al.[8] (2009) observed that the duration of hypothyroidism varied from 6 months to 8 years.

As seen in previous studies, untreated or uncontrolled overt hypothyroidism during pregnancy may increase the incidence of maternal anemia, preeclampsia, spontaneous abortion, low birth weight, fetal death or still birth.[3,5] In this study also the incidence of preeclampsia, IUGR ($P=0.001$) was significantly high in overt hypothyroid group.

In this present study it was observed that mean gestational period at delivery was 36±2.5 weeks ranging from 32 to 39 weeks in sub clinical hypothyroidism patients and 35.8±1.4 weeks ranging from 24 to 38 weeks in overt

hypothyroidism patients. The difference was not statistically significant.

Subclinical hypothyroidism is predominantly seen in women and progression from subclinical to overt hypothyroidism occurs in 3-20% of patients.[9,11] In the past studies it has been shown that these women have higher incidence of preterm delivery, IUGR, placental abruption and perinatal and neonatal morbidity and mortality.[12–14] The overall rate of cesarean section was high in all groups; reason being these were tertiary care teaching hospitals where referrals are sent. Cesarean section as an indication for fetal distress was significantly done among women of overt hypothyroid group (P=0.005). This reinforces the importance of detecting thyroid disorders in pregnancy and to be aware of its maternal and fetal complications.

Thyroid supplements/thyroxin (50µg) of the study patients showed that in group I - 55.2% of the study patients received one tablet of thyroxine per day. However, majority 71.4% of the group II patients received three tablets (150µg) per day. Statistically significant ($p<0.05$) difference was observed in Chi-square test regarding thyroid supplements. This is consistent with other previously reported cases, where mean increases of 42 µg/d to 62 µg/d were observed in 45% to 100% of patients.[15]

In this current study it was observed that the mean TSH level was 12.6±19 µIU/ml ranging from 0.6 to 27.7 µIU/ml in sub clinical hypothyroidism patients during 1st trimester of pregnancy, which was significantly decline during 2nd trimester and 3rd trimester of pregnancy. However, in overt hypothyroidism patients, the mean TSH level was 13.9±10.4 µIU/ml ranging from 6.1 to 49.2 µIU/ml, during 1st trimester of pregnancy which also significantly decline during 2nd trimester and 3rd trimester of pregnancy.

Regarding mean FT_4 level at 1st, 2nd and 3rd trimester of pregnancy was almost identical between two groups, which varied from 0.8 to 2.7 µg/dl in sub clinical hypothyroidism patients and 0.2 to 2.7µg/dl in overt hypothyroidism patients. This is consistent with previously reported cases.[16]

In this present study it was observed that 27.6% and 80.0% babies had low (≥2.5 kg) birth weight in subclinical hypothyroidism patients and overt hypothyroidism patients respectively. Low birth weight and low APGAR score at 1st minute were significantly ($p<0.05$) higher in overt hypothyroidism patients, but others were not significant ($p>0.05$).

Although no significant association was found between maternal TSH and cord TSH. Follow-up beyond newborn period was not possible because after discharge most infants either did not come for follow-up or they were seen in Pediatric clinic.

At present, there is no available recommendation for detecting or screening thyroid dysfunction among pregnant women in Bangladesh. Recent consensus guidelines do not advocate universal thyroid function screening during pregnancy, but recommend testing for high-risk pregnant women with a personal history of thyroid or other autoimmune disorder or with a family history of thyroid disorders.[17]

In conclusion, our study shows effects of thyroid dysfunction, especially overt hypothyroidism among Bangladeshi pregnant women are associated with adverse perinatal outcome. Based on the results of the present study, we, therefore, suggest for a decreased threshold for screening and detection of thyroid dysfunction among Bangladeshi pregnant women attending routine antenatal clinic and to be potentially aware of associated maternal and fetal complications.

This is important because, apart from some exceptions we mentioned, our results confirm that an adequate treatment of hypothyroidism during gestation minimizes risk and in general makes it possible for pregnancies to be carried to term without complications.

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