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Original Research Article

Increased occurrence of hypothyroidism among pregnant women during the first trimester and its correlation with anti-thyroid peroxidase antibody (anti-TPO) and gestational diabetes mellitus in Chattagram region, Bangladesh

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ABSTRACT

Background: The present study was aimed at investigating the prevalence of hypothyroidism in pregnant women in their first trimester in Chattagram, an iodine-sufficient area in Bangladesh. We also studied whether hypothyroidism in pregnancy has any correlation with high titres of anti-thyroid peroxidase (anti-TPO) antibodies and the occurrence of gestational diabetes mellitus.
Methods: Our study included 100 pregnant women at their first antenatal checkup based on certain preselected criteria in two tertiary care hospitals in Chattogram. The levels of serum TSH, FT4, and anti-TPO were estimated to detect thyroid function from the collected blood sample. The oral glucose tolerance test was carried out between 24 and 28 weeks of gestational age. A standard predesigned proforma was used to record a detailed patient history and the findings of general physical examinations.
Results: According to our results, thyroid disorder and GDM affect 19% and 13% of total pregnancies, respectively. Among TD patients, subclinical hypothyroidism (SCH) prevails the most (11%). The majority of the hypothyroid patients with a high titre of anti-TPO positivity (11%) indicate an autoimmune etiology ($p<0.001$). Furthermore, a statistically significant relationship ($p<0.01$) was established between hypothyroidism and GDM. No demographic data was observed to affect GDM and hypothyroidism.
Conclusion: Thyroid disorders affect one in every six pregnant women in the southern part of Bangladesh. Moreover, hypothyroid pregnant women were found to be highly susceptible to GDM. Euthyroid women with a high titre of anti-TPO during their gestation should be closely monitored for the development of hypothyroidism and GDM.

Keywords: Thyroid dysfunction, gestational diabetes mellitus, anti-thyroid peroxidase antibody, subclinical hypothyroidism, oral glucose tolerance test

INTRODUCTION

Every woman experiences different levels of hormonal fluctuation throughout pregnancy to support physiological alterations. One of the most frequently encountered hormones during pregnancy is thyroid hormone, followed by insulin. Thus, the most frequent endocrine abnormalities identified during pregnancy are thyroid problems and gestational diabetes mellitus (GDM).[1,2] A recent study showed that the prevalence of GDM has steadily risen in China and is currently at 14.8%.[3,4] According to statistics from the most recent IDF Diabetes Atlas,[5,6] the frequency of hyperglycemia in pregnancy was 15.8% worldwide, of which gestational diabetes mellitus (GDM) was 83.6%.[6-8] Similarly, thyroid hormones are essential for the survival of all humans, including mothers and children.[3,9,10] Maternal issues, i.e., miscarriage, gestational hypertension, preeclampsia, abruptio placentae, preterm delivery, caesarean section births, and birth trauma, may be associated with both thyroid dysfunction and gestational diabetes.[6,11] In a recent meta-analysis of research, for instance, the frequency of anti-TPO positivity and SCH were reported to be 7.5% and 3.1% respectively.[3,12] The following perinatal and neonatal morbidities are correlated to GDM and thyroid dysfunction: macrosomia, shoulder dystocia, respiratory distress syndrome, neonatal hypoglycemia, polycythaemia, hyperbilirubinaemia, delayed neurodevelopment of the child, and low birth weight.[6,11] The relative amounts of FT4, TSH and anti-thyroperoxidase (anti-TPO) antibodies are frequently used indicators to diagnose a person's thyroid function, such as euthyroidism, subclinical hypothyroidism (SCH), isolated hypothyroxinemia, or hyperthyroidism.[3] Therefore, a greater understanding of the potential etiology and risk factors for TD and GDM is urgently required in order to pinpoint effective control methods. Since thyroid problems are more common in women with type 1 or type 2 diabetes mellitus, TD issues are closely related to diabetes problems.[3,13] There may be a pathophysiological link between diabetes mellitus (DM) and thyroid illness.[6] Regarding insulin sensitivity and requirements, these linkages are influential and have corresponding effects. Glycaemic regulation could be hampered by thyroid dysfunction that has not been diagnosed. Thyroid hormones have been associated with the fundamental pathways that regulate hunger and energy consumption, which are ultimately connected to variations in glycemic control. Patients with TD are substantially more likely to have DM.[6-8] The prevalence of thyroid abnormalities among diabetics is 13.4%, with type 1 diabetes mellitus in women accounting for 31% of cases and type 2 diabetes mellitus for 6.9% of cases.[6] Although there are many studies on pregnancy-related hypothyroidism and GDM, the relationship between GDM and thyroid status (TS) during pregnancy is still a subject of debate and no conclusive evidence has been uncovered to demonstrate how thyroid dysfunction may affect the likelihood of developing GDM.[3,10,14-20] No study was performed specifically in the southern part of Bangladesh, an iodine-sufficient area. Therefore, our research was carried out to study the incidence of undetected hypothyroidism during the first trimester of pregnancy in the Chattagram region and whether it has any correlation with the high titres of anti-TPO Ab and the development of GDM.

METHODS

Current study included pregnant women who came for their first-trimester antenatal check-up and who agreed to participate in our study at the Chattagram Maa-O-Shishu hospital medical college and chittagong medical college hospital from May 2019 to May 2020. Some standard inclusion and exclusion criteria were used to select our study population.

Inclusion criteria

Healthy women with an uncomplicated intrauterine singleton pregnancy (gestation period below 15 weeks) were included in this study. Selected women who were residents of Chittagong, completed a 75 g oral glucose tolerance test (OGTT) at 24-28 gestational weeks and gave written consent to be enrolled in this study were included in the study.

Exclusion criteria

The exclusion criteria for initial screening were multiple pregnancy, history of frequent miscarriage and complicated pregnancies, patient suffering from autoimmune, hepatic or renal diseases or other complex chronic disorders, diabetes or thyroid disease before pregnancy, visible or palpable goiter, etc. Moreover, women receiving thyroid hormone replacement therapy, taking hormone drugs that could affect thyroid function before or during pregnancy, or with incomplete medical histories were not enrolled in this study.

Screening of the study sample

Initially, 111 pregnant women were included in this study. Based on the above-mentioned criteria, the following patients have been excluded: 2 patients with pre-pregnancy diabetes, 1 patient with a surgical history related to the thyroid, 1 patient taking hormone drugs that affect thyroid function, 1 case of twins, 2 cases of abortion, 2 patients without OGTT results, and 2 with abnormal medical reports. The selection process of the study population is shown in (Figure 1).

Workflow

Blood samples (10 mL) were collected in vacutainer tubes from 100 pre-screened, healthy pregnant women attending antenatal clinics. The samples were centrifuged and stored in aliquots at -80 °C until assayed. The samples were analyzed under aseptic conditions for thyroid function tests (TFT), which included TSH, FT4,

and autoantibodies associated with autoimmune thyroiditis (thyroid-peroxidase antibody [TPO-Ab]). The levels of TSH, FT4, and anti-TPO are estimated by chemiluminescence technique using commercially available standard-quality kits (Automated Access 2 Beckman Coulter Immunoassay System, USA). To assess kidney and liver function, serum urea, creatinine, bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were checked by the Humalyzer Primus automated analyzer, USA. Hemoglobin levels and lipid profiles were also estimated. At 24-28 weeks, women were checked for GDM. The predesigned questionnaire was used to get the medical history, results of relevant physical investigations, and written consent of the patients or their attendants. The workflow of this study has been shown in **(**Figure 2).

Evaluation of the thyroid function test

Hypothyroidism, hyperthyroidism, and subclinical hypothyroidism were diagnosed based on the American Thyroid Association (ATA) guidelines in 2011. According to these, the normal values of TSH are 0.1-2.5 mIU/l in the 1st trimester and 0.2-3.0 mIU/l in the 2nd and 3rd trimesters. When TSH was >10 mIU/l, a diagnosis of overt hypothyroidism was made. Sub-clinical hypothyroidism was identified if the range was between 3.1-10 mIU/l.[4,6] Free T4 (FT4) and anti-TPO were considered normal if levels were 0.89–1.76 ng/dL and ≤ 35 IU/ml, respectively.[7] Cases with higher levels of anti-TPO Ab than normal were identified as anti-TPO Ab positive.

Evaluation of GDM

According to the International association of diabetes and pregnancy study groups (IADPSG), all women were screened for GDM at 24-28 weeks of gestation. They underwent a fasting plasma glucose test (FPG) and a 2 h after 75 g oral glucose tolerance test (OGTT). A fasting plasma glucose reading ≥92 mg/dl (5.1 mmol/l) and a value for 2-hour after glucose intake ≥153 mg/dl (8.5 mmol/l) is indicative of GDM.[8]

Statistical analysis

Statistical analysis was performed using SPSS 23 software (SPSS Inc., Chicago, IL). A Chi-square test was used for comparing the variables between different groups as appropriate. A p value of <0.05 was considered to be statistically significant.

RESULTS

The number of pregnant women included in our study was 100, with a gestational age of 4 to 13 weeks. The age range of the study population was between 20 and 40 years (Table 1).

The majority of them belonged to the age group of 21 to 25 years (43%), followed by 26 to 30 years (31%), and 31 to 35 years (13%), respectively. The age group of 21-30 had the highest BMI (28%). Around 16% of patients were found to be anemic, of whom 9% were women between the ages of 26 and 30.

Table 1. Demographic characteristics of study population (n=100).

Age range	≤20	21-25	26-30	31-35	≥35
	19.17±0.98 (7%)	23.09±1.84 (43%)	27.56±1.36 (31%)	32.73±1.19 (13%)	37.8±1.48 (6%)
Body mass index (kg/m^2)	**Low (<18.5)**		**Normal (<25)**		**High (>25)**
	22.93±2.6 (9%)		28.42±4.01 (63%)		18.02±1.8 (28%)
Blood pressure (mmHg)	**Normal (85%)**		**High (10%)**		**Low (5%)**
Systolic	110.89±8.78		142.2±5.36[a]		87±1.87[a]
Diastolic	72.54±7.96		95.4±3.85[a]		49.6±7.3[a]
Hemoglobin level (g/dL)	**Normal**		**Anemia**		
	13.16±1.0 (84%)		10.65±0.47[a] (16%)		
Previous delivery history	**Multiparous**			**Primiparous**	
	Abortion	**NVD**	**C-section**		
	5%	37%	23%	35%	
Educational status	**Primary education**	**Secondary education**	**Higher education**	**Illiterate**	
	55%	24%	17%	4%	
Occupation	**House wife**		**Employed**		
	71%		11%		
Regular drugs taking	**Iron/folic acid taking**		**Iron/folic acid not taking**		
	71%		29%		
Acidity and	**Yes**		**No**		

Continued.

Age range	≤20	21-25	26-30	31-35	≥35
pregnancy related mild complication	89%		11%		
Family history	**With**		**Without**		
Hypertension	6%		94%		
Diabetes	11%		89%		
Thyroid disorder	8%		92%		

Hypertension was reported in 10% of cases, while 5% were found with low blood pressure. The mean age, hemoglobin level, blood pressure, and blood glucose level were given in Table 1. Although age, BMI, family history of diabetes and thyroid disease, etc. may affect GDM and TD, we did not identify any of these as risk factors, probably because of the small number of participants. Additionally, biochemical tests were performed for all the subjects to check their hepatic and renal health. The mean values of serum urea, creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and the complete lipid profile were given in (Table 2).

Table 2: Mean of the results of biochemical tests of study population.

Serum creatinine	Serum urea	Serum Bilirubin	SGPT	SGOT	Total cholesterol	HDL cholesterol	LDL cholesterol	Triglycerides
0.67±0.10	26.73±0.06	1.51±6.94	22.95±7.07	20.82±4.91	146.74±28.36	34.19±3.85	87.44±20.22	133.43±39.25

SGPT- serum glutamic-oxaloacetic transaminase, SGOT- Serum glutamic pyruvic transaminase, HDL- High density lipoprotein cholesterol, LDL cholesterol-Low density lipoprotein cholesterol. All values are expressed as mean±SD.

Table 3: Level of thyroid hormones, anti-TPO and blood sugar among pregnant women.

Parameters			
TSH (mIU/l)	**Normal (84.15%)**	**Medium high (6.1%)**	**High (9.76%)**
	1.49±0.8	3.50±0.38	15.19±7.5
FT4 (ng/dl)	**Normal (85.37%)**	**High (6.1%)**	**Low (8.54%)**
	0.93±0.21	23.28±5.87	0.57±0.03^{ns}
Anti TPO (IU/ml)	**Normal (81.94%)**	**High (18.06%)**	-
	20.72±6.4	60.03±21.13	-
Blood sugar level (mg/dl)	**Fasting**	**2 hr after**	-
Non-diabetic	76.69±6.56	111.9±8.63	-
Diabetic	112.12±4.5	151.18±22.87	-

Table 4: Thyroid status of women with and without gestational diabetes mellitus (GDM) (n=100).

Diabetes status	Thyroid status (%)			
	Euthyroid	**Subclinical hypothyroid**	**Overt hypothyroid**	**Hyperthyroid**
GDM (13%)	7	2	4	0
No GDM (87%)	74	9	2	2
Total	81	11	6	2
Significance	χ^2 = 0.00746,	df = 1, p < 0.01	-	-

GDM- gestational diabetes mellitus. Chi-square test was applied after classifying the women as euthyroid and thyroid patients with and without gestational diabetes mellitus (GDM).

The mean TSH, FT4, anti-TPO Ab, and blood glucose levels of our sample population are shown in (Table 3). Oral glucose tolerance tests were performed for GDM between the 6th and 7th months of pregnancy. In our study population, the incidence of TD was 19% (n = 100), of which the cases of hypothyroidism were 17% and those of hyperthyroidism were only 2%. Among hypothyroid patients, subclinical hypothyroidism (11%) was observed to be more frequent compared to overt hypothyroidism (6%). In the case of overt hypothyroidism, one-half of the patients had high TSH (>10 mIU/l), low FT4, and normal anti-TPO Ab, whereas the other half had high levels of TSH and anti-TPO Ab with low FT4. In the case of the SCH patients, nearly two thirds of women (7%) showed high TSH and low FT4. The remaining one-third had high TSH and normal FT4, as well as normal or elevated anti-TPO Ab. Likewise, the frequency of GDM in our study was seen to be 13%. The coexistence of both GDM and hypothyroidism was noted in six participants (out of 100 samples), which indicates

that about half of the GDM patients also had hypothyroidism. The value of $\chi 2$ ($p<0.01$) showed that there is a statistically significant relationship between hypothyroidism and GDM.

Table 5: Anti-thyroid peroxidase (anti-TPO) antibody status of women with and without thyroid disorder (TD) (n=100).

Thyroid status	Anti-TPO antibody status (%)		Total
	Positive, N=17	Negative, N=83	
Euthyroid	6	74	80
Subclinical hypothyroidism	7	5	12
Overt hypothyroidism	4	2	6
Hyperthyroidism	0	2	2
Significance	χ^2 = 0.000442,	df =1, p<0.001	

Anti-TPO Ab- Anti-thyroperoxidase antibody. Chi-square test was applied after classifying the women as euthyroid and thyroid patients with and without anti-TPO positivity.

Table 6: Anti-thyroid peroxidase (anti-TPO) antibody and thyroid function status of women with and without gestational diabetes mellitus (GDM) (n=100).

Anti-TPO Ab	GDM (%)		Total (%)	Anti-TPO Ab (%)	No GDM (%)		Total (%)
	Euthyroid N=7	TD N=6			Euthyroid N=74	TD N=13	
Positive	2	3	5	**Positive**	4	8	12
Negative	5	3	8	**Negative**	70	5	75
Significance	χ^2 =0.153			df = 1, p>0.05			

GDM- Gestational diabetes mellitus, TD- Thyroid dysfunction, Anti TPO Ab- Anti-thyroperoxidase antibody. Chi-square test was applied after classifying anti-TPO positive patients with and without gestational diabetes mellitus (GDM).

The number of anti-TPO-positive women with and without thyroid disorders is shown in (Table 5). Eleven out of 17 hypothyroid women in our study showed a raised anti-TPO titer in their serum. The presence of anti-TPO Ab in a significant number of thyroid patients, including those

with subclinical (7%) and overt hypothyroidism (4%), suggests that a high titre of anti-TPO Ab contributes to the occurrence of hypothyroidism ($p<0.001$). Furthermore, 6 out of 100 of the study participants with euthyroid status presented anti-TPO positivity. Hyperthyroidism (2%) cases were reported with no GDM and normal anti-TPO Ab levels. The proportion of pregnant women with and without thyroid dysfunction according to GDM and anti-TPO Ab positivity (Table 6). Elevated anti-TPO was found in 17% of women, of whom 11% were diagnosed as hypothyroid, 2% as euthyroid GDM, and 4% as healthy women. A high level of anti-TPO was found in 3% of cases of GDM women with hypothyroidism. The occurrence of anti-TPO positivity was observed in 8% out of 13% of non-GDM hypothyroidism patients. The elevated anti-TPO Ab titre is not associated with the incidence of GDM, as the number of anti-TPO positive GDM patients is not statistically significant ($p>0.05$) compared to anti-TPO negative GDM patients.

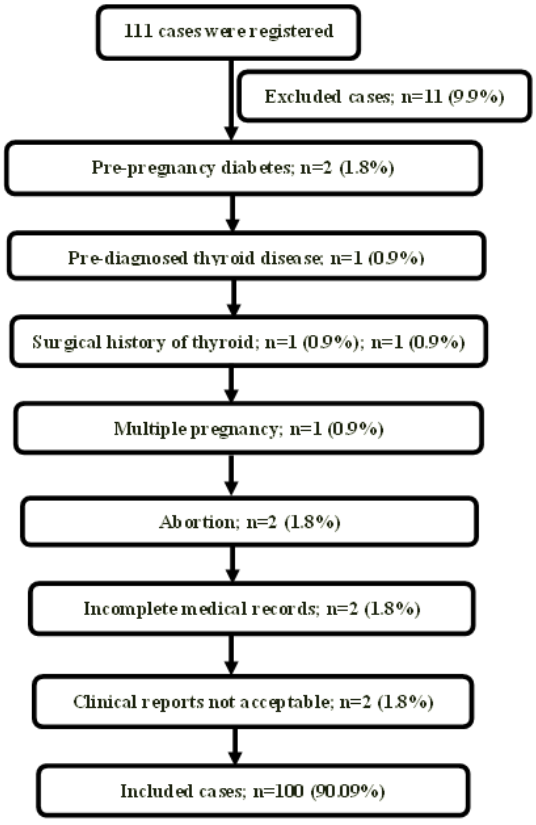

Figure 1: The protocol used to select the study population.

DISCUSSION

Thyroid dysfunction (TD) and gestational diabetes mellitus (GDM) in pregnancy have been an important research area in clinical endocrinology, as both have a huge impact on maternal and fetal outcomes.[21] That's why the majority of developed countries have universal screening for pregnant women for TD and GDM. In our study, GDM was characterized by high blood glucose levels, whereas TD, more specifically hypothyroidism, was assessed by high TSH and low or normal FT4. The purpose of this study was to determine the proportion of hypothyroidism cases during pregnancy in two tertiary care hospitals in Chattogram and whether hypothyroidism is associated with the development of GDM as compared to healthy euthyroid pregnant women. We also investigated if elevated anti-TPO Ab titers contribute to the progression of hypothyroidism.

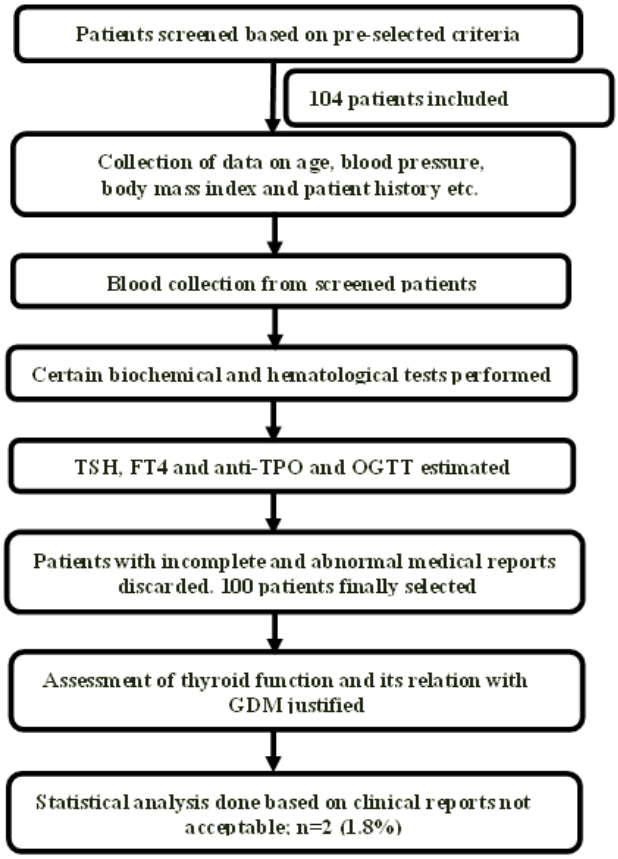

Figure 2: Flow chart of the research method.

Measuring TSH, T3, T4, anti-thyroid peroxidase (anti-TPO) antibodies, and thyroglobulin antibodies is crucial for the proper assessment of thyroid function. Firstly, TSH is considered the most important marker that detects thyroid dysfunction with great sensitivity.[22] Moreover, the presence of thyroid hormone binding proteins in aberrant amounts in physiological conditions such as pregnancy or in conjunction with pharmacological therapy, and anomalies in binding proteins may influence hormone binding. As a result, the FT4 test along with TSH more accurately represents real thyroid health and aids in identifying women with SCH.[23] The varying prevalence of hypothyroidism during pregnancy in different nations is significantly influenced by geographic diversity.[24,25] The incidence of hypothyroidism seems to be higher in Asian countries compared with the West.[26] Furthermore, Asian populations show a higher percentage of diabetic patients than other ethnicities when the BMI is the same.[19]

In contrast to hyperthyroidism, hypothyroidism is relatively frequent during pregnancy , with subclinical hypothyroidism (SCH) being more common.[26] We documented a comparatively higher number of hypothyroid patients, i.e., 17%, where subclinical hypothyroidism was 11% in comparison to hyperthyroidism (2%). Both of which are correlated with the studies of Mandal et al. and Dash et al.[27,28] In our study, thyroid function was analyzed on the basis of TSH and FT4. High FT4 acts as a preventative factor since high TSH raises the likelihood of hypothyroidism. Furthermore, anti-TPO antibodies were found to be more frequent than thyroglobulin (TG) antibodies.[29] SCH is associated with increased TSH levels, low or normal FT4 values, and is more likely to be anti-TPO positive than euthyroid women.[30]

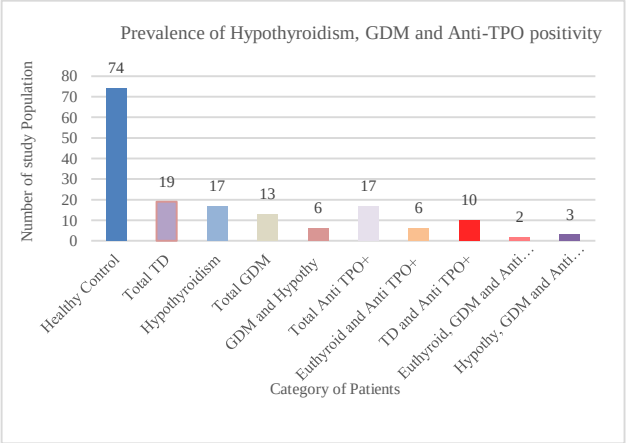

Figure 3: Distribution of the patients with hypothyroidism, GDM, and high titre of anti-thyroperoxidase (anti-TPO) antibodies in the study population. Here, TD- Thyroid disorder, GDM- Gestational diabetes, Hypo- Hypothyroidism, Anti-TPO^{+}- Thyroid peroxidase antibody

Among 17 hypothyroid cases, serum anti-TPO positive results were found in 11 subjects with 7% SCH and 4% OH. Therefore, our study showed a high titre of serum anti-TPO in the majority of hypothyroid cases, which is consistent with Fröhlich et al., Rahman et al., and Dash et al.[1,27,29] According to Siriwardhane et al. OH is characterized by high TSH, low FT4 and is more often associated with an elevated level of anti-TPO.[31] Thus, a high titre of anti-TPO Ab indicates a statistically significant association with hypothyroidism ($p<0.001$) and can be considered as one of the risk factors for

hypothyroidism. The impact of thyroid hormone (TH) on glucose homeostasis has long been recognized. Previous studies have shown that several mechanisms are involved in the thyroid hormone-mediated regulation of glucose metabolism. According to earlier research findings, the growth and function of pancreatic cells are linked with TH action.[32] Furthermore, TH stimulates pancreatic-α cells to secrete more glucagon and pancreatic-β cells to secrete insulin.[32,33] As a biologically active hormone, T3 primarily regulates glucose metabolism.[34] Thus, by inducing insulin resistance, hypothyroidism seems to adversely affect glucose homeostasis.

According to Eom et al. thyroid issues and diabetes mellitus are tightly related.[32] Some reports found such a connection, while others did not get any thus making the results contradictory.[35,36] When compared with euthyroid women, women with hypothyroidism become more susceptible to GDM by further amplifying insulin resistance during pregnancy.[36] Pregnant women diagnosed with GDM and TD were reported to have higher mean TSH and lower FT4 levels as compared to the control group.[37] When the FT4 level increases, the number of GDM and TD decreases gradually, which strongly illustrates that a low FT4 level is an independent risk factor for GDM and TD.[19] According to a study involving 2333 pregnant women, higher TSH levels and positive anti-TPO were associated with an increased risk of GDM progression.[38] In this study, around half of the total GDM patients had thyroid dysfunction, showing a significant link between GDM and hypothyroidism. No cases were found with GDM and hyperthyroidism. Toulis et al. reported an increased incidence of SCH in GDM patients, which is similar to our findings.[1,39] The findings of our investigation are in agreement with those of Gong et al who found a correlation between hypothyroidism and the incidence of GDM.[1,36] There are various studies on thyroid autoimmune disease and the emergence of GDM. Hornnes et al. observed that women who had thyroid autoimmunity were more likely to experience pregnancy-related glucose intolerance, whereas others had opposing views.[1,32,33,35-40] Among 6% of anti-TPO positive euthyroid patients, 2% of cases had GDM. The incidence of GDM, hypothyroidism, and anti-TPO positive cases was 3%. The relative risk of GDM in the presence of an elevated anti-TPO Ab titer indicated no statistically remarkable value ($p>0.05$) in our study.

According to our results, the occurrence of subclinical hypothyroidism is more common among pregnant women. In addition, anti-TPO mediated thyroid autoimmunity acts as a risk factor for the occurrence of hypothyroidism. In comparison to healthy anti-TPO-negative women, euthyroid women with a high level of anti-TPO are more susceptible to hypothyroidism. Furthermore, hypothyroidism is found to be directly linked to GDM. Demographic data had no significant effect on the incidence of GDM and TD. We recommend increasing the sample size to justify the outcome of our study. For early diagnosis and treatment of these disorders, identification of the relationship between hypothyroidism and GDM will be helpful.

CONCLUSION

Maternal thyroid hormone deficiency, or TD, is very common during pregnancy. Earlier diagnosis and easier treatment may yield satisfactory results. Otherwise, it is highly probable that this disease may have serious health consequences for both the mother and the newborn. According to our findings, the prevalence of thyroid dysfunction between the first and beginning of the second trimester was 19% in the pregnant population. Nearly half of the GDM patients were found to have TD. Our results indicate significant associations between hypothyroidism and anti-TPO positivity. Hypothyroid patients with high anti-TPO levels are at greater risk of developing GDM when compared with euthyroid anti-TPO-negative women. Still, anti-TPO-positive euthyroid and non-GDM patients need close monitoring as they also may be susceptible to TD, GDM, or both. These outcomes would recommend that routine assays of thyroid hormones during pregnancy be ensured. Furthermore, the occurrence of TSH and GDM may be interconnected with family history, lifestyle, and many other factors. Our study did not show any demographic or obstetric characteristics (except age and BMI) to influence thyroid function or GDM significantly. We propose further studies with a larger sample size and more data to justify or strengthen our findings.

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