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Research Article

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Evaluation of Thyroid Dysfunction and Thyroid Antibodies Among Subjects with Gestational and Pre-Gestational Diabetes at King Abdulaziz University Hospital, Jeddah: A Retrospective Analysis (2014-2018)

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ABSTRACT

Objective: To evaluate data from a five-year period (2014-2018) regarding the presence of thyroid dysfunction and thyroid antibodies among subjects with gestational diabetes mellitus (GDM) and pre-gestational diabetes mellitus (pre-GDM) at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia (SA). Subjects and Methods: The present retrospective analysis was conducted from January to June 2019; it evaluated five years' (2014-2018) data of patients with GDM and pre-GDM from the patients' electronic record. Results: Of the 485 subjects, 348 (71.8%) were Saudi nationals; whereas, 137 (28.2%) were non-Saudis, and 318 (65.6%) had GDM and 167 (34.4%) had pre-GDM. Five (3.2%) hyperthyroid subjects were in the GDM group as compared to 6 (4.7%) in the pre-GDM group; whereas, 21 (13.3%) hypothyroid subjects were found in the GDM group as compared to 26 (20.3%) in the pre-GDM group. Thyroglobulin antibody (TgAb) was positive among 6 (4.7%) pre-GDM subjects as compared to 2 (1.3%) among GDM subjects (p=0.03). In the GDM group, 5 (3.2%) subjects had positive thyroid peroxidase antibody (TPOAb); whereas, in the pre-GDM group, 7 (5.5%) were TPOAb-positive (p=0.54). TgAb was positive among 1 (0.44%), 3 (27.27%), and 4 (8.51%) euthyroid, hyperthyroid, and hypothyroid subjects, respectively. TPOAb was positive among 4 (1.76%), 4 (36.36%), and 4 (8.51%) euthyroid, hyperthyroid, and hypothyroid subjects, respectively. Thyroid dysfunction was more common in pregnant females of age range 35-44.9 years. Conclusions: Hypo- and hyperthyroid cases were present in both GDM and pre-GDM groups. Thyroid antibodies were found more frequently in the pre-GDM group, and thyroid dysfunction was more common in the older age group.

Key words: *Thyroid peroxidase antibody, Thyroglobulin antibody, Gestational diabetes mellitus, Hypothyroidism, Hyperthyroidism.*

INTRODUCTION

Gestational diabetes mellitus (GDM) and thyroid dysfunctions are two widespread endocrinological problems prevalent among pregnant women [1]. Thyroid disorders are common in pregnancy and have been linked to adverse maternal and fetal outcomes [2]. The incidence of these disorders varies globally; GDM ranges from 12.75% to 30%, and thyroid dysfunction during pregnancy ranges from 2.8% to 16.6% [3-6]. Thyroid dysfunctions among pregnant women have been investigated by many authors [7].

Notably, 15–65% of pregnant women who have elevated thyroid-stimulating hormone (TSH) levels are positive for thyroid antibodies [8, 9]. The frequency of thyroid peroxidase antibody (TPOAbs) varies from 5% to 25%, and that of thyroglobulin antibodies (TgAbs) varies from 3% to 16% [6, 10-12]. The incidence of thyroid

antibodies is related to an augmented threat of unexplained subfertility, repeated miscarriage, premature delivery, and maternal post-delivery thyroiditis [13].

Few pregnancy-induced factors initiate changes in thyroid hormone physiology: (a) a momentary upsurge in human chorionic gonadotropin during the early weeks of pregnancy stimulates the TSH-receptor; (b) during the early weeks of pregnancy, an estrogen-induced increase in T4-binding globulin occurs and continues throughout the pregnancy; (c) during pregnancy, immune system adjustments activate, worsen, or improve hidden autoimmune thyroid disease; (d) augmented breakdown of TH by the placenta; and (e) augmented excretion of iodide in urine, which impairs thyroid hormone synthesis in regions of borderline iodine adequacy [14-16].

GDM is the most common metabolic disorder marked by glucose intolerance that is revealed during gestation because of decreased insulin sensitivity [17]. In Saudi Arabia, GDM is common among Saudi women. A study reported that approximately 30% of pregnant women in Riyadh had either pre-GDM or GDM, and others from Jeddah had a GDM incidence of 12.75% [3, 4]. However, few studies have been conducted to investigate the frequency of thyroid function disorders among women with GDM and pre-GDM. The present study aimed to evaluate data for the presence of thyroid dysfunction and thyroid antibodies among subjects with gestational and pre-gestational diabetes at King Abdulaziz University Hospital (KAUH), Jeddah, SA for a period of five years (2014-2018).

SUBJECTS AND METHODS

The present retrospective analysis was performed at a tertiary care hospital, KAUH, Jeddah, SA, from January to June 2019. The present study evaluated data of five years (2014-2018) from the electronic record of patients who had GDM and pre-GDM, and were followed up at KAUH, Jeddah, SA. All pregnant women with a diagnosis of GDM and pre-GDM were included in the study. Subjects were excluded if they had any other endocrinal problems, such as polycystic ovary syndrome and Cushing's syndrome that may influence fasting plasma glucose (FPG) levels. All subjects receiving thyroid disorder treatment prior to pregnancy were also excluded. All data from the electronic record of the patients were collected on a specially designed proforma. In the electronic file, we found 485 female subjects with GDM, and among them, several subjects had pre-GDM. However, we lacked complete information for several patients; therefore, the 285 subjects who had complete data in the electronic record were further analyzed. All the subjects were divided into four groups according to their BMI, as recommended by the World Health Organization committee [18].

The subjects were divided into two groups: GDM (women who were diagnosed with DM for the first time during pregnancy), and pre-GDM (those who had established DM according to their HbA1c level, FPG, and history of taking DM treatment). The subjects were further evaluated for thyroid profile, and suspected cases were also investigated for thyroid antibodies (TgAbs and TPOAbs).

The proforma was filled with the subjects' age, family history, body weight, height, BMI, residence, education, menstrual history, family history of diabetes, number of children, and previous history of GDM.

Patients were screened during 24–28 weeks of gestation or earlier if they had an increasing risk for GDM. The subjects were classified using one-step approach and the cut-off values of the American Diabetes Association (ADA). GDM was diagnosed at any time in pregnancy if one of the following criteria were met or exceeded [19]:

1. FPG ≥ 5.1 mmol (92 mg/dL).
2. One-hour plasma glucose ≥ 10.0 mmol/L (180 mg/dL) following a 75 g oral glucose load.
3. Two-hour plasma glucose ≥ 8.5 mmol/L (153 mg/dL) following a 75 g oral glucose load.

Ethical approval was obtained from the ethical committee of King Abdulaziz University (Reference No 105-18) and its hospital, and research was performed according to the principles of Declaration of Helsinki for medical research. All study subjects' personal identities were not disclosed.

We used the guidelines of American Thyroid Association (ATA) for the reference range of TSH suggested for the diagnosis and management of gestational thyroid disease. Based on the guidelines, "if trimester-specific reference ranges for TSH are not available in the laboratory, the following reference ranges are recommended: first trimester, 0.1–2.5 IU/mL; second trimester, 0.2–3.0 IU/mL; and third trimester, 0.3–3.0 IU/ mL" [20].

Statistical analysis

All data were analyzed with SPSS version 23 (IBM Inc., Armonk, NY, USA). Frequencies and percentages were used to represent qualitative data, and mean and standard deviations were used for continuous variables, such as age, BMI, and thyroid profile. Several statistical tests, such as the Student's t-test, Chi-square test, and Fisher's exact test, were used accordingly. The significance of the p-value was considered substantial, if it was less than 0.05.

RESULTS

Of the 485 subjects, 348(71.8%) were Saudi nationals; whereas, 137(28.2%) were non-Saudis; 318(65.6%) and 167(34.4%) subjects had GDM and pre-GDM, respectively. The other basic characteristics of patients are represented in Table 1.

For further analysis, 286 subjects [158(55.24%) GDM and 128(44.76%) pre-GDM] were included because of the availability of their complete data in the system. A significant difference in levels of HbA1c and FPG was observed between the GDM and pre-GDM groups ($p<0.001$) (Table 2).

Table 1. Basic characteristics of the subjects

Variables	Mean±S.D
Age (years)	35.39±5.97
Age categories	
<25 years, N (%)	20 (4.1)
25-34.9 years, N (%)	178 (36.7)
35-44.9 years, N (%)	261 (53.8)
>45 years, N (%)	26 (5.3)
BMI (kg/m^2)	33.01±7.14
BMI categories	
Underweight (<18.5 kg/m^2), N (%)	1 (.2)
Normal (18.5-24.9 kg/m^2), N (%)	29 (6.0)
Overweight (25-29.9 kg/m^2), N (%)	76 (15.6)
Obese (>=30 kg/m^2), N (%)	179 (36.8)
Missing	202 (41.5)
Thyroid profile	
TSH (µIU/L)	2.25±1.48
T3 (pmol/L)	4.26±0.79
T4 (pmol/L)	13.40±2.47
Thyroid antibodies	
TgAb (IU/mL)	29±10.13
TPOAb (IU/mL)	22±7.69
HbA1c%	5.89±1.38
FPG (mmol/L)	5.82±1.98
Disease	
GDM, N (%)	318 (65.6)
Pre-GDM, N (%)	167 (34.4)
Nationality	
Saudi, N (%)	348 (71.8)
Non-Saudi, N (%)	137 (28.2)

BMI= Body Mass Index, FPG=Fasting Plasma Glucose, GDM= Gestational Diabetes Mellitus, S.D= Standard deviation, TgAb=Anti-thyroglobulin Abs, TPOAb =Thyroid peroxidase antibody, TSH = Thyroid Stimulating Hormone, T4= Thyroxine, T3= Triiodothronine

According to age categories, 55(34.8%) and 46(35.9%) subjects from the GDM and pre-GDM groups, respectively, were aged 25-34.9 years; while, majority of GDM [93(58.9%)] and pre-GDM [68(53.3%)] subjects were aged 35-44.9 years. Five (3.2%) subjects had hyperthyroidism in the GDM group as compared to 6(4.7%) in the pre-GDM group; whereas, 21(13.3%) subjects had hypothyroidism in the GDM group as compared to 26(20.3%) in the pre-GDM group. TgAb was positive among 6(4.7%) subjects in the pre-GDM group as compared to 2(1.3%) subjects in the GDM group (p=0.03). In the GDM and pre-GDM groups, 5(3.2%) and 7(5.5%) subjects, respectively, were TPOAb-positive (p=0.54) (Table 2).

TgAb was positive among 1(0.44%), 3(27.27%), and 4(8.51%) euthyroid, hyperthyroid, and hypothyroid subjects, respectively; TPOAb was positive among 4(1.76%), 4(36.36%), and 4(8.51%) euthyroid, hyperthyroid, and hypothyroid subjects, respectively (Fig. 1). Thyroid dysfunction was more common in pregnant women aged 35-44.9 years among hypothyroid and hyperthyroid subjects (Fig. 2). However, no significant relationship was found with BMI (not shown in Fig.).

Table 2. Comparison of different variables between GDM and pre-GDM subjects

Variables	GDM (N=158)	Pre-GDM (N=128)	p-value
Age (years)	35.23±5.43	35.66±6.14	0.53
Age categories			
<25 years, N (%)	6 (3.8)	5 (3.9)	0.31
25-34.9 years, N (%)	55 (34.8)	46 (35.9)	
35-44.9 years, N (%)	93 (58.9)	68 (53.1)	
>45 years, N (%)	4 (2.5)	9 (7)	
TSH (µIU/L)	2.23±1.65	2.26±1.23	0.86
T3 (pmol/L)	4.36±0.75	4.12±.81	0.12
T4 (pmol/L)	13.69±2.72	13.32±2.33	0.24
HbA1c%	5.57±.45	6.25±0.99	<0.001
FPG (mmol/L)	5.73±.75	6.39±1.99	<0.001
Thyroid status			
Euthyroid, N (%)	132 (83.5)	95 (74.2)	0.19
Hyperthyroid, N (%)	5 (3.2)	6 (4.7)	
Hypothyroid, N (%)	21 (13.3)	26 (20.3)	
TgAb			
Positive, N (%)	2 (1.3)	6 (4.7)	0.03
Negative, N (%)	15 (9.5)	6 (4.7)	
TPOAb			
Positive, N (%)	5 (3.2)	7 (5.5)	0.54
Negative, N (%)	3 (1.9)	7 (5.5)	
Nationality			
Saudi, N (%)	110 (69.6)	79 (61.7)	.10
Non-Saudi, N (%)	48 (30.4)	49 (38.3)	
BMI (kg/m^2)	32.76±6.84	33.31±7.51	0.52
BMI categories			
Underweight (<18.5 kg/m^2), N (%)	1 (0.6)	0 (0)	0.62
Normal (18.5-24.9 kg/m^2), N (%)	17 (10.8)	12 (9.4)	
Overweight (25-29.9 kg/m^2), N (%)	45 (28.5)	31 (24.2)	
Obese (>=30 kg/m^2), N (%)	95 (60.1)	84 (65.6)	

BMI= Body Mass Index, FPG=Fasting Plasma Glucose, GDM= Gestational Diabetes Mellitus, S.D= Standard deviation, TgAb=Anti-thyroglobulin Abs, TPOAb =Thyroid peroxidase antibody, TSH = Thyroid Stimulating Hormone, T4= Thyroxine, T3= Triiodothronine

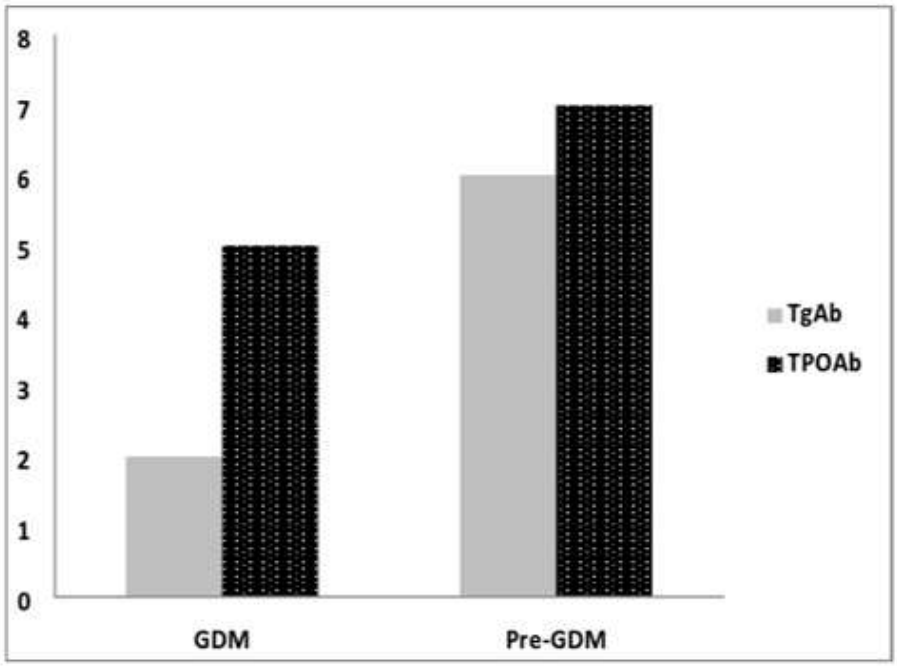

Figure 1: TgAb and TPOAb positive cases among GDM and Pre-GDM subjetcs

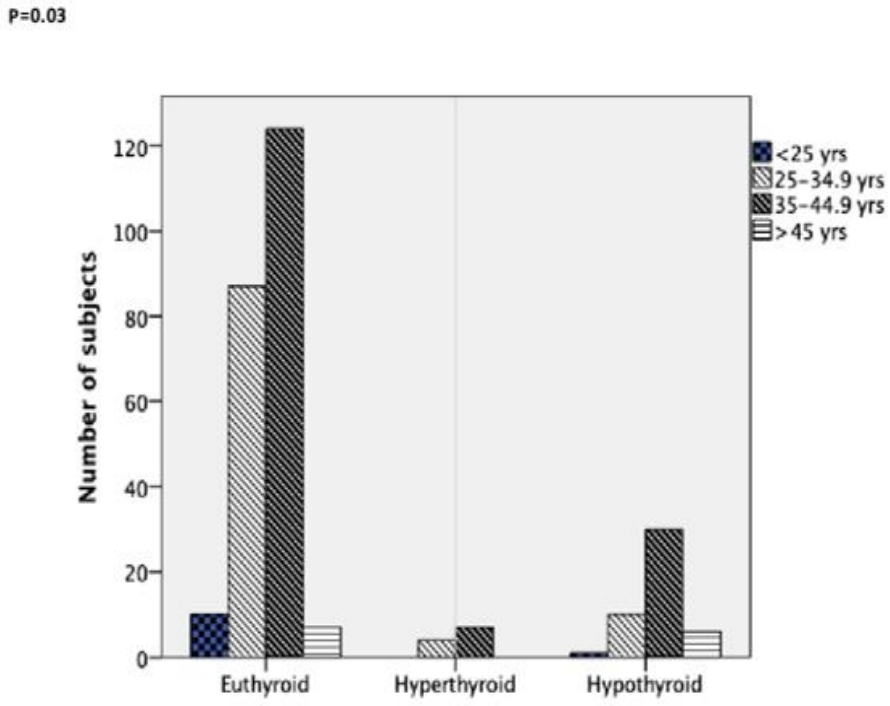

Figure 2 : Comparison of various age categories among euthyroid, hypothyroid and hypothyroid pregnant women

DISCUSSION

In this study, 3.2% and 4.7% of the subjects were hyperthyroid subjects in the GDM and pre-GDM groups, respectively; whereas, 13.3% and 20.3% of the subjects were hypothyroid subjects in the GDM and pre-GDM

groups, respectively. These results are similar to those of a few other studies that have described deranged thyroid function tests among GDM and pre-GDM women [6, 21, 22]. A study reported that 16.6% of the women with GDM had thyroid dysfunction; whereas, 6.1% of the healthy pregnant women had thyroid dysfunction [5]. In India, the incidences of hyperthyroidism and hypothyroidism among pregnant women were 12% and 1.25 %, respectively [23].

TgAb was positive among 4.7% and 1.3% of the pre-GDM and GDM subjects, respectively; whereas, TPOAb was positive among 3.2% and 5.5% of the GDM and pre-GDM subjects, respectively. TgAb was positive among 1(0.44%), 3(27.27%) and 4(8.51%) euthyroid, hyperthyroid, and hypothyroid subjects, respectively, and TPOAb was positive among 4(1.76%), 4(36.36%) and 4(8.51%) euthyroid, hyperthyroid, and hypothyroid subjects, respectively. In our study, the incidence of thyroid antibody-positives was lower than that of an Iranian study that reported the frequencies of TPOAb and TgAb as 12.8% and 8.5%, respectively [24]. Our results are more or less similar to those of a Tunisian study that reported 6.5% incidence of TPOAb positivity among pregnant women, with 3.2% being hypothyroid subjects and 1.3% being hyperthyroid subjects [25]. Our results revealed that the incidence of TPOAb positivity was 3.2% among pregnant women with GDM, which is much lower than that of several studies from other parts of the world, such as Nigeria (25%), Pakistan (13.5%), and Tunisia (6.5%) [6, 25, 26].

The reasons for differences in incidence of autoimmune thyroid dysfunction could be due to variations in assay techniques, use of different cut-off values [6, 27], dissimilar sample sizes, regional variances, race, and iodine deficiency [28]. Many contributing factors for the presence of thyroid antibodies have been reported in literature. These include existence of thyroid autoimmunity disorder in the family, iodine imbalance, old age, and European lineage [10, 11]. A study suggested that hyperglycemia at the time of pregnancy can trigger thyroid autoimmunity [29]. The incidence of thyroid antibodies during pregnancy is dangerous for maternal and fetal health. An Iranian study reported that the incidence of TPOAb positivity among pregnant women was associated with preeclampsia, premature delivery, intrauterine growth restriction, and low first minute Apgar score [24].

Our study revealed that thyroid dysfunction was more common in pregnant women aged 35-44.9 years. These results are consistent with those of another study that reported a higher incidence of hypothyroidism and hyperthyroidism among pregnant women with higher ages [23]. Therefore, it seems that increased maternal age is related to a higher prevalence of thyroid dysfunction. The study also stated that it could be due to late age marriages, and consequently late age pregnancies [23]. Our study results did not find any correlation between thyroid dysfunction and BMI. These results are dissimilar to those of an Indian study that reported a significant association between the TPOAb positive group and BMI [30].

The underlying mechanism of GDM development may be due to placental estrogen levels, which causes high thyroid hormone transport protein levels in the last half of pregnancy.

Thyroid profile screening has been recommended among pregnant women or women at childbearing age with goiter or signs and symptoms of hypothyroidism; subjects with a personal or family history of thyroid disease, history of repeated miscarriages, history of infertility; or exposure to head or neck irradiation [1]. It is suggested that routine thyroid screening should be conducted in subjects with GDM, and thyroid antibodies should be investigated in all subjects with thyroid dysfunctions.

The main limitation of our study was that TgAb and TPOAb levels were not measured in all the subjects. Second, it was a retrospective study; therefore, the detailed histories of subjects were not obtained.

CONCLUSION

Our findings revealed that hypothyroidism and hyperthyroidism cases were present in both GDM and pre-GDM groups. Thyroid antibodies were more in the pre-GDM group than in the GDM group, and thyroid dysfunction was more common in the older age group than in the younger age group. Further larger prospective studies are needed to confirm our results.

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Conflict of interest
All authors declare no conflict of interest.

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