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Prevalence of Thyroid Dysfunction and Autoimmunity among Pregnant Women with Gestational Diabetes Mellitus

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Abstract:

Introduction: Gestational Diabetes Mellitus (GDM) and thyroid complications are the most frequent hormonal disorders observed during pregnancy, and research has shown that they can coexist and affect each other in various ways.

Aim of the Study: Assessing the incidence of thyroid abnormalities and autoimmunity among pregnant females diagnosed with gestational diabetes mellitus.

Subjects and Methods: This study compared 114 individual pregnant women, ranging in gestational age from 24 to 73 weeks. It included 57 singleton pregnancies with GDM and an equal number with a normal 75g OGTT result. The participants received care at the Gynecology and Obstetrics department at Fayoum University Hospital. Thyroid function tests (including Serum TSH, FT4, and TPO antibodies) were administered to all these pregnant women. Additionally, information about family history of Diabetes Mellitus, GDM, and Thyroid disease was collected for both groups and subjected to statistical analysis.

Results: Patients with GDM had a higher average serum TSH level compared to the healthy controls, and factors predicting GDM were evaluated.

Conclusions: Pregnant women with impaired glucose tolerance should be evaluated for thyroid function due to the high prevalence of thyroid disorders and autoimmunity in the GDM group. They face an elevated risk of hypothyroidism, making this evaluation important during pregnancy.

Keywords: Autoimmunity, Gestational Diabetes Mellitus, Pregnancy, Thyroid dysfunction.

1. Introduction

Pregnancy involves complex hormonal changes. Gestational Diabetes Mellitus (GDM) and thyroid disease are the two most commonly encountered endocrine conditions during this time, often coexisting to varying degrees [1].

As reported by the International Association of Diabetes in Pregnancy Study Group, the occurrence of GDM can reach up to 17.5%. Concurrently, thyroid dysfunction, which may present as either hypothyroidism or hyperthyroidism, impacts 10–15% of women during the initial half of their pregnancy [2].

In countries where iodine is plentiful, the size of the thyroid gland increases by about 10% during pregnancy; in areas where iodine is scarce, this increase can reach 20%–40%. As a result, the production of thyroxin (T4) and triiodothyronine (T3) increases significantly—by about 50%—and the daily requirement for iodide also increases by 50% [3].

Pregnancy may occasionally result in the diagnosis of additional thyroid conditions that require treatment, such as thyroid cancer and nodular disease. Pregnancy-related hormonal and metabolic changes include altered thyroid metabolism and elevated iodine levels in the urine. For example, the human chorionic gonadotropin hormone stimulates thyroid-stimulating hormone [4]. As an effect, TSH tends to decrease while an elevation is seen on T4 and T3 levels [5].

The reasons for the change in thyroid functions during pregnancy include elevated thyroid metabolism, elevated plasma volume, increased renal iodine excretion, an increase in estrogen levels, and the corresponding production of thyroid-binding globulin (TBG) [6].

Thyroid hormone, central to human metabolism and neural development, also supports fetal brain growth via maternal transfer [7].

Thyroid Peroxidase Antibody (TPOAB) positivity rates among pregnant women at 16 weeks gestation are approximately 10%, which is consistent with overall population levels. It has been suggested that the presence of TPOAB during pregnancy is strongly linked to an increased risk of developing postpartum thyroiditis and may be linked to hypothyroidism [8].

Unfavourable perinatal outcomes are linked to hypothyroidism, particularly during the first trimester. Gestational hypertension (eclampsia or preeclampsia),

low birth weight, miscarriage, and fetal death are all linked to overt hypothyroidism. However, there is a connection between poor obstetric outcomes and subclinical hypothyroidism [6]. Studies have shown that congenital malformations and perinatal mortality can be linked to maternal hypothyroidism by as much as 20% [5].

Surgical hypothyroidism, post-ablative hypothyroidism in Grave's disease, goitrous or atrophic Hashimoto thyroiditis (idiopathic myxedema), and iodine deficiency are the main causes of hypothyroidism in pregnancy [6].

According to estimates, 4–8.5% of people worldwide suffer from subclinical hypothyroidism (SCH). When TSH levels in the blood exceed the upper limits of the trimester-specific range and serum T4 and T3 levels are normal, it is referred to as gestational hypothyroidism (SCH) [4].

Subclinical hypothyroidism can bring about several complications, including postpartum hemorrhage, anemia, and GDM. Studies have consistently found a link between thyroid issues and GDM, showing that people with GDM often have higher levels of hypothyroxinemia and increased anti-thyroid peroxidase (anti-TPO) antibodies. There's also evidence suggesting that hypothyroidism could make someone

more likely to develop GDM. Furthermore, both gestational diabetes and thyroid dysfunction can harm pregnancy outcomes, negatively affecting the baby's brain development. Overt and subclinical hypothyroidism, often stemming from autoimmune thyroiditis, are especially linked to these adverse outcomes [8].

Based on recent research, women who test positive for thyroid outcomes. antibodies in the early stages of pregnancy typically have higher levels of thyroid-stimulating hormone (TSH) as the pregnancy goes on. Antibody levels are 60% lower in the third trimester compared to the first trimester. Research has linked thyroid antibodies to pregnancy loss, premature labor, postpartum thyroiditis, and placenta disruption. For pregnant women diagnosed with subclinical hypothyroidism, the American Thyroid Association (ATA) released a 2017 recommendation that includes varying treatment recommendations based on thyroid antibody levels [6].

The American Diabetes Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG) suggest using a one-step oral glucose tolerance test (OGTT) for every expectant mother in high-risk categories, like those in

the United Arab Emirates. If the first test comes back clear, the advice is to perform another OGTT between the 24th and 28th weeks of pregnancy. For communities at greater risk, the two-step method that the ADA recommends for places with less GDM isn't seen as cost-effective [8].

2. Subjects and Methods

2.1. Subjects

With the local institution's ethical committee's approval, a case-control study was managed at the outpatient obstetric clinic of Fayoum University Hospital from January 2022 to the end of August.

Inclusion criteria

57 pregnant women with GDM diagnosed according to American Diabetes Association recommendations between 24 and 37 weeks of gestation, an equal number of pregnant women with normal OGTT

Exclusion criteria

Study exclusion criteria encompassed individuals with manifest diabetes, a previous diagnosis of thyroid dysfunction or history of thyroid surgery, prior head and neck irradiation, a history of autoimmune diseases, or those on medications that could affect thyroid function, including lithium, tricyclic antidepressants, anti-epileptics, rifampicin, and selective serotonin reuptake inhibitors. Additionally, women with multiple pregnancies (such as twins) were excluded, as were those who declined to participate in the study.

2.2. Study design

Sample size and intended population

Regardless of their gravidity status, pregnant women who met the eligibility requirements were the target population and attended the obstetrics and gynecology outpatient department.

Sample size

G*Power was used to calculate the sample size, and the effect size was estimated to be 0.7 based on the study by Yanachkova & Kamenov (2021), who wanted to find out whether there were abnormalities in thyroid hormone levels in pregnant women with gestational diabetes [9].

We used a priori analysis software to calculates the independent sample t-test difference between two independent means (two

groups). 90% power was estimated for a sample size of 114 participants, consisting of 57 cases and 57 matched controls. A 10% dropout rate during follow-up and an error probability of 0 points.

According to this calculation, the study included two matched groups:

- Group 1: 57 pregnant women with singleton pregnancies, GDM, ages >18, and between 24 and 37 weeks of gestation who provided informed consent to be included in the study (sample size).
- Group 2: an equivalent number of expectant mothers with a typical 75 g OGTT and a singleton pregnancy (57) in a ratio of 1:1 was chosen in the control group.

2.3. Methods

We performed an anthropometric height and weight assessment along with a thorough clinical examination, focusing on the signs and symptoms of hypothyroidism, obstetric history, family history of diabetes mellitus, and clinical examination. If there was any disparity between fundal height and the Last Menstrual Period (LMP) or if the LMP was uncertain, ultrasonography was conducted to determine the individual's gestational age. To diagnose and rule out GDM, the Oral Glucose Tolerance Test (OGTT) was utilized. Should any of the following plasma glucose levels have been surpassed, a diagnosis of GDM would have been made. The testing criteria for Pregnancy Plasma Glucose (PPG) were as follows:

- Fasting plasma glucose > 92 mg/dL.
- 1st-hour. PPG > 180 mg/dL.
- 2nd-hour. PPG > 153 mg/dL.

Thyroid Peroxidase Antibody (TPO), TSH, and T4 levels were measured in 5 ml of venous blood extracted from the cubital vein of pregnant women enrolled in the study. As per the 2014 American Thyroid Association (ATA) guidelines, a normal serum FT4 level (standard reference range 9–23 mIU/ml) and a TSH between 3 and 10 mIU/ml are considered subclinical hypothyroidism.

Apparent hypothyroidism was defined as either a TSH value $\geq$ 10 mIU/L independent of the FT4 value or a TSH > 3 mIU/L with a combination with a reduced FT4. Clinical hyperthyroidism was diagnosed when there was an elevated FT4 and a suppressed or undetectable serum TSH. Thyroid peroxidase antibodies (TPA) were considered positive if the titer exceeded the upper limit of the standard reference range (<35 IU/mL).

2.4. Statistical Methods

The IBM SPSS Statistical Package version 20 was used to analyze the data after it was collected, processed, coded, and entered.

Quantitative data with a parametric distribution were summarized using means, standard deviations, and ranges. In contrast, qualitative data were presented using frequencies and percentages. To compare qualitative data between two groups where the expected count in any cell was less than five, either Fisher's exact test or the chi-squared test was used. For quantitative data with a parametric distribution, the independent sample t-test compared two independent groups. For quantitative non-parametric data, the Mann-Whitney U test compared two independent groups. Receiver operating characteristic (ROC) curve analysis evaluated the potential of TSH, FT4, and TPO-Ab levels to predict GDM based on sensitivity and specificity. The area under the curve (AUC) was calculated with a 95% confidence interval. There was no predictive ability at 0 points and a full predictive value at 1 point on the AUC scale. Pearson's correlation analysis assessed the linear relationship between thyroid profile measures and other parameters in women with GDM. Only significant correlations with $P < 0.05$ were plotted on correlation graphs. There was a 5% margin of error accepted and a 95% confidence interval set.

3. Results

Table 1 presents the obstetric and demographic characteristics of the two groups under investigation based on whether gestational diabetes was present (GDM+) or not (GDM−). There are no statistically significant differences ($p > 0.05$) between the two groups when it comes to maternal age, gravidity, parity, and BMI. In comparison to pregnant women in good health, the percentage of GDM women who had a family history of the disease was significantly higher (64.9% vs. 7.5%; $p < 0.01$).

Table 1: Study parameters related to both groups' demographics and obstetrics (N= 114).

Variables		Group 1: GDM	Group 2: Healthy	*P-value**
Gestational age (weeks)	**Mean ±SD**	26.4 ±1.4	26.3 ±1.3	0.627[a]
	Range	24.0 -28.0	24.0 -28.0	
Gravidity; times	**Median (IQR)**	3.0 (2.0)	4.0 (2.0)	0.741[b]
	Range	1.0 -7.0	1.0 -5.0	
Parity; times	**Median (IQR)**	2.0 (2.0)	3.0 (2.0)	0.741[b]
	Range	0.0 -6.0	0.0 -4.0	
Family History of GDM (N (%))	**Positive**	37 (64.9%)	4 (7.0%)	**<0.001*[c]**
	Negative	20 (35.1%)	53 (93.0%)	
Age (years)	**Mean + SD**	30.0+4.4	29.9+4.4	0.806
	Range	22.0-40.0	20.0 -40.0	

Data is presented as Mean ±SD or Median (IQR). [a] *Independent sample t-test; Mann-Whitney U test;* [c] *Chi-Square test.* * *Statistically significant.*

The blood glucose test results for the two groups under study are compared in **Table 2** and **Figure 1**. When comparing the blood glucose levels of GDM women to those of healthy controls, there was a significant difference in both the 1st and 2nd-hour postprandial blood glucose ($p < 0.001$), as well as in fasting blood glucose.

Table 2: Comparison of the two groups under study's blood glucose tests (N= 114).

Variables		Group 1 GDM (+) N= 57	Group 2 Controls N= 57	*P-value* [a]
FBG (mg/dL)	**Mean ±SD**	116.9 ±13.8	86.4 ±4.4	<0.001*
	Range	95.0-167.0	80.0-92.0	
1st-hour PPBG (mg/dL)	**Mean ±SD**	203.9 ±29.9	130.8 ±7.3	<0.001*
	Range	140.0 -266.0	120.0-140.0	
2nd-hour PPBG (mg/dL)	**Mean ±SD**	147.9 ±25.4	111.2 ±7.4	<0.001*
	Range	98.0-200.0	95.0-120.0	

*Data are presented as Mean ±SD FBG: Fasting blood glucose, 1st-hour PPBG: 1st-hour post-prandial blood glucose; 2nd-hour PPBG; 2nd-hour post-prandial blood glucose levels. [a] Independent sample t-test. * Statistically significant.*
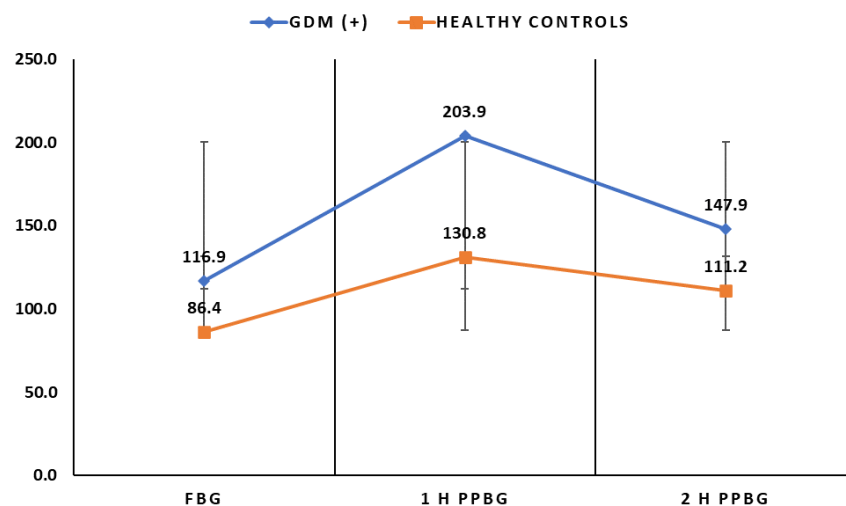
Figure 1: Comparison of Blood Glucose Tests between Both Study Groups.

Table 3 and **Figure 2** present a comparison of the thyroid profiles of the two study groups. Even though the mean serum TSH level in GDM patients was higher than in the healthy control group, the results show that the difference was not statistically significant (2.69 ±0.81 vs. 2.61 ±0.85, p = 0.583). Nonetheless, the pregnant GDM women had higher mean fT4 and mean anti-TPO antibody levels.

Table 3: Comparison of Thyroid profile between both Study groups (N= 114).

Variables		Group 1 (N= 57)	Group 2 (N = 57)	P-value a
FT4 **(ng/ml)**	**Mean ±SD**	1.01 ±0.15	1.09 ±0.23	**0.025***
	Range	0.70-1.55	0.70-2.10	
	Maximum	1.55	2.10	
TSH	**Mean ±SD**	2.83 ±0.89	2.54 ±0.11	0.073
	Range	1.10-4.40	1.05-4.20	
	Maximum	4.40	4.20	
TPO- **AB**	**Mean ±SD**	19.29 ±13.55	10.81 ±1.37	**<0.001***
	Range	6.60-96.00	8.79-15.00	
	Maximum	96.00	15.00	

*Data are presented as Mean ±SD. FT4: free Thyroxine; TSH: Thyrotropin; TPO-Ab: Thyroid Peroxidase Autoantibodies. [a] Independent sample t-test. * Statistically significant.*
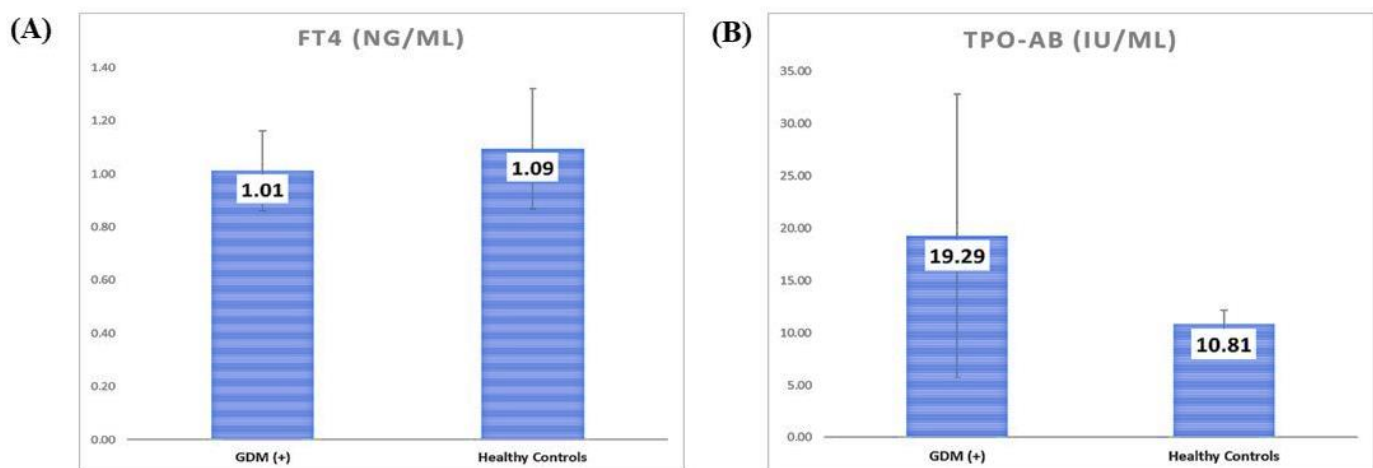
Figure 2: Comparison of thyroid profiles of the two study groups. (A) FT4, (B) TPO-Ab.

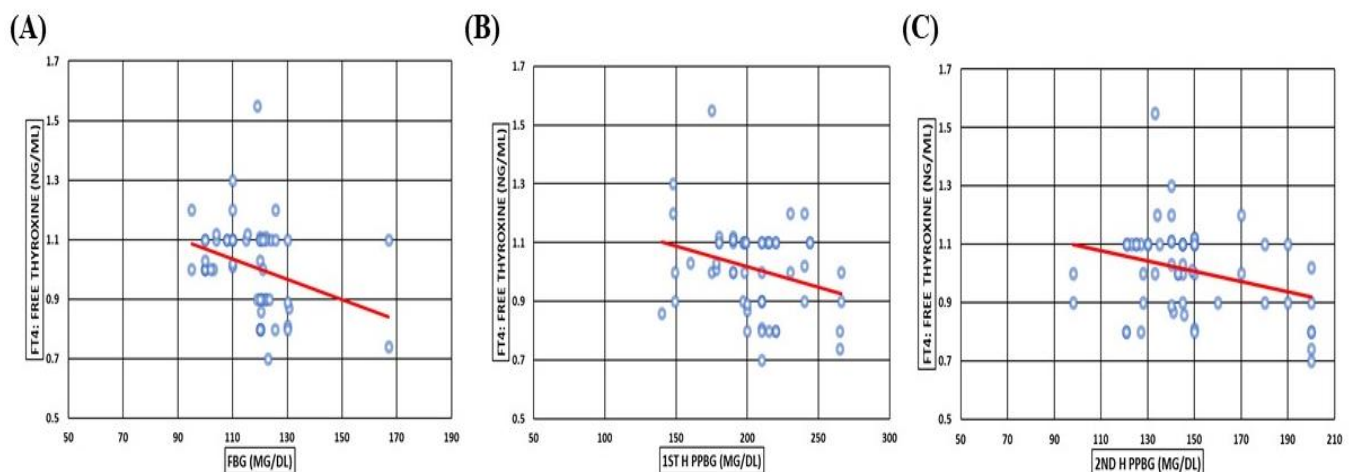The thyroid profile tests and other variables among the pregnant GDM women under study are correlated, as shown in **Table 4** and **Figure 3**. The thyroid profile (FT4, TSH, and TPO-AB) in the current population showed a non-statistically significant linear correlation ($p < 0.05$) with maternal age, gestational age, gravidity, and

parity. FT4 displayed a statistically significant negative linear correlation with 1st-hour PPBG (r = -0.276, p = 0.038), 2nd-hour PPBG (r = -0.295, p = 0.026), and FBG (r = -0.311, p = 0.019). In contrast, TSH and TPO-AB did not exhibit a statistically significant linear correlation with FBG, 1st-hour PPBG, and 2nd-hour PPBG in the current population (p <0.05).

Table 4: Correlation analysis between Thyroid profile tests and other studied variables among studied GDM pregnant women (N= 57).

Variables	FT4	TSH	TPO-AB
Age	0.386	0.935	0.116
Gestational age	0.050	0.198	0.865
Gravidity	0.336	0.202	0.441
Parity	0.336	0.202	0.441
FBG	**0.019***	0.257	0.899
1st-hour PPBG	**0.038***	0.343	0.795
2nd-hour PPHBG	**0.026***	0.755	0.190

Figure 3: Correlation between thyroid profile tests and other variables among the pregnant GDM women. (A) Fasting Blood Glucose (FBG); (B) 1st-hour. Post-Prandial Blood Glucose (1st-hour PPBG); (C) 2nd-hour. Post-Prandial Blood Glucose (2nd-hour PPBG).

The sensitivity and specificity of TSH, FT4, and TPO-AB as markers and diagnostic predictors for GDM were assessed using ROC curve analysis. TSH's area under the curve (AUC) for GDM prediction was 0.587 (95% confidence interval [CI]: 0.40.482–0.692). With a sensitivity of 71% and a specificity of 63%, GDM could be predicted using a cut-off concentration of TSH ≥2.46 mIU/ml. 0.686 (95% CI: 0.587–0.786) was the AUC for FT4. GDM could be ruled out with a sensitivity of 63.2% and a specificity of 60% if the cut-off concentration of FT4 was ≥1.08 ng/ml. 0.779 (95% CI: 0.686–0.872) was the AUC of TPO-AB. With a specificity of 61.2% and a sensitivity of 80.7%, the cut-off concentration of TPO-Ab ≥10.8 IU/ml could be used to predict GDM (**Table 5** and **Figure 4**).

Table 5: Results of ROC curve analysis for sensitivity and specificity of TSH, FT4, and TPO-AB as indicators and diagnostic predictors for GDM (N= 114)

Variables	AUC	95% CI	Cut-off	Sensitivity	Specificity
TSH (μIU/ml)	0.587	0.482 -0.692	≥2.46	71%	63%
FT4 (ng/ml)	0.686	0.587 -0.786	≥1.08	63.2%	60%
TPO-Ab (IU/ml)	0.779	0.686 -0.872	≥10.8	80.7%	61.2%

AUC: Area under the curve, CI: Asymptotic 95% Confidence Interval of AUC, FT4: free Thyroxine; TSH: Thyrotropin; TPO-Ab, Thyroid Peroxidase Autoantibodies.
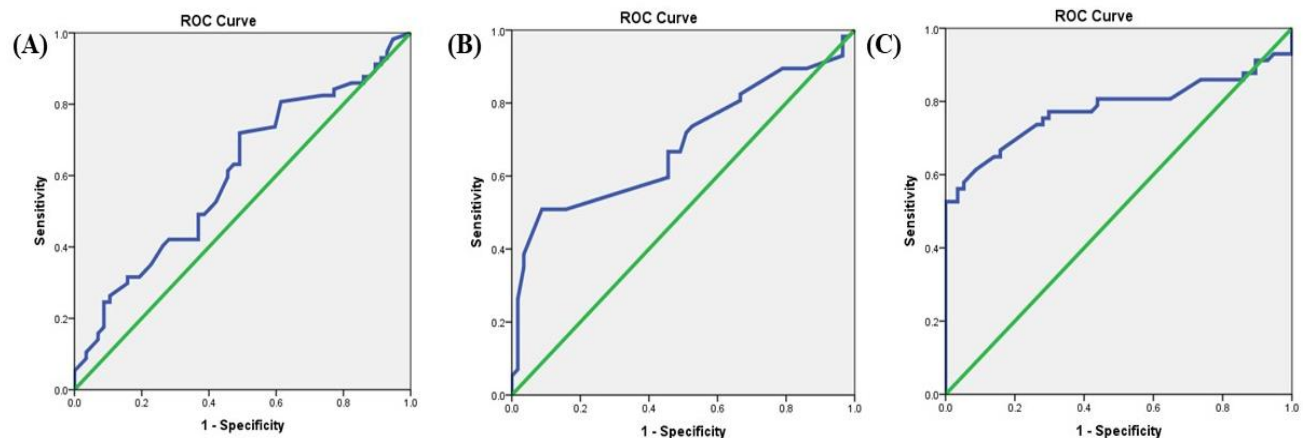
Figure 4: The ROC curve analysis for prediction of GDM. (A) TSH; (B) FT4; (C) TPO-Ab.

4. Discussion

Age is recognized as a factor that elevates the risk of GDM, a finding corroborated by our research. The average age of women with GDM in this study was 30 years, with a standard deviation of 4.4 years, aligning with findings from other research [4, 7, 10].

A significant correlation was observed between GDM patients and a positive family history of diabetes indicating a higher prevalence of such a history in our sample compared to similar studies [11]. Moreover, Yang et al. (2016) highlighted that the likelihood of GDM increases with age and is more prevalent among those with a familial diabetes history [12].

While not statistically significant, GDM patients tended to have higher mean TSH levels, whereas their mean FT4 levels were significantly lower, and TPO-Ab levels were higher compared to healthy pregnant women.

In a recent investigation carried out at a tertiary care facility involving 150 pregnant participants, divided equally between those diagnosed with GDM) and those without, findings revealed elevated TSH levels and anti-thyroid peroxidase (anti-TPO) levels in the GDM group compared to their non-GDM counterparts. Furthermore, the study observed that free thyroxine (FT4) levels were significantly reduced in women with GDM (p ≤0.001). This study encompassed a cohort of 150 women who were between 24 and 28 weeks into their pregnancy [11].

A retrospective case-control study analyzing the medical records of 662 pregnant women revealed elevated TSH and FT3 levels and a higher FT3:FT4 ratio in GDM patients [9].

One more comparable study by Velkoska et al. (2010) was conducted in Macedonia. Thirteen found that the FT4 levels in GDM subjects were lower (11.7 ±2.4 vs. 13.8 ±2.3 pmol/L, p <04) [13].

Our results differ from the Iranian study of 210 pregnant women (105 with GDM, 105 without). The Iranian study found no significant differences in mean TSH (3.43 ± 2.06 vs 1.41 ± 0.69 µIU/ml) or mean FT4 (1.5 ± 0.61 vs 1.74 ± 1.47 ng/dL) between GDM and control groups. In contrast, our study found mean FT4 was significantly higher in the GDM group compared to controls (p =0.023). While the previous study showed no thyroid hormone level differences between GDM and controls, ours demonstrated elevated FT4 levels associated with gestational diabetes [14].

Our results also contrast with the studies by Agarwala et al. (2018) and Ruas et al. (2007) showing comparable FT4 and TSH values between GDM and healthy pregnancies. The high prevalence of iodine deficiency in our baseline study population may explain this discrepancy. While those studies found no thyroid level differences between groups, the iodine deficiency in our cohort may have contributed to the altered thyroid hormones we observed linked to gestational diabetes [15, 16].

Our study demonstrates that low FT4 is an independent risk factor for GDM, evidenced by the statistically significant inverse linear correlation found between FT4 levels and blood glucose. As FT4 increased, the incidence of GDM gradually decreased. A prior study of 2,751 mothers also identified low FT4 as a predictor of GDM risk, with GDM incidence declining as FT4 rose, while TSH and TPO-Ab did not predict GDM. These findings suggest low FT4 confers risk for developing GDM, consistent with our current results. Thyroid hormones play a key role in glucose metabolism. Recent research shows maternal free T3 (FT3) correlates directly with BMI in pregnancy, while FT4 correlates inversely with BMI. 17 Higher FT4 was associated with increasing BMI and FT3, further elevating GDM risk in those with obesity [18].

However, in euthyroid pregnancies, a lower level of FT4 was associated with an increase in the ratio between FT3/FT4 levels and BMI, indicating an increase in peripheral deiodinase activity. This finding was reported in another study [19]. Research has additionally demonstrated that excessive energy intake increases the rate at which peripheral T4 is transformed into T3, indicating that energy intake influences peripheral deiodinase activity [20]. The results of all the aforementioned studies demonstrate the correlation between diabetes and low FT4 levels, which our study also supported.

TPO Ab-positivity is defined in terms of a specific TPO Ab concentration, which is defined in preparation kits. According to several studies, TPO Ab positivity (as opposed to. A higher risk of GDM is linked to negativity [7, 21, 22] and Sub-clinical hypothyroidism may increase this risk even more [23].

The ROC curve analysis showed a TSH level $\geq$2.46 μIU/ml predicted gestational diabetes (GDM) with 71% sensitivity and 63% specificity. This highlights TSH, FT4, and TPO-Ab as potential indicators and predictors for GDM. Additionally, an FT4 cutoff $\geq$1.08 ng/ml excluded GDM with 63.2% sensitivity and 60% specificity. Meanwhile, TPO-Ab $\geq$10.8 IU/ml predicted GDM with 80.7% sensitivity and

61.2% specificity. However, as this was confined to one obstetric center, large-scale multicenter validation is required. The study lacks data on nutritional iodine status and its effect on the thyroid-GDM association, presenting an area for further research.

A key strength is that this is the first study to evaluate first-trimester thyroid dysfunction and autoimmunity prevalence in GDM pregnancies in Fayoum University Hospital's clinic. It represents pioneering research on this topic in this field. However, confirmation through expanded investigations is needed. Analyzing iodine nutrition impacts could provide more insights into the thyroid-GDM relationship in future work.

Conclusion

In conclusion, in the comparative case-control research conducted, it was observed that the average serum TSH levels were elevated in patients with GDM compared to a healthy control group, although the difference did not reach statistical significance. Nonetheless, a statistically significant difference was noted with a p-value of less than 0.05. Furthermore, the analysis revealed that mean FT4 and anti-TPO antibody levels were higher among pregnant women diagnosed with GDM. Our study also identified a correlation suggesting that higher FT4 concentrations were associated with a decreased risk of developing GDM. No significant relationships were established between serum TPO-Ab and TSH levels and the status of GDM. Based on these outcomes, it is recommended that healthcare professionals consider monitoring for relatively lower concentrations of FT4 within the normal range as a preventive measure against GDM, instead of focusing solely on extremely high percentiles or evident low thyroid function.

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