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■ Original Research Article

Comparative Study of Thyroid Hormone Disorders Among Women with Gestational Diabetes and Normoglycemic Pregnant Women

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Abstract

Introduction: Gestational diabetes and thyroid disorders are dual gestational endocrinopathies that can result in adverse maternal and fetal outcomes. **Aims:** To compare the prevalence and types of thyroid hormone disorders in women with gestational diabetes and those without gestational diabetes and to determine the predisposing factors to thyroid hormone disorders. **Settings and Design:** Comparative cross-sectional study. **Methods and Material:** This study was conducted in Jos University Teaching Hospital (JUTH), Jos, Nigeria. Seventy women with GDM and 70 normoglycemic pregnant women were recruited. The serum TSH, fT3 and fT4 were analysed and the results were compared between the two groups groups. Statistical analysis was done using Statistical Package for Social sciences (IBM-SPSS) software (version 26). **Results:** The prevalence of thyroid hormone disorders in the GDM group was 45.7% and this was higher when compared with the normoglycemic group (28.6%). Subclinical hypothyroidism was the most common thyroid hormone disorder among the GDM group and this was statistically significant (34.3%, p value 0.001) when compared with the non-GDM group (1.4%). Gestational diabetics with family history of thyroid disorder were significantly at higher risk (aOR 6.71, 95% CI 1.42-31.80; p=0.016) of hyperthyroidism when compared to normoglycemic group. The risk of hyperthyroidism was significantly lower (aOR 0.07, 95% CI 0.01-0.72) in gestational diabetics with anterior neck swelling than the non-GDM group. **Conclusion:** Subclinical hypothyroidism was the most common thyroid hormone disorder in GDM and this was considerably high and significant than normoglycemic pregnant women. Family history of thyroid disorder is a significant risk factor associated with hyperthyroidism in GDM.

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Introduction

Gestational Diabetes Mellitus (GDM) and thyroid disorders are common endocrinopathies found among pregnant women.[1]GDM is any glucose intolerance with first recognition or onset in pregnancy.[2] The imbalance in thyroid homeostasis can be expressed in pregnancy as overt hypothyroidism, subclinical hypothyroidism, overt hyperthyroidism, subclinical hyperthyroidism and autoimmune thyroid disorder.[3,4]

There are conflicting reports on the association between GDM and thyroid hormone disorders.[4] Physiologic adaptation in pregnancy occurs in multiple organ and metabolic systems which includes thyroid gland and glucose metabolism.[5] These adaptations ensure a healthy balance between the mother and the fetus.[5] The inability of the pancreas to compensate for the physiologic insulin resistance in pregnancy results in GDM.[6] Thyroid hormone disorders may manifest with symptoms and signs of hypothyroidism or hyperthyroidism or remain subclinical.[7]

A multifaceted relationship between GDM and thyroid disorder has been suggested.[8] A direct genetic relationship between GDM and thyroid disorder has been suggested even though not well characterized.[8] High levels of insulin abolishes the nocturnal Thyroid Stimulating Hormone (TSH) response to thyroid-releasing hormone.[8] Also suggested is impairment in the peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3).[8] Insulin resistance with high levels of circulating insulin stimulate thyroid gland growth with increased nodularity.[8] Studies have reported increased risk of thyroid disorders in women with GDM.[9,10] Insulin resistance can also result from hypothyroidism and hyperthyroidism.[8] In hypothyroid state, there is reduced peripheral muscle responsiveness to insulin and increased gluconeogenesis, and reduced glucose disposal by the liver. In hyperthyroid state, there is an exaggerated endogenous glucose production and an elevation in bioactive inflammatory mediators of insulin resistance.[8,11]

Studies have shown that subclinical hypothyroidism is the most common form of thyroid disorder in pregnancy, also a high prevalence of subclinical hypothyroidism has been reported in women with GDM.[5,12] This presents with no clinical feature but detected on biochemical analysis.[3] Even where thyroid disorders are overt, the physiologic change of pregnancy makes clinical diagnosis difficult.[13]

Tirosh and colleagues had referred to the coexistence of GDM and thyroid disorders as a "dual gestational endocrinopathy". They showed that women with GDM had a significantly lower free T4 concentration than healthy pregnant women.[14] Hyperthyroidism has been reported among women with GDM in a case control study, this was however significantly lower than hypothyroidism.[15]

Euthyroidism is important in pregnancy because prior to the 20th week of gestation the mother is the unique source of thyroid hormones.[3] Hypothyroidism is associated with increased risk of impaired cognitive development in the fetus.[16]

Gestational Diabetes and hypothyroidism have been shown to be complicated by hypertensive disorders in pregnancy even after controlling for age, parity and other confounding factors.[14] The mechanism through which these endocrinopathies increase the risk of hypertensive disorders remains complex.[14] Increased incidence of preterm births, abruptio placentae, increased risk of caesarean section are other reported complications.[17] Despite the complications of thyroid disorders in pregnancy, universal screening has remained a topic of controversy.[15] International Federation of Gynaecology and Obstetrics (FIGO) initiative on GDM recommends that "all pregnant women should be tested for hyperglycaemia during pregnancy using a one-step procedure".[18] Because of the prevalence of thyroid disorders especially subclinical and overt hypothyroidism in GDM, screening and treatment have been recommended by some studies.[4,10,16]

Studies have reported a high prevalence of thyroid hormone disorders in women with GDM and established an association.[9,10,14] Even though a study has reported a higher prevalence of thyroid disorders in pregnant women compared to the non-pregnant population[12] studies on the prevalence of thyroid hormone disorders in GDM or association between GDM and thyroid hormone disorders were scarce in this environment.

Identification of thyroid disorders and treatment will help to improve glycaemic control in GDM patients and reduce the maternal and fetal complications associated with these dual endocrinopathies.[8,19] The aim of this study was to

compare the prevalence and types of thyroid hormone disorder among women with and without GDM and ascertain the predisposing factors for thyroid hormone disorders in women with GDM.

Subjects and Methods

***Study Setting and Design*:** This was a cross-sectional comparative study conducted in the antenatal care clinic of the Jos University Teaching Hospital (JUTH), Jos, Nigeria.

***Study Population*:** This study was conducted between July 2020 and January 2021. Women with gestational diabetes (cases) and healthy normoglycemic pregnant women (controls) from a population of women who had oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation were recruited in the study. In this study, blood glucose values recommended by IADPSG were used for the interpretation of OGTT results in pregnancy.[20] Patients with suspected or established thyroid disorders, type 1 or 2 diabetes mellitus, multiple gestations, and women who were on drugs that could affect thyroid function e.g., iodine, amiodarone were excluded from this study.

Sample Size determination: The sample size was determined using the Pocock's sample size formula for comparing proportions.[21] Confidence interval was set at 95%, standard normal distribution was for a significance level of 0.05 and desired level of power of 80%. The reference prevalence of thyroid hormone disorders in GDM and normoglycemic pregnant women derived from a similar study was 0.4852% and 0.1854% respectively.[15] A sample size of 70 for each group was arrived at.

Data Collection: Seventy women with GDM (cases) and 70 non-GDM pregnant women (controls) were consecutively recruited. The controls were matched with cases for age and gestational age. In doing this it was ensured that for every case selected the difference in age for the selected control was ±2 years and the difference in gestational age was ±2 weeks and vice versa. Using the interviewer-administered pretested questionnaire that was formulated, a detailed history was taken with regards to age, parity, marital status, educational qualification, occupation, religion, duration of gestation in weeks. Also, past obstetric history, past history of thyroid disorder, history of head and neck irradiation, use of iodized salt, and whether anterior neck swelling was common in her environment was recorded. Blood pressure of each participant was measured in the sitting position using Accoson mercury sphygmomanometer. Using a needle and syringe, 5mls of venous blood was collected from each participant into a plain anticoagulant-free container. The blood was allowed to clot for a minimum of 30 minutes before centrifugation. The serum was separated into 1ml aliquots in 2 cryovials and immediately stored at -20^{o}C until adequate sample size was reached. A study identification number was given to each participant to protect her identity and eliminate bias during laboratory assessment of their thyroid hormone profile.

The frozen serum samples were thawed and used for the following assay TSH, T3 and T4 using ELISA kit manufactured by Monobind Inc. Lake Forest, CA 92630, USA. The results were interpreted using the values of thyroid function tests recommended by the American Thyroid Association.[7]

Statistical Analysis: Data collected were entered into a Microsoft excel database created. Statistical analysis was performed using IBM-SPSS software (version 26). Frequencies and percentages were computed for demographic and educational characteristics of cases and controls and presented in tables, difference in categorical and numerical variables between GDM patients and controls was done using Chi square and students' t-test. Multiple logistic regression models were built for sociodemographic characteristics and obstetric characteristics. In both, GDM status was used as a covariate to identify independent predictors of thyroid disorder among GDM and non-GDM groups. The results are presented as adjusted odd ratio (aOR) and 95% confidence interval (CI). A P value of <0.05 was taken as significant.

Ethical Consideration: Ethical approval was obtained from the Jos University Teaching Hospital Health Research ethical committee. All participants identified with thyroid hormone disorders were informed and referred to the Endocrinologists for appropriate advice and treatment where necessary.

Results

Demographic Characteristics, Clinical and Laboratory Parameters of Subjects

Table 1 shows there was no significant difference in the sociodemographic characteristics of the 2 groups. The mean serum levels of fT4 was significantly lower in the GDM group than the non-GDM group (1.31mIU/L versus 1.43mIU/L, p= 0.01). There was however no significant difference in the mean TSH and fT3 between the two groups (p=0.154 and 0.64 respectively). There was no significant difference when the other clinical and laboratory parameters were compared between the 2 groups.

Prevalence and types of thyroid hormone disorders

The prevalence of thyroid hormone disorders was higher in the GDM group when compared with the non-GDM group (45.7% versus 28.8%). Subclinical hypothyroidism was the most common type of thyroid hormone disorder among women with GDM accounting for 34.3% of all types of thyroid hormone disorders. The prevalence of subclinical hypothyroidism in the GDM group was higher and statistically significant (p=0.001) when compared with the prevalence among the non-GDM group (1.4%). Among the non-GDM group, subclinical hyperthyroidism accounted for 18.6%, this was

Table 1: Demographic, Clinical and Laboratory variables of study participants

Variables	Cases	Control	χ^2	p-value
Mean Age	33±4.81	32±5.23	1.170	0.244
Mean parity	3±2.27	2±1.84	1.461	0.146
Mean GA(weeks)	30.63±4.17	30.35±3.98	0.421*	0.674
Mean GA at Diagnosis	29.01±4.08	29.51±4.39	0.578*	0.565
Mean SBP(mmHg)	110.25±13.32	108.92±13.04	0.618*	0.538
Mean DBP(mmHg)	65.23±12.55	64.30±11.57	0.470*	0.639
Mean TSH miu/L	2.06±1.44	1.77±0.97	1.432*	0.154
Mean fT4(ng/dl)	1.31±0.51	1.43±0.59	2.606*	0.010

GA=Gestational age, SBP=Systolic Blood Pressure, DBP= Diastolic Blood Pressure, TSH= Thyroid Stimulating Hormone, fT4= Free thyroxine, fT3= Free triodo thyroxine,*t test derived value

Table 2: Prevalence and types of thyroid hormone disorders

Thyroid Hormone Status	GDM n=70(%)	NON-GDM n=70(%)	χ^2	p-value
Euthyroid	38(54.3)	50(71.4)	1.636	0.201
Overt hyperthyroidism	5(7.1)	2(2.9)	1.286	0.257
Overt hypothyroidism	0(0.0)	2(2.9)	-	-
Subclinical hypothyroidism	24(34.3)	1(1.4)	21.160	0.001
Subclinical hyperthyroidism	2(2.9)	13(18.6)	8.067	0.005
Isolated hypothyroxinaemia	1(1.4)	2(2.9)	0.333	0.564

Table 3: Exposure indices for thyroid hormone disorders among participants

Factors	Group		χ^2	p-value
	GDM n=70 (%)	Non-GDM n=70 (%)		
Head and Neck Irradiation				
Yes	2(2.9)	0(0.0)	2.027	0.155
No	68(97.1)	70(100.0)		
Family History of Thyroid Disease				
Yes	8(11.4)	6(8.6)	0000	1.000
No	62(88.6)	64(91.4)		
Anterior Neck swelling				
Yes	12(17.1)	10(14.3)	0.045	0.832
No	58(82.9)	60(85.7)		
Use of Iodised salt				
Yes	66(94.3)	68(97.1)	2.113	0.146
No	4(5.7)	2(2.9)		

*Fisher's exact test

Table 4: Multiple Logistic Regression on the association between exposure indices and hyperthyroidism in study participants

Risk factors	Thyroid disorders	Cases	Control	aOR	95% CI	p-value
Head and Neck Irradiation						
Yes	Hyperthyroidism	0(00.0)	0(0.0)	-	-	-
No	Hyperthyroidism	7(31.8)	15(68.2)			
Family History of Thyroid Disease						
Yes	Hyperthyroidism	3(60.0)	2(40.0)	6.71	1.42-31.80	0.016
No	Hyperthyroidism	4(23.5)	13(76.5)			
Anterior Neck swelling						
Yes	Hyperthyroidism	1(100.0)	0(0.0)	0.07	0.01-0.72	0.026
No	Hyperthyroidism	6(28.6)	15(71.4)			
Use of Iodised Salt						
Yes	Hyperthyroidism	6(28.6)	15(71.4)	2.01	0.19-21.53	0.564
No	Hyperthyroidism	1(100.0)	0(0.0)			

Table 5: Previous Obstetric Characteristics of Study Participants

Variables	Cases	Control	χ^2	p-value
Number of miscarriages				
0	41(58.6)	43(61.4)	0.027	0.869
≥1	29(41.4)	27(38.6)		
Preterm Births				
Yes	7(10.0)	5(7.1)	0.066	0.797
No	63(90.0)	65(92.9)		
Number of still birth				
0	57(81.4)	61(87.2)	0.703	0.402
≥1	13(18.6)	9(12.8)		
No of Macrosomia				
0	44(62.9)	56(80.0)	4.419	0.036
≥1	26(37.1)	14(20.0)		
Previous GDM				
Yes	9(12.9)	4(5.7)	2.106	0.147
No	61(87.1)	66(94.3)		
Irregular menstrual cycle				
Yes	8(11.4)	7(10.0)	0.060	0.806
No	62(88.6)	63(70.0)		

higher and statistically significant (0.005) when compared with the GDM group (2.9%). The other patterns of thyroid disorder are as in Table 2.

Exposure indices for thyroid hormone disorders among participants

There were no exposure indices for thyroid hormone disorder that showed any significant difference between the study groups (Table 3).

On multiple logistic regression there were no exposure indices whose odds were significantly associated with hypothyroidism.

In Table 4, gestational diabetics with family history of thyroid disorder were significantly at higher risk (aOR 6.71, 95% CI 1.42-31.80; p=0.016) of hyperthyroidism when compared with normoglycemic pregnant women. The risk of hyperthyroidism was significantly lower (aOR 0.07, 95% CI 0.01-0.72, p=0.026) in gestational diabetics with anterior neck swelling than the non-GDM pregnant women.

The number of previous macrosomic births were higher and significant in the GDM group than the non-GDM group (37.1% versus 20.0%, p=0.036). The other obstetric characteristics are shown in Table 5.

The odds of developing hypothyroidism were higher (aOR 2.03, 95% CI 0.42-9.52; p=0.378) in gestational diabetics with previous histories of GDM than the non-GDM group, likewise participants in the GDM group with previous histories of still births had more odds of developing hyperthyroidism than the non-GDM group though none of these was statistically significant.

Discussion

In this study, the prevalence of thyroid hormone disorder in women with GDM was higher (45.7%) when compared with normoglycemic women (28.6%). This has been reported to compromise maternal and fetal well-being.[22] Subclinical hypothyroidism was the most common (34.3%) type of thyroid disorder among women with GDM and this was higher and significant when compared with the non-GDM group (1.4%). Overt hyperthyroidism was the second most common thyroid hormone disorder in women with GDM though there was no significant difference when compared with the non-GDM group. The findings in this study are similar to findings in a similar report published by Perham et al where thyroid disorders were assessed in 105 women with and 105 women without GDM.[10] Perham et al using the trimester specific values for thyroid function test recommended by American Thyroid Association (ATA) just like in this study found out that the prevalence of thyroid disorders mostly subclinical hypothyroidism was significantly higher (17.1%, p=0.0193) among women with GDM than normoglycemic pregnant women.[10] There was also a statistically significant difference in the prevalence of clinical hypothyroidism in both groups.[10] Like this study equal number of cases GDM and controls (normoglycemic women) were recruited. Shahin et al compared the thyroid function test of 252 women with GDM and 252 health pregnant controls with similar findings .[23] They found out that there was a significant difference in the prevalence of subclinical hypothyroidism in the experimental group (38.4%) and control group (14.06%).[24] The findings in a study conducted by Esraa et al also showed similar findings.[25] The study involved groups of participants- 40 healthy pregnant women(controls), 15 women with type 1 diabetes(cases) and 40 women with GDM (cases).[25] The study revealed that thyroid dysfunctions especially hypothyroidism was significantly commoner in GDM and type 1 diabetes than the control group.[25] It is now obvious that both overt thyroid dysfunction, and subclinical dysfunction especially subclinical hypothyroidism have adverse effects on maternal and fetal outcomes.[14] Adverse outcomes of maternal hypothyroidism include increased risk of spontaneous abortion, premature delivery, pregnancy induced hypertension, placental abortion, low-birth weight, fetal distress in labor, and impaired neuropsychological development.[14,17] Subclinical hyperthyroidism was the most common form of thyroid disorder in the non-GDM group, this was higher and statistically significant when compared with the GDM group. In a similar study conducted by Shahbazian et al there was no reported case of subclinical hyperthyroidism in the control group (normoglycemic women) nor the GDM arm.[26] This may be because the control arm was disproportionately smaller than the experimental group.[26] Treatment for subclinical hyperthyroidism is not warranted during pregnancy because it is not associated with adverse pregnancy outcomes.[23]

The findings in this study were however different from that by Shabazian et al where the rates of thyroid disorders were compared between 35 normoglycemic pregnant controls and 61 cases that included 22 GDM and 39 pregestational diabetic patients.[26] The prevalence of thyroid disorders among the GDM and control groups was not statistically significant.[26] In a study to assess the association between subclinical hypothyroidism and GDM among 68 GDM patients and 74 normoglycemic pregnant women, there was no significant difference in terms of the prevalence between both groups.[27] Inacil et al prospectively compared the thyroid function in 45 pregnant women with GDM with 180 normoglycemic pregnant women that were recruited as controls, thyroid hormone disorder was found in 26.7% of cases and 20.5 % of the controls.[28] The authors concluded that there was no association between GDM and thyroid hormone disorder.[28] The difference observed may be due to the difference in the study populations as well as the sample size used for the study. Also, it appeared there was no matching of the groups in the study with the GDM group. The reference ranges used for these studies like that by Shahbazian et al[28] differ from the reference ranges by ATA which was used in this study. The serum iodine levels of the population and the variations in the interpretation of the results from the various kits used and different geographical regions may account for these differences.

Family history of thyroid disorder was the only risk factor for thyroid disorder in this study that was found to be significantly associated with hyperthyroidism in gestational diabetics (aOR 6.71, 95% CI 1.42-31.80; p=0.016). The risk of hyperthyroidism was significantly lower (aOR 0.07, 95% CI 0.01-0.72) in gestational diabetics with anterior neck swelling than the non-GDM pregnant women. No other exposure index for thyroid disorder was significantly associated with hypothyroidism or hyperthyroidism group when the 2 groups were compared. Jiri et al reported that family history of thyroid disorder was the most common (31%) risk factor for thyroid disease while personal history of thyroid disorder accounted for 8%.[29] A study in China also revealed that family history and personal history of thyroid disorder as risk factors for thyroid disorder showed statistical significance.[30]

In addition, this study revealed a high but insignificant mean serum TSH level among women with GDM than the non-GDM group. The mean serum fT4 was lower among the GDM group and showed statistical significance when compared with the non-GDM group. The findings stated above was even though the prevalence of subclinical hypothyroidism was significantly higher in women with GDM. In the study conducted by Perham et al the mean serum TSH was significantly higher among women with GDM when compared with normoglycemic pregnant women.[10]

The strengths of the study include the following: Firstly, it was a comparative study that included women with GDM and normoglycemic pregnant women that were matched for age and gestational age. The trimester specific reference ranges were used for interpretation of results. Secondly, confounding effects were avoided using a regression model, as a result independent associations of thyroid disorders in GDM were identified.

Limitations exist in this study that merit careful consideration. The local trimester specific reference ranges of thyroid function parameters for the general population were not used as it was not available. Also, there was no follow-up to determine fetomaternal effects of abnormal thyroid hormones.

Conclusion

The prevalence of thyroid disorder particularly subclinical hypothyroidism in women with GDM is considerably high and significant than normoglycemic pregnant women. Family history of thyroid disorder is a significant risk factor associated with hyperthyroidism in women with GDM.

We recommend that women with GDM particularly those with family history of thyroid disorder may be considered for screening for thyroid disorders. A larger multi-centre study with follow up for fetomaternal outcome is recommended to further substantiate the findings in this study. Also, local trimester-specific values for thyroid hormones should be established for our population because racial, ethnic or geographical variability may affect interpretation of results.

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