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Original Research Article

Evaluation of the Risk of Gestational Diabetes Mellitus in Women with Hypothyroidism

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Abstract

Background: Gestational diabetes mellitus and hypothyroidism can affect both maternal and fetal outcome if not controlled. Thyroid disease and diabetes mellitus seems to be connected in pathophysiological aspect. Unrecognised thyroid dysfunction may cause impairment of the glycemic control. Early diagnosis and management are necessary to prevent fetomaternal complications. We aim to evaluate risk of gestational diabetes with hypothyroidism.

Aims and Objectives: To find whether hypothyroid antenatal patient are high risk for developing gestational diabetes mellitus.

Methods: A prospective observational study was done in a tertiary care hospital in New Delhi, India where in antenatal patients attending OPD were screened for hypothyroidism before 22 weeks of pregnancy. Thyroid function test was performed including fT3, fT4, TSH and anti-TPO antibody at the first antenatal visit and segregated into 2 groups based on their TSH value that is group A and B, with 210 patients in each group and followed up till 24 weeks of gestation after which oral glucose tolerance test by DIPSI criteria was performed and the diagnosis of gestational diabetes mellitus in these patients was made accordingly.

Results: Prevalence of GDM was in hypothyroid group was 15.7% compared to 5.7% in euthyroid group. The relative risk for developing GDM was 1.98 (95% CI: 1.20-3.24). The result was statistically significant ($p<0.0001$). Additionally, the mean T3 and T4 level were significantly lower in GDM patients (1.89±0.81 & 0.54±0.30 respectively) compared to patients without GDM (2.27±0.90 & 0.65±0.27 respectively).

Conclusion: It was observed that a significant association exists between hypothyroidism and diabetes melilites in antenatal patients. Furthermore, the study highlights the needs for vigilance in early gestation in obese and older hypothyroid patients for development of gestational diabetes mellitus.

Key words: Hypothyroidism, Gestational diabetes mellitus, Indian population.

Introduction

Gestational diabetes mellitus (GDM) and hypothyroidism constitute two most common endocrine pathologies encountered in pregnancy [1]. GDM is defined as 'carbohydrate intolerance with recognition or onset during pregnancy', irrespective of the treatment with diet or insulin [2]. The prevalence of gestational diabetes mellitus that is observed from various parts of India falls in between 3.8 to 17.9%. The utmost importance of diagnosing GDM early in pregnancy is that poorly controlled diabetes can lead to complications such as spontaneous abortion, congenital malformations, macrosomia, polyhydramnios, sudden fetal demise, fetal growth restriction in case of diabetic vasculopathy.

Normal pregnancy state is characterised by mild fasting hypoglycaemia, postprandial hyperglycaemia, and hyperinsulinemia [3]. There is

reduced insulin sensitivity, which is caused due to numerous endocrine and inflammatory factors. However, as pregnancy progresses, a surge of local and placental hormones, including estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone together promote a state of insulin resistance. While GDM usually resolves following delivery, it can have long-lasting health consequences not only in mother like increased risk for type 2 diabetes (T2DM), cardiovascular disease (CVD), but also in child like future obesity, CVD, T2DM, and GDM [4].

Second common metabolic disorder in pregnancy with adverse fetal outcome is hypothyroidism, incidence range from 2% to 5%[(1)]. Hypothyroidism can be of two types, that is Overt hypothyroidism and Subclinical hypothyroidism. If there are positive thyroid antibody titres, it reflects autoimmune thyroid disease. The thyroid gland of fetus starts creating little amount of thyroid hormone at about ten weeks of pregnancy, until production plateaus at about thirty-five weeks. Thus, specifically for the first trimester of gestation, the fetus depends solely on maternal trans-placental thyroid hormone. Hypothyroidism can result in miscarriages, recurrent pregnancy losses, anaemia, pre-eclampsia, abruptio placentae, postpartum haemorrhage, increased caesarean sections due to fetal distress, and rarely myopathy and even congestive heart failure (CHF) in severe cases [5]. In pregnancy, blood glucose level is closely related to the levels of estrogen, thyroid binding globulin, human chorionic gonadotropin, placental insulin enzyme, and placental lactogen, which are all affected by maternal thyroid function [6].

As GDM is related to multiple adverse maternal and perinatal outcomes, early prediction and enhanced diagnosis of this pathology can help in better optimisation. There is paucity of studies showing an association between gestational diabetes mellitus and hypothyroidism in women, especially in India.

Aims and Objectives

To assess whether hypothyroidism in women increases the risk of gestational diabetes mellitus.

Material and Methods

This was a prospective case control observational study which was conducted in the department of Obstetrics and Gynaecology, ANC OPD at Atal Bihari Vajpayee Institute of Medical Sciences & Dr RML Hospital, New Delhi. Ante-natal women who had come for their first antenatal visit in the OPD (till 22 weeks) were selected. Patients were explained about the purpose of study and informed written consent was taken from them and those who were willing to participate in study were included.

Exclusion Criteria: multiple pregnancies, women over 22 weeks of pregnancy and the women who were overt diabetic at the time of conception

A detailed history, and relevant investigation was done for all the patients. Around 5 ml of blood was drawn into red-capped vacutainer by phlebotomy. Thyroid profile (FT3, FT4, TSH) and test for thyroid peroxidase antibody were performed on the sample. These patients were divided into two groups based on their thyroid profile. For the first trimester, the cut off for serum TSH was taken as 2.5mlIU/L. And for the second trimester the cut of was taken as 3mIU/L. The study was conducted on a total of 420 antenatal patients, encompassing 210 patients in each group based on the inclusion and exclusion criteria. Women with serum TSH concentrations higher than the trimester specific reference range represented as Group A, and women with serum TSH concentrations within the reference range were considered as other group (B).

All the patients who were diagnosed with sub-clinal hypothyroidism were treated according the latest guidelines.

They were followed up to 24 weeks of gestation and were subjected to oral glucose tolerance test between 24 and 28 weeks. In accordance with DIPSI criteria, a 2-hour value was obtained for these patients. The diagnosis of GDM was made if the value of blood glucose was found to be above 140 mg/dl after 2hour.

Results

We observed no significant disparity in the two groups in terms of age, parity, BMI, educational status, anti-TPO status and HbA1c Level.

Mean age in hypothyroid study group was 28.31±3.90 years while mean age in euthyroid group was 27.70±4.12 years (Table 1).

Table 1: Comparison of mean age between both groups

	Hypothyroid Group (N=210)	Euthyroid Group (N=210)	Unpaired T Test	P Value
Mean Age in Years	28.31±3.90	27.70±4.12	1.54	0.12

Among hypothyroid group, 74 (35.2%) antenatal patients were primigravida and 136 (64.8%) were multigravida, while in euthyroid group 82 (39.0%) antenatal patients were primigravida and 128 (61.0%) patients were multigravida.

In hypothyroid group, 84.8% subjects had BMI <25, and 15.2% had BMI ≥25 kg/m^2 while in euthyroid group, 92.9% subjects had BMI <25, and 7.1% had BMI ≥25 kg/m^2. The difference was found statistically non-significant (p value = 0.01).

A significantly higher number of patients developed gestational diabetes mellitus in hypothyroid study group. In hypothyroid study group, out of 210 patients, 33 patients developed gestational diabetes mellitus whereas in euthyroid study group, 12 patients developed gestational diabetes mellitus. Prevalence of GDM was significantly higher in Hypothyroid group (15.7%) compared to euthyroid group (5.7%) (Table 2).

Gestational Diabetes mellitus	Hypothyroid group (n=210)	Euthyroid group (n=210)	Chi square value	p value
No	177 (84.3%)	198 (94.3%)	**10.97**	**0.001**
Yes	33 (15.7%)	12 (5.7%)		

Table 2: Distribution of study groups according to prevalence of gestational diabetes mellitus

The relative risk for developing GDM was 1.98 (95% CI: 1.20-3.24). The result was statistically significant (p<0.0001) (figure 1).

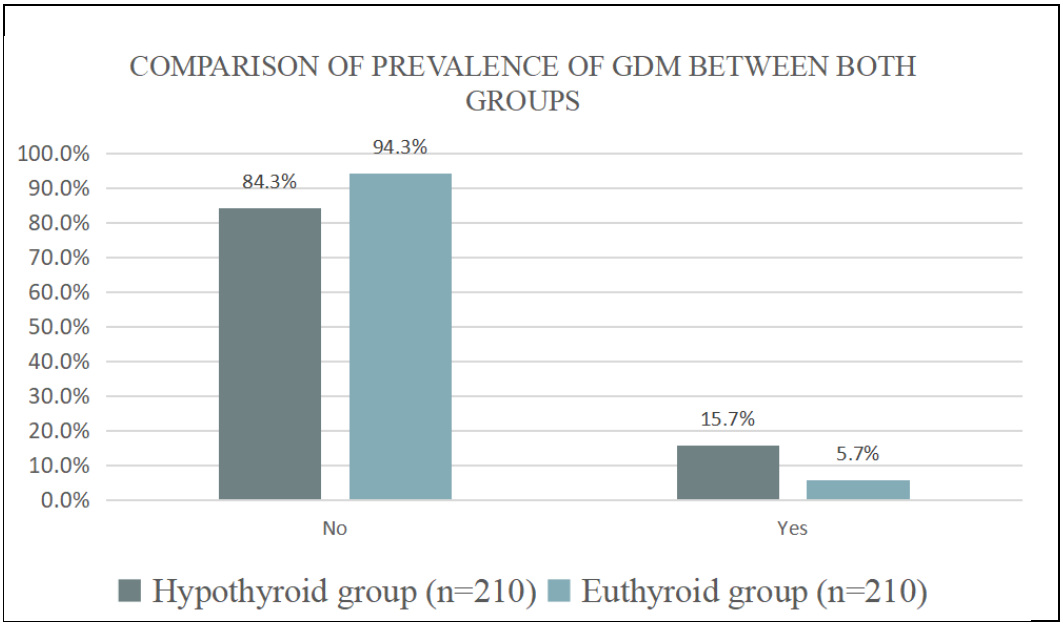

Figure 1: Distribution of study groups according to prevalence of gestational diabetes mellitus

In GDM group 15.6% subject was anti-TPO positive while in subjects without GDM 10.7% subjects were anti-TPO positive. There was no significant difference between the 2 groups in terms of anti-TPO status (p value =0.31) (Table 3).

Anti-TOP antibody	GDM		Chi square value	p value
	No GDM	Yes		
Negative	335 (89.3%)	38 (84.4%)	0.96	0.31
Positive	40 (10.7%)	7 (15.6%)		

Table 3: Association of anti-TPO antibody with development of GDM

In hypergylcemic group 68.9% subjects had BMI <25, and 31.1% had BMI ≥25 kg/m^{2}while in euglycemic group 91.2% subjects had BMI <25, and 8.8% had BMI ≥25 kg/m^2. This shows that BMI ≥25 kg/m^2 was significantly higher in GDM group compared to without GDM.

The Mean oral glucose tolerance test (OGTT) value in group A was found to be 119.23±22.53, whereas in euthyroid group (B) mean OGTT level was 112.21±18.95. There seems to be substantial difference between the 2 groups about OGTT level with hypothyroid group having significantly higher

	Hypothyroid group (n=210)	Euthyroid group (n=210)	Unpaired t test value	p value
OGTT	119.23±22.53	112.21±18.95	3.45	**0.001**
HbA1C	5.18±0.64	5.14±0.56	0.70	0.47

Table 4: Comparison of mean OGTT and HbA1c between both groups

Mean HbA1C levels were also compared. HbA1c levels in group A was 5.18±0.64 while mean HbA1C in group B was 5.14±0.56. There was no statistically significant variation between the 2 groups in terms of mean HbA1c (p value =0.47).

We perceived considerably higher number of patients developing gestational diabetes mellitus in the hypothyroid group in later pregnancy. The prevalence of GDM in group A was 15.7% compared to 5.7% in euthyroid group. The relative risk for developing GDM was 1.98 (95% CI: 1.20-3.24). The results were statistically significant (p<0.0001). Additionally, the mean T3 and T4 level were found to be significantly lower in GDM patients (1.89±0.81 & 0.54±0.30) compared to patients without GDM (2.27±0.90 & 0.65±0.27). (figure 2).

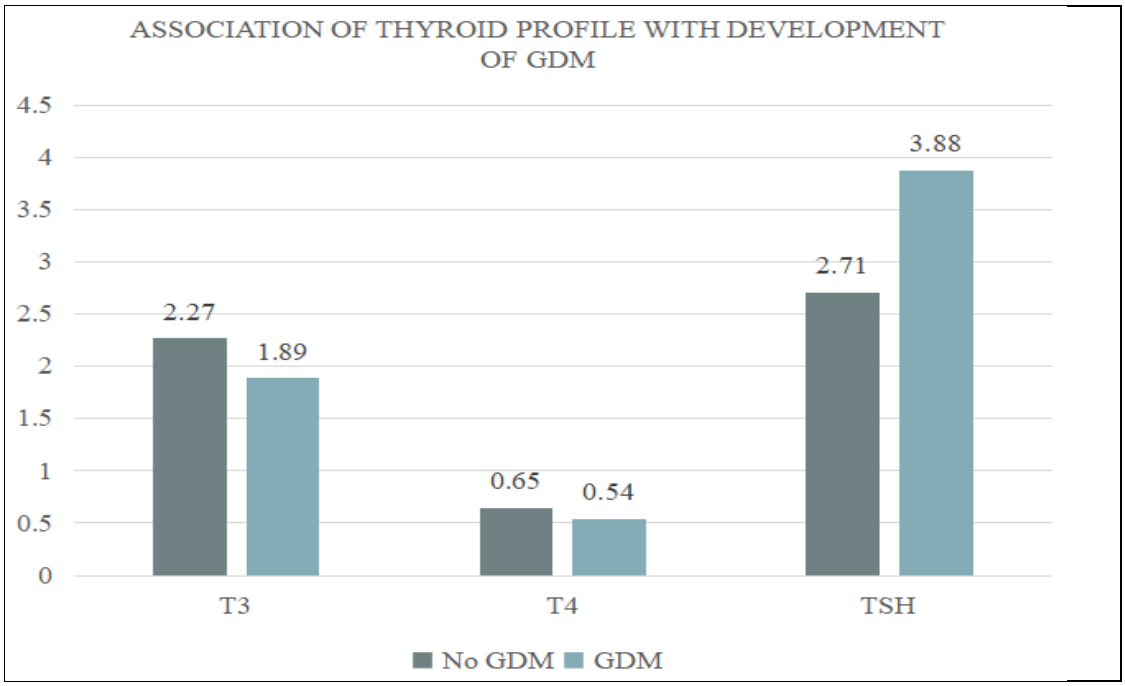

Figure 2: Association of thyroid profile with development of GDM

	P value	Adjusted Odds ratio	95% CI	
			Lower	Upper
Age in years	**0.001**	**1.20**	**1.10**	**1.31**
BMI	0.18	1.11	0.94	1.31
T3	0.31	.77	0.47	1.27
T4	0.81	0.85	0.23	3.09
TSH	**0.001**	**1.487**	1.16	1.89

Table 5: Multivariate logistic regression analysis for predictor of GDM

After doing multivariate analysis, age in years [adjusted odds ratio -1.20 (95% CI:1.10-1.31)] and TSH level [adjusted odds ratio -1.48 (95% CI:1.16-1.89)] were found to be significant predictor of GDM (Table 5).

Discussion

Carbohydrate intolerance is one of the most common metabolic complication that occurs during pregnancy and along with thyroid dysfunction constitutes for the most predominant endocrinopathies that influence the pregnancy outcomes. Various studies had been done worldwide and still ongoing to identify the risk factors in pregnant female that leads to development of GDM and to improve the fetal and maternal outcome. The screening for GDM in women having significant risk factors allows a swift initiation of diet, insulin treatment, or both as required and the decline of both maternal and fetal morbidity during gestation. It has been shown that hypothyroidism negatively affected glucose

homeostasis by inducing insulin resistance. It is well known that marked insulin resistance progressively increases with gestational age during pregnancy. Because of the similar effects of thyroid hormone and pregnancy on glucose metabolism, it seems reasonable to presume that women with either abnormally high or low levels of thyroid hormones would be more likely to develop gestational diabetes.

The main observation in our study is the association between higher TSH values and occurrence of GDM during pregnancy. The prevalence of GDM was observed significantly higher in the hypothyroid group where 33 patients (15.7%) developed GDM when compared to the euthyroid group where only 12 (5.7%) patients were diagnosed with GDM. The relative risk in the present study for development of GDM during their present pregnancy was calculated to be 1.98 (95% CI: 1.20-3.24) and was found to be significant.

This conclusion was also made by a study conducted in 2012 in 24,833 pregnant patients by Carmen M. Tudela et al [7]. They observed a positive association between increasing serum thyrotropin concentrations and the likelihood for having gestational diabetes. Their study supported the finding that subclinical hypothyroidism poses a significantly greater risk for GDM when compared with the cohort of euthyroid women.

Our present study correlated lower levels of T3 and T4 with the incidence of GDM. The mean T3 and T4 levels in GDM were 1.89±0.81 & 0.54±0.30 respectively when compared to 2.27±0.90 & 0.65±0.27 in patients without GDM. A study done in Chinese population by Shuai Yang et al in 2016, also observed a similar association between lower levels of FT4 in early pregnancy in women with GDM than in non-GDM women ($p = 0.24$ and $p<.0001$) and concluded that FT4 played a significant role in predicting GDM and low levels of FT4 served as an independent risk factor for GDM [8].

P Karakosta and colleagues conducted a study in 1170 pregnant patients in Greece to see an association between thyroid dysfunction and thyroid autoantibodies with risk of gestational diabetes [9]. A per-unit increase in TSH value increased the risk of GDM and the relative risk calculated by them was 1.1 for the occurrence of gestational diabetes mellitus in hypothyroid women. Also, in this same study, presence of TPO antibody was associated with higher risk of GDM.

A recent study by Deng et al, conducted in 2019 correlated thyrotropin and TPO antibody to the development of GDM [10]. A positive correlation was found between TSH and TPO antibody for the risk of diabetes. A parallel observation was made by Ying et al in 2016 between thyroid profile and TPO antibody status with occurrence of GDM and higher TSH combined with positive TPO antibody status was associated with a three-fold increased risk of GDM [11].

In antenatal women with thyroid disorders, especially hypothyroidism there is higher incidence of impaired glucose tolerance. Das Bishnu Prasad et al observed more incidence of GDM in hypothyroid group (8%) as compared to the control group (1%) ($p =0.0349$) [12]. This finding can also by deduced from the present study where OGTT levels in hypothyroid group was 119.23±22.53 while OGTT levels in euthyroid group was 112.21±18.95. There was a significant difference between the 2 groups in terms of OGTT values where hypothyroid group had significantly higher level of glucose impairment (p value $=0.001$).

In 2020 Fahimeh Hassani et al suggested in their study that thyroid dysfunction is more common in women with GDM as compared to the non-diabetic pregnant women which was also consistent with the findings of the present study [13]. The study also concluded that hypothyroidism is associated with the higher levels of TPO antibody, but it had no major clinical significance and does not define any fetal or maternal complication and findings were comparable to the present study where no statistically significant association was found between the levels of TPO antibody positivity and the incidence of GDM (p value $= 0.31$).

A retrospective study of 2849 Chinese pregnant women in 2022, done by Geng-dong et al to assess the relation of thyroid dysfunction and GDM concluded that negative association between the TSH concentration or hypothyroid status and GDM which were not consistent with the findings of the present study in-which a positive association was found [14].

A latest study was published by Praktuti Dash et al in 2022, done in 382 pregnant women in India in tertiary care hospital and observed that both subclinical hypothyroidism and gestational diabetes mellitus can progress to overt clinical conditions subsequently and both conditions can have adversely affected maternal and fetal outcome [15]. Therefore, there is a need for vigilant screening and monitoring of the patients associated with GDM and subclinical hypothyroidism so that in the subsequent pregnancies both the mother and the fetal can have a better outcome.

Our study provides a substantiation that proves a direct correlation between increasing serum thyrotropin concentrations and the probability of having GDM.

Conclusion

There were more patients of hypothyroidism with high BMI as (N=32, 15.2%) compared to euthyroid patients (N=15, 7.1%). The mean T3 and T4 level were significantly lower in GDM patients as compared to patients without GDM. Mean TSH level was significantly higher in GDM study group when compared to patients without GDM. After doing multivariate analysis, we can conclude hypothyroidism is a predictor of GDM.

Limitation

Limitation of the study was that the Sample size of the study was only 410, which was very less compared to other studies to affirm the correlation between TSH levels and gestational diabetes mellites.

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