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Study of Subclinical Hypothyroidism and It's Association with Anti-Thyroperoxidase Antibody and Gestational Diabetes Mellitus in Pregnant Women

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Abstract

Background: Subclinical hypothyroidism (SCH) and gestational diabetes mellitus (GDM) are common endocrinological disorders related to pregnancy. Raised anti-thyroperoxidase antibody (Anti-TPO Ab) titer increases the risk of progression of subclinical hypothyroidism into overt hypothyroidism. Both conditions are known to affect maternal and fetal outcomes adversely.

Aim and Objective: To determine the prevalence of subclinical hypothyroidism in pregnant women and it's association with anti-thyroperoxidase antibody and gestational diabetes mellitus.

Methods: This cross-sectional study was conducted in department of obstetrics and gynaecology in SMS medical college, Jaipur from November 2022 till March 2024. Pregnant women coming for their antenatal check-up and fulfilling the inclusion criteria were included, after taking informed and written consent. Thyroid profile (S. TSH, Free T4, Anti-TPO Ab) and 2hr, 75gm, oral glucose tolerance test were performed. The result obtained were analyzed in SPSS.

Results: showed the prevalence of subclinical hypothyroidism was 40.56%, out of that 45.20% were anti-thyroperoxidase antibody positive. In our study the prevalence of GDM was 11.11%. Among SCH patients, 19.18% had glucose levels between 140-199 mg/dl compared to 5.6% euthyroid patients who had level between this range. Conversely, 80.82% SCH patients had levels below 140 mg/dl, while 94.39% euthyroid patients had glucose levels below 140mg/dl. The relative risk of developing GDM with SCH is 3.42 (95% CI: 1.38–8.49), with a p-value of 0.008 which was statistically significant.

Conclusion: Our study showed high prevalence of subclinical hypothyroidism in pregnant women. A

significant number of SCH cases were associated with elevated anti thyroperoxidase antibodies titres. Our study found a significant association between SCH and GDM.

Keywords: SCH, Anti-TPO Ab, Pregnancy, GDM, OGTT, S.TSH, FT3, FT4

Introduction

Subclinical hypothyroidism (SCH) in pregnancy is characterized by elevated serum thyroid-stimulating hormone (TSH) levels beyond the upper threshold of the pregnancy-specific reference range, while free thyroxine (FT4) levels remain within the pregnancy-specific reference range[1]. It has been suggested that the anti-thyroperoxidase (anti-TPO Ab) antibody, may impact foetal growth[2]. Euthyroid pregnant women with elevated anti-TPO antibody titers have been associated with several adverse obstetric and foetal outcomes.[3]

The prevalence of Gestational diabetes mellitus is ranging from 9.4% to 10.6%,[4] and is linked to various adverse outcomes for both the fetus and the mother.

Insulin resistance has been correlated with autoimmune thyroid dysfunction, indicated by elevated anti-thyroid peroxidase antibody levels, suggesting a possible association between autoimmune thyroid dysfunction and GDM. While some studies have reported an increased risk of GDM with hypothyroidism and elevated anti-TPO antibody levels,[5] others have found no significant association between GDM and autoimmune thyroid disorders during pregnancy.

Yang et al., in their meta-analysis, demonstrated a significant but not robust association between thyroid antibodies and GDM risk.[6]

In the study by Prasad et al., the prevalence of GDM was 8% in pregnant women with hypothyroidism compared to 1% in the control group, with a statistically significant p-value of 0.034.[7]

Conversely, Shahbazian et al. found that the incidence of thyroid disorders in the case group was lower than in the control group (4.5% vs. 8.6%).[8]

Furthermore, Sharifi et al. reported that the odds ratio for individuals with GDM to develop clinical hypothyroidism was lower than that of the control group.[9]

Moreover, there is a lack of comprehensive data on the prevalence of hypothyroidism and autoimmunity in women with gestational diabetes mellitus (GDM). Therefore, the study aimed to investigate the prevalence of subclinical hypothyroidism (SCH) during pregnancy and its relationship with Anti-TPO Ab levels and the occurrence of gestational diabetes mellitus.

Materials and Methods

This hospital based observational study was a cross - sectional study conducted in the department of obstetrics and gynaecology and 180 eligible pregnant women coming for antenatal checkup (ANC) between 24-34 weeks of gestation were enrolled in the study.

Apparently healthy pregnant women aged between 21-40 years, singleton live pregnancy between 24-34 weeks gestational age, body mass index (BMI) < 25 provided informed and written consent were included in the study.

Women with pre-pregnancy diabetes or thyroid disorders or other endocrine disorders or surgical history related to the thyroid, having family history of thyroid disease or taking hormone drugs that affect thyroid function and patients with polycystic ovarian syndrome, conceived by assisted reproductive technique were excluded from the study.

After institutional ethical committee approval detailed history was taken, general and obstetric examination was done. Thyroid profile (S. TSH, Free T4, Anti-TPO Ab) and 2hr, 75gm, oral glucose tolerance test were performed. Thyroid profiles were done by the

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chemiluminescence method in MAGLUMI Fully automated chemiluminescence immunoassay (CLIA) analyzer.

Quantitative analysis of thyroid hormone was performed by using trimester specific reference range for S. TSH during pregnancy. For this study, upper limit value for S.TSH was taken as < 3mIU/ml (for second and third trimester). Patients with TSH levels higher than this upper limit and normal freeT4 levels was diagnosed with Subclinical hypothyroidism. Anti-TPO level < 60 U/L was taken as normal upper limit. Level more than 60U/L was considered a raised anti-TPO titer. GDM was diagnosed using 2hr, 75gm, oral glucose tolerance test with DIPSI criteria. Outcome variables was Subclinical hypothyroidism (SCH), with or without positive Anti-TPO Ab and Gestational diabetes mellitus with or without SCH.

Data was entered in the excel sheet, tabulated and analysed using SPSS version 22.0. Quantitative data was summarized using mean and standard deviation. Qualitative data was summarized in percentage and proportion. Significance of difference of proportion was calculated by 'Chi square test'. Significance of difference in mean +/- standard deviation was calculated by 'student t test' and ANOVA test. P value <0.05 was considered as statistically significant.

Observations and Results

Table 1: Prevalence of Subclinical Hypothyroidism

TSH	No of patients	Percentage
Euthyroid	107	59.44
SCH	73	40.56

Here, 107 patients (59.44%) were euthyroid, while 73 (40.56%) had subclinical hypothyroidism (SCH).

Table 2: Prevalence of Gestational Diabetes Mellitus

2 Hrs 75gm Oral Glucose tolerance test	No of patients	Percentage
<140 mg/dl	160	88.89
140-199 mg/dl	20	11.11
>199 mg/dl	0	0.00
Total	180	100.00

The results of the 2-hour 75g Oral Glucose Tolerance Test (OGTT) showed that 160 patients (88.89%) had blood glucose levels less than 140 mg/dl. 20 patients (11.11%) had blood glucose levels between 140-199 mg/dl, indicating impaired glucose tolerance.

Table 3: Distribution of patients according to Thyroid stimulating hormone and Anti- Thyroperoxidase Antibody (Anti-TPO Ab)

Thyroid stimulating hormone	ANTI THYROPEROXIDASE ANTIBODY			
	<60U/L (138)		≥60 U/L(42)	
	No. of Patients	Percentage	No. of Patients	Percentage
Euthyroid	98	91.58	9	8.41
Subclinical Hypothyroidism	40	54.79	33	45.20

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In analysis, among patients with Anti TPOAb levels less than 60U/L (n=138), 98 (91.58%) were euthyroid and 40 (54.79%) had subclinical hypothyroidism (SCH). Conversely, in the group with Anti-TPOAB levels greater than or equal to 60U/L (n=42), 9 (8.41%) were euthyroid and 33 (45.20%) had SCH.

Table 4: Relative risk of Gestational Diabetes Mellitus compared with Subclinical Hypothyroidism and controls (no SCH).

Parameter		Subclinical Hypothyroidism	Euthyroid
2 HRS 75gm OGTT	≥ 140-199 mg/dl	14	6
	<140 mg/dl	59	101
Relative Risk of Gestational Diabetes Mellitus		3.42	
95% CI (Confidence interval)		1.3782 to 8.4875	
P-value		0.0080	

In the context of gestational diabetes mellitus (GDM) and thyroid function, the data showed that 14 patients with subclinical hypothyroidism (SCH) had glucose levels between 140-199 mg/dl, compared to 6 euthyroid patients in the same range. Conversely, 59 SCH patients had glucose levels below 140 mg/dl, while 101 euthyroid patients fell into this category. The relative risk of developing GDM associated with SCH was 3.42 (95% CI: 1.38 to 8.49), with a statistically significant p-value of 0.008.

Table 5: Relative risk of Gestational Diabetes Mellitus compared with Subclinical Hypothyroidism with Anti-Thyroperoxidase antibody positive and Subclinical Hypothyroidism with Anti-Thyroperoxidase antibody negative

Parameter	SCH with ATPO positive	SCH with ATPO negative
GDM	4	10
Non GDM	29	30
Relative Risk of GDM	0.48	
95% CI	0.244 - 1.384	
P-value	0.22	

In patients with subclinical hypothyroidism (SCH), those who were anti-thyroid peroxidase antibody (ATPO) positive, 4 had gestational diabetes mellitus (GDM) while 29 had no GDM. Those who had SCH with ATPOAB negative status, 10 had GDM while 30 patients had no GDM. The relative risk of GDM in patients with SCH and ATPO positivity was 0.48, indicating a lower risk of GDM in this group compared to those who are ATPO negative.

Discussion

This study focused on assessing the prevalence of subclinical hypothyroidism (SCH) in pregnant women at a tertiary level hospital. The study also aimed to evaluate the occurrence of elevated anti-thyroid peroxidase antibody (anti-TPO Ab) titre and to explore relationship between gestational diabetes mellitus (GDM) with SCH.

In present study, 59.44% of patients were euthyroid, while 40.56% had subclinical hypothyroidism (SCH). So in our study prevalence of SCH was 40.56%.

In our study we found a comparatively higher prevalence of SCH which is almost similar to the study done by Dash P et al.[10] reported a prevalence of SCH in pregnancy of 37.69% (144 out of 382 participants). But this prevalence is quite high compared to other studies. Martínez P F et al.[11] found SCH in 284 patients and euthyroidism in 1,267 patients (prevalence 18.31%).

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Yanachkova V et al.[12] reported 142 cases of SCH and 407 cases of euthyroidism (prevalence 25.86%).

In the present study, the 2-hour 75g Oral Glucose Tolerance Test (OGTT) revealed that 88.89% of patients had blood glucose levels below 140 mg/dl, while 11.11% had levels ranging from 140-199 mg/dl, indicating impaired glucose tolerance. No patients had levels exceeding 199 mg/dl.

In our study the prevalence of GDM was similar to the study conducted by Dash P et al[10] GDM prevalence of 12.04%. Saeedi et al[13] (2021) reported the global prevalence of GDM was 14.7%. Based on the International Association of diabetes and pregnancy study groups (IADPSG) criteria the most used screening method world-wide.

In our analysis of TSH and anti-thyroid peroxidase antibodies (Anti-TPOAb), among patients with anti-TPO Ab <60IU/ml (n=138), 91.58% were euthyroid and 54.79% had SCH. For anti-TPO Ab ≥60 (n=42), 8.41% were euthyroid and 45.20% had SCH.

The percentage of SCH cases having anti-TPO antibody positive was found lower than many other studies but closer to the study done by Dash P et al[10] observed among 382 patients, 238 were euthyroid with 27.73% having anti-TPO titers >60 U/L. Among 144 SCH patients, 49.31% had anti-TPO titers >60 U/L. Mandal et al[14] reported 32.94% SCH in pregnant mothers, with 33.93% of SCH women having positive anti-TPO Ab.

Huang K et al[15] found among 242 euthyroid individuals, 30% had ATPOAB values >60 U/L, while 71.4% of 112 SCH individuals had ATPOAB values >60 U/L. Compared to Gayathri et al[16]., Aggarwal et al[17]., and Dhanwal et al[18], our study had a lower percentage of SCH cases with anti-TPO positivity, likely due to iodine deficiency being the primary cause.

We observed that 14 SCH patients had glucose levels between 140-199 mg/dl, compared to 6 euthyroid patients. Conversely, 59 SCH patients had levels below 140 mg/dl, while 101 euthyroid patients had glucose levels below 140mg/dl. The relative risk of developing GDM in SCH is 3.42 (95% CI: 1.38–8.49, p = 0.008).

Ozisik H et al[19] identified SCH as a GDM risk factor, noting hypothyroxinemia's role in GDM development. Deng S Q et al[20] found that TSH(H) (high S.TSH) women had a higher GDM risk (P = 0.0015, OR: 2.09, 95% CI: 1.34– 3.28) and that increased TSH levels correlated with higher GDM risk in later pregnancy. Huang K et al[15] reported incidence of GDM 14.90%. Indicated a nonlinear relationship between TSH level and GDM (p <0.05); when S. TSH level less than or equal to 1.24miu/L, the occurrence of GDM was elevated with increasing S.TSH levels but when S.TSH > 1.24 mIU/L this trend was not obvious. Shuang et al[21] noted that GDM risk increased 1.15 times per year for women aged ≥35. Pregnant women with SCH have a 50% increased GDM risk compared to euthyroid women.[21] Ying H et al[22] showed subclinical hypothyroidism in early pregnancy is linked to increased GDM risk.

In our analysis, among SCH patients 4 ATPO-positive patients had gestational diabetes mellitus (GDM) compared to 10 ATPO-negative patients. Among SCH patients, 29 ATPO-positive individuals had no GDM versus 30 ATPO-negative individuals. The relative risk of GDM in ATPO-positive SCH patients is 0.48, indicating a lower risk compared to ATPO-negative ones. Our results were similar to the study done by Dash P et al, Sharman F et al.

Dash P et al[10] found no increased GDM risk with SCH and raised anti-TPO Ab titer. Relative risk assessment showed no significant value, contrary to many studies documenting increased GDM risk with high anti-TPO Ab

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titers during pregnancy.[10] Sharmen F et al[23] found no significant relative risk of GDM with elevated anti-TPO Ab titer (p>0.05).

Huang K et al[15] found women with isolated positive anti-TPOAb had a higher GDM risk, with RR (95%CI) of 2.603 (1.067–6.351). After adjusting for variables, RR (95%CI) for TPOAb was 2.541 (1.037–6.226). Zhou Y et al[24] found that GDM risk is positively correlated with SCH and TPOab (+), increasing GDM risk by 3.646 times for TPOab (+) and 3.08 times for SCH. A meta-analysis[25] showed SCH increased GDM risk by 1.558 times. TPOab (+) is a specific indicator of autoimmune thyroid disease and predicts GDM risk.

Conclusions

Our study showed high prevalence of subclinical hypothyroidism and it’s association with elevated anti-thyroid peroxidase antibody titer, and high prevalence of gestational diabetes mellitus along with significant association between SCH and GDM.

Routine screening for thyroid status, GDM, Anti-TPO Antibody in all pregnant patients is required.

Timely diagnosis and treatment of these two conditions can have good impact on maternal and foetal outcomes.

Limitations

The study was conducted at a single centre and was hospital based, meaning it’s results cannot be generalised to the broader community.

Conducting the study on a larger scale could lead to more robust conclusions and greater impact.

As it was a cross-sectional study, not good for causal association.

So further longitudinal studies with larger cohort may help to establish a causal association between the two most common endocrine disorders observed during pregnancy.

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