

Gestational Diabetes Mellitus with autoimmune subclinical hypothyroidism in pregnancy in relation to gravida

Prakruti Dash¹, Rajlaxmi Tiwari¹, Saurav Nayak¹, Saubhagya K. Jena²,
Manaswini Mangaraj¹

Departments of ¹Biochemistry and ²Obstetrics and Gynecology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) and hypothyroidism are the most common endocrinological abnormalities associated with pregnancy. The association of gravida with incidence of autoimmune subclinical hypothyroidism (SCH) and GDM in pregnancy has not been studied extensively with availability of very limited data in this context. So, this study was done to find out the association between GDM and autoimmune SCH in pregnancy as per gravida status of the study population. **Materials and Methods:** 382 antenatal cases, both primi and multigravida, were screened for thyroid dysfunction and GDM in their first ANC coming to a tertiary level health care institution. 75 gm GCT was used for diagnosis of GDM and serum TSH, FT4, and anti-TPO antibody were measured for assessment of thyroid dysfunction. Prevalence of SCH was evaluated taking the ATA 2011 guidelines. Data obtained was also compared with ATA 2017 recommendations. Anti-TPO antibody level more than 60 U/L was considered to be raised value. **Observation:** The percentage of GDM was higher in autoimmune SCH participants compared to euthyroid cases with raised anti-TPO Ab Titer. GDM, SCH, and raised anti-TPO Ab titer were overall more prevalent in multigravida cases compared to primigravida participants. **Conclusion:** GDM and SCH with high anti-TPO Ab titer were more prevalent in multigravida participants compared to primigravida cases though not statistically significant. As occurrence of SCH varies with nutritional and geographical factors, hence internal trimester specific range should be calculated and used in practice as recommended by ATA 2017 guidelines.

Keywords: Anti-TPO Ab, ATA guidelines, GDM, prevalence, SCHs

Introduction

Incidence of high-risk pregnancies and associated adverse fetal outcomes are high in India which needs more close monitoring, regular checkups, and adequate antenatal checkups and institutional care. Gestational diabetes mellitus (GDM) and subclinical hypothyroidism (SCH) are commonly associated with pregnancy

and contribute to adverse maternal and fetal outcomes putting them into high risk category. Incidence of high-risk pregnancies are affected by socioeconomic status and access to health care and lack of proper education regarding the associated endocrinal disorders.^[1]

In India, the prevalence of GDM is 4--18%.^[2,3] GDM has been found to be related to gravida with prevalence more in multigravida cases compared to primigravida women in some studies.^[4,5] Progression of GDM to T2DM vary between 2.6% and 70% within a follow-up period of 6 years to 28 years after the first pregnancy as reported in studies.^[6,7]

Address for correspondence: Dr. Prakruti Dash,

Department of Biochemistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha - 751 019, India.

E-mail: biochem_prakruti@aiimsbhubaneswar.edu.in

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Prevalence of clinical hypothyroidism is 1--5% and SCH is 4% up to 40% as per various documented statistics from India.^[8-14] The risk of SCH progression to overt hypothyroidism is 2--6% per year. The risk is higher in women when the TSH level is greater than 10 mIU/ml and associated with raised titer of anti-TPO antibody.^[15] Diseases having an autoimmune basis, many often running in families, mainly affect women in their reproductive years and has a substantial effect on reproductive outcomes.^[16] Autoimmune hypothyroxinemia is registered to be more commonly associated in pregnancy with high titer of anti-TPO antibody.^[17]

Frequent screening is advocated for high-risk groups such as high-risk pregnant women since undetected SCH and the presence of thyroid autoantibodies during pregnancy may adversely affect the survival of the fetus.^[18]

Few studies have documented a positive association between autoimmune hypothyroidism and GDM.^[19-21] Causal association between both the conditions is seen in pregnancy being contributed by autoimmunity and some common factors resulting in adverse maternal and fetal outcome. Again, the frequency of their appearance together may affect further on subsequent pregnancy to both mother and fetus as both the conditions progresses and predisposes to clinical T2DM and overt hypothyroidism with time. Not much data is available on the association between autoimmune SCH, GDM in relation to gravida of pregnancy.

Hence, with the hypothesis that autoimmune SCH and GDM possess relation with gravida of pregnancy, this study was conducted to appraise any association between GDM, SCH, and raised anti-TPO antibody titer in relation to the gravida status of the study participants.

Materials and Methods

This study was a cross-sectional study done in the department of Biochemistry in collaboration with Department of Obstetrics and Gynecology. Apparently, healthy pregnant women both primigravida and multigravida with singleton pregnancy in their first antenatal checkup were included. The study proposal was approved by the Institute Ethics Committee and written informed consent was obtained from all participants.

Exclusion criteria

Known case of thyroid diseases or any other endocrine disorders, pre-existing Diabetes mellitus, hormone replacement therapy, other metabolic or chronic disorders, multiple pregnancies and bad obstetric history with a known cause were excluded from this study.

After general and gynecological examination, fasting blood samples was collected and analyzed for 75 gm GCT and Thyroid profile (TSH, fT4, Anti-TPO antibody) from 382 pregnant women coming for their first antenatal checkup.

The biochemical parameters were done with commercially available kits in Beckman Coulter 5800 Autoanalyzer. Thyroid profile was done by Chemiluminescence method in Siemens Advia Centaur Immunoassay analyzer. TSH value more than the trimester specific level with a normal fT4 value were diagnosed as cases with SCH. For this study, the prevalence of SCH in pregnancy was calculated as per both ATA 2011 and ATA 2017 guidelines and analysis was made between the number of cases fulfilling the two guidelines. ATA 2011 guidelines recommended the TSH cut off to be 2.5 mIU/mL for first trimester and 3 mIU/mL for second and third trimester.^[22] In India, the current practice is to use the reference limits set by ATA as per 2017 guidelines with an upper reference limit of ~4.0 mIU/mL.^[23]

Anti-TPO level <60 U/L was taken as normal upper limit as per manufacturer's protocol. Level more than 60 U/L is considered as raised anti-TPO antibody titer. For 75 gm GCT, fasting blood sugar (FBS) more than 92 mg% and 2-h post glucose blood sugar (PGBS) more than 153 mg% were diagnosed as GDM as per IADPSG guidelines.^[24] Association of GDM, SCH, and raised anti-TPO antibody titer was evaluated in relation to gravida status of the participants. All the results obtained were statistically analyzed with SystatVersion 13.2.

Observations

In our study, there were 234 (61.25%) multigravida cases and 148 (38.74%) primigravida participants. The prevalence of SCH in our study was found to be 37.59% as per ATA 2011 guidelines [Figure 1]. We calculated the prevalence considering ATA 2017 guidelines with upper normal limit of TSH in all trimesters as 4 mIU/mL and the prevalence was observed to be 14.39%. Looking at the gross difference in the two prevalence rates as per the two guidelines, it appears logical to have the internal trimester specific range to prevent over and under diagnosis of SCH in pregnancy. To generate the internal trimester, specific range has also been recommended by ATA 2017 guidelines.

Number of participants with SCH and raised anti-TPO Ab titer (autoimmune SCH) was observed to be in higher in

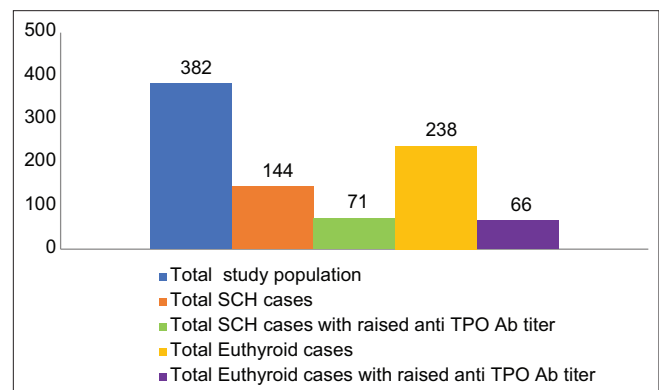


Figure 1: Prevalence of SCH and raised anti TPO Ab in the study population

multigravida cases ($n = 41$) compared to primigravids ($n = 30$). We also registered a higher number of euthyroid cases with raised anti-TPO Ab titer in multigravidas ($n = 50, 21.26\%$) compared to primigravids ($n = 16, 10.8\%$) [Table 1].

Occurrence of GDM was also found to be higher in multigravida cases (12.39%) compared to primigravida participants (11.48%) in our study [Table 2]. Similarly, GDM with SCH having raised anti-TPO titer was also seen to be more frequent in multigravida cases than the primigravids. GDM with only raised anti-TPO Ab titer was also found to be more in numbers in multigravida participants in comparison to primigravida women in our study population [Figure 2].

Compared to GDM with normal anti-TPO titer, TSH and FT4 values were higher in GDM with raised anti-TPO Ab titer and it was found to be statistically significant ($P < 0.01$) [Table 3].

Discussion

GDM and SCH are the most frequent endocrinal abnormalities in pregnancy. Both the disorders are associated with adverse obstetric outcomes and fetal abnormalities. SCH in mother during pregnancy is associated with mental sluggishness of the child as per literature.^[25] GDM during pregnancy increases the risk of development of Type 2 Diabetes Mellitus subsequently.^[6,7,26,27] Similarly, SCH predisposes to overt clinical hypothyroidism in future and more so in subsequent pregnancies.^[15,28] Raised anti-TPO Ab titer is an influencing factor for development of overt hypothyroidism in future.^[29,30] In this context, we can hypothesize that multigravida cases will be more affected than primigravida women and few studies have also documented the same.^[31,32] but not enough data is available to substantiate this association.

Similarly, raised anti-TPO Ab titer resulting in autoimmune hypothyroidism has been documented in many literatures as a risk factor for development of GDM in pregnancy.^[19,20,21,33]

In our study, along with prevalence of SCH and autoimmune SCH in the study population, we have evaluated the association of GDM in autoimmune SCH in pregnancy by measurement of anti-TPO Ab titer. We also assessed the difference in prevalence of SCH and GDM in relation to anti-TPO Ab titer as per gravida status of the study population.

Prevalence of SCH in our study was documented to be 37.59% as per ATA 2011 criteria.^[22] We also calculated the prevalence taking into consideration ATA 2017 guidelines^[23] and was found to be 14.39% [Figure 1].

Prevalence of SCH in various studies has been varying from 4 to 40%. Many of the studies have taken 4 mIU/mL or 4.5 mIU/mL as cut off of TSH for diagnosis of SCH and documented a lower prevalence than found in our study (as per ATA 2011)^[11,12] but it is at par with the prevalence that we have calculated

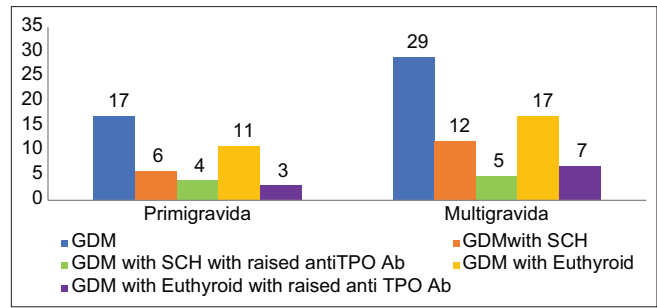


Figure 2: Occurrence of GDM in association with SCH and raised anti-TPO titer as per gravida

Table 1: Percentage of occurrence of SCH and raised anti-TPO Ab titer as per gravida in the study population

| Gravida | Parameters | Frequency | Percent Value |
|----------------------|--------------------------------------|-----------|---------------|
| Multigravida (n=234) | Euthyroid Patient with ATPO Negative | 102 | 43.590 |
| | Euthyroid Patient with ATPO Positive | 50 | 21.368 |
| | SCH Patient with ATPO Negative | 41 | 17.521 |
| | SCH Patient with ATPO Positive | 41 | 17.521 |
| | Total | 234 | 100.000 |
| Primigravida (n=148) | Euthyroid Patient with ATPO Negative | 70 | 47.297 |
| | Euthyroid Patient with ATPO Positive | 16 | 10.811 |
| | SCH Patient with ATPO Negative | 32 | 21.622 |
| | SCH Patient with ATPO Positive | 30 | 20.270 |
| | Total | 148 | 100.000 |

Table 2: Participants with occurrence of GDM as per gravida

| Gravida | GDM + | GDM - | P |
|---------|-------------|-------------|------|
| Primi | 17 (11.48%) | 131 (88.5%) | 0.79 |
| Multi | 29 (12.39%) | 205 (87.6%) | |

Table 3: Comparison between GDM and Normoglycemic Patients for ATPO data

| Variables | ATPO Positive | ATPO Negative | P |
|----------------|------------------|------------------|-------|
| GDM Positive | | | |
| TSH | 3.34 (0.30-6.38) | 1.85 (0.47-3.23) | 0.051 |
| FT4 | 1.18 (0.91-1.45) | 1.04 (0.85-1.43) | 0.017 |
| Normoglycaemic | | | |
| TSH | 2.62 (0.42-4.82) | 2.13 (0.33-3.53) | 0.517 |
| FT4 | 1.18 (0.86-1.34) | 1.15 (0.87-1.43) | 0.219 |

taking 4 mIU/mL as the cut off (ATA 2017). Mandal *et al.*^[14] has compared their results taking two cut off of 2.5 mIU/mL and 4.5 mIU/mL for TSH and registered their prevalence rates as 32.94% and 13.92%, respectively, which is similar to our observations. Looking at the gross difference in prevalence rate as per the two guidelines, it is very likely that there may be either over or under identification of prevalence of SCH in pregnancy with ATA 2011 and ATA 2017 guidelines. Thyroid dysfunction is known to be affected by geographical and nutritional factors.^[9] From our results we may conclude that it is vital to have internal trimester specific range to avoid over or under diagnosis of

Thyroid disorders which is also a recommendation for ATA 2017 guidelines.

In our study, occurrence of SCH with raised anti-TPO Ab titer (autoimmune SCH) was registered to be 49.30% [Figure 1]. This is in accordance with observations made by Mandal *et al.*^[14] and Gayathri *et al.*^[29] Autoimmune thyroiditis resulting in hypothyroxinemia is common next to Iodine deficiency and with fortification of food with Iodine, antibodies against Thyroperoxidase enzyme and Thyroglobulin is considered to be the most common cause of decreased thyroid hormone levels.^[30,32] In our study, 21.36% multigravida participants and 10.81% primigravida participants were found to be euthyroid with raised anti-TPO Ab titer [Table 1]. As presence of these autoantibodies predisposes to overt clinical hypothyroidism in future, hence careful monitoring of these cases is required in future, particularly in future pregnancies for early detection and intervention to avoid obstetric and fetal adversities.^[34-36]

The prevalence of GDM in our study was found to be 12.04%. Number of GDM cases with SCH and raised anti-TPO ab titer was registered to be 9 out of the total 46 cases. The prevalence of GDM, SCH, and raised anti-TPO Ab titer was seen to be higher in multigravida cases ($n = 17$) compared to the primigravida participants ($n = 10$) [Table 2, Figure 2]. This is in accordance with other studies that also documented occurrence of GDM and SCH to be higher in multigravida women compared to primigravida cases.^[21,37] The difference in TSH, fT4, and anti-TPO Ab titers was statistically significant between GDM cases compared to normoglycemic cases [Table 3]. This observation is in accordance with that of Nemani *et al.*^[21] and Koner *et al.*^[37]

Anti-TPO antibody acts against Thyroperoxidase enzyme which is responsible for oxidation of Iodine trapped after which it can bind with Tyrosine molecules to form Monoiodotyrosine and Diiodotyrosine for synthesis of thyroid hormones. Once formed, it gradually increases in titer and hampers synthesis of Thyroid hormones T4 and T3 eventually leading to hypothyroxinemia which is of autoimmune type. Hence, it can be presumed that raised anti-TPO antibody titer seen in first pregnancy will subsequently increase the severity of thyroid hormone deficiency and affect the progression of the disease process from SCH to overt clinical hypothyroidism. We have observed a greater number of multigravida participants with SCH, raised anti-TPO Ab titer compared to primigravida cases in our study population which corroborates with the above-mentioned phenomenon. Not much data is however available on this aspect.

GDM in first pregnancy increases the risk of development of Diabetes mellitus in the affected women and also the chances of occurrence of GDM is higher in subsequent pregnancies too.^[6,7,26,38,39] In our study, the GDM cases were higher in multigravida cases compared to primigravida participants which supports the observations made by other studies [Table 2].^[40,41] Autoimmune antibodies are a risk factor for development of Diabetes mellitus and GDM as per literatures.^[42] In our study, we

documented cases with GDM having higher titer of anti-TPO Ab compared to the normoglycemic participants cases but the difference was not statistically significant. The TSH value was higher and the fT4 value was lower in GDM cases with raised anti-TPO Ab titer compared to the normoglycemic cases with normal anti-TPO Ab titer [Table 3]. This indicates a progression in the disease process and gradual decrease in thyroid hormone levels with raised anti-TPO Ab titer in the serum. Compared to primigravida participants, a greater number of multigravida cases were found with GDM, SCH, and high titer of anti-TPO Ab, thus supporting the hypothesis that presence of raised titer of anti-TPO Ab predisposes to development of SCH and GDM with the risk increasing with the gravida status. Our result is similar to that observed by Nemani *et al.*^[21] We detected a positive correlation between the three variables and multigravida status but it was however not statistically significant. Smaller sample size may be a factor for the observations not resulting in statistical significance value. However, the difference in the occurrence of GDM and autoimmune SCH in primigravida and multigravida was prominent.

Multiple pregnancies and lack of proper antenatal and post-natal care is a common problem in India and is mostly related to lower socioeconomic status. Hence, proper information regarding concurrent occurrence of common endocrinal abnormalities like GDM and SCH which shows progression from index pregnancy to subsequent pregnancies and are known to adversely affect maternal and fetal health outcome is necessary for the health care providers to properly educate, monitor and give timely care and attention, especially to these high-risk pregnancies.

Conclusion

From our study we conclude that internal trimester specific range for diagnosis of thyroid disorders in pregnancy is important to avoid over or underdiagnosis of thyroid disorders in pregnancy.

The novelty of our study lies in our assessment of the incidence of GDM and autoimmune SCH in relation to gravida status which has not been studied extensively yet and data in this context is very limited. Appearance of a higher number of GDM with autoimmune SCH cases took place in multigravida in our study. Both GDM and SCH, in particular if associated with raised titer of anti-TPO antibody increases the risk of subsequent development of T2DM and clinical hypothyroidism. Both the condition is known to be associated with maternal and fetal adversities. Hence, we suggest for assessment of anti-TPO antibody titer to be included in the profile for GDM and Thyroid screening in antenatal cases. A prospective study with a larger cohort may help to strengthen the observation.

Both SCH and GDM progresses to overt clinical conditions subsequently. Both the conditions lead to maternal and fetal adversities. Careful screening and more vigilant monitoring for GDM and SCH associated with raised titer of anti-TPO antibody are essential for subsequent pregnancies for better maternal and fetal outcome.

Key points

1. Internal trimester specific range for diagnosis of thyroid disorders in pregnancy is important to avoid over or underdiagnosis of thyroid disorders in pregnancy
2. Prevalence of SCH is higher in our geographical area and higher association with anti-TPO antibody is observed
3. GDM and SCH with raised titer of anti-TPO antibody were found to be more in multigravida cases compared to primigravida participants
4. Many euthyroid cases were found to have raised titer of anti-TPO antibody which is known to predispose to clinical and SCH.
5. Hence, along with screening for GDM and Thyroid hormone status, assessment of anti-TPO antibody should also be considered for every antenatal case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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