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ORIGINAL ARTICLE

Association of Thyroid Dysfunction and Autoimmunity in Pregnant Women with Diabetes Mellitus

Hiralal Konar[1] · Madhutandra Sarkar[2,4] · Manas Roy[3]

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About the Author

Prof. (Dr.) Hiralal Konar an educationist and medical practitioner of acclaim, is currently a professor of the Department of Obstetrics and Gynecology, Calcutta National Medical College and Hospital, Kolkata, India. He has served in the capacity of the chairman of the Indian College of Obstetricians and Gynecologists (ICOG) in 2013, the vice president of the Federation of Obstetric and Gynecological Societies of India (FOGSI) in 2008 and as the president of the Bengal Obstetric and Gynecological Society (2008–2009). He represented the committee in India for the Royal College of Obstetricians and Gynecologists (RCOG), London (2004–2010). His work and contribution in the field has been documented in the form of nine textbooks, thirty book chapters and more than hundred research publications in national and international journals.

Hiralal Konar is in the Department of Obstetrics and Gynecology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India. Madhutandra Sarkar is in the Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. Manas Roy is Obstetrician-Gynecologist in Rampurhat Sub-Divisional Hospital, Rampurhat, West Bengal, India.

✉ Madhutandra Sarkar
dr.madhutandra.sarkar@gmail.com

1 Department of Obstetrics and Gynecology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India

2 Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

3 Rampurhat Sub-Divisional Hospital, Rampurhat, West Bengal, India

4 C-64 Swastik Towers, Lanka Main Road (BHU), Varanasi 221 005, Uttar Pradesh, India

Abstract

Purpose This study was undertaken to find out the proportion of women with thyroid dysfunction in pregnancy complicated by diabetes mellitus; to find out the association, if any, of thyroid dysfunction and of antithyroid peroxidase (anti-TPO) antibodies during pregnancy in women with pregestational (PGDM) and gestational diabetes mellitus (GDM); and to find out the maternal and perinatal outcomes of pregnancies complicated by both diabetes mellitus and thyroid dysfunction.

Methods A cross-sectional observational study was conducted in a tertiary care teaching hospital in Kolkata, India, for a period of 1 year. Sixty-four pregnant women with diabetes, both PGDM and GDM, were recruited from the antenatal clinic. They were managed and followed up till 6 weeks postpartum. Their plasma glucose levels were estimated, and thyroid function was evaluated periodically. All relevant data were recorded and analyzed statistically.

Results Most (81.25%) women had GDM. Forty percent women suffered from some form of thyroid disorder, mostly (37.5%) hypothyroidism. Thyroid dysfunction was not associated with the type of diabetes mellitus (GDM or PGDM) ($p > 0.05$). The higher rate of anti-TPO titers was observed in pregnancies with PGDM compared to pregnancies with GDM; however, this difference was not statistically associated ($p > 0.05$). All pregnant women with combined endocrinopathy delivered by cesarean section, and the most common neonatal complication observed was jaundice.

Conclusions Thyroid disorders are quite common during pregnancy complicated by diabetes mellitus. The study findings warrant routine screening for thyroid abnormalities in diabetic pregnant women. These women have increased rate of maternal and neonatal complications.

Keywords Diabetes mellitus · Perinatal outcome · Pregnancy · Thyroid function · Thyroid autoantibody

Introduction

Pregnancy is a state of relative iodine deficiency that might lead to a small physiological goiter in case of deficient dietary intake of iodine. Hypothyroidism occurs in 1% of pregnant women. Hyperthyroidism affects 0.2% of pregnant women; of these, 95% has a diagnosis of Grave's disease, which is an autoimmune disorder [1].

Ninety percent of diabetes mellitus in pregnancy has been classified as gestational (GDM) and 10% as pregestational (PGDM) [2]. Prevalence of PGDM (type 1 or type 2 diabetes) continues to rise largely due to increases in type 2 diabetes associated with obesity. The increased insulin requirement during pregnancy often precipitates diabetes mellitus leading to a diagnosis of GDM [3].

During pregnancy, numerous hormonal changes and metabolic demands occur, which result in complex effects on carbohydrate homeostasis and thyroid function. The presence of thyroid dysfunction may affect the control of diabetes, not only during pregnancy, but also in the postpartum period.

There is inconsistent evidence regarding the association between thyroid dysfunction and diabetes mellitus in pregnant women. However, an autoimmune, multisystem disorder is thought to be the basis of such pathology. Women with DM1 are found to have higher rate (up to 20%) of antithyroid peroxidase (anti-TPO) antibodies than the background population. GDM is associated with many non-organ-specific autoantibodies [4]. High titers of anti-TPO in a pregnancy complicated by diabetes mellitus could potentially further compromise the maternal and perinatal complications. Moreover, there is an increased risk of development of postpartum thyroid dysfunction (PPTD) among pregnant women with positive anti-TPO in pregnancy.

Despite the complexity and potential serious nature/impact of this problem, not enough attention has been paid in India and in this subcontinent to understand the problem.

With the above background, the study was conducted with the following objectives:

1. To find out the proportion of women with thyroid dysfunction in pregnancy complicated by diabetes mellitus.
2. To find out the association, if any, of thyroid dysfunction during pregnancy in women with PGDM and GDM.
3. To find out the association, if any, of thyroid autoantibodies (anti-TPO antibodies) during pregnancy in women with PGDM and GDM.
4. To find out the maternal and perinatal outcomes of pregnancies complicated by both diabetes mellitus and thyroid dysfunction.

Materials and Methods

Type of Study Hospital-based cross-sectional descriptive study.

Place of Study The study was conducted in the Department of Obstetrics and Gynecology, Nilratan Sircar Medical College and Hospital, Kolkata, India.

Duration of Study One year.

Study Population All pregnant women with diabetes (both PGDM and GDM) attending the antenatal clinic of the above-mentioned hospital.

Inclusion Criteria (1) Pregnant women with PGDM who attended the antenatal clinic directly or were referred from the diabetic clinic of the same hospital and (2) pregnant women with GDM diagnosed by a 75 g oral glucose tolerance test (OGTT).

Exclusion Criteria (1) Pregnant women with a negative OGTT, (2) pregnant women without a definite history and documented record of diagnosis for PGDM before pregnancy, (3) pregnant women with a history of thyroid disease, (4) pregnant women receiving any medication that could influence thyroid function or the immune system.

Study Tools (1) A pre-designed and pretested schedule, (2) present and past health records and investigation reports, if any, (3) all antenatal records regarding present pregnancy, (4) investigation reports for thyroid profile and plasma glucose levels during pregnancy and postpartum,

(5) hospital records, (6) stethoscope and sphygmomanometer.

Study Technique (1) History taking and (2) clinical examination and investigations.

Methodology Ethical clearance for doing this study was obtained from the institutional ethics committee. Informed consent to participate in the study was obtained from all the eligible women. All the pregnant women who satisfied either of the inclusion criteria were included in the study. Initially, 70 women were included, who were followed up during the antenatal period, at the time of delivery and up to 6 weeks postpartum. However, 6 women were lost to follow-up. Therefore, 64 women completed the study and had been included in the final statistical analysis.

High-risk conditions for the development of GDM, as considered in this study, were marked obesity, diabetes in a first-degree relative, history of glucose intolerance, previous macrosomic infant (≥4 kg), persistent glycosuria in present pregnancy. Then, high-risk pregnant women were selectively screened for GDM by 50 g glucose challenge test (GCT). The test was considered positive should the plasma glucose level be ≥140 mg/dl. All women with a positive screening test for GDM were evaluated further for diagnosis using a 2-h 75 g OGTT with a threshold plasma glucose concentration of ≥140 mg/dl at 2 h.

At the first antenatal visit, special attention was given to note personal history of DM1 or other autoimmune diseases, family history of any autoimmune disease. During follow-up visits, at 4 weeks or earlier, special attention was given to note any sign or symptom of thyroid disease, particularly any thyroid swelling.

All the selected cases were evaluated properly for thyroid function. Serum free T3 (FT3), free T4 (FT4) and TSH levels were measured at the first antenatal visit, and it was repeated at 20 and 30 weeks of gestation and at or before delivery. Serum anti-TPO antibody level was measured at the first antenatal visit and then at or before delivery. Treatment was initiated for those who were detected with thyroid disorder, and for them thyroid function was monitored every 4 weeks up to 20 weeks, then at 30 weeks of gestation and at 6 weeks postpartum. Plasma glucose (both fasting and postprandial) to titrate the requirement of insulin was measured during pregnancy at an interval of 2 weeks and at 6 weeks postpartum.

For estimating plasma glucose, glucose oxidase–peroxidase method (GOD–POD) was used. Estimation of FT3, FT4, TSH and anti-TPO antibody was carried out by the electrochemiluminescence (ECL) technique using commercially available kits from Roche Diagnostics (Mannheim, Germany) with Elecsys 1010 analyzer. The laboratory reference ranges were: FT3 (3.7–7.2 pmol/L), FT4 (12.0–23.0 pmol/L) and TSH (0.27–4.2 mIU/L). Anti-TPO was considered elevated if level was >34 IU/mL [5]. All the relevant information was recorded in the schedule.

Analysis of Data Data were collated and analyzed statistically by simple proportions, Chi-square and Student's *t* test.

Results

The age of the pregnant women ranged from 20–40 years. Majority of them (39 or 60.94%) belonged to the age range of 25–29 years, followed by 20–24 years (14 or 21.87%), 30–34 years (8 or 12.5%) and 35 years or older (3 or 4.69%). Most of the women were nulliparous (42 or 65.62%). Only 15 women (23.44%) were primiparous, and seven (10.94%) were of parity 2 and above.

Table 1 shows that, among the 64 diabetic pregnant women, 52 (81.25%) had GDM and 12 (18.75%) had PGDM. Twenty-six women (26/64 or 40.62%) suffered from some thyroid disorder. Forty percent women with GDM (21/52) had hypothyroidism, and only two (3.85%) had hyperthyroidism, whereas 25% (3/12) women with PGDM were in the hypothyroid group. However, thyroid dysfunction was not associated with the type of diabetes mellitus (GDM or PGDM) ($p > 0.05$).

Nine women (9/64 or 14.06%) were anti-TPO antibody positive. Five of them (5/9 or 55.56%) suffered from

Table 1 Distribution of pregnant women with diabetes (GDM and PGDM) according to thyroid status ($n = 64$)

Diabetic status	Thyroid status			
	Euthyroid	Subclinical hypothyroid	Hypothyroid	Hyperthyroid
GDM ($n = 52$)	29 (55.77)	7 (13.46)	14 (26.92)	2 (3.85)
PGDM ($n = 12$)	9 (75)	2 (16.67)	1 (8.33)	–
Total ($n = 64$)	38 (59.38)	9 (14.06)	15 (23.44)	2 (3.12)

Figures in the parentheses indicate percentages

$\chi^2 = 0.8$, df = 1, $p > 0.05$

Chi-square test was applied after classifying the thyroid status as euthyroid and thyroid dysfunction

Table 2 Distribution of study population according to anti-TPO antibody status and thyroid status ($n = 64$)

Thyroid status	Anti-TPO antibody status		Total ($n = 64$)
	Positive ($n = 9$)	Negative ($n = 55$)	
Euthyroid	3 (33.33)	35 (63.64)	38 (59.38)
Subclinical hypothyroid	1 (11.11)	8 (14.54)	9 (14.06)
Hypothyroid	4 (44.45)	11 (20)	15 (23.44)
Hyperthyroid	1 (11.11)	1 (1.82)	2 (3.12)

Figures in the parentheses indicate percentages

Table 3 Distribution of pregnant women with diabetes (GDM and PGDM) according to anti-TPO antibody status and thyroid status ($n = 64$)

Anti-TPO antibody	GDM			PGDM		
	Euthyroid ($n = 29$)	Thyroid dysfunction ($n = 23$)	Total ($n = 52$)	Euthyroid ($n = 9$)	Thyroid dysfunction ($n = 3$)	Total ($n = 12$)
Positive	1 (3.45)	5 (21.74)	6 (11.54)	2 (22.22)	1 (33.33)	3 (25)
Negative	28 (96.55)	18 (78.26)	46 (88.46)	7 (77.78)	2 (66.67)	9 (75)
Significance	$\chi^2 = 4.2$, df $= 1$, $p < 0.05$			$\chi^2 = 0.15$, df $= 1$, $p > 0.05$		

Figures in the parentheses indicate percentages

$\chi^2 = 0.4$, df $= 1$, $p > 0.05$

Chi-square test was applied after classifying the diabetic status as GDM and PGDM and anti-TPO antibody status as positive and negative

hypothyroid disorder. Six out of 26 women with thyroid disorder (23.08%) were anti-TPO positive and majority (5/6 or 83.33%) belonged to the hypothyroid group (Table 2).

Table 3 shows that, among the total nine anti-TPO positive women, six (66.67%) suffered from GDM and three (33.33%) from PGDM. Six women with GDM (6/52 or 11.54%) had positive anti-TPO antibody, whereas three women with PGDM (3/12 or 25%) had the same. However, this difference was not statistically associated ($p > 0.05$).

Among the total six anti-TPO positive women in GDM group, five had thyroid dysfunction, i.e., hypothyroidism (4) and hyperthyroidism (1). Among three anti-TPO positive women in PGDM group, one had thyroid dysfunction (hypothyroidism).

Among 29 euthyroid women in GDM group, one had positive anti-TPO. On the other hand, among 23 GDM patients with thyroid dysfunction, five had positive anti-TPO. This difference is found to be statistically significant ($p < 0.05$). However, this difference is not significant in PGDM group ($p > 0.05$).

Table 4 depicts the maternal and neonatal complications. Maternal complications noted were pregnancy induced hypertension, preterm delivery, postpartum hemorrhage and cesarean delivery.

The most common neonatal complication noted was jaundice, 7.9% in diabetes alone group and 19.23% in combined diabetes and thyroid dysfunction group. One woman with both diabetes and thyroid dysfunction delivered a baby with meningocele. One neonate, whose mother had diabetes alone, developed septicemia. Both babies died during the early neonatal period (0–7 days).

Table 5 depicts the perinatal outcome with respect to birth weight, Apgar score and perinatal mortality. The proportions of babies born with low birth weight (<2.5 kg) and mild depression (Apgar score at 1 min of 4–6) were 6.25 and 12.5%, respectively.

Discussion

The risk of thyroid dysfunction during pregnancy increases with the presence of autoantibodies and the frequency rises further when the women suffer with diabetes mellitus. Once a diabetic pregnant woman is anti-TPO positive, she needs long-term follow-up in order to detect any thyroid dysfunction.

In our study, more than 80% women (81.25%) had been diagnosed with GDM and the rest (18.75%) with PGDM. Other studies [4, 6] also showed a considerable proportion of women being diagnosed with both GDM and PGDM. Our findings indicate that the risk of developing glucose intolerance during pregnancy could also be very high in the Indian subcontinent and a potentially serious problem in this ethnic group/population.

In our study, thyroid dysfunction was present in 40.62% women, most of which was hypothyroidism (37.5%). In the GDM group, 44.23% women had thyroid dysfunction. The corresponding proportion in the PGDM group was 25%. In

Table 4 Distribution of study population with single and combined endocrinopathy according to maternal and neonatal complications ($n = 64$)

Complications	Women with diabetes only ($n = 38$)	Women with both diabetes and thyroid dysfunction ($n = 26$)
Maternal complications		
Pregnancy induced hypertension	2 (5.26)	1 (3.85)
Preterm delivery	1 (2.63)	1 (3.85)
Postpartum hemorrhage	2 (5.26)	1 (3.85)
Cesarean delivery	35 (92.10)	26 (100)
No complication	33 (86.85)	23 (88.45)
Neonatal complications		
Respiratory distress syndrome	1 (2.63)	2 (7.69)
Septicemia	1 (2.63)	–
Jaundice	3 (7.90)	5 (19.23)
Prematurity	1 (2.63)	1 (3.85)
Congenital anomaly	–	1 (3.85)
No complication	32 (84.21)	17 (65.38)

Figures in the parentheses indicate percentages

comparison with another study [6], we found a higher rate of thyroid dysfunction overall and in GDM patients. However, there was no significant difference in thyroid function between the two groups. This is in contrast to the earlier study [6], which showed significantly higher rate of thyroid dysfunction in PGDM than GDM group.

In this study, only 14.06% (9/64) of the study population was anti-TPO antibody positive and 67% (6/9) of them suffered from thyroid dysfunction. The corresponding proportion was 36.36% in case of anti-TPO negative cases. Majority (5/6 or 83.33%) of the anti-TPO positive cases with thyroid disorder belonged to the hypothyroid group. In our study, the mean TSH level was higher in anti-TPO positive cases than that of anti-TPO negative cases (5.37 ± 2.83 vs. 4.60 ± 5.59 mIU/L), though the difference was not statistically significant ($t = 1.99$, df $= 62$, $p > 0.05$). In an earlier study [4], women with anti-TPO positivity had higher fT4 (not statistically significant) and statistically higher TSH. It can be commented from the above discussion that thyroid dysfunction is more common among anti-TPO positive cases. This emphasizes the need for screening for detection of thyroid dysfunction among women with positive anti-TPO on a regular basis, so that early detection and treatment is possible. In our study, women in the GDM group had higher mean TSH level than that in the PGDM group (4.93 ± 5.78 vs. 3.90 ± 2.52 mIU/L), though not statistically significant ($t = 0.99$, df $= 62$, $p > 0.05$).

Anti-TPO antibody was positive in 11.54% women with GDM and 25% women with PGDM in our study. However, the difference was not statistically associated. This finding corroborates with that of Shahbazian et al. [6]. Another study [4] reported statistically significant difference in anti-TPO antibody between healthy pregnant women and women with diabetes type 1 (PGDM). Earlier study [7] did not report a significant difference in thyroid autoimmunity (anti-TPO) in GDM patients as compared to healthy pregnant women. The above discussion shows anti-TPO positive titer in increased frequency among PGDM than that in GDM patients or healthy pregnant women. This suggests that screening for thyroid dysfunction is indicated, especially in women with PGDM, more so in pregnancy with diabetes type 1.

Sixteen percent of the women who are euthyroid and positive for anti-TPO antibody in the first trimester will develop a TSH that exceeds 4.0 mIU/L by the third trimester, and 33–50% of women who are positive for anti-TPO antibody in the first trimester will develop postpartum thyroiditis [8]. In the present study, anti-TPO antibody was

Table 5 Distribution of study population with single and combined endocrinopathy according to perinatal outcome ($n = 64$)

Perinatal outcome	Women with diabetes only ($n = 38$)	Women with both diabetes and thyroid dysfunction ($n = 26$)	Total ($n = 64$)
Birth weight (kg)			
<2.5	1 (2.63)	3 (11.54)	4 (6.25)
≥2.5	37 (97.37)	23 (88.46)	60 (93.75)
Apgar score (at 1 min)			
4–6 (Mild depression)	4 (10.53)	4 (15.38)	8 (12.5)
7–10 (No depression)	34 (89.47)	22 (84.62)	56 (87.5)
Perinatal mortality			
Still birth	–	–	–
Early neonatal death	1 (2.63)	1 (3.85)	2 (3.12)

Figures in the parentheses indicate percentages

positive in 7.89% (3/38) of euthyroid diabetic pregnant women and two of them developed subclinical hypothyroidism at 6 weeks postpartum. The rate of anti-TPO antibody positivity was significantly higher among those with thyroid dysfunction than among those with euthyroid status in GDM group.

In this study, the rate of cesarean delivery was higher among women with combined endocrinopathy than that of women with diabetes alone (100 vs. 92.1%). Similarly, Tirosh et al. [9] showed a higher rate of maternal complications in the patients with the combination of hypothyroidism and diabetes mellitus. In our study, the neonatal complications like jaundice, respiratory distress syndrome and prematurity were noted in higher proportions in women with combined endocrinopathy. This finding supports that of Tirosh et al. [9].

In our study, women with the combined endocrinopathy had delivered higher proportions of low-birth-weight babies (11.54 vs. 2.63%) and babies with mild depression (15.38 vs. 10.53%) than that of women with diabetes alone. Tirosh et al. [9] had the similar observation.

Regarding treatment of the conditions during pregnancy and postpartum follow-up, insulin requirement was increased by 5–20 units/day from the previous doses to control diabetes mellitus in case of women with hypothyroid status when treated with levothyroxine. However, there was no change in insulin requirement when hyperthyroid mothers were controlled with propylthiouracil during pregnancy. Fifty-one out of 52 women in GDM group were on insulin therapy during pregnancy, and only two of them continued insulin therapy for glycemic control at reduced doses (one-fifth of their antenatal doses) at 6 weeks postpartum. Other women returned to euglycemic state with diet control only. All women in PGDM group were on insulin therapy during pregnancy, and almost all of them (11 or 91.67%) continued insulin therapy at 6 weeks postpartum for glycemic control, though at one-third of their antenatal doses. Only one woman returned to euglycemic state with diet control only. All the women with thyroid dysfunction during pregnancy and treated with either levothyroxine or propylthiouracil were in euthyroid state at 6 weeks postpartum.

The limitation of the study was that there was no control group to compare thyroid function in non-diabetic pregnant women with that of diabetic pregnant women. Furthermore, as we have followed selective screening for GDM, few cases in low-risk group could have been missed. Despite of its limitations, this study emphasizes the need for routine assessment of thyroid status for all diabetic pregnant women when they report to the clinic for early detection and treatment of the condition to decrease maternal and neonatal complications and to improve perinatal outcome.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards Ethical clearance for doing the study was obtained from the institutional ethics committee.

Informed Consent Informed consent was obtained from all the eligible women for participating in the study.

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