

ORIGINAL ARTICLE

Relationship between Hypothyroidism and Gestational Diabetes Mellitus: A Prospective Cohort study in Indian Pregnant Women

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Chaitra Narayan, Prasanta Kumar Nayak, Sarita Agrawal. Relationship between hypothyroidism and gestational diabetes mellitus: A prospective cohort study in Indian pregnant women. Indian J Obstet Gynecol. 2026; 14(2): 49-55.

ABSTRACT

Introduction: Gestational diabetes mellitus is a major contributor of perinatal morbidity and mortality. Thyroid hormones play an important role in glucose metabolism and any derangement in its production may lead to development of gestational diabetes mellitus. Thus we aim to find out whether hypothyroidism detected first time in pregnancy is associated with development of gestational diabetes mellitus.

Methodology: Antenatal women visiting our medical college hospital out patient department during first trimester satisfying the inclusion criteria, after informed consent were enrolled in the study and routine antenatal investigations that includes serum TSH was done. Between 24-28 weeks gestation oral glucose tolerance test (OGTT) was done. The incidence of GDM in hypothyroid and euthyroid was calculated, based on the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria for the diagnosis of gestational.

Results: The incidence of gestational diabetes was found to be 46.9% in hypothyroid women when compared to 20.8% in euthyroid women. The chance of developing GDM in hypothyroid antenatal women were 3.35 times more than euthyroid antenatal women. Highest number of diagnosis was made with 1 hour blood sugar values both in hypothyroid and euthyroid women as per IADPSG criteria.

Conclusion: Our study found a significant number of hypothyroid women developed GDM as compared with euthyroid women. Hence identification of Hypothyroidism in first trimester and screening of GDM subsequently in 2nd trimester using a standardised criteria are important in-order to predict and prevent the perinatal morbidity and mortality caused due to GDM.

KEYWORDS

• Diabetes • Hypothyroidism • Antenatal

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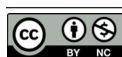
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Received: 18.05.2026

Accepted: 20.06.2026



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INTRODUCTION

Gestational diabetes mellitus (GDM) is a known risk factor for various fetomaternal complications like gestational hypertension, macrosomia, shoulder dystocia etc.¹ The global prevalence of GDM varies from 1% to 20% with an average prevalence of 10.1% in southeast asian countries.^{2,3} Hence, identifying pregnant women with gestational diabetes mellitus followed by appropriate timely treatment can decrease fetal and maternal morbidity.

The second most common endocrinopathy during pregnancy is Hypothyroidism.¹ The prevalence of hypothyroidism being as high as 44.3% in first trimester in India.⁴ Thyroid hormone and pregnancy have similar effect on glucose metabolism, while hypothyroidism induces insulin resistance by affecting the glucose homeostasis negatively, pregnancy would further amplify the resistance and hence overall increasing the risk of GDM. So, it is reasonable to propose that woman with either raised or decreased thyroid hormone would be more likely to develop gestational diabetes.⁵ Either excess or deficient thyroid hormones in the body have profound effect on insulin secretion. When the normal thyroid hormones are restored all its effects of insulin resistance, usually gets reversed. Hence if hypothyroidism is diagnosed in first trimester of pregnancy and subjected to necessary treatment then the development of GDM in later part of pregnancy can be prevented. We have intended to conduct this study as because, the data available on this aspect are less and very few studies are found from developing countries like India. In this study, IADPSG recommendations for screening of GDM which is also endorsed by WHO has been used.^{6,7}

MATERIALS AND METHODS

This is a prospective case control study done at a tertiary care hospital in central India after obtaining written informed consent from the participants. The study was conducted from September 2018 to March 2020 over a period of one and half years. The sample size was calculated to be 230, by considering the prevalence of GDM as 8%.⁶

Sample size calculation with justification:

Sample size was calculated with the formula (based on prevalence of hypothyroidism in GDM taken from results of previous study as mentioned above.

$$N = \frac{Z^2 \times P \times Q}{E^2}$$

In which, Z= 1.96 (at the level of significance 5%)

P = 8% (from Das BP *et al.*)

Q= 100-8= 92%

E = 5%

By substituting the values in the above formula we get 113.8 for cases, rounded off to 115 cases in each group.

Hence the total sample size will be 230 in the case arm- 115 antenatal women with diagnosed hypothyroidism for the first time in pregnancy as per American Thyroid Association criteria in pregnancy-2017 were enrolled after proper consent.⁷ Thyroid function test was done by sandwich assay in direct chemiluminescent assay (CLIA) technology. Screening for GDM was done as per IADPSG recommendations.^{8,9} In the control arm - 115 antenatal women with euthyroid state were enrolled after proper consent. The objective of our study was to determine the association of hypothyroidism with occurrence of gestational diabetes mellitus (GDM). Women who were already a known case of hypothyroidism, known case of diabetes, age <18yrs & >30yrs, having history of GDM in previous pregnancy, multiple gestation, known case of polycystic ovarian syndrome (PCOS), having a history of drug therapy that alter the thyroid functions (amiodarone, lithium, dopamine, bromocryptine) or alter the blood glucose (glucocorticoids, beta blockers, thiazide diuretics, statins, olanzapine, duloxetine) were excluded from the study. Adequate matching between both the groups was done so far as the age, education, socio-economic status and other relevant demographic indices concerned.

Technical information: All enrolled antenatal women were subjected to detailed history and examination, and were followed up in routine antenatal clinic with all necessary investigations as required. As per the institutional protocol these antenatal women were called between 24-28 weeks period of gestation in fasting status and Oral Glucose Tolerance Test (OGTT) was performed with 75 gram anhydrous glucose intake. After collecting fasting venous blood sample (with at least 8 hrs fasting, with at least previous

three days of normal diet intake) 75 grams of anhydrous glucose was dissolved in 250-300ml of water and was instructed to drink at once or at least till 20 minutes after noting time. Venous blood samples were drawn at 1 hour and 2 hours intervals after the glucose intake and was tested for glucose value. The laboratory cut off value used for diagnosis of GDM is ≥ 92 , ≥ 180 , ≥ 153 mg/dl for Fasting, 1 hour and 2 hours blood glucose levels respectively which is as per the International Association of Diabetes in Pregnancy Study Group recommendations (IADPSG).¹⁰ Any one or more blood glucose value equal to or above the cut off levels were considered to have developed gestational diabetes mellitus. Those diagnosed as gestational diabetes mellitus were subjected to medical nutrition therapy and further follow up was done as per institutional protocol.

Statistics: Statistical analysis was performed using a Statistical Package for Social Sciences

software (SPSS version 16). Chi square test was used to see association of the socio-demographic variables between the groups. Independent t test was used to calculate difference of mean age, BMI and weight gain between the groups. Binominal logistic regression was applied on demographic indices to calculate the odds ratio of developing GDM. For all statistical analyses, $p < 0.05$ was considered significant, and $p < 0.001$ was considered highly significant.

RESULTS

A total of 256 antenatal women fulfilling the inclusion criteria were recruited, out of which 26 women could not be followed up due to some reasons like miscarriage, medical termination of pregnancy, migrated to other place, non attendance in OPD due to COVID-19 pandemic etc. Hence a total of 230 antenatal women with 115 in each arm of case and control groups were followed up and analysed.

Table 1: General characteristics of the participants with and without hypothyroidism

Demographic Characteristics		Number of Hypothyroid antenatal women (n=115)	Number of Euthyroid antenatal women (n=115)	Total	Percentage (%)
Age (years)	18-20	8	10	18	7.8
	21-25	36	37	73	31.7
	26-30	71	68	139	60.4
Parity	Primiparous	75	78	153	66.5
	Multiparous	40	37	77	33.4
Education status	Primary	4	3	7	3.0
	Secondary	13	16	29	12.6
	Higher secondary	20	24	44	19.1
	Graduate	51	50	101	43.9
	Post graduate	27	22	49	21.3
Occupation	Housewife	66	99	165	71.7
	Working	49	16	65	28.2
Socio-economic status	Class I	42	40	82	35.6
	Class II	47	56	103	44.7
	Class III	26	19	45	19.5
Area of residence	Rural	16	24	40	17.3
	Urban	99	91	190	82.6
Religion	Hindu	109	111	220	95.6
	Muslim	4	3	7	3.0
	Christian	2	1	3	1.3
BMI(kg/m ²)	Underweight (<18.5)	8	6	14	6.0
	Normal (>18.5-22.9)	36	53	89	38.6
	Overweight(23-26.9)	46	39	85	36.9
	Obese (>= 27)	25	16	41	17.8

As described in Table 1, the majority (60.4%) of women were in age group of 26-30years followed by 31.7% were between 21-25years, primiparous women were 66.5%, education wise 43.9% were graduates followed by 21.3% post graduates, however, 71.7% were housewives and 44.7% belonged to class II of socioeconomic status followed by class I (35.6%) as per B.G Prasad classification of socioeconomic status.¹¹ The majority (82.6%) of women were urban dwellers, and 95.6% women belonged to Hindu religion. Most of the women had normal BMI (38.6%) followed by over weight (36.9%), 17.8% of them were obese while the rest 6% were underweight.

As described in table 2, incidence of GDM was found to be 46.9% in case group while control group showed an incidence of 20.8%, indicating the hypothyroid women had more than double ($P<0.001$) the chances of developing GDM than that of euthyroid women.

Table 2: Comparison of the onset of GDM among hypothyroid and euthyroid women

Outcome	Not developed GDM / (%)	Developed GDM / (%)	Total	P value
Hypothyroid (cases)	61/ (53.0%)	54 (46.9%)	115	<0.001
Euthyroid (controls)	91 (79.1%)	24 (20.8%)	115	

As shown in table 3, highest number of diagnosis was made with 1 hour value of blood sugar both in case and control groups. Overall participants had 1 hour value deranged, hence increasing the diagnostic value of 1 hour blood glucose test.

Table 3: Diagnosis of GDM based on blood sugar levels

Diagnosis made with	Hypothyroid	Euthyroid
FBS value ($>92\text{mg/dl}$)	36	15
1hour BS value ($>180\text{mg/dl}$)	39	15

Table 6: Demographic distribution of participants who developed GDM

Category	No. of GDM cases, n=78 (%)	Odds Ratio	95% CI for OR		P value
			Lower	Upper	
Age $>25\text{yrs}$	52/139 (37.41%)	1.494	0.845	2.642	0.167
BMI $>23\text{kg/m}^2$	60/126 (47.61%)	4.293	2.316	7.957	<0.001
Weight gain $>10\text{ kg}$	40/65 (61.53%)	5.347	2.884	9.913	<0.001
Working women	30/54 (55.55%)	3.333	1.774	6.266	<0.001
Education $\geq$ graduation	59/150 (39.33%)	2.082	1.131	3.832	0.019
SES $>$ class II	13/45 (28.88%)	0.750	0.368	1.528	0.428
Staying in urban area	71/190 (37.36%)	2.813	1.182	6.693	0.019
Multigravida	28/77 (36.36%)	1.177	0.663	2.090	0.578

2hours BS value (153mg/dl)	26	14
Any two values deranged	31	15
All three values deranged	17	4

Among 111 subclinical hypothyroid women, 50 (45%) of them developed GDM while all 4(100%) overt hypothyroid women developed GDM hence showing the significance of hypothyroid status.

Table 4: Hypothyroid cases developing GDM

Hypothyroid status	GDM cases(%)
Subclinical hypothyroidism (n=111)	50 (45%)
Overt hypothyroidism (n=4)	4 (100%)

Highest number of diagnosis was made with 1 hour blood sugar values in both cases (39) and control (15) groups. Overall 51 participants had 1 hour value deranged, hence increasing the diagnostic value of one hour blood sugars. All the three values were deranged in 21 participants, FBS in 49 participants and 2 hour value in 40 participants.

Table 5: Distribution of GDM cases diagnosed based on sugar values

Diagnoses made with	Cases	Controls
FBS value ($\geq 92\text{mg/dl}$)	36	15
1 hour BS value ($\geq 180\text{mg/dl}$)	39	15
2 hour BS value ($\geq 153\text{mg/dl}$)	26	14
All three values deranged	17	4

As described in table 5, applying the binomial logistic regression, odds ratio were calculated for factors like BMI $>23\text{kg/m}^2$, weight gain $>10\text{kgs}$ & working women were observed to have highly significant ($P<0.001$) association with developing GDM with odds/ chances of developing GDM were 4.292, 5.347 & 3.333 respectively.

Education more than graduation and residence in urban areas showed statistical significance $P=0.019$. The odds/chance of developing GDM was 2.082 and 2.813 with respect to education and residence.

However, age, socio-economic status and parity did not show any statistical significance $P=0.167, 0.428, 0.578$ respectively.

DISCUSSION

Gestational diabetes mellitus is one of the very common endocrinological disorder of pregnancy which is known to affect the Fetomaternal outcome. Despite many screening methods and effective interventions and treatment, the fetomaternal outcome in developing countries like India is still not effectively changed.¹² Asian race already known to be at risk for GDM as well as type 2 diabetes, needs universal screening both at first visit as well as in second trimester with an efficient screening method so that no case is missed thereby reducing the morbidity associated with it.

On the other hand we have already mentioned that hypothyroidism being the second most common endocrinological disorder in pregnancy affecting the carbohydrate metabolism.¹ Keeping this in mind, the present study has been taken up to assess the association of one such risk factor i.e hypothyroidism with occurrence of GDM.

Our study done with 230 participants divided into 115 in case & control groups respectively it was observed that the incidence of GDM was found to be 46.95% in case group which was statistically significant when compared to control group 20.8%, $P<0.001$ (Table 2), and also it was found that the incidence in subclinical hypothyroidism was found to be 45% and in overt hypothyroidism as 100% incidence of GDM (Table 4). The odds/chances of developing GDM was 3.357 times more in case group when binomial logistic regression was applied (Table 3). This is in accordance with a study by Das et al showed a statistically significant difference between incidence in hypothyroid and euthyroid groups.⁸ Another study by Manouchehr et al showed a higher prevalence of hypothyroidism in GDM women.¹³ In an umbrella review of meta analysis by Gainnakou et al observed that increased BMI and hypothyroidism had a very significant risk

for development of GDM Similarly in a meta analysis by L.-L.¹⁴ Gong et al similar higher odds of GDM was found in hypothyroid group, however was not statistically significant for subclinical hypothyroidism, but there was statistically significant difference for overt hypothyroidism and GDM.⁵

Highest number of diagnosis of GDM was made with 1 hour blood sugar value both in case and control groups (Table 5) making it a very sensitive value for diagnosis of GDM, thereby indicating IADPSG criteria to be more sensitive than DIPSI criteria which would have missed an effective number of GDM cases. This is in accordance with a study by Mohan *et al* that showed DIPSI criteria would miss 77.4% of GDM cases when compared to IADPSG criteria and 72.3% cases when compared to WHO 1999 criteria.⁶ Similar results in another study by Vijay et al observing 22.36% GDM cases being undiagnosed with DIPSI criteria when compared to IADPSG criteria.¹⁵ Contrary to our study, a research article published where GDM has been diagnosed using IADPSG criteria by P K Nayak et al have shown that maximum number GDM cases were diagnosed based on fasting blood sugar values.¹⁶

In demographic analysis, it was found that some demographic parameters had individual potential in becoming a risk factor for GDM as in our study it was observed the odds of developing GDM in women with $BMI>23\text{kg/m}^2$ was 4.293 times thus making $BMI>23\text{kg/m}^2$ a significant individual risk factor, similar finding in a meta analysis by Chu et al and several other studies.¹⁷⁻²⁰ A gestational weight gain of $>10\text{kg}$ was found to increase the odds of development of GDM by 5.347 times and similar results were also found in a study by Hedderson *et al*, Mac Donald et al study showed chances of GDM increased with every increase in standard deviation of gestational weight gain.^{21,22} It was found that in working women the odds of developing GDM is 3.333 times more than that of housewives, similar to finding in study by Song et al.²³ Apart from these it was found that education above graduation increased the odds of GDM development by 2.82 times similar to study by Rajput R et al, however studies by Bouthoom et al and Song et al showed an inverse association of education with GDM.^{18,23,24} This kind of differences in the outcomes of the studies

can be due to the socio-economic differences of the study population. Another important demographic parameter in our study where it shows that staying in urban areas had 2.813 times more chances of developing GDM than women residing in rural areas which is similar to study results by Carroll X *et al*, Mwanri *et al* and Arora *et al*.²⁵⁻²⁷ However the study by Bhavadharini *et al* showed no statistical difference between urban and rural residents.²⁸ The more incidence of GDM among urban population can be attributed to their life style.

CONCLUSION

Gestational diabetes is a condition of disturbed glucose homeostasis in a pregnant woman which results in hyperglycaemia and its effect on both the maternal health as well as the ongoing pregnancy. Many factors are associated with development of GDM, of which our study found a significant association of hypothyroidism with onset of GDM. The probability of GDM development in hypothyroid women were more than double when compared to euthyroid women in our study. Our study observed the highest diagnosis of GDM with 1 hour value of blood glucose unlike in other studies. Our study also found a significance of subclinical hypothyroid women developing GDM more than euthyroid women unlike many studies till date. However like in other studies, our study also found a significant association of GDM with increased Pre pregnancy BMI, gestational weight gain, higher education, working women and residents of urban areas. Hence hypothyroidism in pregnancy including sub clinical hypothyroidism should be treated on time to prevent the development of GDM.

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