Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 03 Aug 2026
Revised 05 Sep 2026
Accepted 25 Sep 2026

Natural Resources for Human Health 2026, Vol. 6 (23s): 1125-1134

KEYWORDS:
gestational diabetes mellitus; thyroid function; thyroid-stimulating hormone; free thyroxine; free triiodothyronine; pregnancy; India

Thyroid Profile in Pregnant Women with Gestational Diabetes Mellitus Compared with Normoglycaemic Antenatal Women: An Observational Comparative Study

Dr Aishwarya Krishnakumar[1], Dr G Baby Shalini[2*], Dr B Manjulatha[3]

[1]Postgraduate, Department of Obstetrics and Gynaecology, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India, e-mail: zaisha2050@gmail.com
[2]Associate Professor, Department of Obstetrics and Gynaecology, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India. Email: shaluprameela@gmail.com
[3]Professor and Head, Department of Obstetrics and Gynaecology, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India, Email: manjulatha_b@aimsrchittoor.edu.in

ABSTRACT:

Background: Gestational diabetes mellitus (GDM) and thyroid dysfunction are among the commonest endocrine disorders of pregnancy, and thyroid hormones influence glucose metabolism. Published findings on their association are inconsistent and regional data are limited.

Objectives: To compare the thyroid profile (FT3, FT4 and TSH) of antenatal women with and without GDM, to determine the prevalence of thyroid dysfunction in both groups, and to evaluate the need for thyroid screening in women with GDM.

Methods: This observational comparative study was conducted over 18 months at Apollo Institute of Medical Sciences and Research and District Headquarters Hospital, Chittoor, Andhra Pradesh. Of 175 antenatal women assessed, 136 were enrolled and classified by 75 g oral glucose tolerance test into 68 women with GDM and 68 without. Women with known thyroid disorders were excluded. FT3, FT4 and TSH were measured by chemiluminescence immunoassay and interpreted against trimester-specific reference ranges. Groups were compared using the independent-samples t-test and Fisher exact test.

Results: Age, height and weight were comparable between groups. Fasting, 1-hour and 2-hour plasma glucose were significantly higher in the GDM group (all $p < 0.0001$). Mean TSH was 2.09 ± 1.09 versus 1.86 ± 0.77 mIU/L ($p = 0.1701$), FT3 2.39 ± 0.76 versus 2.57 ± 0.72 pg/mL ($p = 0.1503$) and FT4 1.42 ± 0.53 versus 1.49 ± 1.00 ng/dL ($p = 0.6020$) in the GDM and control groups, respectively. An abnormal thyroid profile was present in 11 of 68 women with GDM (16.2%) and in none of the 68 controls ($p < 0.001$). Among women with GDM, TSH showed a non-significant positive correlation with fasting glucose ($r = 0.218$, $p = 0.0756$).

Conclusion: Mean thyroid hormone levels did not differ significantly between groups, but about one in six women with GDM had an abnormal thyroid profile, whereas none of the

controls did. Thyroid function testing may be considered in women with GDM; larger multicentre studies with outcome data are needed.

INTRODUCTION

Gestational diabetes mellitus (GDM) and thyroid dysfunction are the two most common endocrine disorders encountered during pregnancy.[1] GDM, defined as glucose intolerance first recognised during pregnancy,[2] is common in India. A recent systematic review and meta-analysis estimated a pooled national prevalence of 13% (95% CI 9–16%), with higher estimates in urban (12%) than in rural (10%) populations.[3] The consequences extend beyond pregnancy. In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study of 25,505 women, maternal glucose levels below diabetic thresholds showed strong, continuous associations with higher birth weight and cord-blood C-peptide,[4] and women with GDM carry a markedly increased later risk of type 2 diabetes (pooled relative risk 7.43).[5]

Pregnancy also places considerable demands on the thyroid gland. Human chorionic gonadotrophin stimulates the thyroid, oestrogen raises thyroxine-binding globulin and iodine requirements increase, so thyroid function tests must be interpreted against trimester-specific reference ranges.[6,7] Thyroid hormones influence carbohydrate metabolism and insulin sensitivity, and the frequent coexistence of GDM and thyroid dysfunction has been attributed to the insulin-resistant state produced by maternal thyroid dysfunction, to altered placentation and to shared risk factors.[1]

A meta-analysis of 44 studies found that hypothyroxinaemia, overt and subclinical hypothyroidism, overt hyperthyroidism and positive thyroid antibodies were each associated with a higher risk of GDM, whereas subclinical hyperthyroidism was associated with a lower risk.[8] An umbrella review of meta-analyses identified hypothyroidism as one of only four risk factors for GDM supported by convincing evidence.[9] The ratio of free triiodothyronine to free thyroxine (FT3:FT4), a marker of peripheral deiodinase activity, has also been associated with GDM risk.[10,11]

Thyroid dysfunction is itself common among pregnant women in India. In a second-trimester series of 633 women, subclinical hypothyroidism was found in 6.47% and overt hypothyroidism in 4.58%,[12] and in a population-based cohort from North Delhi, 29.2% of 2,317 women had a TSH of 2.5 mIU/L or above in early pregnancy.[13] Hospital-based Indian studies have also reported thyroid dysfunction in a substantial proportion of women with GDM.[14,15] Because both disorders are frequent in the same population, it is relevant to know whether women with GDM in a given setting have an abnormal thyroid profile more often than women without GDM.

Nevertheless, results differ between studies, a discrepancy attributed in part to changing diagnostic criteria and screening strategies for both conditions,[1] and data from our region are limited. Early identification of thyroid dysfunction in women with GDM may allow better monitoring and management during pregnancy. We therefore compared the thyroid profile of pregnant women with and without GDM at a teaching hospital and district headquarters hospital in Chittoor, Andhra Pradesh. The objectives were (i) to compare the thyroid profile (FT3, FT4 and TSH) between antenatal women with GDM and normal antenatal women; (ii) to determine the prevalence of thyroid dysfunction in each group; and (iii) to evaluate the need for further thyroid screening in women with GDM.

METHODS

Study design, setting and period

This observational comparative study was conducted in the outpatient department of Obstetrics and Gynaecology at Apollo Institute of Medical Sciences and Research and District Headquarters Hospital, Chittoor, Andhra Pradesh. The study ran for 18 months from the date of approval by the Institutional Ethics Committee and Scientific Committee Informed consent was obtained from all participants.

Participants

Antenatal women attending the outpatient department during the study period were assessed for eligibility and enrolled consecutively by convenience sampling until the required sample size was reached. Eligible women were classified into two groups: women diagnosed with GDM (cases) and normal antenatal women without GDM (controls).

Inclusion criteria were attendance at the outpatient department of District Headquarters Hospital, Chittoor; spontaneous conception; singleton pregnancy; gestational age of 24–28 weeks or beyond; and age between 18 and 40 years. Women with GDM formed the case group. Exclusion criteria were overt diabetes mellitus and other high-risk factors; age below 18 or above 40 years; multiple pregnancy; a history of infertility treatment; known thyroid disorder; and a family history of thyroid disorders.

Sample size

The study included 136 women, 68 in each group. The sample size was estimated using the formula for comparison of two proportions, $n = (Z\alpha + Z\beta)^2 \times [p1(1 - p1) + p2(1 - p2)] / (p1 - p2)^2$, where $Z\alpha$ is 1.96 (5% significance level), $Z\beta$ is 0.84 (80% power), and p1 and p2 are the estimated prevalences of thyroid dysfunction in the GDM and non-GDM groups, respectively .

Data collection and diagnosis of GDM

Sociodemographic details, clinical examination findings and obstetric history were recorded on a structured proforma. All participants underwent a 75 g oral glucose tolerance test (OGTT) interpreted according to the American Diabetes Association (ADA) and International Federation of Gynecology and Obstetrics (FIGO) criteria. GDM was diagnosed when any one of the following was met or exceeded: fasting plasma glucose ≥92 mg/dL, 1-hour plasma glucose ≥180 mg/dL or 2-hour plasma glucose ≥153 mg/dL.[2,16]

Thyroid function assessment

Blood samples were collected under sterile conditions and serum FT3, FT4 and TSH were measured by chemiluminescence immunoassay (CLIA). Results were interpreted using the trimester-specific TSH reference ranges of the American Thyroid Association (0.1–2.5 mIU/L in the first, 0.2–3.0 mIU/L in the second and 0.3–3.0 mIU/L in the third trimester)[7] together with trimester-specific FT3 and FT4 reference ranges. Women with TSH within the reference range were classified as euthyroid; TSH above 2.5 mIU/L was classified as subclinical hypothyroidism and above 10 mIU/L as overt hypothyroidism. Each woman was categorised as having a normal or an abnormal thyroid profile on this basis.

Study tools and outcome measures

The study tools were a structured questionnaire and patient proforma, clinical examination and recording of obstetric history, the 75 g OGTT for the diagnosis of GDM, and thyroid function tests (FT3, FT4 and TSH) performed by CLIA. The primary outcome was the comparison of FT3, FT4 and TSH between the two groups. Secondary outcomes were the proportion of women with an abnormal thyroid profile in each group, the distribution of abnormal profiles by age group and gravida status within the GDM group, and the correlation between TSH and glucose parameters.

Statistical analysis

Data were entered in Microsoft Excel and analysed using the Statistical Package for the Social Sciences (SPSS), version 21. Continuous variables are presented as mean ± standard deviation and were compared between groups using the independent-samples t-test; categorical variables are presented as numbers and percentages, and proportions were compared using the Fisher exact test. Post-load glucose values were compared across age categories within the GDM group by analysis of variance, and correlation analysis was used to examine the relationship between TSH and glucose parameters. A p value below 0.05 was considered statistically significant.

RESULTS

Study population

Of 175 antenatal women assessed for eligibility, 39 were excluded (known thyroid disorders, n = 14; overt diabetes or multiple pregnancy, n = 13; other criteria not met, n = 12). The remaining 136 women were enrolled and, on the basis of the 75 g OGTT, were classified into 68 women with GDM and 68 without GDM (Figure 1). Thyroid testing was complete for all participants and all 136 were analysed.

Natural Resources for Human Health
eISSN: 2583-1194

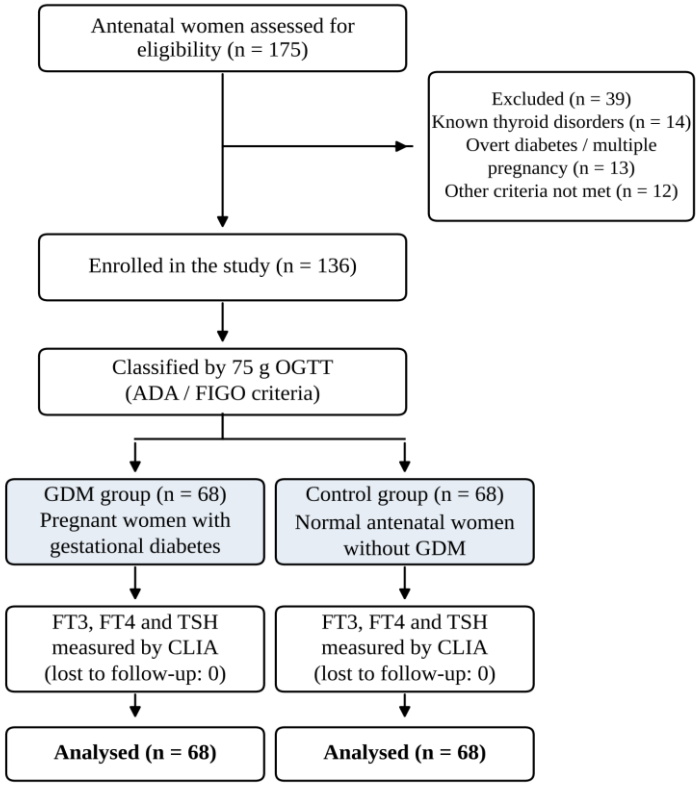


Figure 1. Flow of participants through the study. ADA, American Diabetes Association; CLIA, chemiluminescence immunoassay; FIGO, International Federation of Gynecology and Obstetrics; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

Baseline characteristics

The two groups were comparable at baseline (Table 1). Mean age was 25.19 ± 4.49 years in the GDM group and 24.84 ± 5.07 years in the control group (p = 0.6682). Mean height (156.07 ± 2.76 vs 155.84 ± 3.27 cm; p = 0.6511) and mean weight (62.21 ± 6.89 vs 60.19 ± 8.00 kg; p = 0.1182) did not differ significantly. In both groups, most women were aged 18–25 years (57.4% in each group) or 26–30 years (32.4% in each group).

Table 1. Baseline characteristics of the study groups (n = 136)

Characteristic	GDM (n = 68)	Control (n = 68)	t	p value
Age (years), mean ± SD	25.19 ± 4.49	24.84 ± 5.07	0.430	0.6682
Height (cm), mean ± SD	156.07 ± 2.76	155.84 ± 3.27	0.453	0.6511
Weight (kg), mean ± SD	62.21 ± 6.89	60.19 ± 8.00	1.573	0.1182
Age group, n (%)				
18–25 years	39 (57.4)	39 (57.4)	–	–
26–30 years	22 (32.4)	22 (32.4)	–	–
31–35 years	4 (5.9)	5 (7.4)	–	–
>35 years	3 (4.4)	2 (2.9)	–	–

GDM, gestational diabetes mellitus; SD, standard deviation. Continuous variables compared by independent-samples t-test; age groups are presented descriptively.

Glucose tolerance and thyroid function parameters

As expected from the diagnostic classification, all three OGTT values were significantly higher in women with GDM (Table 2, Figure 2A). Mean fasting plasma glucose was 103.71 ± 14.01 mg/dL in the GDM group and 80.01 ± 9.63 mg/dL in the control group ($t = 11.493$, $p < 0.0001$); the corresponding 1-hour values were 161.25 ± 26.23 and 123.38 ± 20.39 mg/dL ($t = 9.399$, $p < 0.0001$) and the 2-hour values were 135.96 ± 28.43 and 99.69 ± 18.27 mg/dL ($t = 8.849$, $p < 0.0001$). Within the GDM group, post-load glucose values did not vary significantly across age categories ($F = 0.87$, $p = 0.463$).

Mean thyroid function parameters did not differ significantly between the groups (Table 2, Figure 2B). Mean TSH was 2.09 ± 1.09 mIU/L in the GDM group and 1.86 ± 0.77 mIU/L in the control group ($p = 0.1701$). Mean FT3 was 2.39 ± 0.76 versus 2.57 ± 0.72 pg/mL ($p = 0.1503$) and mean FT4 was 1.42 ± 0.53 versus 1.49 ± 1.00 ng/dL ($p = 0.6020$). Numerically, women with GDM had a higher mean TSH and lower mean FT3 and FT4, but none of these differences reached statistical significance. Within the GDM group, TSH showed a positive correlation with fasting plasma glucose that was not statistically significant ($r = 0.218$, $p = 0.0756$).

Table 2. Glucose tolerance test values and thyroid function parameters in the GDM and control groups

Parameter	GDM (n = 68)	Control (n = 68)	t	p value
OGTT plasma glucose (mg/dL)				
Fasting	103.71 ± 14.01	80.01 ± 9.63	11.493	<0.0001
1-hour	161.25 ± 26.23	123.38 ± 20.39	9.399	<0.0001
2-hour	135.96 ± 28.43	99.69 ± 18.27	8.849	<0.0001
Thyroid function				
TSH (mIU/L)	2.09 ± 1.09	1.86 ± 0.77	1.379	0.1701
FT3 (pg/mL)	2.39 ± 0.76	2.57 ± 0.72	−1.447	0.1503
FT4 (ng/dL)	1.42 ± 0.53	1.49 ± 1.00	−0.523	0.6020

Values are mean ± SD; independent-samples t-test. OGTT, oral glucose tolerance test; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

Natural Resources for Human Health
eISSN: 2583-1194

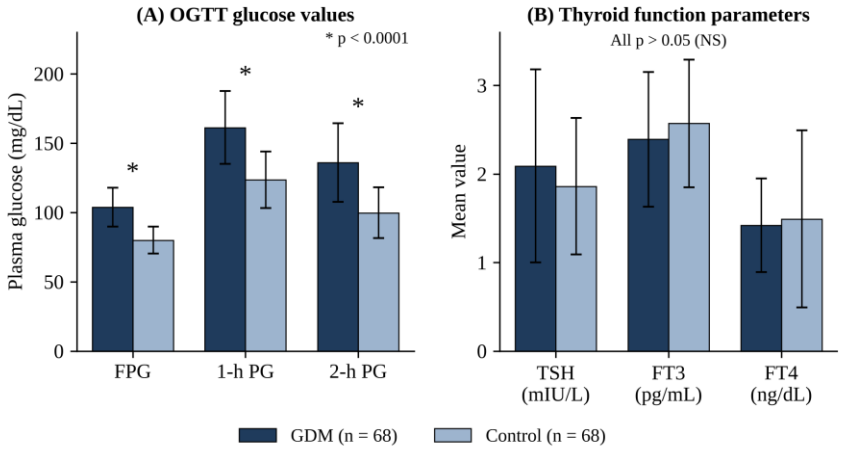


Figure 2. Comparison of (A) OGTT plasma glucose values and (B) thyroid function parameters between women with GDM and controls (mean ± SD). FPG, fasting plasma glucose; PG, plasma glucose; NS, not significant.

Prevalence of abnormal thyroid profile

Thyroid profile was normal in 57 of 68 women with GDM (83.8%) and in all 68 control women (100%). An abnormal thyroid profile was therefore found in 11 of 68 women with GDM (16.2%) and in none of the 68 control women (Table 3); this difference was statistically significant (Fisher exact test, $p < 0.001$). Among women with GDM, the proportion with an abnormal profile was 12.8% (5 of 39) at 18–25 years, 18.2% (4 of 22) at 26–30 years, 25.0% (1 of 4) at 31–35 years and 33.3% (1 of 3) above 35 years (Figure 3A). By gravida status, the proportions were 14.3% (4 of 28) in primigravidae, 16.7% (5 of 30) in women of gravida 2–3 and 20.0% (2 of 10) in women of gravida 4 or more (Figure 3B). The older age groups and the grand multigravida group contained very few women, and the percentages in these subgroups are therefore unstable; no formal comparison across subgroups was made.

Table 3. Thyroid profile status in women with GDM and controls, overall and by age group and gravida status

Group / category	Total (n)	Normal profile, n (%)	Abnormal profile, n (%)
Overall			
GDM	68	57 (83.8)	11 (16.2)
Control	68	68 (100.0)	0 (0.0)
GDM women by age group (years)			
18–25	39	34 (87.2)	5 (12.8)
26–30	22	18 (81.8)	4 (18.2)
31–35	4	3 (75.0)	1 (25.0)
>35	3	2 (66.7)	1 (33.3)
GDM women by gravida status			
Primigravida (G1)	28	24 (85.7)	4 (14.3)

Group / category	Total (n)	Normal profile, n (%)	Abnormal profile, n (%)
Multigravida (G2–G3)	30	25 (83.3)	5 (16.7)
Grand multigravida (≥G4)	10	8 (80.0)	2 (20.0)

Percentages are row percentages. GDM versus control: Fisher exact test, $p < 0.001$. Subgroup rows are descriptive; no formal comparison was made.

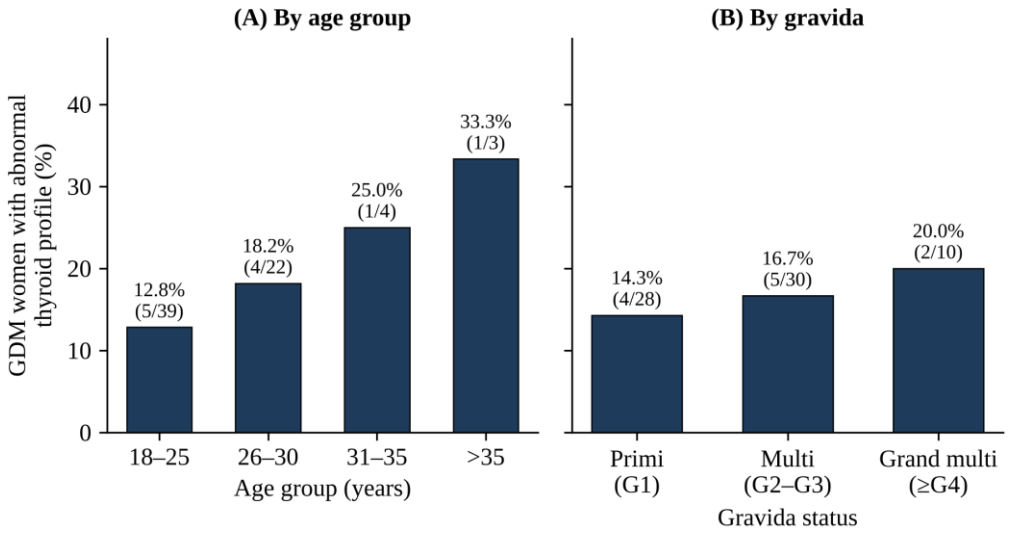


Figure 3. Proportion of women with GDM who had an abnormal thyroid profile, by (A) age group and (B) gravida status. Labels show percentage and number (abnormal/total).

DISCUSSION

In this comparison of 68 women with GDM and 68 without, glucose values differed markedly, as expected from the diagnostic classification, whereas mean TSH, FT3 and FT4 did not differ significantly. Nevertheless, 16.2% of women with GDM had an abnormal thyroid profile compared with none of the controls. The groups were similar in age, height and weight, although body mass index was not assessed. Taken together, our findings do not show a difference in mean thyroid hormone levels but do suggest a higher burden of abnormal thyroid profiles in GDM, which is the signal of most relevance to the question of screening.

The absence of significant differences in mean thyroid hormone levels contrasts with several larger studies. In a retrospective study of 662 women, GDM was associated with higher TSH and FT3, lower FT4 and a higher FT3:FT4 ratio.[17] In a prospective cohort of 26,742 Chinese women, higher TSH and subclinical hypothyroidism were independently associated with GDM (adjusted odds ratios 1.030 and 1.211, respectively), whereas FT4 and thyroid peroxidase antibodies were not.[18] In 24,883 women who had thyrotropin screening at prenatal care, the likelihood of GDM rose with increasing TSH,[19] and in the Rhea cohort of 1,170 women the combination of high TSH and thyroid autoimmunity carried a four-fold relative risk of GDM.[20] Pooled estimates indicate a modest effect: Toulis and colleagues reported an adjusted odds ratio of 1.39 for GDM with subclinical hypothyroidism, although this was not robust to sensitivity analyses,[21] and the larger meta-analysis by Luo and colleagues reported odds ratios of 1.45 for hypothyroxinaemia, 1.54 for subclinical hypothyroidism and 1.80 for overt hypothyroidism.[8] The direction of our TSH and FT4 findings is the same as in these reports. Our numerically lower FT3 is the opposite of the finding of Yanachkova and Kamenov,[17] but agrees with a case-control study from Delhi that found significantly lower mean thyroid function values and higher anti-TPO levels in 40 women with GDM than in 40 without.[22] A study of 60 women with GDM and 60 controls from Puducherry likewise found no significant differences in TSH or FT4, but reported higher FT3 and a higher FT3:FT4 ratio in GDM.[23]

Several features of our design may explain the lack of significant mean differences. Women with known thyroid disorders or a family history of thyroid disorders were excluded, which narrows the range of thyroid values in both groups. Thyroid function was measured once, and mean values may conceal a minority of abnormal results. In addition, with 68 women per group, a comparison at the 5% significance level with 80% power can detect only a standardised difference of about 0.5 standard deviations, so differences of the modest size reported in large cohorts could have been missed.

Women in our study were considerably younger than those in the large Chinese cohort, in which mean age was 33.26 ± 4.01 years in women with GDM,[18] and the two groups in our study were similar in age. Because maternal age and other characteristics vary between populations, thyroid findings should be extrapolated between settings with caution, and the comparison of groups matched for age and body size, as in the present study, removes only part of this uncertainty.

The proportion of women with an abnormal profile is more informative than the group means. The 16.2% observed in our GDM group is of a similar order to the 11.4% reported among 105 women with GDM in a hospital-based Indian study, where dysfunction was predominantly subclinical hypothyroidism,[14] and lower than the 40% of thyroid disorders found in a Kolkata series of 64 pregnant women with diabetes, of whom 81% had GDM.[15] The absence of any abnormal result among our controls is also lower than the community estimates from India cited in the Introduction.[12,13] This probably reflects, at least in part, the exclusion of women with known thyroid disease or a family history of thyroid disorders and differences in reference limits and gestational age at testing; it also means that our control group may not represent the general antenatal population, and the contrast between groups may therefore be exaggerated.

The numerically lower FT4 in our GDM group, although small and not significant, points in the same direction as the association of low FT4 with GDM in the meta-analysis of Luo and colleagues.[8] In a Chinese birth cohort of 6,068 women, higher FT4 in early pregnancy was associated with a lower risk of GDM (odds ratio 0.73 comparing extreme quartiles), whereas a higher FT3:FT4 ratio was associated with a higher risk (odds ratio 1.43).[11] In a Belgian case-control study, a higher FT3:FT4 ratio at 26–28 weeks was associated with GDM (adjusted odds ratio 2.12 for the highest versus the lowest tertile).[10] We did not analyse the FT3:FT4 ratio, and this would be a useful addition in future work, because the ratio may capture altered peripheral thyroid hormone metabolism that individual hormone levels do not.

Within the GDM group, the proportion with an abnormal profile appeared to increase with age and gravidity, but the strata were small and no formal test was performed, so these observations are hypothesis-generating only. In the Indian study cited above, women with GDM and thyroid dysfunction were older and had a higher body mass index than euthyroid women;[14] body mass index was not recorded in our study. The positive correlation between TSH and fasting glucose in women with GDM ($r = 0.218$) did not reach significance ($p = 0.0756$) and should be regarded as no more than suggestive; the Puducherry study found no significant correlation between glucose and thyroid parameters.[23]

Mechanistic explanations for a link between the two conditions include the insulin-resistant state produced by maternal thyroid dysfunction, altered placentation and shared risk factors.[1] Our study was not designed to test these mechanisms. It measured thyroid hormones at one time point in women who already had GDM or normal glucose tolerance, and the direction of any relationship, whether thyroid dysfunction contributes to GDM or the metabolic disturbance of GDM influences thyroid function, cannot be determined from these data.

The American Thyroid Association does not recommend universal thyroid screening in pregnancy and advocates targeted testing of high-risk women.[24] Our finding that about one in six women with GDM had an abnormal thyroid profile, against none in the comparison group, supports considering thyroid function testing in women with GDM, in keeping with the conclusions of Indian studies[14,15] and with the suggestion that the two conditions be assessed together.[1] Measuring FT4 as well as TSH is worthwhile, because low FT4 and hypothyroxinaemia were associated with GDM in a meta-analysis[8] and would be missed by TSH-only testing. Our data, however, cannot show that screening improves maternal or neonatal outcomes, because outcomes were not assessed.

The strengths of this study include measurement of FT3 and FT4 in addition to TSH, which allows detection of abnormalities that a TSH-only approach would miss; classification of both groups by OGTT using the same diagnostic thresholds; use of trimester-specific reference ranges; and complete thyroid data for all enrolled women.

LIMITATIONS

This study has several limitations. The sample was small and drawn from a single centre, which limits statistical power and generalisability. The design was cross-sectional, so causal relationships cannot be inferred, and thyroid function was assessed at a single time point, so changes across trimesters were not evaluated. Known thyroid disorders were excluded, which may have underestimated the true prevalence of thyroid dysfunction in GDM. Thyroid autoantibodies, the FT3:FT4 ratio, insulin levels and insulin resistance indices, body mass index, iodine status and micronutrient status were not assessed, and pregnancy outcomes were not analysed. The criteria for classifying a thyroid profile as abnormal were applied to a small number of women, and the subgroup analyses by age and gravida were descriptive.

CONCLUSION

Women with GDM in this study had significantly higher glucose values than controls, whereas mean TSH, FT3 and FT4 did not differ significantly. However, 16.2% of women with GDM had an abnormal thyroid profile, compared with none of the controls, and TSH showed a non-significant positive correlation with fasting glucose within the GDM group. These findings suggest that thyroid evaluation may be beneficial in women with GDM. Larger, multicentre studies that include thyroid autoantibodies, body mass index and pregnancy outcomes are needed to define whether routine thyroid screening in GDM is justified.

DECLARATIONS

Ethics approval: The study was approved by the Institutional Ethics Committee and Scientific Committee . Informed consent was obtained from all participants.

Funding: No external fund recieved

Conflict of interest: No intrest

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