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Preconceptional thyroid autoimmunity, dysfunction and associated factors in nulliparous Indian women

C. Jayakumari [a], Ashwin Valliyot [b], Sreejith Babu [b], Abilash Nair [b,*], Ravleen Kaur Bakshi [c], P.K. Jabbar [b], K. Amal [b], Chintha Sujatha [d], TS Anish [e], C. Nirmala [f], Lekshmi Vinod [g], Riaz Ismail [h], Bipin Gopal [i]

[a] Department of Emergency Medicine, Govt. Medical College, Thiruvananthapuram, India
[b] Department of Endocrinology and Metabolism, Govt. Medical College, Thiruvananthapuram, India
[c] Division of Reproductive, Biology, Maternal and Child health, Indian Council of Medical Research, India
[d] Department of Community Medicine, Govt. Medical College, Thiruvananthapuram, India
[e] Department of Community Medicine, Govt. Medical College, Manjeri, India
[f] Department of Obstetrics and Gynaecology, Sree Mookambika Medical College, India
[g] Department of Obstetrics and Gynaecology, Govt. Medical College, Thiruvananthapuram, India
[h] Department of Paediatrics, SAT Thiruvananthapuram, India
[i] Kerala Health Services Department, Thiruvananthapuram, India

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ABSTRACT

Background: Hypothyroidism in young women is associated with adverse reproductive outcomes. There are no previous population-based studies regarding the prevalence of hypothyroidism or thyroid autoimmunity in nulliparous preconceptional women. The current study was done to determine the prevalence of thyroid autoimmunity and thyroid dysfunction in newly married nulliparous Indian women.

Methods: Multistage sampling was employed to enrol married nulliparous women of 18–35 years age group from four socio geographic regions of Thiruvananthapuram district (urban, rural, coastal and hilly) based on 'eligible couple register' with the help of community health workers. Trained staff collected demographic and medical information and also conducted limited clinical examination for vital signs, goitre and anthropometric measurements. Biochemical investigations including serum thyrotropin (TSH), total thyroxine(T4), anti-thyroid-peroxidase (TPOAb) antibody were done in all participants.

Results: A total of 1507 women were enrolled, of whom 1379 with complete metabolic, anthropometric, and thyroid profile data were included in the final analysis. The prevalence of overt hypothyroidism was 3.0 % (n = 42) and subclinical hypothyroidism was 9.7 % (n = 134). The prevalence of TPOAb positivity was 19.2 %. In euthyroid, subclinical hypothyroid and overt hypothyroid population, TPOAb positivity was 13.28 %, 42.7 % and 71.8 % respectively. Fasting serum insulin, triglyceride, low-density lipoprotein (LDL) levels were higher in the hypothyroid group compared to euthyroid females. No associations with metabolic parameters were seen for TPOAb positivity.

Conclusion: One in eight preconceptional South Indian women suffer from hypothyroidism. Thyroid autoimmunity contributes to hypothyroidism in participants with higher TSH values whereas insulin resistance may contribute to subclinical hypothyroidism. Screening for hypothyroidism in the preconceptional period is recommended.

* Correspondence to: Department of Endocrinology and Metabolism, Govt. Medical College, Thiruvananthapuram 695011, India.
E-mail addresses: drcjayakumarimch@gmail.com (C. Jayakumari), drashwin@iidkerala.org (A. Valliyot), sreejith.747833@kerala.gov.in (S. Babu), abilashnair@tmc.kerala.gov.in (A. Nair), drravleen01@gmail.com (R.K. Bakshi), drjabbar@iidkerala.org (P.K. Jabbar), amalk47@gmail.com (K. Amal), sujathachintha@gmail.com (C. Sujatha), doctrinets@gmail.com (T. Anish), drnirmalatvm@gmail.com (C. Nirmala), lakshmi_vinodh@yahoo.com (L. Vinod), dr.riaztvm@gmail.com (R. Ismail), bipingopal@yahoo.com (B. Gopal).

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1. Background

Hypothyroidism affects 2–4 % of women of reproductive age group and has been linked to infertility and recurrent abortions [1]. It has been associated to reproductive disorders, including delayed puberty, anovulation, ovarian cysts, irregular menstrual cycles and infertility. During pregnancy there is increased frequency of spontaneous abortions, premature delivery, caesarean delivery and low birth weight [2]. In periconceptional period hypothyroidism can interfere with the process of implantation. Hypothyroidism in early pregnancy may be linked to reduced gray matter volume in offspring an effect not seen with later onset of hypothyroidism [3]. Caesarean section (CS) rates were higher in hypothyroid females compared to euthyroid females [4]. Globally there is limited data on prevalence of preconceptional hypothyroidism from a community based study. In a study done in Iranian population anti thyroid peroxidase antibody (TPOAb) was present in 12.8 % of the population, whereas a multicentre trial from India reported an TPOAb prevalence of 21.85 % [5,6]. TPOAb and Antithyroglobulin antibody (ATG) is found in up to 5–14 % and 3–18 % of pregnant women, respectively [7]. Out of the euthyroid TPOAb positive women, 7 % is likely to develop hypothyroidism in pregnancy [8]. There are studies favouring treatment of euthyroid TPOAb positive women with levothyroxine in pregnancy as it has improved pregnancy outcomes like preterm delivery, however there are studies with conflicting results regarding the same [9,10]. Implementing interventions early in pregnancy has been shown to effectively decrease the risk of maternal and fetal complications. While medical guidelines recommend screening for thyroid dysfunction during pregnancy, there is limited research on preconception screening. However, based on available evidence, it is believed that early screening would be more beneficial than later screening [11]. Early screening enables the initiation of treatment within a critical time frame to effectively address abnormal thyroid function and reduce the potential negative effects on fetal development caused by maternal thyroid dysfunction Against this backdrop, it becomes evident that early detection and treatment of hypothyroidism before conception is a key strategy for improving reproductive health and pregnancy outcomes. The overall prevalence of hypothyroidism reported in India is 10.95 % and prevalence of anti TPO antibody in India is 21.85 % [6]. However there is paucity of data regarding prevalence of thyroid autoimmunity and hypothyroidism in newly married females planning for pregnancy. Without a clear understanding of the prevalence of hypothyroidism in this specific demographic, we might miss opportunities for early intervention and the absence of data limits the formulation of evidence-based guidelines that could potentially mitigate the risks associated with untreated hypothyroidism during pregnancy in our population. The objective of this study was to determine the community-based prevalence of thyroid autoimmunity and dysfunction in newly married females between the ages of 18 and 35 and their associations with anthropometric and metabolic parameters.

2. Materials and methods

This was a community based cross sectional study done from January 1 2022 to December 31 2022, using multistage sampling in Thiruvananthapuram district of South India. Data was obtained as a part of a project on preconceptional community based intervention for prevention of gestational diabetes, sponsored by the Indian council of Medical Research titled Community based cluster randomised lifestyle intervention for prevention of gestational diabetes mellitus in married nulliparous women of 18–35years age". The manuscript was prepared using the preconceptional data obtained from the above mentioned study which was approved by the Human Ethics committee of Government Medical College Thiruvananthapuram vide letter no HEC No. 03/04/2020/MCT. Sample size calculation was done based on previous estimate of hypothyroidism by Unnikrishnan et al. showing a prevalence of 10.95 %,precision of estimate was set at 3.2 %, estimated sample size was 1351 participants. Married nulliparous woman of age group 18–35 years were recruited from four socio geographic regions of Thiruvananthapuram district (urban, rural, coastal and hilly). A total of 14 primary health centres and 107 subcentres were included in the study. Dedicated study staff were recruited and trained for conducting the survey and blood sampling. Additional training sessions were arranged in all PHC's for junior public health nurses, accredited social health activists (ASHA) and awareness was given to them by the investigators regarding recruitment of the participants and study related procedures. The ASHA at each subcentre provided the details of newly married couples from the 'Eligible Couple Register'. The study staff visited the household of all prospective participants with the help of respective ASHA and requested participation after explaining abo the study and procedures.

The inclusion criteria was newly married woman yet to have her first child and not pregnant at present. Women on infertility treatment or suffering from any chronic illness, taking medications like steroids biotin or antiepileptics, having history of pituitary surgery or unwilling to participate in the study were excluded.

After getting written informed consent, detailed history was taken including sociodemographic details, symptoms and family history of thyroid disease or any treatment were enquired and entered in a semi structured proforma. Clinical examination including anthropometric measurements, pulse rate, blood pressure, height, weight, waist circumference, body mass index and examination for goitre was done. An average of 3 seated blood pressure measurements 3 min apart after 5 min of rest using Omron HEM 7120 (Kyoto, Japan) were done. Five ml of blood was drawn under aseptic precautions before 10 am for measuring thyrotropin(TSH), thyroxine (Total T4) and anti-thyroid peroxidase antibody (TPOAb). The collected blood sample was transported to a central laboratory maintaining cold chain as required. Additionally, hemoglobin fasting lipid profile (FLP), plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting insulin, and, glycosylated hemoglobin (HbA1c) was also done in all subjects.

Digital weighing scale (Seca 813. Hamburg, Germany) was used for measuring body weight. Non stretchable tape (Seca 201, Hamburg. Germany). Seca 213 L portable stadiometer (Hamburg, Germany) were used for anthropometric assessment. Serum TSH, Total T4 and TPO antibodies was measured on the Roche e411 immunoassay analyser which employs the electrochemiluminescence immunoassay (ECLIA) sandwich principle for TSH and TPOAb and competitive immunoassay for Total T4. 'Elecsys TSH, Elecsys T4, Elecsys Anti-TPO kit were used which was non-competitive two site assay. The coefficient of variation was 8.7 % at lower values and 1.8 % near TSH values of 10 μIU/ml. Similarly – T4 at lower range 2.2 % and higher range 4.3 %.For anti TPO, coefficient of variation at 15IU/L was 7 % and 4.2 % at mean concentration of 269 IU/ml

In the current study the classification as hypothyroidism was made at a TSH level $>$ 10μIU/ml and as subclinical hypothyroidism when TSH was between 5 and 10 μIU/ml with normal T4 [12,13]. Reference range of TSH assay is 0.27–4.2μIU/ml. Participants with TSH $<$ 0.27 with T4 levels above 12 μg/dl were diagnosed as having hyperthyroidism. Anti-TPO antibody positivity was defined as a value $>$ 34 IU/ml as per the kit reference range. Overweight was defined as those with BMI between 23.0–24.9 kg/m^2 and obesity as those having BMI $\geq$ 25.0 kg/m^2 according to the guidelines for Indian subjects. Participants detected to have subclinical or overt hypothyroidism were referred for appropriate treatment to the Endocrine clinic at Medical College, Thiruvananthapuram.

The demographic, anthropometric, clinical and biochemical data were tabulated in MS Excel 2017. Quantitative variables were summarized as mean and standard deviation SD or median and interquartile range based on the normality of distribution. Statistical analysis was done using SPSS version 28.0.1.0(NY,USA). Qualitative variables like prevalence of hypothyroidism, subclinical hypothyroidism, TPO

antibody positivity etc were expressed as frequency and percentages. Comparison between euthyroid, hypothyroid and subclinical hypothyroid participants were done for various parameters and significance of association was determined using Student t test and chi-square test.

3. Results

A total of 1507 women were enrolled, of whom 1379 had complete anthropometric, metabolic and thyroid profiles and were included in the final analysis. Mean age of study population was 25.08 ± 3.15 years. Urban,rural, hilly and coastal areas constituted 384(24.5 %), 370 (24.2 %), 382(25.7 %)and 368(24.6 %) participants respectively. Mean BMI was 23.4 ± 4.9. Obesity was present in 441(32.1 %)and overweight in 234(17.9 %). Abdominal obesity (Abdominal circumference>80 cm) was present in 635(60.0 %) women.Goitre was present in 0.8 %(11/1399) of study population. Median TSH level was 2.57 μIU/ml IQR (1.84–3.7). Prevalence of anti TPO antibody was 19.2 %(See Table 1). Median anti TPO was 12.9 IU/L (IQR 10.2–21.4).In Anti TPO negative women, the range of TSH was from 0.05 to 75.6 μIU/ml. The prevalence of hypothyroidism was 3 % and subclinical hypothyroidism was 9.7 % (Fig. 1). Mean T4 levels was 8.79 ± 2.14 μg/dl. No statistically significant difference in prevalence of hypothyroidism was noted across 4 regions. The urban, rural, coastal, hilly areas had 51 (14.8),38 (11.0),35 (9.9 %),49(14.4 %) respectively participants with hypothyroidism ($p = 0.09$). Twenty participants were found to have hyperthyroidism (TSH < 0.27μIU/ml) of whom 17 subjects had subclinical hyperthyroidism (i.e. normal T4), whereas 3 had overt hyperthyroidism. The median of anti TPO antibody was 13.7 IU/L. Out of 269 TPOAb positive persons 43.3 % were hypothyroid whereas in TPOAb negative population 7.0 % were hypothyroid (Fig. 2). TPO antibody positivity increased from 13.2% in euthyroid group to 42.7 % in subclinically hypothyroid group and to 71.8% in the overt hypothyroid group (Fig. 3).

Mean fasting triglyceride and fasting insulin levels were higher in hypothyroid group compared to euthyroid females. Body mass index (BMI), abdominal circumference, waist circumference, systolic BP, diastolic BP, AST, ALT, and HbA1c were not significantly different in hypothyroid group compared to euthyroid group (Table 2). Though fasting insulin levels were higher in patients with TSH > 5 μIU/ml, the proportion of patients with insulin resistance as calculated by HOMA IR was not significantly different in patients with normal and elevated TSH levels.

TPOAb positive participants were not statistically different with regard to BMI, Abdominal circumference, waist circumference, Systolic BP, Diastolic BP, AST,ALT, Lipid profile, HbA1c, fasting Insulin, HOMA IR when compared to TPOAb negative group (Table 3).

Table 1
Baseline parameters.

Parameter (n = 1379)	Mean ± SD or Frequency (Percentage)
Age (years)	25.08 ± 3.16
Height (cm)	156 ± 6.8
Weight(kg)	57.4 ± 12.8
BMI (kg/m^2)	23.4 ± 4.9
Systolic Blood pressure (mm Hg)	106 ± 14.3
Diastolic Blood pressure (mm Hg)	77.2 ± 9.45
Waist Cirumference(cm)	81.9 ± 12.8
Hip circumference(cm)	92 ± 11.5
TSH(μIU/ml)	3.36 ± 4.13
Total T4 (mcg/dl)	8.79 ± 2.14
Goitre n (%)	11(0.8 %)
Sub clinical hypothyroidism n (%)	134 (9.7 %)
Overt Hypothyroidism n (%)	42(3.0 %)
Anti TPO Positive n (%)	264 (19.2 %)
TPO Ab Positive in Hypothyroidism [SCH or OH]	90/264 (34.0 %)

Of the 1507 women enrolled,complete anthropometric,metabolic data and thyroid profile were available for 1379 participants.

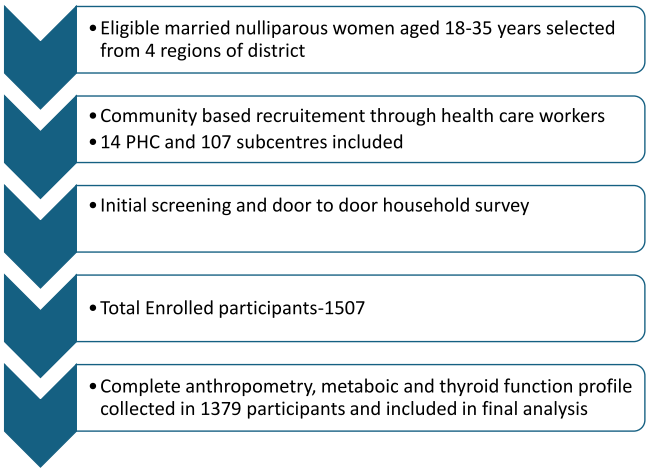

Fig. 1. Study design flow chart.

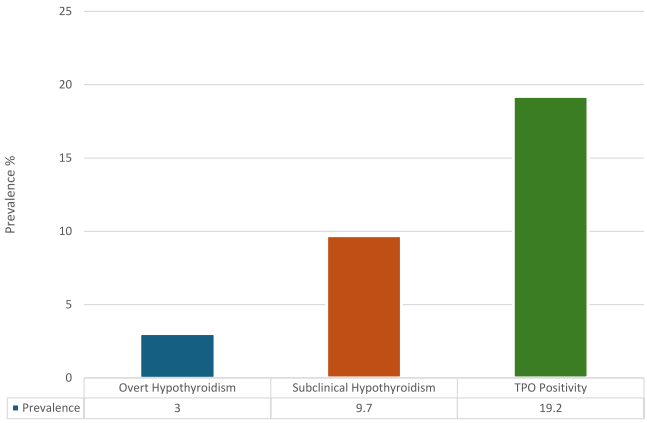

Fig. 2. Prevalence of Hypothyroidism and TPOAb positivity in preconceptional women(%).

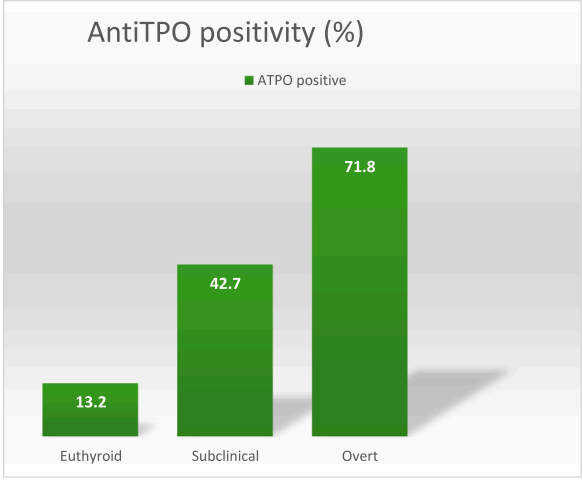

Fig. 3. Anti TPO Antibody positivity among Euthyroid, Subclinically hypothyroid and Overt Hypothyroid participants.

Within the TPOAb negative group, hypothyroid individuals had higher FPG, fasting insulin, serum triglyceride and serum LDL levels and lower HDL levels compared to those who were euthyroid (Table 4) Similar findings were observed in TPOAb positive hypothyroid group who additionally had higher hs CRP compared to those who were

Table 2
Comparison between hypothyroid and euthyroid groups.

Parameter	Euthyroid (Mean ±SD)	Hypothyroid (Mean ±SD)	P value
Weight(kg)	57.5 ± 12.59	58.12 ± 13.0	0.61
BMI	23.46 ± 4.8	23.54 ± 4.7	0.85
Systolic BP(mmHg)	107.27 ± 11.6	107.6 ± 9.6	0.69
Diastolic BP(mmHg)	71.56 ± 17.1	71.42 ± 8.6	0.92
Abdominal Circumference(cm)	78.77 ± 11.1	79.32 ± 11.1	0.54
Waist Cirumference(cm)	81.93 ± 12.74	82.97 ± 12.3	0.32
Hip circumference(cm)	92.17 ± 12.0	92.62 ± 12.3	0.66
Neck circumference(cm)	30.89 ± 2.9	30.6 ± 3.9	0.43
TPOAb	36.8 ± 8	107.0 ± 133.2	**0.0001**
SGOT	24.4 ± 10.8	24.83 ± 9.0	0.68
SGPT	22.9 ± 21.0	22.11 ± 16.3	0.64
Cholesterol(mg/dl)	186.60 ± 33.0	190.96 ± 37.1	0.12
Triglyceride(mg/dl)	85.98 ± 40.1	94.7 ± 41.4	**0.009**
HDL(mg/dl)	49.95 ± 10.5	47.23 ± 9.7	**0.002**
LDL(mg/dl)	120.22 ± 29.9	125.64 ± 34.2	**0.033**
Hemoglobin(g/dl)	12.5 ± 1.3	12.6 ± 1.4	0.69
HbAIC(%)	5.26 ± 0.4	5.28 ± 0.8	0.76
hsCRP(mg/L)	2.72 ± 4.82	2.48 ± 3.0	0.55
FastingInsulin(mIU/L)	11.20 ± 3.7	13.21 ± 12.27	**0.009**
HOMA IR	3.9 ± 4.5	4.5 ± 7.8	0.10
RDW(FL)	14.1 ± 1.9	14.6 ± 2.2	**0.013**
Total Lymphocyte(Cells)	33.4 ± 8.4	35.3 ± 8.2	**0.006**
RBC Count (cells)	4.48 ± 0.41	4.58 ± 0.4	**0.008**

Table 3
Comparison between TPOAb positive and negative group.

Parameter	TPOAb Negative (Mean±SD)	TPOAb Positive (Mean±SD)	P value
BMI	23.46 ± 4.8	23.54 ± 4.7	0.85
Systolic BP(mmHg)	107.69 ± 11.3	105.6 ± 11.7	0.28
Diastolic BP(mmHg)	71.94 ± 17.6	70.10 ± 9.5	0.64
Abdominal Circumference(cm)	78.9 ± 10.9	78.4 ± 11.2	0.49
Waist Cirumference (cm)	82.9 ± 33.8	85.9 ± 62.1	0.18
Hip circumference(cm)	92.2 ± 29.2	137.2 ± 64.1	0.23
Neck circumference (cm)	30.88 ± 6.7	31.3 ± 7.5	0.76
SGOT (IU/L)	24.60 ± 10.8	24.72 ± 10.3	0.56
SGPT (IU/L)	22.87 ± 19.2	22.05 ± 19.5	0.27
Cholesterol(mg/dl)	186.28 ± 32.9	190.7 ± 35.7	0.33
Triglyceride(mg/dl)	86.49 ± 39.7	87.6 ± 38.1	0.39
HDL(mg/dl)	49.6 ± 10.5	49.9 ± 9.7	0.13
LDL(mg/dl)	120.1 ± 29.7	123.28 ± 33.5	0.22
Hemoglobin(g/dl)	12.5 ± 1.3	12.6 ± 1.3	0.85
HbAIC(%)	5.2 ± 0.5	5.27 ± 0.5	0.30
hsCRP(mg/L)	2.66 ± 4.2	2.87 ± 6.18	0.19
FastingInsulin(mIU/L)	11.54 ± 9.3	10.6 ± 8.9	0.65
HOMA IR	4.12 ± 6.9	3.50 ± 6.4	0.13

TPOAb positive euthyroid (Table 5), which may mean that in TPOAb positive subjects, inflammation is associated with progression to hypothyroidism.

On multivariable binary logistic regression analysis only fasting insulin level and HDL level were found to have an independent association with hypothyroidism (Table 6).

4. Discussion

4.1. Prevalence of hypothyroidism and autoimmunity in reproductive age group females

This study was done to determine the prevalence of hypothyroidism, and anti TPO antibody positivity among newly married females planning for pregnancy. It was conducted at community level in a South Indian district. This is an understudied demographic group probably because of the difficulty in locating newly married preconceptional women in a community setting. Notably, we found that one in eight (12.7 %) of the participants had subclinical or overt hypothyroidism. Additionally, 19.2 % tested positive for anti-thyroid peroxidase antibodies which suggests that a significant portion of this population may remain undiagnosed and untreated during pregnancy if proper screening measures are not practiced.

In a previous study by Bjoro et al., hypothyroidism was observed in 4.8 % of females in reproductive age group [14] The prevalence of subclinical hypothyroidism in reproductive age group has been reported from 4 % to 8 % in a study by Krassas et al. [15]. The prevalence of TPO-Ab ranges from 8 % to 14 % in women of reproductive age group. In a retrospective cross sectional study conducted in Spain, the known

Table 4
Comparison TPOAb negative hypothyroid vs euthyroid group.

Parameter	TPOAb Negative Hypothyroid (Mean ±SD)	TPOAb Negative Euthyroid (Mean ±SD)	P value
BMI (kg/m^2)	23.57 ± 5.09	23.43 ± 4.84	0.26
Systolic BP (mmHg)	108.1 ± 9.5	108.2 ± 3.4	0.21
Diastolic BP (mmHg)	71.45 ± 11.15	74.6 ± 4.7	0.63
Abdominal circumference (cm)	79.63 ± 11.8	78.8 ± 10.8	0.25
Hip circumference (cm)	93.87 ± 10.6	92.2 ± 11.9	0.12
Fasting Glucose (mg/dL)	93.6 ± 57.4	85.7 ± 10.58	**0.036**
Fasting Insulin (mIU/ml)	17.53 ± 19	11.7 ± 12.6	**0.05**
HbA1c(%)	5.2 ± 0.9	5.0 ± 0.8	0.51
Triglyceride (mg/dL)	102 ± 48.6	86.1 ± 47.7	**0.02**
HDL (mg/dL)	46.2 ± 9.7	50.5 ± 14.6	**< 0.05**
LDL (mg/dL)	127 ± 30.3	119 ± 29.4	**0.05**
hsCRP	2.97 ± 3.8	2.6 ± 4.3	0.69

Table 5
Comparison TPOAb Positive Hypothyroid vs Euthyroid group.

Parameter	TPOAb Positive Hypothyroid (Mean ±SD)	TPOAb Positive Euthyroid (Mean±SD)	P value
BMI(kg/m2)	23.7 ± 4.0	23.5 ± 4.8	0.84
Systolic BP (mmHg)	106.9 ± 10.03	106.1 ± 17.69	0.15
Diastolic BP (mmHg)	70.33 ± 10.85	69.73 ± 9.0	0.46
Abdominal circumference (cm)	79.63 ± 11.8	78.8 ± 10.8	0.25
Neck circumference (cm)	30.94 ± 2.69	30.63 ± 4.46	0.20
Fasting Glucose (mg/dL)	87.93 ± 57.4	91.±72.02	0.55
Fasting Insulin (mIU/ml)	17.53 ± 19	11.7 ± 12.6	**0.05**
Triglyceride (mg/dL)	102 ± 48.6	86.1 ± 47.7	**0.02**
HDL (mg/dL)	46.2 ± 9.7	50.5 ± 14.6	**< 0.05**
LDL (mg/dL)	127 ± 30.3	119 ± 29.4	**0.05**
HbAIC(%)	5.2 ± 0.6	4.1 ± 2.29	**< 0.001**
hsCRP(mg/dl)	6.8 ± 15.3	3.1 ± 7.72	**0.03**
SGOT(IU/L)	24.3 ± 8.79	25.47 ± 12.09	0.75
SGPT(IU/L)	22.05 ± 15.6	22.74 ± 23.89	0.25

Table 6
Multivariable analysis for independent associations with hypothyroidism in the TPO negative group.

Parameters in the Multivariable Analysis	Unstandardized Coefficient (B)	Odds Ratio (OR)	95 % Confidence Interval (CI) for OR	p-value
Fasting Insulin	0.016	1.016	[1.003, 1.029]	0.01
Triglycerides	0.001	1.001	[0.997, 1.005]	0.56
High-Density Lipoprotein	-0.03	0.97	[0.943, 0.998]	0.02
Low-Density Lipoprotein	0.006	1.006	[0.998, 1.014]	0.13
Fasting Plasma Glucose	0.008	1.008	[0.998, 1.018]	0.1
High Sensitivity CRP	-0.018	0.982	[0.941, 1.025]	0.58
Constant	-2.807	0.06	N/A	0.002

Logistic regression based OR (Odds Ratio) represents the change in the odds of having hypothyroidism for a one-unit increase in the respective parameter, holding all other variables constant. CRP = C-Reactive Protein; TPO = Thyroid Peroxidase.

prevalence of hypothyroidism in the year before conception was 5.09 % [16]. It was also noted that regular thyroid function monitoring was not done year prior to pregnancy in 40 % of this population with thyroid dysfunction. In an Indian study, the overall prevalence of hypothyroidism in women in preconceptional period was 13.2 % [17].

4.2. Impact of maternal hypothyroidism on fetal neurocognitive development

India is currently witnessing the effects of universal salt iodization efforts. Despite this, there remains a significant occurrence of subclinical hypothyroidism, and high prevalence of anti TPO antibodies. In previous studies women with subclinical hypothyroidism had a threefold increased risk of placental abruption complicating their pregnancies. In women with subclinical hypothyroidism, the risk of preterm birth—defined as delivery at or before 34 weeks of gestation—was nearly two times higher [18]. In a previous study done by our group, maternal hypothyroidism was associated with 3.6-fold increased likelihood of experiencing threatened abortion and a 3.8-fold risk of developing gestational hypertension. The risk of caesarean section was also significantly higher in the hypothyroid group [19]. Maternal hypothyroidism affects the neuropsychological development of fetus. The most important evidence for this finding came from the study from Haddow et al., in which serum thyrotropin levels were measured in 25,216 pregnant women. Children of women with high thyrotropin concentrations, particularly those not treated for thyroid deficiency during pregnancy, exhibited slightly lower performance at the age of 7 years on 15 tests related to intelligence, attention, language, reading ability, school performance, and visual-motor skills. Their full-scale IQ scores were notably lower, and 19 % had scores of 85 or less compared to 5 % in the control group [20]. In another study, Jansen *et al.,* investigated association of maternal thyroid function with child brain morphology. An inverted U shaped association was established between maternal TSH levels and offspring's total grey matter volume, with the strongest impact seen around 8 weeks of gestation. Beyond the 14th week of gestation, there was no observed connection between TSH levels and child brain morphology [3]. This study suggests that screening for thyroid deficiency in preconceptional period may be crucial to identify and address undiagnosed hypothyroidism, preventing potential adverse effects on fetal development. According to the results of our study, a significant proportion of women in the preconceptional period have subclinical hypothyroidism without being diagnosed, which could have an adverse impact on the outcome of a pregnancy.

4.3. Thyroid function and metabolic parameters

After stratification for TPO positivity, the participants demonstrated a relation of TSH levels and hypothyroidism with some metabolic parameters notably serum triglyceride levels, LDL levels, HbA1c, FPG, fasting serum insulin levels and inflammatory parameter hs CRP. This is consistent with findings of previous studies which had shown that those with hypothyroidism had significantly higher triglyceride levels [21]. This phenomenon may be attributed to the upregulation of interleukin-6 and tumour necrosis factor-α in adipocytes when TSH levels increase. Both IL-6 and TNF-α can stimulate lipolysis, resulting in insulin resistance and the development of hypertriglyceridemia. Moreover, fasting insulin levels were significantly higher in those with TSH > 5μIU/ml, compared to euthyroid individuals, however there was no statistically significant difference in insulin resistance as assessed by HOMA IR in both groups. Individuals diagnosed with subclinical hypothyroidism (SCH) have an increased likelihood of developing cardiovascular disease (CVD). Hs-CRP is among the inflammatory markers associated with CVD in such cases [22]. A recent metaanalysis, also concluded that subclinical hypothyroidism is associated with increased CRP levels [23]. In current study it was observed that hsCRP is associated with progression with hypothyroidism only in TPOAb positive participants highlighting the role of inflammation in the development of hypothyroidism in TPOAB positive individuals,an effect which is not seen in TPOAb negative individuals. We could not find similar associations from previous studies This association needs to be confirmed by future prospective studies in TPOAb positive individuals

It is important to consider the implementation of community-based pre-conceptional screening for thyroid dysfunction and autoimmunity in females planning for pregnancy. Adopting a universal screening approach could be an effective solution to identify hypothyroidism in this specific demographic group, which when treated will improve the pregnancy outcome, rather than screening for thyroid dysfunction when pregnancy complications are diagnosed. The strength of our study is the community-based house-to-house survey with a large sample size. However, a minor limitation of our study is that the clinical examination was performed by trained paramedical staff and not clinicians. Ultrasound thyroid was done for goitre assessment. Free T4 and antithyroglobulin antibodies were not assessed; use of total T4 may slightly over- or under-estimate thyroid hormone status in some participants.

5. Conclusion

The prevalence of thyroid dysfunction and autoimmunity among women of reproductive age, in south Indian population is high. Metabolic parameters of insulin resistance a have a significant association with thyroid dysfunction. Considering the risk of untreated hypothyroidism in early pregnancy, it is important to screen females planning for pregnancy for thyroid dysfunction to improve maternal and child health.

CRediT authorship contribution statement

Chintha Sujatha: Formal analysis, Data curation, Conceptualization. **TS Anish:** Formal analysis, Data curation, Conceptualization. **Chellamma Nirmala:** Validation, Supervision, Project administration. **Vinodh Lekshmi:** Writing – review & editing, Resources, Project administration. **Riaz Ismail:** Writing – review & editing, Supervision, Methodology. **Chellamma Jayakumari:** Project administration, Methodology, Conceptualization. **Bipin Gopal:** Supervision. **Sreejith Babu:** Project administration. **Abilash Nair:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ashwin Valliyot:** Writing – original draft, Data curation. **Ravleen Kaur Bakshi:** Writing – review & editing, Formal analysis. **P K Jabbar:** Supervision, Resources. **K Amal:** Writing – original draft, Supervision, Project administration,

Investigation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Abilash Nair reports financial support was provided by Indian Council of Medical Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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