ORIGINAL ARTICLE

Association between placental growth factor levels and maternal hypothyroidism at 11–13 weeks of gestation: A hospital-based cross-sectional study (single center) in Vietnam

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ABSTRACT

Background and aim: This study aimed to evaluate the association between maternal placental growth factor (PlGF) levels and thyroid function (FT_4 and TSH), and to assess whether elevated PlGF is associated with hypothyroidism during early pregnancy.

Methods: This hospital-based, single-center, cross-sectional study was conducted at Hung Vuong Hospital, Vietnam, from February to May 2025. A total of 213 pregnant women between 11 and 13 weeks of gestation were enrolled. Hypothyroidism was defined according to the 2017 American Thyroid Association guidelines, including both overt and subclinical hypothyroidism. Marginal effects were estimated and visualized to assess the association between PlGF levels, thyroid hormone concentrations, and the probability of hypothyroidism.

Results: The median maternal age was 32 years. Median PlGF, FT_4, and TSH concentrations were 50.5 pg/mL, 1.10 ng/dL, and 1.05 mIU/L, respectively. The prevalence of hypothyroidism among pregnant women was 10.3%. PlGF was inversely associated with FT_4 concentrations but showed no significant association with TSH. PlGF levels above the 97.5th percentile were associated with a 7.3-fold higher odds of hypothyroidism (95% CI, 1.03–51.4) after adjustment for gestational age, parity, obesity, and education level.

Conclusions: These findings suggest a potential association between placental angiogenic activity and maternal thyroid function, particularly involving FT_4. Extremely elevated PlGF concentrations may be associated with

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thyroid dysfunction and could potentially serve as a novel biomarker for early risk identification or screening. (www.actabiomedica.it)

Key words: placental growth factor, thyroid function, pregnancy, hypothyroidism, Vietnam

Introduction

Maternal hypothyroidism during pregnancy includes both overt and subclinical forms, characterized by insufficient thyroid hormone production to meet the physiological demands of the mother and fetus. Diagnosis is established through elevated thyroid-stimulating hormone (TSH) and low or normal free thyroxine (FT4) concentrations according to trimester-specific reference ranges (1). The clinical relevance of hypothyroidism in pregnancy lies in its potential adverse effects on maternal and fetal health. Untreated cases have been associated with miscarriage, preeclampsia, preterm birth, and impaired neurocognitive development in offspring (2-4). The global prevalence of maternal hypothyroidism ranges from 2% to 5%, depending on iodine sufficiency and population characteristics (5). Early detection and appropriate management are essential to minimize these complications (3, 6). Risk factors contributing to maternal hypothyroidism include advanced maternal age, increased body mass index, multiparity, inadequate iodine intake, and autoimmune thyroid disease (1, 7-10). Placental growth factor (PlGF), an angiogenic member of the vascular endothelial growth factor (VEGF) family, plays a pivotal role in placental vascularization and trophoblast invasion during early gestation (11). Altered PlGF expression has been implicated in various obstetric complications, including preeclampsia and fetal growth restriction (12). Recent evidence indicates that thyroid hormones and angiogenic factors such as PlGF may interact to regulate placental and endocrine adaptation to pregnancy (13). PlGF relates to thyroid function via hCG-mediated TSH-receptor activation and trophoblast angiogenesis, and via endothelial–placental cross-talk whereby PlGF/sFlt-1 modulate thyroid microvascular perfusion and hormone synthesis (13-15). Several studies have demonstrated associations between maternal TSH and FT4 concentrations and circulating PlGF levels, suggesting that thyroid dysfunction may influence placental angiogenesis (16-18). Despite the growing international interest in the interplay between thyroid and angiogenic pathways, there is a paucity of comparable research in Vietnam. Existing local studies have primarily focused on iodine status and thyroid disease prevalence (19, 20), leaving an important knowledge gap regarding the interaction between thyroid function and placental biomarkers. Understanding this relationship during early pregnancy is particularly crucial, as the first trimester represents a critical window for placental and fetal development. Therefore, this study aimed to determine the correlation between maternal PlGF and thyroid hormones (FT4, TSH), and to evaluate the association between PlGF levels and maternal hypothyroidism during early pregnancy (11–13 weeks of gestation). This study tests the hypothesis that, at 11–13 weeks of gestation, higher maternal PlGF concentrations are inversely correlated with FT4 and positively correlated with TSH, and that elevated PlGF is associated with increased odds of maternal hypothyroidism.

Patients and methods

Study design and setting

The cross-sectional study was conducted at Hung Vuong Hospital, a central tertiary maternity facility located in Ho Chi Minh City. Established in 1975 and currently managed by the Ho Chi Minh City Department of Health, the hospital has approximately 900 inpatient beds and nearly 1,300 staff members. It serves as a leading referral center for prenatal diagnostics,

obstetric and gynecologic care, infertility treatment, neonatology, and family planning services, including subspecialties such as pelvic urogynecology and health communication counseling. With over 40,000 deliveries annually, the hospital plays a pivotal role in maternal and perinatal healthcare in southern Vietnam. Its high patient volume and multidisciplinary services make it a suitable setting for research on maternal health outcomes. The research protocol was approved by the Biomedical Research Ethics Committee at the University of Medicine and Pharmacy at Ho Chi Minh City under Decision No. 1189/HDDD-DHYD, dated November 28, 2023. All participating women were fully informed about the objectives and procedures of the study and provided written informed consent before enrollment. This study was conducted and reported in accordance with the STROBE guidelines for observational research (21).

Study participants

The study population consisted of pregnant women with confirmed singleton pregnancies who attended routine antenatal care visits between 11 weeks and 13 weeks 6 days of gestation at Hung Vuong Hospital. Gestational age was determined using crown–rump length (CRL) measured by trained sonographers. Inclusion criteria included a viable singleton intrauterine pregnancy, no prior diagnosis of thyroid dysfunction, and complete clinical and demographic data availability. Exclusion criteria encompassed any history of thyroid disorders before pregnancy, such as hypothyroidism, hyperthyroidism, thyroid nodules, thyroid cancer, or simple goiter or current use of medications known to influence thyroid function. Additional exclusion criteria were the presence of fetal structural abnormalities detected on first-trimester ultrasound and pre-existing severe chronic medical conditions such as type 1 diabetes mellitus, systemic lupus erythematosus, or end-stage chronic kidney disease.

Sample size

The sample size for this study was calculated to ensure adequate power to detect a statistically significant correlation coefficient different from zero (22). The calculation was based on a two-sided significance level of 0.05, a statistical power of 80%, and an expected correlation coefficient of 0.20. Under these assumptions, the initially estimated sample size was 194 participants. To account for potential non-response or incomplete data, a 5% adjustment was applied, resulting in a final required sample size of approximately 204 participants. In this study, we enrolled 213 participants to improve the robustness of the analysis and ensure high data quality in case of missing values or exclusions during data cleaning.

Sampling

The selection of participants was conducted at the outpatient department of Hung Vuong Hospital. Eligible patients were identified during routine prenatal visits based on predefined inclusion and exclusion criteria. Recruitment and data collection were performed on weekdays, with an average of five participants enrolled per day, over the period from February to April 2025. All eligible participants received a detailed explanation of the study objectives and procedures, and written informed consent was obtained before inclusion. Recruitment was terminated once the target sample size required for the study was achieved. Upon enrollment, a trained research team consisting of two nurses collected baseline demographic and clinical history data using a structured questionnaire. Thereafter, participants underwent routine clinical examinations and venous blood sampling in accordance with the hospital's standard protocols.

Variables

In this study, the primary outcome variable was maternal hypothyroidism, defined as a binary variable indicating the presence or absence of hypothyroidism at 11–13 weeks of pregnancy. A pregnant woman was considered to have hypothyroidism if she met the diagnostic criteria for either overt hypothyroidism or subclinical hypothyroidism. As there are currently no officially established reference ranges for TSH and FT_4 levels in pregnant Vietnamese women, we adopted the diagnostic criteria for thyroid dysfunction in the first trimester as recommended by the

American Thyroid Association (ATA) in 2017 (1). Specifically, clinical hypothyroidism was defined as a TSH concentration ≥ 10 mIU/L regardless of FT_4 level, or a TSH level between 2.5 and <10 mIU/L accompanied by a reduced FT_4 level (<0.93 ng/dL). Subclinical hypothyroidism was defined as a TSH level between 2.5 and 10 mIU/L with FT_4 concentrations remaining within the reference range (0.93–1.91 ng/dL) (1). A range of maternal characteristics and biochemical parameters were included as independent variables or covariates in the analysis. Maternal age (years) and gestational age (weeks) at the time of blood sampling were treated as continuous. PlGF concentrations (pg/mL) were examined as a continuous variable and, in parallel, stratified into percentile categories (>90th, >95th, and >97.5th) to evaluate associations with thyroid dysfunction. As assay-specific manufacturer reference ranges for PlGF have not been validated in Vietnamese pregnant populations, fixed cut-offs were not applied. Maternal FT_4 (ng/dL) and TSH (mIU/L) levels were included as continuous variables reflecting thyroid hormone concentrations. The laboratory testing procedures were conducted at the Laboratory Department of Hung Vuong Hospital. Venous blood samples were collected, centrifuged at 4,000 rpm for 10 minutes to separate the serum, and either analyzed within 3 hours at 20 °C or stored at −18 °C for up to 30 days before testing. PlGF, FT4, and TSH concentrations were measured using the Roche Cobas e801 analyzer based on the electrochemiluminescent immunoassay (ECLIA) technique. All reagents, calibrators, and control serum were supplied by Roche Diagnostics. Assay performance was verified according to CLSI EP15-A3 guidelines and met the required precision and accuracy standards. Additional sociodemographic and clinical factors were assessed. Parity was categorized as nullipara, primipara, or multipara. Maternal education level was grouped into three categories: secondary school or lower, high school, and university or higher. Household income was classified into three groups based on monthly income in Vietnamese Dong (VND): ≤10 million, 11–20 million, and >20 million. Maternal obesity status was recorded as a binary variable (yes/no), based on body mass index (BMI), and defined as having a BMI greater than 25.

Statistical analysis

All data were double-entered using EpiData version 3.1 to ensure accuracy. After data cleaning, statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA). A complete-case analysis was applied; participants with missing values for the variables of interest were excluded from the corresponding analyses. Descriptive statistics were used to summarize the characteristics of the study population, with continuous variables presented as medians and interquartile ranges (IQRs), and categorical variables expressed as frequencies and percentages. The normality of continuous variables was assessed by visual inspection of histograms and Q–Q plots and formally tested using the Shapiro–Wilk test. Differences between groups were examined using the Mann–Whitney U test for non-normally distributed quantitative variables and the chi-square test for categorical variables. Marginal effects at different PlGF levels were estimated using the "margins" command in Stata, and the "marginplot" command was subsequently applied to visualize the relationship between PlGF and thyroid hormone levels or the predicted probability of hypothyroidism. Potential confounders were selected a priori based on biological plausibility and published evidence supporting their associations with both placental angiogenic markers and maternal thyroid function. These confounders included gestational age, parity, maternal obesity, and education level. Multivariable linear and logistic regression models were used to adjust for these factors. Furthermore, PlGF concentrations were categorized into percentile groups (>90th, >95th, and >97.5th percentiles) to evaluate the predicted probability of hypothyroidism associated with elevated PlGF levels. Because no official guidelines or standardized cut-off values currently define high PlGF levels in relation to maternal thyroid function, these percentile thresholds were selected on an exploratory basis. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported for each category. Multicollinearity in linear regression models was assessed using the variance inflation factor (VIF), and logistic model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test. A two-sided P value < 0.05 was considered statistically significant.

Results

Table 1 shows the characteristics of pregnant women at 11–13 weeks of gestation. The median maternal age was 32.0 years, and the median gestational age at assessment was 12.1 weeks. The median PlGF level was 50.5 pg/mL, the median FT4 level was 1.10 ng/dL, and the median TSH level was 1.05 mIU/L. Regarding parity, the largest group of women were primiparous (36.2%), followed by nulliparous women (34.7%), with the smallest group being multiparous women (29.1%). Educational attainment showed a similar distribution, with the highest percentage of women having a university degree or higher (36.2%), followed by those with a high school education (35.2%), and the lowest percentage among those with secondary school or less (28.6%).

Table 1. Characteristics of pregnant women at 11-13 weeks of gestation by different factors.

Variables	Median (IQR)
Maternal age (years)	32.0 (10.0)
Gestational age (weeks)	12.1 (0.6)
PlGF (pg/mL)	50.5 (24.6)
FT_4 (ng/dL)	1.10 (0.23)
TSH (mIU/L)	1.05 (1.11)
	N (%)
Parity	
Nullipara	74 (34.7)
Primipara	77 (36.2)
Multipara	62 (29.1)
Education	
Secondary school or lower	61 (28.6)
High school	75 (35.2)
University or higher	77 (36.2)
Income (mil. VND)	
≤10	57 (26.8)
11-20	87 (40.9)
>20	69 (32.3)
Obesity	
No	159 (74.6)
Yes	54 (25.4)

Abbreviations: IQR: Interquartile Range, mil. VND: Million Vietnamese Dong.

In terms of monthly household income, most women belonged to households earning ≤20 million VND (67.7%). Additionally, a notable proportion of women were classified as obese (25.4%).

Table 2 presents the comparison of maternal characteristics according to hypothyroidism status at 11–13

Table 2. Comparison of maternal characteristics by hypothyroidism status at 11–13 weeks of gestation.

Variables	Hypothyroidism	Without hypothyroidism	P value
Maternal age, years, median (IQR)	28.0 (7.0)	32.0 (11.0)	0.10
Gestational age, weeks, median (IQR)	12.1 (0.4)	12.1 (0.7)	0.18
PlGF, pg/mL, median (IQR)	51.2 (25.7)	50.5 (24.6)	0.64
Parity, N (%)			
Nullipara	11 (14.9)	63 (85.1)	0.28
Primipara	6 (7.8)	71 (92.2)	
Multipara	5 (8.1)	57 (91.9)	
Education, N (%)			
Secondary school or lower	6 (9.8)	55 (90.2)	0.02
High school	13 (17.3)	62 (82.7)	
University or higher	3 (3.9)	74 (96.1)	
Income, mil. VND, N (%)			
≤10	2 (3.5)	55 (96.5)	0.02
11-20	15 (17.2)	72 (82.8)	
>20	5 (7.3)	64 (92.8)	
Obesity, N (%)			
No	15 (9.4)	144 (90.6)	0.46
Yes	7 (13.0)	47 (87.0)	
Total, N (%)	22 (10.3)	191 (89.7)	N/A

Abbreviations: mil. VND: Million Vietnam Dong, N/A: Not Applicable, IQR: Interquartile Range, P values were calculated using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

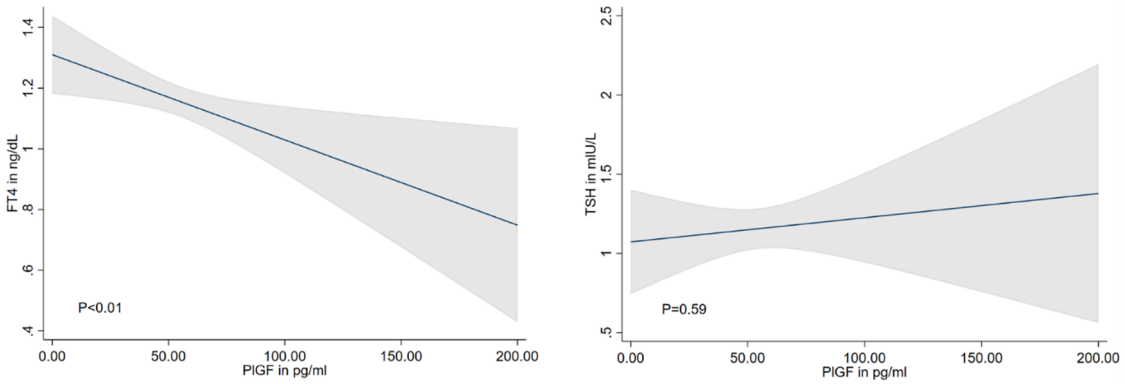

Figure 1. The association of maternal PlGF with TSH and FT_4 levels among pregnant women at 11-13 weeks of gestation. Marginal effects were estimated using linear regression adjusted for gestational age, parity, BMI, and education level. Shaded areas indicate 95% confidence intervals of predicted values.

weeks of gestation. Women with hypothyroidism had a lower median maternal age (28.0 years) compared to those without hypothyroidism (32.0 years), although the difference was not statistically significant (*P=0.10*). The median gestational age was similar between the two groups (12.1 weeks), with no significant difference observed (*P=0.18*). Median PlGF levels were slightly higher in the hypothyroidism group (51.2 pg/mL) compared to the group without hypothyroidism (50.5 pg/mL), but the difference was not statistically significant (*P=0.64*). Regarding parity, the prevalence of hypothyroidism was highest among nulliparous women (14.9%), followed by multiparous women (8.1%) and lowest among primiparous women (7.8%); however, these differences were not statistically significant (*P=0.28*). For education, the prevalence of hypothyroidism was higher among women with a high school education (17.3%) compared to those with secondary school or lower (9.8%) and university or higher education (3.9%), with a significant difference observed (*P=0.02*). In terms of household income, women earning 11–20 million VND per month had a higher prevalence of hypothyroidism (17.2%) compared to those with ≤10 million VND (3.5%) and >20 million VND (7.3%), and this difference was statistically significant (*P = 0.02*). With respect to obesity, the prevalence of hypothyroidism was higher among obese women (13.0%) compared to women without obesity (9.4%), although the difference was not statistically significant (*P = 0.46*). Overall, the prevalence of hypothyroidism in the study population was 10.3%.

Figure 1 illustrates the association between PlGF and TSH as well as FT_4 levels. A significant negative linear association was observed between PlGF and FT_4 levels *(P< 0.01)*, whereas no significant association was found between PlGF and TSH levels *(P = 0.59)*. Additionally, Figure 2 presents the association between maternal PlGF levels and the predicted probability of hypothyroidism. No significant relationship was observed between PlGF levels and hypothyroidism *(P = 0.39)*. The predicted probability of hypothyroidism showed a slight upward trend with increasing PlGF concentrations; however, the 95% confidence interval widened substantially at higher values.

Table 3 presents the association between high PlGF levels and hypothyroidism status among pregnant women at 11–13 weeks of gestation, using logistic regression analysis adjusted for gestational age, parity, obesity, and education level. PlGF levels above the 90^{th} and 95^{th} percentiles were associated with a 2.1-fold and 2.0-fold increase in the odds of hypothyroidism, respectively, although these associations were not statistically significant (*all P>0.05*). In contrast, PlGF levels above the 97.5^{th} percentile were associated with 7.3-fold higher odds of hypothyroidism (P = 0.046).

Discussion

This is the first study conducted in Vietnam to examine the relationship between placental growth factor (PlGF) and thyroid function parameters

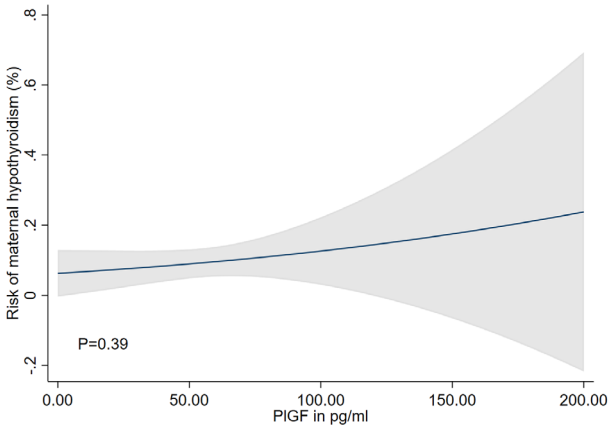

Figure 2. The association of maternal PlGF with hypothyroidism among pregnant women at 11-13 weeks of gestation. Marginal effects were estimated using logistic regression adjusted for gestational age, parity, BMI, and education level. Shaded areas indicate 95% confidence intervals of predicted values.

Table 3. High PlGF levels and hypothyroidism status among pregnant women at 11–13 weeks of gestation.

PlGF levels (pg/ml)	Hypothyroidism	
	OR (95% CI)	P value
>90th percentitle	2.1 (0.6 -7.3)	0.26
>95th percentitle	2.0 (0.4-10.7)	0.41
>97.5th percentitle	7.3 (1.03 -51.4)	0.046

Note: The analysis was performed using logistic regression and adjusted for gestational age, parity, obesity, and education level.

(FT$_4$ and TSH), as well as early gestational hypothyroidism at 11–13 weeks of gestation. We found that 10.3% of pregnant women had hypothyroidism. Higher maternal PlGF levels were significantly associated with lower FT$_4$ concentrations. In addition, PlGF levels above the 97.5th percentile were associated with a 7.3-fold higher odds of hypothyroidism (95% CI, 1.03–51.4; P = 0.046) after adjustment for gestational age, parity, obesity, and education level. These findings underscore the potential role of PlGF as an early marker of thyroid dysfunction in pregnancy. In our study, the prevalence of hypothyroidism at 11–13 weeks' gestation was 10.3%, which is higher than that reported in Western populations but comparable to some South Asian figures. A study in North India reported a high prevalence of hypothyroidism (14.3%) during the first trimester (23). In contrast, data from a Czech first-trimester screening cohort (singleton pregnancies) showed a prevalence of hypothyroidism of 5.3%, which was considerably lower than our estimate (24). Additionally, a study of more than 17,000 pregnant women in Spain reported an overall hypothyroidism prevalence of 6.5%, with regional variations (25). The differences between our findings and those of previous studies may be attributable to variations in diagnostic criteria, reference thresholds, or characteristics of the study population. One notable finding is that we observed a significant inverse association between PlGF levels and FT$_4$ concentrations, which may suggest a potential biological interplay between placental angiogenesis and maternal thyroid function during early gestation. PlGF, a pro-angiogenic factor secreted by the placenta, is a sensitive marker of placental function, while maternal FT$_4$ is essential for fetal neurodevelopment and placental growth in early pregnancy (11,26-28). The inverse relationship identified in our study may reflect a compensatory physiological response or a pathophysiological interaction between placental signaling pathways and maternal thyroid regulation. Several previous studies have shown that abnormal thyroid hormone levels, especially lower FT$_4$, are associated with adverse obstetric outcomes, such as preeclampsia, fetal growth restriction, and preterm birth (7, 29, 30). Additionally, evidence suggests that angiogenic markers like PlGF are affected in pregnancies with thyroid dysfunction, indicating possible bidirectional interactions between placental and endocrine systems (31, 32). Notably, Korevaar et al. reported that elevated PlGF levels may modify the stimulatory effect of human chorionic gonadotropin (hCG) on maternal FT$_4$ production, further supporting the hypothesis that placental-derived factors could influence thyroid hormone dynamics during early pregnancy (13). In this study, we found no significant association between PlGF levels and TSH, suggesting that PlGF may not be closely linked to maternal TSH levels during the first trimester. TSH regulation is mediated by pituitary–thyroid feedback and transiently influenced by hCG in early gestation (27, 33, 34). Although hCG can influence both PlGF and TSH levels through its effects on trophoblastic activity, our data suggest that the regulatory pathways of these two biomarkers may be functionally distinct. One possible explanation is that while hCG stimulates both thyroid hormone production and PlGF expression, the

magnitude and timing of these responses differ, leading to a dissociation between PlGF and TSH levels (13, 35). Furthermore, PlGF expression is mainly localized in the syncytiotrophoblast and may reflect placental vascular development rather than the systemic endocrine feedback mechanisms that regulate TSH secretion (36). Previous studies examining the relationship between angiogenic markers and thyroid function have produced inconsistent results. One study reported that PlGF modified the stimulatory effect of human chorionic gonadotropin (hCG) on FT_4, but not on TSH (13). Our findings are consistent with this observation, supporting the hypothesis that TSH may not serve as a reliable marker for evaluating placental vascular function or PlGF-related pathways. However, other research has demonstrated an inverse association between PlGF and TSH concentrations, indicating that higher PlGF levels were associated with lower TSH levels (16). These discrepancies may reflect differences in study populations, gestational age at assessment, assay methods, or underlying maternal health conditions. We did not observe a significant association between PlGF levels and hypothyroidism, which was inconsistent with a previous study (13). Population-specific factors, differences in diagnostic thresholds, or assay variability may explain this. However, at extreme values, PlGF levels above the 97.5th percentile were positively associated with hypothyroidism, suggesting a possible dysregulation of endocrine–placental interactions. Our findings are consistent with a previous study showing that abnormal levels of placental markers, including elevated PlGF, could interact with maternal thyroid hormone metabolism (13). Furthermore, another study suggested that extreme values of angiogenic factors in early pregnancy may reflect underlying maternal pathophysiological states, including autoimmune or vascular conditions, which have been implicated in the pathogenesis of thyroid disorders (37). This remains a hypothesis, partly supported by studies demonstrating that excessive trophoblast-derived hormones can perturb maternal thyroid regulation (27). In Vietnam, PlGF testing is already part of routine first-trimester preeclampsia screening, while early screening for thyroid dysfunction is not yet recommended. By identifying a potential association between PlGF and thyroid hormones, this study provides baseline data that may support future research and the development of integrated early screening strategies for pregnancy-related disorders. Several limitations of this study should be acknowledged. The cross-sectional design inherently limits causal inference, as the temporal sequence between changes in PlGF and variations in FT_4 could not be determined. The study also did not examine the association between TSH and hCG concentrations, which represents a methodological limitation given the established role of hCG in modulating TSH during early pregnancy. The modest sample size may have reduced statistical power, increasing the risk of type II errors, and the single-center design may limit generalizability. In particular, the study sample was drawn from an urban tertiary care hospital, which may not be representative of pregnant women in rural or community settings, potentially limiting external validity. Given the exploratory nature of this study and the modest sample size, minor violations of linear model assumptions cannot be entirely ruled out. However, the analysis was conducted to explore potential associations rather than to build a predictive model, and the results should be interpreted within this context. In addition, the wide confidence intervals at extreme PlGF levels may reflect low sample density and potential heteroscedasticity, which could affect the precision of the estimates. Finally, residual confounding may be present due to unmeasured factors such as iodine intake and thyroid peroxidase (TPO) antibody status. Future studies with larger, more diverse populations and comprehensive assessments of thyroid autoimmunity and iodine status are warranted to validate these findings.

Conclusion

In this study, we observed that the prevalence of hypothyroidism among pregnant women at 11–13 weeks of gestation was 10.3%. In addition, a significant association was found between maternal PlGF levels and FT_4 concentrations during the same gestational period. PlGF levels above the 97.5th percentile were associated with a higher likelihood of hypothyroidism. These findings indicate an association between elevated PlGF levels and altered thyroid function in early pregnancy, rather than establishing any causal or predictive relationship. Due to the cross-sectional design of this

study, temporal or causal inferences cannot be drawn. Future prospective cohort studies and mechanistic research are warranted to confirm causality, clarify the underlying biological pathways, and explore the potential predictive utility of PlGF in combination with standard thyroid function tests for early risk stratification.

Ethic Approval: The research protocol was approved by the Biomedical Research Ethics Committee at the University of Medicine and Pharmacy at Ho Chi Minh City under Decision No. 1189/HDDD-DHYD, dated November 28, 2023. All participating women were thoroughly informed about the objectives and procedures of the study and provided written informed consent before enrollment.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: Conceptualization and study design: LD, NK; Data collection: LD, PH, PP; Data entry and analysis: LD; Writing – original draft: LD; Review and editing: LD, NK, PH, PP, LN. All authors read and approved the final version of the manuscript.

Declaration on the Use of AI: None.

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