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Prevalence of Subclinical Hypothyroidism among Pregnant Women

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ABSTRACT

Background: Some studies have associated subclinical hypothyroidism with obstetric complications such as preeclampsia, preterm birth, and placental abruption.

Objective: To investigate the prevalence of subclinical hypothyroidism in patients with preeclampsia and normotensive pregnant women ending their pregnancy at Enrique Garces Hospital.

Methods: This is a descriptive cross-sectional study conducted between February 2020 and 2022. The study included pregnant women between 20 and 35 years of age, with singleton pregnancies in the third trimester. The women were in labor and diagnosed with subclinical hypothyroidism and preeclampsia in the current pregnancy. The women underwent blood sampling. Also, the thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels were measured by chemiluminescence.

Results: A total of 639 women were evaluated; Among these women 509 (79.66%) were normotensive, 137 (26.92%) had subclinical hypothyroidism, and 372 (73.08%) did not have subclinical hypothyroidism, 130 (20.34%) had preeclampsia, 34 (26.15%) of them with subclinical hypothyroidism and 96 (73.85%) not having subclinical hypothyroidism. The overall prevalence of subclinical hypothyroidism was 26.76%. In the normotensive group the prevalence of subclinical hypothyroidism was 0.2691 with a 95 % CI (0.2306, 0.3076) and in the preeclampsia group it was 0.2615 with a 95 % CI (0.1859, 0.3370).

Conclusions: A high prevalence of subclinical hypothyroidism was identified among pregnant women, which often goes undiagnosed in the early stages of pregnancy due to the lack of thyroid profile screening protocols for all pregnant women. Regarding the TSH cut-off levels 3mIUI/L there was no statistically significant difference of subclinical hypothyroidism among normotensive pregnant women and preeclampsia women, as literature suggests that TSH levels above 4mIU/L are associated with hypertensive diseases.

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Introduction

Subclinical Hypothyroidism (SCH) is a clinical condition characterized by elevated Thyroid-Stimulating Hormone (TSH) levels above the upper limit of normal in the presence of normal serum free thyroxine (fT4) concentrations, considering trimester-specific reference ranges for the population [1]. The prevalence of Subclinical hypothyroidism in America is estimated at 10-15% among pregnant women, but there is no exact statistic for Latin America due to the lack of routine thyroid hormone testing during prenatal care [2,3]. The diagnosis of subclinical hypothyroidism during pregnancy has been a subject of debate in recent years due to the guidelines set forth by the American Thyroid Association (ATA) in 2011 and 2017[4].

During pregnancy the thyroid gland undergoes significant anatomical, physiological and hormone production changes. These changes include alterations in the concentrations of thyroid hormone-binding globulin due to reduced hepatic clearance and increased estrogen stimulation. Other change is the thyrotropic effect of human gonadotropin-chorionic gonadotropin due to its structural homology with the alpha subunit of thyroid stimulating hormone and its receptors for LH/hCG and thyroid stimulating hormone. There are changes in iodine requirements and clearance; modifications in autoimmune regulation; changes in the role of the placenta in thyroid hormone deiodination, as well as changes in thyroid volume [1].

The impact of subclinical hypothyroidism on adverse obstetric outcomes has not been clearly identified, but some studies have suggested an association between subclinical hypothyroidism and various complications such as preeclampsia, preterm birth, and placental abruption [4,5]. Studies have also suggested that thyroid hormone influences the cardiovascular system through its influence on cardiac contraction and systemic vascular resistance.

This leads to endothelial cell dysfunction which is characterized by decreased nitric oxide production and impaired vasodilation, therefore its relationship with preeclampsia is important [2]. Subclinical hypothyroidism during pregnancy, if diagnosed in the first trimester, increases the risk of hypertensive disorders by 1.79 times; whereas if diagnosed in the second and third trimester the risk of developing hypertensive disorders of pregnancy in the future is more than 1.5 times higher. It has been demonstrated that when thyroid-stimulating hormone levels are below 3 mIU/L, subclinical hypothyroidism in pregnancy is not associated with hypertensive diseases. However, when TSH levels are above 3 mIU/L, the risk increases by 1.67 times, and if the TSH value is 4 mIU/L, above or below this threshold, the risk of developing hypertensive disorders of pregnancy increases [6]. Since there is no consensus on the necessity or benefit of universal screening in the pregnant population, selective screening based on risk factors is recommended by the American Thyroid Association and the Association of Clinical Endocrinology. It is essential to know the incidence of thyroid pathology in each population. In Ecuador, there are no studies conducted on representative samples of pregnant women that would allow us to know the prevalence of thyroid pathology. Local studies have been conducted, but their results cannot be generalized due to small sample sizes relative to the Ecuadorian population. For reference, a study conducted at the Luz Elena Arismendi Hospital in the south of Quito, Ecuador, found a prevalence of subclinical hypothyroidism of 40% Rivera et al, 2016. contrasting with the global prevalence.

Preeclampsia is characterized by arterial hypertension identified twice at 20 weeks of gestation, with a four-hour difference between both measurements, and additionally showing proteinuria ≥ 0.3 g in a 24-hour urine sample or a protein-to-creatinine ratio ≥ 0.3 mg, or the presence of ≥ 2+ on dipstick testing without proteinuria but accompanied by systemic impairment or target organ dysfunction [7-10].

Preeclampsia without signs of severity is characterized by systolic blood pressure greater than or equal to 140 mmHg and less than160 mmHg, with diastolic blood pressure greater than or equal to 90 mmHg and less than 110 mmHg, with proteinuria and without signs of severity or involvement of target organs [7]. The severity criteria and/or involvement of target organs in preeclampsia are characterized by neurological complications: altered mental status, blindness, clonus, severe headaches, or visual disturbances, eclampsia, stroke; pulmonary edema; hematological complications: platelet count<150 000/µl, hemolysis, disseminated intravascular coagulation; acute renal failure: creatinine 90 µmol/L or 1 mg/dL; hepatic involvement: hight levels of aminotransferases, such as ALT or AST > 40 IU/L [8].

The aims of this research were to investigate the prevalence of subclinical hypothyroidism in patients with preeclampsia and normotensive pregnant women attending delivery at Enrique Garces Hospital. Additionally, to describe the sociodemographic data, age, residence, education level, race, occupation, and marital status in pregnant women with preeclampsia and normotensive women.

Methods

This is a descriptive cross-sectional study conducted at Enrique Garces Hospital (a secondary level hospital that provides care for low and moderate-risk deliveries) in the city of Quito, Ecuador, from February 2020 to August 2022. The sample size calculation was performed using SAS version 9.4 software, with a significance level of 5% and a test power of 80%. There was a clinically relevant difference of 15% between the groups and an assumed prevalence of 20% for hypothyroidism, it was estimated that the groups would be unbalanced in a 2:1 ratio, thus requiring a sample size of 318 patients: 106 with preeclampsia and 212 normotensives. However, a total of 639 women were included in the study (509 normotensive and 130 with preeclampsia). Their ages range between 20 to 35 years, with singleton pregnancies in the third trimester, in labor, diagnosed with subclinical hypothyroidism and preeclampsia in the current pregnancy. Women with physical or mental disabilities, chronic hypertension associated with preeclampsia, HELLP syndrome, chronic diseases such as diabetes mellitus, protein-losing nephropathy, antiphospholipid antibody syndrome, hereditary thrombophilia, a history of preeclampsia in previous pregnancies or a family history of preeclampsia, multiple pregnancy, and secondary hypothyroidism were excluded. The women who came from different hospitals, health centers, or arrived at the Enrique Garces Hospital on free demand were divided into two groups: a group of pregnant women with preeclampsia and blood pressure greater or equal to 140/90 mmHg or 160/110 mmHg and one or more crosses on the proteinuria strip test. The other group was a normotensive group with normal blood pressure. A venous blood sample of 10 ml was taken, not in a fasting state, for serological measurement of thyroid-stimulating hormone and free thyroxine (fT4) levels. The measurements were performed using competitive electrochemiluminescence immunoassay (Atellica IM Thyroid-Stimulating Hormone and fT4 from Siemens Healthcare). The TSH assay had an analytical sensitivity of ≤ 0.004 µIU/mL and a coefficient of variation ≤ 16% for samples of 0.020 mIU/L, ≤ 8% (0.300 to 90.000 mIU/L), and ≤ 10% (> 90.000 mIU/L), with a measurement range of 0.008–150.000 mIU/L. The interpretation used the trimester-specific reference range from the American Thyroid Association 2011 (third trimester 0.3-3 mIU/L). The analytical sensitivity of the Atellica IM fT4 assay was ≤ 0.1 ng/dL, with a coefficient of variation ≤ 8.0% for samples of 0.5 to 1.0 ng/dL and < 6.0% for samples > 1.0 ng/dL, with a measurement range of 0.1–12.0 ng/dL and an interpretation range of 0.87-1.76 ng/dL.

The protocol was approved by the Sub-Committee and Ethics Committee of the Universidad Central del Ecuador with codes 0003-FCM-D-2019 and No. 019-CEISH-UCE-2021, respectively, and the research Commission of the Department of Gynecology of the School of Medicine of Ribeirao Preto, USP with protocol No. 654. It also received authorization from the Enrique Garces Hospital, and participants were included in the study after signing informed consent.

Statistics

Statistical analysis was performed using the SAS version 9.4 software. Central tendency and dispersion measurements were used for quantitative variables. Qualitative variables were presented as absolute and relative frequencies. The chi-square test was applied to verify the statistical association of qualitative variables with respect to the groups. The non-parametric Wilcoxon test was used to determine statistically significant differences among the quantitative variables in the study groups.

Results

A total of 639 pregnant women were analyzed, including 509 normotensive women, 137 with subclinical hypothyroidism, and 130 women with preeclampsia: There were 59 with severe signs and 71 without severe signs, and 34 women with subclinical hypothyroidism, 18 of these cases occurred in pregnant women with preeclampsia without severe signs and 16 with severe signs. The prevalence of subclinical hypothyroidism in the sample was 26.76%, with a prevalence of 0.2691 and with a 95% CI: (0.2306-

0.3076). The prevalence was 0,2615 with a 95% CI (0.1859-0.3370) in the preeclampsia group.

Regarding demographic variables, most participants (98.9%) were from the highland region compared to the coast and Amazonia regions. Around 50.39% were single, 91.86% were of mixed race, 66.51% had a secondary education level, and a lower percentage with primary and higher education, while 78.09% were unemployed.

Table 1: Distribution of the Sociodemographic Variables of the Study Population

Residence	No	%
Amazon Region	2	0.31
Coast Region	5	0.78
Inter- Andean Region	632	98.9
Marital Status		
Married	317	49.51
Single	322	50.39
Race		
Mestizo	587	91.86
Others (indigenous and black)	52	8.14
Level of Education		
Primary	104	16.28
Secondary	425	66.51
Superior	110	17.21
Occupation		
Unemployed	499	78.09
Employees	140	21.44

The mean age of the normotensive and preeclamptic patient groups was similar, with 26.07±4.32 years and 26.07±4.17 years, with a p-value of 0.94. The mean number of prenatal visits was 6.17±2.35 and 6.22±1.87 with a p-value of 0.80. The gestational age was 39.13±1.73 weeks in the normotensive group and 38.89±1.68 weeks in the preeclampsia group and a p-value of 0.06. There being no statistically significant differences.

The mean systolic and diastolic blood pressure in normotensive pregnant women were 121.79± 10.11 mm Hg and 74.84 ± 8.85 mm Hg. For preeclampsia 147.75 ± 12.88 mm Hg and 95.12±. 11.11 mm Hg with a p-value <.0001 which is statistically significant.

Cesarean delivery accounted for 52.27% of the entire study group, while cephalon-vaginal delivery accounted for 47.73%.

The mean TSH levels were 3.34±1.85 mIU/L in the normotensive group and 3.59±2.43 mIU/L in the preeclampsia group with a p-value of 0.81. The mean fT4 levels were 1.13±3.11 ng/dL in the normotensive group and 0.95±0.21 ng/dL in the preeclampsia group, p-value of 0.31 which was not statistically significant. TSH in preeclampsia group with severity signs 3.49 ±2.09mUl/L and preeclampsia without severity signs 3.67± 2.69 with a p-value of 0.87. The fT4 levels were 0.93±0.19 and 0.96±0.23 respectively with a p- value of 0.49.

Table 2: Distribution of the Quantitative Variables of TSH and fT4 of the Study Population

Variable	Cluster	N	Mean	Std Dev	Median	P-value
TSH mUI /L	Normotensive	509	3.34	1.85	2.91	0.81
TSH mUI /L	Preeclampsia	130	3.59	2.43	3.03	
Ft4ng/dl	Normotensive	509	1.13	3.11	0.91	0.31
Ft4ng/dl	Preeclampsia	130	0.95	0.21	0.91	
TSH mUI /L	Preeclampsia with signs of severity	59	3.49	2.09	3.05	0.87
TSH mUI /L	Preeclampsia without signs of severity	71	3.67	2.69	3	
Ft4ng/dl	Preeclampsia with signs of severity	59	0.93	0.19	0.91	0.49
Ft4ng/dl	Preeclampsia without signs of severity	71	0.96	0.23	0.93	

There were no statistically significant differences in the prevalence of subclinical hypothyroidism between normotensive and preeclamptic women (26.92% vs. 26.15%, respectively; p-value of 0.86), or between preeclamptic women with severe signs and without severe signs (27.12% vs. 25.35%, respectively; p-value of 0.81).

Table 3: Distribution of Subclinical Hypothyroidism in the Groups of Normotensive-Preeclamptic and Preeclamptic Pregnant Women with and without Signs of Severity and p-value

	Normotensive	Preeclampsia	p- value
Subclinical Hypothyroidism	n / %	n / %	
No	372 (73.08)	96 (73.85)	0.86
Yes	137 (26.92)	34 (26.15)	
	Preeclampsia with signs of severity	Preeclampsia without signs of severity	
Subclinical Hypothyroidism	n / %	n / %	
No	43 (72.88)	53 (74.65)	0.81
Yes	16 (27.12)	18 (25.35)	

No statistically significant differences were found between normotensive and preeclamptic women regarding TSH levels above and below 3 mIU/L (p-value= 0.30), or between preeclamptic women with and without severe signs (p-value=0.83).

Table 4: TSH Cutoff Levels Less than, Equal to or Greater than 3 mIU /L in the Study Population and their p-Value

TSH mIU /L	Normotensive n/%	Preeclampsia n/%	p- value
Less than 3	260 (51.08)	63 (48.46)	0.30
Greater than or equal to 3	249 (48.92)	67 (51.54)	
TSH	Preeclampsia with signs of severity	Preeclampsia psia without signs of severity	
Less than 3	28 (47.46)	35 (49.30)	0.83
Greater than or equal to 3	31 (52.54)	36 (50.70)	

Patients diagnosed with subclinical hypothyroidism were referred to the internal medicine service for follow-up and treatment in the postpartum period.

Discussion

The findings of this study were inconclusive regarding the relationship between subclinical hypothyroidism and preeclampsia, as the TSH cutoff levels were less than 4 mIU/L, and it was found that with TSH levels of 4 mIU/L or higher, the risk of hypertensive disorders increases.

When identifying the prevalence of subclinical hypothyroidism in the sample of this study with 26.76%, it was compared with other reference studies. For example, a prospective case-control study of Mexican women attended during childbirth in Saltillo University Hospital reported a prevalence of 26.7% [2]. Other studies showed lower prevalence rates, such as 21.1% in Mexican women, 15.99% in Colombian women and 13% in Saudi Arabia women [11-13].

In this research, subclinical hypothyroidism was observed in 26.92% of normotensive women and 26.15% of preeclamptic women, with a nearly similar distribution between the two groups. Among preeclamptic women with signs of severity, a higher percentage of 27.12% was observed compared to 25.35% in preeclamptic women without signs of severity. Although, this difference was not statistically significant with a p-value of 0.81. In contrast, another study showed that hypertensive pregnant women had a higher percentage of subclinical hypothyroidism, with 42.3%, while the percentage was 22.8% in normotensive women [11]. Other studies reported lower percentages of subclinical hypothyroidism, such as 8.0% in normotensive women, 18.0% in preeclamptic women, and 17.8% in severe preeclampsia, as well as 15% in preeclampsia without signs of severity and 11.8% in preeclampsia with signs of severity, with a p-value of 0.98 [14-15].

Furthermore, it was found that the prevalence of preeclampsia in women with subclinical hypothyroidism, diagnosed according to the 2017 American Thyroid Association standards, was 5.3%, which was significantly higher than the 2.1 % of prevalence found in the cases of subclinical hypothyroidism diagnosed according to the 2011 American Thyroid Association standards [4,16].

The average age of the pregnant women in this study was 26 years, with gestational termination occurring at 38-39 weeks. Different studies differ in terms of the age of participating pregnant women: 23 years for normotensive women, 24 years for preeclamptic women, and 23 years for severe preeclamptic women. Another group had an age range of 18 to 42 years, the age was 27.7 years ± 5.7, 26.59 years in the preeclampsia group, and 25.67 years in normal pregnant women. Gui et al, 2020, reported higher ages compared to the research on preeclampsia without severity: 31.6 ± 4.4 and preeclampsia with severity: 31.4 ± 5.23, with gestational ages of 39 weeks for normotensive women, 34 weeks for preeclampsia, and 32.5 weeks for severe preeclampsia [12,14,17-18].

The blood pressure measurements in pregnant women showed significantly lower values in normotensive women compared to women with preeclampsia and severe preeclampsia, which aligns with some studies [15,19].

In this research, the results were inconclusive regarding the relationship between subclinical hypothyroidism and preeclampsia, as the TSH cutoff levels were less than 4 mIU/L, but it was found that with TSH levels of 4 mIU/L or higher, the risk of hypertensive disorders increases, as indicated by the meta-analysis and the systematic review [20]. With TSH values above 5 µUI/ml, the risk is 4-5 times higher for developing preeclampsia [21]. According to the data shown in this research, pregnant women with preeclampsia had TSH levels of 3.59 ± 2.43 mIU/L, and normotensive women had TSH levels of 3.34 ± 1.85 mIU/L, but there was no statistical significance with a p-value of 0.81.

Conclusion

The outcomes obtained from this research have allowed the identification of a high prevalence of subclinical hypothyroidism compared to international reports. The study did not directly investigate whether the patients suffered from iodine deficiency or if subclinical hypothyroidism was related to autoimmune thyroiditis. These factors were not analyzed; however, in Ecuador, starting from January 2013, the National Program for the Control of Iodine Deficiency Disorders declared the country free of this deficiency, demonstrating that 98% to 99% of Ecuadorian households consume iodized salt. It is considered necessary to continue conducting further research on more representative samples to establish national universal TSH cutoff levels and ranges of normality for laboratory tests used in the population. This would improve strategies for timely detection and treatment in our country.

Furthermore, it was determined that with TSH cutoff levels of 3 mIU/L, no statistically significant differences in subclinical hypothyroidism were observed between normotensive and preeclamptic women, as several studies indicate that levels >4 mIU/L of TSH are associated with hypertensive diseases.

Declarations

Funding: No funding

Competing Interests: The authors declare they have no competing interests.

Ethics Approval (include Appropriate Approvals or Waivers): The protocol was approved by the Sub-Committee and Ethics Committee of the Universidad Central del Ecuador with codes 0003-FCM-D-2019 and No. 019-CEISH-UCE-2021, respectively, and the research Commission of the Department of Gynecology of the School of Medicine of Ribeirao Preto, USP with protocol No. 654.

Consent to Participate: All authors declare their consent to participate in the manuscript

Written Consent for publication: All participants in this study were given a term of free and informed consent for the voluntary participation of women in the research

Availability of Data and Material: Data can be accessed via the journal's SN Comprehensive Clinical Medicine page on its website if published and also in some cases by an email request to the corresponding author.

Code Availability: Statistical analysis was performed using the SAS version 9.4 software.

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