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ORIGINAL RESEARCH

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# PREVALENCE OF THYROID AUTOIMMUNITY IN A POPULATION OF PREGNANT WOMEN IN SANTA MARTA, MAGDALENA (COLOMBIA)

## Prevalencia de autoinmunidad tiroidea en una población de gestantes de Santa Marta, Magdalena (Colombia)

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## ABSTRACT

**Objective:** To describe the prevalence of thyroid autoimmunity in a hospital-based population of pregnant women, and to explore its frequency in euthyroid and hypothyroid women, as well as the association between autoimmunity and the presence of obstetric complications.

**Materials and methods:** Descriptive cross-sectional study. Accesible population: pregnant women seen at Centros Hospitalarios del Caribe (CEHOCA) in the city of Santa Marta, Magdalena (Colombia), between August 1 and October 31, 2017. Convenience sampling. Sample size: 120 subjects. Thyroid stimulating hormone (TSH), free thyroxine (T4), free triiodothyronine (T3), thyroglobulin (TG) and thyroid peroxidase (TPO) antibodies were determined. Descriptive statistics were used. Prevalence was calculated as the number of women with positive TG or TPO antibodies/ number of women surveyed. Categorization by type of positive antibody and thyroid function (normal or hypothyroidism) was also done.

**Results:** In women with uncomplicated pregnancies, the frequency of thyroid autoimmunity was 14.29%. Five patients (4.5%) had positive TPO antibodies, 14 patients (12.61%) had positive TG antibodies, while 3 of the women were positive for the two types of antibodies. Antithyroglobulin antibodies were the most frequent. Autoimmunity was found in 13.5% of euthyroid women, and in 18.2% of the women with subclinical hypothyroidism. No association was found between the presence of antibodies and miscarriage, pregnancy-associated hypertension or preterm delivery.

**Conclusions:** The presence of antithyroid antibodies was found in 1 out of every 7 pregnant women as a sign of autoimmunity. Further observations are required in order to determine frequencies and normality ranges in the local population, as well as the clinical significance of this thyroid autoimmunity.


**Key words:** Thyrotropin, triiodothyronine, thyroxine, thyroid gland, antibodies.


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## RESUMEN

**Objetivo:** describir la prevalencia de autoinmunidad tiroidea en una población de gestantes de base hospitalaria, y hacer una exploración a la frecuencia en pacientes eutiroideas o hipotiroideas, y de la asociación entre autoinmunidad y la presencia de complicaciones obstétricas.

**Materiales y métodos:** estudio de corte transversal, descriptivo. Población accesible: gestantes atendidas en Centros Hospitalarios del Caribe (CEHOCA), de la ciudad de Santa Marta, Magdalena (Colombia), entre el 1 de agosto y el 31 de octubre de 2017. Muestreo por conveniencia. Tamaño muestral: 120 sujetos. Se determinó hormona tiroestimulante (TSH), T4 libre, T3 libre, anticuerpos antitiroglobulina (ATG) y antiperoxidasa (ATPO). Se utilizó estadística descriptiva. La prevalencia se calculó como número de mujeres con anticuerpos ATG o ATPO positivos/número de mujeres encuestadas, además se categorizó por tipo de anticuerpo positivo y función tiroidea (normal o hipotiroidismo).

**Resultados:** en las gestantes con embarazo sin mención de complicación la frecuencia de autoinmunidad tiroidea fue del 14,29 %. Cinco pacientes (4,5 %) presentaron anticuerpos ATPO positivos, 14 pacientes (12,61 %) anticuerpos ATG positivos, en tanto que 3 embarazadas mostraron positividad para ambos tipos de anticuerpos. Los anticuerpos antitiroglobulina fueron los más frecuentes. Se halló autoinmunidad en el 13,5 % de las gestantes eutiroideas, y en el 18,2 % de las pacientes con hipotiroidismo subclínico. No se encontró asociación entre la presencia de anticuerpos y la presencia de aborto, hipertensión asociada al embarazo o parto pretérmino.

**Conclusiones:** una de cada 7 gestantes mostró presencia de anticuerpos antitiroideos como signo de autoinmunidad. Son necesarias más observaciones a fin de poder establecer frecuencias y rangos de normalidad en la población local y el significado clínico de esta autoinmunidad tiroidea.


**Palabras clave:** tirotropina, triyodotironina, tiroxina, glándula tiroides, anticuerpos..

## INTRODUCTION

Thyroid diseases are known to be more frequent in women. It has also been described that both hypothyroidism and hyperthyroidism may affect pregnant women (1). It is estimated that hypothyroidism occurs in 0.5 to 2.5% of all pregnancies, while thyrotoxicosis is less frequent, with a prevalence ranging between 0.1 and 1%. In a substantial proportion of cases, thyroid disease is associated with immunity disorders (2).

The most frequently found antithyroid antibodies in the general population are antithyroperoxidase antibodies (TPOAbs), which are directed against thyroid mitochondrial peroxidase. They are cytotoxic and have been associated with postpartum thyroiditis and psychiatric symptoms. Other detectable antibodies are antithyroglobulin antibodies (TGAbs), and their determination is important in endemic goiter areas and as markers for thyroid cancer (3). On the other hand, anti-thyroid stimulating-hormone (TSH) receptor antibodies (TRAb) are heterogenous and classified as having stimulating or blocking activity. They may cause hyper as well as hypothyroidism. A third class of neutral anti-TSH receptor antibodies has been described (4).

Environmental risk factors for the development of thyroid autoimmunity include iodine overload and selenium deficiency. Potential immunogenic mechanisms have been proposed in the case of iodine, including the production of pro-inflammatory cytokines, increased oxidative stress and tissue injury, and higher thyroglobulin antigenic activity (5). On the other hand, dietary supplementation with selenium, a micronutrient that participates in biochemical reactions of thyroid hormonogenesis has been found to reduce anti-TPO levels (6). However, evidence remains controversial to this date (7).

Antithyroid antibodies have been detected in close to 50% of pregnant women with subclinical hypothyroidism and in more than 80% with clinical hypothyroidism (8), although some studies show that they may be present in patients with normal TSH and thyroid hormone levels (9). On the other hand, the presence of antiperoxidase or antithyroglobulin antibodies has been reported during pregnancy but not accompanied by overt thyroid disease or subclinical hypothyroidism. Reports vary according to the different authors, with figures ranging between 2 and 20% (8, 10). Moreover, La'ulu and Roberts report ethnic variations in the prevalence of gestational thyroid autoimmunity. Of a total of 3064 serum samples, positive TGAbs were found in 10.6% of Asian patients, 1.8% of black patients, 6.2% of hispanic women and 6.5% of white patients. As for TPOAbs, they were positive in 12.4% of Asian patients, 4.1% of black women, 11.8% of hispanic women, and 12.3% of white patients (11).

Even though subclinical hyperthyroidism has not been associated with obstetric complications, subclinical hypothyroidism and thyroid autoimmunity are a different story (2). Some studies have reported the association between the presence of antithyroid antibodies and lower implantation rates, and a higher frequency of miscarriage in *in vitro* fertilization procedures (12-14). Other studies have suggested an association between positive thyroid autoimmunity and the presence of obstetric complications such as preterm labour (15, 16); however, evidence regarding gestational diabetes and pregnancy-related hypertension is controversial (17, 18). According to the American Thyroid Association (ATA) guidelines (8), evidence is not sufficient to recommend universal screening for thyroid autoimmunity during pregnancy. As of today, testing is reserved for patients with risk factors (e.g., a family history, recurrent miscarriage or other associated autoimmune diseases).

There are few regional reports regarding specific reference hormonal ranges for different population types (mestizo, African descendants and indigenous ethnic groups), just like there is a paucity of studies on the prevalence of gestational thyroid autoimmunity or on the association of anti-thyroid antibodies with obstetric complications. Bearing in mind the ethnic variations mentioned in the literature regarding thyroid stimulating hormone ranges as well as the prevalece of antibodies, and given the absence of available data for our population, the objective of this study is to describe the prevalence of thyroid autoimmunity in a hospital-based population of pregnant women in Santa Marta, Magdalena (Colombia), and to perform an exploratory analysis of the detection of TPO and TG antibodies and the presence of obstetric complications such as miscarriage, threatened or actual preterm delivery, and pregnancy-related hypertensive disorders.

## MATERIALS AND METHODS

*Design and Population.* Descriptive cross-sectional study. The base population consisted of pregnant women seen at Centros Hospitalarios del Caribe (CEHOCA), during the period between August 1 and October 31, 2017. This private healthcare institution provides primary care services and is also a referral center for high complexity patients (adults, children and pregnant women). It receives patients coming from the Department of Magdalena, on the Caribbean coast of Colombia.

The study enrolled patients over 18 years of age with singleton pregnancies coming to the emergency room (at any gestational age) or who went into spontaneous labour (at term), or came for elective cesarean section, and voluntarily agreed to participate in the research. Patients with multiple pregnancy, known past or present thyroid disease (hypothyroidism or hyperthyroidism), or with other pre-existing maternal morbidities were excluded. To estimate the sample size, a base

population of 900 patients, an expected prevalence of gestational thyroid autoimmunity of 10% (18), a 95% confidence level and a margin of error of 5% were used. Sample size: 120 subjects. Convenience sampling was used.

*Procedure*. All the candidates to participate in the study were explained the objectives of the research and invited to participate; once they agreed, they were asked to sign the informed consent. After training the clinical staff on the data collection modality, they were given printed forms to enter the data. The process of sampling, delivering the specimens to the laboratory and treating data confidentially was supported by the institutional staff.

Samples of peripheral venous blood were collected and preserved in vials. Samples that were not processed within the next 48 hours were refrigerated at a temperature of 2-8 degrees Celsius (°C), while samples processed over the next 30 days were stored at -20°C. Free thyroxine (T4), free triiodothyronine (T3) and TSH serum levels were determined in each sample in order to detect patients with unknown pre-existing thyroid disease. TSH ultrasensitive testing was performed using a third generation technique: chemiluminescent microparticle immunoassay (CMIA). Likewise, free T4 and T3 levels were determined using the same methodology. Antithyroglobulin (TGA) and antiperoxidase (TPO) antithyroid antibodies were also determined using chemiluminescent microparticle testing for IgG antibody detection. In order to avoid bias, the staff of the laboratory in charge of processing the samples were blinded at all times to patient clinical data and to the basis of the study.

The 2017 ATA guidelines (Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum) were considered for hormonal ranges (8). These guidelines suggest an upper limit in the reference range of 4 milliunits per liter (mU/L) for TSH, starting in the first trimester. Hypothyroidism was defined as a TSH higher than 4 mU/L with a lower free T4 level, or TSH ≥10 mU/L and normal free T4 level. Hyperthyroidism was defined as TSH suppression (≤ 0,1 mU/L), with high triiodothyronine (T3) or free thyroxine (T4) values (8). Collected data were tabulated for analysis. Peer review was applied in order to ensure the quality of the information.

*Measured variables.* Measured variables included maternal age, parity, gestational age, body mass index (15), socioeconomic bracket, education, marital status, personal and family medical history, TSH and free T3 and T4 levels, TPOAb and TGAb levels, presence of subclinical hypothyroidism and antibody levels in euthyroid and hypothyroid pregnant women, and presence of pregnancy complications (miscarriage, threatened or actual preterm delivery, pregnancy-related hypertension and intra-uterine growth restriction).

*Statistical analysis.* Data were analyzed using the Epi-Info 7® software package (19). Continuous variables were expressed as means and standard deviations, or medians and ranges according to normality. In pregnant women with no complications, 3rd and 97th percentiles were determined for the TSH and free T3 and T4 values. Categorical variables were expressed as proportions. Prevalence was calculated as the number of women with positive TG or TPO antibodies/number of surveyed women, and was categorized by positive antibody type and thyroid function (normal or hypothyroidism). To determine the association with obstetrical complications, the groups of women with positive and negative antibodies were compared using odds ratio (OR).

*Ethical considerations.* The study protocol was approved by the Ethics Committee of Universidad del Magdalena and authorized by Centros Hospitalarios del Caribe (CEHOCA). All the participants signed the informed consent. Confidentiality of the information was ensured. The researchers made the commitment to inform the treating physicians and

the patients in the event thyroid disease was diagnosed, in order to ensure treatment and follow-up.

## RESULTS

A total of 966 pregnant women were seen at Centros Hospitalarios del Caribe (CEHOCA) in the obstetric outpatient clinic or admitted for vaginal term delivery or elective cesarean section between August 1 and October 31, 2017. Of this universe, 117 patients met the study inclusion and exclusion criteria. During the course of the study, 6 participants were excluded due to issues with specimen processing or incomplete data, so the final sample consisted of 111 pregnant women (Figure 1).

The median age in the sample analyzed was 23 years, with a range between 14 and 40. Gestational age at the time of the test ranged between 6 and 41 weeks, spanning the three trimesters of pregnancy. Median parity was 2. Based on the data taken from the clinical records, most of the women had normal weight, followed in frequency by the overweight and obesity groups. The majority of the women reported being in a de facto marital relationship, and the most frequent level of schooling was secondary education (complete or incomplete) (see Table 1). Of the 111 pregnant women, 77 did not have reported pregnancy-related complications, while miscarriage was diagnosed in 11 cases, 6 had threatened or actual preterm delivery, and 17 were diagnosed with hypertensive disorders of pregnancy.

Mean TSH in the 77 patients with uncomplicated pregnancies was 2.2 mU/L, with a standard deviation (SD) of ± 1.56. The mean values for free T3 and T4 were 2.59 pg/ml (SD ± 0.42) and 0.85 ng/dl (SD ± 0.12), respectively. Table 2 shows the distribution of TSH and thyroid hormone values.

Thyroid autoimmunity: 5 patients (4.5%) had positive TPOAbs, 14 patients (12.61%) positive TGAbs, while the two types of antibodies were found to be positive in 3 patients.

The frequency of subclinical hypothyroidism (TSH ≥ 4 mU/L and ≤ 10 mU/L, with normal free T3 and T4 levels) was 9.9%. Using a lower cut-off value (TSH ≥ 3 mU/L and ≤ 10 mU/L), the frequency of subclinical hypothyroidism was 19.82%.

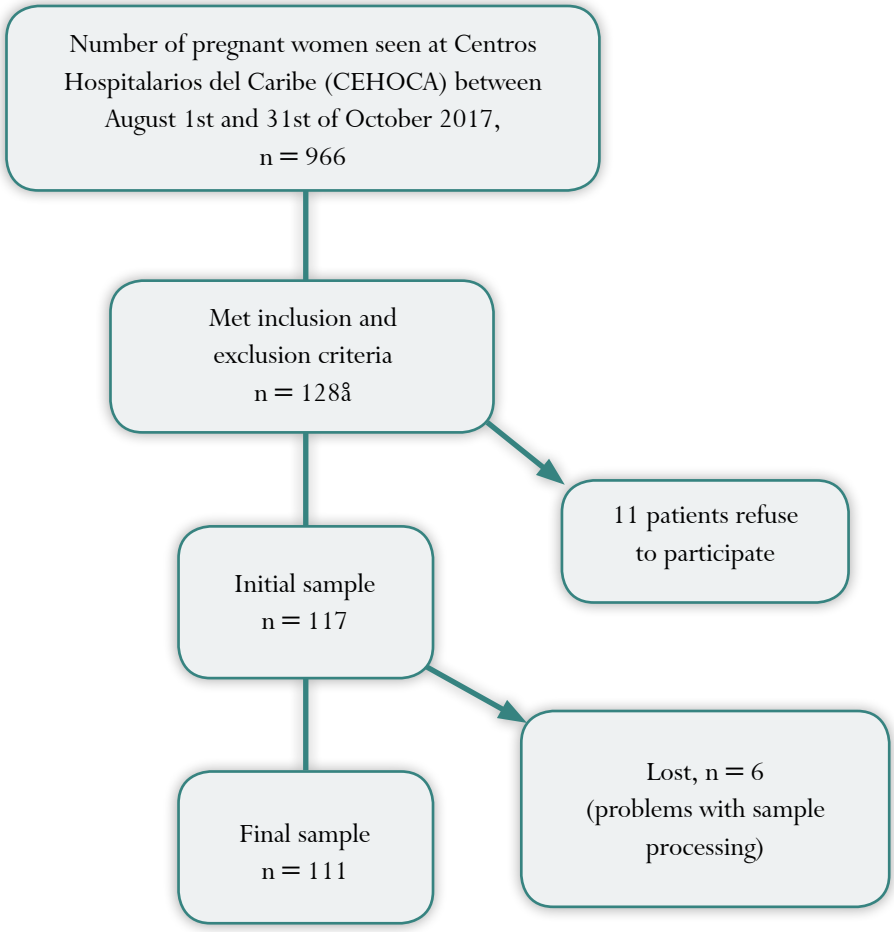
The frequency of positive thyroid autoimmunity was 13.5% in euthyroid patients, whereas in patients with subclinical hypothyroidism (TSH between 3 and 10 mU/L) the frequency was 18.9%. Hormonal and antibody determinations are described in detail in Table 3.

Regarding the association between autoimmunity and obstetric complications, the frequency of thyroid autoimmunity was 14.29% (11/77) in the women with normal pregnancy, and 14.71% (5/34) in women who presented with obstetric complications (OR = 1.03; 95% CI: 0,32-3,24; *p* value 0.95). The frequency of thyroid autoimmunity was 27.3% (3/11) in patients who miscarried, and 11.8% (2/17) in patients with hypertensive disorders. No autoimmunity was detected in patients with threatened or actual preterm delivery, and one of the 2 patients diagnosed with intrauterine growth restriction was positive for antiperoxidase antibodies and had a high TSH value.

## DISCUSSION

This study is an approach to the determination of thyroid autoimmunity prevalence during pregnancy in our setting. Prevalence of positive TPOAb and TGAb was 4.5% and 12.6%, respectively, and 2.7% for the two positive antibodies. The prevalence of subclinical hypothyroidism ranged between 9.9 and 19.82%, depending on the cut-off values used. A 13.5% frequency of thyroid autoimmunity was found in euthyroid women, while in patients with hypothyroidism it was 18.9%. The following values were found in the study population: TSH, 2.18 mU/L (SD ± 1,5); T3, 2.57 pg/ml (SD ± 0,42); and T4, 0.86 ng/dl (SD ± 0,11). No association was found between the presence of autoimmunity and obstetric complications.

**Figure 1.**
Sampling outline




Regarding the presence of TGAb and TPOAb, although the prevalence reported in the literature for antiperoxidase antibodies in the general population is higher (20), our study found higher positivity for antithyroglobulin antibodies, probably explained on the basis of the sensitivity of the analytical methodology and the possibility of ethnic variations.

Regarding the prevalence of subclinical hypothyroidism, our results are consistent with some reports of frequency ranges of 3.5-18%, depending on the TSH values used in the definition (21-23). However, the frequency of subclinical hypothyroidism reported in other studies is much lower, again underscoring the need for local population characterizations (1, 24, 25).

Regarding TSH and free T4 and T3, mean values found in our study are within the range of expected values (8). Of the 111 patients surveyed, 22 (19.82%) had TSH levels ≥ 3 mU/L, the upper limit of the normal reference range mentioned in the old ATA guidelines (20), and all of them were in their third trimester of gestation.

In our exploratory analysis, no association was found between the presence of autoimmunity and

**Table 1.**
**Baseline characteristics of a population of pregnant women of Clínica CEHOCA, Santa Marta (Colombia), studied between August 1 and October 31, 2017**

| | Total | Normal pregnancies | Complicated pregnancies |
|---|---|---|---|
| | n = 111 | n = 77 | n = 34 |
| **Sociodemographic characteristics** | | | |
| Marital status, n (%) | | | |
| Single | 40 (36.04) | 31 (40.3) | 9 (26.5) |
| Free union | 60 (54.1) | 40 (51.9) | 20 (58.8) |
| Married | 11 (9.9) | 6 (7.79) | 5 (14.7) |
| **Education (complete or incomplete) n (%)** | | | |
| Primary | 6 (5.41) | 5 (6.49) | 1 (2.9) |
| Secondary | 102 (91.9) | 70 (90.91) | 32 (94.1) |
| Higher | 3 (2.7) | 2 (2.6) | 1 (2.9) |
| Body mass index, n (%) | | | |
| Low weight | 3 (2.7) | 3 (3.9) | 0 |
| Normal | 80 (72.1) | 57 (74.1) | 23 (67.7) |
| Overweight or obesity | 28 (25.2) | 17 (22.1) | 11 (32.4) |
| | | | |
| Maternal age (median, range) | 23 (14-40) | 23 (14-37) | 26 (15-40) |
| Gestational age at the time of the study (median, range) | 38 (6-41) | 38 (8-41) | 34 (6-38) |
| Parity (median, range) | 2 (1-6) | 2 (1-5) | 2 (1-6) |
| Past Obstetric events, n (%) | 24 (21.62) | 13 (16.88) | 11 (32.35) |
| TSH (mean in mU/L. SD) | 2.2 (1.5) | 2.2 (1.6) | 2.1 (1.4) |

**Table 2.**
**Distribution of TSH and thyroid hormone values in uncomplicated cases studied in a population of pregnant women of Clínica CEHOCA, Santa Marta (Colombia), between August 1 and October 31, 2017**

| | Measurement unit | Median | P3* | P50* | P97* |
|---|---|---|---|---|---|
| TSH | mU/L** | 2.20 | 0.14 | 1.87 | 6.5 |
| Free T3 | pg/ml† | 2.59 | 1.66 | 2.59 | 3.44 |
| Free T4 | ng/dl‡ | 0.85 | 0.66 | 0.85 | 1.11 |

* Percentiles
** milli units per liter
† picogram por milliliter
‡ nanogram per deciliter

**Table 3.**
**Hormonal and antibody determinations in a population of pregnant women of Clínica CEHOCA, Santa Marta (Colombia), between August 1 and October 31, 2017**

| | Normal pregnancies | Miscarriage | Threatened or actual preterm delivery | Hypertensive disorders |
|---|---|---|---|---|
| n (%) | 77 | 11 (32.4) | 6 (17.6) | 17 (50) |
| Mean TSH en mU/L, SD | 2.2 (1.6) | 1.5 (0.8) | 2.4 (1.6) | 2.4 (1.6) |
| Mean Free T3 pg/ml, SD | 2.6 (0.4) | 2.8 (0.4) | 2.3 (0.2) | 2.5 (0.5) |
| Mean Free T4 in ng/dl, SD | 0.9 (0.1) | 1 (0.1) | 0.9 (0.1) | 0.9 (0.1) |
| Antiperoxidase antibodies (TPOAb), n (%) | 4 (5.2) | Undetected | Undetected | 1 (5.9) |
| Antithyroglobulin antibodies (TGAb), n (%) | 10 (13) | 3 (27.3) | Undetected | 1 (5.9) |
| Patients with TSH≥ 2.5 mU/L, n (%) | 23 (29.9) | 3 (27.3) | 3 (50) | 7 (41.2) |

obstetric complications, unlike what other authors have found in larger populations (26-28).

Given that convenience sample was used in this study, the potential risk of selection bias and the fact that the findings cannot be extrapolated to the general population are weaknesses. On the other hand, the methodology used to estimate TSH, free T4 and T3, and antibody levels, may be considered a strength of this study.

## CONCLUSIONS

The prevalence of TPOAb and TGAb positivity was 4.5% and 12.61%, respectively. No association was found between the presence of autoimmunity and obstetric complications. Population studies are needed in order to establish normality ranges in the general population.

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