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Possible association between subclinical hypothyroidism and age at menopause in Colombian women

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ABSTRACT

Objective: To evaluate the association between subclinical hypothyroidism with early menopause, premature menopause, and last menstrual bleeding before the natural age of menopause.

Methods: This was a cross-sectional study conducted in 643 postmenopausal women aged 40–69 years. Groups were formed according to last menstrual episode: ≥45 [Natural age at menopause], 40–44 and [Early menopause], <40 [Premature menopause], and <45 [last menstrual episode before the natural age of menopause]. The Zulewski scale was applied to identify manifestations related to hypothyroidism and subclinical hypothyroidism, diagnosed with a serum TSH > 4.5 µIU/mL plus T4-free between 0.7 and 1.9 ng/dL.

Results: It was found that 24.4% had the last menstrual episode before the natural age of menopause, 18.6% had early menopause, and 5.7% had premature menopause. Subclinical hypothyroidism was diagnosed in 4.5% of patients. Among women with subclinical hypothyroidism, there was a higher frequency of early menopause, premature menopause, and last menstrual episode before the natural age of menopause, than in women without subclinical hypothyroidism ($p < 0.05$). Paresthesia (50%) and dry skin (40.7%) were the most reported hypothyroidism-related manifestations. Early menopause, premature menopause, and last menstrual episode before the natural age of menopause were associated with subclinical hypothyroidism, OR: 3.37 [95% CI: 1.40–8.10], OR: 4.31 [95% CI: 1.24–14.97], and OR: 3.57 [95% CI: 1.57–8.10], respectively.

Conclusions: The last menstrual episode before the natural age of menopause, early menopause, and premature menopause were significantly associated with a higher chance of subclinical hypothyroidism

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Introduction

Subclinical hypothyroidism is characterized by the elevation of the thyroid-stimulating hormone (TSH), with normal preservation of thyroid hormones [1–4]. The condition increases with age and its prevalence may vary from 3 to 18% in the adult population, mainly affecting women, older people, and populations with insufficient iodine intake [2,4,5]. It is a mild thyroid dysfunction, basically asymptomatic, although nonspecific manifestations may occur, such as slow movements or weakness, feeling of thick, dry, or cold skin, weight gain, constipation, decreased sweating, or paresthesia [1,2,4,6]. The importance of subclinical hypothyroidism lies on the potential progression to overt hypothyroidism and the association with lipid alterations, increased coronary risk, congestive heart failure, neuropsychiatric symptoms, and deterioration of muscle strength, especially when blood TSH levels are >10 µIU/mL [2,3,7,8]. The most common cause of subclinical hypothyroidism is Hashimoto's thyroiditis, a chronic autoimmune disorder [6,9].

Immunological, genetic, benign, or malignant utero-ovarian or pelvic diseases and their surgical interventions are recognized as causes for the last menstrual episode to occur before the natural age of menopause [10–12]. Natural menopause occurs between 45 and 55 years of age and is the physiological expression of the exhaustion of the ovarian follicles. Ethnic, environmental, geographic, hormonal, genetic, nutritional, and other factors explain the range of the natural age of menopause [13–15]. Menopause occurring between 40 and 44 years is defined as early menopause and before the age of 40 as premature menopause (spontaneous or surgical) [11,13,16]. The cease of menstrual episodes before the natural age of menopause is associated with osteopenia, osteoporosis and fractures, muscle dysfunction, reduction in gait and physical decline, metabolic syndrome, changes in carbohydrate metabolism and diabetes, cardiovascular disease, cerebrovascular, arterial hypertension, dyslipidemia, adverse emotional, psychosocial and global health impact, cognitive decline, and increased mortality from all causes [11,13,17–27]. There are insufficient studies that explore the association between age at menopause and thyroid disorders, and apparently, they have not been evaluated in Latin American women. Thus, the aim of this study was to evaluate the association between subclinical hypothyroidism and the age at menopause onset.

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Methods

Study design and participants

This was a cross-sectional study belonging to the research project 'Menopause and Thyroid' which was approved by the Institutional Ethics Committee of the University of Cartagena, Cartagena, Colombia (Resolution 01385-2021 and minutes 092-2021). The suggestions and recommendations of the STROBE initiative were considered when structuring the research report [28].

In 2022, women aged 40–69 years who were residents of the Caribbean region of Colombia were invited to participate in the study. They had to have one or more years without menstruation and have been considered postmenopausal in their health care services [29], be able to perform daily tasks, be active at the family level and have the perception of having been healthy in the last month. Participation was carried out in person at meetings of fifty women, anonymously, voluntarily, unpaid, and completing the following phases. First, sign written informed consent. Second, complete a sociodemographic and clinical information form. Third, allow measurement of the ankle reflex and collection of 5.0 mL of peripheral venous blood from the non-dominant forearm in order to measure serum TSH and free-T4. Fourth, attend a talk on menopause and thyroid disease. Women were free to leave at any time and those who did not wish to participate, who had visual or literacy deficits, cognitive disability, diagnosis of benign or malignant thyroid pathology, history of surgery or radiotherapy to the neck, intake of iodinated medications, oncological disease, heart failure, and abnormal free-T4 results were excluded. The information was collected by doctors and interviewers, and venous blood sample was taken by nurses. Invitations and meetings were carried out until the forms were completed according to the calculated sample size.

Used tools and measurements

Measurements were housed in a printed form designed for the study, which had several sections. First, sociodemographic and clinical characteristics were asked: age, occupation, family history of thyroid disease, personal history of high blood pressure, diabetes or dyslipidemia, perception of anxiety or depression in the last month, history of gynecological surgery and age at which the last menstrual episode occurred. Second, the Zulewski scale in Spanish language was applied. This tool assesses manifestations related to hypothyroidism, such as periorbital puffiness, constipation, weight increase, cold skin, paresthesia, hoarseness, dry skin, diminished sweating, impairment of hearing, coarse skin, slow movements, and delayed ankle reflex. One point is assigned to each of the previously mentioned if the manifestation is present and zero when it is absent. Scores are summed and one point is added if the person is <55 years old. The higher the total score, the greater the possibility of hypothyroidism. The tool establishes three categories: euthyroid status [0–2 points], intermediate condition [3–5 points], and possible hypothyroid status [6 and more points]. Sensitivity and specificity of the instrument for the diagnosis of hypothyroidism is 60% [30]. A Kuder–Richardson of 0.56 was calculated among the participants. The third section of the form was reserved to record the ultrasensitive TSH and free-T4 measured serum values, which were performed using third-generation chemiluminescence technique on an Advia Centauros Xp device (Siemens Healthineers Diagnostics Inc., Mishawaka, IN) in the Santa Lucía Clinical Laboratory of Cartagena, Colombia, a certified institution that meets the criteria established by the Colombian legislation. Criteria of the U.S. Preventive Services Task Force was used to diagnose subclinical hypothyroidism, that is if serum TSH was >4.5 μIU/mL with a free-T4 between 0.7 and 1.9 ng/dL [31]. Three groups were established according to the age of the last menstrual episode: ≥45 years (natural age of menopause), 40–44 years (early menopause), and <40 years (premature menopause) [10,16,17,20,32–34]. In addition, a fourth group was structured that included women with premature menopause and early menopause, that is, those who had menopause <45 years of age. This group was called last menstrual episode before the natural age of menopause.

Forms were reviewed weekly and kept in custody; those correctly completed were numbered and transcribed into a Microsoft Excel® data sheet. Incorrectly completed forms were not considered for analysis.

Sample size calculation

Sample size was calculated with OpenEpi, using data from the 2005 Colombian population census that projected a national population of 26,442,213 women by 2022, of which 25.6% would be between 40 and 69 years of age and 4.3% would reside in the department of Bolivar. In this department, that is part of the Colombian Caribbean, that was selected by convenience, it is estimated that a total of 1,137,015 women resided in 2022, with 291,075 between 40 and 69 years of age. A sample size of 385 women was calculated, with a confidence level of 95%, with 50% heterogeneity, and a margin of error of 5%. Of 150 (38.9%) were added to replace women who filled out forms incompletely or inconsistent forms. In addition, the same number of participants was added as a precaution, to replace lost forms, since they would be applied in distant populations. Of 685 forms were printed and available, which were applied until they were exhausted.

Statistical analysis

Statistical analysis was performed with EPI-INFO version 7 (Center for Disease Control and Prevention, Atlanta, GA). Data are presented as continuous variables expressed as mean and standard deviation, and categorical variables expressed as frequencies (%). The significance of the difference between continuous data was calculated with the ANOVA or Kruskal–Wallis test, depending on the distribution of variance based on the Bartlett test. Differences between percentages were evaluated with the Chi-square Mantel–Haenszel test. Bivariate logistic regression was performed between subclinical hypothyroidism (dependent variable) and age at menopause (independent variable). An adjusted logistic regression model was performed with the same variables and also including age, family history of thyroid disease, history of abdominal hysterectomy with or without bilateral oophorectomy, perception of anxiety and depression, and history of diabetes, high blood pressure, and dyslipidemia. For all calculations, a p value < .05 was considered as statistically significant.

Ethical considerations

Women were informed of the study, its objectives and tools to be used, after which they gave written consent of participation without receiving any type of incentive in return. The Declaration of Helsinki on human research, the ethical principles of the Belmont Report and Resolution 8430-1993 of the Colombian Ministry of Health was taken into account at all times. Women who had abnormal TSH tests were promptly referred to their health care services.

Results

A total of 794 women accepted to participate in the study of which 109 (13.7%) had exclusion criteria and 42 (6.1%) form were incorrectly filled out or were incomplete. Finally, analysis was performed on the data of 643 women, a 93.8% of the calculated sample size.

Mean age of the participants was 55.0 ± 5.7 years, average age of menopause onset was 46.8 ± 4.0 years and 75% had their last menstruation at the natural age of menopause. Early menopause was found in 18.6%, premature menopause in 5.7%, and a last menstrual episode before the natural age of menopause in 24.4%. Subclinical hypothyroidism was diagnosed in 4.5% of the participants; these women had a worse score on the Zulewski scale than women without subclinical hypothyroidism. Women with subclinical hypothyroidism had a higher frequency of menopause before the natural age ($p < .05$) (Table 1). Only 5 women (0.7%) had TSH levels > 10 μIU/mL. All manifestations related to hypothyroidism that were explored with the Zulewski scale were more frequent among women with subclinical hypothyroidism as compared to those without ($p < .05$) (Table 2).

The prevalence of subclinical hypothyroidism was 2.9% among participants who had their last menstruation at the natural age of menopause, increasing to 9.1% and 10.8% among those who had early menopause and premature menopause, respectively. When the last menstruation was <45 years, the prevalence of subclinical hypothyroidism was 9.5%. Upon bivariate and adjusted logistic regression, it was found that early menopause and premature menopause were associated three and four times, respectively, with subclinical hypothyroidism ($p < 0.05$). The last menstrual episode before the natural age of menopause was also associated with subclinical hypothyroidism, OR: 3.57 [95% CI: 1.57–8.10] after adjusting for the chosen covariates (Table 3).

Table 1. Sociodemographic and clinical characteristics of all women and according to the presence or not of subclinical hypothyroidism.

	All $n = 643$	With subclinical hypothyroidism $n = 29$ (4.5%)	Without subclinical hypothyroidism $n = 614$ (95.5%)	p Value*
Age (years)	55.0 ± 5.7	53.7 ± 6.3	55.1 ± 5.6	.21[a]
Age at menopause onset (years)	46.8 ± 4.0	44.0 ± 3.7	47.0 ± 3.9	<.001[a]
Time since menopause (years)	8.1 ± 6.4	9.7 ± 6.9	8.0 ± 6.3	.21[b]
TSH (μIU/mL)	2.0 ± 1.8	7.7 ± 4.0	1.7 ± 1.0	<.001[b]
Zulewski Scale Score	2.7 ± 2.0	6.5 ± 2.0	3.0 ± 1.8	<.001[a]
Last menstrual episode ≥ 45 years	486 (75.5)	14 (48.2)	472 (76.8)	<.001[c]
Last menstrual episode between 40 and 44 years	120 (18.6)	11 (37.9)	109 (17.7)	<.01[c]
Last menstrual episode <40 years	37 (5.7)	4 (13.8)	33 (5.3)	.05[c]
Last menstrual episode <45 years	157 (24.4)	15 (72.4)	142 (23.1)	<.001[c]
Work away from home	294 (45.7)	17 (58.6)	277 (45.1)	.15[c]
Abdominal hysterectomy without bilateral oophorectomy	191 (29.7)	8 (27.5)	183 (29.8)	.79[c]
Abdominal hysterectomy with bilateral oophorectomy	91 (14.1)	6 (20.6)	85 (13.8)	.30[c]
Perception of anxiety	107 (16.6)	4 (13.7)	103 (16.7)	.67[c]
Perception of depression	87 (13.5)	4 (13.7)	83 (13.5)	.90[c]
Diabetes	69 (10.7)	3 (10.3)	66 (10.7)	.90[c]
Dyslipidemias	220 (34.2)	9 (31.0)	211 (34.3)	.71[c]
High blood pressure	191 (29.7)	10 (34.4)	181 (29.4)	.56[c]
Family history of thyroid disease	114 (17.7)	7 (24.1)	107 (17.4)	.35[c]

Data are presented as mean ± standard deviations or frequencies n (%).
*p Values as determined with [a]ANOVA, [b]the Kruskal–Wallis test, or the [c]Chi-square – Mantel–Haenszel test.

Discussion

In this group of postmenopausal women residing in Colombia, we found that the frequency of early menopause (18.6%) and premature menopause (5.7%) was higher than the 5% and 1%, respectively, reported by other authors [10,20,22,24,32]. The Study of Women's Health Across the Nation (SWAN) reported a frequency of premature menopause of 1.1% among North American women. Statistical differences were observed according to ethnic groups and the highest frequency (1.4%) was seen among women of Hispanic origin [14]. Our figures are close to those reported by Mishra et al. [15], who in a pooled study of 51,450 postmenopausal women from nine cohort studies, identified early menopause in 7.6% and premature menopause in 2.0%. Golezar et al. [13] in a meta-analysis estimated the global prevalence of early menopause at 12.2% and premature menopause at 3.7%, figures similar to ours. Socioeconomic, nutritional, genetic, ethnic, and lifestyle factors may explain the differences [14,17].

The prevalence of subclinical hypothyroidism of 4.5% found in this study is consistent with that reported by Stuenkel [5], between 4.0 and 8.5%, with an increase to 15% in elderly populations. Likewise, 6.2% has been reported in multiethnic North

Table 2. Symptoms and signs of hypothyroidism as evaluated with the Zulewski scale among all women and the presence or not of subclinical hypothyroidism.

	All $n = 643$	With subclinical hypothyroidism $n = 29$ (4.5%)	Without subclinical hypothyroidism $n = 614$ (95.5)	p Value*
Periorbital puffiness	141 (21.9)	11 (37.9)	130 (21.1)	<.05
Constipation	165 (26.6)	12 (41.3)	153 (24.9)	<.05
Weight increase	138 (21.4)	20 (68.9)	118 (19.2)	<.001
Cold skin	78 (12.1)	18 (62.0)	60 (9.8)	<.001
Paresthesia	323 (50.2)	20 (68.9)	303 (49.3)	<.05
Hoarseness	132 (20.5)	17 (58.6)	125 (20.3)	<.001
Dry skin	262 (40.7)	18 (62.0)	244 (39.7)	<.05
Diminished sweating	123 (19.1)	10 (34.4)	113 (18.4)	<.05
Impairment of hearing	82 (12.7)	11 (37.9)	71 (11.5)	<.001
Coarse skin	67 (10.4)	14 (48.2)	53 (8.6)	<.001
Slow movements	146 (22.7)	20 (68.9)	126 (20.5)	<.001
Delayed ankle reflex	68 (10.6)	12 (41.3)	56 (9.1)	<.001
Possible hypothyroid status	85 (13.2)	19 (65.5)	66 (10.7)	<.001

Data are presented as frequencies n (%); *p values as determined with the Chi-square – Mantel–Haenszel test.

Table 3. Association between subclinical hypothyroidism and type of menopause.

Type of menopause	Age	Age at menopause	Time in postmenopause	Familial history of thyroid disease	Abdominal hysterectomy without bilateral oophorectomy	Abdominal hysterectomy with bilateral oophorectomy	Subclinical hypothyroidism	Logistic regression	
								Crude	Adjusted*
								Odds ratio [95% confidence interval]	
Last menstrual episode ≥ 45 ($n=486$)	55.4 ± 5.1	48.6 ± 2.4	6.8 ± 5.1	77 (15.8)	120 (24.6)	58 (11.9)	14 (2.9)	1	
Last menstrual episode between 40 and 44 ($n=120$)	53.1 ± 6.5	42.7 ± 1.3	10.3 ± 6.3	27 (22.5)	49 (40.8)	24 (20.0)	11 (9.1)	3.40 [1.50–7.69]	3.37 [1.40–8.10]
Last menstrual episode < 40 ($n=37$)	55.6 ± 8.2	37.2 ± 3.1	18.3 ± 9.5	10 (27.0)	22 (59.4)	9 (24.3)	4 (10.8)	4.08 [1.27–13.11]	4.31 [1.24–14.97]
Last menstrual episode < 45 ($n=157$)	53.7 ± 7.0	41.4 ± 3.0	12.2 ± 7.9	37 (23.5)	71 (45.2)	33 (21.0)	15 (9.5)	3.56 [1.68–7.56]	3.57 [1.57–8.10]

Data are presented as mean ± standard deviation or frequencies, *n* (%).
*Covariates: Age, familial history of thyroid disease, abdominal hysterectomy without bilateral oophorectomy, abdominal hysterectomy with bilateral oophorectomy, perception of anxiety, perception of depression, personal history of diabetes, high blood pressure, and dyslipidemias.

American women aged 42–52 [8]. In our study, women with subclinical hypothyroidism more frequently had manifestations related to hypothyroidism, mainly weight gain, paresthesias, and slow movements, and also had a greater possibility of hypothyroid status as determined with the Zulewski scale than women without subclinical hypothyroidism, 65.5% *vs.* 10.7%, respectively. Subclinical hypothyroidism is by definition asymptomatic; however, the affected population usually experiences symptoms of hypothyroidism with low frequency or with subtle intensity [1,2,7]. The magnitude of symptoms is influenced by two characteristics of subclinical hypothyroidism. On the one hand, the ability to evolve over months or years to overt hypothyroidism. Aggarwal and Razvi [7] consider that this behavior is an expression of the aging of the hypothalamus-pituitary-thyroid axis. On the other hand, Somwaru et al. [6] indicate that it is potentially a momentary biochemical condition. In adults over 65 years of age, they observed that only 56% still had elevated TSH values after four years of follow-up. A 46% of those with TSH levels between 4.5 and 6.9 μIU/mL, 10% between 7.0 and 9.9 μIU/mL, and 7% with > 10.0 μIU/mL subsequently normalized [6].

In this study, we found a significant association between subclinical hypothyroidism and early menopause, premature menopause, and last menstrual episode before the natural age of menopause. These findings add to those reported in two studies that identified an association between thyroid immunological disturbances and premature ovarian failure. Thyroid autoimmune disease and elevated thyroid peroxidase antibodies were identified in 20–35% of women with premature ovarian failure [33,34]. In subclinical hypothyroidism, same as with menstrual cessation at an early age or before the natural age of menopause, autoimmune disorders underlie as an important etiological factor. More studies are needed reporting on the simultaneity of alterations of the hypothalamic-pituitary-thyroid axis with dysfunction of the hypothalamic-pituitary-ovarian axis in young women. Interestingly, menopause at an earlier age and subclinical hypothyroidism have been associated with cardiovascular, musculoskeletal, and metabolic disease; in addition to various psychobiological conditions that deteriorate quality of life and favor a greater probability of mortality at an early age [7,8,11,13,17–27]. These facts require further research to better explore the relationship between estrogen deprivation, the age of menopause, and thyroid disorders. It is still not clear how estrogens, hormonal factors, and ovarian follicular cells and fluids are interrelated with thyroid autoimmunity and functional thyroid deficit. However, Kotopouli et al. [35] pointed out an association between early menarche and a greater risk of subclinical hypothyroidism and Brown et al. [1] noted that altered thyroid function is related to menstrual irregularity, polycystic ovary syndrome, infertility, adverse obstetric outcomes, and premature ovarian failure.

Strengths, limitations, and recommendations

The strength of this study is evidencing, with the Zulewski scale, the presence of manifestations related to hypothyroidism in a postmenopausal population that seemed to be healthy from a thyroid point of view. It points out the prevalence of subclinical hypothyroidism, early menopause, premature menopause, and last menstrual episode before the natural age of menopause, situations of which many women have little knowledge and need information that could contribute to therapeutic adherence and perception of satisfaction [36]. Our findings seek to raise awareness and draw attention to the potential relationship between two endocrinological conditions that are separately associated with several morbid conditions [7,8,11,17,19,21,24,27]. Despite this, the study has several limitations. Due to the cross-sectional design, although the associations are statistically significant they do not denote causality. No measurement of gonadotropic hormones or estradiol was performed to document the endocrine profile of the participating postmenopausal women. Antithyroid antibodies were not evaluated, we did not ask about morbid conditions present at the moment of their last menstruation, and it was not possible to identify surgical menopause as we did not ask them when the surgery was performed or menopausal status when operated. Among the participants, a low reliability coefficient was found for the Zulewski scale, so new clinical screening tools should be proposed. Although larger studies with other designs are warranted, it is recommended that women who had their last menstruation before the natural age of menopause have their thyroid hormones and antithyroid antibodies evaluated whether thyroid peroxidase or thyroglobulin antibodies [5]. Governmental and non-governmental agencies that dictate health care protocols should bear in mind the age of menopause when making suggestions on screening for thyroid disorders in women who are adult, mid-aged, or older. Health professionals without

distinction of specialty must remember that physical mental tiredness, the perception of fatigue, emotional lability, mood swings, frequent forgetfulness, intolerance to changes in temperature, changes in the skin and integuments, sleep/wake patterns, and the sensation of palpitations, are among the menopausal symptoms but they also reflect thyroid dysfunction [5]. At the same time, doctors should keep in mind that the American Thyroid Association recommends screening all adults starting at the age of 35 and repeating so every five years. The American Association of Clinical Endocrinologists recommends that older adults, but does not specify the age, be evaluated for thyroid function. The American College of Physicians suggests that women aged fifty or older with an incidental finding of thyroid abnormality should be thoroughly evaluated [5,37]. Finally, there is a need for protocols that take into consideration the age of menopause, and indicate when to explore for subclinical hypothyroidism or other thyroid disorders.

In conclusion, in this group of Colombian postmenopausal women who had not previously been diagnosed with thyroid disorders and surveyed in their community, the prevalence of subclinical hypothyroidism was found similar to that reported in other populations. Clinical manifestations related to hypothyroidism were significantly more reported by women diagnosed with subclinical hypothyroidism than among those without the condition. The presence of last menstrual bleeding before the natural age of menopause was high. Early menopause, premature menopause, and the last menstrual episode before the natural age of menopause were significantly associated with subclinical hypothyroidism.

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Disclosure statement

The author(s) declare having no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

AM-C (conceptualization of the 'Thyroid and Menopause' project, definition of its products, data curation, methodology, and statistical analysis, writing and structuring of the initial draft, argument review, and editing of this article). AM-B (conceptualization of the research line of the project, methodology, and statistical analysis, writing, numerical revision of references, and grammatical adjustment, general revision, and editing). S S-Z (data review, writing, English grammar adjustment, networking activities, and international networking). All authors contributed conceptually and approved the final manuscript.

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Data availability statement

All required information regarding the protocol of the study and collected data will be made available upon a reasonable request to the researchers who provide a methodologically sound proposal. Only the analysis required to achieve the aims in the approved proposal will be permitted. Proposals should be directed to alvaromonterrosa@gmail.com

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