



Original article



EMAS position statement: Thyroid disease and menopause

Gesthimani Mintziori^{a,*}, Stavroula Veneti^a, Kris Poppe^b, Dimitrios G. Goulis^a, Eleni Armeni^c, C. Tamer Erel^d, Ivan Fistonić^e, Timothy Hillard^f, Angelica Lindén Hirschberg^g, Blazej Meczekalski^h, Nicolás Mendozaⁱ, Alfred O. Mueck^{j,q}, Tommaso Simoncini^k, Petra Stute^l, Dorenda van Dijken^m, Margaret Reesⁿ, Leonidas Duntas^o, Irene Lambrinoudaki^p

^a Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece

^b University Hospital CHU St-Pierre UMC, Université libre de Bruxelles (ULB), Belgium

^c Second Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece and Royal Free Hospital, London, United Kingdom

^d Istanbul-Cerrahpaşa University, Cerrahpaşa School of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey

^e Faculty for Health Studies, University of Rijeka, Rijeka, Croatia

^f Department of Obstetrics and Gynaecology, University Hospitals Dorset, Poole, UK

^g Department of Women's and Children's Health, Karolinska Institutet and Department of Gynecology and Reproductive Medicine, Karolinska University Hospital, Stockholm, Sweden

^h Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland

ⁱ Department of Obstetrics and Gynecology, University of Granada, Spain

^j Department of Women's Health, University Hospital Tuebingen, Germany

^k Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100 Pisa, Italy

^l Department of Obstetrics and Gynecology, University Clinic Inselspital, Bern, Switzerland

^m Department of Obstetrics and Gynecology, OLVG Hospital, Amsterdam, The Netherlands

ⁿ Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

^o Evgenideion Hospital, Unit of Endocrinology and Metabolism, National and Kapodistrian University, Athens, Greece

^p Second Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece

^q Beijing OB/GYN Hospital, Capital Medical University, China

ARTICLE INFO

Keywords:

Menopause
Thyroid
Hyperthyroidism
Hypothyroidism

ABSTRACT

Introduction: Thyroid diseases are common in women in their late reproductive years; therefore, thyroid disease and menopause may co-exist. Both conditions may present with a wide range of symptoms, leading to diagnostic challenges and delayed diagnosis.

Aim

To construct the first European Menopause and Andropause Society (EMAS) statement on thyroid diseases and menopause.

Materials and methods: Literature review and consensus of expert opinion (EMAS executive board members/experts on menopause and thyroid disease).

Summary recommendations: This position paper highlights the diagnostic and therapeutic dilemmas in managing women with thyroid disease during the menopausal transition, aiming to increase healthcare professionals' awareness of thyroid disorders and menopause-related symptoms. Clinical decisions regarding the treatment of both conditions should be made with caution and attention to the specific characteristics of this age group while adopting a personalized patient approach. The latter must include the family history, involvement of the woman in the decision-making, and respect for her preferences, to achieve overall well-being.

1. Introduction

Women experience menopause at a particular stage of their lifetime.

On the other hand, subclinical hypothyroidism, mainly due to autoimmune thyroiditis, is a common endocrine disease in women during their reproductive years (the prevalence rate is 6–10 %) [1] and is often

* Corresponding author.

E-mail address: gefsi@auth.gr (G. Mintziori).

<https://doi.org/10.1016/j.maturitas.2024.107991>

present or arises during the menopausal transition.

Many symptoms, including menstrual irregularities, night sweats, flushes, mood swings, muscle and joint pain, anxiety/depression, and insomnia, characterize perimenopause; women may also experience decreased libido, and symptoms related to vulvovaginal atrophy, such as vaginal dryness and dyspareunia [2]. Meanwhile, thyroid symptoms and signs vary in nature and severity and can negatively impact women's quality of life (QoL) at any period, including perimenopause. Given that increased sweating, mood swings, anxiety/depression, decreased libido and menstrual irregularities can also characterize thyroid disease, the differential diagnosis of the two conditions can be difficult. Hypothyroidism and hyperthyroidism affect circulating sex hormone concentrations and dysregulate the autonomic system, which in turn may impair sexual function [3], with, for example, impaired libido, decreased desire and arousal, and dyspareunia.

Suboptimal thyroid function may be associated with age at menopause, although a Mendelian randomization study using the two-sample approach and data from genome-wide association studies (GWAS) found no association between genetically predicted thyroid and ovulatory function [4]. Questions in the field concern the effect of menopausal hormone therapy (MHT) on the natural course of thyroid disease, the impact of levothyroxine (LT₄) replacement or anti-thyroid drugs on menopausal symptoms, and the prevalence and management of thyroid malignancies during perimenopause.

This position paper of the European Menopause and Andropause Society (EMAS) highlights the diagnostic and therapeutic challenges involved in treating women with thyroid disease in perimenopause, in order to increase awareness among physicians (particularly endocrinologists, gynecologists, general practitioners, and internists) of thyroid disorders and menopause-related conditions among their patients, and to assist clinicians and patients in their shared decision-making regarding therapeutic options.

2. Methodology

A literature search was performed by two investigators (GM and SV). The search string was (((("Thyroid Gland" [MeSH]) AND ("Hyperthyroidism" [MeSH] OR "Graves Disease" [MeSH] OR "Hyperthyroidism, Nonautoimmune" [Supplementary Concept])) OR "Hypothyroidism" [MeSH]) OR ("Hashimoto Disease" [MeSH] OR "Thyroiditis" [MeSH])) AND ("Menopause" [MeSH] OR "Postmenopause"[MeSH]) and 179 articles were retrieved and evaluated. The titles and abstracts of the articles were reviewed and evaluated for relevance. Only studies focusing on peri- or postmenopausal women with thyroid disease were eligible for further evaluation.

3. Thyroid function and thyroid disorders

Thyroid function is regulated by the hypothalamus-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) secreted from the hypothalamus stimulates the pituitary to produce thyroid-stimulating hormone (TSH), which in turn targets the thyroid gland and stimulates thyroid hormone secretion. Thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃), exert negative feedback on the secretion of TRH and TSH. Through this mechanism, the body achieves the normal functioning of the thyroid gland. In cases where this balance is disturbed, either hyperthyroidism or hypothyroidism occurs. The diagnosis is made by measuring TSH and thyroid hormone concentrations. Descriptions of the common thyroid disorders are presented in Table 1.

4. Menopausal transition and thyroid disease

Menopause and thyroid dysfunction (hyperthyroidism and hypothyroidism) may be accompanied by similar symptoms, including menstrual irregularities, mood disorders, decreased libido, increased sweating, sleep disturbances, hair loss, and diminished QoL (Table 2).

Table 1
Description of common thyroid disorders.

Thyroid condition	Description
Overt hypothyroidism	Serum TSH concentrations above the reference range, and fT ₄ concentrations below the reference range [5].
Subclinical hypothyroidism	Serum TSH concentrations above the reference range, and fT ₄ concentrations within the reference range [5].
Overt hyperthyroidism	Serum TSH concentrations below the reference range, and fT ₄ concentrations above the reference range [6].
Subclinical hyperthyroidism	Serum TSH concentrations below the reference range, and fT ₄ concentrations within the reference range [6].
Thyroid nodule	A discrete lesion within the thyroid gland [7].
Multinodular goiter	Enlargement of thyroid gland with multiple distinct nodules [7].

fT₄: free thyroxine; TSH: thyroid-stimulating hormone.

Table 2
Symptoms of menopausal transition and of thyroid disease.

Symptoms	Perimenopause/ menopause	Hypothyroidism	Hyperthyroidism
Menstrual irregularities	✓	✓	✓
Anxiety	✓		✓
Depression	✓	✓	✓
Mood disorders	✓	✓	✓
Joint and muscle pains	✓	✓	✓
Muscle weakness	✓	✓ ^a	✓
Tremor			✓
Increased sweating	✓		✓
Sleep problems	✓		✓
Hair problems	✓	✓	
Perceived decreased QoL	✓	✓	✓
Decreased libido	✓	✓	✓

QoL: quality of Life.

^a Only in cases of congenital hypothyroidism due to cerebellar dysfunction.

This common symptomatology comprises the main differential diagnostic challenge for physicians treating women during menopause. Indeed, menopause should be included in the differential diagnosis of hyperthyroidism and hypothyroidism [5]. Without specific signs (e.g., orbitopathy/exophthalmos, periorbital edema, goiter), it is difficult to attribute the symptoms specifically to one disease rather than the other, leading to a delayed diagnosis. Thus, healthcare practitioners working with women of menopausal age should have a low threshold of suspicion for thyroid disease and order hormonal assessment when such symptoms are present.

Thyroid disease affects women's work ability and leads to reduced work hours or leaving work, as occurs in menopause [8]. More specifically, patients with hyperthyroidism are more likely than controls to leave work for a long time within the first year after the diagnosis [9]. Moreover, patients with hyperthyroidism and hypothyroidism have an increased likelihood of receiving a disability pension compared with controls, and patients who do not leave work have a lower income trajectory than controls [8,10].

The main clinical conditions that may be influenced by either menopause or thyroid disease are described below.

5. Clinical conditions influenced by menopause or thyroid disease

5.1. Thyroid nodules and thyroid cancer

The incidence of thyroid nodules increases with age, more markedly among women than men. In iodine-sufficient regions, the prevalence of thyroid nodules is approximately 5 % in women and 1 % in men.

Thyroid cancer occurs in 7–15 % of patients with thyroid nodules and is more common in women than men [11]. The hormonal changes that occur during the menopausal transition contribute to this sexual dimorphism [12,13].

Surgical menopause results in a sudden drop in estrogen concentrations and severe menopausal symptoms [14–16]. It is associated with an increased risk of thyroid cancer [15,16]. This association is of unknown pathophysiology, as natural menopause is associated with a decreased incidence of thyroid cancer [13,15,16]. Early menarche and late natural menopause are associated with thyroid cancer, implying that long exposure to estrogens increases the risk [17]. However, a meta-analysis of 5434 patients with thyroid cancer (615 hysterectomized) concluded that hysterectomy was associated with an increased risk of thyroid cancer later in life (standardized risk ratio [SRR] 1.43, 95 % confidence interval [CI] 1.15–1.78) [18]. This result should be interpreted cautiously since the heterogeneity among studies was high (I^2 47%); the follow-up time might have explained it, since, in one study, the higher risk of developing thyroid cancer was observed only during the first two years after surgery [19]. Furthermore, in a nationwide cohort study in Korea, thyroid cancer incidence was not different if the hysterectomy was performed with or without oophorectomy [14]. Therefore, the precise explanation for this observation might go beyond the decline in estrogen concentrations [18]. Thyroid cancer and indications for hysterectomy may share common risk factors, or screening may be more frequent after surgery. Even without oophorectomy, hysterectomy may be associated with thyroid cancer.

Papillary thyroid cancer has a worse prognosis in postmenopausal than in premenopausal women [20–22]. Additionally, old age *per se* is associated with a worse prognosis in papillary thyroid cancer [23]. The level of estrogen receptor (ER) expression may partly determine papillary thyroid cancer aggressiveness after menopause. ER- α expression increases in the thyroid gland during menopause, which may be associated with activation of specific intracellular pathways involved with thyroid cancer [24]. Although the prognosis remains excellent, postmenopausal status has been associated with the recurrence of differentiated papillary thyroid cancer [25,26]. This period is characterized by estrogen decrease and an increase in follicle-stimulating hormone (FSH), mediated by epidermal growth factor receptor (EGFR) activation. The latter is expressed in papillary thyroid cancer cells more in postmenopausal than in premenopausal women [25].

5.2. Metabolic disease

Thyroid hormones play a key role in metabolism regulation [27]. Their deficiency or excess has been associated with metabolic dysregulation [28]. Low concentrations of free thyroxine (fT₄) have been associated with insulin resistance [29], an association more pronounced in postmenopausal women, implying a synergistic effect with postmenopausal status [30]. On the other hand, hyperthyroidism affects cardiovascular pathophysiology and could cause heart failure and atrial fibrillation [31].

Subclinical hypothyroidism has been associated with increased triglyceride (Tg) levels, elevated total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio, and increased cardiovascular risk [32]. TSH has been positively associated with TC, LDL-C, HDL-C, and Tg [33]. A cross-sectional study on 8565 healthy males and 5350 healthy females reported the effect of TSH on lipids stratified by sex and age. Although young women had lower lipid concentrations than young men, this association was reversed after menopause. Moreover, the positive association of TSH with serum lipids became stronger as age increased [34]. In a cross-sectional study on 2914 women in Italy, menopause status impacted the association between serum TSH elevation and plasma lipid concentrations [35].

The prevalence of hypertriglyceridemia is [much?] higher in women (before or after menopause) with overt hypothyroidism. Hypertriglyceridemia and LDL-C are increased in premenopausal women with

SCH [36]. On the other hand, premenopausal women with hyperthyroidism have reduced TC and LDL-C concentrations, while postmenopausal women are at increased risk of low HDL-C [36].

In a cross-sectional study of 468 euthyroid women, the maximum intima-media thickness (IMT) increased with the progression of menopausal status, and higher serum TSH concentrations were associated with carotid plaques [37]. Moreover, IMT was higher in symptomatic than in asymptomatic postmenopausal women [38]. Clinicians should be aware of this condition and must diagnose and treat subclinical hypothyroidism early in perimenopause, according to the European Thyroid Association (ETA) guidelines [39].

Weight gain affects both women going through the menopausal transition and those who have hypothyroidism [40]. The link between thyroid hormones and energy expenditure as well as body weight is well established; suboptimal thyroid function is known associated with reduced resting energy expenditure, increased levels of cholesterol, reduced gluconeogenesis and lipolysis, and ultimately weight gain [41]. On the other hand, alterations in body composition become noticeable in late perimenopause, preceding the final menstrual period [42,43]. Specifically, there is an increase in fat mass and a decrease in lean mass during the menopausal transition when compared with the premenopausal state [43]. These modifications in body composition persist into the early postmenopausal years [42,43]. Following this timeframe, the changes in fat and lean mass slow down and eventually body composition stabilizes [43,44]. Apart from the overall increase in fat mass, the menopausal transition is linked to an escalation in visceral fat mass [44,45] and a decline in energy expenditure [46], stemming from diminished lipid oxidation [46] and reduced physical activity [47]. Baseline adiposity and ethnicity may influence the extent of the alterations in body composition [48].

Non-alcoholic fatty liver disease (NAFLD) constitutes the leading form of chronic liver disease worldwide and is characterized by steatosis of the hepatocytes without a secondary cause. NAFLD affects 25 % of the global population. The disease can manifest as non-alcoholic fatty liver (NAFL) or non-alcoholic steatohepatitis (NASH) and can lead to fibrosis and cirrhosis [49]. Metabolic syndrome is strongly associated with NAFLD: most patients with NAFLD also have metabolic syndrome [50]. A suggested pathophysiological mechanism is insulin resistance and hepatosteatosis due to the activation of protein kinase C (PKC)- ϵ and fibroblast growth factor 21 (FGF21) in patients on a high-fat diet [51]. Insulin resistance also contributes to liver damage.

In postmenopausal women, the prevalence of NAFLD is 60.2 %, compared with 42.9 % in premenopausal obese women [52]. The decreased estrogen concentrations could explain the increased NAFLD prevalence in women after menopause. Estrogens decrease gluconeogenesis and lipogenesis and increase cholesterol excretion, exercising a protective role in NAFLD [53]. Postmenopausal women who receive MHT have a lower risk of NAFLD and fibrosis than those who do not. TSH and FSH concentrations change with age, and so does the prevalence of NAFLD. Specifically, FSH increases from perimenopause, stabilizes, and then decreases after the woman reaches 70 years of age, on average [54,55]. TSH concentrations are higher in women aged 40–50 years than in younger women [30]. Moreover, NAFLD prevalence increases from the age of 40 years [56]. Increased TSH and FSH concentrations could explain this age dependency. LT₄ supplementation in women with hypothyroidism and MHT in perimenopause and menopause may prevent NAFLD progression [57–59].

5.3. Infertility

Nowadays, more women wish to have children at an older age, often when approaching menopause. Proper guidance and counseling on the likelihood of success and potential problems that may arise should be provided to these women.

Thyroid disorders occur in 30–40 % of women with premature ovarian insufficiency (POI) [60]. Thyroid autoimmunity seems to play a

crucial role. The pathophysiological mechanism of thyroid autoimmunity's effect on ovarian sufficiency has not been elucidated. The fact that several isoforms of thyroid hormone receptor mRNA are expressed in the human oocyte may indicate that thyroid hormone directly affects the oocyte and is involved in folliculogenesis [61]. Anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibodies are present in the follicular fluid on the day of oocyte retrieval in women with thyroid autoimmunity, which led to the hypothesis that they act destructively on folliculogenesis in a direct way [62]. Apart from the association of POI with thyroid autoimmunity, the latter has been associated with ovarian insufficiency in women approaching menopause [63]. Another possibility is that thyroid antibodies are just an epiphenomenon of an undefined immune disorder and that other antibodies destroy the oocytes.

6. Challenges of laboratory thyroid hormone assessments during perimenopause

Apart from vasomotor symptoms, common complaints of postmenopausal women are skin problems (dryness, dark spots, wrinkles), hair loss and hair thinning [64,65]. To reduce the impact of such symptoms on QoL, women are often advised, or even decide by themselves, to use over-the-counter supplements, most of which contain biotin. Biotin is used in many thyroid-related immunoassays as biotin-streptavidin antibodies; thus, consumed biotin may interfere with the immunoassay process and lead to false TSH, fT₃, fT₄ and total T₄ results [66,67] – low values in immunometric assays and high in competitive binding assays [68]. Physicians are encouraged to take a full history, including information on prescribed drugs and over-the-counter formulations. Women should be advised to have thyroid hormone assessments after discontinuing the biotin-containing supplement for 2–3 days.

7. Therapeutic challenges of thyroid disease during perimenopause

7.1. Management of thyroid disease

In menopause, subclinical hypothyroidism can worsen the negative effects of low estrogen concentrations, increasing cardiovascular risk due to dyslipidemia and hypertension. Furthermore, a failure to treat or undertreatment of subclinical hypothyroidism during perimenopause may augment the risk of metabolic abnormalities, including body weight gain and NAFLD, which are increased in the late reproductive years compared with younger ages. Despite the positive impact of LT₄ treatment in women with subclinical hypothyroidism on metabolic parameters and NAFLD, treatment has not been associated with a decreased cardiovascular mortality risk [69].

On the other hand, overtreatment of postmenopausal women with subclinical hypothyroidism can reduce bone mineral density (BMD) and increase the risk of cardiovascular disease. Aging *per se* results in gradual bone loss, as does menopause, due to reduced estrogen production. On top of that, overtreatment of hypothyroidism in (*peri*)menopause is associated with an increased risk of low BMD and osteopenia/osteoporosis. In a cross-sectional study of 1477 perimenopausal Dutch women without thyroid disease, BMD of the lumbar spine of <0.937 g/cm² was associated with fT₄ in the highest quintile of the reference range [70]. Similarly, in a retrospective study of 174 women, low-normal TSH concentrations and anti-TPO were independently associated with osteoporosis [71]. On the other hand, a systematic review of the association of T₄ and TSH concentrations with BMD in postmenopausal women was inconclusive [72].

According to the NICE guidelines, LT₄ treatment should be considered for adults with subclinical hypothyroidism with a TSH of ≥10 mU/l on two separate occasions three months apart [73]. Older patients should have an individualized approach because of possible

comorbidities. A 25–50 µg/day starting dose of LT₄ is suggested for women >65 years with a history of cardiovascular disease, for safety reasons [73].

Some physicians recommend combined LT₄/LT₃ treatment for patients with hypothyroidism who do not respond satisfactorily to the administration of only LT₄. However, there are insufficient data on the administration of the combination in menopausal women to make a recommendation [74,75].

The treatment of hyperthyroidism depends on its cause. Therefore, it is necessary to make a differential diagnosis. Increased serum thyrotropin receptor antibodies (TRAbs) are a criterion for the diagnosis of Graves' disease. If there is no increase, a thyroid scan is required [76]. Hyperthyroidism management includes anti-thyroid drugs, radioactive iodine (RAI) ablation therapy, and thyroidectomy. Methimazole/carbimazole is the drug of choice. In case of an allergy, propylthiouracil can be used. In cases of toxic goiter or toxic nodules, surgery, RAI or radiofrequency ablation are the preferred treatment. Long-term methimazole/carbimazole treatment may be indicated in elderly patients or patients who are not eligible for surgery or RAI. Surgery is avoided for older patients due to increased morbidity [11].

There is no difference between older and younger individuals in managing solitary thyroid nodules. The ETA guidelines for the risk stratification of thyroid nodules in adults do not include age as a criterion [77]. However, in clinical practice, the management of solitary thyroid nodules may differ according to life expectancy or fertility wishes. Furthermore, the American Joint Committee on Cancer TNM staging system has included age as a risk stratification factor, as the mortality rates of thyroid cancer increase after 45 years [11].

7.2. Menopause hormone therapy

MHT was introduced in the 1960s. The first MHT, an equine estrogen preparation sold under the brand name Premarin, had been licensed in the US since 1941 [78]. However, in the early 2000s, the Women's Health Initiative (WHI) study showed no benefit of MHT to health and, in fact, a trend toward early harm [79]. These controversial results and the lack of evidence-based guidance resulted in a radical reduction in MHT prescription [80].

Estrogens constitute the most appropriate therapy for menopausal women [81] as they effectively treat vasomotor symptoms and vaginal atrophy. MHT can be initiated within ten years of menopause or before the age of 60 years as it reduces all-cause mortality [82]. Prescription of MHT may be based on the EMAS 2022 eligibility criteria [83]. In the WHI trial, a trend of decreasing risk of coronary artery disease was reported [84]. MHT helps to prevent hip fractures, a leading cause of morbidity in postmenopausal women [85]. Moreover, no increased risk of stroke with MHT in younger (50–59 years) normotensive postmenopausal women was observed, particularly when lower doses (e.g., <0.625 mg) of conjugated equine estrogens in conjunction with medroxyprogesterone acetate were prescribed [86].

MHT is protective against esophageal, gastric, and colorectal cancer but is associated with an increased risk of venous thromboembolism by the oral route, as well as of breast and ovarian cancer, depending on the route of administration, duration and the timing of treatment. Therefore, it is essential to take a detailed personal and family history. A meta-analysis of nine cohort studies showed no association of MHT with thyroid cancer risk in postmenopausal women [87]. It has been suggested that MHT could influence thyroid autoimmunity over time; however, a population-based Danish study that followed women for 11 years failed to show an association between the MHT duration and changes in anti-TPO concentrations [88]. Notably, normal and neoplastic thyrocytes express ER α and β ; therefore, estrogen administration may influence thyroid function [89,90]. 17 β -estradiol (E₂) has a proliferative effect on benign and malignant thyroid cells. However, the exact mechanism of carcinogenesis has not been elucidated. In this context, the role of estrogen and its binding to thyroid cells may vary,

either through the G protein-coupled estrogen receptor (GPER1) or the ER α and β isoforms [91,92]. In *in vitro* studies, thyroid follicular cells proliferated faster in the presence of estrogens, suggesting that MHT could promote goitrogenesis and nodularity [93]. A study designed to answer this question showed no difference in the size of the thyroid gland and thyroid nodules between postmenopausal women who received estrogen therapy for one year and those who did not [94]. However, one year is a short period for monitoring node progression.

Additionally, there is a difference in the effect on thyroid function of the transdermal and oral estrogens. Oral E₂ in women with hypothyroidism leads to an increase in thyroxine-binding globulin (TBG) concentration. It may cause clinical changes in TSH concentrations, resulting in a need to increase the LT₄ dose [95,96]. In contrast, transdermal E₂ does not affect thyroid function [97–99]. There are also studies showing that even oral estrogens do not affect the thyroid function of menopausal women with subclinical hypothyroidism [100,101]. In addition, no data on interactions between MHT and drugs used to treat thyroid diseases have been reported [83,93,102].

8. Summary recommendations

- Menopause and thyroid dysfunction (hyperthyroidism and hypothyroidism) may be accompanied by general symptoms, including menstrual irregularities, mood disorders, increased sweating, sleep disturbances, and hair loss.
- An increased awareness of the overlap in the symptoms of menopause and thyroid dysfunction on the part of healthcare professionals working with women in menopausal years is needed so that they can more readily detect co-existing thyroid disease.
- Biotin consumption may lead to false TSH, fT₃ fT₄ and total T₄ results when immunoassays are used for thyroid measurements.
- Physicians are encouraged to take a full history, including information on prescribed drugs and over-the-counter formulations. Women taking a biotin-containing supplement should be advised to have thyroid hormone assessments only 2–3 days after they have discontinued taking it.
- Surgical menopause, early menarche and late natural menopause have been associated with the development of thyroid cancer. In the case of papillary thyroid cancer, a worse prognosis in postmenopausal women has been reported.
- We suggest that women with a history of surgical menopause, early menarche, or late natural menopause be evaluated for thyroid nodules. If a nodule is detected, general population guidelines should be followed for their evaluation and follow-up.
- Given that menopausal women and those with thyroid function disorders are at greater risk of dyslipidemia, we suggest that their lipid metabolism is evaluated.
- Menopause interferes with the association between serum TSH concentrations and plasma lipid concentrations. In menopausal women, the prevalence of NAFLD is increased.
- Clinical decisions on the treatment options for menopausal symptoms and thyroid conditions should be made with caution and with attention to the specific characteristics of this age group. A personalized patient approach is suggested, involving the woman in decision-making and respecting her preferences to achieve overall well-being.
- MHT is a safe option to treat women with menopausal symptoms and thyroid conditions.
- In menopause, untreated thyroid disease and overtreatment of thyroid disease can have adverse effects (specifically on cardiovascular risk and bone density). MHT prevents hip fractures, and there is no evidence of any MHT effect on thyroid cancer risk in postmenopausal women.
- LT₄ supplementation and MHT may improve NAFLD.

9. Conclusion

This EMAS position paper highlights the diagnostic and therapeutic dilemmas in managing women with thyroid disease during perimenopause, aiming to increase awareness among healthcare professionals (general practitioners, nurses, obstetricians-gynecologists, endocrinologists) and assist shared decision-making with patients. All clinicians must scrupulously check for the presence of menopause-related conditions or thyroid diseases and treat them if detected. Clinical decisions on the treatment of both conditions should be made with caution and attention to the specific characteristics of this age group, adopting a personalized patient approach.

Contributors

Gesthimani Mintziori, Stavroula Veneti, Leonidas Duntas and Dimitrios G. Goulis prepared and circulated the initial draft to all other named authors (EMAS board members and advisors) for comments and approval. Irene Lambrinouadaki and Margaret Rees coordinated the production.

Funding

No funding was sought or secured for the preparation of this position statement.

Provenance and peer review

This EMAS position statement was not commissioned and was not externally peer reviewed.

Declaration of competing interest

1. Gesthimani Mintziori: none declared
2. Stavroula Veneti: none declared
3. Kris Poppe: none declared
4. Dimitrios G. Goulis: none declared
5. Eleni Armeni: none declared
6. C. Tamer Erel: none declared
7. Ivan Fistonić: none declared
8. Timothy Hillard: Remuneration for talks or consultancy work over the last 5 years from: Theramex, Besins, Astellas, Shionogi
9. Angelica Lindén Hirschberg: consulting fees from Astellas and Gedeon Richter, research support from Besins and Avia Pharma.
10. Blazej Meczekalski: none declared
11. Nicolás Mendoza: Remuneration for talks or lectures by the following laboratories: Adamed, Shionogi, MSD, Procare, Novonordisk, Lacer, Gynea, Exeltis.
12. Alfred Mueck: Grant/research support: Besins/Dr.Kade Company; Consultancies and/or Lectures: Abbott, Bayer, Besins/Dr. Kade, Exeltis, Gedeon Richter, Hexal, Novartis, Jenapharm, MSD, Schaper and Brümmer, Serelys
13. Tommaso Simoncini: consulting fees from Abbot, Astellas, Gedeon Richter, Mitsubishi Tanabe, Sojournix, Estetra, Mithra, Actavis, Medtronic, Shionogi, Applied Medical. Speakers' honoraria from Abbott, Shionogi, Gedeon Richter, Intuitive Surgical, Applied Medical, Theramex
14. Petra Stute: Grant/research support: Schaer Pharma, EFFIK; Consultancies: Theramex, Astellas; Membership of speakers' bureau: Theramex, Jenapharm, Labatec, Exeltis, Besins Healthcare, Astellas, Gedeon Richter, Hexal, Pierre Fabre, Zeller
15. Dorenda van Dijken: none declared
16. Margaret Rees: none declared
17. Leonidas Duntas: none declared
18. Irene Lambrinouadaki: research grant from ITF Hellas.

References

- [1] Y.A. Kim, Y.J. Park, Prevalence and risk factors of subclinical thyroid disease, *Endocrinol. Metab.* 29 (2014) 20–29.
- [2] N. Santoro, C. Roeca, B.A. Peters, G. Neal-Perry, The menopause transition: signs, symptoms, and management options, *J. Clin. Endocrinol. Metab.* 106 (2021) 1–15.
- [3] A.T. Gabrielson, R.A. Sartor, W.J.G. Hellstrom, The impact of thyroid disease on sexual dysfunction in men and women, *Sexual Medicine Reviews.* 7 (1) (2019) 57–70.
- [4] A.D. Kjaergaard, E. Marouli, A. Papadopoulou, P. Deloukas, A. Kuš, R. Sterenborg, et al., Thyroid function, sex hormones and sexual function: a Mendelian randomization study, *Eur. J. Epidemiol.* 36 (3) (2021) 335–344.
- [5] L. Chaker, A.C. Bianco, J. Jonklaas, R.P. Peeters, Hypothyroidism, *Lancet* 390 (2017) 1550–1562.
- [6] S. De Leo, S.Y. Lee, L.E. Braverman, Hyperthyroidism, *Lancet* 388 (2016) 906–918.
- [7] S. Jasim, H. Gharib, Multinodular goiter, in: *Contemporary Endocrinology*, 2018, pp. 135–152.
- [8] V. Leso, I. Vetrani, L. De Cicco, A. Cardelia, L. Fontana, G. Buonocore, et al., The impact of thyroid diseases on the working life of patients: a systematic review, *Int. J. Environ. Res. Public Health* 17 (2020) 1–24.
- [9] M.A. Nexø, T. Watt, J. Pedersen, S.J. Bonnema, L. Hegedüs, A.K. Rasmussen, et al., Increased risk of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning for thyroid patients: a Danish register-based cohort study, *J. Clin. Endocrinol. Metab.* 99 (9) (2014) 3184–3192.
- [10] F. Brandt, M. Thvilum, L. Hegedüs, T.H. Brix, Hyperthyroidism is associated with work disability and loss of labour market income. A Danish register-based study in singletons and disease-discordant twin pairs, *Eur. J. Endocrinol.* 173 (5) (2015) 595–602.
- [11] M.M. Uygur, T. Yoldemir, D.G. Yavuz, Thyroid disease in the perimenopause and postmenopause period, *Climacteric* 21 (2018) 542–548.
- [12] J. Farahati, P. Bucky, T. Parlow, U. Mäder, C. Reiners, Characteristics of differentiated thyroid carcinoma in children and adolescents with respect to age, gender, and histology, *Cancer* 80 (11) (1997) 2156–2162.
- [13] M. Derwahl, D. Nicula, Estrogen and its role in thyroid cancer, *Endocr. Relat. Cancer* 21 (5) (2014) T273–T283.
- [14] M. Kim, B.H. Kim, H. Lee, H. Nam, S. Park, M.H. Jang, et al., Thyroid cancer after hysterectomy and oophorectomy: a nationwide cohort study, *Eur. J. Endocrinol.* 184 (1) (2021) 143–151.
- [15] A.S. Mannathazhathu, P.S. George, S. Sudhakaran, D. Vasudevan, K.M.J. Krishna, C. Booth, et al., Reproductive factors and thyroid cancer risk: meta-analysis, *Head Neck* 41 (12) (2019) 4199–4208.
- [16] J. Luo, M. Hendryx, J.E. Manson, X.Y. Liang, K.L. Margolis, Hysterectomy, oophorectomy, and risk of thyroid cancer, *J. Clin. Endocrinol. Metab.* 101 (10) (2016) 3812–3819.
- [17] S. Shin, N. Sawada, E. Saito, T. Yamaji, M. Iwasaki, T. Shimazu, et al., Menstrual and reproductive factors in the risk of thyroid cancer in Japanese women: the Japan Public Health Center-Based Prospective Study, *Eur. J. Cancer Prev.* 27 (4) (2018) 361–369.
- [18] S. Caini, B. Gibelli, D. Palli, C. Saieva, M. Ruscica, S. Gandini, Menstrual and reproductive history and use of exogenous sex hormones and risk of thyroid cancer among women: a meta-analysis of prospective studies, *Cancer Causes Control* 26 (4) (2015) 511–518.
- [19] R. Luoto, S. Grenman, S. Salonen, E. Pukkala, Increased risk of thyroid cancer among women with hysterectomies, *Am. J. Obstet. Gynecol.* 188 (1) (2003) 45–48.
- [20] P. Brindel, F. Doyon, F. Rachédi, J.L. Boissin, J. Sebbag, L. Shan, et al., Menstrual and reproductive factors in the risk of differentiated thyroid carcinoma in native women in French Polynesia: a population-based case-control study, *Am. J. Epidemiol.* 167 (2) (2008) 219–229.
- [21] J. Jonklaas, G. Noguera-Gonzalez, M. Munsell, D. Litofsky, K.B. Ain, S.T. Bigos, et al., The impact of age and gender on papillary thyroid cancer survival, *J. Clin. Endocrinol. Metab.* 97 (6) (2012) E878–E887.
- [22] D. Zhang, J. Tang, D. Kong, Q. Cui, K. Wang, Y. Gong, et al., Impact of gender and age on the prognosis of differentiated thyroid carcinoma: a retrospective analysis based on SEER, *Horm. Cancer* 9 (5) (2018) 361–370.
- [23] W. Wang, Y. Ding, C. Meng, P. Li, N. Bai, X. Li, Patient's age with papillary thyroid cancer: is it a key factor for cervical lymph node metastasis? *Eur. J. Surg. Oncol.* 49 (7) (2023) 1147–1153.
- [24] G.A. Rubio, P. Catanuto, M.K. Glassberg, J.I. Lew, S.J. Elliot, Estrogen receptor subtype expression and regulation is altered in papillary thyroid cancer after menopause, *Surg (United States)* 163 (1) (2018) 143–149.
- [25] F.A. Candanedo-Gonzalez, A. Gamboa-Dominguez, Postmenopause is associated with recurrence of differentiated papillary thyroid carcinoma, *Med. Hypotheses* 69 (1) (2007) 209–213.
- [26] Zhu X, Yu B, Huang YQ, Zhou JN, Ge MH. Clinicopathological characteristics and prognosis of papillary thyroid carcinoma in naturally menopausal women with various durations of premenarche, reproductive periods, and postmenopausal stages. *Int J. Endocrinol.* 2017;2017.
- [27] R. Mullur, Y.Y. Liu, G.A. Brent, Thyroid hormone regulation of metabolism, *Physiol. Rev.* 94 (2) (2014) 355–382.
- [28] El-Hay GAE-SA, Argoon SA, Mousa NMMA. Evaluation of the frequency and patterns of thyroid dysfunction in patients with metabolic syndrome. *Egypt J. Intern. Med.* 2021;33(1):0–4.
- [29] G. Brenta, Why can insulin resistance be a natural consequence of thyroid dysfunction? *J. Thyroid. Res.* 2011 (2011) 1–9.
- [30] E. Fröhlich, R. Wahl, Insight into potential interactions of thyroid hormones, sex hormones and their stimulating hormones in the development of non-alcoholic fatty liver disease, *Metabolites* 12 (8) (2022).
- [31] P.M. Osuna, M. Udovcic, M.D. Sharma, Hyperthyroidism and the heart, *Methodist DeBakey Cardiovasc. J.* 13 (2017) 60–63.
- [32] G. Goyal, L. Goyal, H. Singla, Arora K. Sheenam, H. Kaur, Subclinical hypothyroidism and associated cardiovascular risk factor in perimenopausal females, *J. Midlife Health.* 11 (1) (2020) 6–11.
- [33] S. Kota, J. Sarangi, S. Jali, L. Meher, S. Raveendranathan, Prevalence of hypothyroidism in patients with metabolic syndrome, *Thyroid Res Pract.* 10 (2) (2013) 60.
- [34] Z. Meng, M. Liu, Q. Zhang, L. Liu, K. Song, J. Tan, et al., Gender and age impact on the association between thyroid-stimulating hormone and serum lipids, *Med (United States)* 94 (49) (2015) 1–10.
- [35] A.P. Delitala, M. Steri, M.G. Pilia, M. Dei, S. Lai, G. Delitala, et al., Menopause modulates the association between thyrotropin levels and lipid parameters: the SardinIA study, *Maturitas* 92 (2016) 30–34.
- [36] Y. Han, C. Wang, L. Zhang, J. Zhu, M. Zhu, Y. Li, et al., Menopausal impact on the association between thyroid dysfunction and lipid profiles: a cross-sectional study, *Front Endocrinol (Lausanne)* 13 (March) (2022) 1–9.
- [37] K. Sakamaki, K. Tsunekawa, N. Ishiyama, M. Kudo, K. Ando, M. Akuzawa, et al., Association between high normal-range thyrotropin concentration and carotid intima-media thickness in euthyroid premenopausal, perimenopausal and postmenopausal women, *Maturitas* 144 (2021) 29–36.
- [38] I. Lambrinoudaki, A. Augoulea, E. Armeni, D. Rizos, A. Alexandrou, M. Creatsa, et al., Menopausal symptoms are associated with subclinical atherosclerosis in healthy recently postmenopausal women, *Climacteric* 15 (4) (2012) 350–357.
- [39] S.H.S. Pearce, G. Brabant, L.H. Duntas, F. Monzani, R.P. Peeters, S. Razvi, et al., 2013 ETA guideline: management of subclinical hypothyroidism, *Eur Thyroid J.* 2 (4) (2014) 215–228.
- [40] I. Lambrinoudaki, E. Armeni, D. Goulis, S. Bretz, I. Ceausu, F. Durmusoglu, et al., Menopause, wellbeing and health: a care pathway from the European Menopause and Andropause Society, *Maturitas* 163 (Sep 2022) 1–14.
- [41] G.A. Brent, Hypothyroidism and thyroiditis, in: S.P. Melmed, P.R. Larsen, H. M. Kronenberg (Eds.), *Williams Textbook of Endocrinology*, Elsevier, Philadelphia, PA, 2012.
- [42] G.A. Greendale, W. Han, J.S. Finkelstein, S.M. Burnett-Bowie, M. Huang, D. Martin, et al., Changes in regional fat distribution and anthropometric measures across the menopause transition, *J. Clin. Endocrinol. Metab.* 106 (9) (2021) 2520–2534.
- [43] G.A. Greendale, B. Sternfeld, M. Huang, W. Han, C. Karvonen-Gutierrez, K. Ruppert, et al., Changes in body composition and weight during the menopause transition, *JCI, Insight* 4 (5) (2019).
- [44] H.R. Banack, J.W. Bea, Z. Chen, R.M. Blew, S. Nicholas, M. Stefanick, et al., Longitudinal patterns of abdominal visceral and subcutaneous adipose tissue, total body composition, and anthropometric measures in postmenopausal women: results from the Women's Health Initiative, *Int. J. Obes.* 47 (4) (2023) 288–296.
- [45] M. Sowers, H. Zheng, K. Tomey, C. Karvonen-Gutierrez, M. Jannausch, X. Li, et al., Changes in body composition in women over six years at midlife: ovarian and chronological aging, *J. Clin. Endocrinol. Metab.* 92 (3) (2007) 895–901.
- [46] J.C. Lovejoy, C.M. Champagne, L. de Jonge, H. Xie, S.R. Smith, Increased visceral fat and decreased energy expenditure during the menopausal transition, *Int. J. Obes.* 32 (6) (2008) 949–958.
- [47] K. Duval, D. Prud'homme, R. Rabasa-Lhoret, I. Strychar, M. Brochu, J.M. Lavoie, E. Doucet, Effects of the menopausal transition on energy expenditure: a MONET Group Study, *Eur. J. Clin. Nutr.* 67 (4) (2013) 407–411.
- [48] K.L. Marlatt, L.M. Redman, R.A. Beyl, S.R. Smith, C.M. Champagne, F. Yi, J. C. Lovejoy, Racial differences in body composition and cardiometabolic risk during the menopause transition: a prospective, observational cohort study, *Am. J. Obstet. Gynecol.* 222 (4) (2020) e1–365.e18.
- [49] J. Maurice, P. Manousou, Non-alcoholic fatty liver disease, *Clin Med J R Coll Physicians London.* 18 (3) (2018) 245–250.
- [50] P. Almeda-Valdes, D. Cuevas-Ramos, C.A. Aguilar-Salinas, Metabolic syndrome and non-alcoholic fatty liver disease, *Ann Hepatol [Internet].* 8 (Suppl. 1) (2009) S18–S24, [https://doi.org/10.1016/S1665-2681\(19\)31822-8](https://doi.org/10.1016/S1665-2681(19)31822-8).
- [51] P. Wainwright, C.D. Byrne, Bidirectional relationships and disconnects between NAFLD and features of the metabolic syndrome, *Int. J. Mol. Sci.* 17 (3) (2016).
- [52] M. Yang, F. Ma, M. Guan, Role of steroid hormones in the pathogenesis of non-alcoholic fatty liver disease, *Metabolites* 11 (5) (2021).
- [53] M. Von-Hafe, M. Borges-Canha, C. Vale, A. Leite, J.S. Neves, D. Carvalho, et al., Non-alcoholic fatty liver disease and endocrine axes—a scoping review. *Metabolites.* 12 (4) (2022).
- [54] Z.R. Xu, A.H. Wang, X.P. Wu, H. Zhang, Z.F. Sheng, X.Y. Wu, et al., Relationship of age-related concentrations of serum FSH and LH with bone mineral density, prevalence of osteoporosis in native Chinese women, *Clin. Chim. Acta* 400 (1–2) (2009) 8–13.
- [55] S.D. Harlow, M. Gass, J.E. Hall, R. Lobo, P. Maki, R.W. Rebar, et al., Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging, *J. Clin. Endocrinol. Metab.* (2012) 1159–1168.
- [56] G.C. Farrell, V.W.S. Wong, S. Chitturi, NAFLD in Asia - as common and important as in the West, *Nat Rev Gastroenterol Hepatol [Internet].* 10 (5) (2013) 307–318.

- [57] M. Hamaguchi, T. Kojima, A. Ohbora, N. Takeda, M. Fukui, T. Kato, Aging is a risk factor of non-alcoholic fatty liver disease in premenopausal women, *World J. Gastroenterol.* 18 (3) (2012) 237–243.
- [58] Liu L, Yu Y, Zhao M, Zheng D, Zhang X, Guan Q, et al. Benefits of levothyroxine replacement therapy on non-alcoholic fatty liver disease in subclinical hypothyroidism patients. *Int J. Endocrinol.* 2017;2017.
- [59] S. Del Ghianda, M. Tonacchera, P. Vitti, Thyroid and menopause, *Climacteric* 17 (3) (2014) 225–234.
- [60] M. Kirshenbaum, R. Orvieto, Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal, *J. Assist. Reprod. Genet.* 36 (11) (2019) 2207–2215.
- [61] S.S. Zhang, A.J. Carrillo, D.S. Darling, Expression of multiple thyroid hormone receptor mRNAs in human oocytes, cumulus cells, and granulosa cells, *Mol. Hum. Reprod.* 3 (7) (1997) 555–562.
- [62] P. Montealeone, D. Parrini, P. Faviana, E. Carletti, E. Casarosa, A. Uccelli, et al., Female infertility related to thyroid autoimmunity: the ovarian follicle hypothesis, *Am. J. Reprod. Immunol.* 66 (2) (2011) 108–114.
- [63] Y.T. Hsieh, J.Y.P. Ho, Thyroid autoimmunity is associated with higher risk of premature ovarian insufficiency-a nationwide Health Insurance Research Database study, *Hum. Reprod.* 36 (6) (2021) 1621–1629.
- [64] T.M. Ortiga-Carvalho, M.I. Chiamolera, C.C. Pazos-Moura, F.E. Wondisford, Hypothalamus-pituitary-thyroid axis, *Compr. Physiol.* 6 (3) (2016) 1387–1428.
- [65] A. LePillouer-Prost, D. Kerob, M. Nielsen, C. Taieb, Mantelet L. Maitrot, Skin and menopause: women's point of view, *J. Eur Acad Dermatology Venereol.* 34 (6) (2020) e267–e269.
- [66] D. Li, A. Radulescu, R.T. Shrestha, M. Root, A.B. Karger, A.A. Killeen, et al., Association of biotin ingestion with performance of hormone and nonhormone assays in healthy adults, *JAMA - J Am Med Assoc.* 318 (12) (2017) 1150–1160.
- [67] R.A. Haddad, D. Giachero, A.L. Barkan, Interpretation of common endocrine laboratory tests: technical pitfalls, their mechanisms and practical considerations, *Clin Diabetes Endocrinol.* 5 (1) (2019) 1–10.
- [68] D. Ylil, S.J. Soldin, B. Stolze, B. Wei, G. Nigussie, H. Nguyen, et al., Biotin interference in assays for thyroid hormones, thyrotropin and thyroglobulin. *Thyroid.* 31 (8) (2021) 1160–1170.
- [69] J.M. Evron, M. Papaleontiou, Decision Making in Subclinical Thyroid Disease vol. 105, Medical Clinics of North America, 2021, pp. 1033–1045.
- [70] L.E. Van Rijn, V.J. Pop, G.R. Williams, Low bone mineral density is related to high physiological levels of free thyroxine in perimenopausal women, *Eur. J. Endocrinol.* 170 (3) (2014) 461–468.
- [71] L. Yang, H. Wang, J. Guo, G. Zheng, D. Wei, T. Zhang, Low normal TSH levels and thyroid autoimmunity are associated with an increased risk of osteoporosis in euthyroid postmenopausal women, *Endocr Metab Immune Disord Drug Targets* 21 (5) (2020) 859–865.
- [72] A.P. Delitala, A. Scuteri, C. Doria, Thyroid hormone diseases and osteoporosis, *J. Clin. Med.* 9 (4) (2020).
- [73] M. Vasileiou, J. Gilbert, S. Fishburn, K. Boelaert, Thyroid disease assessment and management: summary of NICE guidance, *BMJ* (2020) 368.
- [74] R. Ahluwalia, S.E. Baldeweg, K. Boelaert, K. Chatterjee, C. Dayan, O. Okosieme, et al., Use of liothyronine (T3) in hypothyroidism: Joint British Thyroid Association/Society for endocrinology consensus statement, *Clin. Endocrinol.* 99 (2) (2023) 206–216.
- [75] F. Azizi, A. Amouzegar, L. Mehran, H. Abdi, LT4 and slow release T3 combination: optimum therapy for hypothyroidism? *International Journal of, Endocrinol. Metab.* 18 (2020).
- [76] T.F. Davies, A.E. Schwartz, Hyperthyroidism. *Endocr Surg.* (2003) 101–114.
- [77] G. Russ, S.J. Bonnema, M.F. Erdogan, C. Durante, R. Ngu, L. Leenhardt, European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS, *European Thyroid Journal.* 6 (2017) 225–237.
- [78] G.E. Kohn, K.M. Rodriguez, J. Hotaling, A.W. Pastuszak, The history of estrogen therapy, *Sexual Medicine Reviews.* 7 (2019) 416–421.
- [79] U. Menon, M. Burnell, A. Sharma, A. Gentry-Maharaj, L. Fraser, A. Ryan, et al., Decline in use of hormone therapy among postmenopausal women in the United Kingdom, *Menopause* 14 (3) (2007) 462–467.
- [80] R.D. Langer, H.N. Hodis, R.A. Lobo, M.A. Allison, Hormone replacement therapy—where are we now? *Climacteric [Internet].* 24 (1) (2021) 3–10.
- [81] T.S. Mikkola, P. Tuomikoski, H. Lyytinen, P. Korhonen, F. Hoti, P. Vattulainen, et al., Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality, *Menopause* 22 (9) (2015) 976–983.
- [82] R. Karim, R.M. Dell, D.F. Greene, W.J. MacK, J.C. Gallagher, H.N. Hodis, Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization, *Menopause* 18 (11) (2011) 1172–1177.
- [83] N. Mendoza, I. Ramírez, E. de la Viuda, P. Coronado, L. Baquedano, P. Llaneza, et al., Eligibility criteria for Menopausal Hormone Therapy (MHT): a position statement from a consortium of scientific societies for the use of MHT in women with medical conditions, MHT Eligibility Criteria Group. *Maturitas.* 166 (2022) 65–85.
- [84] R.A. Lobo, Postmenopausal hormones and coronary artery disease: potential benefits and risks, *Climacteric* (2007) 21–26.
- [85] G.Q. Zhang, J.L. Chen, Y. Luo, M.B. Mathur, P. Anagnostis, U. Nurmatov, et al., Menopausal hormone therapy and women's health: an umbrella review, *PLoS Med.* 18 (8) (2021) 1–27.
- [86] R.A. Lobo, Menopause and stroke and the effects of hormonal therapy, *Climacteric* (2007) 27–31.
- [87] J.-M. Bae, Hormonal replacement therapy and risk of thyroid cancer in women: a meta-epidemiological analysis of prospective cohort studies, *J Menopausal Med.* 27 (3) (2021) 141.
- [88] L. Bjergved, A. Carlé, T. Jørgensen, H. Perrild, P. Laurberg, A. Krejbjerg, et al., Parity and 11-year serum thyrotropin and thyroid autoantibody change: a longitudinal population-based study, *Thyroid* 26 (2) (2016) 203–211.
- [89] R. Bonacci, A. Pinchera, P. Fierabracci, A. Gigliotti, L. Grasso, C. Giani, Relevance of estrogen and progesterone receptors enzyme immunoassay in malignant, benign and surrounding normal thyroid tissue, *J. Endocrinol. Investig.* 19 (3) (1996) 159–164.
- [90] L. Dalla Valle, A. Ramina, S. Vianello, A. Fassina, P. Belvedere, L. Colombo, Potential for estrogen synthesis and action in human normal and neoplastic thyroid tissues, *J. Clin. Endocrinol. Metab.* 83 (10) (1998) 3702–3709.
- [91] Z. Gong, S. Yang, M. Wei, A.C. Vlantis, J.Y.K. Chan, C.A. van Hasselt, et al., The isoforms of estrogen receptor alpha and beta in thyroid cancer, *Front. Oncol.* 12 (2022).
- [92] P. de A. Manfro, A.P.S. Bertoni, T.W. Furlanetto, GPER1 in the thyroid: a systematic review, *Life Sci.* 241 (2020) 117112.
- [93] D. Manole, B. Schildknecht, B. Gosnell, E. Adams, M. Derwahl, Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms, *J. Clin. Endocrinol. Metab.* 86 (3) (2001) 1072–1077.
- [94] G. Ceresini, B. Milli, S. Morganti, M. Maggio, A. Bacchi-Modena, M.P. Sgarabotto, et al., Effect of estrogen therapy for 1 year on thyroid volume and thyroid nodules in postmenopausal women, *Menopause* 15 (2) (2008) 326–331.
- [95] N.A. Mazer, Interaction of estrogen therapy and thyroid hormone replacement in postmenopausal women, *Thyroid* 14 (2004).
- [96] B.M. Arafah, Increased need for thyroxine in women with hypothyroidism during estrogen therapy, *N. Engl. J. Med.* 344 (23) (2001) 1743–1749.
- [97] J. Kaminski, C.M. Junior, H. Pavesi, B. Drobrzenski, G.M. Do Amaral, Effects of oral versus transdermal estradiol plus micronized progesterone on thyroid hormones, hepatic proteins, lipids, and quality of life in menopausal women with hypothyroidism: a clinical trial, *Menopause* 28 (9) (2021) 1044–1052.
- [98] J.L. Shiffren, N. Rifai, S. Desindes, M. McIlwain, G. Doros, N.A. Mazer, A comparison of the short-term effects of oral conjugated equine estrogens versus transdermal estradiol on C-reactive protein, other serum markers of inflammation, and other hepatic proteins in naturally menopausal women, *J. Clin. Endocrinol. Metab.* 93 (5) (2008) 1702–1710.
- [99] J.L. Shiffren, S. Desindes, M. McIlwain, G. Doros, N.A. Mazer, A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women, *Menopause* 14 (6) (2007) 985–994.
- [100] C.T. Erel, A. Gezer, L.M. Şentürk, A. Somunkiran, S. Kaleli, H. Seyisoglu, Effect of different hormonal therapies on thyroid function in surgical menopause short-term results, *J. Reprod Med Obstet Gynecol.* 52 (12) (2007) 1079–1084.
- [101] W. Xu, Y. Huang, L. Ma, P. Chen, S. Li, K. Chu, et al., Clinical observation of menopause hormone therapy in postmenopausal women with euthyroid and mild subclinical hypothyroidism, *BMC Endocr. Disord.* 23 (1) (2023).
- [102] Fasero M, Quereda F, Andraca L, Coronado PJ, Mendoza N, Ramírez I, et al. Pharmacological interactions and menopausal hormone therapy: a review. *Menopause* 2023;30:873–80.