Integrative Management of Estrogen Dominance, Methylation Impairment, and Histamine Intolerance in Perimenopause: A Case Report

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CASE REPORT

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ABSTRACT

This case report describes the care of a 44-year-old woman who came with a sudden shift in her health, including new abdominal and breast weight gain, mastalgia, extreme fatigue, anxiety, depression, ADHD-related symptoms, digestive upset, insomnia, and an inability to tolerate exercise. Initial laboratory testing showed elevated progesterone metabolites, estrone, estradiol, 2-OH, and 4-OH estrone metabolites, and elevated free DHEA. These findings suggest estrogen dominance or elevated levels of estrogen relative to progesterone, as well as issues with detoxification and adrenal function. The patient's history of celiac disease and Hashimoto's thyroiditis likely contributed to chronic inflammation and micronutrient depletion. To address the interconnected hormonal imbalances contributing to her symptoms, she was treated with a combination of SAMe, methylated B vitamins, DIM, sulforaphane, calcium-D-glucarate, vitex, green tea extract, and DAO enzyme therapy.

Over the course of twelve months, the patient described a 75-80% improvement in anxiety and depression, increased energy, more manageable menstrual cycles, and a self-reported 80% improvement in digestive symptoms after taking DAO. Follow-up testing found improvement in methylation markers, a shift from the genotoxic 4-OH to the favorable 2-OH estrogen pathway, and a 25% reduction of estradiol into the normal range. The patient lost 15 lbs and reported greater emotional stability and improved day-to-day functioning.

The case demonstrates that personalized, root-cause treatment is key to helping women navigate the complex challenges of perimenopause. Addressing factors like estrogen metabolism, methylation, inflammatory load, detoxification pathways, and histamine clearance can meaningfully improve complex perimenopausal symptoms. This case is novel and adds to existing literature as it addresses the compounding effects of autoimmune diseases such as celiac and hashimoto's on the perimenopausal transition. Additionally, there are few studies addressing the effects of elevated estrogen levels on histamine metabolism in early-stage perimenopausal women.

Key Words: Casereport, methylation, estrogen dominance, histamine intolerance, perimenopause, DAO, weight gain, progesterone, estradiol, estrone 2-OH, 4-OH, 16-OH.

INTRODUCTION

Perimenopause is a complex phase of a woman's life driven by fluctuating hormones and a variety of

symptoms that range from insomnia, anxiety, depression, and decreased libido to hot flashes, weight changes, fatigue, and digestive issues. Often, these symptoms aren't connected to perimenopause; they are attributed to other health problems and even overlooked or disregarded. This can lead to symptom-based care without getting to the root cause, leading to a likelihood of increased long-term health risks and unnecessary suffering. Instead, targeted nutrition and herbal support along with lifestyle adjustments like daily movement and stress management. Taking a holistic approach to perimenopause can empower women to navigate this inevitable phase of their lives with knowledge and confidence rather than endure it.

This report details a female patient's experience with a sudden shift in physical, emotional, and cognitive health that significantly affected her quality of life and ability to perform at her job as a project manager. Her history of celiac disease, Hashimoto's thyroiditis, and chronic stress added a complex layer to her hormonal shifts. She continued to struggle with escalating symptoms despite working with doctors who took a more conventional approach. She was motivated to pursue a root-cause strategy rather than symptom-based care.

This patient's year-long clinical progress came under a targeted functional medicine protocol aimed to improve estrogen metabolism, restore methylation capacity, support detoxification pathways, reduce inflammation, and regulate histamine responses. This case offers insight into how individualized nutraceutical interventions can influence hormone balance, symptom expression, and overall function during perimenopause.

NARRATIVE

A 44-year-old female presented in May 2024 with sudden-onset weight gain localized to the abdomen and breasts, mastalgia, digestive discomfort, fatigue, and insomnia without identifiable triggers. The clinical course is summarized in Table 1. Additional symptoms included anxiety, depression, ADHD, inattentiveness, and exercise intolerance. After minimal improvement through conventional interventions, the patient was ready to explore functional medical care, aiming to identify the root cause of her debilitating symptoms.

Born and raised in Bosnia, the patient experienced childhood trauma during the Bosnian War, including loss of the family home and tension surrounding the parents' interfaith marriage. After immigrating to the United States as a teenager, the patient later earned a master's degree from Howard University while working as a civilian in the military. Although achieving professional success, chronic hypervigilance, intrusive anxiety, and intermittent sleep disturbance continued into adulthood.

Past medical history includes celiac disease, Hashimoto's thyroiditis, mitral valve prolapse, osteoarthritis, hirsutism, and visual impairment classified as legal blindness. A 2022 pelvic ultrasound identified uterine cysts and fibroids, but no evidence of polycystic ovaries associated with PCOS. No use of tobacco, alcohol, or recreational drugs was reported.

In May 2024, body weight was 162 lbs with a BMI of 27.8 kg/m^2. Since a COVID-19 infection in 2021, persistent fatigue and sudden weight gain had been reported. Severe exercise intolerance and paralyzing anxiety made it challenging for the patient to complete work tasks. The patient's menstrual cycle consisted of emotionally debilitating symptoms in the premenstrual phase. This was followed by physically debilitating symptoms and bed rest during menstruation. Mastalgia, abdominal bloating, mood instability, and extreme fatigue left the patient "operating on fumes" for nearly two weeks per month. The patient also reported sleeping approximately 6 hours per night.

Initial laboratory testing done in May 2024 included results from a 24-hour urinary hormone panel by Physician's Lab that showed elevated alpha-pregnanediol (720.94 [range 26.00-338.00] ng/mg CR), elevated beta-pregnanediol (3931.22 [range 201.00-1669.00] ng/mg CR), elevated estrone (11.9 [range 1.70-8.50] ng/mg CR), elevated estradiol (4.8 [range 0.80-3.30] ng/mg CR), elevated 2-OH estrone (12.86 [range 2.00-8.40] ng/mg CR), elevated 4-OH Estrone (1.34 [range <=1.20] ng/mg CR) and elevated free DHEA (71.83 [range 6.10-17.30] ng/mg CR) which was more than four times the upper limit of normal.

DHEA-S was reported as “unable to calculate,” indicating that levels were above the measurable range of 38.00-507.00 ng/mg CR. Testosterone was found within range at 6.41 [range 2.30-7.80] ng/mg CR. The overall pattern suggests possible insufficiency in phase I and phase II liver detoxification. It may be worth considering adrenal hyperactivity, which could also be contributing to oxidative stress and histamine sensitivity. Estrogen dominance is defined by elevated estrogen levels in comparison to progesterone levels, meaning that a patient can either have normal estrogen levels coupled with low progesterone levels or the patient can test normal or even high normal progesterone levels coupled with severely elevated estrogen levels.

The patient was prescribed NP Thyroid 30 mg by her primary care physician, and was self-supplementing with Pure Encapsulations P5P (50 mg), Pure Encapsulations Selenium (200 mcg selenomethionine), Pure Encapsulations Zinc (30 mg zinc picolinate), Now Licorice Root (900 mg Glycyrrhizaglabra), Now Oregano Oil (181 mg oregano oil, 17.6 mg ginger oil, 19.3 mg fennel oil), Now Super Enzymes (200 mg betaine HCL, 100 mg oxbile extract, 134 mg pancreatin 11x, 40 mg bromelain, 10 mg acid stable protease, 2 mg papain, 0.1 mg cellulase 0.1), Now Phosphatidyl Serine (100 mg phosphatidyl serine, 100 mg choline, 50 mg inositol), Now NAC (600 mg NAC, 25 mcg selenium-selenomethionine), Ancestral Grassfed Beef Thyroid (30 mg bovine thyroid, 470 mg bovine liver),and Ancestral Grass fed Beef Liver (3000 mg bovine liver). Castor oil packs were applied to the abdomen to assist with detoxification.

Safety risk was considered in altering the regimen for the patient. No prescriptions were altered. All supplements added to the protocol were cross-checked in the Designs for Health software.

(https://www.designsforhealth.com/drug-nutrient-interaction) Patient had 24/7 access to the practitioner to report any adverse response to therapy or request clarification for dosing or timing of the supplement intervention.

In June 2024, self-supplementation was largely discontinued and replaced with a targeted functional protocol consisting of NP Thyroid 30 mg, Designs for Health SAMe-3 capsules (600 mg SAMe, 15 mg P5P, 510 mcg DFE 5-MTHF, 150 mcg methylcobalamin), and Designs for Health Fem Guard + Balance™ 4 capsules (30 mg P5P, 680 mcg DFE 5 MTHF, 400 mcg methylcobalamin, 50 mcg of calcium from calcium D-glucarate, 50 mg magnesium malate, 400 mg calcium D-glucarate, 400 mg chrysin, 200 mg chaste tree extract, 100 mg green tea extract, 100 mg DIM, 100 mg black cohosh extract, 50 mg broccoli blend, 320 mg trans resveratrol).

Natural Vitality CALM® Gummies (330 mg magnesium citrate) were taken on her own, and Horbäach 275 mg potassium citrate per her cardiologist’s recommendation for mild mitral valve prolapses. Because multiple supplements were given at a single time period, we cannot isolate the effects of each individual nutraceutical on the patient’s reported symptom modulation.

The patient followed a dairy and gluten-free diet focused mainly on whole foods, with no alcohol or processed foods. [This was recommended to her by the physician who diagnosed her with celiac disease.] Daily “sanity walks” before and after work, weather permitting, were part of a stress-management routine. Patient reported that walks provided emotional relief and helped regulate mood and energy levels.

Phase II liver detoxification occurs during the conjugation of estrogen metabolites from phase I liver metabolism. Physicians Lab measures the conversion of 2-hydroxy estrone into 2-methoxyestrone, which defines methylation in this specific test. Methylation testing performed during this period revealed poor activity (score 23.3; reference >60). This is likely due to genetic SNPs of the COMT and/or MTHFR genes as per the lab interpretation guidelines. Within several weeks of this new protocol, mild improvement in energy and mood stability, along with modest weight loss, was observed. A 75-80% improvement in anxiety was reported after starting SAMe at a triple dose as directed by a healthcare practitioner.

In July 2024, the patient reported a case of intermittent hives and rashes without being able to identify

the trigger. They were likely related to elevated histamine levels and impaired clearance, as elevated estrogen levels in early perimenopause can impair histamine clearance [1]. In September 2024, Designs for Health DIM-Evail™ was added to the protocol, 100 mg daily to support estrogen metabolism and balance phase I and phase II hepatic detoxification pathways.

In October 2024, Designs for Health Calcium D-Glucarate-2 capsules (150 mg of calcium as calcium D-glucarate) and Designs for Health BroccoProtect™-1 capsule (235 mg broccoli blend: broccoli powder extract, mustard powder) were introduced to support hepatic estrogen detoxification pathways. Following the addition of calcium D-glucarate, menstrual cycles became shorter and irregular, but they normalized after the body adjusted. It took a couple of cycles to get used to the new supplements, but by December, everything felt more balanced. Abnormal breast swelling and tenderness also subsided. Heavy bleeding and increased clotting began initially after starting DIM, but stabilized within a few months. During this time, the patient was diagnosed by her primary care doctor with Crohn's disease and IBS, but the patient insisted that she did not entirely fit the profile for either pathology.

In April 2025, DAO enzyme therapy (NaturDAO 1,000,000 HDU before each meal) was introduced to address ongoing digestive discomfort [2]. High estrogen levels upregulate histamine activity and may impair diamine oxidase activity, preventing histamine metabolism and leading to increased histamine levels [3]. Patient describes an 80% reduction in IBS symptoms (bloating, gas, and postprandial discomfort) was observed within 24 to 48 hours of starting DAO supplementation. She also reported improved tolerance to foods that previously caused reactions. It is a limitation that we did not directly measure serum DAO levels in the patient before and after intervention, and solely relied on the patient's report of symptom improvement.

Patient was retested with the Physicians Lab urinary metabolite test, which showed that generally, hormone levels improved by June 2025, with several markers normalized and others trending toward normal compared with May 2024. Estradiol levels decreased toward the normal range, and methylation capacity normalized.

Free DHEA levels declined significantly, and DHEA-S remained above the detection limit. Although estrone and testosterone both increased, overall, there was a positive shift toward better hormonal balance and more efficient detoxification. In addition, the 2- OH:4-OH estrone ratio favored more efficient estrogen metabolism. Bloodwork by her primary care provider showed the patient's HbA1c was 5.3%, implying a healthy glucose metabolism as she was well below the prediabetic range of 5.7% - 6.4%. The patient also reported improved energy, emotional stability, and exercise tolerance, as well as a 15 lb weight loss and a reduction in BMI to 25.2.

In July 2025, despite improved energy, increased sleep duration, and more manageable menstrual cycles, the patient continued to experience fatigue during menstruation. Follow-up testing revealed low ferritin and iron saturation consistent with iron deficiency. The primary care provider prescribed an iron support regimen consisting of DFH Ferrochel® 27 mg, Mega Food Blood Builder™ Iron supplement (vitamin C as ascorbic acid 15 mg, folate as folic acid 680 mcg DFE (408 mcg folic acid), vitamin B12 as cyanocobalamin 30 mcg, iron as fermented iron bisglycinate 26 mg, organic beetroot 125 mg, food blend 30 mg organic brown rice, organic orange, organic broccoli), and ferric maltol 30 mg/day.

Overall, the patient reported greater control over health, reduced anxiety, steadier energy, improved digestive function, and greater work productivity. While ADHD symptoms and brain fog persisted, weight decreased by 10% and menstrual cycles became more manageable. At the time of writing, goals include addressing ADHD-related challenges that impact work performance and following up with the primary care provider regarding persistently low ferritin levels.

Patient Perspective

I sought care because I was experiencing whole body inflammation that was negatively affecting me both

mentally and physically. Before the intervention, I had low energy, felt frustrated and disinterested, and was severely and chronically apathetic. I was prone to debilitating anxiety, unexplained rashes, and digestive reactions to foods. I was also frustrated that my primary care doctor prescribed Xanax for anxiety instead of trying to find the root cause.

DISCUSSION

Perimenopause is a complex phase of a woman's life driven by fluctuating hormones and symptoms such as insomnia, anxiety, depression, decreased libido, hot flashes, and the genitourinary syndrome of menopause (GSM) [4]. Early perimenopause typically involves a decline in progesterone production, leading to relative estrogen dominance. As estrogen later declines, symptoms such as hot flashes and night sweats begin, particularly in women with a higher body mass index (BMI) [4]. Clinicians use symptoms, along with age and menstrual history, to determine the patient's phase of perimenopause to select the proper intervention. A limitation of this study is that no validated surveys were used to measure improvement, and this study relies on test results and the patient's subjective reports.

The symptoms observed in this case align with those commonly reported during perimenopause. At first glance, one might think PCOS was the main driver due to elevated testosterone and DHEA; however, a previous transvaginal ultrasound ruled out the "pearl necklace" ovarian presentation consistent with PCOS. According to a study of 500 women, 1 in 4 women report forgetfulness or brain fog, 3 in 10 women report lethargy, irritability, anxiety, heavier periods, or delayed cycles [5].

The patient being diagnosed with celiac disease and Hashimoto's thyroiditis makes this case unique since both diseases can cause low iron, low ferriting levels or both leading to a compound effect [6]. Hashimoto's thyroiditis and celiac disease are both associated with chronic inflammation and elevated hepcidin levels, which can indirectly suppress ferritin and limit iron availability. Hepcidin blocks intestinal iron absorption and prevents the release of stored iron (ferritin) from the bloodstream, leading to low serum ferritin and symptoms of iron deficiency, such as fatigue [7]. Iron is also used up quickly during heavy exercise or menstrual bleeding. Low ferritin levels most likely contributed to the patient's continued fatigue during menstruation, even after estradiol, pregnanediol, and thyroid hormone levels normalized. This suggests that micronutrient depletion can continue to drive symptoms despite normalization of sex hormones. It also highlights the importance of retesting after completing protocols to validate progress with measurable data.

In addition to the expected hormonal fluctuations of perimenopause, this case also demonstrates how fluctuating or dominant estrogen levels may elevate histamine levels in the gut [8,9]. The resulting inflammation and histamine-driven symptoms can possibly lead to a misdiagnosis of diseases like IBS, Crohn's, or allergies [10,11]. Elevated estrogen levels maybe the underlying causes in estrogen binds to mast cell receptors and triggers the release of histamine. In addition, elevated estrogen suppresses diamine oxidase (DAO), the enzyme that breaks down histamine [12]. This leads to a buildup of histamine that can cause bloating, flushing, anxiety, headaches, and food sensitivities. In this case, the patient describes that the DAO supplementation led to an 80% improvement in digestive symptoms (bloating, gas, and food intolerance) within 48 hours. This suggests that elevated estrogen levels and poor histamine clearance appear to be the primary drivers of the patient's gastrointestinal discomfort rather than IBS or Crohn's disease. This finding was clinically significant because it redirected care toward estrogen regulation and histamine support.

The protocol for this patient focused on improving estrogen metabolism, supporting methylation, reducing inflammation, enhancing liver detoxification pathways, and stabilizing histamine levels. Interventions utilized included Designs for Health FemGuard + Balance™ (4 capsules daily), Designs for Health SAMe (3 capsules-600 mg daily), CALM® Magnesium Citrate gummies (330 mg), Horbäach potassium citrate (1 capsule-275 mg), Designs for Health DIM Evail™ (1 softgel-100 mg daily), Designs for Health Calcium D-

Glucarate (2 capsules – 150 mg daily), Designs for Health Brocco Protect™ (1 capsule daily), and Natur DAO (1 tablet-1,000,000 HDU before meals).

3,3'-diindolylmethane (DIM) and broccoli seed extract (sulforaphane) were selected because they help modulate estrogen metabolism. DIM has been shown to support healthy estrogen metabolism, especially when detoxification pathways favor the less beneficial 16-OHE1 or 4-OHE1 metabolites [13-15]. DIM has been shown to increase the ratio of 2-hydroxyestrone (2-OHE1) relative to 16α-hydroxyestrone (16-OHE1) and 4-hydroxyestrone (4-OHE1). This shift is considered beneficial because higher ratios of 2-OHE1/16-OHE1 and 2-OHE1/4-OHE1 are associated with reduced risk of breast cancer [13,14].

Broccoli seed extract, rich in glucoraphanin/sulforaphane, is standardized to induce phase II detoxification enzymes and shifts estrogen metabolism from carcinogenic16-OHE1 or 4-OHE1 estrogen metabolites toward the less proliferative 2-hydroxyestrone pathway [16].

Follow-up lab work in June 2025 showed that previously elevated 4-OHE1 metabolites had shifted toward the favorable 2-OHE1 metabolites after twelve months of supplementation. Total estrogen metabolites were almost the same before and after intervention, but estradiol decreased by about 25% into the normal range, while estrone increased. Estrone is a more inactive form of estrogen than estradiol, which could be why the patient feels better. Estrone may be elevated from elevated testosterone levels, aromatizing into estrogen in the abdominal fat. The patient has difficulty with abdominal adiposity, although ith as decreased over the past year. Before intervention, the dominant estrogen metabolite pathways were 4- OHE1, indicating oxidative stress, the presence of free radicals, and potential DNA damage. After the intervention, the detoxification pathways shifted toward a more favorable 2OHE1 pathway. The patient also experienced reduced breast swelling and mastalgia, along with improved mood, which may be attributed to increased levels of 2-hydroxyestrone metabolites, which have anti-inflammatory and antioxidant properties [17].

S-adenosylmethionine (SAMe) and methylated B vitamins, found in the Designs for Health SAMe supplement and FemGuard+Balance™, were also carefully selected for this protocol due to the patient's poor methylation status. Methylation plays a vital role in estrogen clearance and neurotransmitter production. SAMe donates a methyl group to the enzyme catechol-O-methyltransferase (COMT) to convert potentially genotoxic metabolites, primarily the 4-hydroxy estrogens, into methoxyestrogens, which are less biologically active and more readily excreted. Adequate levels of B vitamins also ensure efficient methylation. Folate (vitamin B9) and vitamin B12 are essential cofactors in the one-carbon cycle that generates SAMe.

SAMe is the primary methyl donor in the synthesis and metabolism of monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, which influence mood, anxiety, and depression. Clinical trials and meta-analyses show that SAMe supplementation is superior to placebo and has a moderate therapeutic benefit in alleviating depressive symptoms [18,19]. Folate and B12 are necessary for the methylation reactions involved in the synthesis of serotonin, dopamine, and norepinephrine, while B6 is directly involved in the conversion of precursor amino acids to neurotransmitters. A deficiency in these B vitamins has been linked to depression, anxiety, poor mood, and stress management [20,21].

Within weeks, the patient described a 75-80% improvement in mood symptoms, including anxiety and depression, after starting SAMe and slowly titrating up to a triple dose as directed by the practitioner. Methylation testing initially revealed poor activity (score 23.3; reference >60), but follow-up testing one year later showed normalized methylation capacity (81.3). This is consistent with supplementation with methylated B vitamins and SAMe, as they support one-carbon metabolism, which is involved in neurotransmitter synthesis, estrogen metabolism, adrenal function, and overall neurological health. Folate and vitamin B12 are cofactors in the reactions that generate endogenous SAMe, the primary methyl donor for neurotransmitter production, which may explain the patient’s overall improved mood [21].

June 2025 testing showed dehydroepiandrosterone (DHEA) remained slightly elevated but decreased from 71.83 to 24.5 ng/mg creatinine (range 2.70-20.60 ng/mg CR), while DHEA-sulfate (DHEA-S) increased to above detection limit (range13.70-516.60 ng/mg CR). DHEA is metabolized quickly, whereas DHEA-S consists of DHEA bound to a sulfate ion for longer-term storage that can be converted back into active androgens and estrogens in peripheral tissues. These changes may reflect improved adrenal function and androgen metabolism due to B-vitamin and SAMe supplementation and a stricter adherence to an anti-inflammatory diet following celiac disease diagnosis.

Vitex (chaste tree berry) is an herb included in FemGuard + Balance™ to help balance estrogen and progesterone in conditions like PMS, menopause, PCOS, and infertility. Vitex has been shown to modulate the hypothalamic-pituitary-ovarian axis via dopaminergic pathways that inhibit pituitary prolactin production. Latent hyperprolactinemia due to insufficient dopamine inhibition of the pituitary can lead to cyclic mastalgia, where the patient experiences monthly breast tenderness [22,23]. A systematic review concluded that vitex berry ameliorated breast pain and swelling [24]. Vitex contains diterpenes and triterpenes, which bind to activate dopamine D2 receptors (D2R), suppressing prolactin release by reducing lactotrope activity. Lower prolactin levels help improve breast pain and swelling (mastalgia) in perimenopausal women since prolactin can cause the mammary glands to grow and retain fluid. A systematic review of 25 studies found that Vitex agnus-castus (VAC) was effective in reducing breast pain intensity and lowering elevated serum prolactin levels in patients with cyclic mastalgia aged 18-45 years, with or without premenstrual syndromes [24]. Vitex was appropriate for this patient because she described physically debilitating symptoms, including mastalgia that required bed rest during menstruation. After about four months of supplementation, abnormal breast swelling and tenderness subsided.

Calcium D-glucarate, found in the Designs for Health Calcium-D-Glucarate supplement and FemGuard+Balance™, also supports estrogen metabolism. Calcium D-glucarate helps inhibit beta-glucuronidase, an enzyme that breaks glucuronide conjugates, which can lead to estrogen recirculation and the reabsorption of other toxins back into the bloodstream rather than elimination. Increasing calcium-D- glucarate levels can support phase II detoxification by increasing glucuronidation, promoting detoxification, and enhancing clearance of estrogen metabolites and xenobiotics [25]. Elevated levels of beta-glucuronidase have been associated with increased risk of developing several types of cancer, particularly hormone-dependent cancers, including breast, prostate, and colon cancers [25,26]. Although menstrual cycles initially became shorter and irregular after adding this supplement, they eventually stabilized, and the patient reported an overall improvement in breast tenderness and bloating once the body adjusted.

Green tea extract, an ingredient found in FemGuard+Balance™, was considered for its high catechin content, specifically epigallo catechin gallate (EGCG), which provides potent antioxidant activity, helps modulate inflammatory signaling, and supports phase I and phase II detoxification pathways. EGCG has been shown to increase endogenous antioxidant levels, neutralize harmful ROS, and upregulate phase II detoxifying enzymes, thereby safely excreting toxic substances and waste products from the body by activating the Nrf2 pathway [27-29]. In addition, EGCG inhibits inflammatory signaling pathways, such as nuclear factor-kappa B (NF-κB), by blocking its phosphorylation and nuclear translocation, thereby preventing the activation of pro-inflammatory genes [30,31].

EGCG was an appropriate choice for this case since the patient's initial hormone testing showed elevated 4-OH estrogen metabolites, which are associated with higher oxidative stress and increased risk of DNA damage. With reduced inflammation, the liver may have processed estrogen metabolites more efficiently, which may explain the patient's estradiol levels returning to the normal range on follow-up testing [32]. Diamine oxidase (DAO) supplementation was later added to the protocol to address

digestive discomfort. She previously developed hives and rashes, along with inconsistent digestive symptoms (gas, diarrhea, bloating). She recognized that she could eat some foods during the follicular phase and not tolerate the same foods during the luteal phase. This was possibly due to elevated estrogen levels during the luteal phase, which can increase histamine levels in the gut [33]. Estrogen fluctuations during perimenopause can stimulate mast cells to release histamine and, at the same time, may downregulate DAO activity [8-9].

DAO is the primary enzyme for the metabolism of ingested histamine by forming a barrier along the lumen that breaks down histamine before it reaches the portal circulation. A deficiency in DAO can increase histamine levels, leading to inflammation and hives, and possibly misdiagnosed conditions such as irritable bowel syndrome (IBS), Crohn's disease, or allergies [12]. In this patient, DAO supplementation led to a self-reported 80% improvement in digestive symptoms within 24 to 48 hours, which strongly suggested that fluctuating estrogen and impaired histamine clearance were driving gastrointestinal discomfort [12].

Waking cortisol was slightly elevated before life style modification interventions, and cortisone, the inactive form of cortisol, was elevated after interventions. The patient currently takes morning walks around the neighborhood before work and evening walks after work, totaling 60 to 90 minutes per day, which has likely contributed to improved stress regulation and energy stability over time.

There was no evidence of LH: FSH abnormalities, polycystic ovaries (uterine cysts and fibroids were present on ultrasound in 2022), insulin resistance (HbA1c was below 5.7% at 5.3% in 7/2025), or irregular cycles (24–26 days until October 2024, when calcium D-glucarate was added). Ever since then, they have been irregular and shorter. The patient does not wish to discontinue the calcium D-glucarate because she feels better overall, and she isn't convinced that the supplement is causing irregular cycles; instead, she feels it's her perimenopause progressing due to advancing age. This demonstrates the importance of addressing supplement tolerance during hormonal transition and the need for shared decision-making when navigating treatment.

Overall, this therapeutic approach addressed estrogen metabolism, supporting methylation, reducing inflammation, enhancing liver detoxification pathways, and stabilizing histamine levels, all of which seemed to contribute to the patient's symptoms. The changes seen in repeat labs, along with reduced anxiety and depression, improved cycle symptoms, increased average nightly sleep by one hour, and improvement in digestive issues over the course of one year suggest that these targeted functional interventions successfully supported the physiology driving her symptoms.

CONCLUSION

It would be interesting to see future studies that address estrogen metabolism, methylation support, reduced inflammation, enhanced detoxification, and histamine clearance, and their effects on the complex physiological imbalances contributing to perimenopausal symptoms. After following a targeted protocol for one year, the patient reported a 75-80% improvement in anxiety and depression and described an 80% improvement in digestive symptoms, along with a reduction in breast swelling and mastalgia, increased energy, improved sleep duration (~1 additional hour/night), menstrual cycle stability, and a 15-pound weight loss.

Laboratory findings clinically correlated with the patient's self-reported progress. Estradiol went down about 25% into the normal range, elevated 4-OHE1 metabolites shifted toward the favorable 2-OHE1 metabolites, and methylation capacity normalized. The patient reported feeling more in control of her health because she believed the root causes of her symptoms were addressed, rather than only the symptoms.

While this case focuses on estrogen metabolism and supplement interventions, several other factors could explain the patient's symptoms and improvement. The patient's Hashimoto's thyroiditis could explain many symptoms. Research shows people with this condition have 3.6 times higher odds of depression and 2.3 times higher

odds of anxiety [34], along with fatigue (68-83%), weight gain (24-59%), and cognitive difficulties (45-48%) [35]. Although thyroid medication remained unchanged, thyroid levels were not monitored during the intervention, so thyroid-related contributions cannot be ruled out. Also, the patient's history of childhood trauma during the Bosnian War is a risk factor for adult depression and anxiety (1.61-1.78 times increased lifetime risk) [36]. Also, research shows hormone fluctuations only predict mood problems in women who are also experiencing high life stress [37]. The absence of consistent thyroid monitoring and formal mental health evaluations during this period represents a limitation. Future case reports should include both to better distinguish what drives symptom changes.

Despite these limitations, it can be beneficial for women to know that their hormone levels can shift meaningfully with targeted nutritional, herbal, and methylation support, which may help to address perimenopausal symptoms without relying on prescription bioidentical hormone therapy. This is especially significant for women who prefer non- pharmaceutical options or who wish to begin with a more conservative approach before considering prescription hormone replacement therapy. This case highlights the plausibility of success when implementing a personalized, root-cause approach for women navigating the physiological and emotional challenges of perimenopause. Addressing factors like estrogen metabolism, methylation, inflammatory load, detoxification pathways, and histamine clearance may meaningfully improve complex perimenopausal symptoms.

At the time of writing this paper, the patient wants to focus on managing ADHD as she feels it is affecting her work performance. She is also seeking follow-up care from her primary care provider regarding extremely low ferritin levels at 6 ng/mL (16-232 ng/mL) and % saturation at 10% (16-45%), as per labs taken on 7/17/25. Her primary care provider prescribed an iron support regimen consisting of MegaFood Blood Builder™ Iron supplement (containing iron bisglycinate, vitamin C, folate, vitamin B12, and organic beetroot), and ferric maltol 30 mg daily.

Written informed consent for publication was obtained from the patient in accordance with CARE guidelines.

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PEER REVIEW

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TABLES

Table1: Clinical Timeline

Date	Symptoms/ ClinicalStatus	Testing/ Findings	Interventions	Outcomes
May 2024	New-onset weight gain (abdomen/ breasts), mastalgia, fatigue, anxiety, depression, ADHD symptoms, digestive discomfort, difficulty sleeping, and significant exercise intolerance. BMI 27.8 (162 lbs)	Elevated progesterone metabolites, estrone, estradiol, 2-OH/4-OH estrone, and free DHEA (>4×ULN). Testosterone 6.41 ng/mg CR. DHEA-S" unable to calculate," indicating levels were above the measurable range.	NPThyroid 30mg (primary care physician). Self-supplementation (B6, selenium, zinc, licorice root, oregano oil, digestive enzymes, phosphatidylserine, NAC, and bovine thyroid/liver glandulars).	_
June 2024	Experienced emotional relief, regulated moods and improved energy levels.	Methylation testing revealed poor activity (score 23.3; Reference >60).	Self-supplementation discontinued. Continued NP Thyroid 30 mg. New protocol: Designs for Health SAMe 600 mg, Designs for Health FemGuard + Balance™, Natural Vitality CALM® Gummies 330 mg magnesium citrate, and Horbäach Potassium Citrate 275 mg of potassium citrate.	Modest improvements in energy and weight loss. 75-80% Improvement in anxiety was reported.
July 2024	Intermittent hives and rashes without a known trigger.	Suspected histamine-related	_	
September 2024	_	_	Designs for Health DIM Evail™ 100 mg added.	_
October 2024	Menstrual cycles became shorter and more irregular accompanied by heavier bleeding and increased clotting.	Diagnosed with Crohn's disease and IBS by primary care provider, but did not entirely fit the profile for either pathology.	Designs for Health Calcium D-Glucarate and Designs for Health BroccoProtect™ were added.	By December, the abnormal cycles and heavier bleeding had normalized. Abnormal breast swelling and tenderness also subsided.

April 2025	Ongoing digestive discomfort (bloating and gas)	–	DAO enzyme therapy with NaturDAO was introduced,	Within 24-48 hours an 80% improvement in digestive symptoms, including reduced bloating, gas, and food intolerance.
June 2025	Improved energy, emotional stability, and exercise tolerance, as well as a 15 lb weight loss and a reduction in BMI to 25.2.	A repeat 24-hour urinary hormone panel showed estradiol decreased 25%, testosterone increased, free DHEA decreased, DHEA-S remained above detection limit. Methylation capacity normalized (81.3), HbA1c 5.3%, and a favorable 2-OH: 4-OH shift.	Continued the targeted Designs for Health protocol.	ADHD Symptoms and brain fog persisted.
July 2025	Despite significant improvement in energy and more manageable menstrual cycles, the patient continued to experience fatigue during menstruation.	Ferritin 6ng/mL (ref 16–232) and ironsaturation10% (ref 16–45%)	Iron supplementation initiated by primary care physician: MegaFood Blood Builder™ Iron supplement, Designs for Health Ferrochel® 27 mg, and ferricmaltol 30 mg daily.	

Table 2: Timeline of 24-hour urinary hormone panel by Physician's Lab.

Test	Initial May 2024	Follow-up June 2025
Alpha-Pregnanediol	720.94 ng/mg CR (elevated)	129 ng/mg CR (within range)
Beta-Pregnanediol	3931.22 ng/mg CR (elevated)	828 ng/mg CR (within range)
Estrone	11.9 ng/mg CR (elevated)	17.9 ng/mg CR (elevated)
Estradiol	4.8 ng/mg CR (elevated)	3.8 ng/mg CR (slightly elevated)
2-OHE strone	12.86 ng/mg CR (elevated)	14.5 ng/mg CR (elevated)
4-OHE strone	1.34 ng/mg CR (elevated)	1.4 ng/mg CR (borderline elevated)
16a-OHE strone	1.19 ng/mg CR (within range)	Below the detection limit
Free DHEA	71.83 ng.mg CR (elevated)	24.5 ng/mg (slightly elevated)
DHEA-S	"Unable to calculate, " above measurable range	Above detection limit
Testosterone	6.41 ng/mg CR (within range)	14 ng/mg CR (elevated)
Waking Cortisol	46.2 ng/mg CR (elevated)	30.5 ng/mg CR (within range)
Cortisone	67.38 ng/mg 24hr CR (within range)	104.8 ng/mg 24hr CR (elevated)
Methylation Ratio	23.7 (low)	81.3 (within range)

Table 3: Symptoms report.

Reported Challenges: May 2024	Reported Outcomes: July 2025
Abdominal weight gain	Weight decreased by approximately 10%
Mastalgia and breasts welling	Resolved
Extreme fatigue/low energy	Improved
Anxiety	~75-80% improvement

Depression	~75-80% improvement
ADHD symptoms	Persisted
Brain fog	Persisted
Unmanageable menstrual cycles	Stabilized
Digestive symptoms (bloating, gas)	~80% improvement
Food intolerance	Improved
Insomnia	Improved (~1 additional hour of sleep per night)
Exercise intolerance	Improved