International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2022; 6(5): 24-31
Received: 01-07-2022
Accepted: 05-08-2022

Affiliation all author is given at the end of references section

Expert consensus on the role of nutraceuticals in women's health: Menarche to menopause

Anahita Chauhan, Hemant Thacker, Ashwini Bhalerao Gandhi, Ritu Khanna, PM Gopinath, Kiran Coelho, Nayna Patel, Kamini Patel, Rohit Gutgutia, Srilatha Gorthi, Abhilasha Chaturvedi, Meenakshi Ahuja, Kanika Jain, Sunita Chandra and Anish Desai

DOI: https://doi.org/10.33545/gynae.2022.v6.i5a.1206

Abstract
Throughout life, Women get affected by one or more disorders–dysmenorrhea (young adults), premenstrual syndrome, mastalgia, infertility (reproductive age group), and menopausal symptoms (menopause phase). Although guidelines for these disorders recommend standard drugs, the scientific literature supports the evidence-based use of nutraceuticals. In addition, as life expectancy is rising, there is a renewed focus on nutraceuticals for health and well-being (extending health span, not just lifespan). A group of gynecology experts came together to help leverage the benefits of nutritional science. Their discussion based on peer-reviewed data and clinical experience led to a consensus document on nutraceuticals for women's health. They recommend the use of nutraceuticals for different gynecological disorders. The supporting data and consensus statements will guide clinicians to use nutraceuticals to enhance the health and well-being of women.

Keywords: Dietary supplements, evening primrose oil, amino acids, branched-chain amino acids, cod liver oil, coenzyme Q_{10}

1. Introduction
In a fast-paced VUCA (volatile, uncertain, complex, and ambiguous) world, quick fixes to problems are often challenging. Gynecologists often experience a similar dilemma. Despite advances, there is a considerable lack of consensus on pathogenesis and treatment options for patients with dysmenorrhea, premenstrual syndrome, mastalgia, infertility, menopausal symptoms, etc. Alterations in prostaglandin levels, inflammatory mediators, and estrogen/progesterone ratio have been proposed to contribute to the pathogenesis of these disorders.

Dysmenorrhea is characterized by the turmoil of pain and abdominal cramps, which some menstruating women undergo every month/menstrual cycle; it depict's a high prevalence of 40%, and over 10% report severe restriction of routine activity for one to three days per cycle [1, 2]. Increased concentration of prostaglandins in the menstrual fluid is observed, and approaches to address it have become the principal remedy for primary dysmenorrhea. Premenstrual syndrome (PMS) is associated with bodily, emotional, and behavioral symptoms, mood swings, breast pain, anxiety, depression, acne, fatigue, headache, irritable bowel syndrome, and weight gain. Around 85% of menstruating women are affected by this condition. PMS is characterized by a decline in prostaglandin E_1 levels and increased responsiveness to prolactin which triggers abnormal tissue responses to estrogen and progesterone [8]. Also, an abnormal response to hormonal changes during the menstrual cycle and declining serotonin levels have been implicated. Mastalgia or breast pain occurs in 60-70% of women, and in 10 to 20% of these cases, it leads to significant impairment in daily living [14].

Infertility is a global public health issue, affecting 15% of all couples of reproductive ages. A quarter of male cases result from decreased semen quality [17]. Globally, 70 million couples experience subfertility or infertility. Male patients with infertility often have suboptimal semen quality. It results from altered physiological (elevated levels of reactive oxygen species), environmental, and genetic factors. Oligoasthenoteratozoospermia (OAT) is a common cause of male infertility.

Corresponding Author:
Anish Desai
Clinical Pharmacologist and Pharmaceutical Physician, Director, Intellimed Healthcare Solutions, Mumbai, Maharashtra, India

It results in low count (oligozoospermia), poor movement (asthenozoospermia), and abnormal shape (teratozoospermia) of sperms. Age-related impact and declining ovarian reserve play a crucial etiologic role in female infertility [25]. Both these factors are influenced by oxidative stress.

As a woman transition's into menopause, she experiences vasomotor symptoms - hot flashes and night sweats and symptoms related to other biological systems. These occur due to changes in hormonal levels, especially a decline in estrogen levels. For different gynecology-related disorders, diet and nutraceuticals partner well with standard care. Maintenance and optimal functioning of cells and tissue and diseases' genesis are determined or result from individual dietary habits (quantity and quality of food). Nutraceuticals, yoga and physical activity, traditional home-cooked meals, fresh food, and sleeping habits successfully leverage this linkage between lifestyle and well-being/ disease. The amalgamation of nutraceutical science with modern medicine leads to better outcomes. The resulting clinical practice resonates well with the values and viewpoints of patients and their family members rooted in traditional and nature-based remedies.

1.1. Management of Dysmenorrhoea

The American College of Obstetricians and Gynecologists (ACOG) recommends empiric treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or hormonal therapies, or non-pharmacological therapies (including dietary approach) for primary dysmenorrhea [3]. However, NSAIDs are commonly associated with gastrointestinal and neurological adverse effects, while there is limited data on efficacy with oral contraceptive pills (hormonal approach) for dysmenorrhea. Around 50% of patients with primary dysmenorrhea do not achieve optimal pain relief [1]. Also, the discomfort of side effects suggests a need for different approaches like nutraceuticals to achieve the desired outcomes.

Omega-3 and multivitamin formulations (Cod Liver Oil, Fish Lipid Oil, Vitamin E, and Wheat Germ Oil) are used to manage primary dysmenorrhea. They reduce the intensity and duration of abdominal pain, improve lower back pain, decrease uterine muscle contraction, and reduce the need for NSAIDs. Fish oil supplements provide long-chain Omega-3 fatty acids (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [4-6]. These have anti-inflammatory, antioxidant, and Vaso-protective effects. Vitamin E prevents the peroxidation of phospholipids, the release of arachidonic acid, and prostaglandin formation.

Wheat germ oil is derived from the germ part of wheat. It contains omega-6 (44 and 65% (Linoleic Acid), omega-3 (in a lower proportion, 4-11% (alpha-linolenic acid) fatty acids, and it is known to have the highest tocopherol (Vitamin E) content among other edible oils. It is used widely for its anti-inflammatory properties [7]. Thus, fish oils (Cod Liver Oil, Fish Lipid Oil), Vitamin E, and Wheat Germ Oil act synergistically to control symptoms of primary dysmenorrhea [6].

1.2. Management of Premenstrual syndrome

The Decision-Making Algorithm by The Royal College of Obstetricians and Gynecologists recommends exercise, cognitive behavior therapy, and vitamin B_6 as preferred options for PMS treatment [9]. Other 1st line options proposed are a combined new generation pill and luteal phase SSRI. Halbreich U. *et al*. have shown that a substantial proportion of females (approx. 40%) do not respond to SSRIs or COCs [10]. There is thus a need for alternative treatment approaches, i.e., nutraceuticals.

Evening primrose oil (*Oenothera biennis*) has two types of omega-6-fatty acid - linoleic acid (60%–80%) and γ -linoleic acid (GLA (8%–14%) (essential fatty acids). Linoleic acid and GLA facilitate the production of healthy eicosanoids 1 and 3 (required for normal physiological function). In addition, they reduce the pro-inflammatory eicosanoid 2. It restores the balance in favor of healthy eicosanoids, reduces the production of prostaglandin E_1, and prevents abnormal tissue response to estrogen and progesterone (figure 1).

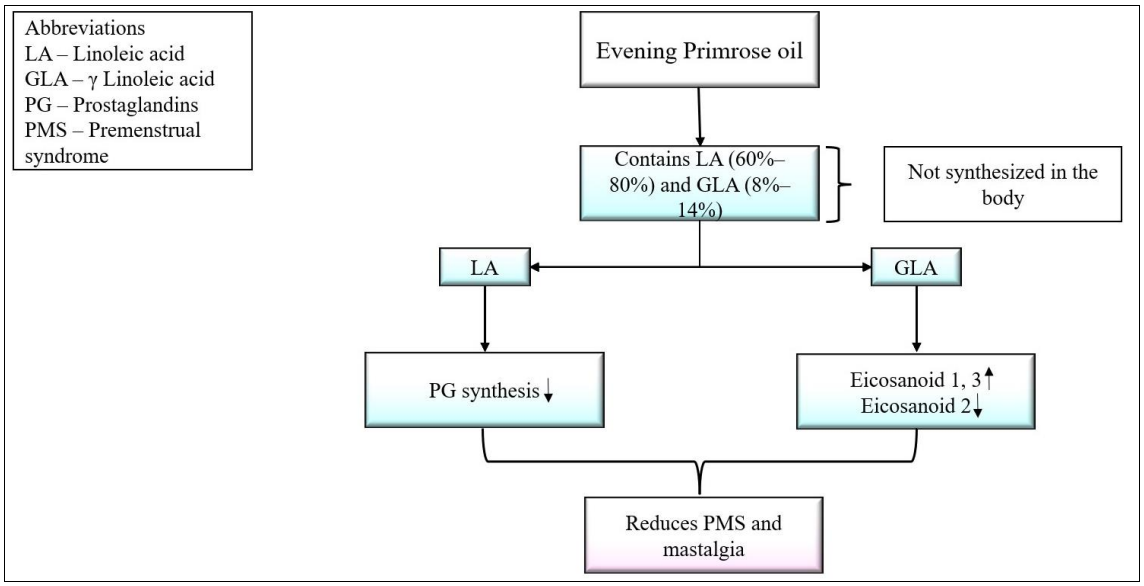

Fig 1: Evening Primrose Oil and its Role in PMS and Mastalgia

Clinical data from different geographies, such as Japan, Finland, and the UK, have shown a direct correlation between PMS and low levels of GLA. Three double-blind, placebo-controlled studies have documented the effectiveness of evening primrose oil in controlling depression and irritability, breast pain and tenderness, and fluid retention observed with PMS [11]. Immediate response in PMS from EPO is unrealistic, as it takes a minimum of 4 to 6 months for effects to manifest.

In PMS, Vitamin E (Tocotrienol (more potent and effective than tocopherol) helps to reduce symptoms by its effect on the central

nervous system and alterations in peripheral endocrine functions [12]. Pyridoxine or Vitamin B_6 is required to synthesize tryptophan and tyrosine (precursors of serotonin and dopamine, respectively); low levels of vitamin B_6 lead to a high level of prolactin, in turn, produce the edema and psychological symptoms associated with PMS [13]. Thus, evening primrose oil, Vitamin E (Tocotrienol), and Vitamin B_6 synergistically manage PMS.

1.3 Management of Mastalgia

The non-pharmacological measures for mastalgia include reassurance and education, a well-fitting bra, and stress, anxiety, or depression management. NSAIDs are preferred for mild symptoms. Tamoxifen (1st line) and danazol (2nd line) are used for moderate symptoms, while goserelin has a role in severe refractory symptoms of mastalgia [15].

Evening primrose oil is effective in mastalgia with good tolerability. It is a preferred treatment option for clinical scenarios where rapid response is not required and patients require repeated courses of treatment [16].

1.4 Management of Male and Female Infertility

Table 1: Pharmacological management of male and female infertility

Hormonal drugs	Non-hormonal drugs	Assisted reproductive technologies
Gonadotropin hormone-releasing hormone (GnRH), Human chorionic gonadotropin (hCG)/ human menopausal gonadotropin (hMG), Follicle-stimulating hormone (FSH), androgens, and anti-estrogens.	Kinin-enhancing drugs, bromocriptine, antioxidants, mast cell blockers, alpha-blockers, systematic corticosteroids and	Intrauterine insemination and IVF (in-vitro fertilization) /ICSI (intracytoplasmic sperm injection (18).

1.4.1 Nutraceuticals for Male Infertility

Coenzyme Q_{10} (CoQ_{10}) has a powerful antioxidant and bioenergetics role (enhances cellular currency, i.e., adenosine triphosphate). It results in positive changes in seminal fluid, sperm count, and motility (Figure 2) [19, 20]. Thus, CoQ_{10} is used for the treatment of idiopathic asthenozoospermia. Ubiquinol is the active reduced form of CoQ_{10}. It is preferred over ubiquinone due to its higher bioavailability. L-carnitine, astaxanthin**,** lycopene, and Zinc are other agents which improve sperm quality, functioning, and pregnancy rates [21, 22]. It results from enhanced energy production, sperm capacitation, acrosome reaction, and hormonal balance.

A high polyunsaturated fatty acids (PUFAs) content is necessary to maintain membrane fluidity for the fusion with the oocyte membrane during fertilization. Omega-3 fatty acids are effective in idiopathic oligoasthenoteratozoospermia as it improves sperm functioning [23]. Selenium (Se), through its antioxidant role, improves sperm fertility parameters (gross count and motility) [24]. It also plays a vital role in ovarian and placental function and fetal development. Supplementation with selenium decreases the risk of pregnancy complications in women at risk of intrauterine growth restriction.

1.4.2 Nutraceuticals for Female Infertility

CoQ_{10} increases CPR (clinical pregnancy) in females seeking ART (Assisted reproductive technology) for infertility (Figure 2) [26]. Supplementation with lycopene, an antioxidant for primary infertility, results in a shorter time to conception [27]. Omega 3 fatty acids influence oocyte quality, essential for cell-to-cell communication, nutrient import and export, and gene regulation [28]. Curcumin is sourced from *Curcumin longa* (Turmeric). It reduces inflammation, oxidative stress, and angiogenesis [29]. It thus helps to resolve infertility in patients with endometriosis.

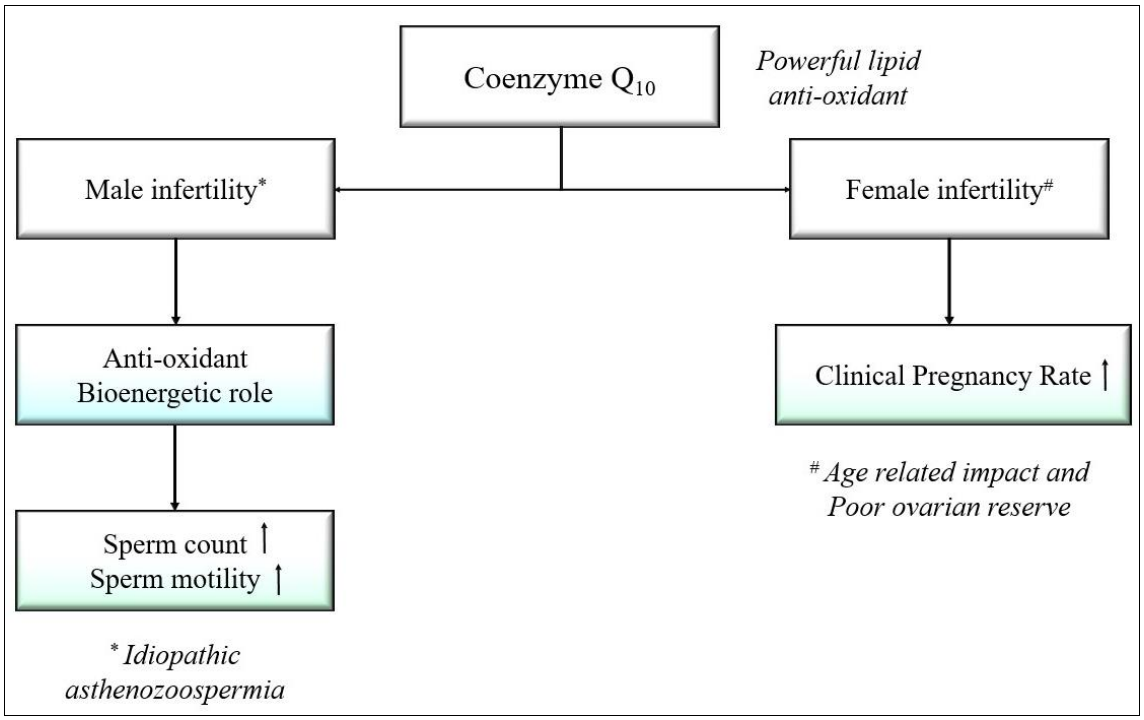

Fig 2: Role of Coenzyme Q_{10} for Male and Female Infertility

1.5 Nutraceuticals for enhancing health and well-being

1.5.1 Modern Medicine and Learnings from Past

The practice of modern medicine is founded on the principles of science and evidence generated using the highest level of scientific rigor. As we strive to achieve the best patient outcomes, we must acknowledge Sir William Osler's familiar quote, "Medicine is a science of uncertainty and an art of probability." [30]. These words beautifully sketch the complexity of medical practice, often an imprecise science. Every physician uses their skills and understanding to refine and practice medicine, which has at its core a craft tailored to meet the preventive needs of the healthcare system ('prevention is better the cure'). A comprehensive lifestyle medicine approach encompasses nutrition, physical activity, sufficient sleep, stress management, social connectedness, and avoiding toxic substances.

Though interwoven, each of the above healthy lifestyle components influences gynecologic health. Ancient India had many celebrated doctors called "Vaidya's," whose job also included educating the people about health and disease and being able to communicate with the lay public and the scholars alike [31].

1.5.2 Preventive Medicine

As we strive to cure/ control a disease, we must acknowledge that every physician, nation, and healthcare seeks to prevent disorders ('prevention is better than the cure'). This motto aligns well with the health promotion concept delivered by physicians to enhance health and well-being across the lifespan. In 1979, the idea of prevention got refined to primordial prevention, which focuses on preventing risk factors for disease and not just prevention of disease [32]. Lifestyle intervention (diet, exercise, etc.) and nutraceutical supplements play a significant role in primordial prevention. In parallel, there has been a rise in global demand for nutraceuticals to enhance health and well-being.

1.5.3 Stress and its management

Stress and anxiety are common mental health challenges that affect women regardless of age. Modern women constantly strive to excel in their multiple roles, which leads to stress. Apart from fulfilling the more traditional female roles, such as being the primary caretaker for children and older family members, spending more time performing household tasks, and serving a more comprehensive range of them than men do, many women now also work outside the family home.

Many women experience feelings of being overwhelmed and increasing levels of stress. There is a requirement for supplementation for optimal cognitive and nervous system functioning. Essential fatty acids (EFAs), B groups of vitamins, vitamin C and minerals (magnesium and Zinc) play a crucial role in the management of stress (prenatal stress, premenstrual and perimenopausal anxiety) [33].

1.5.4 Exercise-Induced Muscle Damage and Muscle Wasting with Aging

Fitness enthusiasts or people with healthier lifestyles perform more frequent physical activity and fitness workouts and require antioxidant supplements to optimize muscle health. In modern sports, high-intensity interval training (HIIT) and downhill running involve target muscles' eccentric contraction (EC). EC exercises (lengthening of muscles during contraction) lead to the generation of ROS (reactive oxygen species) and inflammatory mediators resulting in micro and macro muscle injury. Reduced excitation-contraction coupling, sarcomere disruption, torn myofibers, and microstructural damage are observed [34]. Recent research indicates that supplementing large doses of antioxidants and anti-inflammatory drugs from pharmaceutical sources to suppress EC-induced inflammation is detrimental because they interfere with and inhibit redox signaling pathways that elicit beneficial exercise adaptations [22]. Thus, seeking natural food sources or phytochemicals as dietary supplements with antioxidant and anti-inflammatory properties is highly desirable.

Human proteins are assembled from 20 amino acids, nine of which are considered "essential"; among these are three branched-chain amino acids (BCAAs) - leucine (Leu), isoleucine (Ile), and valine (Val) which are the building blocks for cells and tissues [35]. BCAAs also play an essential role in cellular communication and protein synthesis, facilitating insulin secretion and enhancing muscle protein synthesis and mass during exercise training and aging.

1.6 Nutraceuticals for Menopausal Symptoms

Evening primrose oil has Phyto -estrogenic properties. The mix of agonistic and antagonistic activity at the estrogen receptor relieves menopausal symptoms. Shatavari, also known as *Asparagus racemosus Willd*, is an ancient ayurvedic herb with phytoestrogenic effects. It maintains muscle (ergogenic) and bone health in postmenopausal women [36].

1.7 Nutritional Science and Nutraceuticals for Enhancing Patient Care

Nutraceuticals are an effective tool for all stakeholders in a health care universe to enhance patient care. The International Federation of Gynecology and Obstetrics (FIGO) recommends that all healthcare providers need to "Think Nutrition First"—focusing on optimizing women's health and well-being, starting in the preconception years [37]. To align with these recommendations, every healthcare clinic needs systems and processes to conduct a nutribiography (the effect of an individual's dietary history and supplementation on their clinical signs and symptoms and the pathogenesis of their disorder) to maximize the benefits offered by nutraceutical science. The essential structural and functional elements of cells and tissue are molecules - water, lipid, protein, mineral, vitamins, and carbohydrates [38]. To maintain optimal cellular/ tissue functioning, a healthy and varied diet that provides macro and micronutrients is required.

1.7.1 Pregnancy and Lactation - Nutritional Habits and Linkage with Diseases in Future

Dietary and nutritional habits during pregnancy and lactation lay the foundation for a healthy life from the fetal phase to later phases (adolescents/ young adults/middle-aged and senior citizens). There is a requirement to provide essential amino acids and branched-chain amino acids during pregnancy and lactation to cater to the higher protein requirements of mothers, fetuses, and infants [39-40]. An altered diet or unhealthy nutrition during preconception, pregnancy, perinatal and lactation period influences the epigenetic environment and physiological functioning, thereby sowing seeds for diseases that manifest at later stages. It has led to the concept of critical periods (CPs), Barker Hypothesis, and epigenetic mechanisms for illness [41]. Barker's Hypothesis postulates that prenatal malnutrition (low birth weight) is closely related to mortality due to cardiovascular disease (CVD) in adults and to risk conditions leading to - insulin resistance, metabolic syndrome, obesity, and high blood pressure.

1.7.2 Nutraceuticals for Healthy Pregnancy and lactation and, Fetal and Neonatal development

Supplements with amino acids are integral to cellular proteins and facilitate cellular functioning, multiplication, differentiation, and expansion. They are required for optimal reproduction, gametogenesis, fertilization, implantation, placentation, fetal growth, and development [39]. A healthy diet and supplementation with nutraceuticals are required during pregnancy to ensure a continuous supply of nutrients, especially amino acids (AA), to help drive fetal growth and development [40]. Similarly, supplementation with amino acids during lactation helps milk production, facilitating neonatal survival, growth, and development.

Greater attention is being given to links between poor maternal nutrition and increased risk of later non-communicable diseases (NCDs) in offspring. This approach is a core component of meeting global health goals. Deficient or excessive consumption of macronutrients and micronutrient deficiency results in malnutrition. Micronutrient deficiency results from a diet with insufficient vitamin and mineral density or poor bioavailability of nutrients, or increased body requirements due to infection or growth. A recent concern is the increasing availability and intake of processed, stored, canned, and contaminated food deficient in vitamins and fiber and high in refined carbohydrates and trans fats.

Malnutrition results from overconsumption of non-nutritive calories. Food quality counts as much as food quantity at different phases of women's life – from menarche to menopause. Addressing nutritional needs across all age groups, from menarche to menopause (including the childbearing period), ensures health for adolescents, women, and future generations [37]. Thus, it is necessary to increase awareness of dietary choices and nutrition and their impact on health.

1.8 Patient education and Enhancing Compliance with Nutraceuticals

Many patients are avid users of nutraceuticals, as they are firm believers in their effectiveness with minimal or no side effects. However, they do not disclose this practice to clinicians responsible for their care as often this information is not solicited, or the patient feels that it may elicit a negative response from the doctor.

The need of the hour is to integrate an evidence-based approach with patient expectations by initiating a non-judgmental dialogue. As voluminous data has been generated over the past decade, the physician needs to have an active discourse with patients on treatment outcomes and the safety of nutraceuticals. This interaction will facilitate an individualized treatment plan incorporating nutraceuticals into the standard of care and improve compliance with treatment – dosage and duration. Finally, there is a need for generating clinical data appropriate to nutraceuticals using the rigorous standards applied to standard drugs, i.e., large, phased, randomized clinical trials.

Voluminous data is being generated with nutraceuticals, and their use is rising; the biggest challenge is the lack of stringent regulations (unlike drugs) [42]. It occurs due to the availability of multiple formulations, often with similar constituents and claims at different price points, which leads to quality, safety, and efficacy concerns.

There is an urgent need for changes in regulations to ensure uniformity in the standardization and quality of nutraceuticals. Meanwhile, health care practitioners must enhance their knowledge of nutraceutical science, clinical data, and manufacturing processes. This information will help physicians to select an appropriate quality nutraceutical formulation for improving the health and well-being of their patients.

2. Need for expert consensus

Data from across the globe shows a rising trend in using nutraceuticals. This upswing occurs Attributed to change in consumer behavior. As essential healthcare stakeholders, the benefits offered by nutraceuticals must be leveraged for patients' better health and well-being. In the absence of national and international guidelines, there is an urgent need to generate a consensus document that can help guide clinicians on the role of nutraceuticals in women's health.

3. Methodology

A panel of 14 experts (13 gynecologists and one physician) with experience in research and publications and a speaker at national or regional conferences came together. The objective was to generate a consensus on the role of nutraceuticals in women's health – menarche to menopause. Experts shared their opinions on nutraceuticals in various gynecological disorders. Based on the data discussed and experience shared, three consensus statements were developed, which are provided below, along with data supporting them.

4. Expert Opinion

The expert panel discussed and agreed on the following points:

The correct dose, time, and place for the use of nutraceuticals should be based on the type of disease. The physician and patient need to know why, how long, and the nutraceuticals' effectiveness. Health professionals must also educate patients about nutraceuticals' role in a specific disease condition. Nutraceuticals have received an overwhelming response for their protective role in sub-acute to chronic diseases. They are advised for long-term protection compared to pharmacotherapeutic drugs for acute conditions.

Science-based nutrition is an evolving approach among the public. A proper and well-guided method for nutraceutical consumption can help develop a culture of wellness. It is also the physician's responsibility to inquire and conduct the nutribiography of a patient. It is always recommended to start early and ensure maintenance of good health than wait for an aggravated situation.

In alliance with the benefits of nutraceuticals in the general population, it also significantly impacts women's and child health. Proper and well-balanced nutrition during pregnancy is essential to guard the developing fetus against any adverse non-communicable disease in its later phases of life. Nutraceuticals also have a crucial role in different stages and situations of an adult, including vegetarian females, young females, male infertility, and newlywed women. Finally, physicians should not wait for government guidance or regulations to use nutraceuticals.

5. Expert consensus

1. Integrate the use of nutraceuticals with the standard of care to optimize patient care by use of cod-liver oil and other fish oil formulations for dysmenorrhea, evening primrose oil for the pre-menopausal syndrome, and mastalgia, and coenzyme Q_{10} for male and female infertility.
2. Optimize the use of Nutraceutical to enhance health and well-being.
3. ‘Think Nutrition First’ and optimize nutrition at every stage of women’s life with dietary measures and nutraceuticals.

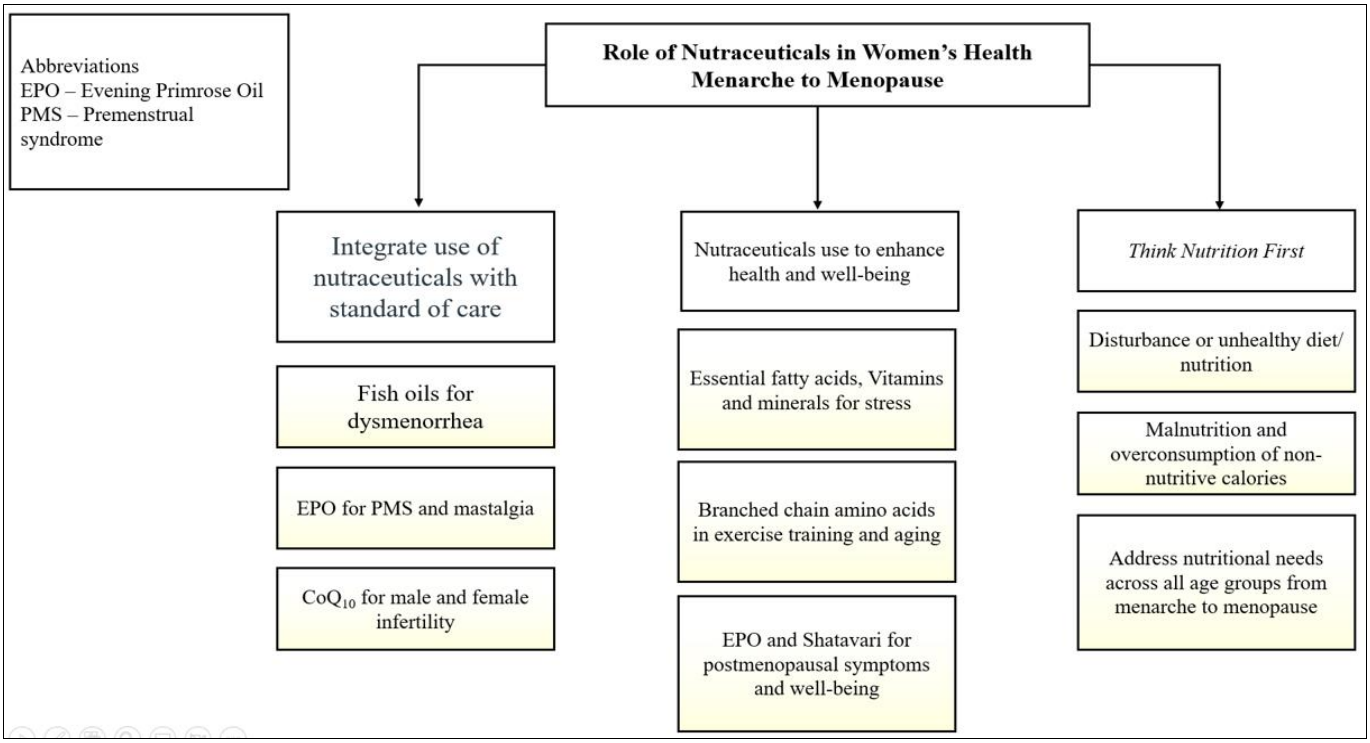

Fig 3: Summary of expert consensus on the role of nutraceuticals – menarche to menopause

6. Conclusion

Diet and nutritional supplements have a considerable role in common gynecology disorders. There is thus a requirement to complement nutraceuticals with the standard of care. Micronutrient deficiencies must be identified and corrected with either a mix of a healthy and varied diet, use of enriched foods, or nutraceuticals. Physicians need to conduct nutribiography and use nutraceuticals to manage different disorders and enhance the health and well-being of their patients.

7. Acknowledgments

7.1 Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

7.2 Medical writing: The authors acknowledge Dr.Manish R Garg, Mr. Hemen Ved, Dr. Sunaina Anand, and Ms. Janice Jacson Mandumpala from Intellimed Healthcare Solutions LLP for medical writing support.

7.3 Funding: The publication fees are paid by Universal Nutri Science (UNS) Pvt. Ltd.

7.4 Compliance with Ethics Guidelines: This article is based on previous studies and does not contain any new studies with human participants or animals performed by any authors.

7.5 Data availability: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

8. References

1. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database of Systematic Reviews; c2015 p.7.
2. Wong CL, Farquhar C, Roberts H, Proctor M. Oral contraceptive pill as treatment for primary dysmenorrhoea. Cochrane Database of Systematic Reviews; c2009.
3. ACOG Committee Opinion No. 760: Dysmenorrhea and Endometriosis in the Adolescent. Obstet Gynecol. 2018;132(6).
4. Zakaria H, Mostafa TM, El-Azab GA, Abd El Wahab AM, Elshahawy H, Sayed-Ahmed NA. The impact of fish oil and wheat germ oil combination on mineral-bone and inflammatory markers in maintenance hemodialysis patients: a randomized, double-blind, placebo-controlled clinical trial. Int Urol Nephrol. 2017 Oct;49(10):1851-1858
5. Liao J, Xiong Q, Yin Y, Ling Z, Chen S. The Effects of Fish Oil on Cardiovascular Diseases: Systematical Evaluation and Recent Advance. Front Cardiovasc Me; c2022. p.8.
6. Sadeghi N, Paknezhad F, Rashidi Nooshabadi M, Kavianpour M, Jafari Rad S, Khadem Haghighian H. Vitamin E and fish oil, separately or in combination, on treatment of primary dysmenorrhea: a double-blind, randomized clinical trial. Gynecol Endocrinol. 2018 Sep 2;34(9):804-808.
7. Yazicioglu B, Sahin S, Sumnu G. Microencapsulation of wheat germ oil. J Food Sci Technol. 2015 Jun;52(6):3590-3597.
8. Yonkers KA, Simoni MK. Premenstrual disorders. American Journal of Obstetrics and Gynecology. 2018 Jan 1;218(1):68-74.
9. Panay N. Treatment of premenstrual syndrome: A decision-making algorithm. Menopause International. 2012; Jun;18(2):90-92
10. Halbreich U. Selective serotonin reuptake inhibitors and initial oral contraceptives for the treatment of PMDD: Effective but not enough. CNS Spectrums. 2008 Jul;13(7):566-72.
11. Horrobin DF. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. J Reprod Med Obstet Gynecol; c1983, 28(7).
12. London RS, Sundaram G, Manimekalai S, Murphy L,

Reynolds M, Goldstein P. The effect of alpha tocopherol on premenstrual symptomatology: A double blind study. ii. endocrine correlates. J Am Coll Nutr. 1984;3(4):351-356.
13. Wyatt KM, Dimmock PW, Jones PW, O'brien PMS. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: Systematic review. BMJ. 1999;318(7195):1375-1381.
14. Kataria K, Dhar A, Srivastava A, Kumar S, Goyal A. A Systematic Review of Current Understanding and Management of Mastalgia. Indian J Surg. 2014;76(3):217-222.
15. Salzman B, Collins E, Hersh L. Common breast problems. Am Fam Physician. 2019 Apr 15;99(8):505-14.
16. Gateley CA, Miers M, Mansel RE, Hughes LE. Drug treatments for mastalgia: 17 years experience in the Cardiff mastalgia clinic. J R Soc Med. 1992;85(1):12.
17. Kumar N, Singh A. Trends of male factor infertility, an important cause of infertility: A review of literature. Vol. 8, Journal of Human Reproductive Sciences. 2015 Oct;8(4):191.
18. Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth A, Weidner W. EAU guidelines on male infertility. Eur Urol. 2005 Nov 1;48(5):703-11.
19. Mancini A, de Marinis L, Oradei A, Hallgass ME, Conte G, Pozza D, *et al*. Coenzyme Q10 Concentrations in Normal and Pathological Human Seminal Fluid. J Androl. 1994 Nov 12;15(6):591-4.
20. Balercia G, Mosca F, Mantero F, Boscaro M, Mancini A, Ricciardo-Lamonica G, *et al*. Coenzyme Q10 supplementation in infertile men with idiopathic asthenozoospermia: An open, uncontrolled pilot study. Fertil Steril. 2004 Jan 1;81(1):93-8.
21. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database of Systematic Reviews; c2019.
22. Fallah A, Mohammad-Hasani A, Colagar AH. Zinc is an essential element for male fertility: A review of zn roles in men's health, germination, sperm quality, and fertilization. Vol. 19, Journal of Reproduction and Infertility. 2018 Apr;19(2):69.
23. Reza Safarinejad M, Safarinejad S. The roles of omega-3 and omega-6 fatty acids in idiopathic male infertility. Asian J Androl. 2012 Jul 1;14(4):514-5.
24. Moslemi MK, Tavanbakhsh S. Selenium-vitamin E supplementation in infertile men: Effects on semen parameters and pregnancy rate. Int J Gen Med. 2011;4:99.
25. Greene AD, Patounakis G, Segars JH. Genetic associations with diminished ovarian reserve: A systematic review of the literature. Vol. 31, Journal of Assisted Reproduction and Genetics. 2014 Aug;31(8):935-46.
26. Florou P, Anagnostis P, Theocharis P, Chourdakis M, Goulis DG. Does coenzyme Q10 supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. Journal of Assisted Reproduction and Genetics. 2020 Oct;37(10):2377-87.
27. Ruder EH, Hartman TJ, Reindollar RH, Goldman MB. Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility. Fertil Steril. 2014 Mar 1;101(3):759-66.
28. Barsky M, Blesson CS. Oocytes, obesity, and omega-3 fatty acids. Fertility and Sterility. 2020 Jan 1;113(1):71-2.
29. Arablou T, Kolahdouz-Mohammadi R. Curcumin and endometriosis: Review on potential roles and molecular mechanisms. Biomedicine and Pharmacotherapy. 2018 Jan 1;97:91-7.
30. Moore-McCann B. Art matters: How art and medicine intersect in the art of Brian O'Doherty/Patrick Ireland. J Med Biogr. 2020 Feb;28(1):46-51.
31. Saini A. Physicians of ancient India. J Fam Med Prim Care; c2016, 5(2).
32. Gillman MW. Primordial prevention of cardiovascular disease. Circulation. 2015 Feb 17;131(7):599-601.
33. McCabe D, Lisy K, Lockwood C, Colbeck M. The impact of essential fatty acid, B vitamins, vitamin C, magnesium and Zinc supplementation on stress levels in women: A systematic review. JBI Database of Systematic Reviews and Implementation Reports. 2017 Feb 1;15(2):402-53.
34. Zhang T, Zhao T, Zhang Y, Liu T, Gagnon G, Ebrahim J, *et al*. Avenanthramide supplementation reduces eccentric exercise-induced inflammation in young men and women. J Int Soc Sports Nutr. 2020 Jul 25;17(1):41.
35. Zhang S, Zeng X, Ren M, Mao X, Qiao S. Novel metabolic and physiological functions of branched chain amino acids: A review. Journal of Animal Science and Biotechnology. 2017 Dec;8(1):1-2.
36. O'leary MF, Jackman SR, Sabou VR, Campbell MI, Tang JCY, Dutton J, *et al*. Shatavari supplementation in postmenopausal women improves handgrip strength and increases vastus lateralis myosin regulatory light chain phosphorylation but does not alter markers of bone turnover. Nutrients. 2021 Nov 27;13(12):4282.
37. Hanson MA, Bardsley A, De-Regil LM, Moore SE, Oken E, Poston L, *et al*. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First" Int. J Gynecol Obstet. 2015 Oct;131:S213-53.
38. Wang ZM, Pierson RN, Heymsfield SB. The five-level model: A new approach to organizing body-composition research. Am J Clin Nutr. 1992 Jul 1;56(1):19-28.
39. Gao H. Amino acids in reproductive nutrition and health. In: Advances in Experimental Medicine and Biology; c2020. p. 111-131.
40. Manta-Vogli PD, Schulpis KH, Dotsikas Y, Loukas YL. The significant role of amino acids during pregnancy: nutritional support. Journal of Maternal-Fetal and Neonatal Medicine. 2020 Jan 17;33(2):334-40.
41. Simeoni U, Armengaud JB, Siddeek B, Tolsa JF. Perinatal Origins of Adult Disease. In: Neonatology. 2018;113(4):393-9.
42. Santini A, Cammarata SM, Capone G, Ianaro A, Tenore GC, Pani L, *et al*. Nutraceuticals: opening the debate for a regulatory framework. British Journal of Clinical Pharmacology. 2018 Apr;84(4):659-72.

Authors Details

Anahita Chauhan
Obstetrician and Gynaecologist, Honorary Consultant, Saifee & St. Elizabeth Hospitals, Mumbai, Maharashtra, India

Hemant Thacker
Consultant Physician & Cardio Metabolic Specialist, Director & HOD Medicine at Bhatia Hospital, Additional Director of Medicine at Jaslok Hospital, Delhi, India