Drug Corner

Pharmacological basis of Evening Primrose Oil in Premenstrual Syndrome — An evidenced based approach

Ashwini Bhalerao Gandhi[1], Anish Desai[2],

Premenstrual Syndrome (PMS) is a recurrent luteal-phase condition associated with somatic emotional and behavioral symptoms. Frequently reported symptoms include breast discomfort, mood swings, fluid retention and food cravings. The exact etiology of PMS is unknown; however, the underlying mechanism is a complex interaction between fluctuations in ovarian steroids and central neurotransmitters as well as peripheral effects of hormones. Therefore, surprisingly a wide range of treatments are not available with satisfactory outcomes. Evening Primrose Oil (EPO) is one of the most popular for the management of PMS. EPO is a valuable fixed oil extracted from the *Oenothera biennis* seeds. It comprises essential fatty acids, including linoleic acid, Gamma-Linolenic Acid (GLA), and Vitamin E, which have been used in various treatments. It has been clinically shown to improve psychological (mood and sleep disturbances) and physical symptoms (breast pain/tenderness, bloating, fatigue) in women suffering from PMS. The rationale put forward for investigating the use of EPO in PMS is thataffected women appear to have abnormal levels of essential fatty acids; hence administrating linoleic acid and GLA in the form of EPO could potentially alleviate the symptoms of PMS.

[*J Indian Med Assoc* 2022; **120(7):** 75-9]

***Key words* : Evening Primrose Oil, Premenstrual Syndrome, GLA.**

The onset of a phase with one or more symptoms before the menstrual cycle that causes an imbalance in a woman's lifestyle and everyday routines is known as Premenstrual Syndrome (PMS). Although most of the symptoms are mild, 5-8% of women experience moderate to severe symptoms that are linked to severe distress or functional impairment. Prospective and retrospective studies report that less than 10% of women with hormonal cycles experience moderate to severe symptoms[1,2]. Moreover, the prevalence of PMS is estimated to vary between 14.3% to 74.4% in India. Surprisingly, adolescents showed a comparatively higher prevalence, negatively impacting their quality of life[3]. Increased irritation, stress, depressed mood, soreness in the breasts, bloating, and weight gain are some symptoms of PMS.Premenstrual disorders significantly affect the quality of life by causing significant distress or interfering with daily activities like work, school, or socializing[4,5]. Treatment options for PMS include hormonal interventions [Gonadotropin-Releasing Hormone (GnRH) agonists and combined oral contraceptives], antidepressants [Selective Serotonin Reuptake Inhibitors (SSRIs)], and lifestyle changes[6].

Editor's Comment :

- Evening Primrose Oil (EPO) is made from the seeds of the flowers of Oenothera biennis, which has traditionally been used to treat various conditions.
- Over the past few years, interest in EPO has risen due to its supposed benefit in managing PMS.
- The oil contains Gamma-Linolenic Acid (GLA) and other omega-6 fatty acids that have both anti-inflammatory and pain-relieving properties.
- Studies demonstrate that EPO helps significantly relieve the symptoms of Premenstrual syndrome (mainly mood disturbances, breast pain, fatigue).

Selecting a suitable treatment option is further complicated due to available therapies' serious side effect profiles.Supplements like Vitamin B6, Calcium, Vitamin D and Magnesium, Psychotherapy and Dietary changes are less researched alternative treatment options for the management of PMS[7]. With current treatment options lacking efficacy and safety, more research into alternative treatments for PMS management is required. Evening Primrose Oil (EPO) is one of the treatment options that has lately been reported to be beneficial in PMS[8]. This article aims to report the characteristics of EPO and its role in the management of PMS.

EPO and Its Applications :

The oil is derived from the evening primrose seeds (Oenothera biennis), which compriselinoleic acid, Gamma-Linolenic Acid (GLA), and Vitamin E. The

[1]MD, DGO, DFP, FCPS, DNB, FICOG, Consultant Gynaecologist, P D Hinduja Hospital, Mumbai.

[2]MD, FCP, PGDHEP, Clinical Pharmacologist & Nutraceutical Physician, Founder & CEO, IntelliMed Healthcare Solutions

Received on : 08/07/2022
Accepted on : 11/07/2022

reputation of EPO is related to its chemical components[9,10]. EPO is currently the most essential source of GLA, which is in high demand for its therapeutic and pharmacological applications due to the presence of essential fatty acid and precursor of prostaglandin E1 and its derivatives. EPO contains two types of omega-6 fatty acids: linoleic acid (60-80%) and GLA (8-14%), both of which are considered essential fatty acids since they are not synthesized in the body[11,12]. Disorders for which EPO has been tested in controlled clinical trials include atopic dermatitis, rheumatoid arthritis, diabetic neuropathy, multiple sclerosis, various cancers, Raynaud's phenomenon, ulcerative colitis, and pre-eclampsia, menopausal flushing, breast cysts, mastalgia, Sjogren's syndrome, schizophrenia and hyperactivity[8,13] (Fig 1).

Management of PMS :

Although the etiology of PMS is unknown, various biological theories have been proposed to explain this syndrome.The gonadal hormones have been proposed as causative factors, with theories involving decreased and increased progesterone levels and changes in estrogen or an imbalance between these two hormones.Prolactin, which rises at the time of ovulation and remains high during the luteal phase, is another hormone that has been implicated[14,15].The findings suggested that women with PMS may have abnormal fatty acid metabolism[16]. According to the results of Watanabe's study from 2005, women with PMS had a significantly lower rate of GLA. Decreased prostaglandin E1 increases sensitivity to luteal phase prolactin and other hormones in women with PMS[17,18]. GLA supplementation is believed to improve microcirculation by improving cell membrane function, which results in decreased viscosity. According to the findings of one study, patients' PMS symptoms could be significantly reduced by herbs comprising GLA acid[15]. Studies have shown that consuming 180 mg of GLA-containing vegetable oil daily reduced PMS symptoms considerably and increased plasma phospholipid GLA levels. The findings of these studies suggest that GLA can effectively treat PMS symptoms and that GLA in plasma phospholipids plays an essential role in the onset of PMS[17,19].

Pharmacology of EPO :

Significant components of EPO include linoleic and GLA, from which GLA, an essential fatty acid, is the crucial active ingredient of this oil. These essential fatty acids are not synthesized endogenously and are necessary for the normal structure of cell membranes[20]. EPO's therapeutic activity is linked to the direct influence of its essential fatty acids on immune cells and an indirect effect on eicosanoid synthesis.The action of highly unsaturated fatty acid in tissues and eicosanoids is hypothesized to be involved in its inflammatory activity[21]. EPO contains essential fatty acids that are essential for the formation of PGE. The presence of GLA allows the synthesis of anti-inflammatory substances such as 15-hydroxy-eicosatrienoic acid and PGE1. Supplementation with EPO is assumed to lead to increased concentrations of GLA and DGLA in blood, thereby supporting anti-inflammatory responses. In fact, studies on the effects of GLA supplementation in humans and rodents have demonstrated that the synthesis of the anti-inflammatory PGE1 was substantially elevated. However, a measurable biomarker for the possible efficacy of EPO has not yet been described[22].

In addition, there is evidence that PGE1, derived from dietary essential fatty acids, is able to attenuate the biological actions of prolactin. Women suffering from PMS may be abnormally sensitive to normal levels of prolactin,and this phenomenon may be related to low PGE1 levels, which in turn may interact with ovarian hormones[23]. Moreover, High prolactin levels associated with low estrogen

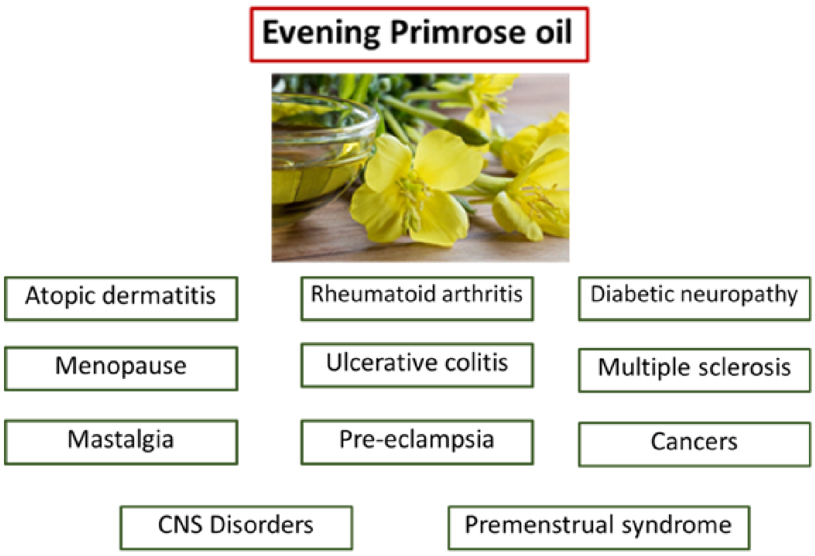

Fig 1 — EPO and its applications

levels may cause mood disturbances and other premenstrual symptoms[24]. The essential acids in the EPO help this oversensitivity to prolactin by decreasing the effect of prolactin.Thus administration of linoleic acid and GLA in the form of EPO could potentially alleviate the symptoms of PMS (Fig 2).

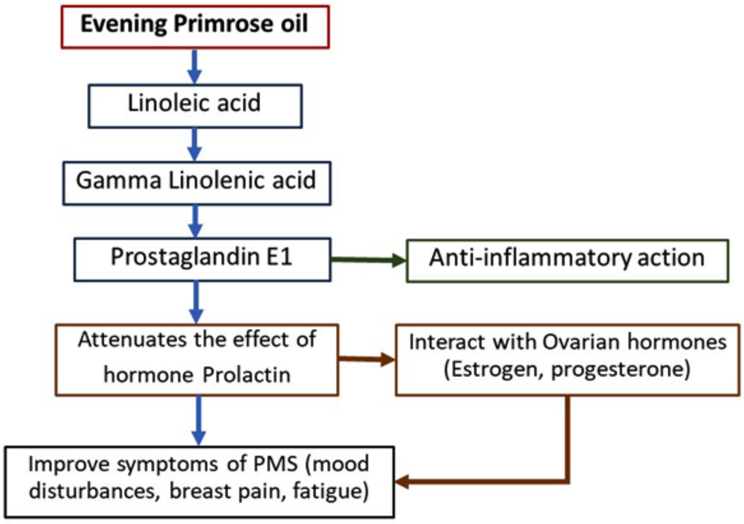

Fig 2 — Mechanism of action of EPO in PMS

Role of primrose oil in PMS :

Many clinical trials have investigated EPO's therapeutic potential in treating PMS (Table 1). Linoleic acid stimulates prostaglandin synthesis and relieves symptoms of PMS. The conclusion of EPO in PMS in clinical trials conducted over the years has been limited[25]. The alleviating effect of 180 mg/day GLA on clinical symptoms of women suffering from PMS in three luteal phases was compared with the placebo in a randomized, double-blind placebo-controlled parallel design.The duration and severity of symptoms were compared in groups using blood samples collected over three cycles. The levels of stearic acid, oleic acid, and Dihomo-Linoleic Acid (DGLA) levels in plasma phospholipids decreased significantly during the follicular and luteal phases. The most common symptom of PMS in women was irritable bowel syndrome, followed by breast swelling, drowsiness, avidity and facial eruption.After treatment, the patients in the GLA group had higher GLA and DGLAlevels in plasma phospholipids compared to the placebo group. Compared to the placebo group, the severity and duration of PMS (Physical, Mental and Social) and irritability improved in the group supplemented with GLA[17]. In another clinical trial, patients were divided into two groups and given either 1.5 g EPO or a placebo daily for three months. EPO significantly reduced PMS severity scores after the intervention when compared to before. After three months of interventions, the EPO and placebo groups saw a significant difference in PMS symptom severity scores[16]. In other studies, 3g of oral EPO or 600 mg of oral vitamin E were given to women

Table 1 — *Clinical trials of EPO in PMS*

Trial	Partici-pants	Intervention	Results
Randomized double-blind placebo-controlled parallel design,	N=28	180 mg GLA orally during the luteal phase	Increase in GLA, DGLA in plasma phospholipid, Improvement of PMS severity and duration ($P<0.05$)[31]
Placebo randomized control trial	N=80	1.5 g EPO for 3 months	Significant reduction in PMS severity score($p<0.001$)[32]
Placebo-controlled,randomized crossover study	N=30	500 mg EPO twice dailystarting on the 15th dayof the cycle and continuing until the nextmenstrual period.	Improvement in PMS score (breast tenderness, abdominal bloating, and breast engorgement)[33]
Double-blind, crossover, placebo-controlled study	N=80	NA	Both psychologicaland physical symptoms improved significantly[26]
Randomized, double-blind, placebo-controlled crossover study.	N=38	500 mg EPO Eight capsules daily for 3 months	Reduced PMS scores after 3 months[28]
Double-blind trial	N=70	1000 mg EPO thrice for 60 days	Significant reduction in stress symptoms ($p=0.004$), sleep disturbance ($p=0.019$), appetite for sweets ($p=0.014$), sore breasts ($p=0.025$), bloating ($p<0.001$)[30]

with cyclical mastalgia as a supplement. Vitamin E or EPO therapy significantly improved breast pain scores and decreased pain intensity[26].

Essential fatty acids, linoleic acid and GLA promote prostaglandin synthesis, which has anti-inflammatory and immune-regulating properties and can alleviate the symptoms of PMS. There is some evidence that prostaglandin E1 (PGE), derived from dietary essential fatty acids, can minimize the biological effects of prolactin which has an outsized impact on the absence of PGE[23,27]. Other studies found that treating PMS with EPO for at least six weeks resulted in a significant difference in scores between the EPO and placebo groups, primarily on mood symptoms, feeling of illness, and breast stimulation.According to studies, a daily intake of 2 mg primrose over a three-month treatment period can reduce breast stimulation more than other PMS symptoms. The results from Cornish's analysis indicated that EPO caused a remarkable reduction in agitation, fatigue and depression after the first treatment cycle[28,29]. Moreover, EPO showed better efficacy in managing the symptoms of PMS when compared to Vitamin E supplementation[30].

Safety of EPO :

Clinical studies on the efficacy of EPO on women's health showed its safe therapeutic potential for PMS. EPO was found to be safe upto 6g daily dose in volunteers with PMS[8,34]. EPO is not associated with severe side effects; however, some patients complain of bloating and gastrointestinal problems, nausea, headache,diarrhea, and weight gain after administration of EPO[35,36]. EPO capsules should be taken with food, milk, or liquid to minimize the risk of side effects. There are no known drug interactions. Steroids and nonsteroidal anti-inflammatory drugs may potentially interfere with essential fatty acid metabolism[37].

Conclusion :

The results from studies show that oral supplementation of EPO is effective in the treatment of PMS.The immediate results should not be expected from EPO; therefore, it should be regularly used for up to 4 or 6 months. EPO, which contains linoleic acid, and a considerable amount of GLA, can reduce and alleviate the symptoms of PMS. Many trials to date have been crossover studies in small numbers of patients. Nevertheless, EPO is an exciting substance with promising outcomes in managing PMS. Designing large multi-center clinical trials on the effectiveness of EPO on different ailments,including PMS among women, is needed for future studies.

Acknowledgement

We want to acknowledge Hemen Ved and IntelliMed Healthcare solutions for providing all the support for drafting the manuscript.

References

1 Yonkers KA, O'Brien PS, Eriksson E — Premenstrual syndrome. *Lancet* 2008; **371:** 1200.
2 Ekholm U-B — Premenstrual Syndrome: A Study of Change in Cyclicity, Severity and Sexuality.
3 Dutta A, Sharma A — Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in India: A systematic review and meta-analysis. *Heal Promot Perspect* 2021; **11:** 161.
4 Buddhabunyakan N, Kaewrudee S, Chongsomchai C — Premenstrual syndrome (PMS) among high school students. *Int J Womens Health* 2017; **9:** 501.
5 Dilbaz B, Aksan A — Premenstrual syndrome, a common but underrated entity: review of the clinical literature. *J Turkish Ger Gynecol Assoc* 2021; **22:** 139.
6 Management of Premenstrual Syndrome. *BJOG An Int J Obstet Gynaecol* 2017; **124:** e73–e105.
7 Kaewrudee S, Kietpeerakool C, Pattanittum P — Vitamin or mineral supplements for premenstrual syndrome. *Cochrane Database Syst Rev*; 2018. Epub ahead of print 18 January 2018. DOI: 10.1002/14651858.CD012933.
8 Mahboubi M — Evening Primrose (Oenothera biennis) Oil in Management of Female Ailments. *J Menopausal Med* 2019; **25:** 74.
9 Stonemetz D — A review of the clinical efficacy of evening primrose. *Holist Nurs Pract* 2008; **22:** 171-4.
10 Barrett ML— The handbook of clinically tested herbal remedies. 2004; 1435.
11 Vahdat M, Tahermanesh K, Mehdizadeh Kashi A — Evening Primrose Oil Effect on the Ease of Cervical Ripening and Dilatation Before Operative Hysteroscopy. *Thrita*; 4. Epub ahead of print 8 September 2015. DOI: 10.5812/THRITA.29876.
12 Hudson BJF — Evening primrose (Oenothera spp.) oil and seed. *J Am Oil Chem Soc 1984 613* 1984; **61:** 540-3.
13 Newall C, Anderson L, Phillipson J — *Herbal medicines. A guide for health-care professionals.*, https://www.cabdirect.org/cabdirect/abstract/19960305478 (1996, accessed 7 July 2022).
14 Horrobin DF, Manku MS — Premenstrual syndrome and premenstrual breast pain (cyclical mastalgia): disorders of essential fatty acid (EFA) metabolism. *Prostaglandins Leukot Essent Fatty Acids* 1989; **37:** 255-61.
15 Cerin A, Collins A, And BL — Hormonal and biochemical profiles of premenstrual syndrome: Treatment with essential fatty acids. *Acta Obstet Gynecol Scand* 1993; **72:** 337-43.
16 Sakip M, Akbarip S, Sakip M — The effect of primrose oil on the premenstrual syndrome among the female students in Lorestan University of Medical Sciences: A triple blind study. *J Nurs Midwifery Sci* 2015; **2015:** 20-6.
17 Watanabe S, Sakurada M, Tsuji H — Efficacy of ã-linolenic Acid for Treatment of Premenstrual Syndrome, as Assessed by a Prospective Daily Rating System. *J Oleo Sci* 2005; **54:** 217-24.
18 Puolakka J, Makarainen L, Viinikka L — Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. *J Reprod Med Obstet Gynecol* 1985; **30:** 149-153.
19 Rocha Filho EA, Lima JC, Pinho Neto JS — Essential fatty acids for premenstrual syndrome and their effect on prolactin

and total cholesterol levels: a randomized, double blind, placebo-controlled study. *Reprod Health* 2011; **8:** 2.

20 Asiri YA — The ABC Clinical Guide to Herbs. *Ann Saudi Med* 2004; **24:** 149.

21 Fan YY, Chapkin RS — Importance of dietary gamma-linolenic acid in human health and nutrition. *J Nutr* 1998; **128:** 1411-4.

22 Simon D, Eng PA, Borelli S — Gamma-Linolenic Acid Levels Correlate with Clinical Efficacy of Evening Primrose Oil in Patients with Atopic Dermatitis. *Adv Ther* 2014; **31:** 180.

23 medicine DH-TJ of reproductive, 1983 undefined. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. *europepmc.org*, https://europepmc.org/article/med/6350579 (accessed 7 July 2022).

24 Carroll BJ, Steiner M — The psychobiology of premenstrual dysphoria: The role of prolactin. *Psychoneuroendocrinology* 1978; **3:** 171-80.

25 Adni LLA, Norhayati MN, Rosli RRM — A Systematic Review and Meta-Analysis of the Efficacy of Evening Primrose Oil for Mastalgia Treatment. *Int J Environ Res Public Health*; 18. Epub ahead of print 2 June 2021. DOI: 10.3390/IJERPH18126295.

26 Budeiri D, Li Wan Po A, Dornan JC — Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials* 1996; **17:** 60-8.

27 De Souza MC, Walker AF — Premenstrual Syndrome. *Encycl Hum Nutr* 1998; 35–42.

28 Khoo SK, Munro C, Battistutta D. Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust* 1990; **153:** 189-92.

29 Hardy ML. Herbs of special interest to women. *J Am Pharm Assoc (Washington, DC 1996)*; 40. *Epub ahead of print* 2000. DOI: 10.1016/S1086-5802(16)31064-6.

30 Masoumi S.Z, Khalili A, Delforooz A — Comparison the effect of evening primrose oil and vitamin E on premenstrual syndrome. *Complement Med J Fac Nurs midwifery* 2017; **7:** 1931-43.

31 Watanabe S, Sakurada M, HT-J of oleo — Efficacy of ã-linolenic acid for treatment of premenstrual syndrome, as assessed by a prospective daily rating system. *jstage.jst.go.jp*, https://www.jstage.jst.go.jp/article/jos/54/4/54_4_217/_article/-char/ja/ (accessed 6 July 2022).

32 Sakip M, Akbarip S, Sakip M — The effect of primrose oil on the premenstrual syndrome among the female students in Lorestan University of Medical Sciences: A triple blind study. *J Nurs Midwifery Sci* 2015; **2:** 20-6.

33 Puolakka J, Makarainen L, Viinikka L — Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. *J Reprod Med* 1985; **30:** 149-53.

34 Kleijnen J. Evening primrose oil. *Br Med J* 1994; **309:** 824.

35 Collins A, Cerin Å, Coleman G — Essential fatty acids in the treatment of premenstrual syndrome. *Obstet Gynecol* 1993; **81:** 93-8.

36 Qureshi S, Sultan N — Topical nonsteroidal anti-inflammatory drugs versus oil of evening primrose in the treatment of mastalgia. *Surgeon* 2005; **3:** 7-10.

37 Brenner RR — Nutritional and hormonal factors influencing desaturation of essential fatty acids. *Prog Lipid Res* 1981; **20:** 41-7.