

The Role of Essential Fatty Acids and Prostaglandins in the Premenstrual Syndrome

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Many of the features of the premenstrual syndrome are similar to the effects produced by the injection of prolactin. Some women with the premenstrual syndrome have elevated prolactin levels, but in most the prolactin concentrations are normal. It is possible that women with the syndrome are abnormally sensitive to normal amounts of prolactin. There is evidence that prostaglandin E₁, derived from dietary essential fatty acids, is able to attenuate the biologic actions of prolactin and that in the absence of prostaglandin E₁ prolactin has exaggerated effects. Attempts were made, therefore, to treat women who had the premenstrual syndrome with gamma-linolenic acid, an essential fatty acid precursor of prostaglandin E₁. Gamma-linolenic acid is found in human, but not cows', milk and in evening primrose oil, the preparation used in these studies. Three double-blind, placebo-controlled studies, one large open study on women who had failed other kinds of therapy for the premenstrual syndrome and one large

open study on new patients all demonstrated that evening primrose oil is a highly effective treatment for the depression and irritability, the breast pain and tenderness, and the fluid retention associated with the premenstrual syndrome. Nutrients known to increase the conversion of essential fatty acids to prostaglandin E₁ include magnesium, pyridoxine, zinc, niacin and ascorbic acid. The clinical success obtained with some of these nutrients may in part relate to their effects on essential fatty acid metabolism.

Introduction

Twelve years ago, in the course of double-blind studies on the effects of prolactin on renal function, I received a number of injections of either ovine prolactin or placebo. After some of these injections I experienced fluid retention, irritability and depression. On breaking the code it was apparent that this response occurred only on my receiving the prolactin and not after the placebo.¹ The similarity between my experience and the features of the premenstrual syndrome (PMS) was striking, and I therefore proposed that elevated prolactin levels might be the key to understanding the syndrome.² My associates and I found some patients with very severe premenstrual syndrome who had prolactin levels that, although not substantially elevated, were definitely higher in the luteal phase than in the follicular phase of the menstrual cycle. Such individuals experienced a spectacular therapeutic response to treatment with the prolactin-suppressing drug bromocriptine.^{3,4} A number of other groups have shown that luteal phase prolactin levels may be modestly elevated in women with PMS and that such patients may respond to bromocriptine, especially as far as breast symptoms are concerned.⁵⁻¹¹

It is apparent that most women with PMS do not have elevated prolactin levels and that in those in whom a prolactin abnormality can be detected the elevation in concentration is almost invariably modest. It is therefore highly unlikely that an elevation of prolactin levels could be a general basis for PMS. However, the concentration of a hormone is only one determinant of hormone action: another is tissue sensitivity, with the same concentration of a hormone able to produce dramatically different effects in different situations. It seemed to me that women with PMS might have an abnormal sensitivity to prolactin, and my research group therefore embarked on a study of the cellular basis of prolactin action.

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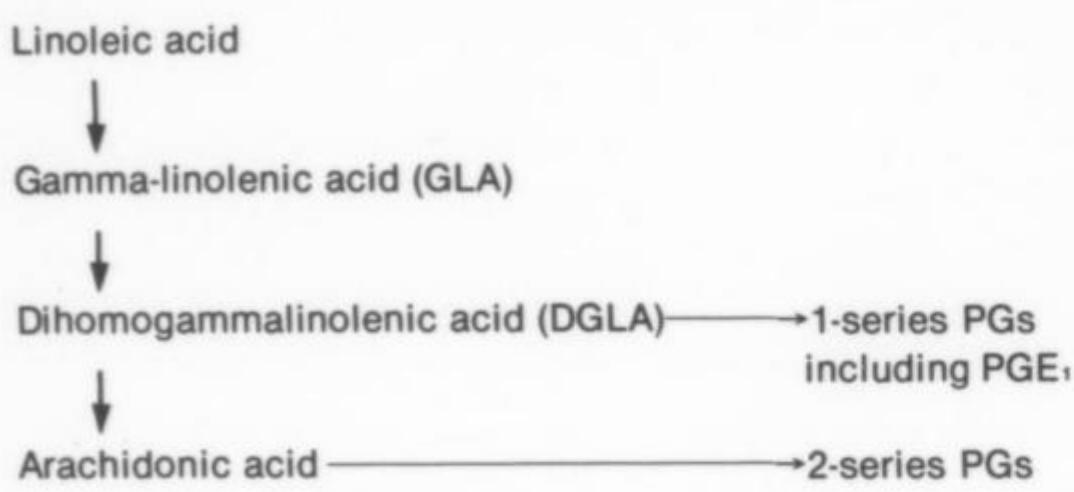


Figure 1
Outline of essential fatty acid metabolism.

We found that one of the effects of prolactin was to stimulate the formation of prostaglandin (PG) E₁ by mobilizing the PGE₁ precursor dihomogammalinolenic acid (DGLA).¹² This PGE₁ appeared, paradoxically, to be able to switch off some of the biologic effects of prolactin. PGE₁ thus appeared to be a form of fail-safe device that would prevent exaggerated biologic consequences of rising prolactin levels. This may account for the fact that many of the actions of prolactin show biphasic dose-response curves, in which an effect of prolactin becomes apparent at intermediate concentrations, only to disappear again at higher ones.¹³ A failure of this fail-safe device, due to inadequate formation of PGE₁, might lead to exaggerated consequences following even small rises in prolactin concentration.

We initiated studies to test the possibility that measures designed to raise endogenous PGE₁ formation would treat PMS by attenuating the biologic effects of prolactin. Three double-blind, placebo-controlled studies, one large open study in patients who had failed other forms of treatment and one large open study in new patients all demonstrated the effectiveness of this approach. Since both pyridoxine and magnesium enhance the conversion of dietary essential fatty acids to PGE₁, the successful use of these nutrients may in part relate to their effects on this aspect of biochemistry.

How Essential Fatty Acids and Prostaglandins Work

Both the essential fatty acids (EFAs) and the PGs were discovered in 1930, but it was not until the 1960s that it was realized that a major function of the EFAs was to give rise to the PGs. An outline of EFA and PG metabolism is shown in Figure 1. The well-known 2-series PGs are formed from arachidonic acid, while the lesser-known 1-series PGs are derived from DGLA. In rats and mice and probably in young humans the main EFA in the diet, linoleic acid, is rapidly converted through to arachidonic acid. In hu-

man adults the situation is very different: the delta-5-desaturase, which converts DGLA to arachidonic acid, seems to have very little activity.¹⁴ In adults, therefore, much of the arachidonic acid used for 2-series PG formation probably comes from dietary sources, notably meat and dairy products. There is little GLA or DGLA in the usual human diet, and DGLA for PGE₁ formation must therefore come from linoleic acid. There are problems in this pathway too, especially in the first step, the conversion of linoleic acid to gamma-linolenic acid (GLA) by the enzyme delta-6-desaturase.¹⁵ This step is highly susceptible to inhibition by a variety of factors. Ones particularly relevant to PMS are diets rich in saturated fats and processed vegetable oils, which contain trans fatty acids; alcohol; and catecholamines released from the adrenal medulla during stress. The enzyme requires zinc, magnesium and insulin to function normally, and a lack of any of these factors may lead to reduced delta-6-desaturase activity.^{15,16} Pyridoxine is a cofactor for the conversion of linoleic acid to DGLA, but it is not yet clear at which of the two steps it operates. Niacin, vitamin C and, again, zinc are all important in the conversion of DGLA to PGE₁.

DGLA and GLA are found in substantial amounts in human milk but not in cows' milk or other foods, suggesting that these EFAs may be of particular importance for human nutrition, especially in infancy, and for human breast function. The only form of GLA readily available for therapeutic use is evening primrose oil, the seed oil from *Oenothera biennis*. Seed oils from this plant have very wide ranges of GLA levels, but one with a consistent content of 9% has been employed in all our studies and is marketed under the trade name Efamol. The other main constituents of this oil are 72% linoleic acid and 12% oleic acid.

The 2-series PGs are familiar to those involved in menstrual cycle research because of their unequivocal involvement in the pains and cramps of dysmenorrhea. Reducing the conversion of arachidonic acid to 2-series PGs with nonsteroidal inflammatory drugs (NSAID) will consistently bring relief to sufferers from dysmenorrhea. In contrast, there is little evidence that the 2-series PGs play much of a part in PMS, and most women and physicians have been disappointed by their experience with NSAID. If the concept proposed here is correct, that a major problem in PMS is defective formation of PGE₁ from EFAs, then NSAID, which will also block PGE₁ production, may actually aggravate some features of PMS.

Clinical Trials of Essential Fatty Acids

The main strategy we have used in an attempt to raise the endogenous formation of PGE₁ is to administer its EFA precursor, GLA. There are so many factors that interfere with the conversion of linoleic acid to GLA, including stress and the typical Western diet, that administration of the usual polyunsaturated, linoleic acid, is likely to require very large doses and to lead to inconsistent results. The studies therefore were performed with Efamol as the source of GLA. Efamol is formulated in 0.5-gm capsules, each containing about 45 mg of GLA. Efamol is a nutritional supplement readily available in the United States, Canada and Europe.

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This study involved 68 women, all of whom had failed to respond to at least one other therapeutic regime and many of whom had failed two.¹⁷ There were therefore few placebo responders in this group, and the majority had severe PMS. Of these very difficult patients, 61% experienced total remission of all symptoms and a further 23%, a partial remission. The whole range of PMS symptoms, both physical and psychologic, responded to therapy. Side effects were minimal and not necessarily related to the Efamol: three patients complained of minor skin blemishes and three of feeling unduly placid. A graduated approach to dosage was used, starting with two 0.5-gm capsules twice per day in the luteal phase only and working up to four capsules twice per day for the whole cycle if there was no initial response. Some of the women in this study have now been treated for up to 18 months, with a sustained response to treatment but with a relapse if it is stopped. Thirty-six of the women experienced breast pain as part of the PMS syndrome. Twenty-six experienced total relief of pain, and five had partial relief; only five showed no improvement. Of nine women with fibrocystic breast disease, six experienced a reduction or disappearance of nodularity, and three showed no response.

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These two studies were identical in design and were organized by breast clinics to which patients were referred for cyclic breast symptoms and pain. The primary focus was therefore on the breast. The study was double blind and placebo controlled, with 42 pa-

tients entered in it. Physicians assessed breast nodularity and tenderness during the premenstrual period, while patients assessed breast pain, tenderness, nodularity and sensation of heaviness, general irritability and general well-being. Assessments were made on a simple scale, and, of course, neither the patients nor the physicians were aware of the treatment group to which the patients were assigned. Half the patients were given Efamol for three months and half, placebo. All eight assessments showed a more favorable response to Efamol than to placebo.^{18,19} The following differences between Efamol and placebo response were statistically significant: nodularity, physician's assessment, $p < 0.05$; nodularity, patient's assessment, $p < 0.05$; tenderness, physician's assessment, $p < 0.0025$; tenderness, patient's assessment, $p < 0.05$; well-being, $p < 0.05$; and irritability, $p < 0.05$. The dose of Efamol used in this study was eight 0.5-gm capsules per day. Again there were no substantial side effects, and no patients dropped out because of them. Some of these patients have continued to take Efamol for up to 18 months, with a continued response. In some there has been full remission of all objective and subjective features of fibrocystic breast disease.

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In this double-blind, placebo-controlled, crossover study the patients received either Efamol or placebo for two cycles and the other treatment for a further two cycles. All the major clinical features of premenstrual syndrome were scored. Most of these patients were new, and, as in any such group, there was a large placebo response. In spite of that there was a clear difference between Efamol and placebo, with an approximately 40% improvement in scores occurring with placebo and 60% with Efamol. There were particularly noteworthy differences in favor of Efamol in terms of irritability and depression.

Britannia Pharmaceuticals, Reigate, England

Most of the patients who reach gynecologists have rather severe PMS and may therefore not be representative of the total PMS population seen in family practice. In an unpublished study, Davies and Morse recruited women with PMS by advertising in the media. After careful scrutiny of menstrual cycle records, 196 women were accepted into the study. These women were then asked to score one cycle prior to treatment with Efamol and two cycles on Efamol. The Efamol was given at a relatively low dose of two

capsules morning and evening during the luteal phase of the cycle. Irritability, depression, headache, breast pain and tenderness, and ankle swelling were scored on a four-point scale. The results were analyzed by the Wilcoxon signed rank test. All five symptoms showed highly significant improvements ($p < 0.001$ in each case) from the initial cycle to the last one. Irritability improved in 77%, depression in 74%, breast pain and tenderness in 76%, headache in 71% and ankle swelling in 63%.

Results of the Studies

These studies, three of them double blind and placebo controlled, demonstrated that modest supplementation with EFAs in the form of evening primrose oil can have a substantial effect in improving PMS symptoms, even in those resistant to other forms of treatment. The effects on breast symptoms were particularly striking and included reversal of the features of benign breast disease. The Britannia study indicated that an exceptionally high response rate may be expected in a new population of patients.

These results are consistent with the hypothesis that a functional deficiency of EFAs, either due to inadequate linoleic acid intake or absorption or to failure of normal conversion of linoleic acid to GLA, leads to abnormal sensitivity to prolactin and the features of PMS. The studies do not, of course, prove that the hypothesis is valid. However, whether or not the hypothesis is correct, its testing has led to a highly effective and safe form of nutritional treatment, without the requirement for drug use or hormonal manipulation.

Other Nutritional Factors

Others have obtained substantial success in the treatment of PMS with pyridoxine¹¹ and with regimes in which magnesium is a major component. Abraham argues convincingly in this symposium that an abnormality of magnesium metabolism is important in PMS and provides convincing experimental evidence to support this view. The use of pyridoxine and magnesium (and also zinc, niacin and ascorbic acid) is fully compatible with the EFA approach since these five substances are important cofactors for the conversion of linoleic acid to PGE₁. In my experience the great majority of PMS patients, perhaps up to 95%, respond to a combined approach using Efamol and these other essential nutrients. No hormonal manipulation is required in these women. The residue of nonresponders probably have genuine abnormalities of hormone secretion of a variety of types that can be

identified by careful hormone assays performed throughout the cycle; these women usually respond to treatment directed at the specific hormonal abnormality.

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