

Differentiating Between Natural Progesterone and Synthetic Progestins. Clinical Implications for Premenstrual Syndrome and Perimenopause Management

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ORIGINAL ARTICLE

Critical differences between natural progesterone and synthetic progestins are often misunderstood. Synthetic progestins should not be used interchangeably with natural progesterone. This article describes their differences and the clinical implications for their use in managing premenstrual syndrome and perimenopause.

Despite a belated introduction in the United States, premenstrual syndrome (PMS) is now increasingly recognized as a distinct clinical entity. PMS was first described in British medical literature in the 1950s in a pivotal article by Raymond Green, MD, and Katharina Dalton, MD. Specific treatment of PMS emerged in the United States in the late 1970s when treatment protocols emphasizing both nutritional therapy and use of natural progesterone were implemented.

This article describes the differences between natural progesterone and synthetic progestins and the clinical implications for their use in the management of PMS and perimenopause.

WHAT IS PROGESTERONE?

Literally, progesterone means "for gestation"-it is the hormone of pregnancy. Produced by the ovaries, progesterone prepares the lining of the uterus for the fertilized ovum and maintains pregnancy. Specifically, progesterone converts the womb lining into a soft, spongy bed to enhance implantation of a fertilized egg. If implantation does not occur, the progesterone also affects the contractions of the fallopian tubes, thickens the consistency of vaginal mucus, and raises body temperature slightly as part of its role in promoting pregnancy.

WHAT IS NATURAL PROGESTERONE?

Progesterone was first isolated in 1934 by a number of researchers. A white or creamy white crystalline powder, progesterone is odorless, stable in air, and nearly insoluble in water. Today, natural progesterone is derived from extracts of yams or soybeans and is chemically identical to the hormone produced naturally by the body.

The term *natural progesterone* is often confused with synthetic progestins. Synthetic progestins are derivatives of progesterone used in such medica

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tions as oral contraceptives or Depo-Provera. They are the chemical analogues of the hormone naturally produced by the body (Figure 1). Although the differences in the chemical structure of natural progesterone and synthetic progestins are slight, their effects in the body are distinctly unmatched and these medications should not be used interchangeably.

Furthermore, so-called "wild yam creams" marketed over the counter contribute to the confusion. These creams are sometimes marketed as "progesterone precursors" or "balancing formulas," and patients are misled into believing that wild yam cream is converted into progesterone in their bodies. Some wild yam creams do contain natural progesterone—the manufacturer has added the prescription medication to the cream. Creams with less than 0.016% natural progesterone added can be marketed over the counter.

HOW THEIR ACTIONS DIFFER

Synthetic progestins can inhibit ovulation, thus suppressing the body's output of its own hormone, progesterone. When synthetic progestins were initially developed nearly 40 years ago, the differences between the synthetic progestins and the natural hormone were less clearly understood. The confusion persists today, although the distinction between progesterone and progestins is now well documented.

When produced by the body, progesterone is secreted by the corpus luteum. It passes from the ovary to the endometrium in increasing amounts, starting with ovulation and reaching a peak at approximately day 21 to 23 of the menstrual cycle. Progesterone levels then fall until menstruation occurs. Progesterone stimulates the endometrium; upon its withdrawal, endometrial bleeding occurs.

Although progesterone causes the formation of the secretory endometrium, the synthetic progestins cause an increased glandular response in the endometrium that leads to secretory exhaustion. This secretory exhaustion is a very useful clinical property in the treatment of both endometriosis and menorrhagia, but is contraindicated in PMS.

It is important to note that synthetic progestins lower the plasma concentration of progesterone. This was first described by Johansson¹ more than two decades ago, when he demonstrated a significantly decreased plasma level of progesterone in the postluteal phase in women treated with 30 mg medroxyprogesterone for 12 days. Further, it was shown that this property was dose-related; increasing the medroxyprogesterone to 60 mg/day caused further quantifiable decline in the blood levels of progesterone.

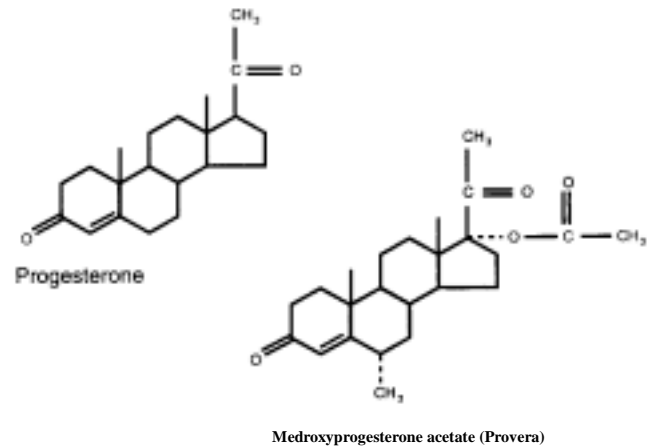


Figure 1.—Differences in the chemical structures of natural progesterone and synthetic progestogens.

The reasons for the differing actions of natural progesterone and synthetic progestins have been suggested by Dalton,² who theorized that the molecule of synthetic progesterone is so similar in shape to natural progesterone that the synthetic progestins bind to progesterone receptors in the endometrium. The synthetics may imitate the action of progesterone in the endometrium but do not bind precisely to progesterone receptor sites in the mid-brain. The competition for these receptor sites serves to decrease the body supply of the natural hormone.

There are other substantial differences between natural progesterone and synthetic progestins. The progestins, especially norethisterone, cause an increase in sodium and water retention. Further, progesterone is synthesized in the adrenal cortex into corticosteroids, whereas progestins cannot be synthesized into other corticosteroids in the adrenal cortex. Progesterone is mildly thermogenic, whereas most progestins are not.

CLINICAL IMPLICATIONS FOR PMS MANAGEMENT

The decline in blood levels of progesterone with the use of medroxyprogesterone is associated with an exacerbation of premenstrual symptomatology with increased depression, headaches, and water retention. Further studies by Johansson and other investigators demonstrated similar effects with other synthetic progestins, including norethisterone, dnorgestrel, and dydrogesterone.

In establishing patient history, physicians and psychotherapists should ask female patients if their premenstrual symptoms were related to the introduction of synthetic progestins. Many women report the

onset of premenstrual syndrome when starting or stopping oral contraceptives. For patients with PMS, the use of synthetic progestins may be inappropriate. The most frequent adverse symptoms experienced when taking synthetic progestins include depression, severe headaches, and weight gain.

Clinical experience also indicates that the routine use of synthetic progestins in hormone replacement therapy for perimenopause or menopause also needs to be reconsidered. If the perimenopausal patient is symptomatic in the premenstrual period, the synthetic progestins should be avoided and natural progesterone can be used alone or as an adjunct to estrogen therapy.

It is also important to note that women in the perimenopausal transition often report that premenstrual symptoms become notably more intense. This may be attributed to the decline in progesterone production by the ovaries, which may begin months or even years before ovarian estrogen output diminishes. Sulak³ describes the perimenopausal woman who may be deficient in progesterone only.

Synthetic progestins may also interfere with the therapeutic action of natural progesterone. It may be necessary for the patient to stop taking the synthetic progestin for 1 to 2 months before starting natural progesterone treatment for PMS.

CLINICAL OBSERVATIONS AT PMS MEDICAL GROUP

For nearly two decades, we have seen many cases of severe PMS precipitated by the use of synthetic progestins. We recommend, whenever possible, that the patient be withdrawn from the synthetic progestin for a minimum of 1 to 2 months before starting natural progesterone therapy for PMS. This allows the clinician to develop an appropriate symptom baseline, and often the patient will improve dramatically during this interval.

In patients younger than 30 years of age, we try to extend the washout period to 3 or more months. During this time we recommend a nutritional approach consisting of eating 6 small meals a day and avoiding simple sugars, caffeine, and alcohol.⁴ We also recommend regular exercise and a vitamin and mineral supplement in some cases.

In some cases, the effects of synthetic progestins tend to linger. We have seen prolonged symptomatology associated with the synthetics that has left the patient refractory to treatment for up to 6 months.

Our clinical experience demonstrates that PMS patients respond to treatment with natural progesterone—often in cases where other modalities, such as treatment with selective serotonin reuptake

TABLE 1

Progesterone Dosage Ranges

Form	Amount	Frequency
Oral micronized capsule	100 mg	2 to 4 times daily
"Even release" tablet	200-300 mg	2 times daily
Suppositories	200-400 mg	2 times daily
Suspension	200-400 mg	2 times daily
Cream, gel, or lotion	10-30 mg	2 times daily
Injection	50-100 mg	Daily or every other day

inhibitors, have failed. In severe cases, immediate intervention with natural progesterone may be in order. The circumstances that most commonly concern us are (1) the presence of suicidal ideation and a past history of suicidal behavior; (2) the possibility of extreme behavior, such as child abuse; and (3) potential impending job loss, marital separation, and/or divorce related to PMS. In these cases, we tend to institute natural progesterone treatment immediately, usually in doses far exceeding the average of 300 mg oral "even release tablets" or 3 cc twice daily of the rectal suspension. We continue to raise the progesterone as much as possible in an effort to overcome the lingering effects of the synthetic progestins on the receptor sites.

When immediate intervention is not necessary, dosage ranges are as listed in Table 1.

These dosage ranges are guidelines. A simple saliva hormone test, performed on day 21 of the menstrual cycle, gives an accurate reading of a woman's progesterone level and can be used as a baseline. Follow-up saliva testing in 30 days can be used to monitor the effectiveness of therapy and titrate dosages as necessary⁵.

Natural progesterone is generally prescribed to be taken during the second half of the menstrual cycle, from ovulation until menstruation begins. It can also be taken only during difficult menstrual cycles; some women do not need natural progesterone every month. In women whose symptomatology is mild, natural progesterone can be used for a few days before menstruation.

CONFUSION CONTINUES

Unfortunately, there is still controversy in the United States concerning the efficacy of natural progesterone in managing PMS. The controversy results from misunderstanding of the differences between

natural progesterone and synthetic progestins, a perceived lack of adequate double-blind studies substantiating the efficacy of natural progesterone, and studies purporting that natural progesterone is ineffective. In addition, difficulties associated with absorption of the vaginal and rectal forms of natural progesterone also contributed in the past to the skepticism surrounding this method of treatment for PMS. However, the development of an effective oral micronized form of natural progesterone has alleviated the absorption difficulty for many patients.⁶ Transdermal natural progesterone is also now available. Topical cream, lotion, or gel is easily absorbed and well-tolerated by most patients, and produces significant symptom relief.

BRAIN MAPPING SHOWS EFFECTS OF ORAL FORM

In a study of the use of the vaginal form of natural progesterone, Freeman et al⁷ contend that this method of treatment for PMS is no more effective than placebo. However, we applied the use of computerized images of the brain, or brain mapping, to document positive effects of oral micronized progesterone. Computerized electroencephalogram allows researchers to view brain activity, including alpha II rhythms and theta II rhythms and increased alpha activity in the brain, with decreased delta and theta activity that follows administration of oral micronized progesterone, can be associated with improved cognition, less depression, and improved mood.

Using well-established database norms gathered over the past decade, we demonstrated in a series of five patients that a 300-mg dose of oral micronized progesterone has an immediate alerting effect on the brain.⁸ This cerebral activating property would appear to confirm that the principal site of action of progesterone results in cerebral dysfunction associated with PMS, such as depression, irritability, and mood swings. This is entirely

consistent with the observed clinical results reported with the use of natural progesterone and would seem to refute the Freeman study. Recent research also suggests that brain response to hormonal fluctuations during the menstrual cycle is a significant variable in PMS symptoms.⁹

CONCLUSION

There is continued confusion regarding the significant differences of action of natural progesterone and synthetic progestins. For women **with PMS**, as well as some perimenopausal women, the use of synthetic progestins can exacerbate premenstrual symptoms. Natural progesterone, **particularly in the oral micronized form**, has been demonstrated to have positive clinical effects. CT

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