

Natural Progesterone: What Role in Women's Health Care?

Whether it's right for your patient depends on the specific setting

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Today's popular women's health literature is replete with suggestions for using natural hormones to prevent and treat a variety of health problems.¹⁻⁶ Natural progesterone is often promoted as an alternative to synthetic progestins for two reasons:

- ◆ It appears to have fewer side effects in many women.⁷
- ◆ It may have more benefit for lipid profile enhancement,⁸ osteoporosis prevention,⁹ and the treatment of menopausal symptoms,¹⁰ premenstrual syndrome (PMS),^{11,12} and endometriosis.¹³

A cultural move toward that which is "natural" and away from man-made chemicals is a current theme voiced by consumers of health care. Many women express the desire to take charge of their own health by eschewing mainstream medical treatment and prescription drugs, and by seeking help from so-called alternative health care providers who recommend nutrition, nutritional supplements, and lifestyle adjustments, as well as natural hormones in the form of creams and phytoestrogens in whole foods. In fact, it has been established that nearly one third of Americans seek care from alternative health care practitioners¹⁴—much of this care for women's health concerns.

Primary care clinicians are confronted daily with questions from patients regarding alternative ap-

ABSTRACT: Natural progesterone (which has a chemical structure identical to that of the hormone produced in humans) is essentially nontoxic, has few side effects, and is less expensive than synthetic progestins. It may be more effective than its synthetic counterparts in certain situations, such as postmenopausal HRT. Its use in other settings, such as osteoporosis prevention and treatment, shows promise. Data are unclear concerning its role in the premenstrual syndrome, affective disorders, menstrual-related allergy symptoms, and benign breast disease. Natural progesterone's various routes of administration allow clinicians to determine the most effective dose and delivery for each patient. (*Women Health Primary Care* 1998;1(8):671-687)

proaches to many women's health problems. This article will provide an overview of mainstream medical research about natural progesterone and its potential uses to help women with a variety of health issues. With such information, primary care clinicians may be better

equipped to answer patients' questions, and may more knowledgeably utilize natural progesterone in those circumstances where it may be appropriate or even preferable to synthetic gestational agents and other drugs.

TERMINOLOGY

First, a word of clarification. The term *natural* in the context of hormone discussions does not necessarily mean that the hormone in question is derived from a source in nature. The term refers to an agent that has a chemical structure identical to that of the hormone molecule produced in the human body. Conjugated estrogens, for example, contain hormones derived from a natural source—horse urine. However, conjugated equine estrogens have a chemical structure different from that of any of the estrogens produced in humans.

Conversely, micronized progesterone is manufactured in a laboratory from chemicals derived from plants (Mexican wild yams and soy), yet it has a molecular structure identical to that of the progesterone produced in humans. Throughout this paper, the term *progesterone* refers to the chemical substance made in humans, which is shown in Figure 1. Synthetic ana-

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logues of progesterone are often labeled *progestogens*, *progestins*, or *progestational agents*. Unfortunately, the medical literature and common usage often interchange these synthetic terms with the word *progesterone*—with much confusion.

Synthetic analogues of progesterone have been developed to make the hormone available orally and to produce longer lasting and more potent effects than would be available from progesterone itself. Most of these compounds were first developed for use as contraceptive agents. Many of them bind to receptors for glucocorticoids, androgens, and mineralocorticoids, as well as those for progesterone¹⁵—thus explaining the diverse side effects many women experience while taking progestins: acne, menstrual irregularities, migraines, striae, and weight gain. Emotional side effects can include depression, mood swings, and irritability.

Progestins commonly in use in American medicine include:

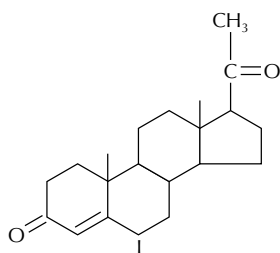
- ◆ Medroxyprogesterone acetate (MPA), which is used to manage dysfunctional uterine bleeding, as a contraceptive (in injectable form), and as an adjunct to postmenopausal hormone replacement therapy (HRT).
- ◆ Norethindrone (or norethisterone) and norethindrone acetate, which are common constituents of oral contraceptives.
- ◆ Megestrol acetate, which is used for cancer treatment.
- ◆ 17- α -hydroxyprogesterone caproate, which is used as a long-acting injectable progestin.
- ◆ Norgestrel, which is often combined with synthetic estrogens in oral contraceptives.¹⁵

The chemical structures of several common progestins are shown in Figure 2.

BIOSYNTHESIS AND BIOCHEMISTRY

Progesterone is manufactured in the corpus luteum of the human

Figure 1. Structure of progesterone



ovary through the conversion of pregnenolone to progesterone. The theca interna cells of the corpus luteum have all the enzymes necessary to convert cholesterol to estradiol, whereas the granulosa cells—which acquire a rich blood supply after ovulation and follicular rupture—convert pregnenolone to progesterone. Thus, a physiologic increase in progesterone occurs during the luteal phase of the menstrual cycle, probably stimulated by the luteinizing hormone (LH) surge at this time. It is thought that LH stimulates the uptake of acetate into the cholesterol molecule, which forms pregnenolone (Figure 3).

Progesterone is also synthesized by the placenta, mainly by hydroxylation of the low-density lipoprotein fraction of cholesterol to pregnenolone, then to progesterone.¹⁶ It is also found in the adrenals and even the uterus in many mammals, including humans. A substantial portion of progesterone is stored in adipose tissue.¹⁷

Plasma concentrations of progesterone in women vary with the menstrual cycle, with levels during the follicular phase being low, generally under 2 ng/mL. During the luteal phase, levels rise to 2 to 20 ng/mL in a surging pattern after ovulation (Figure 4). In the first trimester of pregnancy, blood levels are about 10 to 40 ng/mL, and they rise to 100 to 200 ng/mL near term. Progesterone levels also vary throughout the day; a decline in plasma levels of as much as 15% occurs 1 hour after a meal and in the early morning hours.¹⁶

Progesterone is a key precursor to the biosynthesis of cortisol and the C-18 and C-19 steroids, such as androstanedione, estrone, and estradiol¹⁷ (Figure 3). When progesterone circulates in blood, 90% is bound to an albumin fraction, but a specific binding protein has not been identified. Only 3% circulates unbound. Very little progesterone is present in erythrocytes.

Two thirds of circulating progesterone is metabolized by liver conjugation; there is substantial biliary excretion and reabsorption of its metabolites.¹⁷ Progesterone is excreted primarily by the kidney. Pregnanediol is one of the major specific urinary metabolites of progesterone; its measurement can be used as an index of endogenous progesterone secretion.¹⁵

Progesterone formation appears to be regulated by both the stimulatory and inhibitory effects of other steroids and neurochemicals. Stimulatory modulators include β -adrenergic signals, human chorionic gonadotropin, dehydroepiandrosterone (DHEA), and estrogens. Progesterone has been measured in the adrenal vein of postmenopausal women after corticotropin (ACTH) stimulation. Inhibitory signals come from DHEA-sulfate and androgens.¹⁶

PHYSIOLOGIC ACTIVITY

Progesterone serves many vital functions in the human organism. The hormone interacts both synergistically and antagonistically with estrogens; however, the ratios of the 2 hormones vary widely in different target organs. It is somewhat difficult, therefore, to indicate exactly what effect the various sex steroids have on tissues and organs, since they work together in an intricate relationship.

Reproductive system: It is generally known that progesterone promotes mucus formation in the vagina, participates in mammary gland development,¹⁷ and counter-

acts the breast epithelial cell proliferation stimulated by estrogen.¹⁸ One of its primary functions, of course, is to maintain the uterine lining to support the implantation of a fertilized ovum, as its name implies. Progesterone receptors in the uterus also decrease myometrial sensitivity to oxytocin stimulation. (The antiprogesterone drug, RU-486, negates this uterine quiescent effect in order to induce uterine contractions.¹⁶) Although the data are not entirely clear, it appears that progesterone may also have an effect on transport time of the ovum in the fallopian tube, and it may make the ovum more susceptible to sperm penetration.¹⁷ High levels of progesterone, as are seen in pregnancy, also contribute to suppression of ovulation.

In menstruating women, progesterone is necessary to effect secretory transformation of the endometrium and to produce appropriate withdrawal bleeding.¹⁹

Other systems: In addition to its effects on the reproductive system, progesterone appears to influence other aspects of human physiology. Exogenous administration of progesterone raises body temperature by about 0.3°C (0.5°F)¹⁷ in both men and women. This response seems to disappear after prolonged exposure to progesterone (such as in late pregnancy, when body temperature actually drops). Progesterone administered to rats appears to increase body weight, and it induces a catabolic and natriuretic effect in humans.¹⁷ Possibly because of its natriuretic effect, progesterone has some ability to lower blood pressure. Additionally, it has recently been used to stimulate respiratory drive in patients with the pickwickian syndrome.^{17,20}

In rats, progesterone appears to influence the differentiation and maturation of central nervous system functions that determine future sexual behavior, and it has a favorable effect on insulin utilization

and blood sugar levels.¹⁷ Some studies have found specific progesterone receptors in many areas of the brain, especially (in animals) the hypothalamus. High doses of progesterone can act as an anesthetic agent in humans, and they can lower the seizure threshold.¹¹

Few studies have been performed in humans on the possible effects of progesterone on the thyroid, adrenals, and skeletal system. However, some early work has sparked interest and is discussed further below.

TOXICITY

Rudel and Kincl,²¹ in their review of the international literature, noted that "Nowhere . . . is the oral toxicity of progesterone reported." They therefore undertook a study with rats, administering various doses of progesterone both orally (via gavage) and by subcutaneous injection for 26 weeks. Their only finding was an increase in the body and liver weights of female rats receiving parenteral progesterone.²¹

Not infrequently, women complain of drowsiness, headache, dizziness, or nausea just after ingesting an oral dose of micronized progesterone^{11,22} or transmucosal lozenges. Intravenous administration induces sleep at doses of 250 to 500 mg.¹¹ Synthetic progestins, on the other hand, often cause androgenic side effects (acne, body and facial hair), depression, and weight gain.

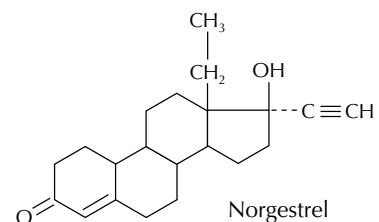
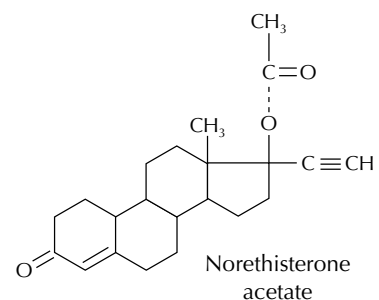
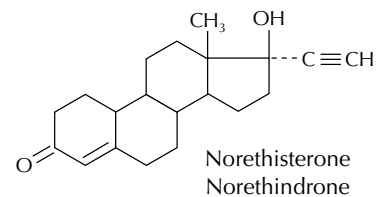
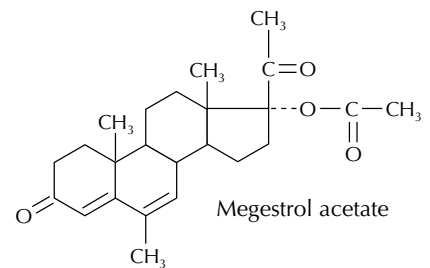
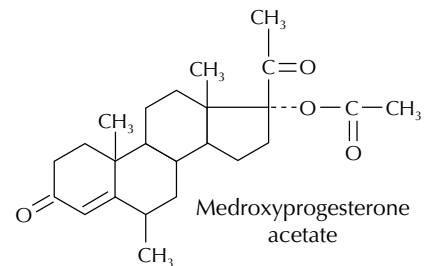
ADMINISTRATION

Progesterone can be administered through a variety of routes, including oral, transdermal, injection, vaginal, rectal, sublingual/buccal, and intrauterine (Table 1).

ORAL

Because oral progesterone is rapidly metabolized by first-pass effects in the liver, oral administration is essentially ineffective. But because of its potential efficacy for a variety

Figure 2. Structure of nonhuman progestins

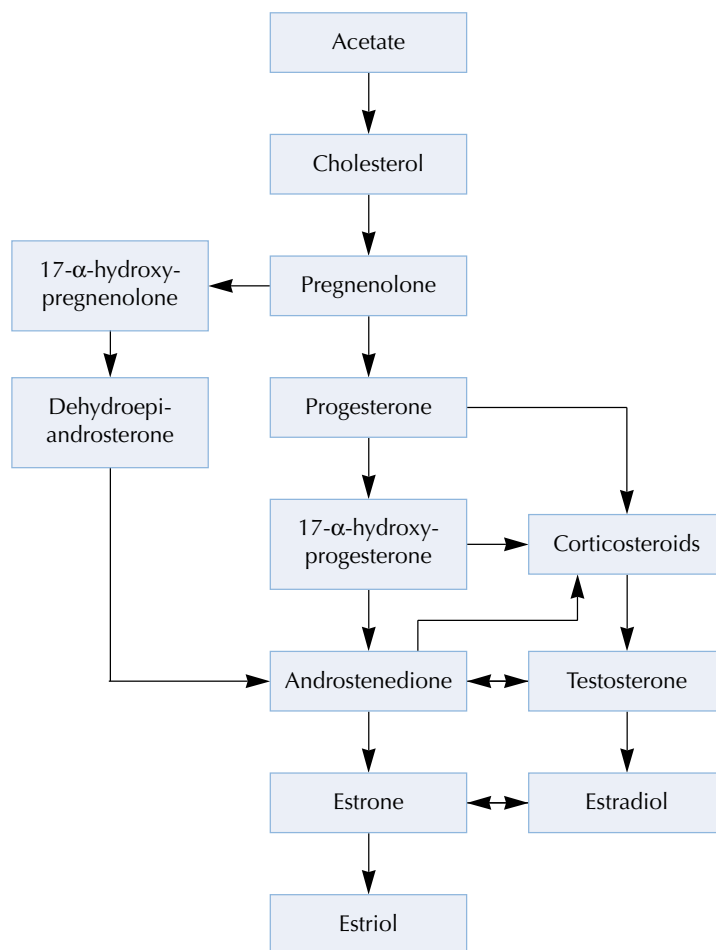


of disorders, synthetic versions were developed during the 40 years after the hormone's discovery in 1934. Micronized progesterone for oral administration became available in the 1980s, first by a French pharmaceutical company and later by an American firm.²³ The American manufacturer produces capsules of 100 mg of progesterone particles (with a mean diameter of 10 μm) suspended partly in oil and partly in solution. Studies have shown that when progesterone is given orally in this fashion, plasma levels peak at about 2 hours and decline to pretreatment levels at about 8 hours.²⁴

Physiologically, micronized progesterone (at a dose of 200 mg/d) has been demonstrated to cause endometrial atrophy in women who were receiving postmenopausal estrogen replacement therapy (ERT) for 21 days monthly, with the other hormone added for 10 days.²⁴ This is a most reassuring finding because estrogen-mediated endometrial cancer is a worrisome side effect of ERT. There is wide consensus that concomitant cyclic or continuous progestin therapy is needed for women with an intact uterus who are receiving ERT.^{25,26} The finding that micronized progesterone can produce this beneficial effect is necessary if we are to consider its use in postmenopausal HRT.

Micronized progesterone has other effects as well. For example, a wealth of evidence demonstrates that it is markedly better at elevat-

Figure 3. Biosynthetic pathway of steroid synthesis



ing high-density lipoprotein levels than are any of the progestins commonly used for HRT.^{8,24} In the Postmenopausal Estrogen/Progestin Interventions trial,⁸ high-density lipoprotein levels increased 3.5 times more in the group using micronized progesterone than in those receiving medroxyprogesterone acetate. Micronized progesterone appears to achieve this effect without producing any adverse effects on hemostasis, blood pressure, or levels of other lipids,²⁴ probably because it has virtually no androgenic side effects.

TRANSDERMAL

Drug delivery through the skin is a rapidly growing area in pharmaceutical development. Transdermal

delivery of steroids has been seen as a real breakthrough, given that patients may experience unacceptable side effects from oral medications. Estradiol, progesterone, and testosterone are good candidates for transdermal delivery because a relatively continuous release of each drug is desirable.²⁷

Progesterone can penetrate the skin but is rapidly metabolized by the 5- α -reductase enzyme, which converts it to 5- α -dihydroprogesterone, thereby lowering plasma progesterone levels. However, when the hormone is applied to the breast directly, high progesterone concentrations can be measured in mammary tissue.²⁸ The implications of this for the treatment of benign breast diseases are discussed below.

Transdermal patches of progesterone are not commercially available, but many progesterone cream preparations are available over the counter (marketed as cosmetics). Higher concentrations can be formulated by compounding pharmacies. Transdermal creams can contain quite variable amounts of progesterone and are not well standardized, as they are not supervised by the FDA. The most potent preparations available without a prescription contain 450 mg progesterone per ounce of cream. Compounding pharmacies can formulate concentrations of up to 900 mg/oz.

Obviously, standardized dosing is difficult in this nonregulated environment. The dosage typically recommended is $\frac{1}{4}$ to $\frac{1}{2}$ teaspoon of

the cream applied to the skin twice daily, but the amount of drug delivered to the patient will vary depending on the cream used.

INJECTION

Plasma levels of progesterone are most reliable and consistent when the hormone is given as an intramuscular injection of progesterone in oil.²⁹ It is rapidly absorbed, and a 100-mg injection produces plasma concentrations of 40 to 50 ng/mL in 2 to 8 hours.¹¹ Plasma progesterone levels remain elevated for up to 72 hours. (These data for the injection of natural progesterone in oil are in marked contrast to the long-acting physiologic effects of the injectable synthetic progestins that are used for contraception.) Although reliable, injectable progesterone is not practical for daily or frequent use.

VAGINAL

Some women find this administration route to be acceptable and convenient; others do not. Progesterone suppositories have been used for years as treatment for some types of infertility and in the management of habitual abortion.²² It was also recommended by clinics specializing in the treatment of PMS during the 1970s and 1980s.¹² (Current use of progesterone for this indication is discussed below.)

Vaginal suppositories of 100 mg progesterone produce a rapid increase in plasma progesterone levels, which peak within 4 hours between 9.5 and 19.0 ng/mL. Over the next 8 hours, there is a gradual fall in plasma levels.²⁹

It is often difficult to place the

suppositories high enough in the vagina; furthermore, they can liquefy at body temperature, resulting in vaginal discharge and vulvar residue. Also, suppositories have been shown to produce high plasma levels of progesterone when first used but declining levels with continued administration.³⁰ Some patients experience irritation, pruritus, vaginal discharge, monilial infections, or other bothersome side effects with vaginal preparations.¹¹

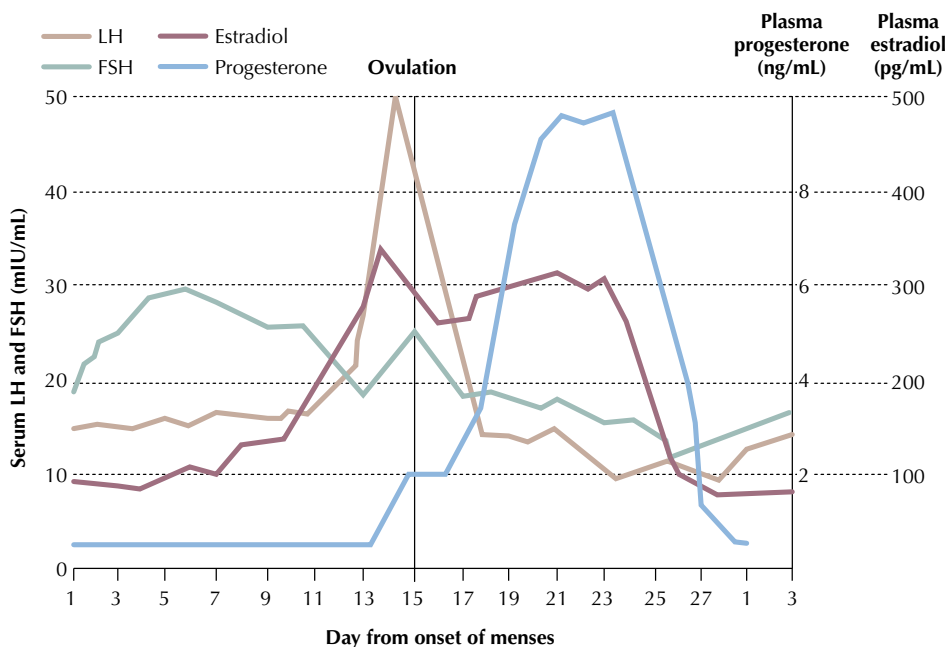
One method developed to overcome the problems with suppositories, and that results in rela-

levels,^{32,33} indicating a direct uterine effect of vaginal administration at doses resulting in lower plasma levels than intramuscular or other systemic routes of administration.

RECTAL

In order to avoid the vaginal symptoms some women experience, rectal preparations have been advocated by some clinicians. Rectal suppositories containing 100 mg progesterone in a variety of bases produce variable results on plasma hormone levels (range, 15.0 to 51.9 ng/mL).²⁹

Figure 4. Hormonal changes during the normal menstrual cycle



LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Adapted from Dalton K. *The Premenstrual Syndrome*. 1964.⁴⁴

tively reliable plasma levels, is a nonliquefying vaginal cream containing micronized progesterone.³¹ More recently, a sustained-release vaginal gel has been developed; this product contains 45 or 90 mg progesterone in 1.1 g of gel with a polycarophil base.³² Several studies of vaginal gels have shown that they prevent estrogen-induced endometrial stimulation, even with relatively low plasma progesterone

SUBLINGUAL/BUCCAL

A sublingual dose of 10-mg progesterone suspension produces a peak plasma level of 5 ng/mL 1 hour after application; return to baseline occurs 24 hours after administration. Transmucosal lozenges or troches may be compounded with natural hormones in a cyclodextrin base, which allows for easy solubility in water and does not enter or damage oral tissues.³⁴ Usual doses

of transmucosal troches are in the range of 50 to 200 mg twice daily to alleviate symptoms of PMS, and 100 to 200 mg twice daily for at least 10 days each month to counteract endometrial hyperplasia in menopausal women on ERT.

INTRAUTERINE

At this time, the only commercially available intrauterine device contains levonorgestrel, a synthetic progestin, which releases 20 µg of levonorgestrel per 24 hours for 5 years. Plasma levels of levonorgestrel achieved with this method are about 200 pg/mL.³⁵ It has been compared favorably with other forms of progesterone administration (vaginal gel and oral micronized progesterone) for postmenopausal HRT^{35,36} because it does not appear to cause as much vaginal bleeding as other methods do.³⁶

THERAPEUTIC USES

Progestational agents are currently used in a variety of clinical settings:

- ◆ Contraceptive pills and devices.
- ◆ Treatment of dysfunctional uterine bleeding, endometriosis, and PMS.

- ◆ Management of threatened habitual abortion and certain types of infertility.
- ◆ Postpartum lactation suppression.
- ◆ Postmenopausal HRT.
- ◆ Treatment of hypoventilation (in selected situations).
- ◆ Management of some types of breast, endometrial, and renal carcinomas.

I will not review all these indications here. Instead, I will focus on the question, “In which clinical situations is natural progesterone useful, or perhaps even preferable to a synthetic progestin?”

MENOPAUSAL HRT

As discussed above, there appears to be ample evidence that daily doses of 200 to 300 mg of micronized progesterone are as effective as standard progestins in protecting the endometrium from the stimulatory effects of estrogen.^{10,37} Furthermore, it appears that micronized progesterone is devoid of the androgenic effects on the lipid profile seen with MPA and other synthetic progestational agents; for that reason, it may be preferable in

HRT protocols for perimenopausal and postmenopausal women.^{8,10,37} Synthetic progestins also have a tendency to increase plasma glucose and decrease plasma insulin levels, whereas natural progesterone does not have these effects.³⁸

One limiting factor to more widespread use of micronized progesterone for HRT is its availability in the US medical marketplace. Most metropolitan areas have at least one compounding pharmacy that will make micronized progesterone capsules or transmucosal lozenges upon a physician's prescription. (Transmucosal lozenges may have certain advantages over the oral drug in terms of bioavailability and elimination of first-pass liver effects.) In addition, there are mail-order compounding pharmacies that will fill prescriptions for micronized progesterone and other progesterone compounds that may not be available in most retail and chain pharmacies.

Based on endometrial proliferation studies, the following combination methods appear to be safe and effective:

Table 1. Natural progesterone: routes of administration

Route	Dose (mg)	Plasma concentration (ng/mL)*	Time to peak (hr)	Availability	References
Oral—micronized	100	3.0 – 6.0	2	Most US pharmacies	10, 23, 24
	200	30.3 ± 7.0	0.8		
Transdermal	45	3.0	Not stated	Health food stores Mail-order companies Compounding pharmacies*	27, 28
Vaginal cream	300	19.2	3.2	Compounding pharmacies*	31
Vaginal gel	90	3.9	7	Most US pharmacies	32, 34
Vaginal suppository	100	9.5 – 19.0	4	Compounding pharmacies*	29, 30
	400	17.0 – 34.5	4		
Rectal suppository	100	15.0 – 51.9	4	Compounding pharmacies*	29
Intramuscular	100	40.0 – 50.0	2 – 8	Most US pharmacies	29
Sublingual/buccal	10	5.0	1	Compounding pharmacies*	35
For comparison, native serum progesterone levels are:				* Information about compounding pharmacies can be obtained from: The International Academy of Compounding Pharmacists (IACP), PO Box 1365, Sugar Land, TX 77487, (800) 927-4227	
< 1.4 ng/mL in the follicular phase					
2.5 – 28.0 ng/mL in the luteal phase					
17.0 – 146.0 ng/mL in midpregnancy					
< 0.7 ng/mL after menopause					

- ◆ Silicon vaginal ring (containing 2 mg micronized 17- β -estradiol) along with a 100-mg progesterone vaginal suppository inserted daily for 7 days each month.³⁵
- ◆ Estradiol (via a patch or in an oral micronized form) with either oral micronized progesterone (100 mg 2 or 3 times daily) or vaginal progesterone (25 to 50 mg/d) for 10 days each month.¹⁹

OSTEOPOROSIS

A fascinating area of research that does not seem to have reached the broad medical literature is progesterone's role as a bone-trophic hormone. On its own—without the influence of estrogen—progesterone could have a significant effect on the prevention and treatment of osteoporosis.^{9,39,40} Popular medical thought widely holds that it is estrogen that is needed to protect perimenopausal and postmenopausal women from the ravages of osteoporosis. In fact, medical consensus suggests that osteoporosis in women is a disease of estrogen deficiency.^{41,42}

However, before the onset of menopause, luteal levels of progesterone decline, whereas levels of estrogen, LH, follicle-stimulating hormone, and other reproductive hormones remain intact.⁴³ We know that bone loss begins in women well before menopause, while ovulation is still occurring and estrogen levels are essentially normal. These facts raise the question: Is it really estrogen loss that is responsible for bone loss, or is progesterone involved, perhaps even more so than estrogen?

The works of Lee^{4,39,40} and of Prior⁹ in the 1980s and 1990s have brought up for discussion, at the very least, the potential of natural progesterone (*not* progestins) as key to the prevention and treatment of osteoporosis. Lee³⁹ studied 100 postmenopausal women with height loss and followed 63 of them with dual photon absorptiometry

for 3 years. The patients were treated with transdermal progesterone cream, exercise, and dietary interventions, but no exogenous estrogen. Lee reported significant increases in bone density (averaging 15.4%) and showed that those with the lowest density at baseline experienced the greatest improvement during the 3 years.

Is it really estrogen loss that is responsible for bone loss, or is progesterone involved, perhaps even more so than estrogen?

There are a variety of ways by which progesterone can affect bone metabolism. For example, the hormone appears to stimulate new bone formation.³⁷ Urinary calcium excretion decreases during progesterone administration.

Progesterone also partially antagonizes dexamethasone-induced osteoblast growth inhibition, indicating that it binds to the glucocorticoid receptor in osteoblasts, and thus it may be especially useful in corticosteroid-induced osteoporosis.⁹ In addition, progesterone appears to increase levels of insulin-like growth factor-1, which promotes bone formation.³⁷

In premenopausal women, the mean length of the luteal phase (when endogenous progesterone levels are normally highest) correlates positively with the percentage annual change in vertebral mineral density. In other words, women with shorter luteal phases had more severe osteopenia than did those with longer luteal phases.⁹

When natural progesterone is used for osteoporosis prevention and/or treatment, a recommended regimen is twice-daily administration of $\frac{1}{4}$ to $\frac{1}{2}$ teaspoon of a progesterone cream that contains 20 mg progesterone per $\frac{1}{4}$ teaspoon.^{2,39}

The cream can be applied anywhere on the body. Usually, the “fleshy parts” (breasts, abdomen, thighs, upper arms) are recommended sites. At this time, there is no standardized dosage or delivery system that has been proved in repeated clinical trials to be effective for preventing or treating osteoporosis. Although there are no

studies to refute the assertion that progesterone has estrogen-independent effects on bone metabolism, more study on its effectiveness is certainly indicated.

PREMENSTRUAL SYNDROME

Use of natural progesterone for PMS was popularized in the 1960s after publication of Dalton's groundbreaking work, *The Premenstrual Syndrome*, in 1964.⁴⁴ In a subsequent book, this author specifically outlined the use of progesterone for PMS,¹² and she later produced further research to support natural progesterone's role in the treatment of PMS.⁴⁵ Dalton stated that “Progesterone is the treatment of choice for patients with severe symptoms which have resisted other forms of treatment, and for those who are at the end of their tether when first reporting for treatment.”¹² She also described PMS as an imbalance in the estrogen–progesterone axis; a relative deficiency of progesterone was held responsible for most of the symptoms women experience. Conversely, she stated that an imbalance in the direction of a relative estrogen deficiency gives rise to dysmenorrhea in many women.

In 1984, progesterone was the most widely recommended treat-

ment for PMS by US and Canadian physicians¹¹; however, clinical trials of progesterone for PMS have provided conflicting results.⁴⁶⁻⁴⁸ Some of these studies had methodologic flaws; others had a high placebo response rate. In all of them, the necessary reliance on subjective means to measure treatment success¹¹ complicates our ability to evaluate results. The only controlled trial that suggested progesterone's superiority over placebo was performed on a relatively small sample of women and used oral micronized progesterone (100 mg in the morning and 200 mg at night for 10 days during the luteal phase in 2 consecutive cycles).⁴⁹

Recently, the psychiatric world

has undertaken numerous studies of psychoactive agents for the management of premenstrual dysphoric disorder (also referred to as late luteal phase dysphoric disorder). In a review of studies designed to look at dysphorias specifically, Gold et al⁵⁰ painted a pessimistic picture of progesterone's effectiveness.

Despite the numerous studies that have been undertaken and the strongly held views of many clinicians and patients that progesterone significantly improves PMS symptoms, there is no convincing evidence yet to provide a strong basis for this treatment approach, nor are there any long-term studies of its safety. Also, the FDA has not approved the use of natural progesterone in the management of PMS.

On the other hand, the use of natural progesterone is relatively benign, and it may be of use for some patients suffering from PMS. Whitaker² recommends progesterone cream (20 mg per ¼ teaspoon) applied transdermally as follows:

- ◆ ¼ teaspoon twice daily on days 15 through 23 of the menstrual cycle.
- ◆ ½ teaspoon twice daily on days 24 through 1.

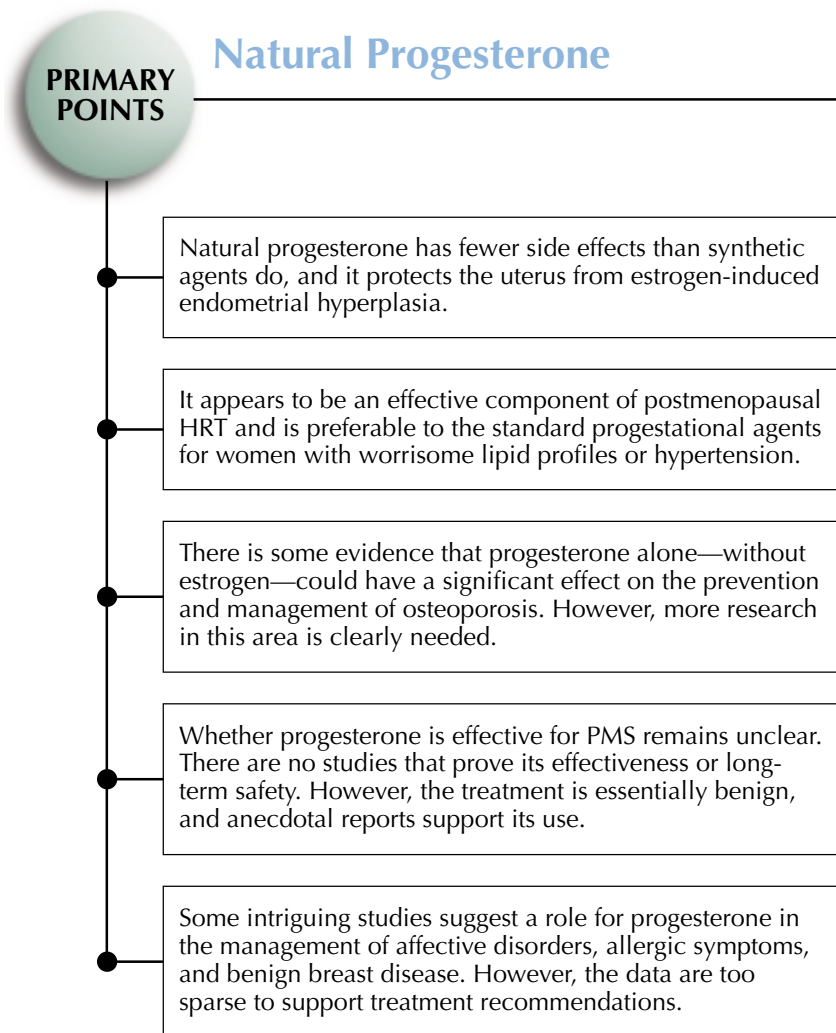
AFFECTIVE DISORDERS

There has also been some interest in the use of sex steroids in the management of various affective disorders. One study showed decreased pregnenolone levels in cerebrospinal fluid of depressed patients, although progesterone levels remained normal.⁵¹ Although this observation is of interest, there is too little research available to date to comment on the use of natural hormones to treat affective disorders. The 1998 *Physicians' Desk Reference* indicates that medroxyprogesterone acetate should be used cautiously in patients with a history of depression; if the depression recurs or worsens, the progestin should be stopped.⁵²

MENSTRUAL-RELATED ALLERGY SYMPTOMS

Only a small number of studies have addressed the use of progesterone desensitization for the treatment of menstrual-related allergy symptoms, such as asthma, allergic rhinitis, headache, urticaria, and vertigo. One study, published in 1974, showed promising results; it used progressively more dilute concentrations of an aqueous progesterone suspension (injected intradermally) to desensitize patients to progesterone and alleviate overt allergy symptoms.⁵³ This technique sounds much like a homeopathic approach and it is not well explained, but nonetheless is a potential area for further research.

A second study, published in



1982, attempted a similar experiment using progressively dilute aqueous progesterone injections to alleviate symptoms felt to be progesterone-related: dysmenorrhea and PMS.⁵⁴ It reported rapid clearing of symptoms. Another study published in 1988 evaluated the effect of intramuscular progesterone on peak flow and the need for corticosteroids in 3 patients with severe premenstrual asthma exacerbations. All 3 had marked improvements with progesterone therapy.⁵⁵

Although these studies are interesting, it appears that little further work has been done in regard to the connection between allergy-immunology and the endocrine system—clearly a field ripe for more research.

BREAST DISEASE

There has been some work published examining the potential relief of mastodynia (breast pain and tenderness) during the premenstrual period using direct application of progesterone cream on the breast tissue.^{12,26,56} In addition, nodularity disappeared in 10% of breasts. Mastodynia is likely an effect of estrogen on breast tissue; estrogen's ability to cause edema can be counteracted by progesterone.

Chang et al¹⁸ noted that progesterone gel applied topically to breast tissue significantly decreased the number of cycling epithelial cells. No studies have compared topical to oral or other routes of progesterone delivery.

With regard to the potential effect of progesterone on breast cancer, an interesting 1981 study⁵⁷ indicated that breast cancer incidence was more than 5 times higher in women with premenopausal progesterone deficiency than in age-matched infertile patients without progesterone deficiency. However, it is not yet known whether progesterone administration can lower the breast cancer risk.

SUMMARY

Natural progesterone appears to be an effective component of postmenopausal HRT and is preferable to standard progestational agents for women with worrisome lipid profiles or hypertension. Natural progesterone has fewer side effects than synthetic agents have, and it protects the uterus from estrogen-induced endometrial hyperplasia. Given the potential toxicities of exogenous estrogen, it is reasonable to speculate whether progesterone, together with a healthy lifestyle, could provide the cardioprotective effects we want for our patients.

As for osteoporosis prevention and treatment, there are certainly some promising data regarding the beneficial effect of natural progesterone on bone formation, particularly in corticosteroid-induced osteoporosis. We need more research on its effects, but if results are positive, there may come a day when women take natural progesterone, follow a healthy diet, exercise—and perhaps avoid exogenous estrogen entirely.

In PMS, the data are confusing. We need more information on the proper route of administration, dosage, and patient selection before we can determine the appropriate role of natural progesterone. More research is also necessary concerning the use of natural progesterone for affective disorders or allergic symptoms. Topical application of progesterone for benign breast disease appears promising, but again, there are insufficient data to clearly know its benefit.

We need more good studies that look critically at the questions raised by existing research. Use of natural progesterone has appeal—it is essentially nontoxic, has few side effects, and is less expensive than synthetic progestins. Perhaps with renewed emphasis on women's health issues, the National Institutes of Health will make more funding available for this needed

research. Unfortunately, since natural progesterone cannot be patented, we are not likely to see much corporate support for this type of research (except for studies investigating patentable delivery systems). We need to know effective doses and routes of administration to manage a variety of women's health problems in this arena, as in many others related to "alternative" and "natural" medicine. ❧

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