Natural Progesterone References


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**Clinical Study Abstracts Evaluating the Benefits and Efficacy of Human-Identical Progesterone**

**Progestosterone and Relief of Menopausal Symptoms**


This randomized, controlled study involving 58 postmenopausal women demonstrated that topically applied progesterone cream (Pro-Gest) had an antiproliferative effect in postmenopausal women who had been given oral estrogens x 14 days prior to progesterone treatment. Treatment with topical progesterone did not differ in effects from vaginally applied progesterone (Crinone), and both progesterone applications demonstrated a significant effect over placebo. Patients preferred the topical application of progesterone cream.

In this study of 35 postmenopausal women, twice-weekly administration of a progesterone vaginal gel (45 mg P4/day) sufficiently protected the endometrium in women receiving transdermal estradiol (0.05 mg/d) as revealed by endometrial thickness and histology. The authors present vaginally applied progesterone as a viable option for hormone replacement therapy at menopause.


This randomized controlled study investigated the effects of acute progesterone administration (25, 50, 100 mg, intramuscularly, 1 dose/wk) on mood. Contrary to the investigators' expectations, very few unwanted behavioral effects were noted, and only in the highest dose (100 mg) did women slightly increase their self-rating of sluggishness?


A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of switching progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women already using hormone replacement therapy (HRT). One hundred seventy-six women who were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1-6 months and had previously received HRT containing MPA were surveyed to assess QOL. Women using micronized progestrone-containing HRT experienced significant improvement in vasomotor symptoms, anxiety, somatic complaints and depressive symptoms. Women reported improved control of menopausal symptoms and perceptions of their vaginal bleeding patterns while on the micronized progesterone-containing regimen. Approximately 80% of women reported satisfaction with the progesterone-containing therapy. A micronized progesterone-containing HRT therapy offers the potential for improved QOL with respect to menopausal symptoms.


Fifteen menopausal subjects were studied to determine the efficacy and safety of hormone replacement therapy with micronized estradiol (E2) and progesterone. Ten subjects were given 0.7-E2 (1.05 mg daily) and progesterone (200-300 mg daily) and evaluated over one year at month 0, 1, 3, 6 and 12. Five subjects were administered conjugated estrogens (0.625mg daily) and medroxyprogesterone acetate (10 mg daily) and evaluated at the same intervals. Results showed all 10 women on E2 and progesterone had a decrease in total cholesterol with an increase in HDLs and sustained amenorrhea with no endometrial hyperplasia or withdrawal bleeding after six months of observation. Four of five women in the conjugated estrogen group continued to have withdrawal bleeding without endometrial hyperplasia. HDLs also increased in this group but no significant change in total cholesterol was found.


In this randomized controlled trial, 102 menopausal women were treated with topical progesterone (Pro-Gest?, 20 mg daily) or placebo and monitored for 1 year. Improvement in vasomotor symptoms was seen in 83% of the women in the treatment group who had experienced hot flashes, compared to 19% in the placebo group (p< .001). There was no difference noted in bone mineral densities between groups after one year. All women studied received a daily multivitamin and 1200 mg calcium.


20 women completed a 1 year randomized, controlled, cross-over study comparing conjugated equine estrogen (Premarin, 0.625 mg) paired with progesterone cream (Pro-Gest, 20 mg) vs conjugated equine estrogen paired with medroxyprogesterone acetate (Prempro). Endometrial biopsies were performed at the end of each 6 month arm of the study. No hyperplasia was found in either group. Incidence of spotting was similar in both groups. Participants preferred the progesterone cream composition (76% vs 5%, p<0.001).

This randomized clinical trial compared the effects of conjugated equine estrogen (CEE) and medroxyprogesterone acetate to CEE and oral micronized progesterone. Twenty-one postmenopausal women were studied in a sleep lab, with results demonstrating an improvement in subjective measures of menopausal symptoms and sleep in both groups. The group receiving natural progesterone had significantly improved sleep efficiency, whereas the medroxyprogesterone acetate group did not, suggesting that the former might better improve sleep in postmenopausal women.


This prospective, multicentre, randomized, parallel-group study enrolled 182 postmenopausal women 45 to 65 years of age and evaluated the quality of life and menopausal symptoms associated with the use of medroxyprogesterone acetate vs oral micronized progesterone when used as a part of a regular hormone replacement therapy. Menopausal symptoms improved in both groups from baseline to 9 months, as did QOL measures. In addition, patients using micronized progesterone had specific improvements in the areas of cognition and menstrual problems whereas the patients using MPA did not. Micronized progesterone was seen as an effective, cost-comparable alternative to MPA as well as being better tolerated.

**Progestosterone Delivery Systems- Transdermal/Topical vs. Oral vs. Vaginal**


This randomized prospective study evaluated and compared the effects of ten days treatment with oral and vaginal progesterone (MP) and medroxyprogesterone acetate (MPA) on glucose metabolism, lipid profiles, and hormonal parameters in 28 patients with polycystic ovary syndrome (PCOS). Oral MPA and oral MP decreased LH (P = 0.028, P = 0.009, respectively) and total testosterone (P = 0.013, P = 0.037, respectively) levels. There was no change in hormonal parameters with vaginal MP. Basal insulin decreased (P = 0.021) and insulin sensitivity increased significantly in the oral MPA group. Low density lipoprotein cholesterol (LDL) and lipoprotein (a) levels decreased only in the MPA group. This study concluded that MPA and oral MP may reduce insulin sensitivity in patients with PCOS. Vaginal MP had no effect on glucose metabolism and lipid profiles.


This pilot study demonstrated a significant increase in serum progesterone levels in 6 women receiving topical progesterone cream (Pro-Gest; 30-60 mg P4/day) and 17beta estradiol (0.05mg patch). The absorption of progesterone via a topical cream correlated well with estrogen absorption (p< 0.001). They concluded that progesterone cream appeared to be a safe and effective route of application.


Twenty estrogen-deprived women were given oral estrogen for 12 days followed by oral estrogen- vaginal progesterone gel for 12 days. Endometrial evaluation occurred before treatment, after the estrogen-only phase and after estrogen-progesterone gel treatment. Atrophy was present before treatment in all patients. Typical proliferative changes occurred after estrogen-only treatment, and secretory transformation occurred after estrogen-progesterone treatment, indicating that sustained-release progesterone gel can effectively counteract the proliferative effects of estrogen treatment in postmenopausal women.
Three different doses of transvaginal progesterone gel were administered to 40 estrogen-deprived women aged 25-41 years. Estradiol was administered orally for 28 days, with progesterone added vaginally on alternate days from days 15-27. Plasma gonadotropins, E1, E2 and progesterone were measured, and an endometrial biopsy was obtained to assess endometrial status and estrogen and progesterone receptor determinations. Transvaginal progesterone induced normal secretory transformation despite low serum progesterone levels, suggesting a direct transit of progesterone into the uterus, or ?first uterine pass effect.?


This small sample study shows that significant serum progesterone levels can be achieved by oral administration of progesterone. Efficacy of absorption is improved using micronization in oil formulations.


The pharmacokinetics are compared between orally administered micronized progesterone, and that administered through a vaginal cream. Oral progesterone is extensively metabolized prior to reaching the target tissues, and progesterone metabolites may comprise a significant amount of progesterone measured in the serum. When compared, vaginal application sustained progesterone levels over a longer period of time than orally administered progesterone.


Twenty-four women participated in this randomized controlled, crossover study comparing the bioavailability and pharmacokinetics of a vaginal progesterone capsule (200 mg/dose) vs a progesterone vaginal gel (90 mg/dose). Both were well tolerated, and no differences were noted with respect to safety. The vaginal capsule delivered more progesterone, however peak concentrations between the two preparations didn’t differ.


Plasma levels of progesterone equivalent to normal luteal phase levels were obtained using 25 mg of injected progesterone or 100 mg via rectal or vaginal administration at 8 hours after administration.


Absorption of progesterone as provided in a topical preparation of ?natural? progesterone cream to 6 premenopausal and 6 postmenopausal women was demonstrated via salivary hormone levels. Salivary progesterone concentrations reached their peak 1-4 hrs after application. A five-fold increase in mean levels was seen in the premenopausal group. Serum progesterone levels were not significantly different from baseline in either group, and serum progesterone was not seen as an effective measure of absorption of topically applied progesterone.


90 mg of vaginal estrogen gel daily was compared to 300 mg oral progesterone daily in a randomized open-label trial of 283 IVF patients. Delivery rates, safety parameters, frequency of spontaneous abortion, ratio of newborn babies to embryo transfer were nearly identical for both groups. The oral progesterone group reported more drowsiness.

Following topical application of a commercially-available progesterone cream, concentrations of fat and water-soluble metabolites of progesterone were measured in various tissues (uterus, kidney, salivary gland, liver) as well as plasma and urine. The topically applied progesterone was demonstrated to be well absorbed and had distribution and metabolism patterns similar to that seen with intravascular progesterone delivery.


This paper discusses the use of micronized progesterone as a safe, effective, and well-tolerated therapy and reviews indications for use. It also includes case studies and issues of patient compliance and the need for an individualized treatment plan for women receiving hormone therapy.


Sixteen estrogen-deficient women were evaluated on a course of transdermal estradiol and transdermal progestogen for five cycles. Regular withdrawal bleeding was noted in all but one patient. Fourteen endometrial biopsies were performed after the fifth cycle, with no evidence of endometrial hyperplasia.

**Progesterone and Cancer**


1,083 infertile women were followed for 14-34 years. Those who were deficient in progesterone showed a fivefold greater incidence of premenopausal breast cancer.


This in vitro study demonstrated that progesterone acts through progesterone receptor B to inhibit endometrial cancer cell invasiveness via the down-regulation of adhesion molecules.


This review emphasizes progesterone’s role in supporting healthy breast homeostasis and opposing the proliferative effects of estradiol in the breast, unlike synthetic progestins.


This study explored the mechanism by which progesterone inhibits breast cancer cell proliferation (growth). In progesterone receptor positive T47-D breast cancer cells, the mechanism of apoptosis appeared to be through the regulation of the genes p53 and bcl-2 by progesterone. These genes control the apoptotic process. It was demonstrated that at progesterone levels that approximate the third trimester of pregnancy, there was a strong antiproliferative effect in at least 2 breast cancer cell lines.

In this study, researchers demonstrated that progesterone administration suppressed cell proliferation and induced apoptosis (programmed cell death) in malignant mesothelioma cells (21). This is consistent with an earlier in vitro study that found administered progesterone induced apoptosis in the breast cancer cell line, T47-D.


In this in vitro study, researchers demonstrated that administered progesterone had a dose-dependent effect causing inhibition of growth of epithelial ovarian cancer cells, suggesting an anti-cancer effect.

Lin VC, Ng EH, Aw SE, Tan MG, Ng EH, Chan VS, Ho GH. Progestins inhibit the growth of MDA-MB-231 cells transfected with progesterone receptor complementary DNA. Clin Cancer Res 1999 Feb;5(2):395-403.

Progesterone is mainly thought to exert its effects via the estrogen-dependent progesterone receptor (PR), the effects of which may be overshadowed by the presence of estrogen. In order to study the independent effects of progesterone on breast cancer cell lines, PR expression vectors were transfected into a PR and ER negative cell line (MDA-MB-231). The growth of these cells was then studied in response to progesterone and several progestins. Progesterone was found to significantly inhibit DNA synthesis and cell growth in a dose-dependent fashion. The results of this study indicate that progesterone and progestins independent of estrogen have an antiproliferative effect on breast cancer cells via the progesterone receptor. This suggests a possible role in the treatment of PR negative breast cancer via re-activation of the PR receptor.


In a culture system, progesterone was found to have an inhibitory effect on breast cell growth. When given following estradiol (E2), it limited the stimulatory effect of E2 on cell growth.


Higher blood levels of progesterone measured during surgical treatment of breast cancers were associated with significantly better survival, especially in women who were node-positive (P<0.01). There was no significant relationship between E2 levels and survival. This study demonstrated that a higher level of progesterone at time of excision is associated with improved prognosis in women with operable breast cancer.


This study evaluated the use of a progesterone-releasing IUD as a feasible treatment for early stage endometrial cancer (IA, grade 1). Twelve subjects were followed for 36 months. Results suggested IUD progesterone appeared to resolve some cases of early endometrial cancer.


This review article outlines the many functions of progestogens in hormone-dependent and independent breast cancer and suggests new clinical applications their use in the treatment of breast cancer.


This cohort study followed 1150 premenopausal French women diagnosed with benign breast disease. Topical progesterone cream, a common treatment for mastalgia in Europe, had been prescribed to 58% of the women. Follow-up accumulated
12,462 person-years. There was no association noted between progesterone cream use and breast cancer risk. Furthermore, women who had used both progesterone cream and an oral progestogen had a significant decrease in breast cancer risk (RR= 0.5) as compared to women who did not use progesterone cream. There was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users. These results suggest there are no deleterious effects caused by percutaneous progesterone use in women with benign breast disease.


The anti-proliferative effects of three different progestins were compared using 3 human uterine cervix cell lines. In one cell line (C-41) devoid of progesterone receptors (PR) all progestagens studied inhibited growth in the following potency - progesterone (56%) > medroxyprogesterone (38%) > megestrol acetate (25%). Sensitivity demonstrated the same order, with progesterone being the most sensitive to inhibiting growth. This suggests there is a non-genomic action of progestagens that is anti-proliferative. The progestins studied also had anti-proliferative effects on the cell lines exhibiting PR.

**Progestosterone and Cardiovascular System**


This 12 month prospective, open, non-comparative study measured the effects progesterone (oral micronized 100mg/day) paired with 0.625 mg conjugated equine estrogens (CEE) and found progesterone had no adverse effects on the lipid profile when combined with CEE. This lack of effect differs from other studies that noted adverse effects on lipid profiles when synthetic progestins were utilized with CEE.


In vitro, progesterone was shown to have antiproliferative effects on vascular smooth muscle after proliferation was induced by models simulating hyperinsulinemia and hyperglycemia. Progesterone may, therefore, have a protective role against the atherosclerotic changes seen with diabetes (type II).


This study evaluated the effects of estradiol and progesterone on cholesteryl ester(CE) formation. Progesterone blocked CE formation, while estradiol had no effect. In comparison, cortisol and prednisolone (a widely prescribed glucocorticoid) both increased CE formation from 2-fold to 5-fold. This study demonstrated a role for progesterone in the decrease of cardiovascular risk factors that was not mediated by the progesterone receptor.


Premenopausal women have a lower mortality from atherosclerotic cardiovascular disease than age-matched men. Progesterone receptors have been found in human and rat aortic smooth muscle cells in vivo and in vitro. This study examined the effect of progesterone on the proliferation of vascular smooth muscle cells. At physiologic levels, progesterone dose-dependently inhibited DNA synthesis and proliferation. RU486, a progesterone antagonist, blocked inhibition. This inhibition of arterial smooth muscle suggests a protective effect of progesterone against atherosclerosis.

This randomized controlled study evaluated the effects of norethisterone (NET) and micronized progesterone (MP) on bleeding disorders in pre-menopausal women. 80 patients were randomized to the trial and all were found via endometrial morphology to need progestogen therapy. They were subsequently treated with NET or MP. In both treatment groups, hyperplastic changes disappeared during the first three cycles, with the duration of treatment being 6 months. NET decreased follicle-stimulating hormone, luteinizing hormone, oestradiol and sex-hormone-binding globulin levels (P < 0.001) whereas no changes were seen during MP treatment. High-density-lipoprotein cholesterol and triglyceride levels were also lowered by NET (P< 0.001-0.02) slightly decreased phospholipids. MP treatment had no effect on lipid profiles suggesting it may be a preferred progestogen for the treatment of bleeding disorders.


Progesterone increased red blood cell membrane fluidity in this in vitro study, in part by a nitric oxide-dependent mechanism. It has been demonstrated that progesterone may play various roles in the regulation of blood pressure and other cardiovascular activities. The findings of this study suggest a positive role for progesterone in the improvement of microcirculation in humans.

**Progesterone and Quality of Life**


This paper reviews the effects of progesterone on the brain, with special focus on its role in the formation of the myelin sheath surrounding nerve fibers. Other roles of progesterone in the brain include activating GABA receptors, which induces a calming effect.


This 3 month, multicentre randomized study evaluated the psychological side effects of a vaginally applied progesterone gel in reproductive aged women treated for hypothalamic amenorrhea or premature ovarian failure. No differences were noted in psychometric measures as evaluated by the Hopkins Symptom Checklist. Natural progesterone in a vaginal gel can be an effective treatment for women requiring hormone therapy.


In this unique randomized controlled study, administration of progesterone (200 mg oral) demonstrated a decrease in craving for and subjective effects of cigarette smoking in female smokers. With progesterone treatment, there was a noted trend to decrease smoking.

**Progesterone - General**


The effect of transdermal estradiol (1.5 mg), transdermal progesterone (25 mg), and combined transdermal estradiol and progesterone (1.5 mg and 25 mg) on human breast epithelial cell cycles was evaluated in vivo. Results demonstrated that estradiol significantly increases cell proliferation, while progesterone significantly decreases cell replication below that observed with placebo. Transdermal progesterone was also shown to reduce estradiol-induced proliferation.

This study investigated the anti-inflammatory effect of injecting progesterone into an arthritic joint. For a month following the injection, 10 out of 12 patients diagnosed with rheumatoid arthritis demonstrated a significant decline in local, but not systemic, joint inflammation. A continued reduction of inflammation was noted in 5 out of 12 patients. During the 2 months following treatment, no important side effects were detected.


This study compares educational attainments of 34 children whose mothers received prenatal progesterone with 37 normal and 12 toxemic controls. Results at ages 17-24 showed that progesterone children were more likely to continue schooling after 16 years, a higher number left school with ?O? and ?A? level grades and more obtained entrance to university. The best academic results were found for children whose mothers had received over 5 grams of progesterone for a minimum of eight weeks, with treatment beginning before week sixteen.


Thirty postmenopausal women were treated daily for four months with 2 mg micronized 17 beta-estradiol and micronized progesterone orally in doses of 50, 100 and 200 mg daily. Serum concentrations of sex hormone-binding globulin (SHBG), corticosteroid binding globulin (CBG), ceruloplasmin, lipoprotein A and liver enzymes were measured. Serum SHBG and CBG increased during treatment with a weak association shown between progesterone and serum CBG. Levels of lipoprotein A and liver enzymes did not change, concluding that natural progesterone supplementation in postmenopausal women does not appear to cause any side effects to the liver.


This paper reviews the use of a transvaginal progesterone gel as a viable option to other routes of application of natural progesterone (intramuscular, oral micronized), and offered it as a viable option to synthetic progestins given the low incidence of side effects noted in existing studies.


The literature reviewed in this tutorial indicates a potential use for oral micronized progesterone for the treatment of secondary amenorrhea, dysfunctional uterine bleeding, luteal phase disorders, premenopausal bleeding disorders, and as a component of hormone replacement therapy that may provide a better safety profile than commonly utilized synthetic progestins.


Progestosterone has a role in increasing blood flow to the uterus during pregnancy. As such, these researchers studied the effect of progesterone treatment to resolve imminent necrosis of a myoma in two cases. Both resolved within several days following oral and vaginal doses of progesterone (300-600 mg/day). Both women went on to deliver healthy, full-term infants.


Although estrogen is known to stimulate the growth of uterine fibroids, the effect of progesterone is unclear. The role of progesterone in the development of uterine fibroids (leiomyoma) is examined in this study in an in vivo in vitro mouse model. Progestins and antiprogestins were utilized to investigate progesterone receptor (PR) signaling in a leiomyoma cell line. Both progestins and antiprogestins inhibited estrogen-mediated growth. PR ligands were also shown to suppress estrogen receptor signaling and leiomyoma cell growth.
Laidlaw IJ, Clarke RB. The proliferation of normal breast tissue implanted into athymic nude mice is stimulated by estrogen, but not by progesterone. Endocrinology Jan 1995;136(1):164-71.

Normal human breast tissue was implanted subcutaneously into athymic nude mice. The mice were then treated with estradiol or progesterone such that serum levels approximated those seen in normal menstruating women. Immunocytochemical measures were made of proliferative activity and steroid receptor expression of the tissue implants. It was found that physiologic levels of estradiol significantly stimulated the proliferation of human breast epithelial cells and increased progesterone receptor expression 10-20-fold. Progesterone failed to affect proliferation alone or after estradiol priming.


In an attempt to better understand the diversity of progesterone’s effects, a novel mouse strain homozygous for the absence of progesterone receptors has been studied. Female PR null mice were found to have extensive reproductive abnormalities, and results provide evidence for progesterone’s diverse role as the coordinator of events that ensure female fertility. Future studies of this animal model may help redefine progesterone’s role as not just a sex steroid, but as a key player and regulator in a variety of physiological processes.


A review of the actions of progesterone and its metabolites demonstrates physiological significance in such biological activities as may have importance in the regulation of stress, post-partum depression, memory, cognition, PMS, and depression, to name a few.


In this long-term controlled study, the safety and efficacy of a progesterone-releasing vaginal contraceptive device was compared to that of the copper-T 380A IUD in nursing mothers. There was no difference in breastfeeding performance or infant growth between groups. The participants using the progesterone-releasing ring had a longer period of lactational amenorrhea than did the group using the copper T. Women were tracked for over 2000 women-months of exposure in both groups. The Chilean government found the progesterone-releasing ring to be a safe and effective contraceptive alternative.


Eighty regularly menstruating women with mastodynia were studied to evaluate the clinical effectiveness of vaginally administered micronized progesterone. Subjects were randomly assigned to one of two groups, with all participating in a control cycle prior to treatment. One group received 4 grams of vaginal cream containing 2.5% natural progesterone for six cycles from day 19 to day 25 of the cycle. The other group was similarly treated with placebo. Both subjective reporting on a daily basis and clinical examination revealed a significant reduction in breast pain, defined as 50% reduction, in 64.9% of subjects receiving progesterone and 22.2% of subjects receiving placebo. Effects of breast nodularity were not significant. No side effects were detected.

**Progesterone and Osteoporosis**


Transdermal progesterone supplementation with and without conjugated estrogens was evaluated in a clinical setting using 100 women aged 38 to 83 years. The average time from onset of menopause was 16 years. 63 women were followed for three years with dual photon absorptiometry. Treatment also included dietary changes, nutritional supplements, and exercise. All individuals followed showed an increase in bone mineral density over the three years, with the greatest increase
occurring in the first year. There was no difference noted between estrogen/progesterone and progesterone only groups. Subjective changes included increased libido, diminished hot flushes, reduced joint pain, and increased mobility and energy. No side effects were noted during treatment protocol.


In this review article, the authors propose that cyclic progesterone both prevents bone loss and acts as a bone-builder. The studies discussed focus on abnormal menstrual cycles as an important risk factor for osteoporotic fractures. Their conclusion is that the first step in preventing osteoporosis is treating ovulation disorders.


A review of the available data indicates that progesterone acts to promote bone metabolism. It appears to be independent of estrogen by either acting directly at progesterone receptors, or indirectly through competition at glucocorticoid receptors in the osteoblasts.

**Progesterone vs. Progestins**


Twenty three early postmenopausal women were randomized to either medroxyprogesterone acetate (MPA) or oral micronized progesterone combined with conjugated equine estrogens (CEE) and followed for 91 days in a sequence of treatments. None of the hormone treatments had any noticeable effect on mood. Participants using MPA experienced more breast tenderness and bleeding than those using progesterone. This study debunks the belief that progesterone depresses mood in healthy individuals.


This article looks at the differing effects of progesterone and synthetic progestogens on the fetus. Of note in this article is evidence that progesterone supplementation may reduce episodes of pre-eclampsia. Synthetic progestogen supplementation during pregnancy may produce a variety of side effects. Several references are made to articles documenting cases of masculinization of external genitalia in female babies. There are two known cases of true hermaphroditism and several cases of behavioral problems developing in adolescent girls whose mothers took oral synthetic progestogens during pregnancy. More problematic may be administration of oral estrogen-progestogen preparations. Side effects may include spina bifida, esophageal anomalies, heart defects and limb reduction deformities.


In this review, the author highlights the differences between progesterone and synthetic progestogens in the breast and cautions that progestogens not be ?all put in the same bag? with respect to safety. A strong case is made for the protective effect of progesterone on the breast.


This review article examines the rationale for selecting oral micronized progesterone over synthetic progestins. It reviews research regarding efficacy and safety and concludes that oral micronized progesterone has fewer side effects than synthetic progestins and is a convenient way to deliver natural progesterone.

Breast cancer risk independently increases with mammographic density. Use of hormone replacement therapy (HRT) postmenopausally is associated with an increase in mammographic density, but the extent of the density increase is unknown. This study evaluated mammograms from 571 of the 875 women enrolled in the PEPI trial at baseline and after 12 months HRT. The women had been randomized to receive placebo, conjugated equine estrogens (CEE) + medroxyprogesterone acetate (MPA) in a continuous or cyclic fashion, or CEE + micronized progesterone (MP). Mammograms were analyzed digitally and a linear regression analysis was utilized to quantify breast density change in all four treatment arms. The adjusted absolute mean changes in mammographic percent density over 12 months were 4.76% (95% confidence interval [CI] = 3.29% to 6.23%), 4.58% (95% CI = 3.19% to 5.97%), and 3.08% (95% CI = 1.65% to 4.51%) for women in the CEE+MPA-cyclic, CEE+MPA-continuous, and CEE-MP groups, respectively. Each of those absolute mean changes was statistically significantly different from the adjusted absolute mean change in mammographic percent density for women in the placebo group, which was -0.07% (95% CI = -1.50% to 1.38%). Greater mammographic density was associated with the use of estrogen/progestin combination therapy, although the micronized progesterone containing arm appeared to induce less of an increase that that with MPA.


Clinical observations demonstrate that patients suffering from PMS respond to treatment with natural progesterone, whereas synthetic progestins may exacerbate the condition. The authors review the differences between natural progesterone and synthetic progestins.


Ovariectomized rhesus monkeys were treated with physiological levels of 17-beta estradiol in combination with either medroxyprogesterone or progesterone (oral micronized) for four weeks. Following pathophysiological stimulation without injury to induce coronary vasospasm, it was shown that progesterone plus estradiol was protective against vasospasm, whereas estradiol plus medroxyprogesterone allowed vasospasm, concluding that medroxyprogesterone increases risk of coronary vasospasm, while progesterone does not.


This randomized trial compared two regimens of estrogen/progestogen therapy on the nocturnal sleep in 21 postmenopausal women. One regimen consisted of conjugated equine estrogens (CEE 0.625mg) and medroxyprogesterone acetate (5 mg). The other utilized oral micronized progesterone (200mg) with CEE. Both groups reported improved subjective measures of sleep and menopausal symptoms. However, sleep efficiency and time spent awake after sleep onset were significantly improved in the micronized progesterone group, but not in the medroxyprogesterone acetate group, suggesting the former may improve sleep quality in postmenopausal women.


Specificity profiles of numerous progestins were evaluated by multivariate analysis. Twenty steroid hormones, including natural progesterone, were tested for anti-estrogenic activity and for binding to the androgen, progesterone, and glucocorticoid receptors.


This study utilizing human umbilical vein endothelial cells (HUVEC?)s demonstrated that progesterone, but not medroxyprogesterone acetate (MPA) inhibited expression of vascular cell adhesion molecule-1 (VCAM-1), demonstrating a role for progesterone in the prevention of atherosclerosis. The differing effects of progesterone and MPA are clinically important, as MPA is widely used in hormone replacement therapy, when, as this research suggests, progesterone might be a more appropriate option.

Fifty-eight postmenopausal women were followed with respect to subfractions of high-density lipoprotein during 3 cycles of unopposed estrogen. The women received either levonorgestrel, medroxyprogesterone acetate, or natural progesterone during the last ten days of the treatment period. Both progestogens significantly lowered HDL cholesterol, whereas natural progesterone had no effect on HDL levels.


Eighteen postmenopausal women were randomized to receive 17-beta estradiol with a synthetic progestin (medroxyprogesterone acetate) or a progesterone vaginal gel for 4 weeks, then crossed over to the alternate treatment. Researchers found through treadmill testing that estrogen plus progesterone significantly increased exercise time before myocardial ischemia, when compared to estradiol plus synthetic progestin. In addition, 2 patients on the synthetic progestin arm had to discontinue due to unstable angina. This research suggests that women at risk for cardiovascular disease need to consider progesterone as a safer alternative to synthetic progestins as a part of their hormone replacement therapy regime.


This article reviews the effects of various synthetic progestins and progesterone on cardiovascular health. Many synthetic progestins, especially 19-nortestosterone and some 17-hydroxyprogesterones, have negative effects on cardiovascular risk factors, whereas natural progesterone does not. Further studies utilizing natural and other steroids should be considered.


The classifications of various progestogens (natural and synthetic) are reviewed in terms of their risks and benefits. This review clearly elucidates the differences in the mode of action of various synthetic progestins as well as progesterone.