Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle.

**Backstrom T.**

Nine periods in seven women with partial epilepsy have been investigated with respect to frequency of fits, and estrogen-progesterone levels in blood plasma. Six cycles with ovulation showed a positive correlation between the number of secondary generalized seizures and the mean estrogen/progesterone (E/P) ratios and a negative correlation to plasma progesterone levels. Three periods without ovulation showed an increase in the number of fits during days of high estrogen. The number of fits seemed not to be correlated to changes in body weight.

PMID: 973554 [PubMed - indexed for MEDLINE]

**Mult Scler 1997 Apr;3(2):105-12**

Comment in:

- **Hum Reprod. 2001 Aug;16(8):1542.**

Neurosteroids, with special reference to the effect of progesterone on myelination in peripheral nerves.

**Baulieu EE, Schumacher M.**

INSERM U 33, Le Kremlin-Bicetre, France.

Some steroids are synthesized within the central and peripheral nervous system, mostly by glial cells. These are known as neurosteroids. In the brain, neurosteroids have been shown to act directly on membrane receptors for neurotransmitters. For example, progesterone inhibits the neuronal nicotinic acetylcholine receptor, whereas its 3alpha,5alpha-reduced metabolite 3alpha,5alpha-tetrahydroprogesterone (allopregnanolone) activates the A gamma-aminobutyric acid receptor complex. Besides these effects, neurosteroids also regulate important glial functions, such as the synthesis of myelin proteins. Thus, in cultures of glial cells prepared from neonatal rat brain, progesterone increases the number of oligodendrocytes expressing the myelin basic protein (MBP) and the 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNPase). An important role for neurosteroids in myelin repair has been demonstrated in the rodent sciatic nerve,
where progesterone and its direct precursor pregnenolone are synthesized by Schwann cells. After cryolesion of the male mouse sciatic nerve, blocking the local synthesis or action of progesterone impairs remyelination of the regenerating axons, whereas administration of progesterone to the lesion site promotes the formation of new myelin sheaths.

Publication Types:

- Review
- Review, Tutorial

PMID: 9291163 [PubMed - indexed for MEDLINE]

**Appl Physiol 1992 Aug;73(2):393-404**

**Central neural mechanisms of progesterone action: application to the respiratory system.**

**Bayliss DA, Millhorn DE.**
Department of Physiology, University of North Carolina, Chapel Hill 27599-7545.

Around the turn of the century, it was recognized that women hyperventilate during the luteal phase of the menstrual cycle and during pregnancy. Although a causative role for the steroid hormone progesterone in this hyperventilation was suggested as early as the 1940s, there has been no clear indication as to the mechanism by which it produces its respiratory effects. In contrast, much mechanistic information has been obtained over the same period about a different effect of progesterone, i.e., the facilitation of reproductive behaviors. In this case, the bulk of the evidence supports the hypothesis that progesterone acts via a genomic mechanism with characteristics not unlike those predicted by classic models for steroid hormone action. We recently, therefore, undertook a series of experiments to test predictions of those same models with reference to the respiratory effects of progesterone. Here we highlight the results of those studies; as background to and precedent for our experiments, we briefly review previous work in which effects of progesterone on respiration and reproductive behaviors have been studied. Our results indicate that the respiratory response to progesterone is mediated at hypothalamic sites through an estrogen- (E2) dependent progesterone receptor- (PR) mediated mechanism requiring RNA and protein synthesis, i.e., gene expression. The E2 dependence of the respiratory response to progesterone is likely a consequence of the demonstrated induction of PR mRNA and PR in hypothalamic neurons by E2. In short, we found that neural mechanisms underlying the stimulation of respiration by progesterone were similar to those mediating its reproductive effects.
Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone.

Beynon HL, Garbett ND, Barnes PJ.
Department of Thoracic Medicine, Brompton Hospital, London.

Three patients with severe premenstrual exacerbations of asthma are reported. None had responded to conventional treatment, including high-dose corticosteroids. In all cases there was a striking fall premenstrually in peak flow rate. The addition of intramuscular progesterone (100 mg daily in two cases and 600 mg twice a week in one) to the regimen eliminated the premenstrual dips in peak flow, and daily doses of prednisolone were reduced in the three patients.

Progesterone and the progesterone receptor.

Bouchard P.
Endocrine Services, Hopital St. Antoine, University Pierre et Marie Curie, 184, Rue du Faubourg Saint Antoine, 75012 Paris, France.

During the 1990s, extensive research has effectively mapped the progesterone receptor-mediated actions of progesterone and has more recently uncovered nonreceptor-mediated effects--the effect of progesterone on uterine sensitivity to oxytocin, for example, involves direct, nongenomic progesterone action on the uterine oxytocin receptor. However, the majority of progesterone effects occur as a result of progesterone-receptor-mediated action, where progesterone behaves as a hormone-dependent transcription factor, probably because these receptors are widely distributed in the body. A distinguishing characteristic of progesterone receptors is the existence of two isoforms, A-form and B-form. In most tissues coexpressing progesterone receptors, estrogen controls the regulation of progesterone receptors, thereby also controlling sensitivity to progestins. Thus,
progesterone receptor expression is upregulated by estrogen and downregulated by progesterone in most target tissues.

Publication Types:
- Review
- Review, Tutorial

PMID: 11392025 [PubMed - indexed for MEDLINE]

**Hum Reprod** 1990 Jul;5(5):537-43

**Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure.**

**Bourgain C, Devroey P, Van Waesberghe L, Smitz J, Van Steirteghem AC.**
Department of Pathology, Akademisch Ziekenhuis, Vrije Universiteit Brussel, Belgium.

In 43 patients without ovaries, endometrial biopsies at day 21 of 75 substituted cycles were studied by light and electron microscopy. The morphology of the endometrium was compared after oral, vaginal or intramuscular administration of progesterone, and correlated with the serum levels of 17-beta oestradiol and progesterone and the pregnancies obtained after oocyte donation. After vaginal application of micronized progesterone, endometrial morphology closely matched that of a natural cycle. This therapy was able to support two ongoing pregnancies. No adequate endometrial response was noted after oral ingestion of progesterone. The maturation of the endometrium after intramuscular injections of progesterone in oil was heterogeneous. It was concluded that the vaginal route for administering micronized progesterone can be advised as the treatment of choice in patients without ovarian function.

PMID: 2394784 [PubMed - indexed for MEDLINE]

**Life Sci** 2001 Aug 24;69(14):1609-17

**Different role of endothelium/nitric oxide in 17beta-estradiol- and progesterone-induced relaxation in rat arteries.**

**Chan HY, Yao X, Tsang SY, Chan FL, Lau CW, Huang Y.**
Department of Physiology, Chinese University of Hong Kong, People's Republic of China.
The present study was aimed to examine the different role of endothelium/nitric oxide in relaxation induced by two female sex hormones, 17beta-estradiol and progesterone in rat isolated aortas and mesenteric arteries. The isometric force of each ring was measured with Grass force-displacement transducers in the organ bathes. 17beta-Estradiol induced both endothelium-dependent and -independent relaxation in the rat aortas but only the endothelium-independent relaxation in the rat mesenteric arteries. In contrast, progesterone induced both endothelium-dependent and -independent relaxation in the rat mesenteric arteries but only endothelium-independent relaxation in rat aortas. N(G)-Nitro-L-arginine methyl ester and methylene blue attenuated the relaxant response to 17beta-estradiol in the aortic rings or to progesterone in the mesenteric arteries. Pretreatment with L-arginine antagonized the effect of N(G)-nitro-L-arginine methyl ester on sex hormone-induced relaxation. The endothelium contribution to relaxation seems to only relate to lower concentrations of 17beta-estradiol and progesterone. In summary, the present results clearly demonstrate a different role of the functional endothelium in the relaxant response to 17beta-estradiol or progesterone in the conduit vessel (aorta) and the resistance vessels (mesenteric artery). Nitric oxide contributes largely to the endothelium-dependent relaxation induced by 17beta-estradiol in the isolated aortas or by progesterone in the mesenteric arteries.

PMID: 11589501 [PubMed - indexed for MEDLINE]

Fertil Steril 1995 Apr;63(4):785-91

Comment in:


Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo.

Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignieres B.
National Taiwan University Hospital, Taipei.

OBJECTIVE: To study the effect of E2 and P on the epithelial cell cycle of normal human breast in vivo. DESIGN: Double-blind, randomized study. Topical application to the breast of a gel containing either a placebo, E2, P, or a combination of E2 and P, daily, during the 10 to 13 days preceding breast surgery. PATIENTS: Forty premenopausal women undergoing breast surgery for the removal of a lump. MAIN OUTCOME MEASURES. Plasma and breast tissue concentrations of E2 and P. Epithelial cell cycle evaluated in normal breast tissue areas by counting mitoses and proliferating cell nuclear antigen immunostaining quantitative analyses. RESULTS: Increased E2 concentration increases the number of cycling epithelial cells. Increased P concentration significantly decreases the number of cycling epithelial cells. CONCLUSION: Exposure to P
for 10 to 13 days reduces E2-induced proliferation of normal breast epithelial cells in vivo.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 7890063 [PubMed - indexed for MEDLINE]

Fertil Steril 1993 Dec;60(6):1020-4

Effects of the repetitive administration of progesterone by nasal spray in postmenopausal women.

Cicinelli E, Cignarelli M, Resta L, Scorcia P, Petruzzi D, Santoro G.
Cattedra di Patologia Ostetrica e Ginecologica, University of Bari, Italy.

OBJECTIVE: To study the effects of 10 days of nasal spray P treatment on P serum levels and the endometrium. DESIGN: Prospective. SETTING: University Medical School. PATIENTS: Eight postmenopausal women received oral conjugated estrogens at a daily dose of 0.625 mg for 4 weeks immediately before vaginal surgery for prolapse. For the first 9 of the last 10 days the patients also received a nasal spray dosage of 11.2 mg P three times a day; on the 10th day they received only one dose. MAIN OUTCOME MEASURES: Blood samples were taken at 8:00 A.M. on treatment days 1, 3, 5, 7, 10, and 11 to follow P serum concentration levels. Endometrial samples for histologic examination were collected before P administration and immediately after surgery to evaluate the end-organ effect. RESULTS: Mean P serum levels increased sixfold after 9 days of nasal spray P administration [from 0.612 +/- 0.280 ng/mL (1.958 +/- 0.896 nmol/L) to 3.925 +/- 1.553 ng/mL (12.560 +/- 4.970 nmol/L)] and declined thereafter, returning to the before treatment levels 24 hours after the last administration. In all subjects, the first histologic evaluation showed proliferative endometrium; the second showed clear secretive changes. CONCLUSIONS: Repetitive nasal spray P administration for 10 days in postmenopausal women led to increasing P serum levels and, when the estrogen stimulation was adequate, to secretory changes in the endometrium (end-organ effect).

PMID: 8243679 [PubMed - indexed for MEDLINE]


Progesterone receptors and human breast cancer.
Clark GM, McGuire WL.

Estrogen receptor protein is known to be an important prognostic factor for patients with breast cancer. The presence of estrogen receptor correlates with response to endocrine therapy in patients with metastatic disease and is associated with prolonged disease-free and overall survival in patients with primary disease. But the correlation between estrogen receptor positivity and endocrine dependence is not perfect. Approximately 40% of estrogen receptor positive tumors fail to regress with endocrine therapy. It has been hypothesized that another protein, progesterone receptor, may be a more effective marker of endocrine responsiveness since progesterone receptor is the end product of estrogen action. We have examined the relationship between progesterone receptor and response of advanced breast cancer tumors to hormonal manipulations. Promising retrospective results indicate the need for new, prospective clinical trials to further define the prognostic value of progesterone receptor for these tumors. We have also analyzed the disease-free intervals of patients with primary disease and found that progesterone receptor was more important than estrogen receptor for predicting time to recurrence. We suggest that both estrogen receptor and progesterone receptor be routinely measured in all breast cancer tumors, and that the results of these assays will help the physician individualize therapy for breast cancer patients.

Publication Types:
- Review

PMID: 6351950 [PubMed - indexed for MEDLINE]


Breast cancer incidence in women with a history of progesterone deficiency.

Cowan LD, Gordis L, Tonascia JA, Jones GS.

In order to investigate the nature of the association of involuntarily delayed first birth and risk of breast cancer, 1083 white women who had been evaluated and treated for infertility from 1945-1965 were followed prospectively through April 1978 to ascertain their breast cancer incidence. These women were categorized as to the cause of infertility into two groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group had 5.4 times the risk of premenopausal breast cancer compared to women in the NH group. This excess risk could not be explained by differences between the two groups in ages at menarche or menopause, history of oral contraceptive
use, history of benign breast disease or age at first birth. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the NH group. The incidence of postmenopausal breast cancer did not differ significantly between the two groups.

PMID: 7304556 [PubMed - indexed for MEDLINE]


**Antagonistic effects of 17 beta-estradiol, progesterone, and testosterone on Ca2+ entry mechanisms of coronary vasoconstriction.**

**Crews JK, Khalil RA.**
Department of Physiology, The Center for Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, MS 39216, USA.

The clinical observation that coronary artery disease is more common in men and postmenopausal women than in premenopausal women has suggested cardioprotective effects of female sex hormones including hormone-mediated coronary vasodilation. The purpose of this study was to investigate whether the sex hormone-induced coronary relaxation is caused by inhibition of Ca2+ mobilization into coronary smooth muscle. The effects of 17beta-estradiol, progesterone, and testosterone on vascular reactivity and 45Ca2+ influx were tested in deendothelialized coronary artery strips isolated from castrated male pigs. Prostaglandin F2alpha (PGF2alpha) (10(-5) mol/L) caused significant, maintained contraction of coronary artery strips. Caffeine (25 mmol/L), an activator of Ca2+ release from intracellular stores, caused transient contraction in Ca2+-free solution whereas membrane depolarization by 96 mmol/L KCl, an activator of Ca2+ entry, caused maintained contraction in the presence of external Ca2+. The 3 sex hormones caused significant and concentration-dependent relaxation of PGF2alpha- and 96 mmol/L KCl-induced contractions with 17beta-estradiol being the most effective. The sex hormones did not significantly affect the transient caffeine contraction in Ca2+-free solution. In contrast, the sex hormones significantly inhibited the PGF2alpha- and KCl-induced 45Ca2+ influx. 17beta-Estradiol caused similar inhibition of PGF2alpha- and KCl-induced contractions with 17beta-estradiol being the most effective. However, progesterone and testosterone caused greater relaxation of PGF2alpha-induced contraction than of KCl-induced contraction. We conclude that in coronary arteries of castrated male pigs, sex hormones inhibit Ca2+ entry from extracellular space but not Ca2+ release from intracellular stores. 17beta-Estradiol mainly inhibits Ca2+ entry, whereas progesterone and testosterone cause coronary relaxation by inhibiting other mechanisms in addition to Ca2+ entry.

PMID: 10195933 [PubMed - indexed for MEDLINE]
Hydrocortisone and progesterone regulation of the proliferation, morphogenesis, and functional differentiation of normal rat mammary epithelial cells in three dimensional primary culture.

Darcy KM, Shoemaker SF, Lee PP, Ganis BA, Ip MM.
Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.

The mechanisms of action of, and resistance to, the steroidal regulators of normal mammary epithelial and breast cancer cell development are only partially understood. A major obstacle to research progress has been the difficulty in supporting physiologically relevant development of normal mammary epithelial cells (MEC) under defined serum-free conditions. A primary culture system was developed in our laboratory that permits nonfunctional rat MEC to undergo extensive proliferation, functional differentiation, as well as multilobular and lobuloductal branching alveolar morphogenesis. In the studies reported here, the contributions of hydrocortisone and progesterone during the coordinate induction of cellular proliferation, organoid morphogenesis, and functional capacity were assessed. Hydrocortisone (0.1-10 microgram/ml) induced alveolar and multilobular branching morphogenesis, suppressed lobuloductal branching morphogenesis, and enhanced casein accumulation. Hydrocortisone also played a role in maintaining alveolar as well as multilobular branching morphogenesis and casein levels. Progesterone (0.01-1 microgram/ml) induced cellular proliferation as well as multilobular and lobuloductal branching morphogenesis, and suppressed casein accumulation. At a supraphysiological concentration (10 micrograms/ml), progesterone inhibited cell growth, alveolar branching morphogenesis, and casein accumulation. MEC cultured without progesterone for up to 1 week retained the ability to respond when subsequently exposed to this steroid. Reversibility studies suggested that progesterone was required for the induction, but not the maintenance of the mitogenic, morphogenic, and lactogenic effects. This physiologically relevant primary culture system can be used to study the factors that regulate steroid responsiveness as well as the cross-talk between steroid and growth factor receptor signaling pathways in normal MEC and breast cancer cells.

PMID: 7706379 [PubMed - indexed for MEDLINE]

Risks and benefits of hormone replacement therapy.

del Lignieres B, MacGregor EA.
Hopital Necher, Paris, France.
Menopause, the permanent cessation of menstruation, is due to ovarian failure, which may lead to oestrogen deficiency diseases, particularly osteoporosis, cardiovascular disease and cerebrovascular disease. Mortality and morbidity caused by these conditions can be modified by using hormone replacement therapy, but the benefits of this therapy must be weighed against the increased risk of breast cancer and the symptomatic side-effects the treatment may cause. The combination of transdermal oestrogen and natural progesterone offers the most favourable risk-to-benefit profile.

Publication Types:
- Review
- Review Literature

PMID: 10997769 [PubMed - indexed for MEDLINE]

Psychoneuroendocrinology 1994;19(5-7):563-79

**Progesterone and the neural mechanisms of hamster sexual behavior.**

DeBold JF, Frye CA.
Department of Psychology, Tufts University, Medford, Massachusetts 02155.

Stimulation of both the ventral medial hypothalamus (VMH) and the ventral tegmental area (VTA) by progesterone is necessary to facilitate sexual behavior in female hamsters. Recently obtained evidence indicates that progesterone exerts its behaviorally relevant actions in the VTA by acting on cell membranes. When progesterone conjugated to bovine serum albumin, which cannot permeate the cell membrane, is applied to the VTA concurrent with free progesterone to the VMH, estrogen-primed hamsters become sexually receptive. Since the reverse treatment is ineffective, this suggests that progesterone's nongenomic effects in the VTA may require concurrent genomic activation by progesterone in the VMH. The nongenomic action of progesterone on sexual receptivity may involve the GABAA receptor complex, as progestins are known to modulate this receptor complex. VTA infusions of GABAA agonists enhance, and antagonists inhibit, progesterone's effectiveness on receptivity. Finally, the behavioral effectiveness of progesterone metabolites in the VTA, concurrent with progesterone in the VMH, is consistent with their relative biochemical efficacy at the GABAA complex. These data suggest that progesterone may exert its behavioral effects in the VTA through GABAA. However, it is not yet clear whether progesterone normally acts directly on GABAA in the VTA. Progesterone may also act at some other membrane binding site and GABAA may represent an indirect mechanism for progesterone.
Progesterone and the premenstrual syndrome: a double blind crossover trial.


A double blind, randomised, crossover trial of oral micronised progesterone (two months) and placebo (two months) was conducted to determine whether progesterone alleviated premenstrual complaints. Twenty three women were interviewed premenstrually before treatment and in each month of treatment. They completed Moos's menstrual distress questionnaire, Beck et al's depression inventory, Spielberger et al's state anxiety inventory, the mood adjective checklist, and a daily symptom record. Analyses of data found an overall beneficial effect of being treated for all variables except restlessness, positive moods, and interest in sex. Maximum improvement occurred in the first month of treatment with progesterone. Nevertheless, an appreciably beneficial effect of progesterone over placebo for mood and some physical symptoms was identifiable after both one and two months of treatment. Further studies are needed to determine the optimum duration of treatment.

Transvaginal administration of progesterone.

Fanchin R, De Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R.
OBJECTIVE: To examine the endometrial effects of three different doses of progesterone administered vaginally. METHODS: Forty women 25-41 years old deprived of ovarian function received estradiol (E2) for 28 days. From days 15 to 27, a new mucus-like vaginal gel of progesterone was administered every other day, randomly, dosed at 45 mg (group A, n = 14), 90 mg (group B, n = 13), or 180 mg (group C, n = 13). Plasma gonadotropins, estrone, E2, and progesterone were measured. An endometrial biopsy was performed on day 20 (n = 20) or 24 (n = 20) for endometrial dating and for estrogen and progesterone receptor determinations. RESULTS: Plasma estrogen levels were in the menstrual cycle range. Mean progesterone levels were lower in group A (2.4 +/- 0.2 ng/mL) than in group B (3.6 +/- 0.2 ng/mL) or C (3.4 +/- 0.4 ng/mL) (P < .005). Plasma FSH and LH decreased significantly during progesterone treatment. In all groups, we observed secretory transformation in the glands (day 20) and stroma (day 24) and the distribution of estrogen and progesterone receptors seen in normal menstrual cycles. CONCLUSION: Transvaginal administration of progesterone induced normal secretory transformation of the endometrium despite low plasma levels, suggesting a direct transit into the uterus or "first uterine pass effect."

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 9277651 [PubMed - indexed for MEDLINE]


Estradiol and progesterone regulate the proliferation of human breast epithelial cells.

Foidart JM, Colin C, Denoo X, Desreux J, Beliard A, Fournier S, de Lignieres B.
University of Liege, Belgium.

OBJECTIVE: To study the effects of estradiol and progesterone on the proliferation of normal human breast epithelial cells in vivo. DESIGN: Double-blind randomized study. SETTING: Departments of gynecology and of cell biology at a university hospital. PATIENT(S): Forty postmenopausal women with untreated menopause and documented plasma FSH levels of >30 mIU/mL and estradiol levels of <20 pg/mL. INTERVENTION(S): Daily topical application to both breasts of a gel containing a placebo, estradiol, progesterone, or a combination of estradiol and progesterone during the 14 days preceding esthetic
breast surgery or excision of a benign lesion. MAIN OUTCOME MEASURE(S): Plasma and breast tissue concentrations of estradiol and progesterone. Epithelial cell cycles were evaluated in normal breast tissue by counting mitoses and performing quantitative proliferating cell nuclear antigen immunolabeling analyses. RESULT(S): Increasing the estradiol concentration enhanced the number of cycling epithelial cells, whereas increasing the progesterone concentration significantly limited the number of cycling epithelial cells. CONCLUSION(S): Exposure to progesterone for 14 days reduced the estradiol-induced proliferation of normal breast epithelial cells in vivo.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 9591509 [PubMed - indexed for MEDLINE]

**Mol Cell Biochem 1999 Dec;202(1-2):53-61**

**Bcl-2, survivin and variant CD44 v7-v10 are downregulated and p53 is upregulated in breast cancer cells by progesterone: inhibition of cell growth and induction of apoptosis.**

**Formby B, Wiley TS.**
Sansum Medical Research Institute, Program in Molecular Oncology, Santa Barbara, CA 93105, USA. bent@sansumres.com

Progesterone inhibits the proliferation of normal breast epithelial cells in vivo, as well as breast cancer cells in vitro. But the biologic mechanism of this inhibition remains to be determined. We explored the possibility that an antiproliferative activity of progesterone in breast cancer cell lines is due to its ability to induce apoptosis. Since p53, bcl-2 and survivin genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90% inhibition of cell proliferation with T47-D breast cancer cells after exposure to 10 microM progesterone for 72 h. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to 10 microM progesterone. The earliest sign of apoptosis is translocation of phosphatidylserine from the inner to the outer leaflet of the plasma membrane and can be monitored by the calcium-dependent binding of annexin V in conjunction with flow cytometry. After 24 h of exposure to 10 microM progesterone, cytofluorometric analysis of T47-D breast cancer cells indicated 43% were annexin V-positive and had undergone apoptosis and no cells showed signs of cellular necrosis (propidium iodide negative). After 72 h of exposure to 10 microM progesterone, 48% of the cells had undergone apoptosis and 40% were annexin V positive/propidium iodide positive indicating signs of necrosis. Control
Untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 h of exposure of T47-D cells to either 1 or 10 microM progesterone, we observed a marked down-regulation of protooncogene bcl-2 protein and mRNA levels. mRNA levels of survivin and the metastatic variant CD44 v7-v10 were also downregulated. Progesterone increased p53 mRNA levels. These results demonstrate that progesterone at relative high physiological concentrations, but comparable to those seen in plasma during the third trimester of human pregnancy, exhibited a strong antiproliferative effect on breast cancer cells and induced apoptosis.

PMID: 10705995 [PubMed - indexed for MEDLINE]


Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53.

Formby B, Wiley TS.
Sansum Medical Research Institute, Santa Barbara, CA 93105, USA.

Progesterone inhibits the proliferation of normal breast epithelial cells in vivo, as well as breast cancer cells in vitro. But the biologic mechanism of this inhibition remains to be determined. We explored the possibility that an antiproliferative activity of progesterone in breast cancer cell lines is due to its ability to induce apoptosis. Since p53 and bcl-2 genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90 percent inhibition of cell proliferation with T47-D breast cancer cells after exposure to 10 microM progesterone for 72 hours. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to these two concentrations of progesterone. After 24 hours of exposure to 10 microM progesterone, cytofluorometric analysis of T47-D breast cancer cells demonstrated 43 percent had undergone apoptosis without signs of necrosis. After 72 hours of exposure to 10 microM progesterone, 48 percent of the cells had undergone apoptosis and 40 percent demonstrated "leaky" membranes. Untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 hours of exposure to either 1 microM or 10 microM progesterone, the expression by T47-D cancer cells of bcl-2 was down-regulated, and that of p53 was up-regulated as detected by semiquantitative RT-PCR analysis. These results demonstrate that progesterone at a concentration similar to that seen during the third trimester of pregnancy exhibited a strong antiproliferative effect on at least two breast cancer cell lines. Apoptosis was induced in the progesterone receptor expressing T47-D breast cancer cells.

PMID: 9846203 [PubMed - indexed for MEDLINE]
Ineffectiveness of progesterone suppository treatment for premenstrual syndrome.

**Freeeman E, Rickels K, Sondheimer SJ, Polansky M.**
Department of Obstetrics/Gynecology, School of Medicine, University of Pennsylvania, Philadelphia 19104.

Progesterone is the most widely used treatment for premenstrual syndrome. To answer definitely the question of whether progesterone suppositories are effective for the treatment of premenstrual syndrome, a randomized, placebo-controlled, double-blind crossover study of 168 women, receiving progesterone in doses of 400 and 800 mg or placebo, was carried out. Premenstrual symptoms were not significantly improved by progesterone compared with placebo in any measure used in the study, including daily symptom reports maintained throughout treatment, clinician evaluation of improvement, and patient global reports of symptoms severity, relief, and disruption of daily activity. No symptom cluster or individual symptom differed significantly between progesterone and placebo treatment. These treatment results were not significantly affected by fluctuations in response during the placebo washout period, pretreatment levels of depression or anxiety at either postmenstrual or premenstrual times, or any of 19 other background, medical history, or symptom variables examined individually as covariates with treatment.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 2194047 [PubMed - indexed for MEDLINE]

**Biol Psychiatry 1994 May 15;35(10):775-80**

CSF neuroactive steroids in affective disorders: pregnenolone, progesterone, and DBI.
George MS, Guidotti A, Rubinow D, Pan B, Mikalauskas K, Post RM.
Biological Psychiatry Branch, National Institutes of Mental Health, Bethesda, MD 20892.

Recently several steroid compounds have been discovered to act as neuromodulators in diverse central nervous system (CNS) functions. We wondered if neuroactive steroids might be involved in affective illness or in the mode of action of mood-regulating medications such as carbamazepine. Levels of the neuroactive steroids pregnenolone and progesterone, as well as the neuropeptide diazepam binding inhibitor (DBI) (known to promote steroidogenesis), were analyzed from cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) from 27 medication-free subjects with affective illness and 10 healthy volunteers. Mood-disordered subjects who were clinically depressed at the time of the LP had lower CSF pregnenolone (n = 9, 0.16 ng/ml) compared with euthymic volunteers (n = 10, 0.35 ng/ml; p < 0.01). In addition, pregnenolone was lower in all affectively ill subjects (n = 26, 0.21 ng/ml), regardless of mood state on the LP day, than healthy volunteers (p < 0.05). No differences were found for progesterone or DBI levels by mood state or diagnosis. Progesterone, pregnenolone, and DBI did not change significantly or consistently in affectively ill subjects after treatment with carbamazepine. CSF pregnenolone is decreased in subjects with affective illness, particularly during episodes of active depression. Further research into the role of neuroactive steroids in mood regulation is warranted.

PMID: 8043707 [PubMed - indexed for MEDLINE]


Physiological action of progesterone in target tissues.

Graham JD, Clarke CL.
Westmead Institute for Cancer Research, University of Sydney, Westmead Hospital, NSW, Australia.

Publication Types:
- Review
- Review, Tutorial

PMID: 9267762 [PubMed - indexed for MEDLINE]
Intermittent progesterone therapy and frequency of complex partial seizures in women with menstrual disorders.

Herzog AG.

We studied eight women who had complex partial seizures and anovulatory cycles or inadequate luteal phases. Progesterone suppositories were given during the premenstrual phase or entire second half of the cycle in doses of 50 to 400 mg q12h. Antiseizure medication levels were kept in the therapeutic range. Average monthly seizure frequency declined by 68% (p less than 0.05, Wilcoxon matched-pairs test) in a 3-month treatment period compared with the 3 months prior to therapy, and six of the eight women had fewer seizures. None experienced more seizures or disruption of menses. Transient tiredness and depression were noted in some when progesterone dosage was raised above minimally effective levels. These symptoms cleared within 48 hours of lowering the dosage. The value of intermittent natural progesterone therapy as a safe, well-tolerated, and effective adjunct to antiseizure therapy should be assessed further.

PMID: 3785677 [PubMed - indexed for MEDLINE]

Protective effects of progesterone and tamoxifen in estrogen-induced mammary carcinogenesis in ovariectomized W/Fu rats.

Inoh A, Kamiya K, Fujii Y, Yokoro K.

The protective effect of progesterone or tamoxifen, an antiestrogenic agent, was investigated in estrogen-induced mammary carcinogenesis. Multiple mammary tumors (MT) of tubular or medullary carcinoma type developed at a high rate following prolonged treatment of ovariectomized W/Fu rats with diethylstilbestrol or 17 beta-estradiol. All MTs were located adjacent to the nipple and were slow-growing. The induction rate, multiplicity and size of estrogen-induced MTs were reduced by the simultaneous administration of either progesterone or tamoxifen. The estrogen-induced pituitary tumorigenesis was effectively inhibited by tamoxifen treatment, but it was not affected by progesterone. The results indicated that the inhibitory effect of progesterone or tamoxifen in estrogen-induced carcinogenesis is attributable to interference with the binding of estrogen to the estrogen receptors on the target cells.

PMID: 3930447 [PubMed - indexed for MEDLINE]
Thrombospondin-1, an inhibitor of angiogenesis, is regulated by progesterone in the human endometrium.

Iruela-Arispe ML, Porter P, Bornstein P, Sage EH.
Department of Pathology, Beth Israel Hospital, Boston, Massachusetts 02215, USA.

Thrombospondin-1 (TSP1), a multifunctional extracellular matrix glycoprotein, has been shown to suppress the angiogenic response in vivo and in vitro. We hypothesized that TSP1 might play a role in the inhibition of capillary morphogenesis during the endometrial cycle and examined its expression in 46 human endometrial specimens. Our results show that the expression of TSP1 in the endometrium is (a) cycle-dependent, (b) associated with periods of low capillary growth, and (c) regulated by progesterone. TSP1 protein was identified in the basement membrane of capillaries of the functional endometrium during the secretory phase. Abundant expression of TSP1 mRNA in the secretory phase was also detected by in situ hybridization, in contrast to the low levels seen in the proliferative phase. These findings were confirmed by Northern analysis of proliferative and secretory endometrium. Transcripts for TSP1 were observed predominantly in stromal cells, but signal was also detected in some endothelial and smooth muscle cells. Since the proliferation of endometrial tissue is regulated by steroid hormones, we tested the effects of estrogen and progesterone on TSP1 expression by stromal cells isolated from human endometrium. We found that levels of TSP1 mRNA and protein were increased after incubation with progesterone. Maximal stimulation of mRNA was observed after 8 h of treatment with 10-50 microM progesterone, and the effect was suppressed by the progesterone antagonist RU-486. Induction by progesterone was cell-specific and equivalent to the stimulation mediated by PDGF. Finally, the levels of TSP1 present in progesterone-stimulated cultures were sufficient to inhibit the migration of endothelial cells in vitro; this effect was nullified by anti-TSP antibodies. We therefore propose that the production of TSP1 at later stages of the endometrial cycle is linked to the inhibition of vessel formation and that TSP1 expression is progesterone-dependent in this tissue.

PMID: 8567961 [PubMed - indexed for MEDLINE]

The clinical usefulness of salivary progesterone measurement for the evaluation of the corpus luteum function.

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The present study was designed to construct reliable daily salivary progesterone profiles throughout the luteal phase to accurately evaluate the corpus luteum function. Furthermore, we investigated the clinical relevance of a simple midluteal salivary progesterone estimation for the diagnosis of luteal phase insufficiency by determining the diagnostic efficiency and cutoff values. A total of 121 women were divided into 3 groups; normal luteal function, luteal phase insufficiency and unclassified group, based on basal body temperature recordings and serum progesterone levels at 3 sampling points during the midluteal phase. Salivary progesterone values across the luteal phase of the normal luteal function group were significantly increased from day 1 to day 4, remained constant from day 5 to day 9 (mean +/- SD, 318 +/- 170 pmol/l on day 5, 287 +/- 169 pmol/l on day 9; urinary LH surge = day 0) and decreased thereafter. Salivary progesterone concentrations in the luteal phase insufficiency group showed significantly lower values compared with those in the normal group between days 3 and 10. The cutoff values of 189 pmol/l in the midluteal phase yielded a sensitivity of 78.0% and a specificity of 76.5%. Our results suggest that daily salivary progesterone profiles during the luteal phase and a simple estimation of midluteal salivary progesterone appeared to be useful for the diagnosis of luteal phase defects.

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PMID: 11803226 [PubMed - indexed for MEDLINE]


**Progesterone induces endothelium-independent relaxation of rabbit coronary artery in vitro.**

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The effect of progesterone on isolated rabbit coronary arteries and its possible mechanism was investigated by measuring changes of isometric tension. Progesterone (1, 3, 10 and 30 microM) induced significant coronary relaxation in K+ (30 mM)-, prostaglandin F2 alpha (3 microM)- or Bay K 8644 (1 microM plus 15 mM K+-) precontracted arteries. There was no difference between endothelium-intact and -denuded coronary arteries from both male and female rabbits, precontracted with these three agents. Haemoglobin, indomethacin, methylene blue, glibenclamide or barium chloride did not affect the relaxation. In endothelium-denuded rabbit coronary arteries, progesterone shifted calcium concentration-dependent constrictor-response curves to the right, the maximal contraction was also reduced. The -log ED50s were 3.6 in control, and 3.3 and 2.9 after incubation with progesterone (3 and 30 microM), respectively. Similar
results were obtained in rat aorta. We conclude that progesterone induces significant endothelium-independent relaxation in rabbit coronary arteries in vitro, possibly by affecting calcium influx.

PMID: 1319340 [PubMed - indexed for MEDLINE]

A complex role for the progesterone receptor in the response to vascular injury.


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Clinical studies of hormone replacement therapy to prevent cardiovascular diseases have heightened interest in the cardiovascular effects of progestins. However, the role of the progesterone receptor (PR) in vascular biology has not been studied in vivo. We studied ovariectomized female PR knockout (PRKO) mice and their wild-type (WT) littermates using the mouse carotid artery injury model. Placebo-treated PRKO mice showed significantly greater vascular medial hypertrophy and vascular smooth muscle cell (VSMC) proliferation in response to vascular injury than did WT mice. Progesterone had no significant effect in the PRKO mice, but worsened the response to injury in WT mice. VSMCs cultured from PRKO mouse aortae were markedly hyperproliferative, and their growth was not affected by progesterone. In contrast to the in vivo findings, progesterone inhibited proliferation of WT-derived VSMCs. Furthermore, reintroduction of PR into PRKO-derived VSMCs using adenoviral methods restored progesterone-mediated inhibition of proliferation to these cells. This effect was reversed by the PR antagonist, RU 486. Thus, the effects of PR and progesterone differ markedly between cultured VSMCs and intact blood vessels. These data demonstrate a direct role for the PR in regulating the response to vascular injury and VSMC proliferation.

PMID: 11518735 [PubMed - indexed for MEDLINE]

Absorption of micronized progesterone from a nonliquefying vaginal cream.

_Kimzey LM, Gumowski J, Merriam GR, Grimes GJ Jr, Nelson LM._
An improved delivery method to achieve sustained physiological P levels would be useful. Based on this single-dose pharmacokinetic study, micronized P prepared in a nonliquefying vaginal cream holds promise as a convenient method to achieve this goal with a single daily application.

PMID: 1936339 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta 2001 Jun 29;1532(3):173-84

**Progesterone inhibits apolipoprotein-mediated cellular lipid release: a putative mechanism for the decrease of high-density lipoprotein.**

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In order to investigate the mechanism for female gonadal hormones to regulate the plasma high-density lipoprotein (HDL) level, the effect of 17 beta-estradiol and progestogens was examined in vitro on the assembly of HDL by free apolipoprotein A-I (apoA-I) with cellular cholesterol and phospholipid. ApoA-I generated HDL particles by removing cholesterol and phospholipid from human fibroblasts, MRC-5. While 17 beta-estradiol did not influence this reaction, progesterone suppressed the removal by apoA-I of both cholesterol and phospholipid, with the extent of the inhibition more for cholesterol than phospholipid. Three other synthetic progestogens showed the similar inhibitory effect on the cellular cholesterol release. Cellular cholesterol de novo-synthesized from mevalonolactone entered more into the acyl-esterified cholesterol compartment and less to the unesterified compartment in the presence of progesterone. On the other hand, progesterone did not influence the overall mass ratio of free and esterified cholesterol in the cell. Cell-surface cholesterol was also uninfluenced by progesterone when probed by extracellular cholesterol oxidase reaction or by diffusion-mediated cellular cholesterol release to cyclodextrin. Neither caveolin-1 nor ABCA1 expression was influenced by progesterone. Progesterone thus seems primarily to alter the specific intracellular cholesterol compartment that is related to the apoA-I-mediated HDL assembly. This mechanism might contribute to the decrease of plasma HDL by administration of progestogen in women under hormone replacement therapy.

PMID: 11470238 [PubMed - indexed for MEDLINE]
Is natural progesterone the missing link in osteoporosis prevention and treatment?

Lee JR.

Conventional treatment with vitamin D, calcium, and estrogen will delay but not reverse osteoporosis. The addition of fluoride may increase bone mass but fails to increase bone strength; fracture incidence is actually increased in non-vertebral bone by fluoride. Clearly, successful treatment of osteoporosis remains an unsolved problem. In women, osteoporosis coincides with menopause. The hypothesis that progesterone and not estrogen is the missing factor was tested in a clinical setting and was found to be extraordinarily effective in reversing osteoporosis.

PMID: 1943883 [PubMed - indexed for MEDLINE]

Progesterone inhibits arterial smooth muscle cell proliferation.

Lee WS, Harder JA, Yoshizumi M, Lee ME, Haber E.
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Mortality from atherosclerotic cardiovascular disease is lower in premenopausal women than in age-matched men. It is also lower in postmenopausal women who take estrogens and progestins together rather than estrogens alone. Progesterone receptors were detected in human and rat aortic smooth muscle cells in vivo and in vitro (in subculture). We examined the effect of progesterone on proliferation of smooth muscle cells, important constituents of atherosclerotic plaques. Progesterone at physiologic levels inhibited DNA synthesis and proliferation in these cells in a dose-dependent manner, and pretreatment with the progesterone receptor antagonist RU486 blocked inhibition. Cyclin A and E messenger RNA levels decreased after progesterone treatment but those of cyclin B and D1 did not change. This cell cycle-dependent inhibition of arterial smooth muscle cell proliferation by progesterone may represent a mechanism for the hormone's protective effect against atherosclerosis.
Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss.

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OBJECTIVE: To determine effectiveness of transdermal progesterone cream for controlling vasomotor symptoms and preventing postmenopausal bone loss.

METHODS: We randomly assigned 102 healthy women within 5 years of menopause to transdermal progesterone cream or placebo. Study subjects and investigators were masked until data analysis was completed. An initial evaluation included complete history, physical examination, bone mineral density determination, and serum studies (TSH, FSH, lipid profile, and chemistry profile). Subjects were instructed to apply a quarter teaspoon of cream (containing 20 mg progesterone or placebo) to the skin daily. Each woman received daily multivitamins and 1200 mg of calcium and were seen every 4 months for review of symptoms. Bone scans and serum chemistries were repeated after 1 year.

RESULTS: Thirty of the 43 (69%) in the treatment group and 26 of the 47 (55%) in the placebo group complained initially of vasomotor symptoms. Improvement or resolution of vasomotor symptoms, as determined by review of weekly symptom diaries, was noted in 25 of 30 (83%) treatment subjects and five of 26 (19%) placebo subjects (P < .001). However, the number of women who showed gain in bone mineral density exceeding 1.2% did not differ (alpha = .05, power of 80%). CONCLUSION: Although we found no protective effect on bone density after 1 year, we did see a significant improvement in vasomotor symptoms in the treated group.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

Comparison of the pharmacokinetics of crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal

OBJECTIVE: Compare the pharmacokinetics of vaginal progesterone gel (Crinone 8%, 90 mg) with that of oral progesterone (Prometrium, 100 mg). DESIGN: Open-label, randomized, parallel-group protocol. SETTING: Outpatient clinic. PATIENT(s): Twelve healthy postmenopausal women. INTERVENTION(s): Six subjects each were randomized to receive progesterone, which was administered either as 90 mg of progesterone gel (Crinone 8%) given vaginally or 100 mg progesterone in a capsule (Prometrium) given orally. MAIN OUTCOME MEASUREMENT(s): Serum progesterone levels were measured by both radioimmunoassay (RIA) and liquid chromatography-mass spectrometry (LC-MS). RESULT(s): Progesterone given vaginally resulted in greater bioavailability with less relative variability in absorption than oral progesterone (mean AUC(0-24) = 1.48 +/- 0.16 ng. h/mL per milligram vs. 0.035 +/- 0.0052 ng. h/mL per milligram). Mean C(max) for oral progesterone was much lower than that of vaginal progesterone (i.e., 2.20 +/- 3.06 ng/mL vs. 10.51 +/- 0.46 ng/mL). Mean T(max) occurred earlier for oral progesterone than for Crinone (1.00 +/- 0.41 hours vs. 7.67 +/- 3.67 hours). Radioimmunoassay is inappropriate for determining serum progesterone levels after oral administration, because it provided erroneously high values that were approximately eightfold higher than those obtained with LC-MS. CONCLUSION(s): Crinone (progesterone gel) given vaginally results in greater bioavailability with less relative variability than oral progesterone, thus providing more reliable delivery of progesterone, compared with oral progesterone. Measuring circulating progesterone with use of direct RIA is not appropriate after oral progesterone administration.
OBJECTIVE: To establish age-stratified reference values for salivary luteal P levels. DESIGN: One hundred thirty-six regularly menstruating women (18 to 48 years of age), screened for weight, exercise, and steroid medication use, collected daily saliva samples for one complete menstrual cycle. Luteal P levels were measured by 3H-RIA, and data were aligned by day of next menstrual onset. Means (+/- 1 SD range) and percentiles, calculated using both untransformed and log transformed data, were calculated for each luteal day and for indices of luteal P production. RESULTS: Reference values for salivary daily luteal P levels and indices of luteal P are presented for three age groups (18 to 24 years, 25 to 39 years, and 40 to 48 years). CONCLUSION: The age-stratified reference values presented here can be used, without collateral clinical procedures, to assess salivary luteal P levels. Salivary monitoring is ideally suited for research and long-term clinical observation, but the characteristics of salivary P data may limit the usefulness of these values for individual diagnosis.

PMID: 8137965 [PubMed - indexed for MEDLINE]

Progesterone differentially regulates the membrane-type matrix metalloproteinase-1 (MT1-MMP) compartment of proMMP-2 activation in MG-63 cells.

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Osteoblast-derived matrix metalloproteinases (MMPs) are considered to play a crucial role in bone formation and initiation of bone resorption by degrading the bone matrix. MMP-2 is constitutively secreted in a latent zymogen by osteoblasts, and requires the process of activation mediated by membrane-type matrix metalloproteinase-1 (MT1-MMP)/tissue inhibitor of metalloproteinase (TIMP-2) complex in the cell surface. Bone is one target tissue for progestins. In the present study, we observed the effects of progesterone on proMMP-2 activation and MT1-MMP expression, and also TIMP-2 levels in osteoblastic MG-63 cells. Gelatin zymograms and ELISA showed that progesterone have no effects on proMMP-2 activation. Using Western immunoblot analysis, we unexpectedly found that treatment with increasing doses of progesterone in MG-63 cells caused a dose-dependent increase in expression of MT1-MMP protein, and after 48h treatment, progesterone at 10(-8)M increased MT1-MMP protein level. Confocal immunohistochemistry analysis also confirmed that progesterone induced MT1-MMP expression in MG-63 cells. The results of Northern blot analysis showed that progesterone at 10(-8)M increased MT1-MMP protein levels after 48 h treatment. We also found that TIMP-2 levels were undetectable in MG-63 cells. In conclusion, progesterone increases MT1-MMP protein and mRNA levels in
MG-63 cells, but has no effects on proMMP-2 activation, which is partly attributable to the undetectable levels of tissue inhibitor of metalloproteinase-2 (TIMP-2). Our studies suggest that TIMP-2 is involved in proMMP-2 activation, and regulation of MT1-MMP by progesterone may contribute to its actions on bone formation.

PMID: 11507673 [PubMed - indexed for MEDLINE]

Reproductive phenotypes of the progesterone receptor null mutant mouse.

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Although progesterone has been traditionally associated with the establishment and maintenance of mammalian pregnancy, a number of studies have implicated physiological roles of this steroid hormone in other reproductive events. At present most of the downstream molecular and cellular mechanisms by which progesterone exerts its effects are unclear; however, the progesterone signal is known to be mediated initially by the progesterone receptor (PR), a member of the nuclear receptor superfamily of transcription factors. In most tissues studied, the PR is induced by ovarian estrogen via the estrogen receptor (ER), thereby implying that many of the observed reproductive physiological responses attributed to PR could conceivably be due to the combined effects of progesterone and estrogen. Therefore, to define clearly the distinct roles of progesterone and estrogen in vivo and to understand better progesterone function in a physiological context, we recently have generated a novel mouse strain in which both forms of the PR were ablated using gene targeting/embryonic stem cell techniques. Surprisingly, both male and female embryos, homozygous for the PR null mutation, developed to adulthood at the normal Mendelian frequency with no deviation in the sex ratio. Although developmental defects have yet to be detected in the adult male PR homozygote, extensive reproductive abnormalities were observed in the female. The reproductive phenotypes consisted of an inability to ovulate, uterine hyperplasia and inflammation, severely limited mammary gland development and an impairment in the induction of a sexual behavioral response. Collectively, these results provide direct in vivo evidence for progesterone's role as a pleiotropic coordinator of diverse reproductive events that together ensure female fertility. Finally, we believe that this animal model will be an invaluable tool in exploring the effects of progesterone in physiological systems other than reproduction and may, in the future, help to redefine progesterone not just as a sex steroid hormone but also as a key regulator of diverse physiological processes.
Treatment of common gynecologic-endocrinologic symptoms by allergy management procedures.

**Mabray CR, Burditt ML, Martin TL, Jaynes CR, Hayes JR.**

The technique of managing allergies by optimum-dose (provocative neutralization) testing and treatment using aqueous progesterone has been studied in 132 women having progesterone-related symptoms due to the menstrual cycle, pregnancy, or exogenous hormone administration. When extremely small doses of progesterone (0.0016 mg or below, up to maximum of 2.5 mg) were administered following determination of specific dose requirement by skin testing, startlingly rapid and effective clearing of symptoms was observed. With these individualized doses, symptoms cleared completely or almost completely within 30 minutes in the majority of patients. A single-blind technique was employed to rule out placebo effect. Some common problems found to respond well to the procedure were nausea and vomiting during pregnancy (100%), premenstrual syndrome (96%), and dysmenorrhea (84%).

**PMID: 7200220 [PubMed - indexed for MEDLINE]**

Investigation of the efficacy of progesterone pessaries in the relief of symptoms of premenstrual syndrome. progesterone Study Group.

**Magill PJ.**
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BACKGROUND. A variety of definitions have been applied to premenstrual syndrome. The severity of the syndrome is also variable. AIM. A study was undertaken to compare progesterone pessaries with placebo in the relief of symptoms of premenstrual syndrome. In this study the condition was
characterized by a wide range of symptoms recurring in the late luteal phase but absent in the follicular phase (that is, the specific definition published by Dalton in 1953). METHOD. A multicentre, prospective, double-blind, randomized, parallel group study was undertaken by 45 general practitioners. Patients were deemed eligible after two prospective menstrual cycles of observation (selection phase) in which a precise definition of symptoms was applied. Patients were randomized to use either progesterone pessaries (400 mg twice a day) or matching placebo, by vaginal or rectal administration, from 14 days before the expected onset of menstruation until the onset of vaginal bleeding, for four consecutive cycles. Baseline data for the outcome variables were determined in the selection phase. The main outcome variables were changes in the severity (categorized as none, mild, moderate or severe) of each patient's most severe symptom, and in the average score of all the patient's symptoms characteristic of premenstrual syndrome. Spontaneous reports of adverse events were recorded. RESULTS. A total of 281 patients were screened for premenstrual syndrome; of these, 141 patients were randomized to treatment or placebo groups. Efficacy was evaluated in 93 patients. Reductions in the scores of the highest scoring, most severe, symptoms and in the average symptom score, were consistently observed in patients receiving progesterone pessaries and in those receiving placebo. The response to progesterone was greater than to placebo during each cycle; the differences were clinically and statistically significant. Adverse events were reported by 51% of patients in the progesterone treatment group and by 43% in the placebo group. Irregularity of menstruation, vaginal pruritus and headache were reported more frequently by patients taking active therapy. CONCLUSION. In this study, progesterone, given as pessaries by vaginal or rectal administration, was more effective than placebo in the relief of symptoms of premenstrual syndrome in a population of patients selected by strict entry criteria.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 8554838 [PubMed - indexed for MEDLINE]


**Diverse modes of action of progesterone and its metabolites.**

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Progesterone and its metabolites have a variety of diverse effects in the brain,
uterus, smooth muscle, sperm and the oocyte. The effects include changes in electrophysiological excitability, induction of anesthesia, regulation of gonadotropin secretion, regulation of estrogen receptors, modulation of uterine contractility and induction of acrosome reaction and oocyte maturation. The latency of the effects vary from several seconds to several hours. Thus, it is not surprising that multiple mechanisms of action are involved. The classical mechanism of steroid hormone action of intracellular receptor binding has been supplemented by the possibility of the steroid acting as a transcription factor after the binding of the receptor protein to DNA. Other mechanisms include influence of the steroids on membrane fluidity and acting through other cell signalling systems, membrane receptors and GABA(A) receptors. Of particular interest are multiple mechanisms for the same types of action. For example the effect of progesterone on gonadotropin release is largely exerted via the classical intracellular receptor as well as membrane receptors, whereas 3(alpha),5(alpha)-tetrahydroprogesterone-induced LH release occurs via the GABA(A) receptor system. The inhibition of uterine contractility by progesterone is regulated by progesterone receptors while the action of 3(alpha),5(alpha)-tetrahydroprogesterone on uterine contractility is regulated by GABA(A) receptors. The regulation of the differences in the pattern of progesterone effects on estrogen receptor dynamics in the anterior pituitary and the uterus in the same animal are also of considerable interest.

Publication Types:
- Review
- Review, Academic

PMID: 8603042 [PubMed - indexed for MEDLINE]

Science 1986 May 23;232(4753):1004-7

Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM.

Two metabolites of the steroid hormones progesterone and deoxycorticosterone, 3 alpha-hydroxy-5 alpha-dihydroprogesterone and 3 alpha, 5 alpha-tetrahydrodeoxycorticosterone, are potent barbiturate-like ligands of the gamma-aminobutyric acid (GABA) receptor-chloride ion channel complex. At concentrations between 10(-7) and 10(-5)M both steroids inhibited binding of the convulsant t-butylidicyclophosphorothionate to the GABA-receptor complex and increased the binding of the benzodiazepine flunitrazepam; they also stimulated chloride uptake (as measured by uptake of 36Cl-) into isolated brain vesicles, and potentiated the inhibitory actions of GABA in cultured rat hippocampal and spinal
Hypothalamic dysfunction.

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A pulsatile GnRH stimulus is required to maintain gonadotropin synthesis and secretion. The frequency and amplitude of GnRH pulses determine gonadotropin subunit gene expression and secretion of pituitary LH and FSH. Rapid frequency (more than 1 pulse per h) GnRH pulses favor LH while slower frequencies favor FSH secretion. During ovulatory cycles, an increase in GnRH frequency during the follicular phase favors LH synthesis prior to the LH surge, while following ovulation, luteal steroids slow GnRH pulses to favor FSH synthesis. Thus, a changing frequency of GnRH stimulation of the gonadotrope is one of the mechanisms involved in differential gonadotropin secretion during ovulatory cycles. In hypothalamic amenorrhea a majority of women exhibit a persistent slow frequency of LH (GnRH) pulses, which reflects excess hypothalamic opioid tone and can be temporarily reversed by opioid antagonists. At the other end of the spectrum, in polycystic ovarian syndrome, LH (GnRH) pulses are persistently rapid and favor LH synthesis, hyperandrogenism and impaired follicular maturation. Administration of progesterone can slow GnRH pulse secretion, favor FSH secretion and induce follicular maturation. Thus, the ability to change the pattern of GnRH secretion is an important factor in the maintenance of cyclic ovulation, and loss of this function leads to anovulation and amenorrhea.
progestins: clinical implications for premenstrual syndrome and perimenopause management.

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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.

Publication Types:
- Review
- Review, Tutorial

PMID: 9669099 [PubMed - indexed for MEDLINE]

Preserved forearm endothelial responses with acute exposure to progesterone: A randomized cross-over trial of 17-beta estradiol, progesterone, and 17-beta estradiol with progesterone in healthy menopausal women.

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Regularly menstruating women are relatively protected from cardiovascular disease. Epidemiological and endothelial function studies attribute this protection to estradiol (E(2)), but both progesterone (P) and E(2) are normally present. A range of vascular effects of added progestins have been described, from neutral to detrimental, but the effects of P per se on endothelial function in humans have not been reported. We therefore investigated the acute effects of E(2), P, and E(2) combined with P, on endothelium-dependent and -independent forearm blood flow responses. Using venous occlusion plethysmography, forearm blood flow (FBF) was measured during acute brachial artery infusions, achieving physiologic levels of 17-beta-E(2), P, and 17-beta-E(2) with P in healthy menopausal women with no cardiovascular disease risk factors. Vehicle or hormones were infused, in random order, on 4 days, 1 week apart. Flow responses were measured during coinusions of hormone with the endothelium-dependent vasodilator acetylccholine and the endothelium-independent vasodilator sodium nitroprusside. Twenty-seven
healthy menopausal women were studied, and all had normal baseline endothelial responses. Small (approximately 15%), statistically nonsignificant increases in endothelium-dependent flow responses were seen after all acute hormone treatments. No impairment in response was seen with P alone or in combination with 17-beta-E(2). In healthy menopausal women without cardiovascular disease risk factors and without baseline defects in endothelial function, acute exposure to physiologic levels of 17-beta-E(2), P, and 17-beta-E(2) with P produced equivalent endothelium-dependent responses. These data suggest that P does not have detrimental vascular effects in humans.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 11134122 [PubMed - indexed for MEDLINE]

**Antiestrogen action of progesterone in breast tissue.**

**Mauvais-Jarvis P, Kuttenn F, Gompel A.**
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This review analyzes recent data from international literature concerning the antiestrogen action of progesterone and progestins at the level of mammary cells in culture from either breast cancer lines or normal breast obtained from reduction mammoplasties. Most data indicate that progesterone and progestins have a strong antiestrogen effect on breast cell appreciated by the decrease of estradiol receptor content, the decrease of cell multiplication and the stimulation of 17 beta-hydroxysteroid activity which may be considered as a marker of breast cell differentiation dependent of progesterone receptor.

Publication Types:
- Review
- Review, Tutorial

PMID: 3331374 [PubMed - indexed for MEDLINE]

In most target tissues of the female genital tract, an adequate cell differentiation can be obtained with the successive and synergistic action of estradiol (E2) and progesterone (P), essentially because the progesterone receptor (PR) synthesis implicates the previous action of E2 via its E2 receptor (ER). In normal breast, E2 stimulates the growth of the ductal system whereas the development of acini depends on P secretion. In other words, when E2 plus P are secreted by the ovaries in balanced proportions, the two hormones permit a complete and harmonious development of the mammary gland. The antiestrogenic activity of P is carried out through the decrease of ER resynthesis and stimulation of 17 beta-hydroxysteroid dehydrogenase enzyme activity, which transforms E2 into its less active metabolite estrone (E1) in the target cells. These biochemical events are well documented concerning the endometrium. They have also been observed in normal mammary cells in primary cultures as well as in breast fibroadenomas with high epithelial cellularity. Moreover, data from literature indicate that E2 could be both a direct and indirect factor of cell multiplication in cancerous cell lines. P as well as progestins have the opposite effect. Recent results from this laboratory indicate that E2 and P also have antagonistic effects on the cell multiplication of normal human mammary cells in primary culture. Therefore, the hypothesis that a lack of P during a long period of the female genital like could be a factor in the promotion of breast cancer must be considered.

Publication Types:

- Review

PMID: 3535636 [PubMed - indexed for MEDLINE]


Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study.

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OBJECTIVE: To determine pharmacokinetic and endometrial effects of vaginally delivered micronized P. DESIGN: Functionally agonadal estrogen-replacement recipients received either micronized P administered vaginally or bi-daily IM injections of P. Hourly blood samples were obtained, from baseline to 6 hours after the initial dose of P and again on simulated cycle day 21 when transvaginal ultrasound (US) measurements and tissue samples of the endometrium were performed. Blood and tissue samples were assayed for P. Endometrial histology, estrogen receptor (ER) and P receptor (PR) contents were evaluated. SETTING: University of Southern California School of Medicine, Los Angeles, California. PARTICIPANTS: Twenty functionally agonadal and four normally ovulating women. MAIN OUTCOME MEASURE: Delivery differences were assessed by [1] endometrial P concentrations; [2] USs; [3] histologic datings; [4] ER and PR contents, and [5] serum P levels. RESULTS: Endometrial P concentrations were higher with vaginally administered P than endometrial concentrations observed in normal ovulatory women or women who consistently had the highest serum P after IM administration (11.50 +/- 2.60 versus 1.40 +/- 0.40 versus 0.30 +/- 0.10 ng/mg protein [36.56 +/- 8.27 versus 4.45 +/- 1.27 versus 0.95 +/- 0.32 nmol/L], respectively). After 7 days of P, no differences between either treatment regimen and control groups were detected by histologic, ultrasonographic, or immunocytochemical receptor analyses. CONCLUSION: Vaginal micronized P enhances P delivery to the uterus compared with a standard IM regimen and results in a synchronous secretory endometrial histology in agonadal women preparing for embryo donation.

PMID: 8062942 [PubMed - indexed for MEDLINE]


Serum progesterone and prognosis in operable breast cancer.

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Several studies have now shown that women with operable breast cancer undergoing tumour excision during the luteal phase of the menstrual cycle have a better prognosis than those having surgery during the follicular phase. As part of a prospective study of prognostic factors in breast cancer, blood was taken at the time of surgery. Between 1975 and 1992 this was available from 289 premenopausal women within 3 days of tumour excision. All were treated by either modified radical mastectomy or breast conservation including axillary clearance and the date of last menstrual period (LMP) was known in 239 (80%) cases. Blood samples were assayed for both oestriadiol (E2) and progesterone (P). Because of the wide inter-individual variation in E2 levels there was no clear relationship between E2 and LMP. However, using a running mean smoothing technique the expected cyclical variation could be discerned. There was no
significant association between E2 and survival. Smoothing of the P data yielded a pattern similar to the normal hormone profile. Those cases with a progesterone level of 4 ng ml-1 or more had a significantly better survival than those with a level < 4 ng ml-1. This was especially clear in node-positive patients (P < 0.01). The possibility of misclassification of menstrual cycle status, because of misreported LMP, has been minimised by applying an independent hormonal measurement (P) of cycle activity. This parameter will also identify women who may be undergoing anovular cycles. Thus this study has confirmed that a raised level of progesterone at the time of tumour excision is associated with an improvement in prognosis for women with operable breast cancer.

PMID: 8664128 [PubMed - indexed for MEDLINE]

**Effect of progesterone on peripheral blood flow in prepubertal female anesthetized pigs.**

Molinari C, Battaglia A, Grossini E, Mary DA, Surico N, Vacca G.

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This study was undertaken to determine the effects of progesterone on the peripheral circulation. In prepubertal female pigs anesthetized with sodium pentobarbitone, changes in the superior mesenteric, left renal and left external iliac flow caused by intravenous infusion of progesterone were assessed using electromagnetic flow meters. Changes in heart rate and arterial blood pressure were prevented by atrial pacing and by connecting the arterial system to a pressurized reservoir containing Ringer solution. In 20 pigs, infusion of 1 mg/kg of progesterone increased mesenteric, renal and iliac flow. In a further 4 pigs, the vasodilatory effects of the hormone were enhanced by graded increases in the dose between 1, 2 and 3 mg/kg. The mechanisms of these responses were studied in the 20 pigs by repeating the experiment after hemodynamic variables had returned to the control values before infusion. In 5 pigs, blockade of adrenergic receptors with propranolol and phentolamine did not affect the responses elicited by progesterone. The increases in mesenteric, renal and iliac flow to progesterone were prevented, respectively, by the injection of N(omega)-nitro-L-arginine methyl ester into the mesenteric (5 pigs), the renal (5 pigs) or the iliac artery (5 pigs). The present study shows that intravenous infusion of progesterone dilated mesenteric, renal and iliac circulations. The mechanism of this response involved the release of nitric oxide. Copyright 2001 S. Karger AG, Basel

PMID: 11740156 [PubMed - indexed for MEDLINE]
Prevention of endometrial hyperplasia by progesterone during long-term estradiol replacement: influence of bleeding pattern and secretory changes.

Moyer DL, de Lignieres B, Driguez P, Pez JP. University of Southern California Medical Center, Los Angeles.

OBJECTIVE: To determine the relative influences of induction of withdrawal bleedings secretory transformation, and reduction of mitosis in glands on prevention of endometrial hyperplasia during long-term hormonal replacement therapy. DESIGN: Observational expanded clinical case report. SETTING: Reproductive Endocrine Department of Hospital Necker, Paris, France, and Pathology Department of Women's Hospital, Los Angeles County and University of Southern California Medical Center, Los Angeles, California. PATIENTS: Postmenopausal women seeking treatment for symptomatic menopause. INTERVENTIONS: Endometrial biopsy and/or ambulatory hysteroscopy. MAIN OUTCOME MEASURE: Endometrial histology including progestational maturation patterns and glandular epithelial mitosis rates. Macroscopic endometrial appearance. RESULTS: The use of larger doses of E2 and P induced more marked secretory changes and more frequent withdrawal bleeding than the lower doses. There was no evidence of endometrial hyperplasia after 5 years of E2/P replacement therapy independently of bleeding pattern or progestational maturation. Consistent reduction of mitosis rates in glandular epithelium was found after 9 or more days of P administration in each cycle. CONCLUSIONS: Control of endometrial growth is mainly related to control of mitosis in glands by a relatively low doses of P. Induction of withdrawal bleeding and endometrial secretory transformation, which require larger doses of Progesterone, do not provide additional benefit for prevention of hyperplasia. Induction of amenorrhea with a relatively low dose of P may be offered to women seeking hormone replacement therapy with similar levels of safety.

PMID: 8486201 [PubMed - indexed for MEDLINE]

Serum progesterone levels following vaginal administration of progesterone during the luteal phase.

Myers ER, Sondheimer SJ, Freeman EW, Strauss JF 3rd, Rickels K.

We measured serum progesterone (P) levels after administration of 400 mg P vaginal suppositories to women during the luteal phase of the menstrual cycle.
Blood samples were obtained before suppository insertion and at five intervals up to 8 hours after insertion. On the first day of treatment with P suppositories, there was a substantial elevation in serum P above baseline after insertion. However, on subsequent days of administration a smaller increment in serum P was observed. In 4 women studied on days 1 and 8 of the same treatment cycle in the luteal phase, a smaller rise in serum P following suppository administration on day 8, compared with day 1, was found. Overall, a highly significant negative correlation between change in serum P from baseline and duration of vaginal suppository treatment was found. This observation does not appear to be related to the achievement of a pharmacokinetic steady state. Possible mechanisms for this observation are discussed.

PMID: 3792576 [PubMed - indexed for MEDLINE]

Maturitas 1993 May;16(3):185-202

Profiles of plasma estrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone.

Nahoul K, Dehennin L, Jondet M, Roger M.
Fondation de Recherche en Hormonologie, Fresnes, France.

Doses of 100 mg of micronized progesterone (P) and of 0.5 mg of micronized estradiol (E2) were administered vaginally and orally, respectively, in the early follicular phase of the menstrual cycle in six premenopausal women. In the second cycle, the same doses were administered in the same subjects, orally for P and vaginally for E2. Serial blood samples were collected and the following steroids were assayed by highly reliable techniques: P, E2, estrone (E1), deoxycorticosterone (DOC), 5 alpha- and 5 beta-pregnanolone and the sulfates of E1, E2, and DOC. Circulating P and E2 levels were higher after vaginal than after oral administration, while those of E1 were similar after either route. Metabolites of P (DOC, DOCS and pregnanolone) were higher after oral administration. Concerning estrogen sulfates, E1S concentrations were similar whichever the route, while those of E2S were lower after oral than after vaginal administration. This study has confirmed that metabolism of ingested P and E2 occurs mainly in the intestine. Moreover, P was predominantly metabolized to 5 alpha-reduced derivatives, whatever the route of administration. In view of the metabolic pathways which are operative and of the peripheral plasma levels which were found, the vaginal route appears to be more adequate than the oral one for hormone replacement therapy.

PMID: 8515718 [PubMed - indexed for MEDLINE]
Comparative bioavailability of orally and vaginally administered progesterone.

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OBJECTIVE: To study the pharmacokinetics of progesterone (P) in healthy premenopausal female volunteers to compare the bioavailability of orally or vaginally administered hormone. DESIGN: Subjects were randomly allocated to receive either oral P or a vaginal pessary then crossed over to the alternate preparation 1 month later. SETTING: The study was conducted in outpatient setting. SUBJECTS: All subjects were healthy, normal female volunteers who underwent a physical and gynecological examination before the study. None were using oral contraceptives. Ten subjects (mean age 32.6 +/- 7.3 years) entered the study and all completed it. INTERVENTIONS: Progesterone was administered as 200 mg of micronized hormone or as a pessary containing 400 mg. MAIN OUTCOME MEASURE: Plasma levels of P were measured by radioimmunoassay to test the apriori hypothesis of similar bioavailability. RESULTS: Peak plasma P concentrations attained within 4 hours after oral administration ranged from 8.5 to 70.6 ng/mL, whereas after vaginal administration the peak levels were attained within 8 hours and ranged from 4.4 to 181.1 ng/mL. Considerable interindividual variation was noted. Area under the plasma concentration-time curve for the two formulations was not significantly different (F = 1.09; P greater than 0.1; ANOVA). CONCLUSIONS: The two formulations had similar bioavailability.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 1743318 [PubMed - indexed for MEDLINE]
were determined in 18 women with premenstrual syndrome and 10 symptomless (control group) women. Plasma progesterone concentration was higher in the women with symptoms during the postovulatory phase of the cycle, and the peak progesterone concentration appeared earlier. The changes in progesterone concentration were accompanied by a natriuresis and diuresis that fell towards preovulatory values in the premenstrual phase. Sodium retention was not confined to any definite period. Mood symptoms occurred after the changes in progesterone and electrolyte concentrations. Progesterone deficiency is probably not the cause of premenstrual syndrome. Thus treatment with progesterone is probably illogical unless a deficiency is detected. Treatment should be aimed at preventing the natriuretic effect of progesterone in the postovulatory phase and the sodium-retaining and water-retaining effects of aldosterone in the premenstrual phase.

PMID: 7190047 [PubMed - indexed for MEDLINE]

Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre- and postmenopausal women.

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OBJECTIVE: The use of topically applied micronised ('natural') progesterone as a substitute for synthetic oestrogens and progestogen preparations is controversial. The aim of this study was to examine the changes in blood and salivary concentrations of progesterone following a single topical application of a progesterone cream. PATIENTS AND MEASUREMENTS: We investigated six premenopausal women in the luteal phase and six postmenopausal women to determine the short-term changes in serum, urinary and salivary progesterone concentrations following a single 64 mg topical application of micronised progesterone. RESULTS: Serum progesterone concentrations did not increase during the first 3 hours after application of progesterone cream, however, salivary values rose significantly in both premenopausal and postmenopausal women, consistent with the view that progesterone is absorbed and transported through the body. Salivary progesterone concentrations were significantly elevated above basal levels by 30-60 minutes and reached peak levels at 1-4 h, with mean levels approximately fivefold higher in premenopausal, than in menopausal women. CONCLUSIONS: Salivary progesterone measurements confirm that topically applied progesterone is absorbed, despite the lack of change in serum progesterone concentrations. However, at the dose administered, serum progesterone levels do not reach those observed after oral or vaginally delivered progesterone preparations. Higher doses may be required to induce biological
responses within the endometrium.

PMID: 11106923 [PubMed - indexed for MEDLINE]


**Serum levels of progesterone and some of its metabolites including deoxycorticosterone after oral and parenteral administration.**

**Ottoson UB, Carlstrom K, Damber JE, von Schoultz B.**

Single 100-mg doses of progesterone were given orally and as intramuscular injections to four women during the follicular phase of the menstrual cycle. After oral administration serum levels of progesterone increased rapidly to reach luteal phase values (mean maximum level 55.6 nM) within 1-4 h and were still elevated after 12 h. The serum concentrations of 20 alpha-hydroxy-4-pregnen-3-one showed a similar pattern while there were only minor transient changes in 17 alpha-hydroxyprogesterone concentrations. The serum levels of cortisol and 4-androstene-3,17-dione were unaffected. In comparison, after intramuscular administration values two to three times higher than by the oral route were achieved. A significant increase in serum deoxycorticosterone was recorded in all women. The mean ratio between the change in deoxycorticosterone and progesterone was increased after oral administration. Oral treatment with natural progesterone may develop into an attractive alternative to synthetic progestogens but the conversion of progesterone into a potent mineralocorticoid may be a potential disadvantage.

PMID: 6498126 [PubMed - indexed for MEDLINE]

Cancer Detect Prev 1999;23(4):290-6

**Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease.**

**Plu-Bureau G, Le MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P.**

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Percutaneous progesterone topically applied on the breast has been proposed and widely used in the relief of mastalgia and benign breast disease by numerous gynecologists and general practitioners. However, its chronic use has never been evaluated in relation to breast cancer risk. The association between percutaneous progesterone use and the risk of breast cancer was evaluated in a cohort study of
1150 premenopausal French women with benign breast disease diagnosed in two breast clinics between 1976 and 1979. The follow-up accumulated 12,462 person-years. Percutaneous progesterone had been prescribed to 58% of the women. There was no association between breast cancer risk and the use of percutaneous progesterone (RR = 0.8; 95% confidence interval 0.4-1.6). Although the combined treatment of oral progestogens with percutaneous progesterone significantly decreased the risk of breast cancer (RR = 0.5; 95% confidence interval 0.2-0.9) as compared with nonusers, there was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users. Taken together, these results suggest at least an absence of deleterious effects caused by percutaneous progesterone use in women with benign breast disease.

PMID: 10403900 [PubMed - indexed for MEDLINE]

**Endocr Rev 1990 May;11(2):386-98**

**Progesterone as a bone-trophic hormone.**

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Experimental, epidemiological, and clinical data indicate that progesterone is active in bone metabolism. Progesterone appears to act directly on bone by engaging an osteoblast receptor or indirectly through competition for a glucocorticoid osteoblast receptor. Progesterone seems to promote bone formation and/or increase bone turnover. It is possible, through estrogen-stimulated increased progesterone binding to the osteoblast receptor, that progesterone plays a role in the coupling of bone resorption with bone formation. A model of the interdependent actions of progesterone and estrogen on appropriately-"ready" cells in each bone multicellular unit can be tied into the integrated secretions of these hormones within the ovulatory cycle. Figure 5 is an illustration of this concept. It shows the phases of the bone remodeling cycle in parallel with temporal changes in gonadal steroids across a stylized ovulatory cycle. Increasing estrogen production before ovulation may reverse the resorption occurring in a "sensitive" bone multicellular unit while gonadal steroid levels are low at the time of menstrual flow. The bone remodeling unit would then be ready to begin a phase of formation as progesterone levels peaked in the midluteal phase. From this perspective, the normal ovulatory cycle looks like a natural bone-activating, coherence cycle. Critical analysis of the reviewed data indicate that progesterone meets the necessary criteria to play a causal role in mineral metabolism. This review provides the preliminary basis for further molecular, genetic, experimental, and clinical investigation of the role(s) of progesterone in bone remodeling. Much further data are needed about the interrelationships between gonadal steroids and the "life cycle" of bone. Feldman et al., however, may have
been prophetic when he commented; "If this anti-glucocorticoid effect of progesterone also holds true in bone, then postmenopausal osteoporosis may be, in part, a progesterone deficiency disease."

Publication Types:

- Review
- Review, Tutorial

PMID: 2194787 [PubMed - indexed for MEDLINE]

J Am Coll Cardiol 2000 Dec;36(7):2154-9

**Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women.**

**Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P.**

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OBJECTIVES: We sought to compare the effects of estrogen/transvaginal progesterone gel with estrogen/medroxyprogesterone acetate (MPA) on exercise-induced myocardial ischemia in postmenopausal women with coronary artery disease or previous myocardial infarction, or both. BACKGROUND: Estrogen therapy beneficially affects exercise-induced myocardial ischemia in postmenopausal women; however, women with an intact uterus also take progestin to protect against uterine malignancies. The effects of combination estrogen/progestin therapy on myocardial ischemia are unknown. METHODS: Eighteen postmenopausal women (mean +/- SD age 59 +/- 7 years) were given 17-beta-estradiol in single-blinded manner for four weeks (1 mg/day for three weeks then 2 mg/day for one week). Estradiol (2 mg/day) was then continued, and the patients were randomized (double-blind) for 12 days to either transvaginal progesterone gel (90 mg on alternate days) and oral MPA placebo (10 mg/day), or vice versa. After another two weeks on estradiol alone, the patients crossed over to progestin treatment and repeated the protocol on the opposite treatment. Patients underwent treadmill exercise testing after each estradiol phase and at day 10 of each progestin phase. RESULTS: Exercise time to myocardial ischemia increased after the first estrogen phase as compared with baseline (mean difference with 95% confidence interval [CI]: 72 s [34 to 110], p = 0.001), and was increased by combination estradiol/progesterone therapy as compared with estradiol/MPA therapy (92 s [35 to 149], p = 0.001)). Two patients (11%) were withdrawn while taking estradiol/MPA owing to unstable angina. CONCLUSIONS: Combination estrogen/transvaginal progesterone gel increases
exercise time to myocardial ischemia, as compared with estrogen/MPA. These results imply that the choice of progestin in women at higher cardiovascular risk requires careful consideration.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 11127455 [PubMed - indexed for MEDLINE]

**Br Med J (Clin Res Ed) 1985 Jan 5;290(6461):13-4**

**Natural progesterone and antihypertensive action.**

**Rylance PB, Brincat M, Lafferty K, De Trafford JC, Brincat S, Parsons V, Studd JW.**

In a placebo controlled, double blind crossover study natural progesterone was given by mouth, in increasing doses, to six men and four postmenopausal women with mild to moderate hypertension who were not receiving any other antihypertensive drugs. When compared with values recorded before treatment and during administration of placebo progesterone caused a significant reduction in blood pressure, suggesting that progesterone has an antihypertensive action rather than a hypertensive one as has been previously thought. This possible protective effect of progesterone should be investigated further.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 3917316 [PubMed - indexed for MEDLINE]

**Arterioscler Thromb Vasc Biol 1997 Nov;17(11):3071-8**

**Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial.**

**Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M.**
INSERM-Cardiovascular Epidemiology Unit U258, Hopital Broussais, Paris,
Postmenopausal hormone replacement therapy is associated with a reduction in the incidence of coronary heart disease. However, inconclusive results have been reported with respect to the risk of stroke, and recent studies consistently showed an increased risk of venous thromboembolism in postmenopausal women using oral estrogen. There are surprisingly few interventional studies to assess the true effects of estrogen-progestin regimens on blood coagulation and fibrinolysis, and the impact of the route of estrogen administration on hemostasis has not been well documented. Therefore, we investigated the effects of oral and transdermal estradiol/progesterone replacement therapy on hemostatic variables. Forty-five healthy postmenopausal women, aged 45 to 64 years, were assigned randomly to one of the three following groups: cyclic oral or transdermal estradiol, both combined with progesterone, or no hormonal treatment. Hemostatic variables were assayed at baseline and after a 6-month period. Pairwise differences in the mean change between the three groups were compared using nonparametric tests. Oral but not transdermal estradiol regimen significantly increased the mean value of prothrombin activation peptide (F1 + 2) and decreased mean antithrombin activity compared with no treatment. Differences in fragment F1 + 2 levels between active treatments were significant. The oral estrogen group was associated with a significant decrease in both mean tissue-type plasminogen (t-PA) concentration and plasminogen activator inhibitor (PAI-1) activity and a significant rise in global fibrinolytic capacity (GFC) compared with the two other groups. A transdermal estrogen regimen had no significant effect on PAI-1, t-PA, and GFC levels. There were no significant changes in mean values of fibrinogen, factor VII, von Willebrand factor, protein C, fibrin D-dimer, and plasminogen between and within the three groups. We conclude that oral estrogen/progesterone replacement therapy may result in coagulation activation and increased fibrinolytic potential, whereas opposed transdermal estrogen appears without any substantial effects on hemostasis. Whereas these results may account for an increased risk of venous thromboembolism in users of oral postmenopausal estrogen, they emphasize the potential importance of the route of estrogen administration in prescribing hormone replacement therapy to postmenopausal women, especially to those at high risk of thrombotic disease.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 9409295 [PubMed - indexed for MEDLINE]

Calcif Tissue Int 2000 Jul;67(1):47-52

Effects of estrogen and progesterone on tibia histomorphometry in
The present study was performed to evaluate possible interactions between estrogen and progesterone on peak cancellous bone mass. Ovariectomized (OVX) growing rats were treated with 17beta-estradiol (4.8 microg/day), progesterone (4.8 mg/day), a combination of the two sex steroids, or with vehicle for 14 days beginning 7 days after OVX. The tibiae were removed for histomorphometric analysis of the proximal metaphysis. OVX and growth each resulted in net resorption of cancellous bone at a sampling site adjusted for longitudinal bone growth. Estradiol and progesterone treatment each antagonized bone loss by inhibiting the decrease in trabecular number. Estradiol increased but progesterone had no effect on trabecular thickness. Progesterone did not influence either osteoclast number or the resorption of the pretreatment fluorochrome label. Estradiol reduced osteoclast number and inhibited label resorption, the latter change being accentuated by combination treatment. Estradiol reduced and progesterone enhanced the mineral apposition and bone formation rates. The results indicate that estradiol and progesterone have independent activities on cancellous bone turnover during growth. Whereas estradiol reduced bone turnover, progesterone had a stimulatory effect on bone formation. These findings suggest that progesterone has a role in establishing and maintaining peak cancellous bone volume during growth.

PMID: 10908413 [PubMed - indexed for MEDLINE]

Micronized progesterone: vaginal and oral uses.

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Publication Types:

- Review
- Review, Tutorial

PMID: 8616985 [PubMed - indexed for MEDLINE]
Ovarian hormones elicit phosphorylation of Akt and extracellular-signal regulated kinase in explants of the cerebral cortex.

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Estradiol and progesterone both have been demonstrated to afford neuroprotection against various insults. In an attempt to identify potential mechanisms underlying these neuroprotective effects, two key elements within signal transduction pathways linked to neuroprotection were evaluated. In mouse cerebral cortical explants, both estradiol and progesterone elicited the phosphorylation of Akt, a downstream effector of the phosphoinositide-3 (PI-3) kinase pathway. Progesterone also elicited the phosphorylation of extracellular-signal regulated kinase (ERK), a component of the mitogen-activated protein kinase (MAPK) pathway. These effects were not inhibited by the progesterone receptor antagonist, RU486. However, inhibition of either MAPK/ERK kinase with PD98059 or PI-3 kinase with LY294002 successfully inhibited progesterone's actions on ERK and Akt, respectively. Collectively, the data offer novel mechanisms for both progesterone and estrogen action in the central nervous system, demonstrating the functional and mechanistic diversity of gonadal hormones and supporting their neuroprotective potential for such neurodegenerative disorders as Alzheimer disease.

PMID: 11444439 [PubMed - indexed for MEDLINE]

Role of progesterone in normal breast physiology.

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The extant literature indicates that progesterone significantly influences normal mammary growth and differentiation. However, most breast tissue research is conducted using malignant cells, in which the progesterone activity differs greatly from that in normal cells. Although progesterone has been demonstrated to support cyclic proliferation in the breast during the menstrual cycle and pregnancy, in vitro studies have been inconsistent in their assessments of progesterone's role in proliferation. Similarly, mitotic activity in the breast reaches its peak during the progesterone-dominant luteal phase of the menstrual

PMID: 10231049 [PubMed - indexed for MEDLINE]
cycle, and therefore some researchers claim that progesterone plays a major role in breast cancer; however, several clinical observations have found evidence dismissing progesterone as a key factor. Thus, researchers seek to expand our current understanding of the role of progesterone in breast physiology.

Publication Types:
- Review
- Review, Tutorial

PMID: 11392028 [PubMed - indexed for MEDLINE]

J Reprod Med 1999 Feb;44(2 Suppl):141-7

**Pharmacokinetics of progesterone administered by the oral and parenteral routes.**

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Progestogens, which include the natural hormone, progesterone, and synthetic steroid derivatives, are used to treat a variety of reproductive disorders. Since synthetic progestogens are often associated with undesirable side effects, improved formulations and modes of administration of progesterone have been sought. In order to find an optimal therapeutic agent, different progesterone formulations and routes of administration have been studied. This paper explains several methods of measuring progesterone levels and summarizes clinical data on the pharmacokinetic profiles of natural progesterone administered by the oral, intramuscular, vaginal, intranasal, percutaneous, sublingual and rectal routes.

Publication Types:
- Review
- Review, Tutorial

PMID: 11392023 [PubMed - indexed for MEDLINE]

Hum Reprod Update 2000 Mar-Apr;6(2):139-48

**Comparison between different routes of progesterone administration as luteal phase support in infertility treatments.**
Different routes of natural progesterone supplementation have been tried as luteal phase support in infertility treatments. Orally administered progesterone is rapidly metabolized in the gastrointestinal tract and its use has proved to be inferior to i.m. and vaginal routes. Progesterone i.m. achieves serum progesterone values that are within the range of luteal phase and results in sufficient secretory transformation of the endometrium and satisfactory pregnancy rates. The comparison between i.m. and vaginal progesterone has led to controversial results as regards the superiority of one or the other in inducing secretory endometrial transformation. However, there is increasing evidence in the literature to favour the use of vaginal progesterone. Vaginally administered progesterone achieves adequate endometrial secretory transformation but its pharmacokinetic properties are greatly dependent on the formulation used. After vaginal progesterone application, discrepancies have been detected between serum progesterone values and histological endometrial features. Vaginally administered progesterone results in adequate secretory endometrial transformation, despite serum progesterone values lower than those observed after i.m. administration, even if they are lower than those observed during the luteal phase of the natural cycle. This discrepancy is indicative of the first uterine pass effect and therefore of a better bioavailability of progesterone in the uterus, with minimal systematic undesirable effects.

Publication Types:

- Review
- Review, Tutorial

PMID: 10782572 [PubMed - indexed for MEDLINE]

**Gynecol Obstet Invest 1993;36(4):234-8**

**Progesterone reduces sympathetic tone without changing blood pressure or fluid balance in men.**

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There is scant information on the effects of progesterone on circulation. Changes in catecholamine levels, blood pressure and transcapillary fluid balance were measured in 12 men before and during administration of natural progesterone (Utrogestan). Before administration, systolic blood pressure was significantly correlated with venous adrenaline ($r = 0.67$, $p = 0.01$). There was a significant decrease ($p = 0.004$) in venous noradrenaline during progesterone administration,
and systolic blood pressure was significantly correlated with the arteriovenous difference for noradrenaline (r = 0.66, p = 0.02). Serum progesterone, which attained levels similar to those found in women during the luteal phase, did not significantly alter blood pressure, body weight or intra- to extravascular fluid shift. It is concluded that progesterone may have a direct action by increasing the uptake of noradrenaline from the synaptic cleft or by decreasing the nerve firing rate. Interestingly, the pretreatment finding of a significant correlation between blood pressure and adrenaline was less evident during progesterone administration.

PMID: 8300009 [PubMed - indexed for MEDLINE]

Follow-up examination at the age of 15 months of extremely preterm infants after postnatal estradiol and progesterone replacement.

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A randomized controlled pilot study was performed with a sample of extremely preterm infants to evaluate the impact of postnatal estradiol and progesterone replacement on postnatal bone mineral accretion. Twenty-five of 30 infants in the pilot study survived, and of these, 24 infants were available for the follow-up examination at a median chronological age of 18.1 months (minimum-maximum, 17.0--20.6) corresponding to a corrected age of 14.8 months (minimum-maximum, 12.9--17.4). Somatic growth data and bone mineralization showed no differences between the hormone-treated and control group infants. The deviation of the skeletal age from the corrected age was 0.0 months (minimum-maximum, -7.7 to 7.4) for hormone-treated infants compared with -1.7 months (minimum-maximum, -7.5 to 5.9) for the control group. The Bayley scales mental and psychomotor developmental indexes were 89 (minimum-maximum, 71--107) and 101 (minimum-maximum, 49--121) for the hormone-treated infants and 93 (minimum-maximum, 49--111) and 71 (minimum-maximum, 49--121) for the control group infants, respectively (mental developmental index, P = 1.0; psychomotor developmental index, P = 0.14). The normal psychomotor development in the hormone-treated infants compared with the below average development in the control group infants is encouraging and indicates the potentially important integrative role of sex steroids for the developing brain. Larger studies on the effects of the postnatal replacement of estradiol and progesterone in extremely preterm infants are warranted.
Management of the extremely preterm infant: is the replacement of estradiol and progesterone beneficial?

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This review presents data to suggest that postnatal estradiol and progesterone replacement therapy may be beneficial in preterm infants. During pregnancy, maternal plasma levels of estradiol and progesterone increase up to 100-fold compared to the nonpregnant status. The fetus is also exposed to these increasing hormone levels. After delivery, estradiol and progesterone levels drop by a factor of 100 within 1 day. Whereas this is a physiological condition for an infant born at term, preterm delivery means withdrawal from the placental supply of these hormones at an earlier developmental stage. Seventy years ago, the idea was raised that preterm infants may benefit from the replacement of estrogens. Studies in which estrogen was injected subcutaneously showed only a slightly better bodyweight gain compared to placebo-treated controls and therefore routine use was not established. The effective treatment of postmenopausal osteoporosis with hormone replacement therapy led to a pilot study of estradiol and progesterone therapy to prevent osteopenia of prematurity. The highest median bone mineral accretion rate was found in the replacement group when the supplementation with calcium and phosphorus was also sufficient. None of the previous studies dealing with estrogen replacement controlled for achieved plasma levels of estradiol in the infants. In our controlled randomised pilot study with 30 preterm infants (15 in each group), we aimed to maintain intra-uterine plasma levels of estradiol and progesterone. Preterm infants with replacement of estradiol and progesterone for 6 weeks postnatally showed trends to higher bone mineral accumulation. In addition, a trend towards a lower incidence of chronic lung disease was found. Neurodevelopmental follow-up showed normal psychomotor development in infants given estradiol and progesterone, whereas the untreated infants (controls) showed a trend towards delayed development. Recent research emphasises that estradiol and progesterone may be important for brain development. Thus, while there is data indicating that postnatal estradiol and progesterone replacement therapy may be beneficial in preterm infants, experience with this new therapy is
limited and extensive research is needed to address the potential benefits and to rule out adverse effects.

Publication Types:

- Review
- Review, Tutorial

PMID: 11688594 [PubMed - indexed for MEDLINE]

Ann Med 2000 Dec;32(9):608-14

The replacement of oestradiol and progesterone in very premature infants.

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The idea of replacing 17beta-oestradiol (E2) and progesterone (P) in preterm infants is based on the observation that during pregnancy E2 and P plasma concentrations rise in the mother and the fetus by a factor of 100. Disruption of the placental supply of these hormones is a physiological event for an infant delivered at term. A preterm infant is deprived from this supply at an earlier developmental stage. In vitro and in vivo data are discussed, and they highlights the potential benefit of E2 and P on the development of different organ systems. The postnatal replacement of E2 and P has the aim of maintaining in utero plasma concentrations. In the first randomized clinical study in 30 extremely preterm infants, E2 and P were replaced postnatally for a total of 6 weeks. With a median intravenous replacement of 8.4 micromol/kg/day of E2 (4.2-22.9) and 67.4 micromol/kg/day of P (35.7-87.0), plasma levels of E2 and P were maintained within the intrauterine reference values of 7.3-22.0 nmol/L and 0.95-1.9 micromol/L, respectively. Three- to sixfold higher dosages were needed via the transepidermal route. Trends towards an improved postnatal bone mineral accretion and a reduced incidence of chronic lung disease were found. Further studies are warranted to clarify the potentially important role of E2 and P for the postnatal development of an extremely preterm infant.

Publication Types:

- Review
- Review, Tutorial

PMID: 11209968 [PubMed - indexed for MEDLINE]
Uptake of progesterone by red blood cells in the rat.

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This work examined the extent to which progesterone (P) in whole blood is transported in association with red blood cells (RBC) in the rat. The effects of plasma P concentration and changes in the source of whole blood on this association were also assessed. Initially, the RBC uptake of [3H]P was measured in vitro in blood from either adrenalectomized-ovariectomized (Ax-Ox) rats, thus rendered effectively P-free, and from rats at Day 16 of pregnancy. In blood from Ax-Ox rats, almost 10% of [3H]P was located within the RBC fraction, and this percentage increased with the addition of exogenous P (range of mean RBC uptake 9.4-18.9% over a plasma P concentration range of approximately 100-4500 ng/ml). A similar though less marked effect of exogenous P was observed in blood from pregnant rats (mean RBC uptake 11.7-14.8% over a similar plasma P concentration range), suggesting that plasma from pregnant rats had a greater capacity to bind P. To assess the RBC uptake of P in vivo, arterial blood samples were obtained during constant infusion of [3H]P in Day 16 pregnant rats with or without prior P supplementation (20 mg P per day over 4 days). The mean RBC uptake of P in control rats was 18.8 +/- 0.7%, but was reduced (p less than 0.05) to 16.2 +/- 0.5% after P supplementation. This reduction may have been due to the increase in the P-binding capacity of plasma known to occur after P supplementation. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 3207803 [PubMed - indexed for MEDLINE]

Progesterone and sexual behavior in males.

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Previous investigations into the effects of progestins on copulatory behavior have suggested that progesterone inhibits the expression of androgen-dependent sexual behaviors in males. However, virtually all of those studies utilized pharmacological dosages of progesterone. Such experiments, although essential for understanding the behavioral effects of progesterone, yield little insight into the function of endogenous progesterone in masculine sexual responses. In this
brief review, attention is focused on the role of physiological levels progesterone in copulatory behavior in male reptiles and mammals. Efforts are made to promote a reevaluation of the behavioral effects of progestins in males, similar to ongoing studies which are reexamining neural mechanisms involved in progestin-mediated reproductive behavior in the female.

Publication Types:

- Review
- Review, Tutorial

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Comment in:


Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women.

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BACKGROUND: Transdermal progesterone is being used in some countries as a purported treatment for menopausal symptoms, either alone or prescribed in conjunction with estrogen, but little information exists regarding the biological activity and effectiveness of this method of delivery of progesterone in protecting the endometrium from excess proliferation. This study was designed to evaluate the use of sequential transdermal progesterone. End-points evaluated included endometrial cellular response and bleeding pattern as well as plasma hormone levels and salivary progesterone estimations. METHOD: Twenty-seven postmenopausal women were treated with continuous transdermal estrogen (28-day cycle) and a cream containing 16, 32 or 64 mg of progesterone in each 4-cm extrusion from a tube of Pro-Feme administered daily in a sequential (days 15-28 of cycle) regimen. Blood and endometrial samples were analyzed for progesterone response prior to therapy, after the first 14 days of unopposed transdermal estrogen and following 14 days of transdermal progesterone. Saliva samples were taken during the last 14 days of the 84-day study, when the final
progesterone cream therapy was being applied. RESULTS: Hormone assay indicated that physiological levels of estradiol were achieved, but progesterone levels were insufficient to induce any detectable change in the endometrium. Only one patient experienced bleeding during the study period. Levels of salivary progesterone were so variable as to be considered completely unreliable in determining the potential influence on biological activity. INTERPRETATION: Pro-Feme transdermal progesterone administered in a 16-, 32- or 64-mg daily dose for 14 days in a sequential regimen does not appear to be effective in inducing a secretory change in a proliferative endometrium. Salivary progesterone levels were not of value in managing the therapy of postmenopausal women.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

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**Serum progesterone levels correlate with decreased cerebral edema after traumatic brain injury in male rats.**

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Previous animal research suggests that progesterone may have powerful neuroprotective effects in traumatic brain injury (TBI). This experiment tested the hypothesis that progesterone levels correlate with decreased cerebral edema in male rats with bilateral medial frontal cortex injuries. Three groups of male Sprague-Dawley rats were used: injured given progesterone (4 mg/kg), injured given vehicle (oil), and uninjured controls given vehicle. Progesterone or vehicle was administered intraperitoneally at 1, 6, and 24 h postinjury. At 48 h postinjury, the rats were killed, brains extracted, and assayed for edema. Percent difference in water content of the area surrounding the lesion was compared to posterior cortex. A strong inverse relationship was found between serum progesterone levels and percent cerebral edema; the higher the progesterone levels, the lower the percent edema. Both progesterone and oil-treated animals had some edema compared to sham-operated controls. The brains of the injured animals given control solution were higher in water content than either the uninjured group or injured progesterone-treated rats 48 h postinjury. These findings confirm that progesterone significantly decreases cerebral edema after TBI in adult male subjects.
Apoptosis induced by progesterone in human ovarian cancer cell line SNU-840.

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Progesterone has been used as an ingredient of anticancer drug for patients with ovarian carcinoma. However, the mechanism of anticancer effects by progesterone has not been understood. In this study, the effects of progesterone on ovarian cancer cells, SNU-840, were investigated. After the incubation with progesterone, the viability of the cells was evaluated by MTT assay. As a result, 45% of the cells were viable after 48 h of incubation with 100 microM progesterone. In addition, [(3)H]thymidine incorporation assay showed that the proliferation of the cells was completely inhibited by progesterone after 48 h of incubation at 100 microM concentration. Colorimetric TUNEL assay revealed the fragmentation of the chromosomal DNA, suggesting that the process of the cell death was apoptosis. The level of the p53 mRNA was determined by northern blotting assay, since many apoptosis processes are mediated by up-regulation of the p53 expression. The level of the p53 mRNA was determined by northern blotting assay, since many apoptosis processes are mediated by up-regulation of the p53 expression. The level of the p53 mRNA reached its maximum at 12 h and decreased after 24 h of incubation with progesterone. In conclusion, progesterone inhibits the proliferation and elicits apoptosis of SNU-840 cells. Also, it up-regulates the p53 mRNA transiently. Copyright 2001 Wiley-Liss, Inc.
risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial.

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OBJECTIVE--To assess pairwise differences between placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women. DESIGN--A 3-year, multicenter, randomized, double-blind, placebo-controlled trial. PARTICIPANTS--A total of 875 healthy postmenopausal women aged 45 to 64 years who had no known contraindication to hormone therapy. INTERVENTION--Participants were randomly assigned in equal numbers to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 d/mo; (4) CEE, 0.625 mg/d plus consecutive MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/d for 12 d/mo. PRIMARY ENDPOINTS--Four endpoints were chosen to represent four biological systems related to the risk of cardiovascular disease: (1) high-density lipoprotein cholesterol (HDL-C), (2) systolic blood pressure, (3) serum insulin, and (4) fibrinogen. ANALYSIS--Analyses presented are by intention to treat. P values for primary endpoints are adjusted for multiple comparisons; 95% confidence intervals around estimated effects were calculated without this adjustment. RESULTS--Mean changes in HDL-C segregated treatment regimens into three statistically distinct groups: (1) placebo (decrease of 0.03 mmol/L [1.2 mg/dL]); (2) MPA regimens (increases of 0.03 to 0.04 mmol/L [1.2 to 1.6 mg/dL]); and (3) CEE with cyclic MP (increase of 0.11 mmol/L [4.1 mg/dL]) and CEE alone (increase of 0.14 mmol/L [5.6 mg/dL]). Active treatments decreased mean low-density lipoprotein cholesterol (0.37 to 0.46 mmol/L [14.5 to 17.7 mg/dL]) and increased mean triglyceride (0.13 to 0.15 mmol/L [11.4 to 13.7 mg/dL]) compared with placebo. Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10 g/L compared with -0.02 to 0.06 g/L); differences among active treatments were not significant. Systolic blood pressure increased and postchallenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment. Compared with other active treatments, unopposed estrogen was associated with a significantly increased risk of adenomatous or atypical hyperplasia (34% vs 1%) and of hysterectomy (6% vs 1%). No other adverse effect differed by treatment assignment or hysterectomy status. CONCLUSIONS--Estrogen alone or in combination with a progestin improves lipoproteins and lowers fibrinogen levels without detectable effects on postchallenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, CEE with cyclic MP has the most favorable effect on HDL-C and no excess risk of endometrial hyperplasia.
Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

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