

## 2010 Trial: Hormones (HRT)

### Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns

Link: <https://pubmed.ncbi.nlm.nih.gov/20575654/>

Year published: 2010

Pubmed classification: Randomised Controlled Trial.

**Objective:** To evaluate the effects on bleeding pattern of two different doses of natural progesterone (NP) administered per os or per vagina in association with transdermal estradiol in a continuous, sequential estrogen-progestin therapy.

**Blind/double blind?** Unknown.

**Randomised?** Yes.

**Placebo?** No.

**Participant information:** 100 patients.

**Treatment length:** 12 cycles.

**Drug and dosage:** Each group received transdermal 17beta-estradiol treatment at the dose of 50 microg/day. Groups A and B received NP per os at the dose of 100 mg/day and 200 mg/day, respectively. Groups C and D received NP per vagina at the dose of 100 mg/day and 200 mg/day, respectively.

**Side-effects assessment:** No significant differences were observed in endometrial thickness between groups, suggesting that all treatments are effective in balancing the effects of estradiol on endometrium.

Regarding bleeding control, patients in Groups C and D showed a higher number of episodes of regular bleeding than patients in Groups A and B and fewer episodes of spotting. The better control of bleeding was associated with a higher treatment compliance in patients who received vaginal NP, with a larger percentage of women completing the study.

**Conclusion:** Transdermal estrogen replacement therapy combined with 100 mg of micronized NP administered per vagina from the 14th day to the 25th day of each 28-day cycle leads to good cycle control and provides excellent patient satisfaction without serious side-effects.

**Considerations for future:** This therapy could be a treatment of first choice in early postmenopausal patients.

## **2010 Trial: Hormones (Combination)**

**A novel regimen of combination transdermal estrogen and intermittent vaginally administered progesterone for relief of menopausal symptoms**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/20486879/>

**Year published:** 2010

**Trial information:** Retrospective chart review.

**Objective:** To determine the safety and efficacy of a novel regimen of transdermal estrogen and vaginally administered progesterone for treatment of menopausal symptoms.

**Participant information:** 41 menopausal patients aged 46-65, who had been using an oestradiol patch and vaginally administered prometrium for at least 1 year. 17 patients were lost to follow-up or discontinued therapy within 1 year.

**Trial length:** 1 year assessment.

**Drug and dosage:** Estrogen patch ranging from 25 to 100 µg twice weekly and vaginal prometrium either continuously 3-5 days weekly (36 patients), or sequentially 12 days/month (5 patients).

**Measuring scales:** Available transvaginal ultrasound (TVUS) measurements of endometrial thickness and endometrial biopsy results after at least 1 year of treatment were collated. Symptom relief, bleeding and side effects were reviewed.

**Efficacy outcomes:** All patients had relief of menopausal symptoms.

**Side-effects assessment:** Only 23.5% (4/17 patients) of patients who had a TVUS after 1 year (or sooner if bleeding occurred) had a thickened endometrial lining on ultrasound (>5 mm), and all of these had normal endometrial biopsies. By 1 year of follow-up, 91.7% of patients were amenorrhoeic.

**Conclusion:** Vaginal administration of progesterone as part of combined estrogen plus progestin therapy has the potential for decreasing side effects while maintaining endometrial safety and amenorrhoea.

**Considerations for future:** Larger prospective trials are warranted.

## **Trial 2003: Hormones (Estrogens)**

### **Increase in prefrontal cortex serotonin 2A receptors following estrogens treatment in postmenopausal women**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/12900319/>

**Year published:** 2003

**Pubmed classification:** Clinical trial.

**Objective:** This study investigated the effect of estrogen on brain serotonin 2A (5-HT(2A)) receptors in postmenopausal women and whether there was any correlation of receptor changes with cognition and mood.

**Participant information:** 10 participants, post-menopausal.

**Further methodology information:** Positron emission tomography measurements of 5-HT(2A) receptor binding with [(18)F]deuteroaltanserin occurred before and after estrogen replacement therapy.

**Efficacy outcomes:** 5-HT(2A) receptor binding was significantly increased after estrogen replacement therapy in the right prefrontal cortex (right precentral gyrus [Brodmann's area 9], inferior frontal gyrus [Brodmann's area 47], medial frontal gyrus [Brodmann's area 6, 10] and the anterior cingulate cortex [Brodmann's area 32]).

In the inferior frontal gyrus [Brodmann's area 44]), receptor up-regulation was correlated with change in plasma estradiol. Verbal fluency and Trail Making Test performance, but not mood, were significantly improved by estrogen without correlation with receptor changes.

**Conclusion:** Estrogen increases 5-HT(2A) receptor binding in human prefrontal regions.

## **Trial 2001: Hormones (GnrH analogues)**

### **Use of Luprolide acetate plus Tibolone in the treatment of severe premenstrual syndrome**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/11172843/>

**Year published:** 2001

**Pubmed classification:** Clinical trial.

**Objective:** To evaluate the effectiveness of GnRH agonist (GnRH-a) plus tibolone in the treatment of severe premenstrual syndrome (PMS).

**Blind/double blind?** Double-blind.

**Randomised?** Unknown.

**Placebo?** Placebo group.

**Participant information:** 30 patients affected by severe PMS, aged 23-29 years (mean age +/- SD, 25.3 +/- 2.9 years) in the Naples region.

**Treatment length:** 2 cycles.

**Drug and dosage:** Leuprolide acetate depot (3.75 mg IM for 28 days) in association with tibolone (2.5 mg/d orally); or placebo (1 tablet per day).

**Measuring scales:** The mean severity of each symptom and sign of PMS was evaluated using a visual analog scale during the last 7 days of each treatment cycle in comparison with the last 7 days of the cycle before treatment.

**Efficacy outcomes:** Mean scores for each of the adverse psychological/physical and positive psychological symptoms were significantly improved during treatment. No statistically significant difference was detected between patients treated with tibolone and placebo.

**Side-effects assessment:** A significantly lower number of hot flushes per day was observed in groups treated with GnRH-a and tibolone in comparison with GnRH-a and placebo.

**Conclusion:** Tibolone administered in association with GnRH-a does not reduce the therapeutic effect of GnRH-a in women affected by PMS. Tibolone used in association with GnRH-a may provide long-term medical treatment for women with PMS.

## **Trial 1993: Hormones (GnRH analogues)**

**The prevention of bone loss in young women treated with GnRH analogues with "add-back" estrogen therapy**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/8416441/>

**Year published:** 1993

**Pubmed classification:** Clinical trial.

**Objective:** To determine whether the addition of a low dose of oral estrogen replacement therapy (ERT) taken daily can prevent the bone loss associated with continuous GnRH analogue use.

**Blind/double blind?** Double-blind.

**Randomised?** Yes.

**Placebo?** Placebo-controlled.

**Participant information:** 60 participants, aged 21-45 years old. The drop-out rate was 32%.

**Treatment length:** 6 cycles.

**Drug and dosage:** Three treatment groups: Placebo implant every 4 weeks plus placebo ERT tablets daily; Zoladex (goserelin 3.6 mg) implant every 4 weeks plus placebo ERT tablets daily; or Zoladex (3.6 mg) implant every 4 weeks plus estradiol valerate, 2 mg/day, with norethisterone 5 mg from days 22-28.

**Measuring scales:** A dual x-ray bone density scan was performed before treatment and again after six treatment cycles. The percentage bone change with respect to the initial bone density was calculated.

**Side-effects assessment:** There was a significant loss of bone density at both the lumbar spine and proximal femur in the group receiving Zoladex plus placebo after 6 months compared with both pre-treatment values and with the group receiving placebo plus placebo.

The addition of Estrogen "add-back" therapy to GnRH analogue treatment (Zoladex plus ERT) resulted in no significant change in bone density compared with either pre-treatment values or the group receiving placebo plus placebo.

**Conclusion:** The addition of "add-back" estrogen therapy to continuous GnRH analogue use can prevent bone loss.

## **Trial 1989: Hormones (HRT)**

**Treatment of severe premenstrual syndrome with Oestradiol patches and cyclical oral Norethisterone**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/2570971/>

**Year published:** 1989

**Pubmed classification:** Clinical trial.

**Blind/double blind?** Unknown.

**Randomised?** Yes.

**Placebo?** Placebo controlled - crossover.

**Participant information:** 40 patients with premenstrual symptoms.

**Treatment length:** 3 months active drug or placebo; 3 months active drug or placebo.

**Drug and dosage:** Transdermal oestradiol patches (2 x 100 micrograms) to suppress ovulation; or placebo patches. Norethisterone 5 mg was given in each group from day 19-26 of the cycle to ensure a regular withdrawal bleed.

**Measuring scales:** Patients completed the Moos menstrual distress questionnaire (MDQ) and the premenstrual distress questionnaire (PDQ) daily throughout the study.

**Efficacy outcomes:** After 3 months, both groups showed improvement in MDQ and PDQ scores. In general, between 3 and 6 months, patients who switched from active treatment to placebo had deteriorating scores while patients who switched from placebo to active treatment maintained or improved upon their initial gains.

Significant improvements occurred after changing to active treatment in five of six negative MDQ symptom clusters and in six of ten PDQ symptoms. There was 1 withdrawal because of considerable improvement with the initial (active) treatment.

**Side-effects assessment:** 4 participants withdrew due to skin reactions (treatment group unknown).

## **Trial 1988: Hormones (Serotonin)**

**Alteration of platelet serotonergic mechanisms and monoamine oxidase activity in premenstrual syndrome**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/3390499/>

**Year published:**1988

**Classification:** Unknown

**Objective:** Determination of Platelet uptake and content of 5-hydroxytryptamine (5-HT), platelet monoamine oxidase (MAO) activity, and plasma free and total tryptophan levels for patients with PMS

**Participant information:** Patients diagnosed with premenstrual syndrome.

**Measuring scales:** Measurement of platelet uptake and content of 5-hydroxytryptamine (5-HT), platelet monoamine oxidase (MAO) activity, and plasma free and total tryptophan levels in relation to cycle timings.

**Outcomes:** The Vmax of 5-HT uptake and 5-HT content in platelets of PMS patients were significantly decreased during the premenstrual phase (cycle days -9 to -1) compared to control subjects. Platelet MAO activity was significantly lower post-menstrually (cycle days 5-9) in PMS patients compared to the premenstrual phase. There were no differences in plasma free and total tryptophan levels between PMS patients and control subjects during either interval.

**Conclusion:** As platelets are believed to be a peripheral model for central serotonergic neurons, the results suggest that PMS symptomatology may be related to alterations in serotonergic neuronal mechanism

## **1986 Trial: Hormones (HRT)**

**Treatment of the premenstrual syndrome by subcutaneous estradiol implants and cyclical oral norethisterone: placebo controlled study**

Link: <https://pubmed.ncbi.nlm.nih.gov/3087550/>

**Year published:** 1986

**Pubmed classification:** Clinical trial.

**Further trial information:** Longitudinal study.

**Objective:** The hypothesis that the many non-specific changes normally associated with cyclical ovarian activity are the primary aetiological factors in the premenstrual syndrome was tested by suppressing ovulation with subcutaneous oestradiol implants.

**Blind/double blind?** Unknown.

**Randomised?** Unknown.

**Placebo?** Placebo group.

**Participant information:** 68 women with proved premenstrual syndrome.

**Treatment length:** Up to 10 months.

**Drug and dosage:** Subcutaneous oestradiol implants (33); or placebo (35). Active treatment was combined with cyclical oral norethisterone to produce regular withdrawal periods.

**Measuring scales:** Symptoms were monitored with daily menstrual distress questionnaires, visual analogue scales, and the 60 item general health questionnaire.

**Efficacy outcomes:** Of the 35 women treated with placebo 33 improved, giving an initial placebo response rate of 94%. The placebo effect gradually waned, but the response to the active combination was maintained for the duration of the study.

Analysis of the prospective symptom ratings showed a significant superiority of oestradiol implants over placebo after two months for all six symptom clusters in the menstrual distress questionnaire. Changes seen in the retrospective assessments were less significant but the trend was the same.

**Conclusion:** Treatment with oestradiol implants and cyclical rogestogen was well tolerated and appears to be both rational and effective for severe cases of the premenstrual syndrome.



## **Trial 1985: Hormones (Prostaglandin)**

### **Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors**

**Link:** <https://pubmed.ncbi.nlm.nih.gov/3839018/>

**Year published:** 1985

**Pubmed classification:** Clinical trial.

**Objective:** The clinical and biochemical effects of a prostaglandin synthesis precursor (Efamol) were studied.

**Blind/double blind?** Unknown.

**Randomised?** Unknown.

**Placebo?** Placebo group.

**Participant information:** 30 women with severe, incapacitating premenstrual syndrome.

**Treatment length:** Unknown.

**Drug and dosage:** Prostaglandin synthesis precursor (Efamol) containing linoleic acid and its metabolite, gamma-linolenic acid; or placebo.

**Efficacy outcomes:** Efamol treatment alleviated the premenstrual symptoms in general, and depression especially, better than placebo. The capacity of platelets to release thromboxane B<sub>2</sub> during spontaneous clotting was decreased in patients undergoing Efamol treatment (141 +/- 59 ng/ml, mean +/- SD), as compared to those undergoing placebo treatment (186 +/- 44 ng/ml, p less than 0.01), and control subjects (176 +/- 40 ng/ml, n = 25, p less than 0.05). No changes were found in plasma 6-keto-prostaglandin F<sub>1</sub>alpha or in FSH, LH, prolactin, progesterone, estradiol and testosterone.

**Conclusion:** The data suggest that prostaglandins might play a role in the pathophysiology of the premenstrual syndrome.