

**Medroxyprogesterone and Conjugated Estrogen are Equivalent for Hot Flashes—  
a one-year randomized double blind trial following premenopausal ovariectomy**

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**Short title: Progestin and Estrogen Equal for Hot Flashes**

**Key words:** night sweats, vasomotor symptoms, surgical menopause, conjugated equine  
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**Background:** Estrogen therapy is the gold standard treatment for hot flushes/night sweats, but it and estrogen/progestin are not suitable for all women. Medroxyprogesterone reduces hot flushes but its effectiveness compared with estrogen is unknown.

**Methods:** Oral estrogen and medroxyprogesterone were compared for their effects on hot flushes in a planned analysis of a secondary outcome for a 1-yr, randomized double blind parallel group controlled trial in an urban academic medical centre. Participants were healthy, menstruating women prior to hysterectomy-ovariectomy for benign disease. Forty-one women (aged 45 +/- [SD] 5) enrolled; 38 women were included in this analysis of daily identical capsules containing conjugated equine estrogen 0.6 mg/day or medroxyprogesterone 10 mg/day. Demographic variables did not differ at baseline. Daily data provided number of night and day flushes compared by group. Vasomotor symptom day-to-day intensity change was assessed by therapy assignment.

**Results:** Hot flushes/night sweats were well controlled in both groups—one occurred on average every third day and every fourth night. Mean/day daytime occurrences were 0.363 and 0.187 respectively on estrogen and medroxyprogesterone with no significant difference ( $P = 0.156$ ). Night sweats also did not differ ( $P = 0.766$ ). Therapies were statistically equivalent (within one event per 24-h) in control of vasomotor symptoms. Day-to-day hot flush intensity decreased on medroxyprogesterone and tended to remain stable on estrogen ( $P < 0.001$ ).

**Interpretation:** This analysis demonstrates that medroxyprogesterone acetate and conjugated equine estrogen are equivalent and effective in control of the number of hot flushes/night sweats immediately following premenopausal ovariectomy.

### ***Introduction***

Conjugated equine and other estrogens provide effective treatment for hot flushes and night sweats—these are collectively called vasomotor symptoms. A systematic review of randomized double-blind placebo-controlled trials concluded that estrogen therapy reduces the frequency of hot flushes and night sweats by 75% [1].

However, use of estrogen for menopausal treatment has recently become problematic. Conjugated equine estrogen with medroxyprogesterone acetate therapy caused significantly more harm than benefit compared with placebo in primarily asymptomatic menopausal women in the Women's Health Initiative randomized controlled trial [2]. In the estrogen-only arm of the Women's Health Initiative, women who had undergone hysterectomy also received no benefit in preventing coronary heart disease and had an increase in stroke compared with placebo [3]. A meta-analysis of randomized controlled menopausal hormone therapy trials showed that estrogen therapy over five years caused harm exceeding benefit in one of 230 women aged 50-59 [4], the age range in which most vasomotor symptoms are treated. Estrogen therapy, even for severe vasomotor symptoms, is currently contraindicated for women with breast cancer, thrombophilias or active liver disease. Finally, largely asymptomatic menopausal women discontinuing estrogen/progestin therapy after the Women's Health Initiative were almost six times more likely to experience moderate-to-severe hot flushes than were women randomized to placebo [5].

Hormone therapy was discontinued by half of hormone-treated women in New Zealand and the U.S.A. following results of randomized controlled hormone therapy trials [6-8]. Women over age 65 in Ontario also filled 32% fewer hormone prescriptions [9]. However, with discontinuation of estrogen, many women re-develop hot flushes. Therefore, 18% of women report restarting hormone therapy, 76 percent of these for recurrence of severe hot flushes or night sweats [6]. Others reported intense hot flushes that alternate therapies did not adequately control [10].

Oral progestins, like estrogens, have been shown to be effective for vasomotor symptoms in randomized placebo-controlled trials from the 1980s [11-14]. There are also few head-to-head trials of progestins versus estrogens. Two such trials tested androgen-derived progestins and high doses of ethinyl estradiol [15;16]. In one, ethinyl estradiol and estradiol/d-norgestrel were more effective than d-norgestrel alone—all hormone arms were more effective than placebo [15]. In the other trial, although ethinyl estradiol was effective, and results of the two hormone arms were not different, norethindrone also did not differ from placebo [16]. No randomized comparative trials for hot flushes have tested currently used doses of conjugated equine estrogen and medroxyprogesterone.

Data to support the choice of a minimal clinically significant difference in vasomotor symptoms are scarce. However, in a review of data from a series of vasomotor symptom cross-over studies, Sloan et al. [17] found that those women who expressed a preference reported a median of 1.3 fewer hot flushes per 24-hour day, while those who expressed no preference differed by 0.4 hot flushes per day. This observation, and clinical experience, led us to use a difference of one or fewer hot flush event per day as our criterion for equivalence. This is less than the criterion for improvement of 50% used by Sloan and colleagues, which corresponds to about 2 events per day in their highly symptomatic population [17].

The purpose of this study was to compare medroxyprogesterone acetate in a luteal phase equivalent dose (10 mg/day) and conjugated equine estrogen in a standard menopause dose (0.6 mg/day) for their effects in controlling the number and intensity hot flushes and night sweats (hot flushes during sleep). The treatments were hypothesized to be similarly effective. This report analyzed women's daily experience of day and night flushes during a 12-month trial starting from the time of hospital discharge following pre/perimenopausal hysterectomy and ovariectomy for benign disease.

### ***Methods***

This was a randomized double blind parallel group trial of two hormonal therapies taken daily [18]. The current analysis was a pre-planned analysis of a secondary endpoint in a

randomized controlled trial examining bone mineral density changes [18]. The primary outcome variable was the number of hot flush/night sweat vasomotor symptom episodes per 24-hour period. A placebo arm was not included in this study because placebo-treated women lose bone rapidly following premenopausal ovariectomy [19]. Human ethics committees at the University of British Columbia and participating hospitals approved the protocol. Prior to enrolment all women provided written informed consent.

Women were enrolled between 1989 and 1991 and randomized as previously described [18]. Briefly, women scheduled for hysterectomy with bilateral ovariectomy were identified from preoperative lists at four teaching and one community hospital. Following permission from the operating gynecologist, the study nurse visited each woman to provide information about the study and to screen women for eligibility. Participants were pre- or perimenopausal women (who had menstruated within four months) and were not using hormonal therapy. They had undergone hysterectomy with bilateral ovariectomy for a benign condition, and had no contraindications to hormone therapy [18].

Participants were assigned to one of the two therapies using a randomization table administered by the Vancouver General Hospital research pharmacist who dispensed study medications and maintained the therapy assignment code. They received conjugated equine estrogen in a dose of 0.6 mg/day or medroxyprogesterone acetate in a dose of 10 mg/day each dispensed in two identical, powder-filled capsules to be taken once a day. Investigators remained blinded to therapy assignment until completion of data collection and construction of an accurate database.

Participants recorded their experiences in the Daily Menopause Diary<sup>©</sup>, an instrument with short-term reproducibility [20], that allowed documentation of both the number and the intensity of daytime hot flushes as well as night sweats that occurred during sleep. Participants were seen monthly over the first six-month interval and then every three months until study completion.

Statistical analysis [21;22] used the number of vasomotor symptom episodes per 24-hour period as the primary outcome variable. The secondary outcome was the intensity of hot flushes/night sweats on a zero-to-four scale. Possible explanatory variables for number of hot flushes included body mass index (weight in kilograms divided by height in meters squared), age at menarche and gynecological age (years from menarche).

Primary analyses were based on calculations of the number of vasomotor symptoms/day following enrollment. To describe the relation between the incidence of vasomotor symptoms and therapy, each person's follow-up was divided into a series of consecutive one-month periods. The episode rate was calculated as the number of events divided by the total number of observed woman-days in that month for each woman. Poisson regression models with adjustment for overdispersion (Splus, Insightful, version 6.1) were used to quantify the relation between treatment and vasomotor symptom rates by month. All the variables were treated as fixed at their values at the start of the study. The Poisson log-linear regression modeled the number of vasomotor symptoms as a function of these variables, a mean value per month following enrollment by treatment category, and with the logarithm of the observed patient-days included in the model as an offset to account for differential follow-up periods over participants. Corrections for overdispersion and within-patient correlation between the repeated events were included with the use of generalized estimating equations.

Equivalence testing of the two therapies for control of vasomotor symptoms was performed using the null hypothesis that the difference in daily frequency of vasomotor symptoms (total of both day and night) was greater than one event per 24-hour period. Tests were two-tailed, and alpha was set at 0.05.

Changes in hot flush intensity from day-to-day and night-to-night by therapy assignment were also analyzed using Markov chain modeling. This analysis provided the potential to track the progression of the hot flush intensity level (on a 0 through 4 scale) over time, by treatment group.

## *Results*

Forty-one women whose mean age was  $45 \pm 5$  ( $\pm$  standard deviation) years were enrolled and randomized. Flow of participants through the trial is shown in **Figure 1**. Eligibility criteria and indications for hysterectomy with ovariectomy have been reported [18]. Only three women did not provide data for this analysis: one woman decided against participation immediately following randomization and without taking any study drug. A second discontinued at one week because of difficulty swallowing the large gelatin capsules. The third was a medical withdrawal at four months for acute hyperthyroidism—this condition alters temperature control and is in the differential diagnosis of hot flushes. Most women completed at least 360 days; the early study withdrawals for five of the women are described in **Figure 1**. Within the period of data collection, Daily Menopause Diary© were 94% complete. Thus data from 38 of the 41 randomized participants contributed to this analysis.

**Table 1** shows the baseline demographic characteristics of participants. Women randomized to the estrogen and medroxyprogesterone treatment groups did not differ with regard to any documented characteristics. Participant adherence by capsule count was >90% and equal by therapy [18].

Both estrogen and medroxyprogesterone therapies were well tolerated following surgical menopause. Hot flushes and night sweats were generally well controlled in both groups. After the first six weeks, 45 percent of the study population was free of daytime hot flushes and 30 percent were free of night sweats. No participant experienced thrombophlebitis, myocardial infarction, stroke or breast cancer during the study (or a systematic 1-yr follow-up) (unpublished data, J. C. Prior). However, weight gain was nearly universal and averaged  $3.2 \pm 4.0$  kg over the year and significantly greater on conjugated equine estrogen than on medroxyprogesterone acetate [18]. One woman on medroxyprogesterone discontinued at four months with severe hot flushes and dyspareunia. Three women on estrogen withdrew, despite good hot flush control, after one

to five months with complaints of low energy, trouble sleeping and headaches. Data from these four discontinuing women were included in this analysis.

The mean rate of hot flushes was very low for the entire year but also somewhat variable over time. For both therapy groups, the overall mean rate was 0.282 hot flushes per day, and 0.268 night sweats per night, which created a total mean of 0.556 vasomotor symptoms per 24-hour period. These rates were significantly affected by body mass index, but not gynecological age or age at menarche. The figures show rates as adjusted for body mass index. The mean overall, daytime and nighttime daily rates of hot flushes for women on the estrogen arm are shown as a horizontal line in **Figure 2**. The mean and 95% confidence intervals for rates for each month on estrogen therapy are superimposed on that estrogen-therapy mean.

The tendency for fewer vasomotor symptoms per day for those randomized to MPA was not statistically significant (24-hour RR 0.74, 95% CI 0.27, 2.00; daytime RR 0.56, 95% CI 0.20, 1.55; and nighttime RR 1.02, 95% CI 0.35, 2.99). A formal test of equivalence (defined as no greater than one vasomotor symptom event difference per 24-hour period) found the therapies were significantly equivalent ( $P < 0.01$ ). Of the other covariates considered, only body mass index was statistically significant for number of overall and nighttime hot flushes and was associated with an increase in the rate of 24-hour overall, daytime, and nighttime hot flushes (overall RR 1.19, 95% CI 1.02, 1.39; daytime RR 1.17, 95% CI 0.99, 1.38; nighttime RR 1.19, 95% CI 1.02, 1.40). Other covariates considered include age at menarche (overall RR 1.01, 95% CI 0.69, 1.46; daytime RR 1.07, 95% CI 0.78, 1.49; nighttime RR 0.97, 95% CI 0.61, 1.53) and gynecological age (24-hour RR 0.98, 95% CI 0.90, 1.07; daytime RR 1.00, 95% CI 0.91, 1.10; nighttime RR 0.96, 95% CI 0.87, 1.07).

Vasomotor symptom-free days were common on both therapies throughout this 1-year study. For women on estrogen, 82 percent of days and 85 percent of nights were without hot flushes. For women on medroxyprogesterone, 90 percent of days and 87 percent of nights were without hot flushes.

Monthly patterns over the course of a year are illustrated in **Figure 3**. The difference and 95% confidence intervals between therapy arms for overall 24-hour vasomotor symptoms, after adjusting for body mass index, are plotted in the top panel of **Figure 3**. The horizontal dark line represents an equal experience by therapy. Values lying above zero indicate fewer hot flushes in the medroxyprogesterone arm. **Figure 3** also shows the estrogen minus medroxyprogesterone hot flush rates for daytime and night sweat rates as the lower two panels.

For the most part, rates of overall, day or nighttime vasomotor experiences did not significantly differ between the estrogen and medroxyprogesterone groups, with one month with a marginally significant difference during the year. The mean differences between estrogen and medroxyprogesterone in hot flush numbers per day corrected for body mass index are shown in **Figure 3** as light horizontal lines representing 0.277 vasomotor symptoms per 24-hour period ( $P = 0.30$ ), 0.182 hot flushes per daytime ( $P = 0.20$ ), and 0.062 hot flushes per nighttime ( $P = 0.67$ ).

This study also evaluated changes in hot flush intensity from day-to-day or night-to-night. Days of high daytime hot flush intensities (rated 2, 3 or 4) tended to come in runs for those in the estrogen arm, while those taking medroxyprogesterone were more likely to switch to a lower intensity level on the subsequent day. The probability of a transition from a high daytime hot flush intensity to a lower intensity on the next day was 56 percent for women on medroxyprogesterone but only 20 percent for those on estrogen ( $P < 0.001$ ). The same trend for alternating rather than clustered intensities was true for night sweats for women on medroxyprogesterone compared with those on estrogen ( $P < 0.001$ ).

Intense hot flushes or night sweats occurred on less than one percent of days or nights during the year, no matter whether women were randomized to estrogen or medroxyprogesterone therapy (**Figure 4**). The proportion of days or nights on which hot

flushes and night sweats of each intensity level occurred did not differ by estrogen or medroxyprogesterone therapy.

### *Discussion*

This 1-year trial has found that medroxyprogesterone acetate is equivalent to conjugated equine estrogen in the control of vasomotor symptoms for women treated immediately following pre/perimenopausal surgical menopause. Both treatments were effective during this double blind randomized study.

Women experiencing a premenopausal ovariectomy tend to have more intense hot flushes/night sweats than do women with natural menopause [23]. However, women in this study, all of whom were treated from the day of hospital discharge, in general did not develop troublesome symptoms. Only one perimenopausal woman had reported experiencing hot flushes before enrolment. That the expected intense symptoms, as are usually reported in women with surgical menopause [10], were not experienced in this study suggests that both therapies can be highly effective. The small differences in day and night hot flushes between therapies, 95% confidence intervals around the differences in the rates for the two treatments and formal equivalence testing all indicate that estrogen and medroxyprogesterone are similarly effective in control of the number of hot flushes.

To our knowledge, this is the first randomized, controlled trial to directly compare hot flush control with medroxyprogesterone versus estrogen. Randomized placebo-controlled trials from the 1980s showed that medroxyprogesterone effectively reduced hot flushes [11-13]. Two previous studies that compared androgen-derived progestins with ethinyl estradiol, produced variable results. Dennerstein found d-norgestrel to be more effective than placebo but less effective than estrogen or combined estrogen and d-norgestrel [15]. Nordin found that norethisterone was no more effective than placebo and less effective than estrogen in a three-week study [16]. These trials, however, are of limited current applicability because of the very high doses of ethinyl estradiol that were used.

The strengths of this study are its one-year duration, its double-blind character, and the completeness of the data analyzed over one year. Further, participation of initially premenopausal/perimenopausal women who were just discharged following bilateral ovariectomy and hysterectomy eliminated any major differences in endogenous ovarian hormone levels that might have confounded the effects of therapy on hot flushes/night sweats.

It is not clear what triggers hot flushes and night sweats but it has been assumed to relate to estrogen exposure and decreasing estrogen levels—it does not require elevated gonadotrophins [24]. Decreased serotonin and norepinephrine levels are implicated [25], hence the therapeutic use of agents acting through these neurotransmitters [26]. Medroxyprogesterone may control hot flushes by different pathways than estrogen. Medroxyprogesterone, acting through hypothalamic mechanisms, modulates LH pulse frequency [27], increases core temperature [28] and stimulates respiration [29]. Thus medroxyprogesterone acts on the hypothalamus, the central site at which hot flush generation is understood to occur.

One limitation was the lack of pre-surgical baseline data. Potential participants were identified using surgical slates and were only eligible for study enrollment following surgery. Given the major physiological changes caused by premenopausal ovariectomy itself, and that all except one woman had never previously experienced hot flushes, it could be argued that inclusion of information from pre-operative baseline measurements, even if these were available, may not be entirely appropriate. However investigating the usefulness of such measures would have been helpful.

As far as possible, this resembles an intent-to-treat analysis. Only three randomized women's data were not analyzed—one took no medication, one took it for only one week, and the third had hyperthyroidism that developed during the first four months of the trial. Because hyperthyroidism may cause sweating and heat intolerance, her data were judged to be potentially confounded by her illness.

Use of medroxyprogesterone therapy for vasomotor symptoms may raise concerns about metabolic changes. Data from participants in this randomized, blinded one-year trial are available to describe changes in weight, blood pressure, percent body fat, lipids, electrolytes, hepatic and renal function during conjugated estrogen compared with medroxyprogesterone acetate therapy. Weight gain during conjugated estrogen therapy exceeded that on medroxyprogesterone acetate [18]. In addition women recorded 16 other experiences daily, including depression, which we are analyzing using factorial analysis. We anticipate submitting these data for publication shortly.

One consideration in selecting medroxyprogesterone or conjugated estrogen as therapy for menopausal hot flushes is the effect of each on venous thromboembolism (VTE), lipids, endothelial function, cardiovascular disease and strokes. Long-term placebo-controlled trials of medroxyprogesterone alone are needed and not available. The best synthesis of available data suggest that oral conjugated estrogen therapy doubled the relative risk for thrombosis [2;3], tripled it in older women with heart disease [30] and quadrupled it in those with cancer . A multicentre long-term trial of high dose medroxyprogesterone (1200 mg/d) in 42 women with advanced breast cancer showed no coagulation/fibrinolysis changes compared with chemotherapy-treated controls [31], suggesting no increased thrombosis risk. Although supposedly cardio-protective increases in HDL cholesterol occur with oral estrogen therapy, this lipid change did not prevent heart attacks in recent controlled trials [2;3;30]. Medroxyprogesterone with estrogen caused a significant but probably not biologically important decrease in HDL cholesterol [32]. Both progestin and estrogen cause beneficial decreases in LDL and total cholesterol, however only estrogen causes a detrimental increase in triglyceride levels. Therefore the lipid changes of each, although different, appear similar in cardiovascular impact. Estrogen causes improvements in endothelial function that may [33-35] or may not [36] be modified by varying doses of medroxyprogesterone. Multiple controlled studies show no effect of either hormone on blood pressure. The incidence of stroke was similar in the estrogen-with-progestin and estrogen-only arms of controlled trials [2;3] suggesting no excess stroke risk from medroxyprogesterone therapy.

Whether or not medroxyprogesterone increases the risk for breast cancer is unknown although data showing lower risk for breast cancer following pelvic surgeries such as hysterectomy [37] suggest that the apparent increased risk for breast cancer with combined hormones versus estrogen alone may represent confounding by indication. A large international case-control study has found no increased risk of breast cancer with depot medroxyprogesterone acetate used for contraception [38].

In summary, in this one-year randomized, double blind study, both conjugated equine estrogen, the gold standard, and medroxyprogesterone acetate effectively and equivalently controlled night and daytime hot flushes for women treated immediately following premenopausal ovariectomy. This parallel therapy trial showed equivalent control of the number of hot flushes and night sweats between estrogen- and progestin-treated women. Medroxyprogesterone caused a greater decrease in hot flush intensity change from day-to-day compared with estrogen. For these reasons medroxyprogesterone offers an alternative to estrogen treatment for intense hot flushes/night sweats in women for whom estrogen is either contraindicated or undesirable. This important study adds to evidenced-based information available to women and clinicians on effective treatment of vasomotor symptoms. Larger trials are indicated to confirm these findings.

(Word Count = 3378)

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## Legends for Figures

**Figure 1:** CONSORT figure for this randomized therapy trial comparing conjugated equine estrogen (0.6 mg/day) with medroxyprogesterone acetate (10 mg/day) as therapy for vasomotor symptoms for women undergoing premenopausal ovariectomy for benign disease. The figure shows the flow of individuals from initial screening and secondary eligibility through to enrolment and randomization to one of two therapies. The figure also enumerates the women who contributed partial data, or who were excluded from the analysis.

**Figure 2:** Vasomotor symptoms (as rate per 24-hour period) over 1 year following premenopausal ovariectomy for benign disease. Month 1 is the month immediately following surgery and study enrollment. Points are estimated average daily rate for women in the estrogen reference group (0.6 mg/day), adjusted for body mass index, and shown with 95% confidence intervals for each month. Analysis was by Poisson regression model with adjustment for overdispersion. Panels show the overall rate (top), daytime only (middle panel) and during sleep only (bottom panel). The light horizontal lines represent the estimated daily average rate during estrogen therapy during the full year.

**Figure 3:** Difference between therapies in the daily rate of vasomotor symptoms. Points are the estimated difference in the daily rate of vasomotor symptoms per month between conjugated equine estrogen (0.6 mg/day) and medroxyprogesterone acetate (10 mg/day) with 95% confidence intervals, adjusted for body mass index. Analysis was by Poisson regression model with adjustment for overdispersion. There was no significant difference between the therapies, and the two therapies were statistically equivalent (within 1 event per day of one another,  $P < 0.01$ ). Panels show the overall rate (top), daytime only (middle panel) and during sleep only (bottom panel). The dark horizontal lines represent equality. Positive values indicate fewer vasomotor symptoms for women randomized to take medroxyprogesterone acetate. The light horizontal lines are the estimated average daily

differences by therapy in hot flushes over the year in these women following premenopausal ovariectomy for benign disease.

**Figure 4:** This stacked bar graph shows the percentage of days with each intensity level of vasomotor symptoms (hot flushes or night sweats) over 1-year for both daytime and nighttime hot flushes and night sweats during therapy with conjugated equine estrogen (0.6 mg/day, n = 18 women) and medroxyprogesterone (10 mg/day, n = 20 women) following premenopausal ovariectomy. Increasing intensities of hot flushes and night sweats (range 0-4) are shown by increasing density of hatching, and the height of the bars reflects the proportion of days/nights with any vasomotor symptoms.

**Table 1:** Baseline demographic data for women providing Daily Menopause Diary© records by random assignment to conjugated equine **estrogen** (0.6 mg/day) or **medroxyprogesterone** acetate (10 mg/day) during a double blind parallel trial of hot flushes and night sweats following premenopausal hysterectomy and ovariectomy. These summary statistics include 38 women and are presented as mean (standard deviation) or as counts. There were no differences in participant characteristics between the treatment groups.

<b>Variables</b>	<b>Estrogen</b>	<b>Medroxyprogesterone</b>
N	18	20
Age	43.8 (6.1)	45.5 (3.3)
Weight (kg)	63.3 (8.3)	61.2 (9.6)
Height (cm)	163.3 (5.1)	160.8 (6.6)
BMI (kg/m <sup>2</sup> )	23.7 (2.8)	23.7 (3.6)
Menarche age (yr)	12.4 (1.7)	12.7 (1.8)
Gynecological age (yr)	30.6 (6.6)	32.1 (3.7)
*Days since surgery	6.3 (4.5)	6.9 (4.8)
Ethnicity (Caucasian/Asian)	16/2	14/6
Missing data (% of days)		
Daytime	8.0% (17.6%)	3.7% (13.1%)
Nighttime	8.5% (16.5%)	3.5% (13.1%)

\*Days following ovariectomy at which they were discharged from hospital and randomized therapy began.

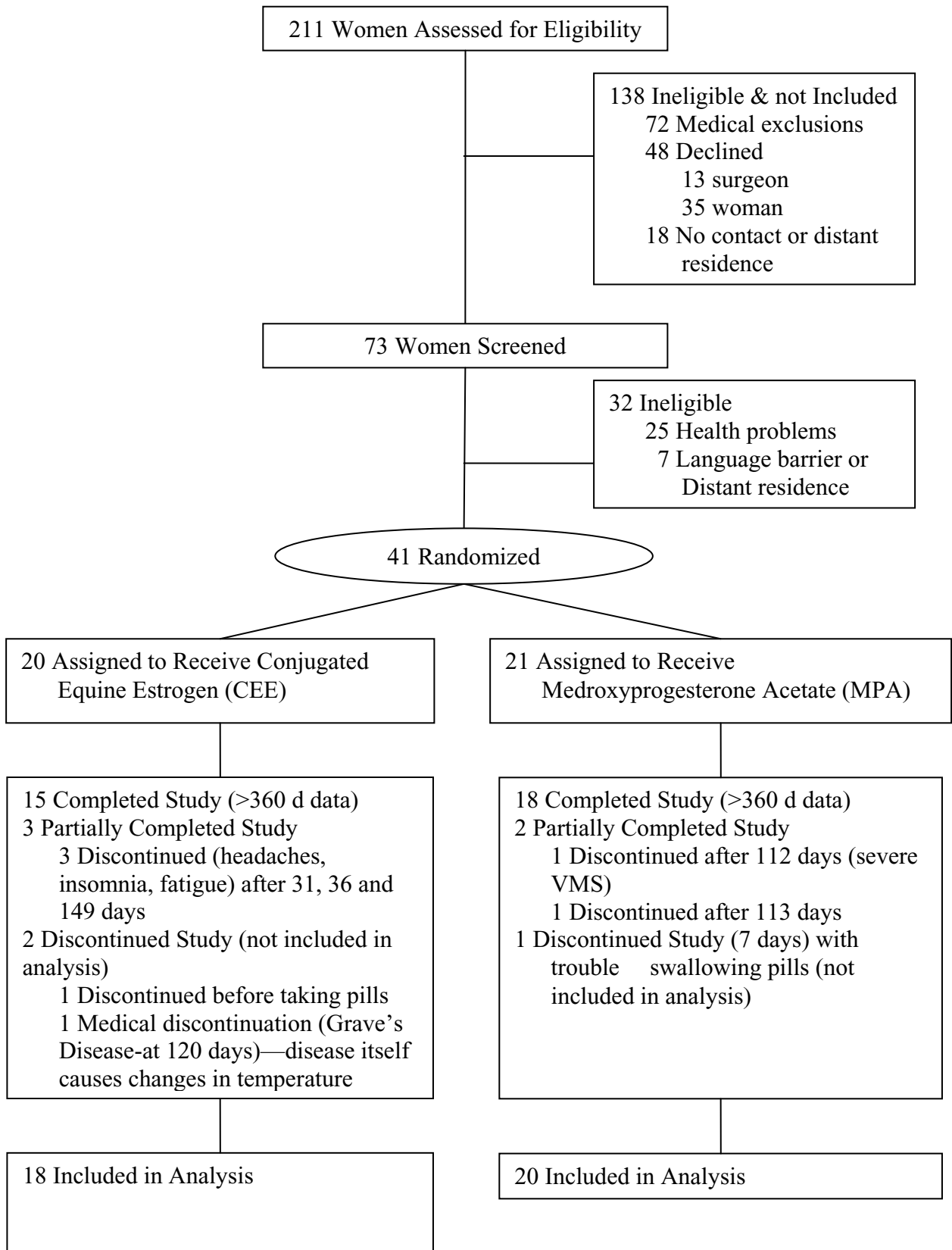
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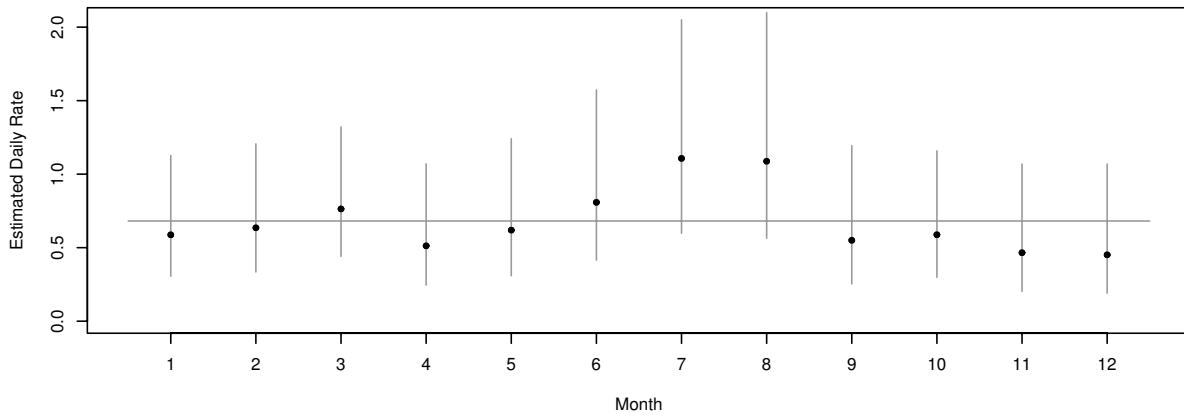
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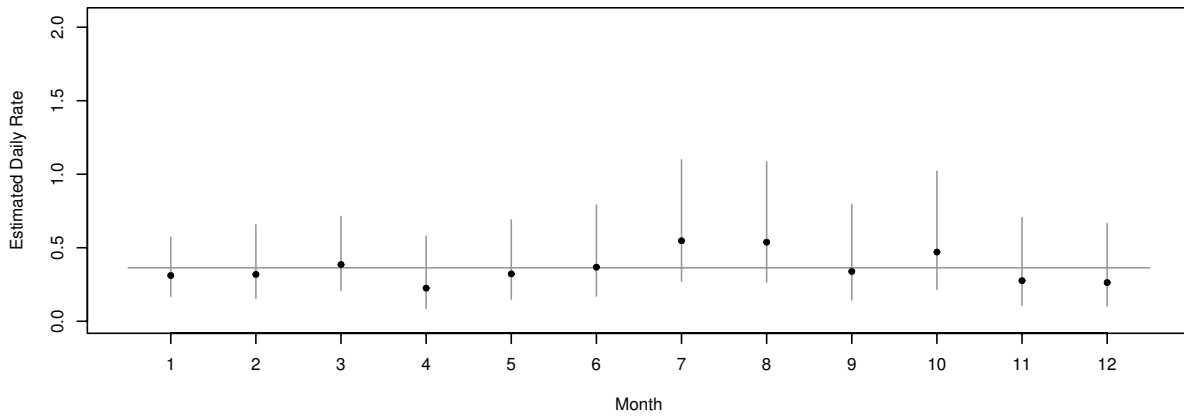
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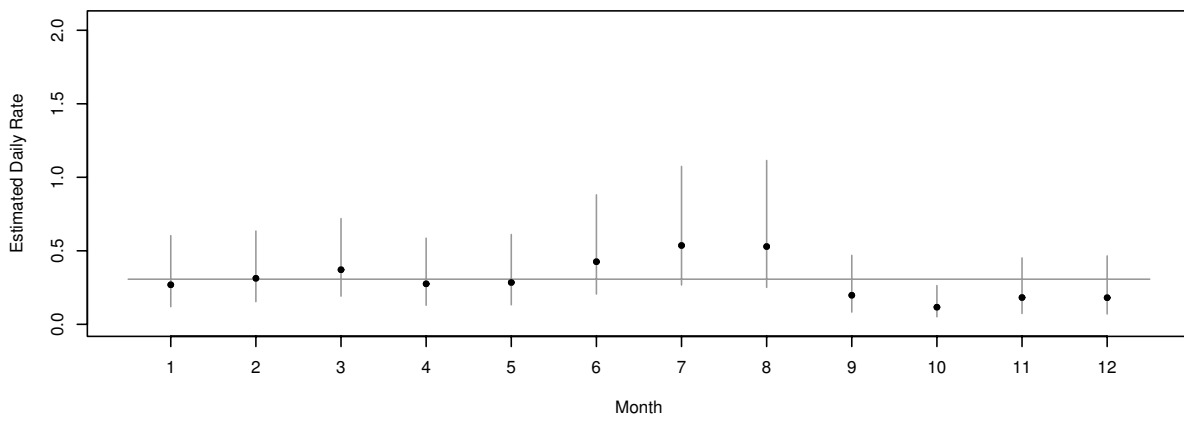
24-Hour Rates for Estrogen Arm by Month



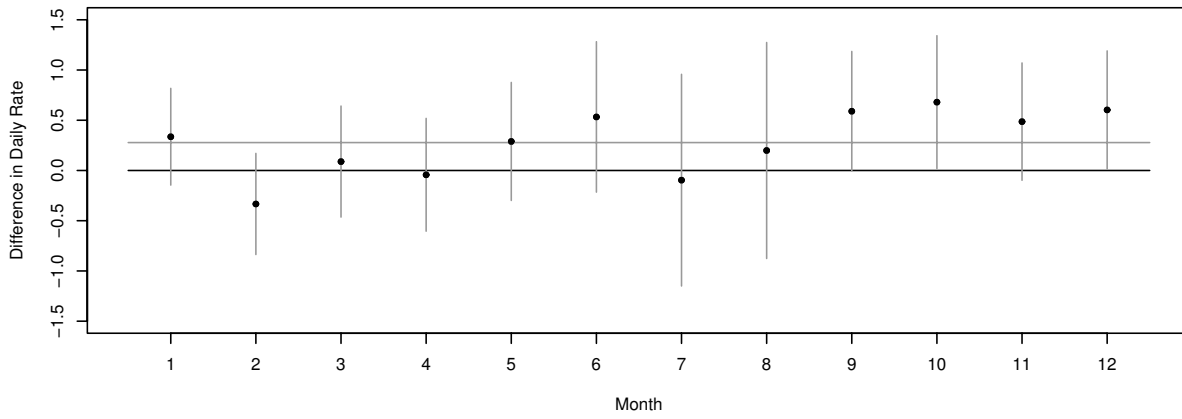
Daytime Rates for Estrogen Arm by Month



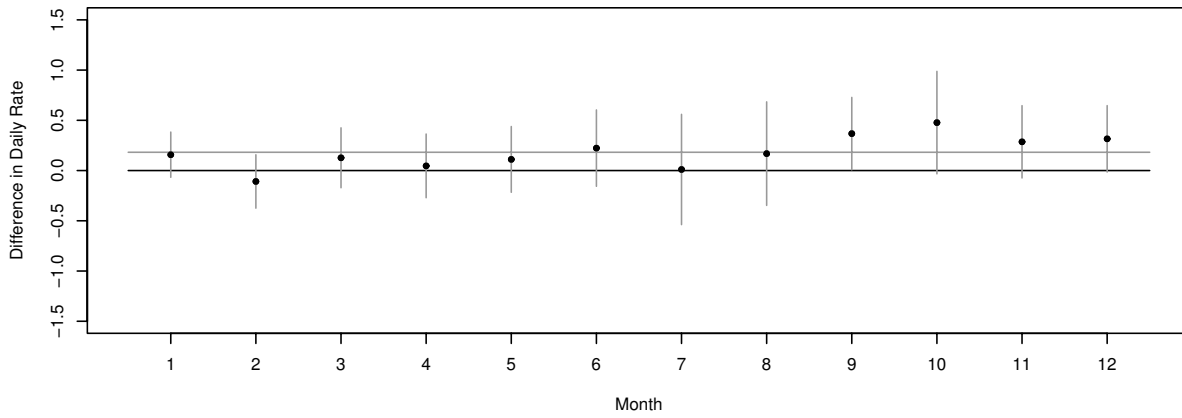
Nighttime Rates for Estrogen Arm by Month



Estrogen – Medroxyprogesterone 24–Hour Rate Difference by Month



Estrogen – Medroxyprogesterone Daytime Rate Difference by Month



Estrogen – Medroxyprogesterone Nighttime Rate Difference by Month

