Short-term oral progesterone administration antagonizes the effect of transdermal estradiol on endothelium-dependent vasodilation in young healthy women

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Submitted 22 April 2011; accepted in final form 12 August 2011


Am J Physiol Heart Circ Physiol

WITH OVER 73% OF childbearing-aged women in the United States taking exogenous hormones for contraceptive and gynecological purposes (49a), the exploration of how exogenous hormones affect cardiovascular health is imperative. Although research on sex hormones has mainly focused on the effects of estrogen and manufactured progestins, there is relatively little known regarding the effect of progesterone on the vasculature. With progesterone production occurring naturally within the body and its bioidentical exogenous form being one of the most frequently prescribed progestogens, the need to understand the influence of progesterone on cardiovascular health is great.

One of the primary methods used to investigate the effect of sex hormones on vascular health is via flow-mediated dilation (FMD). FMD, measured as the percent change in brachial artery diameter in response to an increase in shear stress, has been widely used as a noninvasive technique to assess endothelial function and is known to parallel endothelial function in the coronary arteries (2). FMD can be used as a predictor of future cardiovascular events across many different ages and disease states (16, 18, 27, 29, 35, 39, 53) and adds independent prognostic value in determining cardiovascular risk in women (35).

FMD values have been shown to vary between sexes (21), and the technique has been used to investigate changes in endothelial function during the menstrual cycle (13, 51). FMD is lowest during menstruation (low-estrogen, low-progesterone phase) (13) and has been shown to vary with the rise and fall of estrogen throughout the menstrual cycle (13, 51). However, it is unclear whether the lower FMD during the mid-luteal phase, compared with the ovulation phase (high estrogen, low progesterone), is due to the rise in progesterone or the lowered estrogen during this phase. The administration of estradiol has also been demonstrated to increase FMD compared with hormone-suppressed values (5, 10, 11, 25, 26, 47). However, cardiovascular responses to different types of exogenous progestogen administration widely vary (1, 7, 23, 36). Our laboratory has previously shown that levonorgestrel, desogestrel, and medroxyprogesterone acetate (MPA) all antagonized the effects of ethinyl estradiol on FMD (25, 26, 47). Conversely, etonorgestrel (via a vaginal ring) and drospirenone did not (24, 48). Whereas various progestins produce different effects on the vasculature, it is unknown what effect progesterone itself might have on endothelial function.

Research on the effects of unopposed progesterone administration on the vasculature of young healthy women is nonexistent. Therefore, this study aimed to evaluate the effects of progesterone, both in combination with estradiol and without, on endothelial function in healthy young reproductive-aged women. Through our design of suppressing endogenous sex hormones and then adding back hormones exogenously, we hypothesized that the beneficial effects of estradiol on endothelial function would not be antagonized by progesterone and that progesterone administration alone would not decrease endothelial function.
METHODS

Subjects. Seventeen healthy, recreationally active females (exercise limited to 1–3 days/wk for <1 h/day), between the ages of 18 and 29 yr, completed the protocol. All subjects were nonsmokers, had a body mass index (BMI) < 25, and were not taking any medications, with the exception of combined hormonal contraceptives (n = 13). Subjects taking contraceptives discontinued use and began menstruating before starting gonadotropin-releasing hormone antagonist (GnRHa) suppression. Before the subjects participated in the study, a physician specializing in gynecology screened all the women for a history of cardiovascular disease, hypertension, hypercholesterolemia, diabetes, medical allergies, clotting disorders, endocrine and/or menstrual disorders, and recent surgical procedures. Subjects were required to take a pregnancy test, demonstrating negative results, at the beginning of each testing session. Subjects abstained from exercise, alcohol, vitamins, and over-the-counter medications for 24 h before each trial. Additionally, subjects abstained from caffeine for 12 h, and subjects were either fasted for 12 h before each trial (if the subject was under hormone suppression) or instructed to eat a light, low-fat meal no less than 2 h before the start of the protocol (after afternoon studies, to prevent a hypoglycemic episode). All testing was conducted in a temperature-controlled room (21 to 23°C), and each testing session was conducted at the same time of day across trials for each individual subject (time of sessions was counterbalanced across conditions). Approval for this study was granted by the Institutional Review Board at the University of Oregon, and each subject provided written and oral consent for the protocol before enrolling in the study.

Study design. After a successful screening interview, subjects initiated endogenous female sex hormone suppression via 250 μg/0.5 ml subcutaneous injection of the GnRHa, ganirelix acetate (Organon International, Roseland, NJ), on the first day of their next menstruation (day 1 of study). Subjects continued GnRHa suppression daily for the entirety of their participation in the study (10–12 days in total). Within 36–48 h of beginning GnRHa treatment, endogenous estrogens and progesterone are fully suppressed (31). On day 4 of the study, subjects came into the laboratory to participate in trial 1 (hormone suppression condition). Upon completion of testing on this day, subjects continued endogenous sex hormone suppression and were randomly assigned to one of two exogenous hormone add-back conditions. These conditions consisted of supplementation with either 200 mg progesterone orally each evening (n = 8) or 0.1 mg estradiol transdermally (n = 9) per day. Estradiol (Mylan Pharmaceuticals, Morgantown, WV) was given as a weekly 31-mm2 transdermal patch that contains 3.88 mg of estradiol (United States Pharmacopeia), ultimately delivering 0.1 mg of estradiol per day. The progestosterone administered (Prometrium; Solvay Pharmaceuticals, Marietta, GA) is a bioidentical equivalent to endogenous progesterone. On study day 7, subjects returned to the laboratory to participate in trial 2 (progesterone-first or estradiol-first conditions), and we then began the administration of both estradiol and progesterone at the dosages stated above. Subjects returned for trial 3 (combined hormone condition) on day 10. Figure 1 provides a schematic diagram of our study design.

After the conclusion of this original study, we discovered subjects had lower serum levels of estradiol than predicted in our combined hormone condition in the estradiol group. To explore this issue further, we conducted a follow-up study in which we suppressed endogenous hormones in four additional subjects, studying them on day 4 for the hormone suppression condition. We then administered 0.2 mg of transdermal estradiol (double estradiol group) and studied them again during a combined hormone condition (double dose of estradiol and single dose of progesterone) on day 10. Subjects were also instructed to replace the patches every 3 days to avoid modulation of the medication dose. The results and discussion for this follow-up study are included in appropriate sections below.

Protocol. Subjects entered the laboratory for each trial and were instrumented with a five-lead electrocardiogram (ECG) and a blood pressure cuff on the left brachium. Heart rate was continuously monitored throughout the protocol (CardioCap, Datex-Ohmeda, Louisville, CO) and was recorded during baseline, during each subsequent 20-min resting period, and after completion of testing. Blood pressure was noninvasively measured from the left arm via automated brachial oscillation (CardioCap 5, Datex-Ohmeda) and was recorded simultaneously with heart rate.

To measure FMD, an inflatable occlusion cuff was placed on the right forearm ~2 cm distal to the antecubital fossa. With the use of a high-resolution Doppler ultrasound machine (Terson t3000cv, Teratech, Burlington, MA), a 10.0-MHz linear array ultrasound transducer probe was placed on the brachial artery (using an insonation angle of 60°) between 3–10 cm proximal to the antecubital fossa. Probe placement, occlusion cuff placement, and arm-trunk angle were recorded to ensure consistency between trial days. Endothelial function testing was performed as previously described by Celermajer et al. (8), followed the guidelines suggested by Corretti et al. (9) and Thijsen et al. (43), and are summarized below.

After a clear image of the brachial artery was obtained and the subject rested for a minimum of 20 min, measurements of brachial artery diameter and blood velocity were recorded. After 1 min of baseline measurements, an occlusion cuff (Zimmer, Dover, OH) was rapidly inflated to 300 mmHg (E20 Rapid Cuff Inflator, D. E. Hokanson, Bellevue, WA). The occlusion was maintained for a continuous 5 min, and recording continued for 3 min postrelease. Upon release, brachial artery blood flow was increased, causing a shear stress on the vessel walls. In response to this shear stress, nitric oxide (NO) is released from the endothelium, causing a reactive vasodilation, known as FMD (17). FMD was assessed as the percent change in brachial artery diameter from baseline to peak dilation. After a 20-min supine rest, a second FMD test was conducted.

Doppler ultrasound data were collected at 20 frames/s (Camtasia Studio, TechSmith, Okemos, MI). After completion of an entire study day, data files were transferred to a computer that operates a custom-designed edge-detection and wall-tracking analysis software (DICOM, Perth, Australia), which can track the vessel walls, measuring the average of all diameters throughout the entire cardiac cycle and the peak blood velocity tracing in real time. These synchronous measurements allow blood flow (product of cross-sectional area and Doppler velocity) to be calculated (52). FMD is calculated as the percent change between baseline diameter and peak dilation postocclusion cuff release: FMD = [peak diameter (in mm) – baseline diameter (in mm)]/[baseline diameter (in mm)] × 100. This software has demonstrated the ability to detect a 1.5–2.0% change in dilation within eight subjects with a power of 80%, requiring fewer subjects than other methods of analysis (52).

Since peak dilation may not be achieved until 40 to 90 s post-cuff release, we continued recording and analyzing 3 min postrelease (6, 43). We calculated shear rate as the product of four times the velocity divided by the diameter. By plotting shear rate as a function of time

<table>
<thead>
<tr>
<th>Study Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>GnRHa</td>
<td>GnRHa + P₄</td>
<td>GnRHa + P₄ + E₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>GnRHa</td>
<td>GnRHa + E₂</td>
<td>GnRHa + P₄ + E₂</td>
<td></td>
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</tr>
</tbody>
</table>

Fig. 1. Study design. Subjects are tested under hormone suppression, progesterone-first or estrogen-first, and combined progesterone-estrogen conditions. Testing occurred on days 4, 7, and 10. GnRHa, hormone suppression via gonadotropin release hormone antagonist; P₄, progesterone; E₂, estradiol.
and estradiol group

Baseline characteristics in the progesterone group

Rate and FMD percentage within the progesterone-first group (until peak dilation (34, 43). There was no correlation between shear dilation shear rate area under the curve, which is the relevant indicator (until peak dilation is reached), we determined the time to peak dilation.

Age, yr 21
Weight, kg 61.18 ± 2.40
Height, cm 161.33 ± 2.36
Body mass index, kg/m² 23.52 ± 1.07
Heart rate, beats/min 61 ± 5
Baseline diameter, mm 3.2 ± 0.2
Systolic BP, mmHg 111 ± 2
Diastolic BP, mmHg 71 ± 2
Mean arterial BP, mmHg 85 ± 2

Values are means ± SE; n = 8 subjects in progesterone group, and n = 9 subjects in estradiol group. BP, blood pressure.

H1718 PROGESTERONE ANTAGONIZES ESTROGEN IN FMD

RESULTS

Subject characteristics. Baseline characteristics for both study groups are displayed in Table 1. Between groups, subjects did not differ in age, height, weight, BMI, baseline brachial artery diameter, baseline heart rate, or baseline blood pressures.

Within each group (those who received progesterone vs. estradiol first during the study protocol), there were no significant differences in height, weight, BMI, heart rate, or diastolic blood pressure across the three trial days (see Table 1 for baseline data). However, within the estradiol group, systolic blood pressure was significantly higher during the hormone suppression condition, compared with the estradiol-first (P = 0.014) and combined hormone (P = 0.006) conditions. Mean arterial pressure was also significantly higher in the hormone suppression condition, compared with the combined hormone condition (P = 0.014). No blood pressure differences were found within the progesterone group across study days. Additionally, within each group there were no differences in baseline brachial artery diameters across trial days. See Tables 2 and 3 for blood pressure and heart rate data across trial days.

Endogenous estradiol and progesterone levels were suppressed during trial 1 (hormone suppression condition) in both groups (Tables 2 and 3). In both groups there was an increase in estradiol levels between trials 1 and 2 (progesterone first, P = 0.007; and estradiol first, P < 0.001), although the small increase in estradiol in the progesterone-first condition would not indicate any physiological significance. Progesterone levels remained consistent between trials 1 and 2 in the estradiol-first group. However, as expected, we saw a rise in progesterone levels in the progesterone-first condition (P = 0.002) between trials 1 and 2. This elevated level of progesterone remained stable within the progesterone group for the combined hormone condition (still significantly different from hormone suppression, P < 0.001). Within the progesterone group, estradiol levels significantly rose in the combined hormone condition and were significantly different from both hormone conditions.

Table 2. Endothelial function and subject characteristics in the estradiol group

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone suppression</td>
<td>Estradiol first</td>
<td>Combined hormones</td>
</tr>
<tr>
<td>Baseline diameter, mm</td>
<td>3.31 ± 0.17</td>
<td>3.29 ± 0.12</td>
</tr>
<tr>
<td>Peak diameter, mm</td>
<td>3.57 ± 0.18</td>
<td>3.61 ± 0.13</td>
</tr>
<tr>
<td>Shear rate (AUC) (10²)</td>
<td>17.30 ± 2.89</td>
<td>21.06 ± 3.77</td>
</tr>
<tr>
<td>GTN, %</td>
<td>19.33 ± 2.13</td>
<td>19.12 ± 2.31</td>
</tr>
<tr>
<td>Progesterone, ng/ml</td>
<td>2.0 ± 0.1</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>Estrrogen, pg/ml</td>
<td>16.3 ± 1.5*</td>
<td>122.2 ± 19.9†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 5</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>113 ± 2*</td>
<td>109 ± 2</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>71 ± 2</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Mean arterial BP, mmHg</td>
<td>85 ± 2</td>
<td>83 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9 subjects in estradiol group. AUC, area under the curve; GTN, nitroglycerine administration. *Significantly different from trials 2 and 3; †significantly different from trial 3; significantly different from trials 1 and 2.
Table 3. Endothelial function and subject characteristics in the progesterone group

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone suppression</td>
<td>Progesterone</td>
<td>Combined hormones</td>
</tr>
<tr>
<td>Baseline diameter, mm</td>
<td>3.17 ± 0.18</td>
<td>3.23 ± 0.20</td>
</tr>
<tr>
<td>Peak diameter, mm</td>
<td>3.41 ± 0.18</td>
<td>3.44 ± 0.22</td>
</tr>
<tr>
<td>Shear rate (AUC) (10^5)</td>
<td>21.99 ± 3.64</td>
<td>22.86 ± 4.32</td>
</tr>
<tr>
<td>GTN, %</td>
<td>18.63 ± 1.31</td>
<td>18.27 ± 2.26</td>
</tr>
<tr>
<td>Progesterone, ng/ml</td>
<td>1.9 ± 0.1*</td>
<td>5.4 ± 0.7</td>
</tr>
<tr>
<td>Estrogen, pg/ml</td>
<td>13.0 ± 1.3*</td>
<td>17.2 ± 1.3†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>57 ± 3</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>110 ± 2</td>
<td>111 ± 1</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>70 ± 2</td>
<td>69 ± 2</td>
</tr>
<tr>
<td>Mean arterial BP, mmHg</td>
<td>64 ± 2</td>
<td>83 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 subjects in progesterone group. *Significantly different from trials 2 and 3; †significantly different from trial 3.

FMD in the progesterone-first condition was significantly lower than in the estradiol-first condition (P = 0.038).

Endothelium-independent vasodilation. There were no significant differences in nitroglycerine-mediated vasodilation (GTN%) within or between the progesterone or estradiol groups across the different hormone conditions (P > 0.05, Tables 2 and 3).

Follow-up study. In the follow-up study, the administration of 0.2 mg of estradiol (double estradiol group) increased serum estrogen levels in the additional subjects compared with the original study, and estradiol levels were significantly higher in the double estradiol group during the combined hormone condition (133.7 ± 23.5 pg/ml) compared with the single estradiol group (P = 0.021). FMD values during the combined hormone conditions between the double estradiol group and the single-dose of estradiol group displayed the same trend, indicating that the lower serum levels of estradiol in the single-dose study did not change the FMD response in trial 3 (see Table 4).

**DISCUSSION**

The goal of this study was to explore the effects of progesterone on endothelial function. In contrast to our hypotheses, we found that a combined administration of estradiol and progesterone decreased endothelial function, measured via FMD, compared with the increase in FMD with estradiol-only administration. There was no statistically significant decrease in FMD with unopposed progesterone administration compared with endogenous sex hormone suppression or combined progesterone and estradiol conditions, although we did observe
a trend. These findings suggest that oral progesterone alone does not profoundly reduce endothelial function yet antagonizes the beneficial effects of estrogen.

Changes in endothelial function in response to various exogenous progestogens have produced mixed results in previous studies. Our laboratory has previously shown a negative impact of desogestrel, levonorgestrel, and MPA (all combined with varying doses of ethinyl estradiol) on FMD levels (25, 26, 47). Lizzarelli et al. (22) also discovered similar responses in FMD in young women, showing that levonorgestrel (when combined with ethinyl estradiol) and depot MPA decrease FMD, compared with that in age-matched controls. Alternatively, our laboratory found an increase in FMD upon the administration of transvaginal etonogestrel (48) and oral drospirenone when combined with ethinyl estradiol (24), compared with that of their respective placebo weeks. We suspect the specific form of progestogen may cause the varying effects on the cardiovascular system (38) and may be related to variable effects of hormones on NO production and possibly endothelin-1 (25).

It has been shown that the FMD response after a 5-min occlusion is predominately mediated by the release of NO (9, 12, 30). Increased endothelial function that is documented with estrogen administration is largely attributed to increased endothelial NO synthase expression and NO production (33, 42, 44, 50). Some progestins, such as drospirenone, also seem to increase the synthesis of NO in endothelial cells, as reported by Simoncini et al. (40), and lead to enhanced vasodilation. This may account for the increase in FMD our laboratory has found during combined drospirenone and ethinyl estradiol administration (24). The deleterious effects of MPA on endothelial function may relate to its vasoconstricting properties, caused by a decrease in NO release (37) or an increase in production in endothelin-1 (25).

Natural progesterone appears to stimulate NO synthesis through transcriptional and nontranscriptional pathways, both in human endothelial cells and in ovarioctomized rat abdominal aortas (41). Progesterone has also shown several other beneficial effects on the vasculature. It protects against atherosclerosis by inhibiting smooth muscle proliferation in human and rat aortic smooth muscle cells (19, 20), which may be mediated via a p53-dependent pathway (15). In ovarioctomized rats with pulmonary hypertension, treatment with progesterone decreased the severity of hypertension, decreased vascular remodeling, and decreased mortality (45). We hypothesized that these improvements in vascular function would also extend to increases in FMD in our young healthy women.

Contrary to our results, Gerhard et al. (11) showed an increase in FMD with both estradiol-only and estradiol-progesterone administration in postmenopausal women. However, the dose and route of administration of progesterone in our study (200 mg orally) differed from the Gerhard et al. study (300 mg vaginally), suggesting that the difference in responses may be due to the dose or the route of administration of progesterone. When taken orally, progesterone undergoes first pass metabolism in the liver. The route of administration, and subsequent change in chemical structure, may alter which receptors are activated at the target organs and potentially could cause the effects to be more closely akin to progesterin-like responses. We have previously observed this phenomenon in women using MPA, in which the oral form of MPA antagonized the effects of estrogen (25), but estrogen administration resulted in improvements in endothelial function in women taking the intramuscular injection form of MPA (46).

Arterial smooth muscle walls contain progesterone receptors (19, 20, 38). A study conducted by Toth et al. (49) on human umbilical vein endothelial cells discovered that progesterone specifically acts on progesterone receptor A and implied that other progestins, such as MPA, may not act on this specific receptor. Future research on progesterone receptors may help us to solve the mystery on why different progestogen administrations result in variable (positive and negative) effects.

Negative effects of progestogens on FMD have also been found in postmenopausal women. Faludi et al. (10) showed that norethisterone acetate administration decreased FMD compared with unopposed estradiol. The Women’s Health Initiative trials (1, 23, 36) ended the conjugated estrogens-MPA study arm early because of the number of increased cardiovascular events observed compared with the estrogen-only and placebo arms. These studies suggest that progestogens may antagonize the effects of estradiol in the postmenopausal woman as well. However, similar to our results, Honisett et al. (14) found that unopposed oral progesterone did not decrease FMD compared with baseline measurements in postmenopausal women, showing that progesterone alone does not decrease endothelial function compared with the menopausal hormone state.

The effects on FMD from exogenous hormone administration in the current study seem to mimic FMD changes that have been found with endogenous estrogen and progesterone fluctuations during the menstrual cycle (13, 51). The design of our study, by continuing estradiol supplementation while adding progesterone (during trial 3), allows interpretation that the high level of progesterone during the mid-luteal phase of the menstrual cycle may be antagonizing the effects of estradiol on the vasculature, possibly accounting for the decrease in FMD observed during this phase. However, as pointed out above, differences in oral administration versus naturally occurring, or delivered via an alternative route, make this conclusion tenuous.

Study limitations. One limitation in our study was the lower than expected levels of serum estradiol in response to the 0.1-mg transdermal dose observed in trial 3 of the estradiol-first group. We did conduct a follow-up study where we administered 0.2 mg of estradiol (double estradiol group) in place of the dose used in the original study. As shown in the results, serum estrogen levels in these subjects were increased from the original study and no longer decreased between trials 2 and 3. Furthermore, similar FMD values were observed during the combined hormone conditions of the double and single-dose estradiol groups.

An additional limitation of our study was that through the random assignment process, our data approached a significant difference in BMI between the progesterone-first and estradiol-first groups (P = 0.07). As shown in previous studies, a larger BMI is associated with a lower FMD value (32). The intent of this study was to have no differences between the two groups at baseline, yet through random assignment, there was a trend of the progesterone-first group to have a slightly higher BMI. However, all women fell within a normal range of BMI, and there were no differences in FMD values or blood pressure between the two groups at baseline, which leads us to conclude that the near-significant difference in BMI did not translate into
FMD results and have no effect on the interpretation of the results of this study.

Lastly, FMD tended to be lower when women were administered progesterone alone, compared with hormone suppression or combined hormone conditions. However, the decrease was not statistically significant. As discussed above, we would need to study a large number of women to achieve statistical significance, which simply is not feasible due to the cost of the GnRHa injections and the time required to study that large of a sample size. It is not clear how important this trend toward a lower FMD is, since the difference was only ~1%.

**Conclusions and perspectives.** In this study, we verified that the administration of unopposed estradiol improves endothelial function, as measured by FMD. This increase in endothelial function is abolished when progesterone is added to the regimen, indicating that oral progesterone antagonizes the effects of estradiol on the endothelium in young healthy women.

Ongoing studies, such as the Kronos Early Estrogen Prevention Study (KEEPS), are currently using oral progesterone in menopausal supplementation protocols (i.e., 200 mg oral micronized progesterone for 12 days/mo) in hopes of having more beneficial outcomes than the Women’s Health Initiative studies did with MPA administration (28). Our hypothesis of progesterone eliciting differing vascular responses than previously found with MPA administration did not transpire exactly as we expected. Although progesterone alone did not decrease FMD values, it did antagonize the effects of estrogen on the FMD. Therefore, further research is needed to expand our basic understanding of the specific effects of progesterone on the vasculature and whether these changes translate to differences in cardiovascular risk and outcomes.

**ACKNOWLEDGMENTS**

We would like to extend our gratitude to the individuals who participated in this study. Statistical consultation was provided by Dr. Keith Smolkowski.

**GRANTS**

This research was supported by the National Heart, Lung, and Blood Institute Grant HL-081671.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**REFERENCES**


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