Modification of angiogenic factors by regular and acute exercise during pregnancy

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1Department of Obstetrics, Gynecology and Reproductive Science, and 2Magee-Womens Research Institute, University of Pittsburgh, Pittsburgh, Pennsylvania; and 3Department of Obstetrics and Gynaecology, Queen’s University, Kingston, Ontario, Canada

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Weissgerber TL, Davies GAL, Roberts JM. Modification of angiogenic factors by regular and acute exercise during pregnancy. J Appl Physiol 108: 1217–1223, 2010. First published March 11, 2010; doi:10.1152/japplphysiol.00008.2010.—This cross-sectional study examined mechanisms through which exercise might alter preeclampsia risk by estimating the effects of acute and chronic exercise on angiogenic markers in healthy pregnant women with different amounts of regular exercise participation. Serum-soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PIGF), and soluble endoglin (sEng) were measured before and after 20 min of moderate-intensity cycle ergometry in normotensive, nonsmoking pregnant (16 active, 9 inactive, 34.1 ± 1.6 wk gestation) and nonpregnant (15 active, 12 inactive, midlate luteal phase) women. Inactive women did not regularly exercise at an intensity that was sufficient to cause sweating. Active women exercised for at least 3 h/wk. Inactive pregnant women had significantly lower PIGF concentrations [median (interquartile range): 268 (159, 290) vs. 278 (221, 647) pg/ml, P = 0.014] and higher sFlt-1 [5,180 (4,540, 5,834) vs. 4,217 (2,014, 5,481) pg/ml, P = 0.005] and sEng concentrations [9.1 (7.7, 16.7) vs. 7.8 (6.5, 10.1) ng/ml, P = 0.025] than active pregnant women. This effect of regular exercise participation was not observed in nonpregnant women. Acute exercise in pregnancy was not associated with angiogenic changes that might contribute to preeclampsia; rather, there was a small, but statistically significant, increase in PIGF following acute exercise in active pregnant women [278 (221, 647) vs. 335 (245, 628) pg/ml, P = 0.014]. sFlt-1 increased significantly following acute exercise in inactive nonpregnant women [90 (86, 100) vs. 106 (101, 116) pg/ml, P = 0.012], but not in active nonpregnant women. Regular exercise during pregnancy is associated with higher serum PIGF and lower sFlt-1 and sEng concentrations in late gestation, a difference that is unlikely to have predated the pregnancy.

preeclampsia; non-pregnant women

PREECLAMPSIA IS DIAGNOSED after 20-wk gestation on the basis of new onset hypertension and proteinuria (42). This syndrome affects 2–7% of pregnancies (8, 11) and is a leading cause of maternal (42) and fetal (2) morbidity and mortality, accounting for ~15% of preterm births (17). The only cure is delivery. Prospective (23) and retrospective studies (15, 24, 25, 29) indicated that women who exercised regularly were 20–60% less likely to develop preeclampsia, depending on the amount and intensity of exercise. Recreational physical activity significantly reduced the risk of preeclampsia among Norwegian women with a preconception body mass index (BMI) <25 kg/m², but was not protective in overweight or obese women (14). In contrast, regular exercise did not reduce preeclampsia risk in the Danish National Birth Cohort (21). The risk of severe preeclampsia was increased among women exercising >270 min/wk, compared with women who did not exercise (21).

The multitude of underlying causes of preeclampsia (34) suggests that any proposed preventive intervention will be effective in some patients and not others. We propose that physiological studies identifying mechanisms through which acute and chronic exercise may alter preeclampsia risk could be beneficial for three reasons. First, positive results would justify further study of the relationship between preeclampsia and exercise. Second, identifying mechanisms by which exercise may alter preeclampsia risk could allow investigators to select women for future intervention studies who are likely to benefit. Third, mechanistic knowledge would assist exercise physiologists to optimize exercise prescriptions to enhance potential beneficial effects and prevent potential harmful effects.

Recent evidence suggests that excessive antiangiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), contribute to the pathophysiology of preeclampsia (16). sFlt-1 reduces angiogenesis by binding the proangiogenic ligands vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). As nonsignaling decoys (19), sFlt-1 and sEng may impair pregnancy-induced adaptation in maternal placental bed vessels and contribute to systemic maternal endothelial dysfunction (19). The purpose of this study was to determine whether either regular exercise or acute moderate-intensity exercise would affect proangiogenic (PIGF, VEGF) or antiangiogenic (sFlt-1, sEng) factors in nonpregnant women, and whether the effects of exercise were different in pregnancy.

We hypothesized that active pregnant women would have higher serum PIGF concentrations and lower serum sFlt-1 and sEng than inactive pregnant women in the third trimester. Furthermore, we hypothesized that sFlt-1, sEng, PIGF, and VEGF would not change immediately following acute moderate-intensity exercise in nonpregnant or pregnant women.

MATERIALS AND METHODS

Data were collected during a study examining the effects of pregnancy, acute exercise, and regular exercise on conduit artery vascular function conducted between February 2006 and April 2007 (33). This study included extensive evaluation of exercise habits and physical fitness; therefore, ultrasound screening and medical approval were required for participation, and the number of subjects was limited. Serum sFlt-1, sEng, PIGF, and VEGF were retrospectively measured to examine the potential effects of exercise on angiogenesis. This preliminary analysis sets the stage for a larger, less complex study of the role of angiogenic factors in the exercise effect on the risk of preeclampsia and identifies future targets for research in this area.

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Subjects. Subjects were 16 active pregnant, 9 inactive pregnant, 15 active nonpregnant, and 12 inactive nonpregnant healthy, nonsmoking women, age 22–40 yr, who were not taking hormonal contraception or medications. Women with preexisting cardiovascular disease or hypertension, previous hypertension in pregnancy, or hypertension or proteinuria during the current pregnancy were excluded. Inactive women did not regularly exercise at an intensity that was sufficient to cause sweating, while active women exercised for at least 3 h/wk at an intensity that was sufficient to cause sweating. Nonpregnant women had regular menstrual cycles between 25 and 32 days in length and were tested between menstrual cycle days 20 and 28. Pregnant women were tested between 30 and 36 wk gestation. Participants were recruited through flyers and contact with local obstetricians and midwives.

Pretest screening. Women completed standardized screening forms (Physical Activity Readiness Questionnaire or PARmed-X for Pregnancy, http://www.csp.ca/forms.asp) to confirm that they had no contraindications to exercise. The doctor or midwife of each pregnant participant reviewed the form to verify that she could exercise safely. A transabdominal ultrasound was performed to ensure that the pregnancy was singleton and uncomplicated and that the fetus was not small for gestational age. An obstetrician (G. A. L. Davies) provided medical clearance for exercise testing after examining the screening form and ultrasound results. The Health Sciences Research Ethics Board at Queen’s University approved the study protocol, and all subjects provided written, informed consent before participating.

Physical activity indices. Subjects completed a 3-day physical activity record (5) on consecutive days (1 weekend day, 2 weekdays) within 2 wk of the test to evaluate current physical activity. Chronic physical activity was evaluated using the Kaiser Physical Activity Survey, which has been validated in nonpregnant (1) and pregnant (27) women. The survey was administered once to nonpregnant subjects, to assess activity during the past year, and twice to pregnant subjects, to assess activity during pregnancy and for 1 yr before conception. Mean voluntary physical activity (5) and the sports and exercise index (1, 27) were calculated, as described previously (1, 5, 27).

Exercise test. Subjects avoided caffeine and strenuous exercise for 12 and 24 h before testing, respectively, and consumed a standardized meal at the test site at 9:45 AM. A blood sample was drawn immediately after the meal. The participant sat quietly for 10 min, while heart rate (Polar Vantage Heart Rate Monitor) and breath-by-breath respiratory measurements (VMAX II, Cardinal Health or Moxus Modular Metabolic System, AEI Technologies) were collected. After a 3-min warm-up on the cycle ergometer (Sensor Medicis Model 800S, Cardinal Health), women completed a 90-s ramp work rate increase until a rating of perceived exertion (RPE) of 13 on the 6–20 Borg scale was reached. This intensity corresponds to a verbal descriptor of “somewhat hard” and was maintained for 20 min. RPE was the primary indicator of intensity, as pregnancy does not alter RPE during weight-supported exercise (40). Steady-state heart rates of ~130 beats/min in nonpregnant subjects and 140 beats/min in pregnant subjects were used to confirm that subjects were exercising at the desired intensity. Resting heart rate increases by 10–15 beats/min during pregnancy (40). This decreases heart rate reserve; therefore, pregnant women typically need to exercise at higher heart rates than nonpregnant women to reach the same RPE during low- and moderate-intensity exercise. A postexercise blood sample was collected within 3 min of exercise cessation. Pregnancy outcome data were obtained from medical records.

Measurement of analytes relevant to angiogenesis. Blood samples for serum VEGF, PGF, sFlt-1, and sEng determination were collected in serum separator tubes (Becton Dickson Vacutainer Systems), clotted on ice for 1.5–2 h, and centrifuged at 4°C for 10 min at 2,500 rpm. Serum was collected, frozen at ~80°C, and subsequently assayed. Serum concentrations of free VEGF, PGF, and sFlt-1 were determined in triplicate, and serum concentrations of sEng were measured in duplicate by ELISA using commercially available kits (R&D Systems, Minneapolis, MN). The kit interassay coefficients of variation were 7% for VEGF, sFlt-1, and sEng, and 9% for PGF.

Statistical analysis. Gestational age, weight gain from preconception, gestational age at delivery, birth weight, and menstrual cycle day in active and inactive groups were compared using Mann Whitney U-tests. Fisher’s exact test was used to compare parity and the odds of delivering a male infant, across subject groups. Comparisons of mean voluntary physical activity in active and inactive subgroups were performed using Wilcoxon’s rank-sum test. Age, BMI, and the sports and exercise index (preconception/nonpregnant) were compared using a 2 × 2 ANOVA with pregnancy (nonpregnant vs. pregnant) and activity (active vs. inactive) as between-subjects factors. Pregnancy-induced changes in the sports and exercise index were examined using a 2 × 2 repeated-measures ANOVA, with pregnancy status (nonpregnant vs. pregnant) as the within-subjects factor, and activity as the between-subjects factor. Serum VEGF, PGF, sFlt-1, and sEng were log-transformed to provide a normal distribution for repeated-measures parametric analysis. The effects of acute exercise, pregnancy, and chronic physical activity on angiogenic markers and respiratory responses to exercise were assessed using a 2 × 2 × 2 repeated-measures ANOVA, with acute exercise as the within-subjects factor (pre vs. post) and pregnancy status and activity as the between-subjects factors. Where significant main effects were present, simple main effects were assessed using paired or independent sample t-tests, with the Sidak correction for multiple comparisons. All analyses were performed using SPSS 16.0 (SPSS). Statistical significance was determined by a two-sided P value < 0.05.

Serum samples were collected during a more extensive study examining the effects of pregnancy and acute and chronic exercise on endothelial function (33). Sample size calculations were based on the primary outcome measures for that study. Retrospective power calculations revealed that the sample size was sufficient to detect a 50% difference in PGF, a 60% difference in sFlt-1, and a 70% difference in sEng between active and inactive pregnant groups, with P = 0.05 and 80% power. Previous studies have reported that PGF is 30–80% lower, sFlt-1 is 40–150% higher, and sEng is 75–150% higher among women with preeclampsia compared with normotensive pregnant women (30, 37). Among nonpregnant women, the sample size was sufficient to detect a 20% difference in PGF, a 25% difference in sFlt-1, and a 30% difference in sEng between active and inactive groups.

RESULTS

Subject characteristics and pregnancy outcome. Age did not differ between groups (Table 1). Gestational age and weight gain from preconception were similar in active and inactive pregnant groups. Cycle day did not differ between active and inactive nonpregnant groups. Preconception BMI was significantly greater in inactive pregnant women than in active pregnant women. BMI was significantly greater in inactive nonpregnant women than in active nonpregnant women. Inactive women were more likely to be multiparous than active women.

Pregnancy outcome data were unavailable for one active woman who delivered at home and was lost to follow-up. One inactive woman developed gestational hypertension. All participants delivered healthy infants after 37-wk gestation. Birth weight [active: 3,584 ± 355 g (mean ± SD); inactive: 3,540 ± 292 g], gestational age at delivery (active: 39.9 ± 1.2 wk; inactive: 39.5 ± 1.3 wk), and the odds of carrying a male fetus (active: 40%; inactive: 44%) did not differ between active and inactive women.

Regular exercise participation. The activity questionnaires confirmed the activity levels of the participants. Low mean
Effects of pregnancy on angiogenic markers. In accordance with previous studies (16, 30), serum concentrations of sFlt-1, PlGF, and sEng were significantly higher in pregnant women than in nonpregnant controls (P < 0.001) due to increased VEGF binding by increased sFlt-1 (16, 19). Baseline PIGF concentration was significantly lower (P = 0.014), and sFlt-1 (P = 0.005) and sEng concentrations were significantly higher (P = 0.025), in inactive pregnant women than in active pregnant women. There was a significant inverse correlation between PIGF and sFlt-1 (Pearson r² = 0.30, P = 0.005). The strength of this correlation was attenuated by controlling for BMI, infant birth weight, and gestational age and was no longer statistically significant (r² for partial correlation = 0.18, P = 0.061).

Acute exercise significantly increased heart rate, \( \dot{V}O_2 \), \( \dot{V}CO_2 \), \( \dot{V}O_2 \) in milliliters per kilogram per minute, ventilation (VE), tidal volume, and breathing frequency in active and inactive pregnant women (P < 0.001 for all main effects and pairwise comparisons, Table 3). sFlt-1 and sEng did not change following acute exercise in active or inactive pregnant women (Fig. 1). Serum PIGF concentrations increased in active (P = 0.014), but not inactive, pregnant women.

Effects of acute and chronic exercise in nonpregnant women. In contrast to the findings in pregnant women, baseline serum VEGF, PIGF, sFlt-1, and sEng concentrations did not differ between active and inactive nonpregnant women (Fig. 1).

Acute exercise significantly increased heart rate, \( \dot{V}O_2 \), \( \dot{V}CO_2 \), \( \dot{V}O_2 \) in milliliters per kilogram per minute, VE, tidal volume, and breathing frequency in active and inactive nonpregnant women (P < 0.001 for all main effects and pairwise comparisons, Table 3). VEGF decreased immediately postexercise in active (P = 0.008) and inactive (P = 0.010) nonpregnant women (Fig. 1G). The magnitude of the exercise-induced decrease in VEGF did not differ between active and inactive nonpregnant women (acute exercise \( \times \) regular exercise participation: P = 0.200). sFlt-1 increased significantly following acute exercise in inactive nonpregnant women (P = 0.012), but this effect was not observed in active nonpregnant women.

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active Pregnant</th>
<th>Inactive Pregnant</th>
<th>Active Nonpregnant</th>
<th>Inactive Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>9</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Age, yr</td>
<td>32.0 ± 3.7</td>
<td>31.2 ± 3.9</td>
<td>32.8 ± 5.1</td>
<td>33.1 ± 4.4</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>34.0 ± 1.3</td>
<td>34.4 ± 2.1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cycle day</td>
<td>N/A</td>
<td>N/A</td>
<td>25 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Preconception/nonpregnant BMI, kg/m²</td>
<td>22.7 ± 2.9</td>
<td>25.7 ± 4.6*</td>
<td>22.6 ± 2.8</td>
<td>26.1 ± 4.0*</td>
</tr>
<tr>
<td>Weight gain from preconception, kg</td>
<td>12.6 ± 4.5</td>
<td>14.9 ± 6.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Parity, %nulliparous</td>
<td>81</td>
<td>56*</td>
<td>87</td>
<td>33*</td>
</tr>
<tr>
<td>Nonsmokers, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian (n)</td>
<td>14</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Asian (n)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. Self-reported weight before conception was used to calculate body mass index (BMI) before conception and weight gain. N/A, not applicable. Significant difference from active group of same reproductive status: *P < 0.05.

### Table 2. Physical activity characteristics of subjects

<table>
<thead>
<tr>
<th>Activity</th>
<th>Active Pregnant</th>
<th>Inactive Pregnant</th>
<th>Active Nonpregnant</th>
<th>Inactive Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean voluntary physical activity, kcal</td>
<td>257 ± 131</td>
<td>7 ± 22†</td>
<td>578 ± 314</td>
<td>61 ± 148‡</td>
</tr>
<tr>
<td>Sports and exercise index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preconception/nonpregnant</td>
<td>4.4 ± 0.4</td>
<td>2.8 ± 1.3*</td>
<td>4.4 ± 0.4</td>
<td>1.6 ± 0.6†</td>
</tr>
<tr>
<td>Pregnant</td>
<td>4.1 ± 0.3</td>
<td>1.6 ± 0.8‡</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Mean voluntary physical activity and the sports and exercise index were available for 9 and 11 out of 12 inactive nonpregnant subjects, respectively. Significant difference from nonpregnant group of same activity level: *P < 0.01; from active group of same reproductive status: †P < 0.01; and from preconception: ‡P < 0.01.
Postexercise increases in sFlt-1 were correlated with decreases in VEGF (Pearson $r^2 = 0.25$, $P = 0.009$). Serum PI GF and sEng concentrations did not change significantly following exercise in active or inactive nonpregnant women.

The inactive pregnant participant who later developed gestational hypertension had sFlt-1 concentrations similar to the maximum values observed in the inactive pregnant group, sEng concentrations within the range observed in the inactive pregnant group, and PI GF concentrations similar to the minimum values observed in the inactive pregnant group. This subject was included in all analyses.

**DISCUSSION**

This preliminary analysis examined the effects of acute and chronic exercise on sFlt-1, PI GF, and sEng in apparently healthy, nonsmoking pregnant and nonpregnant women. During pregnancy, serum PI GF was lower, and sFlt-1 and sEng were higher, in sedentary women, compared with exercising women. This effect was not present in nonpregnant women. This suggests that the differences observed in pregnant women were unlikely to have predated the pregnancy, supporting the hypothesis that regular exercise during pregnancy contributes to a proangiogenic serum profile in late gestation. This effect may contribute to the reduced risk of preeclampsia among pregnant women. This effect was not present in nonpregnant women. This suggests that the differences observed in pregnant women are mediated by the placenta or by pregnancy-induced changes in regulatory mechanisms of other tissues.

**Effects of regular exercise on angiogenic makers.** The higher PI GF and lower sFlt-1 and sEng concentrations associated with regular exercise during pregnancy could contribute to the reduced preeclampsia risk among active women reported in some epidemiological studies (15, 23, 24, 29). Although mean sEng differed significantly between active and inactive groups, the data distribution illustrates the heterogeneity of the response (Fig. 1). Higher mean sEng in inactive pregnant women was due to high concentrations in three subjects, as concentrations in the six remaining subjects were within the range observed for active pregnant women (Fig. 1). Future studies should determine whether exercise has different effects in different subpopulations of women.

Aerobic exercise, particularly in early pregnancy (10), increases placental growth (6, 7) and vascularity (7, 10) and reduces the proportion of nonvillous placental tissue (7, 10). Researchers hypothesize that exercise-induced reductions in placental blood flow stimulate vascular growth (6) to prevent future reductions in substrate and oxygen supplies (6). Enhanced placental vascularity could prevent placental hypoxia or hypoxia and reperfusion (35), which contribute to preeclampsia by stimulating placental release of sFlt-1, sEng, and other substances that promote endothelial damage, oxidative stress, and inflammation (22). Future studies should determine whether exercise-induced placental adaptations contribute to lower sFlt-1 and sEng in active pregnant women (6). There are three potential limitations to our observation that regular exercise was associated with higher PI GF, and lower sFlt-1 and sEng concentrations. Acute exercise caused antiangiogenic changes in nonpregnant women, but not in pregnant women. Future studies should determine whether the differing responses in pregnant women are mediated by the placenta or by pregnancy-induced changes in regulatory mechanisms of other tissues.

**Table 3. Respiratory data at rest and during exercise**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th></th>
<th></th>
<th>Exercise</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Pregnant</td>
<td>Inactive Pregnant</td>
<td>Active Nonpregnant</td>
<td>Inactive Nonpregnant</td>
<td>Active Pregnant</td>
<td>Inactive Pregnant</td>
</tr>
<tr>
<td>$n$</td>
<td>16</td>
<td>9</td>
<td>15</td>
<td>12</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Rating of perceived exertion</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>85 ± 10$^b$</td>
<td>93 ± 11$^{b,c}$</td>
<td>62 ± 8</td>
<td>77 ± 6$^d$</td>
<td>142 ± 13$^{c,e}$</td>
<td>143 ± 15$^a$</td>
</tr>
<tr>
<td>$V_{O2}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>3.9 ± 0.5</td>
<td>3.5 ± 0.4</td>
<td>4.1 ± 0.6</td>
<td>3.7 ± 0.4$^e$</td>
<td>17.6 ± 2.4$^{b,a}$</td>
<td>12.6 ± 2.3$^{a-c,d}$</td>
</tr>
<tr>
<td>$V_{CO2}$, l/min</td>
<td>0.38 ± 0.03</td>
<td>0.30 ± 0.03</td>
<td>0.26 ± 0.04</td>
<td>0.26 ± 0.04</td>
<td>1.36 ± 0.19$^a$</td>
<td>1.05 ± 0.11$^{a-d}$</td>
</tr>
<tr>
<td>$V_{CO2}$, l/min</td>
<td>0.27 ± 0.03</td>
<td>0.28 ± 0.04</td>
<td>0.23 ± 0.04</td>
<td>0.24 ± 0.04</td>
<td>1.34 ± 0.19$^a$</td>
<td>1.09 ± 0.12$^a$</td>
</tr>
<tr>
<td>$Ve$, l/min</td>
<td>10.7 ± 10$^b$</td>
<td>11.7 ± 2.4$^b$</td>
<td>8.8 ± 1.6</td>
<td>9.1 ± 1.3</td>
<td>44.1 ± 8.6$^a$</td>
<td>39.2 ± 6.6$^a$</td>
</tr>
<tr>
<td>Tidal volume, liters</td>
<td>0.72 ± 0.16</td>
<td>0.72 ± 0.10</td>
<td>0.60 ± 0.13</td>
<td>0.67 ± 0.18</td>
<td>1.61 ± 0.37$^a$</td>
<td>1.42 ± 0.39$^a$</td>
</tr>
<tr>
<td>Breathing frequency, breaths/min</td>
<td>16 ± 3</td>
<td>17 ± 5</td>
<td>15 ± 3</td>
<td>14 ± 3</td>
<td>28 ± 5$^a$</td>
<td>30 ± 9$^a$</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$, no. of subjects. $V_{O2}$, $O_2$ uptake; $V_{CO2}$, $CO_2$ production; $Ve$, ventilation. Significance different from rest: $^aP < 0.001$; from nonpregnant group of same activity level: $^bP < 0.01$, $^cP < 0.05$; and from active group of same reproductive status: $^dP < 0.01$, $^eP < 0.05$. 

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**Table 3. Respiratory data at rest and during exercise**

$P = 0.303$
If sFlt-1 is higher in nulliparous than in multiparous women throughout gestation, the effect of regular exercise on sFlt-1 would have been underestimated. Third, angiogenic differences during pregnancy may have been attributable to the higher BMI in inactive women. There is little information available on this topic. In nonpregnant individuals, there are reports of a positive relationship of BMI and VEGF in two small studies (18, 28). A larger study did not confirm this relationship, nor was there a relationship with sFlt-1 (26). One study of pregnant women also found no relationship of BMI to PIGF or s-Flt-1 at the gestational age at which subjects in our study were tested (13). Nonetheless, with this limited data, we cannot exclude the relevance of BMI to angiogenic factors.
Effects of acute exercise on angiogenic markers. One epidemiological study reported an increased risk of severe preeclampsia among women exercising >270 min/wk (21). The authors hypothesized that acute exercise increases preeclampsia risk by exacerbating pathophysiological processes that lead to preeclampsia (21). Antiangiogenic changes that could contribute to preeclampsia did not occur immediately following 20 min of moderate-intensity exercise in pregnant women in the present study. PIgf actually increased among active pregnant women postexercise, supporting the hypothesis that exercise-induced reductions in placental blood flow stimulate placental vascular growth (6). However, antiangiogenic changes could occur later in recovery. Future studies should also examine the acute effects of longer duration or higher intensity exercise. Intensity and duration in the present study were selected based on Canadian guidelines, which recommend 15- to 30-min sessions at an RPE of 12–14 (39). Most active pregnant women in the present study regularly exceeded 20-min duration, and 44% regularly exceeded the recommend intensity.

Among nonpregnant women, postexercise increases in sFlt-1 were correlated with decreases in VEGF ($r = 0.50, P = 0.009$) and may have contributed to postexercise decreases in serum VEGF. Similarly, decreased VEGF and increased sFlt-1 were observed following maximal exercise in previous studies of men (4). However, other studies report no change (20, 36), or increased (9, 12, 32, 41), circulating VEGF postexercise. All studies used the same assay; therefore, other factors must explain the diverse results. For example, VEGF uptake by nonexercising tissues may decrease circulating VEGF during large muscle mass exercise when samples are not drawn from the vein draining the exercising muscle (32).

Conclusions. This study demonstrates that regular exercise participation had no effect on sFlt-1, sEng, PIgf, or VEGF in nonpregnant women; however, it was associated with higher concentrations of PIgf and lower concentrations of sFlt-1 and sEng in the third trimester. This suggests that the differences observed in pregnant women were unlikely to have predated the pregnancy and were probably caused by placental adaptation or another pregnancy-specific mechanism. The proangiogenic serum profile observed in active pregnant women could contribute to the reduced risk of preeclampsia among exercising women reported in some epidemiological studies (15, 23, 29). Larger studies are needed to replicate these findings. Studies that include women with preeclampsia are also needed to examine the clinical significance of the observed effects. Twenty minutes of moderate-intensity exercise in the third trimester did not cause antiangiogenic changes that could increase preeclampsia risk, and PIgf actually increased postexercise in active pregnant women. Future studies should examine the effects of longer duration and higher intensity exercise. Physiological studies are also needed to examine the acute and chronic effects of exercise on other physiological processes that influence preeclampsia risk.

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DISCLOSURES

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

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