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Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide

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Submitted 23 December 2004; accepted in final form 24 January 2005

Jensen, Dennis, Larry A. Wolfe, Lubomira Slatkovska, Katherine A. Webb, Gregory A. L. Davies, and Denis E. O’Donnell. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am J Physiol Regul Integr Comp Physiol 288: R1369 –R1375, 2005.—This study examined the effects of human pregnancy on the central chemoreflex control of breathing. Subjects were two groups (n = 11) of pregnant subjects (PG, gestational age, 36.5 ± 0.4 wk) and nonpregnant control subjects (CG), equated for mean age, body height, prepregnant body mass, parity, and aerobic fitness. All subjects performed a hyperoxic CO₂ rebreathing procedure, which includes prior hyperventilation and maintenance of iso-oxia. Resting blood gases and plasma progesterone and estradiol concentrations were measured. During rebreathing trials, end-tidal Pco₂ increased, whereas end-tidal Po₂ was maintained at a constant hyperoxic level. The point at which ventilation (Ve) began to rise as end-tidal Pco₂ increased was identified as the central chemoreflex ventilatory recruitment threshold for CO₂ (VRTCO₂). Ve levels below (basal Ve) and above (central chemoreflex sensitivity) the VRTCO₂ were determined. The VRTCO₂ was significantly lower in the PG vs. CG (40.5 ± 0.8 vs. 45.8 ± 1.6 Torr), and both basal Ve (14.8 ± 1.1 vs. 9.3 ± 1.6 l/min) and central chemoreflex sensitivity (5.07 ± 0.74 vs. 3.16 ± 0.29 l·min⁻¹Torr⁻¹) were significantly higher in the PG vs. CG. Pooled data from the two groups showed significant correlations for resting arterial PCO₂, central chemoreflex sensitivity, and the VRTCO₂. The VRTCO₂ was also correlated with progesterone and estradiol concentrations. These data support the hypothesis that pregnancy decreases the threshold and increases the sensitivity of the central chemoreflex response to CO₂. These changes may be due to the effects of gestational hormones on chemoreflex and/or nonchemoreflex drives to breathe.

human gestation; hyperoxia; chemoreflex sensitivity; ventilatory recruitment threshold

HUMAN PREGNANCY IS CHARACTERIZED by a rise in minute ventilation (Ve) that begins before weeks 6–7 of gestation (7, 27). As a result, arterial (Paco₂), alveolar, and cerebrospinal fluid Pco₂ decrease throughout pregnancy (11, 15, 16). In addition, arterial Po₂ (PaO₂) is either unchanged (11) or slightly increased (16). The pregnancy-induced respiratory alkalosis is partially compensated for by increased renal excretion of bicarbonate and a lowering of plasma bicarbonate concentration (16). Consequently, arterial pH (pHₐ) is increased to ∼7.46 (34).

The mechanism of the increased Ve and reduced Paco₂ is poorly understood but is due, at least in part, to the effects of gestational hormones on respiratory sensitivity to CO₂ (34). Circulating progesterone levels rise progressively during pregnancy and are always preceded or accompanied by an increase in circulating levels of estrogen (31). In addition, progesterone administered alone, or in combination with estrogen, to men (5, 15, 29, 35) and ovarioly hysterectomized women (28) significantly increases the sensitivity of the central ventilatory chemoreflex response to CO₂. However, the effects of exogenous progesterone and estrogen on the central chemoreflex threshold for CO₂ are unclear, as some (13, 15, 23, 28, 29) but not all (5, 10, 35) studies have reported a significant decrease.

Limited information exists regarding the effects of pregnancy on characteristics of the central chemoreflex control of breathing. Some studies have demonstrated an increase in the sensitivity and decrease in the threshold of the central ventilatory chemoreflex response to CO₂ (15, 22), whereas Moore et al. (21) observed no effect. In addition, Hannhart et al. (11) reported that central chemoreflex sensitivity was greater in pregnant vs. nonpregnant cats. However, the threshold for CO₂ was similar in the two groups. Thus it is unclear whether the increased Ve and reduced Paco₂ observed during pregnancy is the result of changes in the sensitivity or threshold of the central chemoreflex response to CO₂ or a combination of both. Previous reports have also suggested that endogenous and exogenous increases in progesterone markedly increase both the Ve and carotid body neural output response to hypoxia (10, 11, 22, 33). These effects appear to be intrinsic to the carotid body (i.e., peripheral chemoreflex) (10, 11) and potentiated by increased plasma estrogen concentrations (10).

This study examined the effects of pregnancy on the central chemoreflex ventilatory recruitment threshold for CO₂ (VRTCO₂) as well as the ventilatory response below (i.e., behavioral drives) and above (i.e., central chemoreflex sensitivity) this threshold. Relationships between central ventilatory chemoreflex control characteristics, resting blood gases, and circulating gestational hormone concentrations were also examined to provide insight into the mechanism(s) responsible for pregnancy-induced respiratory adaptations. It was hypothesized that central chemoreflex sensitivity would be higher and that the VRTCO₂ would be lower in healthy pregnant vs. nonpregnant women and that these changes would be due to increased gestational hormone levels. Furthermore, it was postulated that Paco₂, measured in late gestation and in the...
midluteal phase (LP) of the menstrual cycle in the nonpregnant state, would be significantly correlated with changes in central ventilatory chemoreflex control characteristics and circulating hormone levels.

**METHODS**

**Subjects.** Subjects were two groups (n = 11) of healthy, nonsmoking, physically active pregnant (pregnant group; PG) and healthy, nonpregnant, eumenorrheic women (control group; CG) with similar physical and demographic characteristics. Prospective subjects were recruited via media advertisements, posted announcements, and contact with local obstetricians and midwives. Before participation, pregnant subjects completed the Physical Activity Readiness Medical Examination for Pregnancy (available online at www.csep.ca/forms.asp) and obtained medical clearance from the physician or midwife monitoring their pregnancies. In addition, during the week before laboratory testing, pregnant subjects underwent a fetal ultrasound examination and biophysical profile to accurately date their pregnancies and verify normal fetal development. Nonpregnant subjects were screened using the revised Physical Activity Readiness Questionnaire (available online at www.csep.ca/forms.asp). Written, informed consent was obtained from all subjects before participation in the study. The study protocol and consent form were approved by the Research Ethics Board, Faculty of Health Sciences, Queen’s University.

Basic physical measurements included body height and body mass. Body-mass index (BMI) was calculated as body mass/body height^2 (in kg/m^2). The PG and CG were equated for mean age, body height, prepregnant body mass and BMI parity, and aerobic fitness. Members of the PG were tested between 34 and 38 wk of gestation. Subjects in the CG were tested in the mid-LP of their menstrual cycle and had not used oral contraceptives for at least 6 mo before they were tested. Menstrual cycle status was calculated using the first day of the last menstrual cycle and average length of the cycle. Plasma progesterone and estradiol measurements were used to confirm menstrual cycle status.

All subjects performed a progressive cycle exercise test on a constant work rate cycle ergometer (model 800s, SensorMedics, Yorba Linda, CA) to evaluate aerobic working capacity (12, 24). Respiratory responses were measured breath-by-breath as previously described (12, 24).

**Modified rebreathing protocol.** Subjects refrained from aerobic and muscular conditioning exercise as well as caffeine and alcohol on the day of testing. A rebreathing procedure that was modified to include prior hyperventilation and maintenance of a constant (iso-oxia) end tidal O2 tension (PETO2) was used to evaluate central ventilatory chemoreflex control characteristics (8, 14). Subjects breathed room air for 5 min, using a slow and deliberate breathing pattern to avoid the short-term potentiation effect described by Folgering and Durlinger (9). Prior hyperventilation lowered the body stores of CO2 below 25 Torr, thereby allowing the VRTCO2 to be identified, as end-tidal PCO2 and PETCO2 were measured at the mouth with a respiratory mass spectrometer (Perkin-Elmer, MGA, 1100). Iso-oxia was maintained by a flow of 100% O2 to the bag side of the T valve. The data-acquisition software calculated breath-by-breath measures of VE, VT, f, PETCO2, PETO2, SaO2 and HR.

**Data analyses.** Data from rebreathing experiments were imported to an analysis program designed specifically for this purpose (14). Measured volumes were corrected to body temperature and pressure, saturated (BTPS). Data from the first equilibration at the start of rebreathing and any aberrant points were excluded from further analyses. Subsequently, breath-by-breath PETCO2 was plotted against time and fitted with a least-squares regression line, whose slope depends on the metabolic rate of production of CO2. The equation for this line provided a predicted value of PETCO2 vs. time, thereby minimizing interbreath variability due to measurement. Thereafter, VE, VT, and f were plotted against the predicted PETCO2.

Each of these plots was fitted with a model made up of the sum of two segments separated by one breakpoint. All segments were fitted through an iterative process, whereby the breakpoint and other parameters were varied to obtain an optimal fit to the observed data by minimizing the sum of squares (Levenberg-Marquardt algorithm) using commercial software (Sigmamplot 7.0, SPSS). Figure 1 is an example of the lines fitted to the VE response of a representative subject during an iso-oxic hyperoxic CO2 rebreathing procedure. The first segment of the response was an exponential decline to a final value (i.e., basal VE), estimating behavioral drives to breathe, independent of the ventilatory chemoreflex (30). This value was taken as a measure of VE, VT, and f below the VRTCO2, respectively. Rarely, a short-term potentiation of breathing was observed after hyperventilation, and its waning was modeled as an exponential decay.

The point at which VE, VT, and f began to rise in a linear fashion in conjunction with a rise in PETCO2, was taken as the VRTCO2 (Fig. 1). The slope of the line fitted to VE, VT, and f responses above the VRTCO2 was taken as a measure of central chemoreflex sensitivity (Fig. 1). On the basis of the modeling of Duffin et al. (8), we assumed that VRTCO2 and sensitivity parameters measured during iso-oxic hyperoxic CO2 rebreathing originated from the central chemoreflex alone, since hyperoxia abolishes virtually all peripheral chemoreflex activity (8).

**Blood biochemistry.** Before rebreathing experiments had started, an experienced nurse specialist inserted an in-dwelling catheter into a dorsal hand vein situated as far from the thumb as possible. The hand and lower arm were placed in a Plexiglas box and heated by warm circulating air to promote vasodilation and to allow for arterIALIZATION of venous blood. Blood samples for determination of PCO2, PaO2, and pHi were collected with a syringe containing lyophilized heparin (Monovette, Sarstedt, Ville St-Laurent, PQ) and analyzed immediately with a Radiometer ABL-5 acid-base analyzer (Radiometer/
Copenhagen) at a standard temperature of 37°C. Next, blood for plasma 17β-estradiol ([estradiol]) and progesterone ([progesterone]) concentration determinations was collected in a Vacutainer containing no additives and stored on ice for 0.5–1.0 h to allow time for clotting. The blood was later centrifuged for 10 min at 2,500 revolutions/min and frozen at −80°C for later analysis by radioimmunoassay. Currently, evidence suggests that estrogen is required to increase the number and availability of hypothalamic progesterone receptors, which are essential to the increased central respiratory drive produced by progesterone (1, 2, 4, 6). Therefore, the [progesterone]-to-[estradiol] ratio was calculated for each subject and used as an index of progesterone receptor availability. In this regard, it was hypothesized that a decrease in the [progesterone]-to-[estradiol] ratio would represent an increase in progesterone receptor availability and explain pregnancy-induced changes in central chemoreflex control characteristics.

Minimum sample size estimate. Minimum sample size was calculated based on 80% power and a confidence interval of 0.05 using an unpaired subject formula for the comparison of means (25). The resulting critical sample sizes were estimated to be 6 and 10 for sensitivity and VRTCO₂ parameters using standard deviations from Jensen et al. (14). The resulting critical sample sizes were estimated to be 6 and 10 for sensitivity and VRTCO₂ parameters, respectively. Therefore, a sample size of 11 subjects per group was adequate for this study.

Statistical analyses. Unpaired Student’s t-statistics were used to identify significant between-group differences among measured variables (SigmaStat 3.0). Pearson’s product-moment correlation coefficients (Pearson’s r) were calculated to detect correlations among criterion variables. Stepwise linear regression analyses for PaCO₂, with basal Ve, the VRTCO₂, Ve chemosensitivity, [progesterone], [estradiol], and the [progesterone]-to-[estradiol] ratio as the independent variables were performed for pooled data from both groups and within each group, respectively. Results for all statistical tests were considered significant if \( P < 0.05 \). Values are presented as means ± SE.

RESULTS

Physical characteristics. Subjects in both groups were non-smoking, physically active women between the ages of 20 and 40 yr. The mean gestational age for the PG was 36.5 ± 0.7 days. There were no significant differences between groups in age, height, parity, or pre-pregnant body mass and BMI (Table 1). As expected, body mass and BMI were significantly greater in the PG vs. CG. There was also no significant between-group differences in oxygen uptake at peak exercise, indicating that the two groups had similar levels of aerobic fitness.

[Progesterone] and [estradiol] were significantly higher in the PG compared with that in the CG (Table 1). The [progesterone]-to-[estradiol] ratio was significantly lower in the PG vs. CG. At rest, PaCO₂ was lower and pH₄ was higher in the PG vs. CG. Values for these variables were in the expected range for both groups (31).

Effects of pregnancy on central ventilatory chemoreflex control characteristics. Basal Ve and f were significantly greater in the PG vs. CG (Table 2). Both Ve and VT recruitment thresholds for CO₂ were ~5 Torr lower in the PG vs. CG. Both Ve and VT chemoreflex sensitivities to CO₂ were significantly greater in the pregnant state.

Table 1. Physical characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>30.0±0.7</td>
<td>27.0±1.3</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>163.7±1.4</td>
<td>165.0±1.8</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>75.3±1.6</td>
<td>59.2±2.1*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1±0.6</td>
<td>21.8±0.8*</td>
</tr>
<tr>
<td>Prepregnant body mass, kg</td>
<td>60.6±1.8</td>
<td>N/A</td>
</tr>
<tr>
<td>Prepregnant BMI, kg/m²</td>
<td>22.6±0.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Parity</td>
<td>0.5±0.2</td>
<td>0</td>
</tr>
<tr>
<td>VO₂peak, l/min</td>
<td>2.1±0.1</td>
<td>2.1±0.1</td>
</tr>
<tr>
<td>PaCO₂, Torr</td>
<td>31.8±0.7</td>
<td>38.0±0.6*</td>
</tr>
<tr>
<td>pH₄</td>
<td>7.45±0.01</td>
<td>7.40±0.003*</td>
</tr>
<tr>
<td>[P]-to-[E] ratio, pmol/pmol</td>
<td>0.013±0.002</td>
<td>0.086±0.016*</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; PaCO₂, arterial PCO₂; pH₄, arterial pH; VO₂peak, oxygen uptake at peak exercise; N/A, not applicable; [P], plasma progesterone concentration; [E], plasma estradiol concentration. *Significant between-group difference (\( P < 0.001 \)).

Table 2. Effects of pregnancy on the central ventilatory chemoreflex response to carbon dioxide

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>14.8±1.1</td>
<td>9.3±1.6*</td>
</tr>
<tr>
<td>VT, ml/4 min</td>
<td>793±63</td>
<td>784±130</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>18.1±1.1</td>
<td>11.6±1.0†</td>
</tr>
<tr>
<td>Ventilatory recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>threshold for CO₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ve, Torr</td>
<td>40.5±0.8</td>
<td>45.8±0.7†</td>
</tr>
<tr>
<td>VT, Torr</td>
<td>40.6±2.0</td>
<td>45.8±0.8†</td>
</tr>
<tr>
<td>Sensitivities to CO₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ve, l/min-Torr</td>
<td>45.3±2.1</td>
<td>47.4±1.6</td>
</tr>
<tr>
<td>VT, ml/min-Torr</td>
<td>5.07±0.7</td>
<td>3.16±0.29*</td>
</tr>
<tr>
<td>f, breaths-min-Torr</td>
<td>228.39±33.19</td>
<td>143.26±14.77*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Ve, minute ventilation; VT, tidal volume; f, respiratory rate. *Significant between-group difference (\( P < 0.05 \)). †Significant between-group difference (\( P < 0.001 \)).
Table 3. Pearson’s product-moment correlation grid of relationships between chemoreflex control characteristics, arterial blood gases, and gestational hormones within the pregnant group

<table>
<thead>
<tr>
<th>Variable</th>
<th>VRTCO₂</th>
<th>Sensitivity</th>
<th>PaCO₂</th>
<th>pH₄</th>
<th>[P]</th>
<th>[E]</th>
<th>[P]-to-[E] Ratio, nmol/pmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal VE, l/min</td>
<td>0.06</td>
<td>0.12</td>
<td>0.23</td>
<td>0.13</td>
<td>0.23</td>
<td>0.46</td>
<td>−0.07</td>
</tr>
<tr>
<td>VRTCO₂, Torr</td>
<td>−0.63 *</td>
<td>0.80 *</td>
<td>−0.55</td>
<td>−0.50</td>
<td>0.50</td>
<td>−0.40</td>
<td>0.63 *</td>
</tr>
<tr>
<td>Sensitivity, 1·min⁻¹·Torr⁻¹</td>
<td>−0.75 *</td>
<td>0.64 *</td>
<td>−0.13</td>
<td>0.27</td>
<td>0.27</td>
<td>−0.24</td>
<td>−0.24</td>
</tr>
<tr>
<td>PaCO₂, Torr</td>
<td>−0.71 *</td>
<td>0.24</td>
<td>−0.15</td>
<td>0.31</td>
<td>0.31</td>
<td>0.24</td>
<td>0.31</td>
</tr>
<tr>
<td>pH₄</td>
<td>−0.16</td>
<td>0.63 *</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
<td>−0.49</td>
</tr>
<tr>
<td>[P], nmol/l</td>
<td>−0.31</td>
<td>0.77 *</td>
<td>0.77</td>
<td>0.77</td>
<td>0.77</td>
<td>0.77</td>
<td>−0.81 *</td>
</tr>
<tr>
<td>[E], pmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VRTCO₂, central chemoreflex ventilatory recruitment threshold for CO₂; *Significant correlation at the P < 0.05 level.

Relationships between central chemoreflex control characteristics, blood gases, and gestational hormones. No significant correlations were observed between basal VE and the VRTCO₂ or basal VE and VΕ chemosensitivity within the PG (Table 3), CG (Table 4), or pooled data. However, a significant negative correlation was observed between the VRTCO₂ and VΕ chemosensitivity characteristics within the PG (Table 3), CG (Table 4), and pooled data (r = −0.71).

Within the PG, PaCO₂ was correlated with the VRTCO₂, VΕ chemosensitivity, and pH₄. In addition, pH₄ was positively correlated with VΕ chemosensitivity and [estradiol], whereas the VRTCO₂ was significantly related to the [progestrone]-to-[estriol] ratio (Table 3). Stepwise linear regression analysis revealed that the central chemoreflex VRTCO₂ accounted for 45.6% of the variance of PaCO₂, with the addition of [progestrone] improving this to 84.5%.

**DISCUSSION**

The primary findings of this study support the original hypothesis that pregnancy significantly lowers the threshold and increases the sensitivity of the central ventilatory chemoreflex response to CO₂. Findings suggest that these changes may be due to the effects of gestational hormones on chemoreflex and/or nonchemoreflex drives to breathe.

**Critique of methods.** A comprehensive critique of the modified rebreathing procedure has been described in previous reports (8, 14, 17, 18, 20). A limitation of the present study is that it used a cross-sectional approach to examine the effects of pregnancy on the ventilatory response to CO₂. Therefore, it is possible that selection factors may have contributed to our findings. However, equating groups for important physical and demographic characteristics minimized this possibility. Nevertheless, controlled longitudinal studies are needed to confirm the findings of the present study.

**Effects of pregnancy on the central chemoreflex control of breathing.** Limited information exists concerning the effects of pregnancy on the central chemoreflex control of breathing (11, 15, 21, 22). Findings of the present study confirm that central chemoreflex sensitivity is significantly greater in pregnant compared with nonpregnant women, as reflected by differences in the slope of the VΕ and VT response to hyperoxic CO₂ rebreathing. In addition, both the VE and VT threshold for CO₂ were significantly lower in the PG vs. CG. These data are...
consistent with previous reports demonstrating concomitant pregnancy-induced changes in both the sensitivity and threshold of the central ventilatory chemoreflex response to CO₂ (15, 22). Together, these findings confirm the original hypothesis that central chemoreflex sensitivity is higher and the VRTCO₂ is lower in pregnant vs. nonpregnant women.

In theory, an increase in the sensitivity and decrease in the threshold of the central chemoreflex response to CO₂ would stimulate VE at any given PaCO₂. Therefore, we hypothesized that pregnancy-induced changes in central ventilatory chemoreflex control characteristics may explain, at least in part, the higher VE and lower PaCO₂ observed during pregnancy. Indeed, linear regression analyses of pooled data from both groups as well as the PG revealed significant relationships between PaCO₂ with VE chemosensitivity and the VRTCO₂. In fact, the central chemoreflex VRTCO₂ accounted for 65% and 76% of the variability of PaCO₂ at rest within the PG and pooled data, respectively. In addition, central chemoreflex sensitivity predicted 46% of the variance of PaCO₂ within the CG. However, this relationship could be a statistical artifact, since measures of PaCO₂ were relatively homogeneous among non-pregnant subjects. Furthermore, strong correlations between PaCO₂ with [progesterone], [estradiol], and the [progesterone]-to-[estradiol] ratio within the pooled data from both pregnant and nonpregnant subjects confirmed the widely held view that gestational hormones increase ventilatory drive (34).

Pregnancy-induced changes in central chemoreflex sensitivity have been attributed to an estrogen-dependent progesterone receptor-mediated central neural mechanism (1–4, 6). However, no significant relationships were observed between central chemoreflex sensitivity with [progesterone] and the [progesterone]-to-[estradiol] ratio within either group. Nevertheless, this is the first study to demonstrate strong correlations between the VRTCO₂ with [progesterone] and [estradiol]. Furthermore, [progesterone] was found to be a significant predictor of changes in the VRTCO₂ within the pooled data. In addition, the relationship between the VRTCO₂ and [progesterone]-to-[estradiol] ratio within the pooled data supports the hypothesis that progesterone receptor availability is an important determinant of pregnancy and gestational hormone-induced changes in ventilatory control (1–3, 6). These data suggest that the effects of gestational hormones on the chemical control of breathing during human pregnancy may be expressed, at least in part, through their influence on the central chemoreflex VRTCO₂. However, it is unclear whether gestational hormones act directly on central chemoreceptors and/or other central neural sites involved in the processing of chemoreceptor activity to increase the ventilatory response to CO₂ (1).

Pregnancy is also reported to increase peripheral ventilatory chemoreflex responsiveness to hypoxia (11, 21, 22). This appears to be due to a direct effect of progesterone on the
carotid body, independent of descending central neural influences (10, 11). In this regard, endogenous and exogenous increases in circulating [progesterone] significantly increase both the $V_E$ and carotid body neural output response to hypoxia (10, 11, 21, 22, 33). The stimulatory effect of progesterone on the peripheral chemoreflex appears to be potentiated by estrogen via central neural mechanisms (10).

Nevertheless, it is difficult to justify how the hyperventilatory response to pregnancy could be the result of changes in the central and peripheral chemoreflex control of breathing because the increased $V_E$ occurs despite decreased chemoreceptor stimuli (i.e., reduced $P_{aCO_2}$, increased $P_{aO_2}$). The only logical way in which the ventilatory chemoreflex may be responsible for the ventilatory changes observed during pregnancy is if the $V_{R T C O_2}$ decreased and/or chemoreflex sensitivity increased before a significant change in $V_E$ and $P_{aCO_2}$. Unfortunately, our data do not permit confirmation of this hypothesis, and further studies will be needed to test it.

Effects of pregnancy on the ventilatory response to hypocapnia. This is the first study to demonstrate that the ventilatory response to hypocapnia (i.e., basal $V_E$), an index of nonchemoreflex drives to breathe, is greater in pregnant compared with nonpregnant women. In addition, significant correlations between basal $V_E$ with [progesterone], [estradiol], and $P_{aCO_2}$ were observed within the pooled data. This suggests that progesterone may act alone or in combination with estradiol to increase $V_E$ and reduce $P_{aCO_2}$ at rest via stimulation of central neural sites involved in the control of breathing, independent of the central ventilatory chemoreflex. In this regard, progesterone and estradiol are capable of crossing the blood-brain barrier (16) and directly stimulating $V_E$ through central neural mechanisms (1) in the absence of peripheral ventilatory feedback influences (1, 2). Indeed, Bayliss and colleagues (1–3) identified both the medulla oblongata and diencephalon, which comprises the thalamus and hypothalamus, as critical neuroanatomic structures involved in the central ventilatory response to progesterone. Estrogen also appears to increase the number and availability of hypothalamic progesterone receptors, which are essential to the increase in central ventilatory drive produced by progesterone (1, 2, 4, 6).

As previously discussed, this relationship is reflected by significant correlations between $P_{aCO_2}$ with [progesterone], [estradiol], and the [progesterone]-to-[estradiol] ratio within the pooled data. Taken together, these data support the hypothesis that progesterone and estradiol act synergistically to stimulate $V_E$ and reduce $P_{aCO_2}$ through an estradiol-dependent progesterone receptor-mediated central neural mechanism, independent of the central chemoreflex.

We postulate that the early and progressive rise in $V_E$ and reduction in $P_{aCO_2}$ observed during pregnancy is due, at least in part, to the stimulatory effects of progesterone and estradiol on nonchemoreflex drives to breathe. Elevations in progesterone are always preceded or accompanied by increases in estradiol during pregnancy and throughout the menstrual cycle (31). Unpublished observations from this laboratory suggest that neither the $V_{R T C O_2}$ nor sensitivity of the central chemoreflex response to $CO_2$ differs between the follicular phase and LP of the menstrual cycle, despite significant differences in resting $V_E$, $P_{aCO_2}$, [progesterone], and [estradiol]. Therefore, progesterone and estradiol may act on nonchemoreflex drives to breathe to stimulate $V_E$, thereby altering maternal blood gases and acid-base status and causing a remodeling (i.e., increase sensitivity, decrease threshold) of the central ventilatory chemoreflex. Thus changes in central and peripheral chemoreflex control characteristics may be the result, rather than the cause, of maternal hyperventilation, secondary to an increase in plasma [progesterone] and [estradiol]. Further study is needed to test this hypothesis.

Conclusions. The present study confirms the hypothesis that pregnancy significantly increases the sensitivity and decreases the threshold of the central ventilatory chemoreflex response to $CO_2$. These changes appear to be due, at least in part, to the effects of gestational hormones on the central chemoreflex. Findings also support the involvement of hormone-mediated increases in nonchemoreflex drives to breathe to reduce resting $P_{aCO_2}$ in late gestation. Further study is required to better understand the underlying mechanism(s) of pregnancy-induced changes in ventilatory control.

ACKNOWLEDGMENTS

We acknowledge the support of Christine Rafuse, Penny Lowe, and Sarah McMlen (Queen’s University).

GRANTS

This work was supported by grants from the Ontario Thoracic Society and William M. Spear Research Endowment Fund (Queen’s University). D. Jensen was supported by an Ontario Graduate Scholarship for Science and Technology.

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