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Chemical and mechanical adaptations of the respiratory system at rest and during exercise in human pregnancy

Dennis Jensen, Katherine A. Webb, and Denis E. O'Donnell

Abstract: Human pregnancy is characterized by significant increases in ventilatory drive both at rest and during exercise. The increased ventilation and attendant hypocapnia of pregnancy has been attributed primarily to the stimulatory effects of female sex hormones (progesterone and estrogen) on central and peripheral chemoreflex drives to breathe. However, recent research from our laboratory suggests that hormone-mediated increases in neural (or non-chemoreflex) drives to breathe may contribute importantly to the hyperventilation of pregnancy. This review challenges traditional views of ventilatory control, and outlines an alternative hypothesis of the control of breathing during human pregnancy that is currently being tested in our laboratory. Conventional wisdom suggests that pregnancy-induced increases in central respiratory motor output command in combination with progressive thoraco–abdominal distortion may compromise the normal mechanical response of the respiratory system to exercise, increase the perception of exertional breathlessness, and curtail aerobic exercise performance in otherwise healthy pregnant women. The majority of available evidence suggests, however, that neither pregnancy nor advancing gestation are associated with reduced aerobic working capacity or increased breathlessness at any given work rate or ventilation during exhaustive weight-supported exercise.

Key words: pregnancy, exercise, control of breathing, chemoreflex, progesterone, estrogen, respiratory mechanics, breathlessness.

Résumé : Au cours de la grossesse chez la femme, on observe une augmentation significative du débit ventilatoire tant au repos qu'à l'exercice physique. Cette augmentation du débit ventilatoire associée à l'hypocapnie serait due aux effets stimulants des hormones sexuelles (progestérones et oestrogènes) sur la commande nerveuse centrale et périphérique de la respiration. Cependant, des études récentes menées dans nos laboratoires suggèrent que l'augmentation de la commande respiratoire neural médiatisé par les hormones (pas par les chimioréflexes) contribue de façon importante a l'hyperpnée de la grossesse. Cet article-synthèse conteste les interprétations classiques à propos du contrôle de la ventilation et propose une hypothèse alternative du contrôle de la respiration durant la grossesse chez la femme, une hypothèse qui fait l'objet de vérification dans nos laboratoires. D'après la sagesse populaire, l'augmentation de la commande motrice dans les centres respiratoires au cours de la grossesse combinée à la compression progressive des cavités thoraco-abdominales semble nuire à la mécanique normale de l'appareil respiratoire, augmenter la perception de l'essoufflement à l'effort et réduire la performance aérobie chez la femme enceinte en bonne santé. D'après la majorité des études scientifiques, on n'observe aucune diminution de la capacité aérobie de travail ni une augmentation de l'essoufflement durant la grossesse quelle que soit l'intensité de travail ou l'importance de la ventilation, et ce, au cours d'un exercice physique de port de poids.

Mots-clés : grossesse, activité physique, contrôle de la respiration, chimioréflexe, progestérone, oestrogènes, mécanique respiratoire, essoufflement.

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Introduction

Human pregnancy is characterized by significant changes in cardiovascular, metabolic, thermoregulatory, respiratory, and other important physiologic control systems both at rest and during exercise (Weinberger et al. 1980; Lotgering et al. 1984, 1985; Wolfe et al. 1989; Elkus and Popovich 1992; Wolfe and Mottola 1993; Crapo 1996; O'Toole 2003; Wolfe

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and Weissgerber 2003; Wolfe et al. 2005; Weissgerber and Wolfe 2006; Wise et al. 2006). The majority of these changes are (*i*) initiated and maintained by gestational hormones, (*ii*) almost fully established by the end of the first trimester, and (*iii*) necessary to accommodate the increased demands of the growing fetus and, to a lesser extent, maternal organs and tissues (Weissgerber and Wolfe 2006). This review summarizes the available research concerning chemical and mechanical adaptations of the respiratory system at rest and during exercise in human pregnancy. The physiological mechanisms of these adaptations will be discussed and an alternative hypothesis of ventilatory control during human pregnancy will be presented.

It is certainly reasonable to assume that progressive changes in the shape and configuration of the abdomen, diaphragm, and chest wall (secondary to the gravid uterus) may compromise the mechanical response of the respiratory system during exercise, increase the perception of exertional respiratory discomfort (breathlessness), and decrease aerobic working capacity in otherwise healthy pregnant women. This does not appear to be the case, however, as the majority of available evidence suggests that neither pregnancy nor advancing gestation affects aerobic working capacity (i.e., maximal or peak O_2 uptake ($V\dot{O}_{2\ max}$ or $V\dot{O}_{2\ peak}$, expressed in litres per minute (L/min)) or the perception of breathlessness at any given work rate or ventilation during weight-bearing (i.e., treadmill) or non-weight-bearing exercise (i.e., stationary cycling, swimming) (Sady et al. 1989, 1990; Lotgering et al. 1991; McMurray et al. 1991; Jaque-Fortunato et al. 1996; Spinnewijn et al. 1996; Lotgering et al. 1998; Ohtake and Wolfe 1998; Heenan et al. 2001; Jensen et al. 2006*a*, 2006*b*). The physiological mechanisms of this preservation are incompletely understood and are the focus of recent research in our laboratory (Jensen et al. 2006*a*, 2006*b*). We are currently testing the hypothesis that mechanical adaptations of the respiratory system, including changes in resting and dynamic operating lung volumes and reduced airway resistance, may help to preserve neuromechanical coupling of the respiratory system and allow healthy pregnant women to achieve their maximal aerobic working capacity without an increase in breathlessness, despite significant increases in central respiratory motor output command.

Ventilatory control during human pregnancy

Arguably the most consistent and striking physiological effect of human pregnancy is that of an increased ventilatory drive observed both at rest and during exercise. In this regard, minute ventilation (V_E) increases by 3–4 L/min (35%–55%) at rest and by 4–13 L/min (10%–40%) during standard submaximal exercise throughout pregnancy (Guzman and Caplan 1970; Knuttgen and Emerson 1974; Pernoll et al. 1975; Edwards et al. 1981; Sady et al. 1989; Field et al. 1991; Lotgering et al. 1991; Pivarnik et al. 1992, 1993; Spatling et al. 1992; Wolfe et al. 1994; Jaque-Fortunato et al. 1996; Spinnewijn et al. 1996; Lotgering et al. 1998; Ohtake and Wolfe 1998; Heenan and Wolfe 2000, 2003; Charlesworth et al. 2006; Jensen et al. 2006*b*; Weissgerber et al. 2006). The increased V_E is explained by increases in tidal volume (V_T) with little or no change in respiratory frequency (Knuttgen and Emerson 1974; Pernoll et al. 1975; Field et al. 1991; Lotgering et al. 1991; Pivarnik et al. 1992, 1993; Spatling et al. 1992; Wolfe et al. 1994; Jaque-Fortunato et al. 1996; Spinnewijn et al. 1996; Ohtake and Wolfe 1998). V_E at maximal or peak exercise is either unchanged (McMurray et al. 1991; Wolfe et al. 1994; Jaque-Fortunato et al. 1996; Spinnewijn et al. 1996; Heenan et al. 2001; Jensen et al. 2006*b*) or slightly increased (Sady et al. 1989; Lotgering et al. 1991, 1998) in the pregnant versus non-pregnant state. Pregnancy-induced increases in V_E are greater than those typically observed for O_2 uptake ($V\dot{O}_2$) and CO_2 production ($V\dot{C}O_2$) and, therefore, the ventilatory equivalents for O_2 ($V_E/V\dot{O}_2$) and CO_2 ($V_E/V\dot{C}O_2$) are increased both at rest and during exercise throughout pregnancy (Knuttgen and Emerson 1974; Lotgering et al. 1991; Pivarnik et al. 1992, 1993; Wolfe et al. 1994; Jaque-Fortunato et al. 1996; Ohtake and Wolfe 1998; Heenan and Wolfe 2000, 2003; Heenan et al. 2001; Jensen et al. 2006*b*; Charlesworth et al. 2006; Weissgerber et al. 2006).

Alveolar ventilation (V_A) is also increased at rest and during exercise in human pregnancy (Pernoll et al. 1975; Pivarnik et al. 1992, 1993; Spatling et al. 1992; Ohtake and Wolfe 1998; Heenan et al. 2001). Consequently, arterial (P_aCO_2), alveolar, and cerebrospinal fluid ($P_{CSF}CO_2$) PCO_2 are reduced by 5–10 mmHg at rest during pregnancy (Lyons and Antonio 1959; Eng et al. 1975; Machida 1981; Moore et al. 1987; Pivarnik et al. 1992; Spatling et al. 1992; McAuliffe et al. 2001; Heenan and Wolfe 2003; Jensen et al. 2005; Charlesworth et al. 2006; Weissgerber et al. 2006), whereas arterial PO_2 (P_aO_2) is either unchanged (Eng et al. 1975; Hannhart et al. 1989) or slightly increased (Templeton and Kelman 1976; Machida 1981; McAuliffe et al. 2001). Furthermore, direct and indirect measures of P_aCO_2 during steady-state (Pernoll et al. 1975; Pivarnik et al. 1992; Spatling et al. 1992; Charlesworth et al. 2006) and progressive (Heenan et al. 2001) exercise are reportedly lower during pregnancy.

In accordance with conventional acid–base theory, the respiratory alkalosis of pregnancy is only partially compensated for by a lowering of plasma and cerebrospinal fluid bicarbonate concentrations ($[HCO_3^-]$) (Eng et al. 1975; Machida 1981; Pivarnik et al. 1992; Blechner 1993; Kemp et al. 1997; Heenan and Wolfe 2000; McAuliffe et al. 2001) such that arterial and cerebrospinal fluid $[H^+]$ is reduced at rest during pregnancy (Templeton and Kelman 1976; Machida 1981; Pivarnik et al. 1992; Blechner 1993; Kemp et al. 1997; Heenan and Wolfe 2000, 2003; McAuliffe et al. 2001; Jensen et al. 2005; Charlesworth et al. 2006; Weissgerber et al. 2006). However, consistent with Stewart's physicochemical analysis of acid–base balance (Stewart 1981, 1983), the reduced arterial $[H^+]$ observed at rest during pregnancy is the net result of reductions in P_aCO_2 and total weak acid (which tends to decrease $[H^+]$), which is partially offset by the acidifying effects of a reduced strong ion difference (Kemp et al. 1997; Wolfe et al. 1998; Heenan and Wolfe 2000; Charlesworth et al. 2006).

Role of female sex hormones in the control of breathing during pregnancy

Unfortunately, the time course and mechanism(s) of the

aforementioned changes are not completely understood. Pregnancy-induced increases in V_E at rest and during exercise are almost fully established by 7–8 weeks of gestation (Clapp et al. 1988; Rees et al. 1990; Spatling et al. 1992; Weissgerber et al. 2006) with smaller progressive increases continuing through the second and third trimesters (Guzman and Caplan 1970; Contreras et al. 1991; Lotgering et al. 1991; Wolfe et al. 1994; McAuley et al. 2005; Jensen et al. 2006*b*). The increased V_E of pregnancy has been attributed primarily to the combined stimulatory effects of progesterone and estrogen (both of which increase throughout gestation) on ventilatory drive (Dempsey et al. 1986; Tatsumi et al. 1995; Wolfe et al. 1998; Saaresranta and Polo 2002; Behan et al. 2003). In this regard, significant negative correlations have been observed between plasma progesterone concentrations ([progesterone]) and P_aCO_2 at rest in pregnant and non-pregnant women (Machida 1981; Heenan and Wolfe 2003; Jensen et al. 2005; Slatkovska et al. 2006; Weissgerber et al. 2006). Several studies have also observed significant increases in V_E and reductions in P_aCO_2 and $P_{CSF}CO_2$ at rest following the administration of the synthetic progestins — medroxyprogesterone acetate and chlormadinone acetate — to men, women, and laboratory animals (Lyons and Antonio 1959; Skatrud et al. 1978; Zwillich et al. 1978; Schoene et al. 1980; Robertson et al. 1982; Hosenpud et al. 1983; Kimura et al. 1984; Hohimer et al. 1985; Tatsumi et al. 1986; Bayliss et al. 1987; Bonekat et al. 1987; Morikawa et al. 1987; Okita et al. 1987; Mikami et al. 1989; Regensteiner et al. 1989; Javaheri and Guerra 1990; Vos et al. 1994; Saaresranta et al. 1999, 2002*a*, 2002*b*; Wagenaar et al. 2002, 2003). Surprisingly, neither the dose, duration of treatment, or luteinizing activity of the synthetic progestin seems to have an effect on the magnitude of change in V_E and P_aCO_2 (Skatrud et al. 1978; Morikawa et al. 1987; Mikami et al. 1989), suggesting that progesterone's effect on ventilatory drive may be a receptor-mediated phenomenon.

The ventilatory effects of progesterone observed at rest are also present during exercise. In this regard, V_E/VCO_2 (index of ventilatory drive) is reportedly higher, and P_aCO_2 lower, during steady-state (Skatrud et al. 1978) and progressive (Robertson et al. 1982; Bonekat et al. 1987) cycle ergometer exercise following the administration of medroxyprogesterone acetate to healthy men. Similarly, Regensteiner and co-workers (1989) found that the combined administration of progesterone and estrogen significantly increased (versus placebo) the V_E response to mild exercise in ovariohysterectomized women.

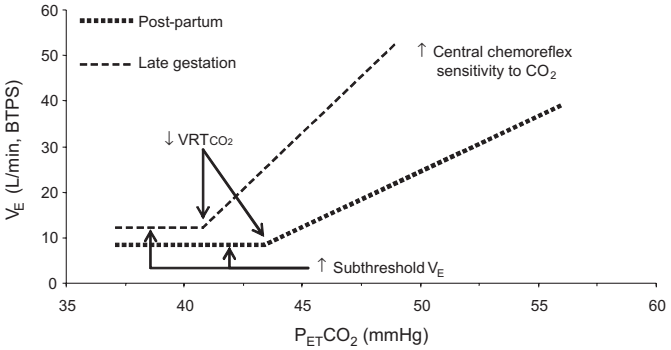
In the natural setting of pregnancy, increases in [progesterone] are always preceded or accompanied by increases in circulating levels of estrogen ([estrogen]). Studies conducted in both humans (Regensteiner et al. 1989; Jensen et al. 2005) and animals (Brodeur et al. 1986; Bayliss et al. 1987, 1990, 1991; Hannhart et al. 1990; Tatsumi et al. 1991; Bayliss and Millhorn 1991, 1992) suggest that the ventilatory response to progesterone is mediated by estrogen through its ability to increase the number and availability of progesterone receptors within respiratory-related areas (i.e., hypothalamus, medulla) of the central nervous system (Bayliss and Millhorn 1991, 1992; Bayliss et al. 1991).

In a series of detailed and elegant studies, the findings of which have been summarized in detail elsewhere (Bayliss and Millhorn 1992), Bayliss and colleagues found that normal physiological doses of progesterone had no effect on phrenic nerve activity (neural equivalent of V_E) in cats pretreated with a progesterone-receptor antagonist (Bayliss et al. 1987). Conversely, repeated doses of a progesterone-receptor agonist caused a dose-dependent increase in phrenic nerve activity (Bayliss and Millhorn 1992). These investigators (Bayliss et al. 1990) also found that progesterone evoked a dose-dependent increase in phrenic nerve activity in estrogen pre-treated cats only, and that the administration of either an estrogen- or progesterone-receptor antagonist attenuated this response. These experiments were conducted in anaesthetized and paralyzed carotid- and vagus-denervated cats under isocapnic conditions. Therefore, the collective results of these studies suggest that progesterone may increase ventilatory drive via an estrogen-dependent progesterone-receptor-mediated central neural mechanism independent of central and peripheral chemoreceptor feedback influences.

Although female sex hormones contribute importantly to the increased ventilatory drive of pregnancy, the physiological mechanism(s) of their action has not yet been determined. The presence of progesterone and estrogen in the arterial blood and cerebrospinal fluid (Backstrom et al. 1976; Skatrud et al. 1978; Hirabayashi et al. 1995) permits their interaction with both central and peripheral sites involved in the chemical and neural control of breathing (Dempsey et al. 1986; Bayliss and Millhorn 1992; Tatsumi et al. 1995; Behan et al. 2003; Saaresranta and Polo 2002). Mahamed et al. (2001) recently demonstrated that, in humans, approximately 40% and 25% of resting V_E may be accounted for by central and peripheral chemoreflex drives to breathe, respectively, with the balance (35%) provided by non-chemoreflex influences, including central neural and state-dependent (or "wakefulness") drives to breathe. Thus, pregnancy-induced increases in chemical and (or) non-chemical drives to breathe, secondary to increased circulating female sex hormone levels, may account for the increased V_E and reduced P_aCO_2 observed at rest and during exercise in pregnancy.

In accordance with the results of previous studies (Lyons and Antonio 1959; Eng et al. 1975; Liberatore et al. 1984; Moore et al. 1987; Hannhart et al. 1989), we recently observed a 60% increase in the sensitivity and a 5 mmHg decrease in the threshold of the central chemoreflex response to CO_2 in pregnant versus non-pregnant women (Fig. 1) (Jensen et al. 2005). In that study, pooled cross-sectional data from pregnant (36.5 ± 0.4 weeks gestation) and non-pregnant women revealed significant correlations between P_aCO_2 with central chemoreflex sensitivity, central chemoreflex ventilatory recruitment threshold for CO_2, [progesterone], [estrogen], and the [progesterone]:[estrogen] ratio (a crude index of progesterone-receptor availability). Significant associations were also observed between the central chemoreflex ventilatory recruitment threshold for CO_2 with [progesterone] and the [progesterone]:[estrogen] ratio; however, no such relationships were observed between central chemoreflex sensitivity and each of [progesterone], [estrogen], and the [progesterone]:[estrogen] ratio. These data suggest that pregnancy-induced increases in V_E at rest and during exercise may be due, at least in part, to the combined

Fig. 1. Central ventilatory chemoreflex response to hyperoxic hypercapnia in a representative subject in late pregnancy (35 weeks gestation) and 18 weeks post-partum. V_E, minute ventilation; $P_{ET}CO_2$, end-tidal PCO_2; $VRTCO_2$, central chemoreflex ventilatory recruitment threshold for CO_2. Note the pregnancy-induced (*i*) increase in subthreshold V_E (representing neural or non-chemoreflex drives to breathe), (*ii*) decrease in the central chemoreflex ventilatory recruitment threshold for CO_2, and (*iii*) increase in central chemoreflex sensitivity. With data from the laboratory of D.E. O'Donnell.



effects of progesterone and estrogen on the central chemoreflex ventilatory recruitment threshold for CO_2 and, to a lesser extent, central chemoreflex sensitivity. The way female sex hormones alter the threshold and sensitivity of the chemoreflex response to CO_2 during pregnancy is not known and is the focus of ongoing research in our laboratory (discussed below).

Peripheral chemoreflex responsiveness to hypoxia is also increased throughout gestation (Moore et al. 1986, 1987; Hannhart et al. 1989) and was estimated to account for approximately 30% of the increased V_E in pregnant cats (Hannhart et al. 1989). Endogenous and exogenous increases in circulating [progesterone] have been shown to increase the carotid body neural output response and consequently the V_E response to hypoxia (Hannhart et al. 1989, 1990; Tatsumi et al. 1997). These effects appear to be intrinsic to the carotid body (Hannhart et al. 1989, 1990; Tatsumi et al. 1997) and potentiated by estrogen via central neural mechanisms (Hannhart et al. 1990). Collectively, these data support the widely held view that pregnancy-induced increases in female sex hormone concentrations may increase V_E and reduce P_aCO_2 via their direct (i.e., effect on chemoreceptor cells) and (or) indirect (i.e., facilitation of neurons involved in integrating signals from chemoreceptor cells) stimulatory effects on central and peripheral chemoreflex drives to breathe.

However, it is difficult to justify how the hyperventilatory response of pregnancy could be the result of hormone-mediated changes in central and peripheral chemoreflex responsiveness, since the increased V_E occurs despite reductions in chemoreceptor stimuli (i.e., reduced arterial and cerebrospinal fluid [H^+], and slightly increased P_aO_2).

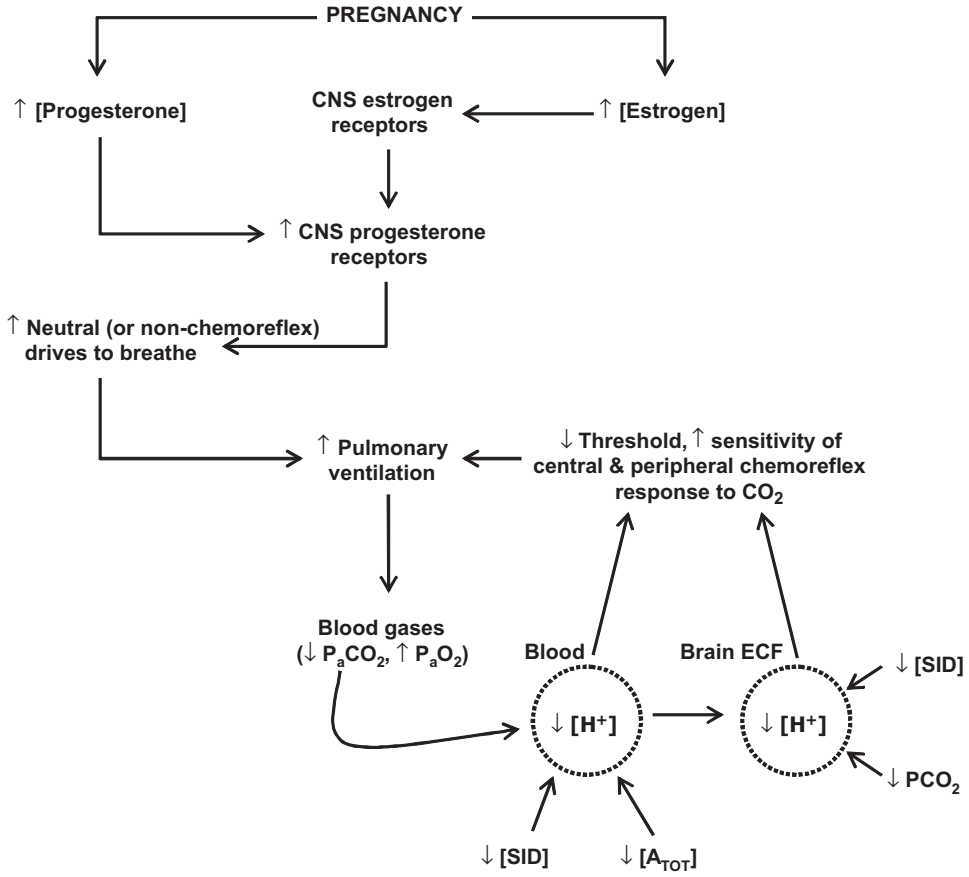
The majority of published studies have found that neither medroxyprogesterone acetate nor chlormadinone acetate therapy alter the threshold or sensitivity of the central chemoreflex response to CO_2, despite significant increases in V_E and reductions in P_aCO_2 (Schoene et al. 1980; Kimura et al. 1984; Tatsumi et al. 1986; Bonekat et al. 1987; Morikawa et al. 1987; Regensteiner et al. 1989; Wagenaar et al. 2002, 2003). Furthermore, most studies have found that medroxyprogesterone acetate and chlormadinone acetate therapy only increase the V_E response to progressive hypoxia when $P_{ET}CO_2$ is restored to pre-treatment (i.e., normocapnic) levels (Zwillich et al. 1978; Schoene et al. 1980; Tatsumi et al. 1986; Morikawa et al. 1987; Regensteiner et al. 1989; Wagenaar et al. 2003). Although these findings suggest that progesterone may increase peripheral chemoreflex sensitivity, one must consider that the hypocapnia induced by medroxyprogesterone acetate and chlormadinone acetate is compensated for by reductions in arterial and cerebrospinal fluid [HCO_3^-], such that the buffering capacity of the arterial blood and brain extracellular fluid for CO_2 is reduced. Therefore, the increased V_E response to progressive hypoxia following synthetic progestin therapy may not reflect an increased peripheral chemoreflex responsiveness to hypoxia per se, but rather an exaggerated arterial and central (or brain extracellular) [H^+] stimulus, secondary to the restoration of $P_{ET}CO_2$ to normocapnic levels. Furthermore, Skatrud and associates (1978) found that medroxyprogesterone acetate administered to 5 healthy men for 14 days significantly reduced both arterial and cerebrospinal fluid [H^+], but had no effect on the V_E response to hypercapnia or 100% O_2 — convincing evidence that progesterone may stimulate ventilation via some central neural mechanism, independent of either central or peripheral chemoreceptor feedback influences.

An alternative hypothesis of ventilatory control during human pregnancy

Consistent with the above, we recently found that the V_E response to hyperoxic hypocapnia, representing neural (or non-chemoreflex) drives to breathe, was 60% (or 5.5 L/min) higher in pregnant than in non-pregnant women (Fig. 1), and that this change was negatively correlated with resting P_aCO_2 and positively correlated with both plasma [progesterone] and [estrogen] (Jensen et al. 2005). Based on these results, we hypothesized that pregnancy-induced changes in the threshold and sensitivity of the central (and presumably also peripheral) chemoreflex response to CO_2 may be the result, rather than the cause, of maternal hyperventilation and attendant hypocapnia, secondary to the stimulatory effects of progesterone and estrogen on neural (or non-chemoreflex) drives to breathe (Fig. 2). In accordance with this hypothesis, we recently demonstrated that phasic menstrual cycle changes in non-chemoreflex drives to breathe may account for the increased V_E and reduced P_aCO_2 during the luteal (or high female sex hormone) versus follicular (or low female sex hormone) phase of the normal human menstrual cycle (Slatkovska et al. 2006). In that study, menstrual cycle phase had no significant effect on the threshold or sensitivity of either the central or peripheral chemoreflex response to CO_2, despite cyclic changes in V_E, P_aCO_2, [progesterone], and [estrogen].

Duffin (2005) recently demonstrated that acid–base disturbances, such as occur during human pregnancy (Kemp et al. 1997; Wolfe et al. 1998; Heenan and Wolfe 2000; Charlesworth et al. 2006), change the relationship between PCO_2

Fig. 2. A novel hypothesis of ventilatory control during human pregnancy. Refer to text for details. CNS, central nervous system; P_aCO_2, arterial PCO_2; P_aO_2, arterial PO_2; [SID], strong ion difference; [A_{TOT}], total weak acid; [H^+], hydrogen ion concentration; ECF, extracellular fluid.



and [H^+], the actual stimulus to the chemoreceptors, which alters the threshold (and sensitivity) of the chemoreflex response to CO_2 and thus resting (steady-state) V_E and P_aCO_2. Consistent with this idea, we suggest (and are currently testing the hypothesis) that pregnancy-induced increases in female sex hormones increase V_E and reduce both arterial and central (or brain extracellular) PCO_2 via stimulation of neural (or non-chemoreflex) drives to breathe (Fig. 2). The attendant arterial and central alkalosis initiates a compensatory (i.e., renal) reduction of arterial and central [SID] (strong ion difference; the concentration difference of strongly dissociated positive and negative ions in solution), which partially restores arterial and central [H^+] (Fig. 2). Consequently, the PCO_2 at which CO_2 begins to stimulate V_E (i.e., the ventilatory recruitment threshold for CO_2) is significantly reduced and the sensitivity of the V_E response to CO_2 is significantly increased during human pregnancy (Fig. 2), even though the threshold and sensitivity in terms of [H^+] does not change.

Mechanical adaptations of the respiratory system during pregnancy

Many cross-sectional (Norregaard et al. 1989; Das and Jana 1991; McAuliffe et al. 2002; Kolarzyk et al. 2005) and longitudinal (Rubin et al. 1956; Gee et al. 1967; Knuttgen and Emerson 1974; Eng et al. 1975; Baldwin et al. 1977; Milne et al. 1977*b*; Alaily and Carrol 1978; Craig and Toole 1975; Gilroy et al. 1988; Berry et al. 1989; Contreras et al. 1991; Puranik et al. 1994) studies have examined the effects of human pregnancy and advancing gestation on pulmonary function and respiratory mechanics at rest. As a result of uterine enlargement and abdominal distension, diaphragmatic mid-position is elevated by 4–5 cm and the circumference of the thorax is increased 5–7 cm (Thomson and Cohen 1938; Gilroy et al. 1988; Contreras et al. 1991). These changes are partially compensated for by relaxation of ligamentous attachments of the ribs such that chest wall compliance and, therefore, total respiratory system compliance is reduced during human pregnancy; however, lung compliance does not change (Gee et al. 1967; Contreras et al. 1991). Despite progressive thoraco–abdominal distortion, inspiratory and expiratory muscle strength is preserved (Gilroy et al. 1988; Contreras et al. 1991) and diaphragmatic excursion is not impaired (McGinty 1938; Thomson and Cohen 1938). The preservation of inspiratory muscle strength during pregnancy may be due in part to optimization of the length–tension relationship of the diaphragm, secondary to increased diaphragmatic mid-position. The oxygen cost of breathing, however, is reportedly increased during pregnancy (Bader et al. 1959) as evidenced by a 55% increase in the tension–time index of the diaphragm (Contreras et al. 1991).

Lung volumes and capacities

Pregnancy-induced reductions in chest wall compliance (secondary to progressive thoraco–abdominal distortion) significantly reduce both end-expiratory lung volume (EELV; relaxation volume of the respiratory system) and expiratory reserve volume (ERV); however, residual volume (RV) is generally preserved during pregnancy (Cugell et al. 1953; Gee et al. 1967; Knuttgen and Emerson 1974; Eng et al. 1975; Baldwin et al. 1977; Alaily and Carrol 1978; Craig and Toole 1975; Gilroy et al. 1988; Berry et al. 1989; Norregaard et al. 1989; Contreras et al. 1991; Puranik et al. 1994; McAuliffe et al. 2002). Reductions in EELV are compensated for by reciprocal increases in inspiratory capacity (IC) such that total lung capacity (TLC) does not change (Cugell et al. 1953; Gee et al. 1967; Knuttgen and Emerson 1974; Baldwin et al. 1977; Craig and Toole 1975; Gilroy et al. 1988; Berry et al. 1989; Contreras et al. 1991; Puranik et al. 1994). Since pregnancy has no effect on either RV or TLC, vital capacity is preserved (Gee et al. 1967; Baldwin et al. 1977; Alaily and Carrol 1978; Craig and Toole 1975; Gilroy et al. 1988; Berry et al. 1989; Das and Jana 1991; Puranik et al. 1994; McAuliffe et al. 2002).

Pulmonary diffusing capacity

Pulmonary diffusing capacity (D_L) depends on the diffusing capacity of the alveolar capillary membrane (D_M), pulmonary capillary blood volume (V_C), and the concentration of circulating haemoglobin ([Hb]), all of which may be altered during pregnancy. Pregnancy-induced increases in cardiac output and plasma volume (Wolfe et al. 1989) may decrease D_M (tend to decrease D_L) and increase V_C (tend to increase D_L). In addition, the hypervolemia of pregnancy lowers circulating [Hb] by 2–3 g/dL (Knuttgen and Emerson 1974; McAuliffe et al. 2002, 2003), which may decrease D_L. Despite these changes, neither pregnancy nor advancing gestation has been shown to alter either D_M, V_C, or D_L (absolute or corrected for [Hb]) (Bedell and Adams 1962; Krumholz et al. 1964; Gazioglu et al. 1970; Milne et al. 1977*a*; Norregaard et al. 1989; McAuliffe et al. 2002, 2003).

Central and peripheral airway function

Briscoe and DuBois (1958) previously demonstrated that airway conductance, the reciprocal of resistance, is linearly and positively related to the degree of lung inflation (or deflation). In this regard, pregnancy-induced reductions in EELV should, at least in theory, increase flow resistance in the central and peripheral airways. Breathing at low lung volumes, such as occurs during human pregnancy, has also been shown to increase airway hyper-responsiveness (Ding et al. 1987; Torchio et al. 2006). Despite reductions in EELV, neither pregnancy nor advancing gestation have an effect on forced expiratory volumes (Rubin et al. 1956; Knuttgen and Emerson 1974; Eng et al. 1975; Baldwin et al. 1977; Milne et al. 1977*b*; Alaily and Carrol 1978; Berry et al. 1989; Norregaard et al. 1989; Das and Jana 1991; Puranik et al. 1994; Garcia-Rio et al. 1997; McAuliffe et al. 2002; Kolarzyk et al. 2005) or peak expiratory flow rates (Rubin et al. 1956; Norregaard et al. 1989; Das and Jana 1991; McAuliffe et al. 2002; Kolarzyk et al. 2005). In fact, airway resistance is reportedly unchanged (Milne et al. 1977*b*; Liberatore et al. 1984; Garcia-Rio et al. 1997) or even slightly reduced (Rubin et al. 1956; Gee et al. 1967; Garrard et al. 1978) during human pregnancy, suggesting bronchodilation.

Peripheral airway function is also well maintained during human pregnancy. Expiratory flows at lower lung volumes (i.e., 75% of FVC maneuver) tend not to change during pregnancy or throughout gestation (Baldwin et al. 1977; Norregaard et al. 1989; Das and Jana 1991; Kolarzyk et al. 2005). Moreover, closing capacity, which represents the absolute lung volume at which dynamic compression of the airways occurs, is not significantly different at any stage of pregnancy (Craig and Toole 1975; Russell and Chambers 1981). However, pregnancy-induced reductions in EELV encroach on closing capacity such that airway closure occurs closer to EELV than to RV in the pregnant versus nonpregnant state (Bevan et al. 1974; Craig and Toole 1975; Russell and Chambers 1981). This effect, combined with the anemia of pregnancy, may compromise ventilation–perfusion relationships of the lung (i.e., widen the alveolar–arterial O_2 gradient), predisposing otherwise healthy pregnant women to the development of arterial hypoxemia, particularly during strenuous exercise. Preliminary results from our laboratory, however, suggest that healthy pregnant women do not develop arterial hypoxemia (i.e., arterial O_2 saturation <93%–95%) during progressive symptom-limited exercise testing in late gestation (Jensen et al. 2006*a*), suggesting that alveolar gas exchange is generally preserved during exhaustive exercise in this population. To our knowledge, no published study has examined the incidence or severity of arterial hypoxemia during strenuous exercise in healthy human pregnancy.

The lack of anticipated change in central and peripheral airway function during pregnancy may be explained by the relaxant effect of progesterone on airway smooth muscle. Popovic and White (1998) observed progesterone-dependent increases in upper airway dilator muscle (i.e., genioglossus) activity in postmenopausal women following 2 weeks of synthetic progestin administration. In that study, genioglossus muscle activity was also greater in pre- versus post-menopausal women (Popovic and White 1998). Furthermore, studies conducted in laboratory animals have demonstrated that progesterone potentiates isoprenaline-induced relaxation of pig bronchus (Foster et al. 1983) and prevents histamine- and carbachol-induced contraction of guinea pig trachea (Perusquia et al. 1997). Thus, pregnancy-induced increases in [progesterone] may help to preserve (or improve) central and peripheral airway function by increasing both genioglossus muscle activity and β-adrenergic activity, and decreasing cholinergic (vagal) airway tone.

Respiratory limitation to exercise tolerance during human pregnancy: fact or fiction?

It is reasonable to assume that the aforementioned changes in ventilatory drive and respiratory mechanics may compromise the normal mechanical ventilatory response to exercise, increase the perception of respiratory discomfort (breathlessness), and curtail aerobic working capacity during pregnancy. Several studies have reported that 60%–75% of

healthy pregnant women with no history of cardiorespiratory disease complain of increased breathlessness during activities of daily living such as walking and stair climbing by 30–36 weeks gestation (Cugell et al. 1953; Milne et al. 1978; Moore et al. 1987). Despite the high prevalence of breathlessness during pregnancy and the fact that it may reflect mechanical maladaptation of the respiratory system, systematic studies into its etiology are limited and the results are conflicting (Bader et al. 1959; Gilbert et al. 1962; Gilbert and Auchincloss 1966; Field et al. 1991; Garcia-Rio et al. 1996; Jensen et al. 2006*b*). The perception of breathlessness during exercise in pregnancy has been shown to increase in some (Field et al. 1991), but not all (Ohtake and Wolfe 1998; Jensen et al. 2006*b*), studies.

Breathlessness during exercise in human pregnancy

Several theories have been put forward to explain the etiology of gestational breathlessness. First, it has been attributed to the normal awareness of maternal hyperventilation (Cugell et al. 1953; Field et al. 1991), secondary to increased central and peripheral chemoreflex drives to breathe (Moore et al. 1987; Garcia-Rio et al. 1996). Second, it has been suggested that breathlessness may be the consequence of an exaggerated central perception of normal V_E or respiratory effort (Gilbert et al. 1962; Gilbert and Auchincloss 1966). Finally, Bader et al. (1959) proposed that progressive reductions in chest wall compliance, secondary to thoraco–abdominal distortion, may compromise the mechanical response of the respiratory system such that more work (or effort) may be required to achieve a given V_E during exercise, which would provoke an increase in breathlessness.

In pulmonary disease states, the intensity of perceived respiratory discomfort is positively correlated with the level of V_E (absolute or relative to maximal ventilatory capacity) and inspiratory effort (absolute or relative to maximal inspiratory pressure) during exercise (Leblanc et al. 1986; Marciniuk et al. 1994). Therefore, pregnancy-induced increases in exercise V_E would be expected to increase ratings of exertional breathlessness. Consistent with this hypothesis, Field et al. (1991) found that V_E, V_T, inspiratory esophageal pressure swings (index of inspiratory effort), and Borg ratings of breathlessness were significantly greater during standard submaximal cycle exercise in late pregnancy (33 ± 2 weeks gestation) versus the post-partum state (12 ± 3 weeks post-partum). In addition, pregnancy had no effect on the relationship between (*i*) inspiratory effort and V_T or (*ii*) breathlessness intensity and inspiratory effort during exercise. These data suggest that pregnancy-induced increases in exertional breathlessness may reflect the normal awareness of increased V_E and inspiratory effort during maternal exercise. In that study, however, comparisons were made at a standardized work rate of only 48 W, corresponding to an exercise V_E of only 31 and 24 L/min in the pregnant and post-partum states, respectively. Similarly, Borg ratings of perceived breathlessness were only 1.8 (“very slight” to “slight”) and 1.0 (“very slight”) at this low work rate in the pregnant and post-partum states, respectively. In addition, the investigators reported that in the third trimester, all women experienced some respiratory discomfort (2.7 ± 1.0 Borg units; “slight” to “moderate”) at end-exercise (i.e., 70% of predicted maximum heart rate), but did not consider it unpleasant or exercise limiting. Given the low breathlessness intensity ratings and the fact that third trimester exercise tests were stopped well in advance of symptom limitation or achievement of physiological maximum, it is unclear whether these women actually experienced significant respiratory discomfort. Furthermore, it is reasonable to suggest that the exercise testing protocol employed in that study was too conservative to unmask a potential mechanical ventilatory constraint to exercise tolerance in healthy pregnant women.

In contrast to the above, Ohtake and Wolfe (1998) reported no significant effect of pregnancy or advancing gestation on ratings of perceived respiratory effort (RPEr) during 6 min of steady-state cycle ergometer exercise at 20, 45, and 65 W, despite pregnancy-induced increases in V_E, V_T, V_E/VO_2, and V_E/VCO_2 at each work rate. In fact, these investigators reported a significant decrease in the RPEr–V_E relationship at each work rate in the pregnant (37.2 ± 0.1 weeks gestation) versus post-partum state (14.0 ± 0.5 weeks post-partum). Again, comparisons were made at modest submaximal steady-state work rates corresponding to Borg RPEr ratings between 8 (“extremely light” to “very light”) and 12 (“light” to “somewhat hard”) and exercise V_E between 15 and 35 L/min. Furthermore, in that study, RPEr (and not specifically breathlessness) was quantified only as a secondary outcome variable and the end points of Borg’s 6–20 scale were not anchored prior to exercise, making it difficult to appreciate the significance of these results.

We recently tested the hypothesis that the perception of exertional breathlessness would increase with advancing gestation and would also be greater in pregnant versus non-pregnant women during progressive symptom-limited cycle ergometer exercise, reflecting both an increased ventilatory drive and restricted ventilatory mechanics (Jensen et al. 2006*b*). However, consistent with the results of Ohtake and Wolfe (1998), we found that neither pregnancy nor advancing gestation were associated with reduced peak exercise performance (i.e., $VO_{2\ peak}$ (L/min)) or increased exertional breathlessness at any given work rate, despite significant and progressive increases in exercise V_E, V_E/VO_2, and V_E/VCO_2. Since pregnancy-induced increases in exercise V_E and ventilatory drive are almost fully established by the end of the first trimester, we also hypothesized that the intensity of breathlessness at a standardized exercise V_E would increase throughout pregnancy, reflecting progressive mechanical ventilatory constraints. To our surprise, however, neither pregnancy nor advancing gestation had an effect on Borg ratings of breathlessness at a standardized exercise V_E of 40 L/min. In fact, the intensity of breathlessness was approximately 1 Borg unit lower at iso-V_E in late gestation (36.2 ± 0.3 weeks) compared with the non-pregnant state, suggesting that mechanical adaptations of the respiratory system during pregnancy have no deleterious effect on the perceptual response to exercise.

The collective results of Ohtake and Wolfe (1998) and Jensen et al. (2006*b*) suggest that neither pregnancy nor advancing gestation has an effect on the perception of breathlessness during steady-state or progressive weight-supported

exercise, despite significant increases in central ventilatory drive. In addition, it appears that pregnancy and advancing gestation have no appreciable effect on breathlessness–V_E relationships during exercise, despite progressive thoraco–abdominal distortion. The mechanisms of this preservation are poorly understood and are the focus of recent research in our laboratory (Jensen et al. 2006*a*).

Mechanical ventilatory response to exercise in healthy, non-pregnant volunteers

During exercise in health, ventilatory work and the O_2 cost of breathing are minimized through several acute physiological adaptations, including control of operating lung volumes, reduced airway resistance (or bronchodilation), increased V_T expansion, and improved matching of ventilation and perfusion (Sheel et al. 2002; Dempsey et al. 2006). Progressive expiratory muscle recruitment reduces dynamic end-expiratory lung volume (EELV) and increases dynamic IC during exercise, which allows V_T to expand by encroaching equally on the expiratory and inspiratory reserve volumes (Younes 1991). This ensures that V_T remains positioned on the linear (or compliant) portion of the respiratory system's sigmoidal pressure–volume curve during exercise, where the relationship between respiratory effort and V_T expansion is preserved and the elastic work of breathing is minimized; that is, the least amount of negative intrathoracic pressure has to be generated by the inspiratory muscles to achieve a given increase in V_T (Younes 1991). Furthermore, increases in circulating catecholamines (Warren and Dalton 1983) and feedback from pulmonary (vagal) stretch receptors (secondary to increased V_T expansion) during exercise decrease cholinergic tone of airway smooth muscle, which helps to minimize the resistive work of breathing despite large increases in inspiratory and expiratory flow rates (Warren et al. 1984; Dempsey et al. 1996, 2006). These dynamic ventilatory adaptations ensure that ventilatory capacity exceeds demand even during the most strenuous exercise and that the respiratory system does not limit aerobic working capacity, at least in healthy, untrained, non-pregnant volunteers (Dempsey 1986).

Mechanical ventilatory response to exercise during pregnancy

Pregnancy-induced increases in exercise V_E and central ventilatory drive combined with progressive reductions in chest wall compliance may alter the normal mechanical response of the respiratory system during exercise, increase the work and O_2 cost of breathing, increase the perception of breathlessness, and curtail exercise performance in otherwise healthy pregnant women. For example, without bronchodilation, pregnancy-induced reductions in resting EELV may increase the degree of expiratory flow limitation during exhaustive exercise, since V_T is positioned closer to residual volume where the capacity of the respiratory system to generate flow is constrained. Given this scenario, it is possible that expiratory flow limitation could lead to dynamic hyperinflation (i.e., progressive increase in EELV during exercise), which would eventually constrain V_T expansion despite progressive increases in central respiratory motor output command, and increase the elastic work of breathing. Such alterations in operating lung volumes could have negative sensory consequences at higher levels of V_E during maternal exercise.

As previously discussed, however, neither pregnancy nor advancing gestation are associated with increased exertional respiratory discomfort (Ohtake and Wolfe 1998; Jensen et al. 2006*b*) or reduced aerobic working capacity (Sady et al. 1989, 1990; Lotgering et al. 1991, 1998; McMurray et al. 1991; Jaque-Fortunato et al. 1996; Spinnewijn et al. 1996; Heenan et al. 2001; Jensen et al. 2006*b*). We postulate that mechanical adaptations of the respiratory system, including recruitment of resting and dynamic inspiratory capacity and reduced airway resistance (or bronchodilation), may account for the lack of anticipated increase in exertional breathlessness and decrease in aerobic working capacity by minimizing expiratory flow limitation and preventing both dynamic hyperinflation and neuromechanical uncoupling of the respiratory system during exhaustive weight-supported exercise in human pregnancy (Jensen et al. 2006*a*, 2006*b*). These mechanical adaptations would also be expected to help preserve cardiopulmonary interactions during exercise and allow healthy pregnant women to achieve the same absolute maximal (or peak) $V\!O_2$ as their non-pregnant counterparts. We suggest, therefore, that the increased perception of breathlessness experienced by many healthy pregnant women during activities of daily living reflects the normal awareness of increased central respiratory motor output command and not derangement (or maladaptation) of ventilatory mechanics. These hypotheses are currently being tested in our laboratory.

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