The respiratory response to pregnancy

J. A. MILNE
M.A., M.B., Ch.B., M.R.C.O.G.

Department of Obstetrics and Gynaecology, University of Cambridge

Summary

The respiratory response to pregnancy appears to be largely mediated by the action of progesterone and, perhaps to a lesser extent, oestrogens, at least in the first and second trimesters. The mechanical effects of the gravid uterus cause relatively little change in pulmonary mechanics, although finer changes in airways function require further investigation.

Dyspnoea during pregnancy is also probably hormone-mediated but the exact temporal relationship between hormone status, functional change and the development of symptoms is not yet clearly defined.

Introduction

The specialized changes in physiological function during normal pregnancy have aroused much interest and research, primarily on the organs of reproduction but also on several other organs and systems. Although some of these changes are well documented (Hyttten and Leitch, 1971), this is not so of respiratory function in normal pregnancy (Woolcock and Read, 1972).

Many previous studies have employed measurement techniques with poor reproducibility and have studied small numbers of subjects at infrequent intervals throughout pregnancy. An attempt is now made to review what is known about changes in respiratory function during normal pregnancy, particularly in relation to the occurrence of dyspnoea and also the possible aetiological role of progesterone and oestrogens in these changes.

The role of the sex hormones in respiration

Progesterogens

It was the demonstration of hyperventilation very early in gestation that first suggested that hormonal rather than mechanical factors might be involved (Hassellbach and Gammeltoft, 1915). Since that study, much evidence has accumulated to suggest that progesterone is responsible. It has been shown that ventilation is significantly greater in the luteal phase of the ovulatory cycle than the oestrogen-dominated follicular phase (England and Fahri, 1976; Milne, Pack and Coutts, 1977d), Fig. 1).

Furthermore, subjects taking an oral contraceptive preparation containing the progestogen, norethisterone, have a significantly greater minute ventilation than normal ovulatory subjects at all stages of their cycles, apart from late in the luteal phase (Fig. 1). This would seem to add weight to the case for a progestogen effect, although Tyler (1960) was unable to demonstrate a respiratory stimulant effect when norethisterone was administered parenterally to hypercapnic emphysematous subjects. When progesterone itself was substituted, however, ventilation increased.

This latter finding is well known because administration of progesterone to volunteers, both male and female (Goodland et al., 1953) and to patients with chronic hypercapnic states (Lyons and Huang, 1968; Tyler, 1960) consistently increases ventilation and lowers alveolar carbon dioxide tension ($P_{A,CO_2}$).

Progesterone probably exerts its effect on ventilation by increasing the sensitivity of the respiratory centre to changes in $P_{CO_2}$ (Lyons and Antonio, 1959).
Oestrogens

The effect of the oestrogens on the respiratory system is less well defined, although Goodland et al. (1953) have demonstrated in males that simultaneous administration of oestradiol can prolong, although not enhance, the hyperventilation caused by progesterone.

With respect to gas transfer across the alveolar-capillary membrane, Pecora, Putnam and Baum (1963) demonstrated a fall in pulmonary transfer factor (Tlco) for carbon monoxide after intravenous administration of the equine oestrogen, Premarin, to volunteers. It was postulated that this was caused by an increase in acid mucopolysaccharides in the alveolar-capillary membrane and thus an increased diffusion path. While there is also evidence of a fall in transfer factor during pregnancy, as will be discussed later, its relationship to oestrogen status is not so obvious (Milne et al., 1977a).

In the light of this background knowledge of the role of the sex hormones in respiration, the respiratory function changes during normal pregnancy will now be discussed.

Ventilation and gas exchange

Resting ventilation

There is almost universal agreement that a significant increase in resting minute ventilation takes place from very early on in pregnancy (Bonica, 1973). There is, however, considerable disagreement as to the time-course and, to a lesser extent, the magnitude of this increase. This results from lack of attention to attaining basal measurement conditions in many earlier studies (Plass and Oberst, 1938; Widlund, 1945) and to conclusions being drawn from the mean values of widely scattered results on small numbers of subjects (e.g. Pernoll et al., 1975).

Previous studies have either shown a linear increase (of up to 40%) in ventilation and a consequent fall in PA,CO₂ throughout pregnancy (Widlund, 1945; Cugell et al., 1953; Knutten and Emerson, 1974; Pernoll et al., 1975) or a significant change in the first trimester which is maintained but not increased as pregnancy progresses (Bonica, 1973; Templeton and Kelman, 1976; Guzman and Caplan, 1974; Milne et al., 1977b; Alaily and Carrol, 1978). In the Glasgow study of 31 subjects, a mean increase of 24% was demonstrated in resting minute ventilation (Fig. 2). This was established before the end of the first trimester but did not increase throughout pregnancy. This trend was mirrored by the fall in capillary PCO₂ (Fig. 2).

Most authors, however, seem agreed that the increase in ventilation is mediated by a raised tidal volume, respiratory frequency remaining constant (Bonica, 1973).

It may be that the failure of ventilation to increase after the first trimester can be explained in terms of the maternal respiratory response anticipating the ventilatory demands which later gestation will bring.

Gas transfer

In view of the increased volume of gas flowing in and out of the lungs during pregnancy, it is of interest now to consider how this is reflected in terms of gas transfer across the alveolar-capillary membrane.

While it is the transfer (or diffusion) of oxygen which is of concern during pregnancy, this process is relatively slow and its direct measurement is technically difficult. Carbon monoxide (CO) on the other hand, diffuses more easily, binds preferentially with haemoglobin, and its diffusing capacity can be readily measured (Ogilvie et al., 1957). Any measurable decrease in carbon monoxide diffusing capacity will certainly indicate impairment of oxygen transfer.

There have been very few studies of pulmonary transfer factor (Tl) in normal pregnancy. Krumholz, Echt and Ross (1964) measured Tl twice, at 14 and 27 weeks' gestation, and found no difference. However, no post-partum measurements were made. Similarly, Gazioglu et al. (1970) found no significant change in Tl at 10, 24 and 36 weeks' gestation, the values being no different from those obtained post partum. Lehmann (1975) also made serial observation of Tl in 23 subjects and was the first to suggest that this parameter fell during pregnancy. Milne et al. (1977a) measured Tl serially in 57 subjects and found
that it decreased significantly from the first trimester until around 27 weeks' gestation with no further fall thereafter (Fig. 3). Interestingly, Tl had not even returned to its first trimester level 12 months post partum. Unlike Pecora et al. (1963), these workers were unable directly to correlate the fall in Tl with oestrogen status.

In summary, it seems that the increase in ventilation during pregnancy may be offset to some extent by decreased efficiency of gas transfer, although the exact temporal relationship between the two require further investigation.

**Pulmonary mechanics**

Instinctively, this is the aspect of pulmonary function most obstetricians expect to be altered by the enlarging gravid uterus.

**Static lung volumes**

There is a plethora of data on this topic stretching from the middle of the nineteenth century to the present day. This is summarized by Woolcock and Read (1972) and more recently by Alaily and Carrol (1978).

The end expiratory volume, functional residual capacity (FRC) and the irreducible residual volume (RV) have consistently been shown to decrease steadily from early in gestation. Figure 4 shows the results of a recent serial study of 61 subjects. A mean decrease in FRC of 0.6 l was demonstrated between

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**Fig. 3.** Pulmonary transfer factor during normal pregnancy and post partum. Mean values for 57 subjects.
- - Corrected for Hb and alveolar volume; ---- observed values; T = term; PP = post partum.

**Fig. 4.** Static lung volumes during normal pregnancy and post partum. Mean values (No. = 61).
- - Total lung capacity; O----O vital capacity; ▲----▲ functional residual capacity; ▲----▲ residual volume; bar = s.e. mean.
the first trimester and term which agrees well in time-
course and magnitude with that shown by Alail and
Carrol (1978) in their study of 38 subjects. Residual
volume showed a mean decrease of almost 0·4
litre, also starting from early pregnancy.

Although not a primary lung volume, vital
capacity (VC) has been the parameter of pulmonary
function most frequently measured during preg-
nancy and, despite the deficiency of many previous
studies, which have variously demonstrated an
increase, decrease and no change, it seems unlikely
that there is any significant alteration in this para-
meter throughout pregnancy. Alail and Carrol
(1978) showed no alteration in their study of 38
subjects and the author's own results are in agree-
ment with these (Fig. 4). Similarly, total lung capacity
(TLC) remained virtually unaltered.

It is likely that the tendency of the raised dia-
phragm to reduce TLC is offset by an increase in the
antero-posterior and transverse diameters of the
chest (Bonica, 1973).

Large airways function

A reduction in resting lung volumes such as occurs
during pregnancy will tend to increase the flow
resistance of the airways (Briscoe and Du Bois,
1958). Similarly, it has been shown that reduction in
$P_{A}CO_{2}$, such as occurs in pregnancy, leads to an
increase in airways resistance (Newhouse et al.,
1964). Opposing this, the possible direct action of
progesterone as a bronchodilator during pregnancy
should be considered, for this hormone is known to
increase β-adrenergic activity (Raz, Zeigler and

Furthermore, the possibility of an effect of the
prostaglandins (PGE$_2$, PGF$_{2a}$) or their metabo-
listes on airways calibre during pregnancy should be
considered in view of their known bronchodilator (E$_2$) and
bronchoconstrictor (F$_{2a}$) properties (Fanburg, 1973).

Whenever airways function has been assessed
during pregnancy by forced spirometry, no change in
function has been noted (e.g. Cameron, Bain and
Grant, 1970; Sims, Chamberlain and de Swiet, 1976;
Milne et al., 1977c). However, there is disagreement


table 1. Large airways function during normal pregnancy and post partum.

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Post partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>$sGaw$ (kPa·sec·l$^{-1}$)</td>
<td>1·84</td>
</tr>
<tr>
<td>FEF$_{25}$ (litres)</td>
<td>3·12</td>
</tr>
<tr>
<td>FEF$_{25}$/FVC (per cent)</td>
<td>84·0</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>30</td>
</tr>
</tbody>
</table>

Paired t-tests: in all cases $P < 0·1$.

Key: $sGaw$ = Specific conductance;
FEF$_{25}$ = Forced expiratory volume in 1 sec;
FVC = Forced vital capacity.

Table 1. Large airways function during normal pregnancy and post partum.

as to what happens to airways resistance ($R_{aw}$)
measured during quiet respiration. This has variably
been shown to increase, decrease or remain un-
changed during pregnancy. It appears that poor
measurement techniques and the failure to normalize
for changes in lung volume have both contributed to
the conflicting results.

The advent of body plethysmography has greatly
improved matters and using this method in a recent
study, 30 subjects have had specific conductance
($sGaw$), the reciprocal of airways resistance
normalized for lung volume change, measured serially
throughout pregnancy (Table 1). No significant
change was demonstrated (Milne et al., 1977c). As
with other studies, no significant change was shown
in forced expiratory volumes. It would seem likely,
however, as discussed earlier, that the constancy of
large airways function in pregnancy is a balance
between factors tending to increase and those tend-
ing to decrease airways resistance.

Small airways function

Obstruction to airflow in the tracheo-bronchial
tree was considered for long to be a simple phenome-
on easily investigated by the techniques described
earlier. However, recent work has shown that air-
ways resistance may be partitioned into that offered
by airways greater than 2 mm in diameter (90% of
the total) and that offered by those less than 2
mm in diameter (Macklem and Mead, 1967). Thus,
there may be extensive disease or dysfunction of
these smaller airways before it becomes detectable
by the standard methods for assessment of
airways function (Hogg, Macklem and Thurlbeck,
1968). Levine et al. (1970) have demonstrated that
such small airways dysfunction may lead to measur-
able abnormalities of gas exchange.

It is now possible to investigate the function of
these peripheral airways with the use of measure-
ments such as 'closing volume', the lung volume at
which the dependent lung zones cease to ventilate
owing to small airway closure.

Using the single breath nitrogen technique
(Anthonisen et al., 1969), there have been a limited
number of attempts to measure closing volume (CV) in pregnancy. Unfortunately, most studies have in some way been deficient owing to the many factors which influence its determination, e.g. posture, influence of smoking, standardization of the expiratory manoeuvre.

Bevan et al. (1974) measured CV once between 36 weeks and term and found that in 50% of their subjects, airways closure occurred during normal tidal ventilation (i.e. above FRC). They suggested that this might lead to impairment of gas exchange in pregnancy although no post-partum measurements were made. Garrard, Littler and Redman (1978) found a linear increase in CV during pregnancy, although by stating that their subjects found difficulty with measurement of vital capacity (VC), the reliability of these findings must be in question.

Craig and Toole (1975) and Baldwin et al. (1977), however, found that the point of airways closure was unaltered in pregnancy. There remains a need, therefore, for more detailed investigation of this potentially interesting area of lung function during normal pregnancy.

Dyspnoea during normal pregnancy

It is well known that a significant number of healthy pregnant women complain of dyspnoea at some stage during pregnancy (Thomson and Cohen, 1938; Cugell et al., 1953). The incidence and time-course of the symptom have been documented in a recent study (Milne, Howie and Pack, 1978), (Fig. 5). This showed that almost 50% of subjects complained of dyspnoea before 20 weeks’ gestation. Findings such as these have suggested a hormonal rather than a mechanical aetiology for the symptom, although direct evidence for this is scanty. However, in relation to the previously discussed role of progesterone in modifying the respiratory response to changes in $P_{CO_2}$, Gilbert and Auchincloss (1966) showed that dyspnoeic pregnant subjects were more sensitive to changes in $P_{CO_2}$ than non-dyspnoeic subjects and that they exhibited an inappropriately great ventilatory response which may be experienced as dyspnoea.

These authors also showed that pregnant dyspnoeic subjects had a greater difference between their pregnant and non-pregnant $P_{CO_2}$ levels than did those with no symptoms.

Another theory has been put forward by Lehmann (1975) who suggested that hyperventilation in pregnancy is a secondary response to an oestrogen-mediated fall in gas transfer. He demonstrated that dyspnoeic subjects tended to have lower $T_l$ values in pregnancy than did non-dyspnoeic subjects and postulated that this may in part be responsible for the symptom.

While the exact aetiological mechanism and the temporal relationship of functional change to the development of symptoms still remain to be clarified, there is growing evidence that dyspnoea during pregnancy is in some way related to the individual's adaptation to the inevitable hyperventilation which accompanies the gravid state. It is unlikely that mechanical factors are involved, certainly in the first and second trimesters.

![Fig. 5. Incidence, time-course and severity of dyspnoea during normal pregnancy (No. = 62). NP = not pregnant; T = term.](http://pmj.bmj.com/)

Grade 1 $\square$ = dyspnoea present on climbing hills or more than one flight of stairs;
Grade 2 $\square\square$ = dyspnoea present: (a) on climbing one flight of stairs; (b) walking at an even pace on level ground; (c) during routine performance of housework;
Grade 3 $\square\square\square$ = dyspnoea on slightest exertion or at rest.
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