Respiratory and Acid-Base Changes During Pregnancy

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MUCH of our knowledge of respiratory and acid-base changes in pregnancy stems from studies made more than ten years ago and even that material is limited and incomplete. This is surprising when one considers that pregnancy constitutes one of the most severe states of physiologic adaptation. Incongruously, the effect upon lung function of a number of exceedingly rare diseases has been studied exhaustively from every aspect, and by the most modern techniques, whereas the effect of pregnancy, where we are confronted with an ever-growing and inexhaustible supply of clinical material, has been explored so incompletely. Actually, more attention has been paid to states of pathologic stress upon pregnancy such as heart disease, tuberculosis and following chest surgery than to the physiologic norm.

Pregnancy would seem to be an ideal condition in which to study the effects of abdominal distention upon mechanics of breathing. Nevertheless, alterations of abdominal and intrathoracic pressures have not been measured, nor are there data on airway resistance, compliance of the lungs, or the mechanical work of breathing. The effect of hypervolemia upon pulmonary capillary blood volume and the diffusing capacity of the lung membrane also remains unexplored. The striking alterations in the control of respiration during pregnancy have received scant attention since Hasselbalch's fundamental work, and much has to be inferred from a few experimental pharmacologic studies. Indeed, several recent reviews on the control of respiraiton do not even mention hormonal influences.

In this review an attempt will be made to correlate available data on normal pregnancy. Whenever possible, these findings will be compared to other conditions or pathologic states to facilitate a discussion of mechanisms and to lend some perspective to the observed alterations.

Lung Volumes

In 1831, Velpeau [1] stated in his treatise on midwifery, "The diaphragm itself being pushed upward into the thorax, whose base it enlarges, while its vertical diameter is lessened, is in some degree hindered from executing its contractile movement." He suggested that the growing abdominal contents interfered not only with diaphragmatic movement but also caused a reduction in the size of the thoracic content. Early measurements of lung volumes during pregnancy were limited to the vital capacity which was found unaltered,[2-4] increased [5, 6] or decreased.[7, 8] Alterations were always small, however, and in any given series there were variations both in the size and direction of the changes. In a careful study, Thompson and Cohen [5] noted a tendency towards an increase in vital capacity in 31 pregnant women compared to 9 controls.

Bittdorf and Forschbach [7] were the first to measure the residual volume by an open-circuit, hydrogen technique. Since then there have been few references to the lung volume profile in pregnancy [6, 7, 9] and serial observations were not made until 1953.[10]

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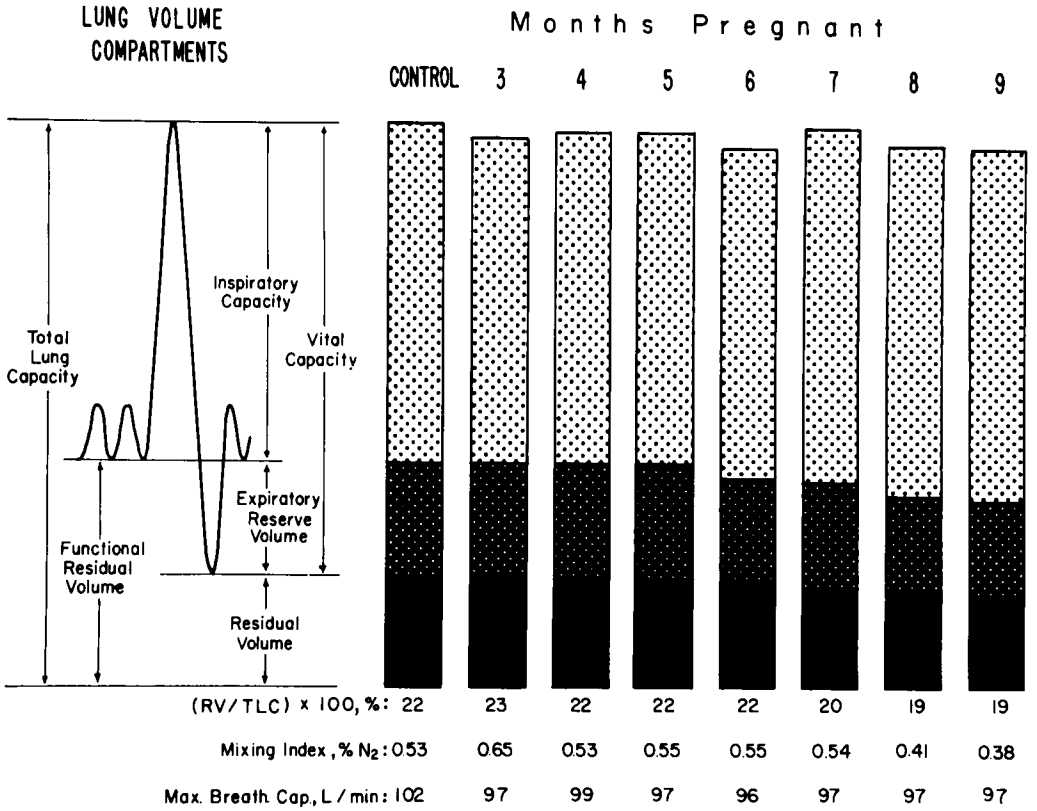

FIG. 1. Serial measurements of lung volume compartments, pulmonary mixing indices and maximal breathing capacities during normal pregnancy. Control values were obtained from the same women 4 to 9 months postpartum. Mean values for 9 subjects from data of Cugell *et al.*[10]

Progressive changes in the lung volume profile of 9 healthy women studied in our laboratory are shown in figure 1. Baseline measurements were obtained four to nine months postpartum when, it was assumed, normalcy had been restored. Significant alterations are not observed until the fifth to sixth months. Thenceforth, there is a progressive decrease of both the expiratory reserve volume (E.R.V.) and the residual volume (R.V.). At term, the sum of these two volumes, which is the functional residual capacity (F.R.C.), is decreased some 17 per cent. However, there is a concomitant increase of the inspiratory capacity (I.C.) with the result that the vital capacity (V.C.) and the total lung capacity (T.L.C.) remain unaltered. Due to the progressive diminution of the R.V., in the face of an unchanging T.L.C., the ratio R.V./T.L.C. diminishes during the last trimester.

It is quite apparent that the only significant change in the lung volume profile is a reduction of the F.R.C., or the position at which the lungs and surrounding structures come to rest at the end of a quiet expiration. This position is determined by an equilibrium between two opposing elastic forces, the recoil of the lungs tending to reduce the F.R.C., and the outward and downward pull of the thoracic cage and abdominal contents which tend to increase the F.R.C. Important changes of the F.R.C. are usually associated with pathologic conditions of the lungs. For example, the resting position is increased by diminished lung recoil, as with emphysema, or it may be decreased, as with lung fibrosis. However, the F.R.C. may be significantly altered by changed elastic recoil of the parietes even though the lungs are anatomically normal. The effects of a number of such conditions are compared in figure 2. The increased intra-abdominal pres-

sure of pneumoperitoneum has the same effect upon the lungs as does pregnancy.[11] The downward pull of the diaphragm is diminished, the intrapleural pressure becomes less negative and the resting lung volume is reduced. Yet, in both conditions the lungs are normal and the range of motion of the diaphragmatic and thoracic musculature is unimpaired. Hence the total lung capacity remains unchanged. A similar reduction of the downward pull of the diaphragm can also be achieved by assuming the supine position.[12] In all three conditions "lung tension" is relaxed which has been shown to favor healing of tuberculous cavities. It is of historical interest that, because of this, both the recumbent position and pneumoperitoneum have been used to treat this disease; and the tendency towards healing of lesions during pregnancy has been attributed, in part, to a degree of "collapse" or reduction of F.R.C. Conversely, the commonly observed breakdown of tuberculosis after delivery has been thought to result partly from the increase of the resting lung volume; therefore pneumoperitoneum has been used immediately postpartum to prevent this sudden lung distension.[11]

Figure 2 depicts other conditions which may affect the tension equilibrium between lungs and parietes. Abdominal binding increases the intra-abdominal pressure but limits, to some extent, the range of motion of the inspiratory musculature. The net effect is a reduction of both the F.R.C. and the I.C.[13] Severe obesity largely causes a decreased mobility of the thoracic cage and diaphragm.[14] Hence the F.R.C. is not greatly affected but the inspiratory capacity is markedly diminished. In this respect the effect is similar to that of kyphoscoliosis.[15]

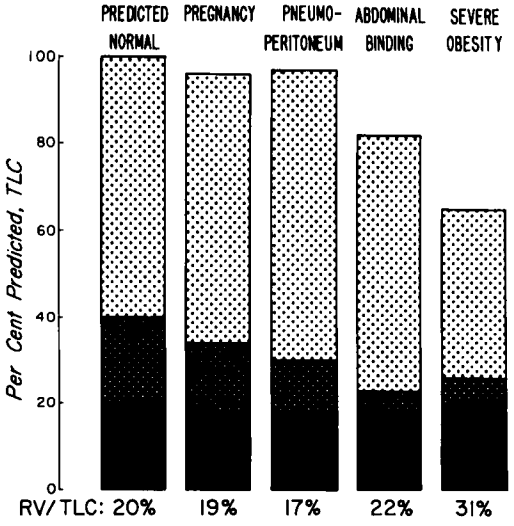

FIG. 2. The effect upon lung volume compartments of various conditions causing increased intra-abdominal pressure. Data for "pregnancy" are those at 9 months from figure 1; "pneumoperitoneum" from 5 women of Patton *et al.*[11]; "abdominal binding" from 3 cases of Caro *et al.*[13]; and "severe obesity" from 17 cases of Hackney *et al.*[14] The code is the same as that in figure 1.

Dynamics of Breathing

The performance of the respiratory pump is related to the effectiveness and coordination of the muscles of respiration and to the resistances imposed by the airways and tissues and the elastic structures of the lungs and parietes. The maximal breathing capacity (M.B.C.) is a good test of the overall performance of this pump and affords some information as to its reserve capacity. However, the value of the M.B.C. depends upon technical details and is subject to variations in individual motivation. During the early months of pregnancy, morning sickness and nausea may interfere with maximal effort, and voluntary hyperventilation may produce a more profound alkalosis in pregnancy than in normal controls thereby interfering with performance. Further, this test, like all others requiring maximal voluntary participation, is useless in the immediate postpartum period.

Rubin, Russo and Goucher[16] found the M.B.C. increased during pregnancy compared to 7 to 14 weeks postpartum; Cugell *et al.*[10] found virtually no change (fig. 1); and Ihrman[17] found a lower value in 50 pregnant women than in nonpregnant controls. The latter maintained that his nonpregnant control subjects were better motivated and more enthusiastic than the pregnant group and suggested that the M.B.C. was a poor test during pregnancy. Nevertheless, serial changes of the M.B.C. have been exceedingly small (fig. 1) and certainly do not suggest that either muscular efficiency or resistance to breathing is importantly altered. Perhaps a better index of the function of the respiratory pump is the timed vital capacity volume ($F.E.V._1$), or that

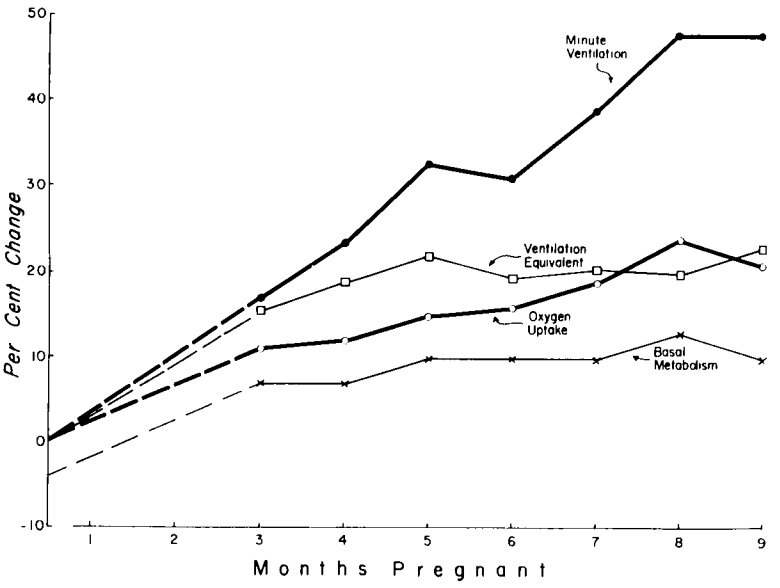

FIG. 3. Per cent changes of minute ventilation, oxygen uptake, basal metabolism and the ventilation equivalent for oxygen at monthly intervals throughout pregnancy. The subjects are the same as those in figure 1.

portion of a rapidly delivered V.C. which can be exhaled during the first second. Here again serial studies showed very little change, but in many individuals the usually excellent correlation between F.E.V.$_1$ and M.B.C. did not hold which again suggests that the M.B.C. may have been encumbered by less-than-optimal effort.[10]

Relatively little is known concerning details of mechanics of breathing. A single study of total lung resistance unfortunately made use of the somewhat unpredictable technique of Vuilleumier but it suggested that, in 8 women, resistance was somewhat lower during, than 2 to 3 months after, pregnancy.[16] It was speculated that this may have been due to the action of corticosteroids and relaxin upon the smooth musculature of the airways which runs counter to the fact that asthmatics find little relief during pregnancy.[18] At any rate, these findings, together with the unchanged M.B.C. and F.E.V.$_1$ suggest that an increase of the airway resistance, usually associated with diminution of the F.R.C.,[19] does not occur during pregnancy. Diaphagmatic motion is not diminished by the full-term uterus and, if anything, excursions may be larger than in the postpartum period.[20] The oxygen cost of breathing is considerably higher than during the nonpregnant state.[21]

Ventilation and Metabolism

In 1904 Magnus-Levy[22] observed an increase in resting ventilation ($\dot{V}_E$) during pregnancy. Soon thereafter, Zuntz[23] found this value, and the oxygen uptake ($\dot{V}_{O_2}$), considerably larger during pregnancy than postpartum and suggested that this was a "specific reaction of pregnancy." Hasselbalch[6] noted that these changes were accompanied by a decreased alveolar carbon dioxide tension ($P_{A_{CO_2}}$) and suggested that was due to an increased irritability of the respiratory center.

The increase in minute ventilation at rest constitutes one of the earliest and most obvious respiratory changes of pregnancy and has been confirmed by numerous investigators. The sequential changes of $\dot{V}_E$, $\dot{V}_{O_2}$ and basal metabolic rate (BMR) are shown in figure 3. Increments of ventilation exceed those of $\dot{V}_{O_2}$ and BMR throughout gestation. At term $\dot{V}_E$ is 48 per cent above normal, $\dot{V}_{O_2}$ is increased 21 per cent and BMR only 14 per cent. The ventilation equivalent for oxygen (the ventilation in liters required for each 100 ml. of $\dot{V}_{O_2}$) is thus persistently raised.[10]

The hyperventilation of pregnancy has been attributed to increasing abdominal girth with upward displacement of the diaphragm, to changes in lung volumes, to hypervolemia and

increased cardiac output and to increasing O_2 demand of the fetus. However, an increase of as much as 20 per cent of $\dot{V}_E$ has been noted as early as the third month [10, 24–26] before any of the above changes have occurred and at a time when the fetus is of microscopic size. A slight increase in $\dot{V}_{O_2}$ at this time (fig. 3) may well be related to the work of hyperventilation.[21]

The usual causes of hyperventilation associated with lung disease are absent in pregnancy. There is no enlargement of either anatomic or physiologic deadspace. In fact, the effect of the anatomic deadspace tends to be reduced because the F.R.C. is reduced and because minute ventilation is augmented by tidal volume rather than rate. Nor is there any evidence to suggest uneven distribution of inspired gas. Figure 1 shows, on the contrary, that pulmonary washout, as reflected by the "mixing index," is actually accelerated with hyperventilation. The diffusing capacity of the lung is unaltered [27] and arterial O_2 tension and saturation tend to be increased, rather than decreased.[28] Even during later pregnancy the increased abdominal pressure cannot be responsible for hyperventilation because this does not occur with pneumoperitoneum, which produces identical changes.[11] With these facts in mind, attention as to the cause of hyperventilation must be diverted to factors outside of the cardiopulmonary apparatus.

Hormones and Respiration

Ovarian Hormones. Much attention has been paid to a possible humoral factor being responsible for the hyperventilation of pregnancy. The first clue came from Hasselbalch and Gammeltoft [29] who found a decrease in $P_{A_{CO_2}}$ not only during pregnancy but also during the luteal phase of the menstrual cycle. This observation provided a link between endocrine changes of menstruation and of pregnancy. These findings were confirmed by others who showed that the cyclic variations of the $P_{A_{CO_2}}$ disappeared with menopause.[30, 31] Subsequent workers attempted to associate these respiratory changes with specific hormones.

Following conception, excretion of estriol, estrone, estradiol and pregnanediol increases rapidly during the first half of gestation, then rises more slowly until parturition and falls off abruptly after delivery.[32] The stimulus for this secretion is mediated through the pituitary.

The effects on respiration of progesterone, the hormone of the luteal phase of the menstrual cycle, have been studied extensively. There is no question that it acts as a mild respiratory stimulant. Heerhaber *et al.*[33] compared its effect to that of other hormones in 5 men and 1 postmenopausal woman. A maximum response was noted 24 hours after injection when the $P_{A_{CO_2}}$ was decreased by 4 mm. of mercury which corresponded to a 10 per cent increase of $\dot{V}_E$. Lyons and Antonio [34] studied the effects of progesterone in normal individuals and found a decrease of $P_{A_{CO_2}}$ as early as 3 hours after administration. This action of progesterone on respiration has been confirmed by several investigators and has been demonstrated as well in patients with emphysema and CO_2 retention.

Progesterone administration was not associated with a demonstrable increase of BMR and it could not be reproduced by injection of testosterone, corticosterone, estradiol or gonadotropic hormone.[33] Progesterone causes a rise in basal temperature much like the rise which occurs following ovulation. It has been thought that this may lead to hyperventilation, but Döring *et al.*[35] found little change in ventilation after the administration of pyrogens. An occasional rise in BMR with progesterone has been attributed to its catabolic action [36] but this is not large enough to explain the respiratory changes. Estrogens also act by stimulating growth and energy build-up in specific end organs [37] and thus, like progesterone, may have a direct action on ventilation by raising the BMR.[38]

Heerhaber [39] demonstrated changes in CO_2 sensitivity during the luteal phase of the menstrual cycle. Examining 6 women through repeated cycles she showed both a lowered threshold of the respiratory center for CO_2 and an increase in the steepness of the slope. The latter has been termed "increased irritability" of the center. Identical changes of decreased threshold and increased irritability have been demonstrated following progesterone administration. Döring, Loeschcke and Ochwadt [35] studied CO_2 response curves in

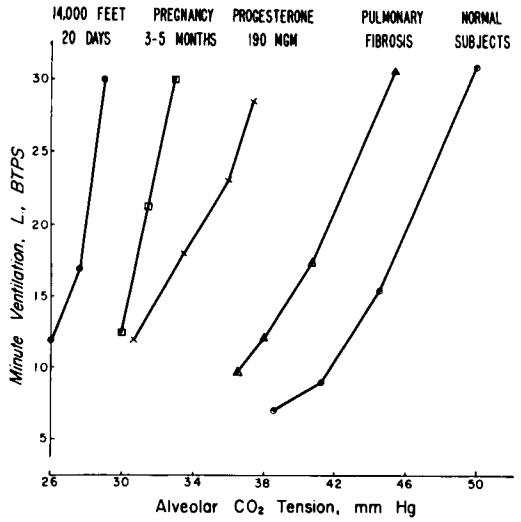

FIG. 4. Carbon dioxide sensitivity curves in various conditions associated with hyperventilation. Normal values are from 33 subjects of Lambertsen [41]; "pulmonary fibrosis" from 3 cases of Lindgren *et al.*[43]; the "progesterone" study is from one case of Wilbrand [40]; "pregnancy" represents average values 17 women of Lyons and Antonio [34]; and the high altitude studies show average values of 3 subjects studied by Kellogg.[42]

5 subjects before and after administration of progesterone, of estrogen or of both hormones together. They found that the changes produced by progesterone were prolonged, if not increased, by the simultaneous administration of estrogen. This suggested that the major action of progesterone is to decrease the threshold of the respiratory center while estrogens may increase its irritability.[40] The effect of both drugs appeared to be additive. Whatever the mode of action of these hormones, the effects on respiration of the latter half of the menstrual cycle, of pregnancy and of progestrone administration are the same.

Carbon dioxide sensitivity curves in a number of different conditions are illustrated in figure 4. For orientation, an average normal curve is shown of 33 young men of Lambertsen.[41] In these individuals the initial $P_{A_{CO_2}}$ averaged 38 mm. of mercury and the slope indicates an increase of about 1.5 liters/minute of ventilation per 1 mm. of mercury rise of $P_{A_{CO_2}}$. As can be seen, all the illustrated conditions including high altitude,[42] pregnancy,[34] progesterone effect,[40] and the "alveolar-capillary block" syndrome,[43] are associated with a decreased threshold to CO_2, as indicated by a shift to the left of the curves. In two types of hyperventilation, one endocrine stimulated (progesterone) and the other probably largely stimulated by hypoxemia (pulmonary fibrosis), the slopes of the curves, and hence the "irritability," are normal. In pregnancy, however, the data of Lyons and Antonio,[34] much as the German studies, show a much steeper slope with a rise of 6 liters/minute, instead of the normal 1.5 liters/minute, for each 1 mm. of mercury rise of $P_{A_{CO_2}}$. This slope is similar to that observed by Kellogg [42] in normal men acclimatized for 20 days to an altitude of 14,000 ft.

These changes in position and slope are probably related to the concomitant alterations of acid-base balance which will be dealt with elsewhere.

Basal Metabolism and Thyroid Hormone. An increase in metabolic rate during pregnancy was noted in 1897 by Magnus-Levy [44] and has been confirmed by many subsequent investigators.[10, 24, 45, 46] The BMR may be elevated as early as the sixth week and certainly by the twelfth to eighteenth week (fig. 3). Increased thyroid activity increases the O_2 requirement of the organism and consequently the ventilatory requirement. During pregnancy there are striking biochemical abnormalities of thyroid function. A high serum protein-bound iodine and increased ^{131}I uptake,[47] a high rate of conversion of iodide to thyroxine,[48] and the occasional appearance of a goiter may all indicate thyroid overactivity. However, despite these, the peripheral utilization of thyroxin is diminished,[49] the half-life of thyroxin is prolonged some 50 per cent, and the amount of free thyroxin is diminished.[50] In addition, hyperthyroidism is often ameliorated during pregnancy.[51] These paradoxical changes are attributed to increased thyroxin binding which occurs after the natural or artificial adminstration of estrogens irrespective of the level of thyroid activity.[51]

These changes in thyroid activity occur early in pregnancy without demonstrably affecting basal metabolism. Therefore thyroid hormone probably plays little part in altering the respiration in pregnancy. It has been suggested that when the surface area of the fetus is taken into account there is, in fact, no increase in maternal BMR.[49]

Adreno-corticosteroids. Plasma 17-hydroxycorticosteroids are raised early in pregnancy and achieve a roughly linear increase with the duration of gestation.[52] During later pregnancy steroid production is 2 [53] to 4 times normal.[52] The mode of action of these hormones upon normal respiration is unknown. The 17-hydroxycorticosteroids are catabolic in action and may increment the need for O_2, though this effect is not demonstrable in early pregnancy. When alterations in lung volumes occur late in pregnancy, the adrenocorticosteroids may play a part in altering the mechanics of breathing.

Acid-Base Changes

The term "acidosis of pregnancy" was introduced by Hasselbalch and Gammeltoft [29] when *p*H, measured by the iso-P_{CO_2} titration technique, was found lower in pregnant women than in nonpregnant controls. This seemed to confirm an earlier observation by Zangemeister [54] who showed that the total blood alkalinity was reduced. It also lent support to Leimdorfer's [55] suggestion that increased lactic acid production may play a part in the control of respiration in pregnancy.

Subsequent workers continued their search for an acid factor in pregnancy because of the propensity for pregnant women to develop ketosis and for pre-existent diabetes mellitus to worsen during pregnancy. Proponents for the acid theory were encouraged by the findings of Schultze [56] and of Bokelmann [57] of raised lactic acid levels during labor, and by Loeser [58] who found an increased placental lactic acid production in experimental animals. However, doubt as to this theory was expressed by Seidentoff and Eissner [59] and by Behrendt *et al.*,[60] who found the lactic acid content to be low during pregnancy. In a careful analysis, Samueloff *et al.*[61] could find no evidence for the accumulation of fixed acid during pregnancy except during labor.

A drop in the plasma bicarbonate was often observed [59, 60, 62-65] but the *p*H was usually normal or alkaline. In addition, a fall in the total plasma cation content was noted.[60] These findings led Austin and Cullen [63] to state, "The rise in *p*H would indicate a tendency to increased pulmonary ventilation late in pregnancy and the slight lowering of the bicarbonate may well be considered, therefore, a secondary effect of hyperventilation rather than a true acidosis." Undoubtedly, much of the early confusion can be attributed to the study of venous blood and to lack of precise methods for determination of *p*H.

It is now generally accepted that the changes in acid-base metabolism observed during pregnancy result from hormone-stimulated hyperventilation. The probable sequence of events is as follows: The increase in tidal volume causes a drop in the $P_{A_{CO_2}}$ with a transient respiratory alkalosis. This in turn is compensated for by a lowering of the plasma bicarbonate concentration causing the *p*H to readjust to normal levels. The net result of the primary respiratory and secondary renal mechanisms is a lowering of both the total acid and the total base by some 5.0 mEq./liter.[65] Renal excretion of bicarbonate compensates for the lowered P_{CO_2} and does not appear to be affected by changes in *p*H [66] or plasma bicarbonate.[67]

Döring and his co-workers demonstrated beautifully that the changes in acid-base metabolism begin immediately after conception. They are, in fact, related to a continuation of the luteal phase of the menstrual cycle. Figure 5 shows serial changes in one woman studied almost daily for several months prior to conception, during pregnancy and for 18 months thereafter. This figure is a composite of data published in two different papers.[68, 69] Alveolar CO_2 tension drops rapidly after ovulation and remains low throughout the gestational period. This is accompanied by a slower drop in the buffering capacity of the blood, the arterial *p*H remaining unchanged. When the menstrual cycles resume some months later, the fluctuations in $P_{A_{CO_2}}$ mark the two phases, follicular and luteal, and fluctuations in body temperature move in the opposite direction of $P_{A_{CO_2}}$.

Much confusion in the literature concerning the term "alkali-reserve" prompted Prystowsky *et al.*[70] to reassess this value using the strict definition of "the total CO_2 concentration of the blood plasma at a CO_2 tension of 40 mm. Hg with the blood fully oxygenated." With these criteria, comparison between pregnant and nonpregnant subjects could be made. Both the bicarbonate and total CO_2 contents

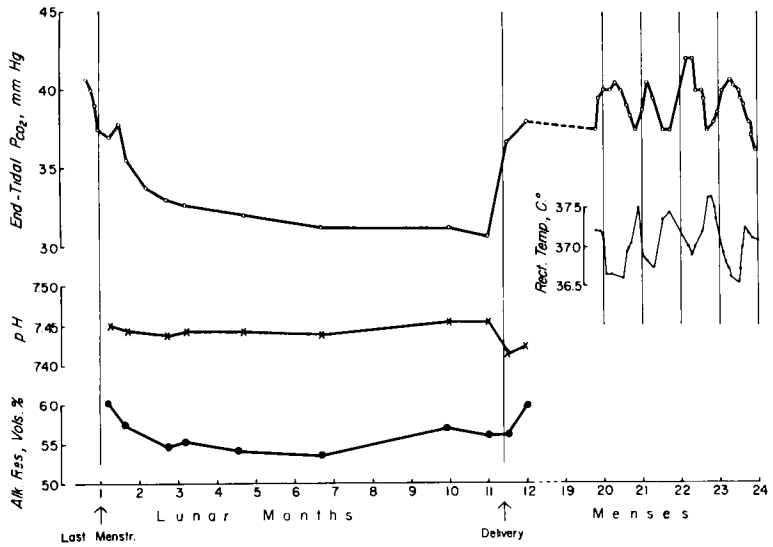

FIG. 5. Progressive changes of alveolar carbon dioxide tensions, *p*H, alkali reserve and rectal temperature of one individual studied repeatedly before conception, throughout pregnancy and for many months after resumption of menstruation. Consecutive data from the same normal woman were extracted from two publications of Döring [69] and of Döring and Loeschcke.[68]

were found to be reduced 3.1 m*M*/liter. However, equilibrating blood of a low bicarbonate content with a gas of "normal" P_{CO_2} results in a marked shift of *p*H to the acid side and this probably accounts for the original assumption of an "acidosis of pregnancy."

The data of Oberst and Plass [65] show that reduction of both bicarbonate and proteinate ions constitute the drop in alkali reserve while chloride increases slightly during pregnancy. The reduction in base is solely due to sodium loss. The changes in the extracellular fluid compartment are reflected in the red blood cells where the total acids are reduced.[65]

The changes in respiratory dynamics and acid-base metabolism seem to allow for an optimal environment for the fetus. The low P_{CO_2} and high P_{O_2} of the mother furthers optimal gaseous exchange at the placenta. The effects of *p*H and P_{CO_2} also tend to superimpose the oxyhemoglobin dissociation curve of the adult upon that of the fetus, and the low bicarbonate would tend to prevent wide fluctuations in acid-base changes in the newborn. These phenomena are dealt with elsewhere in this volume.

The Dyspnea of Pregnancy

Some shortness of breath is noted by 60 to 70 per cent of pregnant women, often during the first and second trimesters. In most conditions dyspnea is experienced as the result of an abnormally great work of breathing.[71] The latter may be caused by a decreased breathing capacity (M.B.C.) or by an abnormally increased ventilatory demand ($\dot{V}_E$). A relation between the two is expressed by the dyspnea index, ($\dot{V}_E$/M.B.C.) × 100, which indicates the percentage of the maximal ventilatory capacity required for a stated degree of activity. In pregnancy, the M.B.C. remains virtually unchanged and, during a mild standard exercise, the dyspnea index increases only from a normal 15 per cent to 20 per cent at term.[10] This figure is well below that of 35 to 50 per cent found in patients with pulmonary disease who complain of dyspnea. Apparently, mechanical changes of breathing are not responsible for this complaint and we have found no correlation between subjective dyspnea and altered lung volumes or dynamics of breathing in pregnancy.[10] Although the oxygen cost of breathing is higher than normal, this could bear some relation to shortness of breath only during the last trimester.[20] Certainly, this complaint bears no relation to alteration in lung volumes which are of no greater magnitude than those associated with pneumoperitoneum where dyspnea does not occur [11] nor does it bear any relation to altered intrapulmonary distribution of gas [10] or diffusing capacity.[27]

Gilbert *et al.*[72] have thought that this complaint may be related to an alteration of re-

spiratory control and that women with a high P_{CO_2} before pregnancy are more prone to develop dyspnea during pregnancy. They believed that dyspnea is more likely to occur when there is a marked change of P_{CO_2}. This suggests that women with normal mechanics of breathing are more likely to develop dyspnea than those with impaired lung function. Perhaps this is borne out by our observations that women with pre-existing pulmonary impairment do not complain of breathlessness as often as normal women.[73]

Dyspnea occurs early during pregnancy when the discrepancy between ventilation and O_2 consumption is greatest. Changes in acid-base metabolism and the buffering capacity of the blood and cerebrospinal fluid may well be related to this sensation. These changes are like those observed after acclimatization to altitude[74] and those seen in patients with the "alveolar-capillary block" syndrome,[43] though the stimulus is different. In all these conditions ventilation is increased, bicarbonate is reduced, sensitivity to CO_2 increased (fig. 4) and recovery requires weeks. Though there is no evidence as yet, it may be that the drop in the buffering capacity of the blood results in a reduction of the buffering capacity of cerebrospinal fluid such as occurs during acclimatization to high altitude.[75] This may cause a change of intracellular *p*H and the membrane potential and excitability at the surface of those brain cells concerned with respiration. This finer adjustment of the respiratory center may cause a greater than normal stimulus to respiration during exercise and during CO_2 inhalation and may be related to the sensation of dyspnea.[74, 76, 77] At any rate, in pregnancy, just as at altitude and with "alveolar-capillary block," the stimulus for greater ventilation is present at all times, not only during exertion, and dyspnea is out of proportion to the usual indices relating ventilatory requirement to breathing capacity.

Pregnancy in Patients with Pulmonary Impairment

Numerous clinical reports of full term delivery in women with limited breathing capacity suggest that an impaired respiratory apparatus is more competent in dealing with the additional respiratory demands than the damaged heart is in meeting the increased circulatory demands. Artificial pneumothorax was often continued during pregnancy[78] and even with bilateral pneumothorax the incidence of dyspnea was surprisingly low.[79] Thoracoplasty, lobectomy, moderate kyphoscoliosis and other restrictive disorders do not increase significantly the hazards of pregnancy and a number of reports have appeared of uneventful pregnancy after pneumonectomy.

We have followed 17 women with pneumonectomy who, together, had 34 pregnancies. The incidence of abortion, miscarriage, difficult labor and delivery by section was no greater than that of women with normal lung function, and complaints of dyspnea were rare.[80] Serial studies of 7 patients with diminished pulmonary function due to tuberculosis and operative collapse or resection showed that their tendency to hyperventilation was less marked than that of normal subjects and it was absent in those with greatly impaired function.[73] The increased O_2 requirement was met by greater tidal volume in all but the most severely impaired, and the effect of pregnancy on ventilatory capacity and lung volume was the same as in normal subjects. None of these patients had extremely severe restriction. Anthony and Hansen[12] believed that pregnancy might well produce respiratory decompensation and hypoxia in such patients. In women with nonselective lateral thoracoplasties labor was often accompanied by a very high pulse rate and cyanosis and operative intervention was often required to hasten delivery.[81] We have seen a few young women who had such severe respiratory impairment from cystic fibrosis or extreme kyphoscoliosis that pregnancy could not be carried to a successful conclusion. Nevertheless, we believe that patients with restrictive ventilatory impairment, who are not dyspneic at rest, will tolerate pregnancy without difficulty.

Summary

Pregnancy causes no significant alterations in the lung volume profile. During the last trimester there is a slight reduction in the functional residual capacity which, however, is compensated for by an increase of the inspiratory capacity so that vital and total lung capacities remain unchanged. The effect of late

pregnancy upon lung volumes is therefore similar to that induced by recumbency or by pneumoperitoneum.

The dynamics of respiration, as measured by maximal breathing capacity, are not altered even in late pregnancy, suggesting that airway resistance and the efficiency of the respiratory musculature most likely remain unchanged. The intrapulmonary distribution of gas and the diffusing capacity of the lungs are probably unaffected.

Both minute and alveolar ventilations are significantly increased as early as the first trimester. These increments exceed the augmented oxygen requirement throughout pregnancy. Hyperventilation is not related to altered mechanics of breathing; rather it appears to be stimulated by the ovarian hormones, progesterone and estrogen. This effect is a continuation of the luteal phase of the menstrual cycle and disappears soon after parturition.

Renal excretion of bicarbonate compensates for the respiratory alkalosis. The acid-base changes render the respiratory center more sensitive to the carbon dioxide stimulus much as occurs after acclimatization to high altitude. Dyspnea, a common complaint of pregnant women, is unrelated to changes in mechanics of breathing and may be due to the altered respiratory center threshold and sensitivity.

Restrictive pulmonary impairment is not a contraindication to pregnancy, unless the mother is dyspneic at rest. An impaired respiratory apparatus is more competent in dealing with the additional stress of pregnancy than is the impaired heart.

This review largely served to emphasize important gaps in our knowledge concerning respiratory and acid-base changes during pregnancy. Alterations of abdominal and intrathoracic pressures have not been measured nor is there information concerning their effects upon airway resistance, lung complicance or the mechanical work of breathing. The effect of hypervolemia upon pulmonary capillary blood volume and membrane diffusing capacity is unknown; and the action of hormones upon the control of breathing have only been tentatively explored.

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