BRONCHOPULMONARY RESISTANCE IN PREGNANCY

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THIS PAPER is concerned with observations of expired bronchopulmonary resistance values in normal pregnant women, in those with evidence of pre-eclamptic toxaemia, and in pregnant asthmatics. The importance to anaesthetists of increases in bronchopulmonary resistance in pregnancy revolves around its appearance as a dominent feature in a syndrome with which nearly all have had either direct or indirect experience, the acid-aspiration syndrome, or Mendelson's asthmatic-like reaction.[1]

This syndrome was described by Mendelson in a paper 15 years ago. He differentiated between the pulmonary sequelae of the aspiration of solid vomitus and those of the aspiration of liquid vomitus during general anaesthesia for obstetrics. These latter he referred to as the asthmatic-like reaction. Since then this syndrome has generally become known as Mendelson's syndrome. These cases, in some of whom the actual inhalation of vomit was not noticed, developed cyanosis, tachycardia, and dyspnoea; the chest showed rales and rhonchi over the affected areas of the lungs and radiography revealed no evidence of pulmonary lobar collapse but of diffusely scattered opacities. The author advised that treatment should be directed to the relief of the bronchiolar spasm and the ensuing cardiac embarrassment. In a further paper,[2] Parker described the autopsy findings in four such cases of pulmonary death following obstetric anaesthesia. In these there was no evidence of airway obstruction, only small quantities of aspirate being found in the bronchial tree. The history of these cases revealed that the vomiting had occurred prior to or during anaesthesia, but that the onset of the fatal symptoms might come later, the patient being in an apparently satisfactory condition in the interval. It was as a consequence of personal experience of two such cases, one fatal, that a search of the literature was made in an attempt to uncover any unusual situation in pregnancy which might lead to these pulmonary sequelae in apparently fit young women.

That a unique disturbance exists in pregnancy which might facilitate the appearance of the reaction is suggested by the work of Kapeller-Adler.[3] She has shown that strong histaminase activity is found in the blood of pregnant women, whereas no such activity is detectable in that of the non-pregnant. The source of the enzyme has been shown by Swanberg[4] and others to be the placenta. Kapeller-Adler's figures show that in normal pregnancy there is little alteration in the histamine content of the blood cells and plasma accompanying the increased histaminase content of the serum. In the toxaemias, however, as the severity of

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the condition increases, histaminase activity falls and there is an apparent shift of histamine from the cells to the plasma (Fig. 1). This she attributes to the

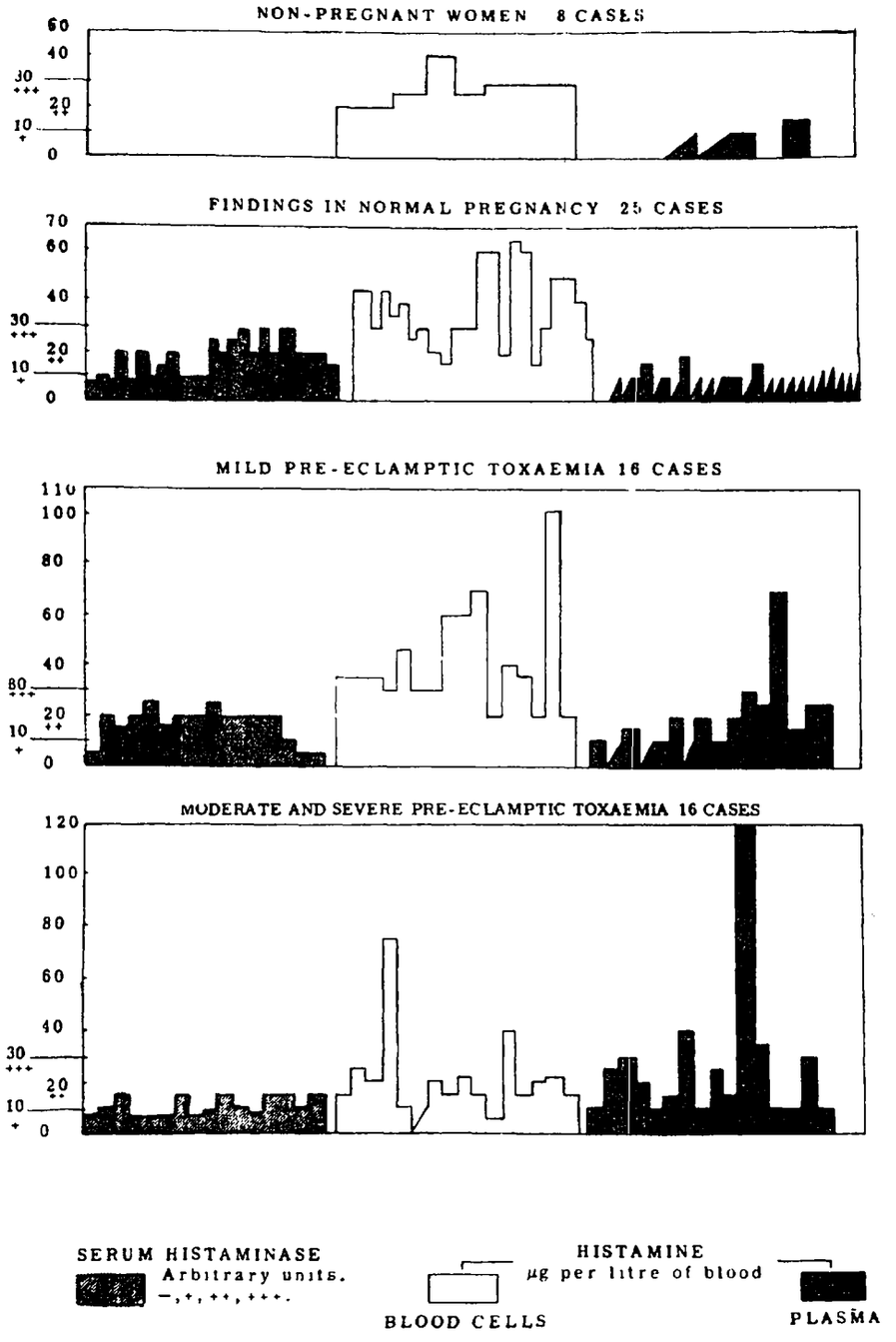

FIGURE 1. Histamine and histaminase levels in normal pregnancy and pre-eclampsia. This histogram is composed from the figures given by Kapeller-Adler. The abscissae represent the number of women concerned, the columns in each item correspond in order to the same patient. (By kind permission of Dr. Kapeller-Adler and the editor of the Lancet.)

increased facility of the histamine to move from within the cell to the tissue fluids. In the advanced toxaemias, situations may arise in which the plasma histamine level may exceed that of the cells. She concludes that the histaminase

might serve as a protective measure against histamine intoxication and that the amount circulating is proportional to the amount of living placental tissue.[5] This being so, a fall in the serum histaminase level following the removal of its source, with a concurrent slow fall in the plasma histamine, might lead to a critical level, with pulmonary symptoms, being attained after an interval.

In order to investigate the hypothesis[6] that this elevated plasma histamine level might be indicted as the cause of the bronchospasm in Mendelson's syndrome, a project was set up to make measurements of bronchopulmonary resistance in pregnancy. It also seemed possible that the elevated histamine in the plasma in the pre-eclamptic toxaemias might cause changes in the bronchopulmonary resistance in the course of pregnancy. For this reason, both normal and pre-eclamptic patients would be studied, and in both groups the effects of the administration of an antihistamine on the lungs would be investigated. Tripelennamine was selected for the purpose as it possesses slight central depressive effects and minimal adrenaline reversal activity.

The method of measuring the bronchopulmonary resistance was that of Clements,[7] utilizing a repetitive interrupter technique. This technique analyses solely expiration, and the results are expressed as cm. H_2O/L./sec., at 1 L./sec. This is necessitated by the exponential character of human airway resistance, the value, determined by Ainsworth, being 1.6.[8] The interrupter used in this investigation had a coefficient of resistance of 3.94 cm. H_2O/L./sec. and an exponent of 1.54. Patients were observed at intervals from about the seventh month of their pregnancy until term, additional records being taken when possible during labour and following delivery. The great majority of the post-delivery measurements were made in the first few hours. Unfortunately, a few were not obtained until some 24–48 hours had elapsed. All women were carefully screened for evidence of pulmonary and cardiac conditions which might influence the results.

The first group was of eighteen normal pregnant women who showed no evidence of pre-eclamptic toxaemia at any time during the period of observation. They received no drugs other than vitamins during their pregnancy. Sedation during labour excluded all phenothiazine derivatives and antihistamines. The values obtained for each patient were tabulated according to the week of the pregnancy in which the record was made. In order to do this, it was assumed that parturition took place at the fortieth week. From these tables the average results obtained from the records on each particular week were calculated and reduced to the nearest half centimeter of water. The maximum value obtained from this group of patients at any time was 3.5 cm. H_2O/L./sec. and the minimum 1.5 cm. H_2O/L./sec. The averages obtained at each of the weeks fell between 3 and 2 cm. H_2O/L./sec.

The second group of 11 women, with normal pregnancies, were given tripelennamine 50 mg. t.i.d. during the latter month of their pregnancies. Only one of these patients reported drowsiness and her dosage was reduced to 50 mg. b.i.d. Two of these patients were given intramuscular doses of tripelennamine 25 mg. during labour. The recordings were made on the same schedule as the first group and calculated in the same manner. The maximum reading obtained was 3.5 cm.

H_2O/L./sec. and the minimum 2.0 cm. H_2O/L./sec. The averages obtained at each week was 3 cm. H_2O/L./sec. during pregnancy and labour, falling to 2.5 cm. H_2O/L./sec. after parturition.

Five of the women from these first and second groups were seen again six weeks following delivery and their non-pregnant bronchopulmonary resistance averaged 2.5 cm. H_2O/L./sec. with a maximum and minimum respectively of 3.0 and 2.0 cm. H_2O/L./sec. (Fig. 2).

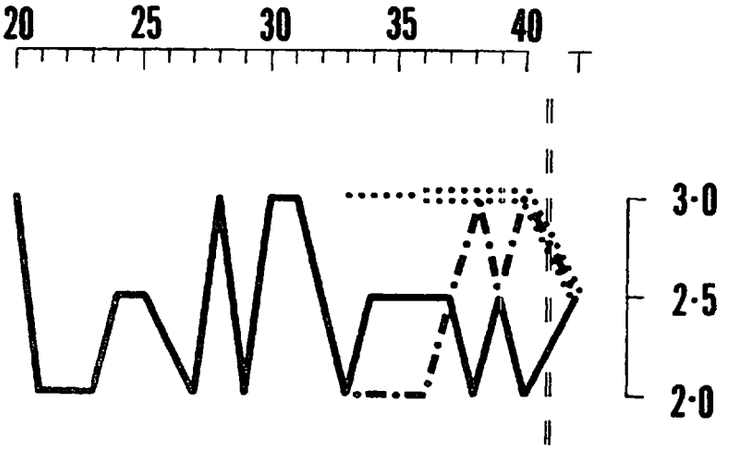

FIGURE 2. Bronchopulmonary resistance in pregnancy. Abscissa, week of pregnancy; ordinate, cm. H_2O/L./sec.; —— values obtained in normal pregnant women; .... values obtained in normal pregnant women and : : : : during the period of oral administration of tripelennamine; –·–· values obtained in women with evidence of pre-eclamptic toxaemia. The time of parturition is denoted by the interrupted vertical lines.

From these results it was concluded that expired bronchopulmonary resistance was unaffected by normal pregnancy, and was of a value of 2.0 to 3.0 cm. H_2O/L./sec. when obtained by this method. Furthermore, the administration of tripelennamine appeared to have no effect on these values.

A third group of 8 patients who showed evidence of pre-eclamptic toxaemia were then observed. The average figures, obtained in the same manner as in the previous groups, showed their bronchopulmonary resistance to be between 2.5 and 2.0 cm. H_2O/L./sec. with a maximum reading of 5.0 and a minimum of 1.5 cm. H_2O/L./sec. Two of these cases were treated with a low salt diet, two with a diuretic and a low salt diet, two by diuresis and tripelennamine, and two by tripelennamine alone. Such a variety of treatment in so small a series denies the possibility of arriving at any finite conclusion as to the relationship between bronchopulmonary resistance and toxaemia of pregnancy. These toxaemias, it must be pointed out, were all of the mildest order. The more advanced cases of toxaemia are not suitable for study in the manner here used, as the necessary sedation renders the patients unable to co-operate adequately. However, one point of interest does arise from the figures obtained; the only recordings where the bronchopulmonary resistance exceeded the value of the maximum obtained in either of the foregoing normal groups were in an untreated case, or in one in which a low salt diet alone was used. The remainder of the figures were within

the range of the normal averages. The values obtained in one patient treated by diuretics and low salt intake diet demonstrated the effect of adequate weight control. Her resistance fell progressively from 5.0 cm. H_2O/L./sec. at the twenty-sixth week of pregnancy, when treatment was instituted for excessive weight gain, to 2.0 cm. H_2O/L./sec. at term.

The observations on this group of patients do little other than suggest that toxaemia may be associated with increased bronchopulmonary resistance. This may be due to passive swelling of the lining cells of the bronchioles.[9]

The following case histories, excluded from the previous groups for reasons which will be apparent, are given to illustrate the effects of tripelennamine when used for the treatment of bronchospasm which was clinically evident.

Case 1

This 24-year-old primiparous woman was first seen at the thirty-fifth week of pregnancy. She gave a history of a facial dermatitis following both sulphonamide and penicillin therapy, and at the time had suffered an acute coryza which she stated had begun one week previously, but was resolving. Her bronchopulmonary resistance was then 3.5 cm. H_2O/L./sec., and on auscultation of the lungs expiratory rhonchi were heard. After a week taking tripelennamine mg. 50 t.i.d. the value was 3.0 cm. H_2O/L./sec. and the chest was clear of rhonchi. At the thirty-seventh week, still taking tripelennamine, the value was again 3.5 but the chest remained clear; this rise coincided with the first appearance of albuminuria and hypertension. Early in her labour which began two weeks later, the resistance rose to 5.0 cm. H_2O/L./sec. and her chest once again contained rhonchi; an intravenous dose of tripelennamine was given at the time and immediately following this the rhonchi disappeared and the resistance fell to 4.0 cm. H_2O/L./sec. Her post-partum record gave a value of 3.5 cm. H_2O/L./sec.

Case 2

This patient, who was first seen at the thirty-third week of pregnancy, had had five previous pregnancies which all miscarried. She was aged 34 years and gave no history of pulmonary or cardiac conditions, nor of asthma or other sensitivity. She complained that as this pregnancy had proceeded she had become wheezy and was coughing, especially at night. Her bronchopulmonary resistance was 6.0 cm. H_2O/L./sec. She was given Promethazine mg. 10 q.i.d. for a week and this value fell to 3.0 cm. H_2O/L./sec. She was advised to continue taking the promethazine, but this she failed to do and on her next weekly visit she was extremely wheezy and was given promethazine mg. 20 orally at that time. Later the same day she appeared at the hospital with gross dyspnoea and cyanosis; coarse rhonchi were heard in her lung fields. The resistance had reached 15.5 cm. H_2O/L./sec. Ten mg. promethazine were given intravenously and a quarter of an hour later a resistance of 7.5 cm. H_2O/L./sec. was recorded. In a further fifteen minutes, she was breathing freely and left the hospital. Unfortunately, no further recordings were made, but she continued to take promethazine for the rest of her pregnancy which she carried uneventfully to term. It is to be noted that dependent oedema was found at all of this patient's prenatal clinic visits.

Case 3

This 26-year-old multiparous woman had had asthma for years; in each of three previous pregnancies which she carried to term, the asthma had become much worse. When first seen, she had been in hospital for four days in status asthmaticus and had proven refractory to aminophylline and cortisone therapy; she was in her thirty-ninth week of pregnancy, orthopnoeic, exhausted, and unable to sleep. In addition, she had produced a melaena and was anaemic. At this time, her bronchopulmonary resistance was about 19.0 cm. H_2O/L./sec. (repeated records were not feasible in this case). Intravenous tripelennamine mg. 25 was given; subjective relief was immediately obtained, but clinically there was no evidence of resolution of the bronchospasm. The resistance, 20 min. after the injection, had fallen to 11 cm. H_2O/L./sec. Intramuscular tripelennamine was maintained until after her delivery, but occasional intravenous booster doses had to be given. Three weeks after her delivery, her bronchopulmonary resistance was 10.0 cm. H_2O/L./sec. and at this time she stated that she was as well as at any time in recent years.

Case 4

In this case, it was not possible to obtain any measurements, initially because of the patient's critical condition, and later on account of a language barrier and lack of co-operation. The woman was in labour in her fifth pregnancy, in the later stages of which her uterine contractions had become violent; she suddenly collapsed, her pains ceased, and the foetal heart was no longer heard. A diagnosis of a ruptured uterus was made and an immediate laparotomy performed. During induction of anaesthesia, she regurgitated stomach contents which were sucked out under direct laryngoscopy; the hypopharynx was cleared and the vocal cords were noted to be in spasm; these relaxed with administration of a depolarizing agent. No vomitus was seen in the upper trachea, and a cuffed endotracheal tube was inserted. Anaesthesia was maintained on cyclopropane and oxygen with succinyl-dicholine relaxation and intermittent positive pressure respiration. At the end of the procedure, her blood pressure was satisfactory, her colour good, her chest clear on auscultation, and she was conscious within a few minutes. The blood loss had been heavy and she had received a 1,500 ml. transfusion. On transfer to the recovery room, a further 500 ml. of blood containing hydrocortisone mg. 100 was set up. One hour later she became cyanosed and her breathing became laboured; examination of the chest revealed widely scattered rhonchi and rales. Aminophylline gm. 0.35 was given intravenously but little effect was noted. Forty-five minutes after this, her blood pressure had fallen to 90/50 and her cyanosis and laboured respirations were unchanged despite oxygen therapy. At this time, tripelennamine mg. 25 was given intravenously; there was an immediate and complete release of the bronchospasm; on auscultation of the lungs, only rales could be detected. Approximately twelve hours later, there was some return of the rhonchi but these resolved with a further intravenous dose of tripelennamine. From this time onwards, she was maintained on intramuscular injections of the drug until she was able to take oral doses. In addition, she was digitalized, given antibiotics, diurectics, and continued cortisone therapy. After

two days, when she showed evidence of a pulmonary lobar collapse, she coughed well and produced some bloodstained sputum. From then on she improved more rapidly and eventually left the hospital with a clinically and radiologically clear chest. Sputum specimens were examined without success for evidence of amniotic fluid embolus, and electrocardiograms showed no evidence of coronary occlusion; changes due to anoxia and some right ventricular strain were noted, however. This case was considered a classic example of Mendelson's syndrome and the dramatic resolution of the bronchospasm by the administration of tripelennamine was noted.

Discussion

The values for bronchopulmonary resistance in normal pregnancy have been recorded, using a direct measurement technique. That the administration of an antihistamine to normal pregnant women does not alter these values has been demonstrated.

A small group of women with evidence of pre-eclamptic toxaemia was investigated; a variety of treatments to these patients precluded an assessment of the effects of the pre-eclampsia upon the bronchopulmonary resistance, but it was noted that higher values occurred in this group.

Four selected cases in which antihistamines were used successfully for the treatment of bronchospasm occurring in association with pregnancy are also presented. One of these cases was a known asthmatic. The use of antihistamines in the treatment of asthma aggravated in pregnancy must be considered both in the light of the abnormal plasma histamine levels and Dale's[10] theory of cellular response to histamine. Dale postulates that cells may respond to intrinsically as well as extrinsically released histamine, the latter being carried from distant cells to the effector cells in the body fluids. In asthma the bronchial muscle responds to intrinsically released histamine which accounts for the lack of response to antihistamines.[11] In pregnancy these cells are exposed to additional histamine borne by the plasma, and it would seem that the exposure of these same cells to a specific antihistamine via the same route would result in rendering the cellular surface unsusceptible to any histamine reaching it. This is also the basis for advocating the use of antihistamines to protect the lungs of pregnant women, with or without evidence of pre-eclampsia, from the raised plasma histamine levels and the part played by antihistamines in its control. It is, however, considered to be of greater importance to the toxic patient. Examination of the autopsy reports[12] of seven maternal deaths attributable to anaesthesia revealed that five had pathological evidence of pre-eclamptic toxaemia; the lungs in three of these five cases were similar to those described by Parker. Two of the seven cases, without evidence of pre-eclampsia, also gave the same picture. In only one of these subjects was vomiting known to have occurred. In the one case of Mendelson's syndrome here reported the successful action of intravenous tripelennamine is shown.

The other two recorded cases demonstrated the action of antihistamines used to treat bronchospasm occurring in the course of pregnancy.

Conclusion

Measurement of bronchopulmonary resistance in mild toxaemias does not reveal deviation from the normal range. Further work is necessary, in the severer degrees of toxaemia to elucidate the effect of the condition upon bronchopulmonary resistance.

The four case reports are considered to suggest that antihistamines may be effective in the treatment of bronchospasm associated with pregnancy and obstetric anaesthesia, and use of these drugs is advocated.

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Résumé

En employant une technique de mesure directe, nous avons établi les valeurs de résistance bronchopulmonaire au cours de la grossesse normale. Nous avons démontré que l'administration d'un antihistaminique à des femmes enceintes normales ne change en rien ces valeurs.

Nous avons examiné un petit groupe de femmes manifestant des signes de toxémie pré-éclamptique. Différents traitements chez ces malades laissaient prévoir une diminution des effects de la prééclampsie sur la résistance bronchopulmonaire, mais nous avons observé des données plus élevées dans ce groupe.

Nous avons également présenté quatre cas choisis, chez qui le traitement aux antihistaminiques a été un succès pour vaincre le bronchospasme survenant au cours de la grossesse. Une de ces malades était une asthmatique connue. L'usage des antihistaminiques dans le traitement de l'asthme, aggravé par la grossesse, doit être étudié en songeant au double aspect de la présence de taux anormaux d'histamine dans le plasma et de la théorie de Dale sur la réponse cellulaire à l'histamine. Dale postule que les cellules peuvent répondre aussi bien à une libération intrinsèque qu'à une libération extrinsèque d'histamine; dans cette dernière éventualité, l'histamine peut être apportée par les liquides de l'organisme de cellules situées à distance à des cellules effectrices.

Dans l'asthme, le muscle bronchique répond à une libération intrinsèque d'histamine. C'est pourquoi on n'obtient pas de réponse à l'administration d'antihistaminique.

Au cours de la grossesse, ces cellules sont inondées par une quantité additionnelle d'histamine apportée par le plasma, et il semblerait que si ces cellules reçoivent de la même façon un antihistaminique spécifique, leur surface cellulaire deviendrait insensible à toute histamine qui pourrait les atteindre. C'est en nous basant sur ces données que nous employons des antihistaminiques pour protéger les poumons des femmes enceintes, avec ou sans signes de prééclampsie, contre les taux élevés d'histamine dans le plasma, et à cause de la part jouée par les antihistaminiques sur leur contrôle.

Cependant, cela semble plus important chez les malades intoxiquées. L'analyse des rapports d'autopsie de sept morts maternelles attribuables à l'anesthésie nous apprend que cinq d'entr'elles présentaient des signes pathologiques de toxémie prééclampsique; les poumons de trois de ces cinq malades ressemblaient à ceux qu'a décrits Parker. Deux des sept malades, exemptes de signes de prééclampsie, ont présenté le même tableau. Chez une seule de ces malades, nous avons constaté des vomissements. Dans le seul cas de syndrome de Mendelson rapporté ci-contre, nous avons observé l'action bienfaisante du trépelennamine intraveineux.

Les deux autres cas rapportés illustrent l'action des antihistaminiques pour traiter le bronchospasme survenant au cours de la grossesse.

L'évaluation de la résistance bronchopulmonaire chez les cas de toxémie légère ne dévie pas beaucoup de la moyenne. Il faudra pousser la recherche davantage chez les cas de toxémie plus grave pour préciser les effets de cette pathologie sur la résistance bronchopulmonaire.

Les quatre cas rapportés nous incitent à affirmer que l'emploi des antihistaminiques peut être efficace pour le traitement du bronchospasme au cours de la grossesse et de l'anesthésie obstétricale, et nous préconisons l'usage de ces médicaments.

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