Of labour and the lungs

Failure of normal adaptation of the lungs at birth may take one of two main forms, albeit with some overlap both in aetiology and clinical manifestations. Transient tachypnoea in the newborn is thought to be due to delayed clearance of lung liquid and characteristically runs a benign self-limiting course. Delay in lung liquid absorption may be a feature of hyaline membrane disease (HMD) but surfactant deficiency, consequent upon prematurity, is of primary aetiological importance. However, even when allowance is made for gestational age, certain other factors increase the incidence and severity of the disease which remains the single most important cause of morbidity and mortality in the newborn period. One such risk factor, apparently related to the absence of labour rather than to the route of delivery, is elective caesarean section (CS). Evidence accumulated in recent years gives a reasonably clear picture of the final stages in adaptation of the lung to air breathing in which catecholamines, secreted by the fetus during labour, play a central role both in initiating the absorption of fetal lung liquid and promoting surfactant secretion. The evidence for this conclusion, which may have a direct bearing on clinical practice, is derived from observations in animals and humans and provides a convincing example of how the two investigative approaches can be complementary.

### HMD and mode of delivery

Any comparison of different studies is bedevilled by variable and loose definitions of HMD and the failure of some authors to distinguish emergency from elective CS. In these respects the work of Fedrick and Butler is the most satisfactory; there is little ambiguity of diagnosis since the data are expressed in terms of the incidence of hyaline membranes present at necropsy. Compared with babies delivered vaginally those born by CS, particularly before the onset of labour, run a much greater risk of death from HMD (Table).

The conclusions of Usher et al. are broadly comparable, but Jones et al. found that there was a significant increase in the incidence of HMD after CS but only in infants of greater than 34 weeks' gestation. In neither of these two studies was the CS group subdivided according to presence or absence of labour. Whether the risk of HMD after elective CS extends to term infants is disputed. However, there is no doubt that this form of delivery significantly retards the rate at which even the mature newborn infant attains normal blood gases.

The considerable influence of labour on postnatal lung function is due to its inter-related effects on lung water and surfactant.

### Lung volume, lung water, and labour

Measurements of lung volumes, both crying vital capacity and thoracic gas volume, by reverse plethysmography have shown that the highest values are to be found in babies born vaginally and the lowest in those born by elective CS (at equivalent gestations). Not only is crying vital capacity, normalised for chest circumference, some 20% higher in the former group but its rise during the first 24 hours of life is much faster (16% v 7%). The difference in initial thoracic gas volume is even more striking: 33 ml/kg after vaginal delivery, 20 ml/kg after CS. As with the observations on crying vital capacity, babies born by emergency CS form an intermediate group between elective CS and vaginal delivery.

Dynamic compliance varies directly with thoracic gas volume and differences persist for 48 hours. It is concluded that the proportion of lung volume occupied by liquid is greater in babies born by elective CS and that it may account for the increased incidence of transient tachypnoea associated with this form of delivery.

It is certainly true that in rabbits total lung extravascular water is lowest (by about 13%) in newborn rabbits that have experienced labour, irrespective of the mode of delivery. Furthermore the differences remain even 24 hours after birth.

### Surfactant production and labour

Data on this topic are surprisingly scanty. Cabero et al. reported lecithin/sphingomyelin ratios in amniotic fluid during human labour (34–43 weeks)
that were roughly twice those obtained before the onset of labour. That the release of surfactant brought about by labour is accompanied by increased synthesis may be inferred from work in term rabbits\(^{19}\) in which measurements have been made of the concentrations of cholinephosphotransferase (the enzyme which catalyses the penultimate step in the synthesis of disaturated phosphatidyl choline) and lung lavage phospholipid. Whereas lung cholinephosphotransferase concentration at birth is already increased by 90\(\%\), the effect of labour on the concentration of lung lavage phospholipid (of which the main constituent is disaturated phosphatidyl choline) is not seen until age 3 hours but thereafter, during the first 24 hours of life, it remains at 2 to 3 times the level found in newborn rabbits delivered before the onset of labour.

The work discussed so far stresses the importance of labour in lung adaptation at birth but gives no intimation as to how this effect is mediated. The evidence which follows points to the critical role of adrenaline.

Catecholamines, lung liquid, and surfactant

These observations were made in chronically catheterised fetal lambs in which term is 147 days.

Exogenous adrenaline and noradrenaline. The work of Brown \textit{et al.}\(^{20}\) shows that after 130 days' gestation the response of the fetal lung to intravenous infusions of adrenaline at rates of 0·5–1·0 \(\mu g/min\) (which give blood levels comparable with those found during labour) is characterised by absorption of lung liquid—the rate of absorption increasing as term approaches. Earlier than 130 days lung liquid secretion is slowed or halted. This effect, which cannot be reproduced by equimolar amounts of noradrenaline,\(^{21}\) can be blocked by propranalol.\(^{21}\) Others\(^{22}\) have reported that inhibition of lung liquid secretion is accompanied by an increase in surfactant release in mature fetal lambs infused with adrenaline (3 \(\mu g/min\)).

Endogenous catecholamines in labour.\(^{20}\) During labour lung liquid secretion progressively slows. Absorption begins at about the time that fetal parts become visible at the vulva and thereafter accelerates to 20–40 ml/hour. Fetal plasma catecholamine levels rise correspondingly reaching, at their peak, mean levels roughly 4 (noradrenaline) and 100 (adrenaline) times prelabour values. The correlation between the response and adrenaline concentration is exponential and highly significant both during labour and during adrenaline infusion (and the parameters of the two regression lines are similar). There is no correlation of lung liquid absorption with noradrenaline concentration.

It may well be that in the human, absorption of lung liquid occurs at an earlier stage of labour than in the sheep in which the process of birth is generally less stressful.

Synthetic \(\beta\) agonists

Effects on surfactant and lung liquid. There is no doubt that \(\beta\)-mimetic drugs, when administered to rabbit fetuses shortly before premature delivery, have a potent effect on the lung. Intramuscular injection, 3 hours before delivery, of isoxsuprine\(^{23}\) (0·5 mg) or terbutaline\(^{24}\) (0·1 mg) into fetal rabbits of 28 days' gestation (term is 31 days) reduces the amount of liquid which can be aspirated from the lungs at birth by 60–65\(\%\). These same drugs increase air retention during deflation (at 10 cm\(H_2\)O) by 30\(\%\) in the sheep in which 60\(\%\) respectively. Furthermore, isoxsuprine has been shown to double the lecithin/sphingomyelin ratio of fetal lung liquid while reducing its surface tension by 50–60\(\%\). Consistent with these findings \textit{in vivo} are the observations that in fetal rabbit lung slices isoxsuprine accelerates the incorporation of choline into disaturated phosphatidyl choline\(^{26}\) (indicating increased surfactant synthesis) while in preparations of rat alveolar type II cells\(^{27}\) the release of radiolabelled disaturated phosphatidyl choline is increased about 3-fold by 10 mmol/l terbutaline or isoprenaline (and more than 2-fold by an equimolar concentration of adrenaline).

Evidence, albeit indirect, for a similar effect of \(\beta\)-mimetics on lung surfactant production in the human fetus comes from a study\(^{28}\) in which ritodrine (40 mg daily), administered orally to pregnant women between 33 and 35 weeks' gestation, resulted in an increase of some 70\(\%\) in the palmitic acid concentration of amniotic liquid measured at the end of the treatment period.

Prevention of HMD. The efficacy of \(\beta\)-adrenergic drugs in reducing the incidence of HMD after premature delivery is far less clear than may be expected from the evidence of their effect on the lungs of animals. This is not for lack of papers on the subject\(^{29–32}\) but because of the need for a properly controlled large-scale prospective trial. The whole question is further complicated by uncertain diagnostic criteria for HMD and uncertainty about the timing of the last dose of \(\beta\)-mimetic drugs before delivery. The consensus in published work supports the conclusion that \(\beta\)-mimetic drugs (including specific \(\beta_2\) agonists such as terbutaline\(^{28}\) and
salbutamol) when administered to women during preterm labour, appreciably decrease the incidence of HMD.

Conclusions

That labour has a beneficial effect on subsequent lung function is beyond doubt. However, there are some who argue that these changes in the lung are mediated by the surge in fetal cortisol secretion which occurs during labour. Given that the maximum effect of cortisol on most tissues (including the premature lung) is seen after 24–48 hours, this particular hormone seems ill fitted for the role. Indeed, in fetal lambs, we have not seen evidence of any acute effect of cortisol on lung liquid secretion either given alone or with adrenaline, and others have concluded that a sudden increase in endogenously-secreted cortisol is not a stimulus for increased surfactant production. In this context it should be remembered that exogenous steroids have no effect in preventing HMD unless given at least 24 hours before delivery.

Steroids may be important, apart from their effect on lung maturation, in priming the adrenergic system before labour, both by increasing the capacity of the adrenal medulla to secrete and by increasing the number of β adrenergic receptors in the lung.

The place of β-mimetic drugs in the prevention of HMD is not clear. None the less, there seems to be sufficient evidence of a beneficial effect on lung function to warrant a proper clinical study of their use, particularly in those at greatest risk—premature babies delivered by elective CS.

References


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Of labour and the lungs.

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doi: 10.1136/adc.56.9.659

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