



FETAL LUNG MATURITY

Fetal lung maturity has always been a challenge to the obstetrician and pediatrician in cases of preterm labor and preterm premature rupture of membranes (PROM). With preterm babies, hyaline membrane disease has always been the main cause of neonatal death and solution to the immaturity of fetal lungs is a primary concern. The introduction of corticosteroids for fetal lung maturity by Liggins and Howie ¹ in patients at risk of preterm labor was a major milestone in reducing neonatal morbidity and mortality from respiratory distress syndrome (RDS).

Pulmonary surfactant is produced by type II alveolar cells. It spreads in the lung tissue-air interface, preventing alveolar collapse during expiration and allowing the alveoli to open easily at the next inspiration. HMD occurs due to inadequate production of pulmonary surfactant and is seen if labor occurs before 32-34 weeks of pregnancy. The alveoli will collapse during expiration and each inspiration will require considerable effort. This situation rapidly leads to fatigue, decreased respiratory effort, hypoxia, cyanosis, acidosis and eventually death.

The surfactant is a heterogeneous mixture of lipids and proteins. Dipalmitoyl phosphatidyl choline (DPPC) is the main component of the pulmonary surfactant. It is possible to assess the biochemical maturation of fetal lungs by studying the amniotic fluid phospholipid composition.

Evaluation of the presence of surfactant has been studied and used extensively in the past. Some of the bedside tests which have been used are :

- a) *Shake Test* : After shaking a mixture of amniotic fluid and ethanol, the stability of the bubbles formed is estimated qualitatively. It has 100% positive predictive value.
- b) *Tap Test* : 1 mL of amniotic fluid is mixed with one drop of 6 N HCl and 1.5 mL of diethyl ether. The test tube is briskly tapped creating bubbles in the ether layer. If the lungs are mature, the bubbles will rise to the surface and breakdown. If the lungs are immature, the bubbles will remain stable or break down slowly. It has 98-100% positive predictive value ².

- c) The laboratory evaluation of L/S ratio in amniotic fluid prior to planned early delivery has been an established test. Ratio > 2:3 suggests lung maturity ³.
- d) Determination of presence of DPPC in the amniotic fluid and its quantitative measurement. DPPC more than 500 µg/dL is predictive of lung maturity .

In the days gone by, the mainstay of treatment in intensive care unit was maintenance of oxygen saturation and prevention of respiratory acidosis by sodium bicarbonate injections. This caused a lot of economic burden on the patients, as the neonatal ICU stay was long and the ultimate outcome was poor. But the work of Liggins and Howie ¹ of using glucocorticoids for improving fetal lung maturity not only decreased the neonatal mortality, and morbidity due to RDS but also lessened the need for neonatal intensive care and use of exogenous surfactant therapy causing economic savings.

Steroids cause premature liberation of surfactant from the alveoli perhaps by induction of an enzyme concerned with the biosynthesis of surfactant . The steroids used are usually dexamethasone or betamethasone. They are identical biologically and readily cross the placenta. They have little mineralocorticoid activity and are relatively weak in immune suppression. Dosage recommended by Howie and Liggins is two doses of 12 mg bethamethasone given 24 hours apart or four doses of 6 mg dexamethasone given 12 hours apart ⁴. Betamethasone is widely used because of patient compliance. It is used between 24 to 34 weeks of gestation . Before 24 weeks the type II pneumocytes are not sufficiently formed to release the surfactant, and after 34 weeks the risk of RDS is low and its severity less. Antenatal corticosteroids, apart from reducing RDS, also reduce intraventricular hemorrhage and neonatal mortality ⁵.

The best neonatal respiratory results come after a complete course of injections and delivery 3-7 days after this completed course is ideal. Tocolytics can be used simultaneously to delay labor so as to allow the steroids to act fully. The above recommendations are in line with the RCOG guidelines ⁵ and ACOG committee opinion ⁶.

Some clinicians are of the view that reduction in RDS associated with antenatal steroids is not statistically significant in the sub-group of babies who deliver more than 7 days after a single course of treatment. Hence the practice started of repeating the course of treatment at weekly intervals for women who do not go into labor but remain at risk for a preterm delivery. This administration of repeated steroids has never been subjected to proper randomized trials and there is no evidence that multiple courses of steroids are more effective than a single course. Interestingly both, the RCOG guideline ⁵ and ACOG Committee ⁶ stressed the point that there was no evidence that repeated doses after 7 days were useful. One randomized controlled trial of single vs multiple courses of corticosteroids involving 502 pregnant women between 24 and 32 weeks of gestation concluded that weekly courses of antenatal steroids did not reduce composite neonatal morbidity compared to single course of treatment ⁷.

In a recent paper published by French et al ⁸ from Western Australia, the relevant data show great improvement in respiratory function after one course of antenatal steroids over use of no steroids, but there is no improvement among those women who had two, three or more courses at weekly intervals. Polypharmacy is always to be discouraged as although the risks of repeated steroids to the mother are small, they will increase with each dose. Multiple dose therapy is associated with decrease in the birth weight ⁹. Study by Dunlop et al ¹⁰ states that repeated prenatal steroids delay myelination of the CNS axons in sheep. Further research has now established that the repeated doses in fact are harmful to the fetus, since myelination suffers drastically. CT and MRI studies of fetuses have shown flattening of the cerebral hemispheres ¹¹.

There are a few relative contra-indications to giving antenatal steroids. They are -

- a) PPRM before 28 weeks of pregnancy with birth weight less than 1000 g and of more than 24 hours duration, because the risk of infection is higher. But some authors believe that the use of steroids and improvement in lung maturity outweigh the risk of infection.
- b) Diabetic mothers who have poor glycemic control as steroid administration not only increases the risk of infection but also causes instability of diabetic control. One should give the steroids to help the fetus and after that look into the fine tuning of diabetic control with insulin ¹².
- c) Tuberculosis in the mother has a risk of flare up after steroid administration but this could be covered by the newer and more rapidly acting anti-tubercular drugs if available.

There are no long term side effects seen on the mother or the child in any of the studies which followed up the children up to 6 to 12 years ¹³⁻¹⁵.

The outcome of babies with HMD has changed dramatically with the development of surfactant replacement therapy ¹⁶. Both natural and artificial surfactants have been used. Natural surfactant can be obtained from human amniotic fluid and cow, calf and pork lungs. Survanta is a natural surfactant obtained from bovine lungs. The best known artificial surfactants are exosurf and ALEC.

Surfactant can be used as soon as a preterm baby is delivered and before the development of HMD ¹⁷. It is administered via endotracheal tube. The response to therapy is immediate and it results in a decrease in the oxygen concentration necessary to ventilate the infant and a decrease in the ventilatory pressure. Repeated doses may be necessary.

The role of the obstetrician in preterm labor prevention has been limited with the drugs available. Atosiban is effective in delaying preterm labor but is expensive. It can be used with nifedipine. The sole purpose is to buy time for steroids to act on fetal lung and improve lung maturity. The neonatologists have contributed immensely towards neonatal survival in cases of preterm labour and RDS.

Conclusion

Incidence of RDS due to HMD is now decreasing due to increasing use of corticosteroids in women at risk of preterm labor. The RCOG guideline on antenatal corticosteroids has concluded that currently there is no evidence to recommend multiple courses of antenatal corticosteroids ¹⁸. The NIH consensus statement of 1994 concluded that "The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health".

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