Alternative methods for promoting lung maturation

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Many experiments have been carried out for promoting lung maturation. The effect of adrenal hormones on the cellular differentiation of alveolar epithelium was studied by BUCKINGHAM (1), and the clinical studies of LIGGENS (26) have provided a base for an established relation between the application of glucocorticoids and induction of fetal lung maturation. Side effects of glucocorticoid application have been also observed. Combined therapy with corticosteroids and tocolysis may lead in some cases to severe, and even fetal interstitial pulmonary oedema of the pregnant patients (18, 41). Therefore, alternative methods for inducing lung maturation have been recently considered. The effects of beta-mimetics on the lung maturation have been investigated by many research groups. HAYDEN (17) reported about the effect of the beta-mimetic Isoxsuprine on the lung maturation of rabbits fetuses. ENHORNING (6) in his study was able to detect higher L/S-ratio in extracted fetal lungs after injecting pregnant rabbits with Isoxsuprine in glucose solution. Similar results were supported by KANJANAPONE (19). The previously mentioned experimental studies have been opposed by clinical observations.

DUDENHAUSEN (3, 4) observed after long time therapy with the beta-mimetic Fenoterol between the 33th - 39th week of gestation a statistically significant decrease in the amniotic fluid lecithin concentration. GÖSER (9) in another clinical study was not able to detect such a negative effect of tocolysis on the lung maturation. SALZER (37) found neither positive nor negative effects of beta-mimetics on the fetal lung maturation.

KAROTKIN (20) observed a significant increase in the phospholipid content of the lung lavage material after intrafetal application of Aminophyllin. CORBET (2) published also similar increase in the phospholipid content of lung alveoli after intraperitoneal injection of Aminophyllin in the pregnant rabbits. A clinical information was provided by HADJIGEORGIOU (14). By comparing 67 cases of premature deliveries before the 35th week of gestation previously treated with Aminophyllin, with 75 control cases, the perinatal mortality rate in the first group was found to be 7.1%, compared to 17.9% in the second group.The incidence of RDS in the Aminophyllin group (10%) is clearly less than that of the second group (29.5%).

The effect of the hormones on fetal lung maturation was also thoroughly investigated. WU (42) observed a positive effect of Thyroxine on the lung maturation.

FISCHBACH (7) proved an increase in the DPPC of the fetus after giving Thyroxine to the pregnant wistar-rats. The clinical application of Thyroxine was studied by MASHIACH (31, 32). T_4 was injected intraamniotically. He observed 16 cases of premature deliveries before the 34th week of gestation, 15 cases showed no evidence of RDS.

The above concept was opposed by the clinical study of SCHREYER (38). Trijodthyrenin (T_3) was injected intraamniotically to 15 pregnant women with hypertension. The gestational age was in average the 32.4th week by the time of delivery. 10 cases with low Apgar score were recorded. RDS was observed in 7 cases, and 3 babies died. Here, it should be noticed that T_3 and TSH concentrations in the fetal blood showed no evidence of T_3 reaching the fetal compartments.

Another group of investigators have proposed a relationship between estrogen and lung maturation. KHOSLA (21) found an increase in the phospholipid concentration in the fetal lung lavage material after injecting pregnant rabbits with 17ß-estradiol intramuscularly and a better alveolar epithelium from type II and I, and decrease in the undifferentiated epithelial cells, in addition, a better lung vasculature was seen (22). MOAWAD (33) concluded out of his experiments on rabbits, that estrogen administration is followed by increase in the beta-adrenergic receptors.

HAMOSH (16) applied prolactin intramuscularly on the 24th day of gestation to the rabbits fetuses, and was able to detect a significant increase in the total phospholipid, lecithin and dipalmitoyl-lecithin content. VAN PETTEN (36) examined the pressure volume relationships of premature lungs of rabbits after intrafetal application of prolactin and found no changes. SMITH (39) compared the prolactin level in the umbilical cord blood of prematures with and without RDS. The level was lower in those suffering from the RDS.

HALLMAN (15) infused pregnant rabbits with insulin in the latter third of pregnancy. Fetal blood glucose and insulin levels were found to be low, while at the same time there was accelerated fetal lung maturation.

LOHNINGER (27) described the body own betain Carnitin as an interesting alternative for prevention of RDS.

Bromhexine-Metabolite VIII has recently received a great attention. GERNER (8) only discussed a stimulant effect on surfactant secretion. VAN PETTEN (35) reported a positive effect of Ambroxol on lung maturation after his research work on lambs and rabbits fetuses.

The electronmicroscopic study of the human fetal lung tissue cultures from the first trimester of pregnancy

showed a significant stimulant effect of Ambroxol on lamellar corpuscles formation of the pneumocyte type II (43). The clinical observations of LORENZ (28, 29) showed a significant rise of L/S-ratio in amniotic fluid and rise in the palmitic acid level. No significant decrease in the morbidity and mortality of RDS after Ambroxol application was noticed (30). Better results in 106 cases were reported by WAUER (40). Application of Ambroxol was followed by increase in the total phospholipids, P/S- and L/S-ratio, and increase in the surface tension parameters of the amniotic fluid. The incidence of pulmonary hyaline membrane disease was reduced by about 50%. No side effects were detected. In a retrospective study on premature babies previously treated with Prednisolone, the incidence of RDS was also reduced. However, an increase in neonatal mortality during the first 28 days of life due to increased infection mortality could not be avoided.

In our department in Lübeck we have been trying to stimulate surfactant formation by providing a substrate. Our research was carried out on rabbits and mini-pigs (5, 11, 24, 25, 34). Radioactive labelled lecithin applied to the pregnant animals was found not to cross the placenta. On the other hand, 6 hours after its intra-amniotic application, lecithin was detected in the alveolar surface. It was concluded, that lecithin applied intraamniotically is first swallowed by the fetus, then absorbed from the intestine, metabolized in the liver and lastly synthetisized and concentrated in the lungs. This concept was also applied in 3 special clinical cases (10, 12, 13, 23). Lecithin was detected as before in the lungs.

Patients with threatened premature delivery between the 29th and 35th week of gestation were given 60 ml Intralipid, which is a fatty acid solution with high content of lecithin, under ultrasound control provided that the membranes were still intact. The table shows the results obtained up till now. Out of 51 cases of Intralipid application, 44 babies showed no signs of RDS. In 27 cases delivery could be inhibited till more than the 36th week. From the premature babies who showed no signs of RDS, one was born in the 30th week, eight were born between the 30th and 33th week, and eight were born between the 34th and 36th week. 6 premature babies born between the 34th and 36th week showed a transirorial RDS. Complications or side effects of Intralipid application could not be detected.

In a comparable collection of betamethasone treated babies, 14 premature out of 19 showed no signs of RDS. However, 2 premature babies developed a I-degree RDS,

2 developed a II- and III-degree, on one case a IV-degree RDS was observed.

Incidence of R D S after intralipidapplication

gestational age (weeks) / R D S	< 30	30 - 33	34 - 36	> 36	total
∅ R D S	1	8	8	27	44
transitorial			6		6
R D S I°					
R D S II°			1		1
R D S III°					
R D S IV°					
total	1	8	15	27	51

Table

The complications and contraindication of corticosteroid application for induction of lung maturation make it necessary to research for alternative methods. There are some very interesting observations, but still we need more clinical results.

(References demanded)

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