New technique for artificial lung maturation Direct intramuscular fetal corticosteroid therapy

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Summary

The aim of this study was to present a new technique of administration of antenatal corticosteroid therapy in order to cause fetal lung maturation.

A single dexamethasone dose of 4 mg was applied directly to the fetal gluteal musculature by ultrasound-guided intramuscular injection 48 h before delivery. This technique of fetal corticosteroid therapy was applied in six cases. Our patients had high risk pregnancies (preeclampsia diabetes mellitus, intracranial hemorrhage, epilepsy, hyperthyreosis). The pregnancies were terminated in the mother's vital interest. The lecithin/sphyngomyelin (US) ratio was <1.5:1. There were no procedure-related complications. The fetuses were delivered by cesarean, 48 hours later except for the vaginal delivery in the patient in which fetal death occurred in utero. In five cases an uneventful outcome of fetuses indicated that direct fetal corticosteroid treatment improved postnatal lung function in preterm fetuses.

A new technique of corticosteroid application successfully prevents respiratory distress in preterm infants decreasing the risk of maternal complications. To our knowledge, this is the first report of fetal intramuscular corticosteroid therapy in the human population.

Key words: Respiratory distress syndrome; Corticosteroid; Fetal intramuscular therapy; Lung maturation.

Introduction

Preterm labor is one of the major ethiological factors which give rise to neonatal morbidity and mortality. The leading cause of death and significant morbidity in preterm neonates is respiratory distress syndrome (RDS). Hyaline membranes were described in relationship with respiratory-associated deaths of the newborn in 1929 [1]. During the fifties presence of surfactant was proven in the foam of pulmonary oedema [2], and in the lung extract [3]. RDS has been known to be associated with surfactant deficiency since Avery and Mead's report in 1959 [4].

It is well known that surfactant is produced and secreted by type II epithelial cells in lung alveoli. It is composed of a monolayer of phospholipid that stabilizes the alveoli and consequently prevents alveoli to collapse at low volumes. Although the production of surfactant is noticable starting with the 20th week of gestation, it is found in larger concentrations around the 32nd week, when for the first time the ratio of lecithin and sphingomyelin reaches one.

Pulmonary maturity depends not only on the synthesis and secretion of adequate amounts of surfactant, but also on the development of sufficient gas exchange surface. The formation of competent structural matrix for airway and alveolar function with on adequate ratio of elastine and colagen increases lung compliance. Development of an endothelial and epithelial barrier is necessary for pulmonary functioning while the growth of lymphatic pathways allows efficient control of the fluid and protein fluxes in and out of the lungs. Maturation of pulmonary metabolic activities such as antioxidant systems, is essential for normal respiratory function. The pulmonary vascular epithelium normally has vasoactive substance clearance pathways.

In addition, other organ systems must function in concert to permit sufficient gas exchange. Maturity of the central nervous system and breathing musculature, as well as control of head position and pharyngeal musculature are obligatory for adequate postnatal lung function.

Following Liggin's observation that fetal corticosteroid treatment results in early lung maturation in sheep, there were numerous clinical trials on that subject [5]. Antenatal corticosteroid therapy given to the mother has improved the outcome of the preterm infant by reducing the risk of respiratory distress syndrome (RDS) and other major causes of morbidity such as intraventricular hemorrhage and necrotizing enterocolitis. Many studies have subsequently demonstrated that corticosteroids accelerate, in vitro and in vivo, the physiological, biochemical and morphological maturation of the fetal lung. The mechanisms of action are complex, with different effects on lung morphology and biochemistry which are likely to be dependent on gestational age.

In spite of strong evidence in favor of the use of antenatal corticosteroid therapy, there is wide variation as to their use in clinical practice. Less than 20% of preterm infants have been antenatally exposed to corticosteroids. The main reason for this situation is the fear from risks of maternal corticosteroid treatment. Special concern has been expressed that the corticosteroids might initiate or aggravate hypertension in mothers.

An alternative technique of corticosteroid application

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could overcome this problem. The aim of the study is to present a new technique of corticosteroid administration. The authors investigated the possibility of a single-dose, ultrasound-guided intramuscular corticosteroid treatment for fetal lung maturation on preterm fetuses.

Materials and Methods

We used a free hand technique with a Toshiba Eccossee 2000, with color Doppler mapping in order to avoid maternal and fetal blood vessels. A single dexamethasone dose of 4 mg (approximately 2.0 mg/kg) was administered directly to the fetus by transabdominal ultrasound-guided intramuscular injection 48 h before delivery. The site of application was the fetal gluteal musculature. A 22G needle was used. The mothers were sedated during intervention (Diazepam). The duration of the interventions was between one and two minutes. There were no incidents during corticosteroid applications. This technique of fetal corticosteroid therapy has been applied in six cases so far.

The protocol was approved by the Local Ethical Committee. After informed consent patients were enrolled in the study.

Results

A summary of basic characteristics of the pregnancies involved is given in Table 1. All of the fetuses had a L/S ratio which indicated that the fetal lungs were immature at the time we decided to terminate the pregnancies. They were all jeopardized by hypoxia. The first time we decided to apply corticosteroids directly to the fetus, the mother had suffered from intracranial bleeding a month before. She also had diabetes mellitus, and the L/S ratio was 1.5/1. Four patients had preeclampsia. One of our patients in addition to preeclampsia had a pregnancy which was complicated by epilepsy and hyperthyreosis. Two of our patients had fetuses with growth retardation. One patient (number 5) had diabetes mellitus with preexisting hypertension as well as nephrotic syndrome and superimposed preeclampsia. Patient number 6 had oligoamnion at admission; the fetus was growth-retarded and had evident signs of suffering.

Outcome of the pregnancies is shown in Table 2.

Table 1. — *Summary of cases treated with intramuscular fetal corticosteroid therapy.*

Case	HBD)	Diagnosis	CTG	Doppler flow analysis	L/S	Isolette (0_2)
1	38	St. post. hem. intracranial PIH Diabetes mellitus	non reactive	Pathological redistribution	1.5:1	1 hour
2	35	EPI Pre eclampsia Hyperthyreosis	non reactive	AED	1.3:1	3 days
3	33	IUGR PIH	non reactive	RED	1.3:1	2 days
4	33	IUGR PIH	non reactive DIP II	AED	mecon.	2 days
5	33	Diabetes Sy nephroticum Hypertensio art. Pre eclampsia	non reactive	pathological redistribution	<1:1	3 days
6	32	Anamnion IUGR	non reactive	pathological redistribution	<1:1	0

PIH = pregnancy-induced hypertension
IUGR = intrauterine growth retardation
AED = absence of diastolic flow in umbilical artery
RED = reverse diastolic flow in umbilical artery

Table 2. — *Outcome of cases treated with intramuscular fetal corticosteroid therapy.*

Case	Mode of delivery	Weight	HBD	SEX	TSR	Apgar at 1 and 5 min	Clinical outcome
1	CS	4200	39	M	15s	5/7	Uneventful
2	CS	3000	36	M	30s	6/7	Uneventful
3	CS	1100	34	F	30s	3/6	Uneventful
4	CS	1700	33	M	60s	1/3	Uneventful
5	CS	1750	33	F	60s	1/3	Uneventful
6	vag	1100	32	M	0s	0	FMU

TSR-time elapsed to spontaneous respiration

Five patients had a cesarean while the patient where fetal death occurred in utero had a vaginal delivery. We did not have RDS amongst the newborns. The intensive care unit stay was short. Morbidity was usual for babies of their gestational age. In one of the neonates (no. 4) a mild stage of intraventricular hemorrhage was diagnosed which was treated conservatively. The ultrasound examination of the central nervous system of the other neonates showed signs of hypoxic ischemic changes, due to early onset of intrauterine hypoxia. One of the neonates had hyperbilirubinemia. None of the newborns had an infection.

Discussion

It is likely that endogenous corticoids influence normal lung development; possible sources of cortisol include the fetal adrenal gland, maternal adrenal gland, and conversion of cortisone to cortisol by amniotic membranes and lung fibroblasts [6]. For almost 30 years since the first clinical reports appeared on prenatal corticosteroid treatment to enhance fetal lung maturation, this treatment has been studied in thousands of preterm newborns. These studies have demonstrated that prenatal steroid treatment reduces RDS among premature newborns at 26 to 34 weeks gestation [7].

The fetal lung responses to corticosteroids are multiple and affect many different systems that could influence a functional maturational response. The properties of glucocorticoid action are consistent with enzyme induction mediated by interaction of steroids with cytoplasmatic glucocorticoid receptors. Receptors are present in the lungs of many species, including the human fetus, and in both pulmonary fibroblasts and type II cells. Corticosteroids induce type II cell maturation by increasing surfactant phospholipid synthesis, as well as the production of surfactant associated proteins. They also induce lung structural maturation, influencing the

mechanical properties of the lung that are independent of alveolar surfactant. Corticosteroids increase the content of elastin in the fetal lung and decrease serum protein leakage into the airspace. Gas exchange surface area is increased as it is reflected by lung volume measurements. Corticosteroids accelerate maturation of the antioxidant system in the fetal lung.

The problem of maternal, transplacental administration is that corticosteroids must cross the placenta. The placenta is rich with 11-ß-ol-dehydrogenase which converts active steroids into inactive 11-ketosteroids. Therefore, the question has been brought up as to whether certain corticosteroids given to the mother reach the fetus in sufficient quantities to elicit their biologic effects, e.g. acceleration of fetal lung maturation [8]. The potent fluorinated steroids, betamethasone and dexamethasone, are more effective in accelerating lung maturation than are the less potent corticosteroids, cortisol, cortisone, and prednisone. Betamethasone crosses the placenta to the extent that fetal concentrations reach 33% of the maternal levels. Dexamethasone is a known ligand for type 2 glucocorticoid receptors, but is a relatively poor substrate for the placental 11-ß-dehydrogenase-2 enzyme, so it might possibly escape inactivation.

The advantageous effects of antenatal corticosteroid therapy need to be balanced with potential risks of treatment for the mother or baby. The potential suppression of maternal immunity with a corresponding increase in maternal and neonatal risk of infection is a repeatedly stated concern when using corticosteroids. Cases of pulmonary edema and maternal death have been reported in women receiving a combination of corticosteroid and tocolytic drugs or magnesium sulfate [9, 10, 11].

Hypertensive disease is a frequent indication for preterm delivery. Corticosteroids might initiate hypertension in normotensive women and aggravate it in those with already elevated blood pressure. The 48-hour postponement of delivery required to complete antenatal corticosteroid therapy may be unacceptable because of maternal risk of preeclampsia, aggravated by corticosteroid therapy [12].

Potentially harmful side-effects of corticosteroids have led to the testing of other drugs capable of accelerating fetal lung maturity. Ambroxol has been shown to significantly reduce RDS compared to a placebo, without causing important adverse effects either on the mother or the baby. Experimental studies on aminophylline and inositol have shown that those drugs exert only minor beneficial effects on fetal lung maturation and surfactant production [13, 14].

Other agents such as catecholamines, thyrotropin-releasing hormones, oestradiol, heroin and cyclic AMP also influence pulmonary phospholipid metabolism. Thyroid hormones have similar effects to corticosteroids, but they seem to influence different biochemical steps. Synthetic analogues of triiodothyronine (T3) are available which readily cross the placenta, in contrast to T3 and thyroxine, and accelerate surfactant synthesis and release. Thyroid hormones probably act through nuclear receptors which are present in the lungs of both animals and humans. Thyroid treatment in utero also appears to accelerate lung maturation and prevent RDS in premature infants [15].

All of the fetuses had immature lungs at the time we decided to conclude the pregnancy duration. They were jeopardized by hypoxia as was shown by non-invasive diagnostic procedures, cardiotocography and Doppler examination of fetal circulation. Three patients had preeclampsia (which was complicated by epilepsy and hyperthyreosis in one case and IUGR in the two other cases). The first time we decided to apply the corticosteroids directly to the fetus was because the mother had suffered from severe intracranial bleeding (previous month), had diabetes mellitus and an L/S ratio of 1.5/1.

Due to the risk of aggravation of hypertension, which has been brought up in the literature [12], we decided to take a less dangerous path for the mother – direct administration of corticosteroids. All pregnancies were terminated operatively due to inadequate conditions for labor induction as well as preexisting fetal hypoxia.

The outcome was extremely successful. We did not have a single case of RDS. The intensive care unit stay duration was very short. Morbidity was usual for the neonates of similar gestational age. In one of the neonates intraventricular hemorrhage of a mild stage was diagnosed which was treated successfully in a conservative manner. Ultrasound examination of the central nervous system of the other neonates showed signs of hypoxic ischemic changes as the result of an early beginning of intrauterine hypoxia. One of the neonates had hyperbilirubinemia. None of neonates had any infection.

Conclusion

Direct intramuscular fetal corticosteroid therapy could overcome these problems. With this new technique of fetal corticosteroid administration we bypass the placenta, avoiding 11-ß-ol-dehydrogenase conversion into inactive 11-ketosteroids. This technique enables us to predict the concentration of the medication in the fetal blood, as it is independent of placental degradation.

Harmful potential side-effects of corticosteroids to the mother, such as suppression of the immune system and risk of infection, interaction with other drugs (tocolytic drugs or magnesium sulfate), or aggravation of hypertension can be avoided using this new technique.

A simple technique for induction of fetal lung maturation has been described. We had no procedure-related complications. In all our cases an uneventful outcome of fetuses indicated that ultrasound-guided single fetal corticosteroid treatment improved postnatal lung function in preterm fetuses.

To the best of our knowledge, this is the first report of fetal intramuscular corticosteroid therapy for lung maturation in the human population.

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