Artificial fetal lung maturation - Prevention of antenatal complications in premature deliveries

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Summary

Keeping in mind the frequency of preterm deliveries as well as the morbidity and mortality of the newborn population, many ways of bringing about faster maturation of the fetus have been. Today, we can say that after the 24th week of gestation, when the pneumocites time 2 are anatomically formatted, medical treatment of the fetus for maturation not only of the lungs but all the vulnerable organs is available. By stimulating the pneumocites to make surfactant and sphingomyeline and phosphatidilinositol and phosphatidilglycerol, we can reduce respiratory distress syndrome. Moreover, the frequency of intracranial haemorage is lowered. We have performed many studies with all of their positive and negative effects, including: use of corticosteroids, thyroxine, aminophilline, surfactant, inositole and beta adrenergic agonist.

Key words: Artificial fetus maturation; Corticosteroids; Thyroxine; Aminophilline; Surfactant; Inositole; Beta-adrenergic agonist.

Introduction

In all situations when pregnancy should be ended prematurely, whether because of maternal or fetal indications, or indications of the fetoplacental unit, it is necessary to choose the most efficient and proper way of artificial maturation.

Artificial fetal lung maturation is usually conducted by corticosteroid therapy given to the mother prenatally or directly to the fetus under ultrasound control, but also by the use of thyroxin, aminophylline, oxytocine and surfactants.

Glucocorticoids

It has been known for many years that neonates born before term, in conditions where mothers suffer from chronic blood vessel diseases, show a greater degree of maturity than in conditions where those deliveries are ended by surgery.

Our conclusion was that glucocorticoids do not directly influence fetal lung acceleration, but lead to biochemical changes that secondarily provoke uterine contractions and fetal oxygen fluctuations, leading to acceleration of fetal lung maturation.

Among all glucocorticoids, bethamethasone and dexamethasone are the preferred hormones used in antenatal therapy. They have identical biological activity and cross the placenta immediately in their biological forms. Both of them are known ligands for type 2 glucocorticoid receptors, but both preparations are modest substances for placental 11 beta-HSD type 2 enzymes to avoid inactivation.

Bethamethasone crosses the placenta, so 33% of maternal concentration value is present in fetal circulation.

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Both hormones have relatively low immunosuppressive activity and a longer period of activation compared to cortisol and prednisone. In experimental rat models, both bethamethasone and dexamethasone were pharmacologically identical. However, in fetal surfactant production, bethamethasone has greater potential.

Glucocorticoids lead to increased synthesis of surfactant proteins, increasing the process of transcription of proteins SP-A and SP-B.

Conclusions of indications, methods, doses and effects of prenatal corticosteroids

There is a direct decrease in respiratory distress syndrome (RDS) - mortality and intraventricular hemorrhage (IVH).

All fetuses between the 24th and 34th week of gestation - in danger of premature delivery should undergo artificial fetal lung maturation, as recommended by the USA National Health Institute in 1995 to establish a general recommendation for the use of glucocorticoids (GC) in inducing fetal lung maturity (FLM) in fetuses at risk of premature delivery.

In newborns born between the 29th and 34th week of gestation, antenatal corticosteroid treatment evidently decreases the incidence of RDS and mortality.

Antenatal corticosteroid therapy used between the 24th and 28th week of gestation does not significantly decrease the incidence of RDS. However, it does evidently decrease the incidence of IVH in this group. All fetuses between the 24th and 34th week of gestation with suspected premature delivery are candidates for corticosteroid therapy at the 34th week of gestation, the risk of neonatal mortality, RDS and IVH is small. The analysis of antenatal corticosteroid therapy in this group is limited. Thus, corticosteroids are generally not used in artificial fetal lung maturation above the 34th week of gestation, except in conditions of confirmed lung immaturity.

The use of corticosteroid therapy does not depend on gender or race, and it is not related to further need of surfactants.

Patients undergoing tocolytic therapy have to be subjected to corticosteroid therapy with caution.

Therapy effect is achieved by the application of two doses of 12 mg of bethamethasone IM every 24 hours, or four doses of 6 mg of dexamethasone every 12 hours. Optimal benefits are achieved after 24 hours from the initial dose and last for seven days. In practice, these doses enabled decreased RDS incidence in newborns in the studies. With these doses, 75% of receptors sensitive to corticosteroid therapy are occupied. Larger doses do not increase the efficiency of the therapy but corticosteroid therapy shows effects 24 hours after the initial dose and it has been proved that even the initial application of corticosteroids decreases neonatal mortality, RDS and IVH to a certain degree. However, corticosteroids should be started even if delivery starts by premature rupture of membranes between the 30th and 32nd week of gestation. In the absence of chorioamnionitis, glucocorticoids are applied primarily to prevent IVH and to achieve effects at least 24 to 48 hours are necessary. The most adequate effect is in the next 3 to 4 days.

In complicated pregnancies up to the 34th week of gestation, if there is danger of premature delivery, corticosteroid therapy gives evident results.

At the European Congress of Perinatal Medicine held in Brussels in 1982, it was presented that diasoxide can partially postpone premature delivery, and if postponed more than 72 hours the percentage of RDS in children born weighing 800 to 1300 g is significantly decreased. If delivery is postoponed for less than 48 hours, the relative frequency of RDS is 52%.

We use diasoxide as a tocolytic agent because it does not have negative effects on neuromuscular junctions nor does it disturb fetal breathing movements.

Keeping in mind that the fetus should be kept intrauterine for 72 hours after steroid administration, no specific system of maturation is needed except endogenous release of RTH-TSH-T3 and T4 which would lead to maturation. It is not yet clear if this therapy increases neonatal or maternal infection, nonetheless, the risk of death is higher than the risk of infection.

Data obtained by following children until the age of 12 do not show complications in their growth or psychomotor development.

Antenatal corticosteroid therapy is indicated in all maternal conditions at risk of premature delivery and it leads to decreased neonatal mortality and morbidity, and evident decreases in healthcare costs.

The use of corticosteroids in artificial fetal lung maturation is one of the rare decreasing: that enhances health conditions of the population and evidently decreases the costs of healthcare.

Among all hormones used in fetal lung maturation acceleration, glucocorticoids given to the mother are most effective in

- Infant respiratory disease syndrome (IRDS);
- Intraventricular hemorrhage (IVH);
- Periventricular leukomalatia (PVL);
- Retinopathy of prematurity (ROP);
- Necrotizing enterocolitis (NEC);
- Persistent ductus arteriosus (PDA).

Type of corticosteroids

Dexamethasone and bethamethasone are the most adequate corticosteroids for antenatal therapy. These two components are identical in biological activity and cross the placental barrier actively in their biologically active forms. They are free of mineral corticoid activity and have very weak immunosuppressive activity, thus having a longer activation time than cortisol and methylprednisolon. They are also the most studied corticosteroids in artificial fetal lung maturation.

Time evaluation

Large positive effects of corticosteroid therapy begin within 24 hours and last up to seven days. Possible benefits or risks of repeated doses after seven days are unknown. Human fetal lung in in vitro experiments show that induced biochemical changes disappear within seven days, but newly formed structural changes persist.

Preterm premature rupture of membranes (PPROM)

The use of antenatal corticosteroids to decrease newborn morbidity remains controversial. Antenatal application of corticosteroids has reduced the incidence of RDS in PROM in randomized controlled trials, even though the amplitude of RDS reduction is not as high as in conditions where membranes are intact. However, there is significant evidence of decreases of IVH between the 30th and 32nd week of gestation, thus the use of antenatal corticosteroids in conditions where there is no chorioamnionitis is justified.

Other conditions

Data about treating patients with hypertension and diabetes mellitus are not reliable enough. If there are no evident contraindications or side-effects of corticosteroid usage, they belong to the same group of corticosteroid application as in those conditions with the danger of premature delivery. In pregnancies burdened with hypertension, the use of corticosteroids decreases the possibility of HELLP syndrome but it is necessary to follow the basic principles of corticosteroid therapy and to eliminate any contraindications.

Also, in conditions with multiple gestations, intrauterine growth retardation and fetal hydrops, patients should undergo antenatal corticosteroid therapy.

Indications for early delivery in relation to maternal condition are preconditions for artificial fetal lung maturation, observing basic principles and contraindications.

Among possible maternal complications, pulmonary edema should be kept in mind if glucocorticoids are applied together with tocolytic therapy. The mechanisms of glucocorticoid and betamimetic interactions include:

- Increased electrolyte retention and retention of water in the lungs;

– Increased medium arterial pressure;
– Disturbance of membrane forms;
– Decreased blood vessel resistance.

The possibility of maternal pulmonary edema increases in cases of multiple gestations and maternal infections. There are many reports about maternal deaths in cases where glucocorticoids were combined with tocolytic therapy.

The relation between glucocorticoids and maternal estriols is evident. When maternal estriols begin to fall, there is no RDS. However, estriol values that remain unchanged or are increased cause fetal RDS.

Glucocorticoids also influence fetal behavior. They level the diurnal rhythm of fetal hormones. Bethamethasone leads to decreased fetal breathing, fetal movements and fetal heart rate. When the therapy is stopped, all described effects disappear. Dexamethasone leads to increased frequency of FHR.

Among all hormones used in fetal lung maturation acceleration, glucocorticoids given to the mother are the most effective in decreasing:
– IRDS incidence;
– IVH;
– PVL;
– ROP;
– NEC;
– PDA.

Recommendations for the use of corticosteroid therapy

Generally the US National Institute of Health official guidelines are followed on the use of glucocorticoids in fetuses in cases of preterm deliveries:

1) Indications: Pregnancies between the 24th and 34th week of gestation where delivery is estimated within 24 hours.

Pregnancies above the 34th week of gestation with proven fetal lung immaturity.

2) Absolute indications: chorioamnionitis, peptic ulcer and tuberculosis.

3) Dosage - Bethamethasone, 12 mg (50% phosphate, 50% acetate) IM for 24 hours, divided into the next three days (pregnant patients under 70 kg of body mass according to body mass index, 0.2 mg/kg).

All fetuses between the 24th and 34th week of gestation can be potential candidates for this method. The exception is a case when delivery may start within the next 24 hours or if there are maternal contraindications. If PPROM starts before the 30th or 32nd week of gestation and if there is no chorioamnionitis, glucocorticoids are recommended in order to decrease the possibility of IVH.

To achieve the desired effects of corticosteroid therapy, it is necessary to wait 24 to 48 hours after administration for the delivery.

Our clinical experience shows the great efficacy of corticosteroid therapy.

Artificial fetal lung maturation by thyroxin

The data has shown significant effects, thus this therapy has started to be applied in humans after animal models.

However, prenatal therapy by thyroxin has not been examined in detail like glucocorticoids. Therapy is applied by injection of 500 μg of levo-thyroxin sodium into the amniotic cavity, with repetition of the same dose after three to five days. The efficacy is almost identical to steroid therapy.

The multifold efficacy of corticosteroids in combination with TRH has been proven.

Side-effects of TRH were found when TRH stimulation was conducted in the period that is crucial for development of the fetal nervous system and fetal brain.

Nonetheless the results of combined thyroid hormones and glucocorticoids were negated in the large Austrian study with 1,234 women between the 24th and 31st week of gestation. By administering 200 μg of thyroid hormone in four individual doses in combination with glucocorticoids, a significant decrease in RDS was obtained together with reduced need of assisted ventilation of premature neonates. On the contrary, maternal side-effects, such as nausea, vomiting, headache and hypertension (140/90 mmHg) were significant in relation to the positive effects of this combined therapy.

Artificial fetal lung maturation by aminophylline

Aminophylline and betamimetics

Even though good effects have been obtained by prenatal aminophylline, this approach needs additional research. It is supposed that aminophylline acts through the increased concentration of cyclic adenosine 5-monophosphate (cAMP) to intracellular surfactant synthesis, but also to the indirect surfactant depot discharging out of the pneumocytes.

Aminophylline acts as a central breathing stimulator, smooth muscle relaxant (uterus, bronchia and blood vessels), leading to bronchodilatation in immature lungs. Aminophylline increases fetal breathing pocesses thus it can be useful in the prevention of fetal pulmonary hypoplasia in the increased possibility of entering surfactants in utero application, and in treating apnea and immaturity. Aminophylline is a promising solution but its application in decreasing IRDS needs further study.

Aminophylline increases fetal breathing activity and it can help the effects of artificially administered injected surfactant.

Artificial fetal lung maturation by surfactants

Surfactants

By applying surfactants the incidence of respiratory tract insufficiency is prevented, but immaturity of other organs is not influenced. Very often, if there are technical and material possibilities, the combination of these two methods is applied.

Treatment includes administration of surfactants into the lower trachea by the endotracheal tube in newborns with a body weights from 600 to 2000 g who show clinical and radiological signs of RDS, and require intermittant positive pressure ventilation (IPPV) determined by FiO2 more than 40% and less than 60%.

In order to achieve the desired effects, the following criteria should be satisfied:

1. Surfactant is injected by the needle for amniocentesis under ultrasound control near the nostrils or mouth of the fetus and its spread into the upper respiratory paths can be observed.
2. Fetal breathing movement (FBM) is increased by giving aminophylline to the mother.
3. To a certain extent, aminophylline leads to smooth muscle relaxation and decreased resistance to surfactant passage through the trachea.
4. Part of the surfactant enters the fetal gastrointestinal tract.

Administration includes giving bolus aminophylline (240 mg) to the mother for ten minutes in the form of IV infusion 0.1-0.2 mg/kg/min. By subsequent color Doppler increased fetal breathing activity can be confirmed, and when breathing movements appear, the needle for amniocentesis is placed near the fetal mouth and 80-120 mg of Curosurf surfactant is applied.

Some aspects undoubtedly show the positive effects of surfactant intraamnional application in combination with aminophyline infusion given to the mother:

1. Surfactant injected near the fetal nostrils or mouth enters the fetal trachea.
2. Aminophylline given to the mother increases fetal breathing movements which is confirmed by subsequent color Doppler.
3. The decrease of bronchial smooth muscle resistance enables the passage of surfactants.
4. Surfactants are partially swallowed by the stomach.
5. Surfactant distribution is continued to the smallest fetal lung alveoli.

Artificial fetal lung maturation by inositole

Basic study

Inositole, alcohol sugar, is a preparation similar to vitamins, and is included in the growth and determination of cell membranes responsible for signal spreading.

Because of a glucocorticoid effect to lung growth and body mass indexes, inositol was given in combination with glucocorticoids to pregnant animals and the effects of the growth parameters were observed. Animal studies show that inositole administration increases surfactant secretion in the lungs of pregnant rabbits. There is an increase in the weight of the lungs, protein contents and DNA. A special significance of inositole administration can be seen in male neonates where inositole together with bethamethasone leads to decreased IRDS statistically more often than with bethamethasone alone.

Artificial fetal lung maturation by beta adrenergic agonists

The mechanism of fetal lung maturation by betamimetic agents has been studied in many experimental studies and it includes:

1. An increase of uterine blood flow and placental phospholipid transfer from mother to fetus.
2. Decrease or suppression of collagen synthesis in the lungs, influencing the mechanical characteristics of fetal lungs.
3. Decreased lecithin precursor incorporation in pneumocytes type 2; under in vitro conditions ritodrin leads to a choline increase or plamitat decrease, while inoxsuprine leads to a mild decrease of both precursors.
4. Production and secretion of surfactants in type 2 epithelial cells.
5. Synergism in other markers of fetal maturity.

References

[1] Liggins G.C., Howie R.N.: "A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants". *Pediatrics*, 1972.
[2] Cosmi E.V., Caldeyro-Barcia R.: "Fetal Homeostasis". In Cosmi E.V.: ed. "Obstetric Anesthesia and Perinatology". New York: Appleton Century Crofts, 1981, 103.
[3] Cosmi E.V., Anceschi M.M., Piazze J.J. *et al.*: "Prevention of fetal and neonatal lung immaturity". In: Kurjak A. (ed.). Textbook of Perinatal Medicine. Camdon, UK, Parthenon Publishing, 1998, 1382.
[4] Anceschi M.M., Palmerini M., Codini M. *et al.*: "Collagen and elastin in rabbit fetal lung: Ontogeny and effects of steroids". *J. Dev. Physiol.*, 1992, *18*, 233.
[5] Robertson B.: "Corticosteroids and surfactants for the prevention of neonatal IRDS". *Ann. Med.*, 1993, *25*, 285.
[6] Ervin M.G., Seidner S.R., Leland M.M. *et al.*: "Direct fetal glucocorticoid treatment alters postnatal adaption in premature newborn baboons". *Am. J. Physiol.*, 1998, *274*, R1169.
[7] Witlin A.G., Saade G.R., Mattar F. *et al.*: "Predictors of neonatal out-come in women with severe preeclampsia of eclampsia between 24 and 33 weeks' gestation". *Am. J. Obstet. Gynecol.*, 2000, *182*, 607.
[8] Elimain A., Verma U., Canterino J. *et al.*: "Effectiveness of antenatal steroids in obstetric subgroups". *Obstet. Gynecol.*, 1999, *93*, 174.
[9] Chitrit Y., Caubel P., Herrero R. *et al.*: "Effects of maternal dexamethasone administration on fetal doppler flow velocity waveforms". *Br. J. Obstet. Gynaecol.*, 2000, *107*, 501.
[10] Piazze J.J., Anceschi M.M., La Torre R. *et al.*: "Effect of antenatal betamethosone therapy on maternal-fetal doppler velocimetry". *Early Hum. Dev.*, 2001, *60*, 225.
[11] Dodie M., May C.N., Wintour E.M. *et al.*: "An early prenatal exposure to excess glucocorticoid leads to hypertensive offspring in sheep". *Clin. Sci.*, 1998, *94*, 149.
[12] Anwar M.A., Schwab M., Poston L. *et al.*: "Betamethasone-mediated vascular dysfunction and changes in hematological profile in the bovine fetus". *Am. J. Physiol*, 1999, *276*, H1137.
[13] Shelton S.D., Boggess K.A., Murtha A.P. *et al.*: "Repeated fetal betamethasone treatment and birth weight and head circunference". *Obstet. Gynecol.*, 2001, *97*, 301.
[14] Abbasi S., Hirch D., Davis J. *et al.*: "Effect of single versus multiple courses of antenatal steroids on neonatal outcome". *Am. J. Obstet. Gynecol.*, 2000, *182*, 1243.
[15] Banks B.A., Cnaan A., Morgan M.A. *et al.*: "Multiple courses of antenatal corticosteroids and outcome of premature neonates". *Am. J. Obstet. Gynecol.*, 1999, *181*, 709.
[16] Haynes R.C. Jr.: "Adrenocorticotropic hormone: Adrenocortical steroids and their synthetic analogs. Inhibitors of the synthesis and actions of adrenocortical hormones". In: Goodman L.S., Gliman A., Rall T.W. (eds.): "The Pharmacological Basis of Therapeutics", 8th ed. New York: Pergamnon Press, 1990, 1431.
[17] Helal K.J., Gordon M.C., Lightener C.R. *et al.*: "Adrenal suppression induced by betamethasone in women at risk for premature delivery". *Obstet. Gynecol.*, 2000, *96*, 287.

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