NEW ASPECTS OF ANTENATAL CORTICOSTEROID THERAPY FOR FETAL MATURATION;WHICH STEROIDS TO GIVE AND REPEAT COURSE VALIDITY: REVIEW

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SUMMARY

Prematurity is the major cause of neonatal death and antenatal corticosteroid administration is one of the main, sometimes the only positive intervention that the obstetrician is able to offer to improve the outcome of the premature infant. The current benefit and risk data are insufficient to support routine use of repeat or resque courses of antenatal corticosteroids in clinical practise. We searched literature for new aspects of antenatal corticosteroid therapy for fetal maturation and evidence obtained was reviewed and evaluated

Key Words: Antenatal corticcostroids, fetal maturation

FETAL LUNG MATURATION

During the final prenatal period of fetal lung development in humans, important maturational processes occur, including the production of surfactant necessary to decrease surface tension at the air-liquite interface of alveoli.[1] During early gestation, the glucocorticoid receptor is expressed in the fetal lung, and glucocorticoids stimulate the production of surfactant associated proteins and increase phospholipid synthesis by enhancing the activity of phosphatidylcholine. Recently it was suggested that glucocorticoids are also important in postnatal pulminonary development and may be related to the development of the neotanal lung disease in preterm infants.[2] Surfactant deficiency that can be prevented by antenatal corticosteroid treatment causes infant respiratory distress syndrome and requires mechanical ventilation. Ventilation by itself or in combination with high levels of oxgewn, fluid overload, pulmonary infections,sepsis and air leak syndrome causes an acute pulmonary inflammatory reaction that may result in chronic lung disease or bronchopulmonary dysplasia.[3] Glucocorticoids are effective in the treatment of the chronic lung disseace of prematurity and regulate the inflammatory response by the interaction with tracription factors such as nuclear factor of chemokines and cytokines in bronchoalveolar fluid which decrease after dexamethasone treatment. However treatment of fetuses and preterm infants with repeated and/or high doses of corticosteroids may have considerable long term side effects on somatic, brain and lung growth. The difficult balance between short term gain and the possible long-term side effects of glucocorticoidsin preterm remains as difficult issue.[4]

BENEFITS OF CORTICOSTEROIDS USED ANTENTALLY

In 1972 Liggins and Howie described the beneficial effects of corticosteroid administration to accelerate lung maturity in premature infants. Since then corticosteroids have been used to reduce morbidity and mortality in preterm neonates with great success.[2,5] Corticosteroids are poverful regulaturs of differentiation and maturation in the central nervous system. They regulate maturation of oligodentrocytes and hence myelination and can alter brain development. Most studies agree that the effects of steroids correspond to their dose. Till the results of the proposed randomized trials are available, obstetricians need to temper their enthusiasm for repeated administration of antenatal corticosteroids.[6] Pregnant who are thought to be at risk of preterm delivery are

routinely offered a short course of corticosteroids because there is compelling evidence that this intervention reduces neonatal death, respiratory distress syndrome, and neonatal intraventricular hemorrhage without causing any harmfull long therm side effects.[7] The administration of corticosteroids to accelerate fetal lung maturity has become the standart of care in the world for nearly all women at risk of preterm delivery between 24 and 34 weeks of gestational age and are not limeted by the infant's gender of race. Review of meta-analyses based on randomized trials supports general option that premature infants whose mothers received corticosteroids before delivery are less likely to develop RDS and this complications. In the presence of premature rupture of membranes or better with intact membranes,antenatal corticosteroids reduce frequency of intraventricular hemorrhage (IVH)and finally mortality and morbidity.[6,7]

The beneficial effects of corticosteroids are the best pronounced after more than 24 hours from the begining of the treatment.Noteworthy is the threapy less than 24 hours of duration may also improve. Recent data showed that benefits derived from antenatal corticosteroids (ANS) are additive to those of surfactant therapy, rendering the latter more effective. Follow up of children up to 12 years of age indicate that ANS do not impair physical growth or psychomotor development. Short term adverse effects including maternal infection,maternal pulmonary edema were not clearly demonstrated. Pulmonary edema has not been reported when ANS were used alone (i.e not in combination with betamimetic tocolytics). No long term unwanted effects on maternal adrenal function have been observed.[1,3,6,7]

There is no serious maternal risk resulting from immunsuppressive effect of corticosteroid therapy on maternal ımmune system. Alhtough glucocorticoid therapy is likely to provoke insulin resisdance, and thereby deterioration in diabetic control, and potentially causes cortisol resistance in the fetal lung,the results of scarce ramdomized trials are not conclusive. Current available data are not indicative of higher risk of fetal mortality in association with maternal hypertensive disease and ANS.[5,6,7]

HARMFUL EFFECTS AND RISKS

We also reviewed current animal and human data regarding possible adverse fetal effects and risk from antenatal steroid treatment. Data have also raised concerns that relate to a transient increase in bone resorption and osteonecrosis of the maternal femoral head.[8] In addition, a recent Australian cohort study of 477 preterm neonates reported that fetal growth restriction in 9% of babies whose mothers were given repeated doses of corticosteroids antenatally.[9] The potential risk of multiple doses of steroids are possible suppression of fetal hypothalamic adrenal axis,growth retardation or neurodevelopmental delay. Newborn infants whose mother's had received multiple corticosteroids for lung maturity exhibited an appropriate response to external stresses such as infection allaying the fear about fetal hyphothalamic adrenal axis suppression. Animal studies have shown retardation of brain development with the use of antenatal steroids however the animals used were small the dosage used was higher and for prolonged duration with a shorter period gestation.[9,10,11] A recent nonrandomized analysis of 710 neonates enrolled in the North American Thyrotropin-Releasing HormoneTtrial showed that more than two courses of antenatal steroids were associated with a small decrease in fetal growth, did not improve survival and there was no change in the head circumference.[12]

SINGLE VS WEEKLY COURSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN AT RISK OF PRETERM DELIVERY

We evaluated studies of single versus repeat courses of antenatal corticosteroids for benefits and risk thought a review of published literature and data presented during the consensus conferences. The clear evidence that a single course of antenatal corticosteroids improve neonatal outcome has led obstetricians to give futher courses to women who remain at risk of preterm delivery 7-14 days after their first course.[1] The optimal benefits of antenatal corticosteroids are seen 24 hours after administration, peak at 48 hours, and continue for approximately seven days. If therapy for preterm labor is succesful and the pregnancy continues beyond 1 week,there appears to be no added benefit with repeated courses of corticosteroids. In fact, multiple courses may be associated with delayed pyschomotor development in the infant.[2,7,12] In many units some women could receive weekly courses of corticosteroids from 24 weeks until 34 weeks (11 courses) or in some cases even longer. No unbiased evidence exists that this practice is of benefit and recent animal studies have shown that it has the potential to cause harm.[7]

There is evidence that there may be a decrease in the incidence of RDS secondary to the use of multiple doses of antenatal corticosteroids: However, a concomitant increase in neonatal deaths may also occur. A single course of corticosteroids reduces perinatal mortality, respiratory distress syndrome, and intraventricular hemmorrhage. Information regarding repeat courses of corticosteroids is limited and conflicting, with many studies being retrospective and nonrandomized.[13] Some studies suggested a reduction in respiratory distress syndrome with repeat courses, but some found increased rates of neonatal and maternal infections adrenal suppression; decreased fetal or neonatal somatic and brain growth; and incresead perinatal mortality.[14,15] Growning number of studies have demonstrated harmful effects that have been associated with multiple courses of antenatal steroids. Despite this, it should not be forgotten that multiple courses of antenatal steroids may have benificial effects and the assumption underlying their widespread use may be correct. It is possible that both beneficial and harmful effects could be caused simultaneously.[16] A greater number of recent studies have suggested harm than have suggested benefit but this could be because more studies have investigated adverse outcomes or there has been selective reporting of results suggesting harm.[17] In 2001 Thorp JA et al have made a study. This study was undertaken to determine whether prolonged betemedhasone therapy is, as an has been suggested, associated with adverse maternal or neonatal outcomes. A randomized controlled trial was performed to determine whether duration of betamethasone therapy was associated with adverse maternal or neonatal outcomes. They found that prolonged antenatal betamethasone therapy was not associated with higher risk of antenatal maternal fever, chorioamnionitis, reducedbirth weight, neonatal adrenal suppression, neonatalsepsis, and neonataldeath.[18] However, another very recent randomized, double blind placebo controlled trial conducted in 13 centers to evaluate the efficacy of weekly administration of antenatal corticosteroids compared with a single course in reducing the incidence of neonatal morbidity and to evalu ate potential complications of weekly treatment showed that weekly courses of antenatal corticosteroids did not reduce neonatal morbidity compared with a single course of treatment. So, they resulted in that weekly courses of antenatal corticosteroids should not be routinely prescribed for women at risk of preterm delivery.[19] There is no good evidence that repeated courses reduce death or respiratory distress syndrome more than a single course. Moreover there is a possibility that they may be harmful. Recent evidence from animal studies has suggested that repeated courses may have a variety of detrimental effects on the fetus including neurodevelopmental delay, growth delay, and adrenal suppression. Evidence from randomized controlled trials in animals suggests that repeated doses of antenatal corticosteroids may have beneficial effects in terms of lung function but may have adverse effects of brain function and fetal growth.[13] Because of the differences between animals and humans it is difficult to extrapolate directly the results of theses studies to humans. A recent cohort study was carried out in mothers of singleton infants who had more than five courses of betamethasone (80-120 mg cumulative dose). Patients were compared to concurrent controls who had taken one course of corticosteroid therapy. There was no significant difference between groups in head circumference, length, and body weight at birth and at age 4 years. The ability to sit and to walk without assistance and to use two-word phrases was attained at similar ages. The use of glasses or hearing aids, allergies, asthma or recurrent upper respiratory infections were not reported more frequently in repeated course group.[20]

This study failed to ascertain adverse long-term effects of repeated antenatal corticosteroids administration in infants and children to the age of 4 years. Therefore, more randomized, controlled trials in humans are needed to assess the effects of pregnant women who are at increased risk of preterm birth in terms of important perinatal, neonatal and maternal outcomes.

So it would be prudent to minimize antenatal steroid treatments to a single course with repeated dosing only if there is a persistent threat of preterm delivery. The practice of giving weekly infections of steroids starting at fetal viability and continuing into the third trimester is not supported.

Another aspect from the literature suggest that improvement in lung function after repeated courses depends on the reduction of the treatment/birth interval and not to the rise of cumulative dose. These benefits must be balanced against the risk of decreased birth weight induced by repeated courses. A recent retrospective chart review of 204 patients showed that Apgar scores, neonatal hospital stay, specific neonatal morbidity and combined morbidity were not different between the two groups. Combined neonatal morbidity was higher after three courses antenatal steroids. Weekly antenatal steroids did not improve neonatal morbidity.[21] In preterm animals, multiple doses of antenatal corticosteroids improve lung function when compared with a single dose. These benefits include improved lung mechanics and gas exchange as well as increased lung volume and

surfactant pools.[13] No published data on any of the possible benefits to humans of repeat courses of antenatal corticosteroids were available from randomized controlled trials and the data from nonrandomized controlled trials were limited in quality. Despite their limitations these studies suggested possible benefits in reduction of the incidence and severity of respiratory distress syndrome and reduction in the incidence of patent ductus arteriosus. There is little or no evidence to support other possible benefits including a reduction in mortality rate or reductions in the incidence of intraventricular hemorrhage, chronic lung disease, sepsis, necrotizing entercolitis or retinopathy of prematuriety. With the usage of multiple courses of corticosteroids no increase in cerebral palsy and no consistent effect on intraventricular hemorrhage was apparent from the available data.[22,23]

Neurodevelopmental follow-up studies suggest an increase in psychomotor delay and behavioral problems. Data from studies on both animals and humans raise questions about the safety of repeat doses of antenatal corticosteroids. Animal studies have also shown dhat repeat courses of antenatal corticosteroids have deleterious effects on lung growth and organization of cerebral myelination, the function of the hypothalamic pituitary adrenal axis and retinal development. In addition there is evidence for a dose dependent effect on fetal growth and persistence of immature lung architecture. Evidence from human studies on both the short and long term adverse effects of repeat doses of corticosteroids is contradictory and therefore inconclusive.[22,23,24]

WHICH STEROID TO USE

A single course of steroids, 24 mg betemethasone or dexamethasone, given in 2 to 4 doses does not seem to result in long term adverse effects although relatively few follow-up studies have been carried out. However betamethasone causes a temporary – yet considerable – reduction in fetal heart rate variation as well as in fetal breathing and body movements. Familiarity with this phenemenon prevents unnecessary medical intervention (because of presumed fetal distress).[25]

The effect of betamethasone versus dexamethasone on fetal biophysical parameters are searched in clinical observations, which suggest that betamethasone reduces maternal perception of fetal movements and short term variability, but that this dose not occur after treatment with dexamethasone. A recent randomized, prospective study in 2001 has shown that when comparing the effect of betamethasone and dexamethasone on fetal biophysical parameters, unlike betamethasone, dexamethasone does not induce a decrease in fetal movements. Dexamethasone might, therefore, be preferred for enhancement of lung maturation in imminent preterm labor.[26] But in another study, a placebo controlled comparison between betamethasone and dexamethasone for fetal maturation; differences in neurobehavioral development of mice offspring were evaluated (to determine whether antenatal betamethasone or dexamethasone is the preferred drug for neurobehavioral development assesment of exposed mice offspring). In this study, corticosteroid treatment did not induce significant changes in sensory, motor, motivation and learning performances or in reproductive capability and progeny development. Subtle differences in offspring performances of neurobehavioral development tasks favored antenatal betamethasone rather than dexamethasone. This finding, along with the knowledge that dexamethasone is less potent in accelerating lung maturity in the fetal mouse, suggests that betamethasone may be the preferred corticosteroid to use when human preterm delivery is imminent.[27] Both dexamethasone and betamethasone appear to be ideal corticosteroids for enhancing fetal maturation when they are given between 24 and 34 weeks gestation. These drugs are similar in structure and function have a long half life (up to 72 hours) and cross the placenta in biologically active forms.

Treatment should consist of either two doses of 12 mg betamethasone intramuscularly given 24 hours apart or four doses of 6 mg of dexamethasone intramuscularly given 12 hours apart. Optimal benefits begin 24 hours after administration of therapy and last for 7 days.[28]

Differential effects of maternal betamethasone and cortisol on lung maturation and growth in fetal sheep was searched in pregnant sheep, maternal betamethasone decreased the birthweight by 16% and induced lung maturation. Fetal cortisol or betamethasone induced only lung maturation. Maternal cortisol treatments had no apparent effects on the fetus, suggesting that growth restriction caused by betamethasone may result from unidentified effects on the maternal-placental unit.[29] There is limited information about alternatives to bethamethasone and dexamethasone for the enhancement of fetal lung maturity in women at risk of preterm delivery. However, in the absense of these two preferred drugs, hydrocortisone can be given at a dose of 500 mg intravenously every 12 hours for four doses for this indication.[30]

Recommendation

The literature was examined for evidence regarding a dose response of the benefits and detriments of antenatal corticosteroids. Here, we present the last point which was the world opinion come for antenatal corticosteroid therapy for fetal maturation (American College of Obstetricians and Gyneco logists, The National Institute of Child Health and Human Development and the Office Medical Applications of Research of the National Institutes of Health convened conferences in 1994 and 2000 and Maternal Fetal Medicine committee of the Society of Obstetricians and Gynaecologists (Canada assessment in 2003).[6,12,31,32]

1. All pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 dats should be considered candidates for antenatal treatment with a single course of corticosteroids.

2. Treatment should consist of two 12 mg doses of betamathasone given in 24 hours apart, or four 6 mg doses of decamethasone given in 12 hours apart. There is no proof of efficacy for any other regimen.

3. Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids including so-called "rescue therapy" should not be routinely used but should be reserved for women enrolled in clinical trials.

Also in 2002 from California University, Caughey AB and Parter JT have made another logical decision analysis which was very near to the above recommendation. They reviewed the evidence regarding multiple versus single courses of antenatal corticosteroids. 138,000 patients who presented between 27-34 weeks of gestation at risk for preterm delivery, with 91,915 deliveries were assessed.[33]

On the basis of their results, They recommended the following:

1- All fetuses between 24 and 34 weeks' gestation at risk for preterm delivery should be given the first course.

2- If there is a persisting risk of preterm delivery subsequent to this, the next course should be given two weeks later.

3- No more than 2 courses should be given. These recommendations need to be examined in a randomized controlled trial.

CONCLUSION

The collective international data continue to support unequivocally the use and efficacy a single course of antenatal corticosteroids using the dosage and interval of administration specified in the 1994 and 2000 Consensus Development Conference report. The current benefit and risk data are insufficient to support routine use of repeat or rescue courses of antenatal corticosteroids in clinical practice. Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.

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