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# Risks and Benefits of Antenatal Corticosteroid Therapy Prior to Preterm Birth in Pregnancies Complicated by Fetal Growth Restriction

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The antepartum administration of fluorinated corticosteroids (bethametasone and dexamethasone) for fetal maturation represents the most important clinical contribution so far in the struggle against prematurity. This treatment reduces the risk of neonatal death and handicap. It is also known that upon corticosteroid exposure, the fetus is subjected to transiently increased physiologic and metabolic demands. Healthy fetuses are able to cope, although, emerging evidence suggests that this may not be the case with severely growth restricted fetuses. Concerns have been raised that corticosteroids administration when preterm delivery is anticipated could be harmful in this setting.[1] A hypoxic growth restricted fetus with diminished reserves may be just coping when unchallenged, but exposure to corticosteroids may tip the balance.

Data originating from the pioneering study on antenatal corticosteroids conducted by Liggins and Howie[2] suggested an excess of fetal death in cases of pregnancy-related hypertension and fetal growth restriction (FGR) treated with corticosteroids. Consequently, many of the subsequent clinical trials on the effect of antenatal corticosteroids excluded pregnancies with such complications. In recent clinical practice however, the indication for antenatal corticosteroids has been extended to almost all pregnancies at risk for delivery before 32 to 34 weeks gestation. The cumulative evidence so far has served to alleviate the concerns specifically related to pregnancy-related hypertension,[3] but the potential adverse effects of corticosteroid administration in growth restricted fetuses continue to be debated.[4]

## Benefits of Antenatal Corticosteroids in FGR

In the absence of randomized studies specifically designed to assess the effects of antenatal corticosteroids in preterm growth restricted fetuses, the efficacy considerations are based on observational and retrospective data. Further complicating the interpretation are the inconsistent results published in the literature. For instance, a large study in preterm infants born between 25 and 30 weeks gestation appeared to document benefit with antenatal corticosteroids even in growth restricted cases, at a level comparable to that observed in appropriately grown infants.[5] Still another study of growth restricted babies born between 26 and 32 weeks gestation suggested increased intact survival at 2 year follow-up in those babies who had received betamethasone (BTM) compared to untreated controls.[6] However, the authors of a systematic review of all available reports (as of 2007) on antenatal corticosteroid treatment in small for gestational age or growth restricted preterm fetuses concluded that the corticosteroids had no effect on neonatal morbidity or mortality.[7] The same lack of short-term neonatal benefit was noted in a retrospective cohort of severely growth restricted fetuses with abnormal Doppler ultrasound evaluation.[8] The authors suggested that in the absence of demonstrable benefit and given the potential for long-term adverse effects, corticosteroids should not be administered routinely in growth restricted fetuses. They also called for a randomized controlled trial.

For a long time it has been speculated that the already elevated endogenous corticosteroid levels in growth restricted fetuses would interfere and dampen any demonstrable beneficial effect of the additional exogenous corticosteroids.[9] Although such an opinion may be supported by the observation that increased endogenous corticosteroids lead to accelerated lung maturation in experimental animals, in human growth restricted fetuses, elevated endogenous corticosteroid levels may not necessarily translate into accelerated pulmonary maturation.[10]

## Risks of Antenatal Corticosteroids in FGR

Corticosteroids stimulate tissular maturation and differentiation essentially through genomic effects, but may depress tissular growth in different organs via dose-dependent nongenomic effects. Examples of adverse corticosteroid nongenomic effects are the interference with bioenergetics of cellular metabolism,[11] increased apoptosis, and inhibition of mitosis. According to Buttgereit et al,[12] low doses of corticosteroids produce exclusively genomic effects, whereas with increasing doses, additional nongenomic effects become evident.

In the clinical context of antenatal corticosteroid administration, with relatively brief exposures, the fetal effects are most likely genomic in nature. With increased doses, or a more prolonged exposure, the relative contribution of the nongenomic effects increases, enhancing the risk for iatrogenic harm. As previously stated, FGR may be associated with elevated endogenous corticosteroid levels. When these fetuses become exposed to exogenous corticosteroids in anticipation for preterm delivery, the magnitude of exposure is exagerated. It appears that dexamethasone (DXM) is more potent than BTM in eliciting nongenomic effects.[11,12] Ozdemir et al have demonstrated a greater reduction in lung and liver weight in mice with repetitive doses of DXM, rather than BTM.[13]

### *Antenatal corticosteroids and the placental barrier function*

The uteroplacental perfusion is increased by the administration of corticosteroids and corticosteroid-induced FGR cannot be therefore attributed to a reduction in placental perfusion. It has been speculated that FGR is a consequence of reduced expression and function of 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD 2) in the placenta.[14] Severe FGR is associated with reduced 11beta-HSD 2 activity and mRNA expression, consequently with less cortisol to cortisone conversion, favorizing excessive fetal transplacental exposure to maternal endogenous corticosteroids.[14,15] The addition of pharmacological doses of fluorinated corticosteroids increases the degree of exposure and may also further impact the activity of 11beta-HSD 2.[16,17]

An interesting observation has been made with direct fetal administration of corticosteroids to the ovine fetus. In spite of the higher plasma corticosteroid levels obtained in the fetus with direct fetal administration, even after repetitive administration, there was no FGR, in contrast to the decrement in growth noted with an equivalent maternal (transplacental) administration.[18] It appears that the fetal somatic growth depressor effect observed with corticosteroids is mediated through the cointervention of a placental factor or event, possibly the downregulation of 11beta-HSD 2.

The sustained action of 11beta-HSD 2 late in pregnancy is important in order to maintain fetal cortisol concentrations several times lower than the maternal ones.[19] The hypocortisolic fetal milieu is presumed to be crucial for the development of fetal hypothalamo-pituitary-adrenal (HPA) axis and may also be neuroprotective.[20] HPA axis functional balance can be affected by corticosteroid exposure in a dose- and time-dependent manner[21] and the concern is that severe growth restricted fetuses exposed to larger doses of corticosteroids may have greater potential for adverse effects of early HPA axis programming. In rodents, impaired placental 11beta-HSD 2 function has been linked to reduced birthweight and long-term unfavorable programming leading to hypertension and altered behavior.[22]

### *Antenatal corticosteroids and feto-placental hemodynamics*

Recent sheep experiments have indicated that maternally administered corticosteroids have distinctly different effects on cardiovascular function in normally grown and growth restricted fetuses, most likely reflecting a fundamental difference in the regulation of vascular tone even in cases with only mild fetal hypoxia.[23] Where vasoconstriction with decreased total cardiac output was seen in healthy controls, vasodilation with increased blood flow to all major organs was noted in growth restricted fetuses. The blood flow to the heart was 4-fold higher, with increased cardiac output. The increased cardiac output, especially if sustained, may overload the fetal heart which works close to the upper limit of the ventricular function curve and has only limited function-

al reserve available to increase stroke volume via the Frank-Starling mechanism.

In healthy and growth restricted human fetuses, provided that diastolic flow in umbilical artery is present, it is considered that corticosteroids have no major effect on Doppler blood flow in fetal vessels, and do not induce fetal hypoxemia or acidemia.[24-26] However, in severely growth-restricted fetuses with absent end-diastolic flow in the umbilical artery, the fetal hemodynamic changes may be similar to those observed in the sheep FGR experiments. These growth restricted fetuses with abnormal Doppler flow patterns and altered responses to corticosteroids may be a group of significant concern.

Researchers from Australia first reported in 1999, in a small retrospective human study, that in a majority of FGR cases with absent end-diastolic flow in the umbilical artery, the flow throughout diastole will be temporarily regained after corticosteroid administration.[27] They confirmed the finding in a subsequent prospective cohort study[28] and other investigators have independently verified the same phenomenon in Canada,[4] Germany,[29] and Brazil.[30] The cumulative evidence so far, on 161 cases, indicates that the return of end-diastolic flow may be expected to occur within 24 hours after corticosteroid injection in about 62% of cases, lasting for a median of 3 days, range up to 10 days. Even in multiple pregnancies discordant for absent end-diastolic flow, the administration of BTM was associated with return of umbilical artery end-diastolic flow in 50% of cases, for a median of 5 days.[31] The mechanism underlying these changes and their impact – beneficial vs deleterious – are still unknown. The return of end-diastolic flow may not necessarily equate with improved gas exchange.[32] In fact, several researchers,[29,32] have found that the return of end-diastolic flow in the umbilical artery is accompanied by a decrease in the middle cerebral artery velocity, change that is consistent with blood redistribution to the brain as part of the fetal response to a more advanced stage of hypoxia.

In a prospective study, Simchen et al observed a better perinatal outcome in fetuses showing return of end-diastolic flow after corticosteroids (n=10) compared with those with persistent absent or reverse end-diastolic flow (n=9).[4] In the latter subgroup, 2 died and 2 were severely acidotic at birth. No such outcomes (death or severe acidosis) occurred in the subgroup with transient return of end-diastolic flow. More recently, Robertson et al confirmed, in a larger study group (92 cases), the higher risk of neonatal morbidity associated with lack of return of end-diastolic flow after corticosteroids administration in the growth restricted fetus.[33] Although clinicians should be particularly wary of the growth restricted fetuses that fail to show the transient return of diastolic flow in response to corticosteroids,[33] even in the subgroup with end-diastolic flow return, there is still a 40% acute deterioration rate, suggesting an overall poor tolerance to corticosteroids.[4]

***Antenatal corticosteroids and the brain of growth restricted fetuses***

There is evidence that the brain of the growth restricted fetus is particularly at risk of damage. Healthy fetuses are estimated to acquire an average of 173 million cells per day in the cerebral cortex in the second half of pregnancy. Growth restricted fetuses acquire only half of that.[34] The subsequent smaller cortical volume may explain the decreased academic and professional ability in adulthood of former FGR infants. It has been suggested that corticosteroids further contribute to neuronal injury in hypoxic growth restricted fetuses by affecting the ability of the brain to withstand hypoxia-ischemia.[35] Experiments conducted in fetal rat hippocampal cultures have demonstrated that exposure to corticosteroids may enhance both hypoxic and hypoglycemic neuronal and astroglial injury.[36]

Miller et al, in a sheep experimental model of FGR, showed that administration of BTM was associated with disturbed neuronal integrity and enhanced cell death in the brain due to increased cerebral oxidative stress.[1] This study used twin pregnancies to provide internal age-matched controls and provided the first in vivo experimental evidence that maternally administered corticosteroids may have detrimental effects on the brain of the growth restricted fetus. Three hours after BTM administration, a decline in brain perfusion in both control and growth restricted fetuses was first noted lasting for 3 hours. Following that, a significant rebound reperfusion, persisting for 4 hours, was noted only in growth restricted fetuses. It has been hypothesized that this exaggerated reperfusion would lead to overproduction of reactive oxygen species in mitochondria, causing lipid peroxidation. In the hypoxic growth restricted fetal brain, lipid peroxidation results in generation of excess free radicals, with possible brain injury.[37] The brain is particularly vulnerable to oxidative damage due to its high lipid composition and relatively low content of antioxidant enzymes. The increased oxidative stress also increases apoptosis in the fetal brain.

Similar brain hyperperfusion and oxidative stress may be present after antenatal corticosteroid administration in the severely growth-restricted human fetus,[23] placing the developing brain at risk for profound neurological deficits. Unfortunately, the effects of antenatal corticosteroids on the brain of human growth restricted fetuses remain largely understudied.

## What Advice Can be Offered?

The effects of corticosteroids on the growth restricted fetus are necessary future research directions, not only from the perspective of efficacy, but most importantly, from that of safety. Until more relevant information becomes available to guide the clinical use of antenatal corticosteroids in pregnancies complicated by fetal growth restriction, based on available evidence, the following precautions should be observed:

- If possible, corticosteroids should not be administered to a growth restricted fetus without prior evaluation of feto-placental hemodynamics by Doppler sonography.
- Caution should be exercised when corticosteroids are used in growth restricted fetuses with absent end-diastolic flow, and continuous electronic fetal monitoring may be necessary for up to 3 days after administration.
- When the Doppler evaluation is indicative of increased placental resistance and more advanced stages of fetal hypoxemia such as suggested by fetal circulatory redistribution towards brainstem centers and abnormal venous flow dynamics, expedited delivery becomes necessary and corticosteroids administration may be hazardous or impractical.
- In the absence of a prior evaluation, Doppler assessment performed only after corticosteroids administration may be falsely reassuring in those cases with temporary regain of the blood flow throughout diastole. The clinician would not recognize the true degree of fetal compromise and may schedule inappropriate fetal surveillance.
- Because DXM is more potent than BTM in eliciting potentially unfavorable nongenomic effects, when available, BTM should be preferred to DXM.
- Because of the conflicting reports and lack of good quality data to confirm or refute the efficacy of antenatal corticosteroids in FGR, discontinuation of this practice cannot be advocated.

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