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Judicious use of antenatal glucocorticoids: putting the risks into the balance

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Abstract

The administration of a course of antenatal glucocorticoids (AG) to improve neonatal outcome after preterm birth is a prime example of evidence-based medicine, but the current clinical application of AG is too broad. AG override the glucocorticoid enzymatic placental barrier in order to elicit fetal lung maturation at a pre-physiological gestational age. Yet the maturation benefit is accompanied by a number of undesirable phenomena, most of which are transient (lasting for at least 24-48 h after the last injection). These include metabolic effects in both mother and fetus and signs of reduced fetal wellbeing. In addition, the fetal growth rate slows down depending on the number of AG courses. Multiple courses may increase the risk of cerebral palsy, as neonatal dexamethasone treatment does. There are no randomised trials on the benefit-risk balance of AG in pregnancies complicated by diabetes or intra-uterine growth restriction (IUGR). Animal studies indicate that AG are associated with an inadequate response to acute hypoxaemia and different brain development. Judicious use of AG includes avoidance of multiple courses, and a case-based approach in pregnancies with (pre)gestational diabetes, IUGR or equivocal fetal condition, until more data become available. In addition, better prediction models of preterm birth are needed.

Key words: antenatal glucocorticoids, fetal growth, fetal wellbeing, hyperglycaemia.

Antenatal glucocorticoids: current practice

No obstetrician-gynaecologist in her or his right mind could be against the rational use of antenatal glucocorticoids (AG). The evidence that AG improve neonatal outcome in preterm births for up to 7 days after treatment is supported by systematic reviews. AG reduce neonatal death by ~30% and serious neonatal morbidity (respiratory distress syndrome, cerebroventricular haemorrhage, necrotising enterocolitis, systemic infections) by 35-55%. This conclusion is valid for pregnancies complicated by preterm labour, preterm ruptured membranes, and pregnancy-related hypertension (Roberts & Dalziel, 2010).

Courses of AG typically consist of either betamethasone (12 mg i.m., 2 doses 24 h apart) or dexamethasone (6 mg i.m., 4 doses every 12 hours). These pharmacological glucocorticoids are relatively unaffected by the placental 11β-hydroxysteroid dehydrogenase type-2 (HSD11B2), the enzyme that functions as the physiological glucocorticoid barrier between mother and fetus.

But every medal has a reverse side. Medical students are taught that glucocorticoids are potent hormones with beneficial and detrimental effects. Regarding the latter, glucocorticoids suppress growth and bone acquisition or preservation; they cause insulin resistance which affects glucose, lipid (depot-dependent) and protein metabolism. Fetuses are not much different from postnatal individuals, as I will expound below.

Representative figures and trends of the sales volume of glucocorticoids for obstetrical indications are lacking, but the overall impression is one of intense use. In many centres, AG are used in gravidas at risk of preterm birth up to 36 weeks; weekly or two-weekly administration is common, as is a "rescue" course (*i.e.*, a second or yet another course of AG before scheduled delivery prior to 34 or

37 weeks); and AG are given to healthy as well as compromised fetuses. Part of the pregnancies in which one or more courses of AG have been administered continue until term. Again, representative figures on the important issue of (retrospectively) unnecessary courses of AG are lacking.

Maternal-fetal cortisol physiology

In the fetus, a functional pituitary-adrenal axis with significant adrenal secretion of steroids – mainly DHEAS, starts at an early gestational age (8-10 weeks). The fetal adrenal steroid production is, of course, critical for the placental production of oestrogens, and the coordination between the fetal adrenal cortex and the placenta is traditionally believed to play a role in the onset of parturition. However, the *de novo* production of cortisol in the fetal adrenal cortex is delayed until late gestation (≥35 weeks GA) because of the late maturation of the enzymatic machinery necessary for cortisol synthesis (Murphy, 1982; Ishimoto & Jaffe, 2011).

Maternal cortisol concentrations, both total and free, rise gradually during pregnancy but the fetus is shielded from this excess by the placental HSD11B2 which inactivates 80-90% of the cortisol into cortisone. Fetal cortisol concentrations are 5-10 times lower than maternal concentrations (Lockwood *et al*., 1996).

However, some interaction between maternal and fetal cortisol is likely: a correlation between maternal and fetal plasma cortisol was documented at the time of cordocentesis (Lockwood *et al*.,1996; Gitau *et al*., 2001). Several studies have documented that chronic maternal stress or anxiety engenders behavioural and cognitive alterations in the offspring, and cortisol is believed to mediate at least some of these effects (Glover *et al*., 2010). A partial and gestational age-dependent interaction between fetus and mother has also been documented for other hormonal axes (*e.g*., the thyroid axis), but our current knowledge regarding the adrenal axis is less advanced.

Hormonal regulation of fetal lung maturation

The endogenous cortisol surge in late gestation is critical for lung maturation, acting through the glucocorticoid receptor. A recent study using mutant mice found that the glucocorticoid receptor in lung mesenchyme-derived cells is more important than the receptor in the alveolar epithelial cells (Habermehl *et al*., 2011). Other hormones, particularly the thyroid hormones, are important for fetal maturation including lung maturation; severe hypothyroidism in both mother and fetus results in a striking delay of lung maturation (de Zegher *et al*., 1995). In the past, maternal administration of thyrotropin-releasing hormone was used to accelerate fetal lung maturation.

Lung and cerebral maturation are delayed in fetuses of diabetic mothers. Direct inhibition of lung surfactant synthesis by the hyperglycaemic (and hyperinsulinaemic) *milieu* is at least partly responsible (Weindling, 2009), yet there is also suggestive evidence of indirect effects through lower cortisol and/or thyroid hormone levels (Rotenberg & Gewolb, 1993).

Older literature and wide clinical experience show that chronic intrauterine stress, as experienced by fetuses with intra-uterine growth restriction (IUGR) owing to reduced uteroplacental blood flow, is accompanied by advanced *in utero* maturation (for references, see van Stralen *et al*., 2009). Since stress activates the hypothalamic-pituitary-adrenal axis, the endogenous cortisol surge appears to be switched on at an earlier gestational age. However, higher endogenous cortisol should not be considered as overall beneficial: in a study of 350 intubated neonates with a birthweight of 500-999 g, a high level of cortisol 12-48 h after birth was associated with more cerebral morbidity (Aucott *et al*., 2008).

Possible harmful effects of a course of AG on mother and fetus

Transient catabolism and oxidative stress. A course of AG suppresses maternal ACTH and cortisol concentrations for at least 4-6 days with the lowest levels on day 2 (Koenen *et al*., 2005). As expected, AG raise maternal glucose levels for at least 24 h, which is more pronounced in twin pregnancies (Foglia *et al*., 2008). We have repeatedly documented raised fetal glucose levels for 24-48 h after the last injection of AG, which is accompanied by higher insulin concentrations and indices of insulin resistance (Verhaeghe *et al*., 2005; 2007; 2009). This effect is the probably the result of both maternal hyperglycaemia and a direct effect of glucocorticoids on fetal glucose disposal (Tappy *et al*., 1994). Transient (24-48 h after last injection) insulin resistance is also suggested by proteolysis with increased concentrations of aminoacids, particularly glutamine and alanine, and lipolysis with increased free fatty acids (Verhaeghe *et al*., 2007; Marconi *et al*., 2010).

The metabolic changes may be related to AG-induced oxidative stress. A course of betamethasone is accompanied by lower levels of the antioxidant enzyme glutathione peroxidase-3 for ~24 h after the last injection and higher levels of malondialdehyde, a measure of lipid oxidative damage, for at least 72 h (Verhaeghe *et al*., 2009).

Transient reduction in fetal wellbeing. Both betamethasone and dexamethasone interfere with the diurnal rhythm in fetal movements with ~50% fewer recorded movements for 1 or 2 days; the number of breathing movements also decreases (Magee *et al*., 1997; Mulder *et al*., 1997; Koenen *et al*., 2005). Basal fetal heart rate is slightly decreased (Magee *et al*., 1997; Lunshof *et al*., 2005; Schneider *et al*., 2010) or increased (Rotmensch *et al*., 2005) but all changes are less than 10 bpm. More importantly, long-term heart rate variability is reduced with less accelerations, and the heart rate pattern becomes more complex (Rotmensch *et al*., 2005; Schneider *et al*., 2010). The changes are suggestive of sympathetic suppression (Schneider *et al*., 2010).

There is some evidence that repeated administration of AG perturbs brain development. The U.S. randomised trial of weekly antenatal betamethasone (2-12 courses in total, median of 5) documented 6/206 children with cerebral palsy at 2-3 years compared with 1/195 in the single-course arm (relative risk (RR) = 5.7, CI 0.7-46.7, $P = 0.12$) (Wapner *et al*. 2007). This outcome is not unexpected, because early-neonatal dexamethasone treatment – administered to prevent bronchopulmonary dysplasia – also increases the risk of cerebral palsy (RR = 1.8, CI 1.2-2.6, $P = 0.004$); because of this and other risks (hypertension, gastrointestinal complications), neonatal dexamethasone is no longer recommended for routine clinical practice (Doyle *et al*., 2010). In another randomised trial of weekly antenatal betamethasone (Australasian trial, median of 3 or 4 courses in total), there was no difference in the cerebral palsy incidence compared with single-course betamethasone, but a mild increase in attention problems was found (RR = 1.9, CI 1.0-3.4, $P = 0.04$) (Crowther *et al*., 2007). Interestingly, attention problems are also more frequent among the children of gravidas with high levels of stress or anxiety (Glover *et al*., 2010).

Fetal growth. Weekly or two-weekly antenatal betamethasone is associated with a small decrease in biometric parameters (weight, length and head circumference) at birth compared with a single course (Peltoniemi *et al*., 2011). For birthweight, the difference is ~100 g (Wapner *et al*., 2006; Murphy *et al*., 2008). No differences in weight and height were observed at 2-3 years of age (Wapner *et al*., 2007). A dose-related inhibition of the fetal growth rate (Wapner *et al*., 2006) is an expected finding. Mechanisms include: possible interference with the transplacental transport of nutrients such as aminoacids (Audette *et al*., 2011); the catabolic effects in the fetus previously alluded to; and the reduction in the concentration of insulin-growth factor-I, one of the most important growth factors in the fetus. After a single course of AG, IGF-I was suppressed for ~48 h after the last injection (Verhaeghe *et al*., 2007).

The fetal growth pattern and birth biometric markers predict the size and mineral content of bones in children and adults (Harvey *et al*., 2010). Multiple courses of AG might hinder pre- and postnatal bone development in the same way as neonatal dexamethasone treatment does (Wang *et al*., 2006).

Impact of AG on fetal physiology: additional insights from animal models

Inadequate response to *in utero* hypoxaemia. Fetal sympathetic suppression owing to AG (Schneider *et al*., 2010) may be detrimental in case of hypoxaemia. Fetal sheep subjected to acute hypoxaemia showed a lower catecholamine response with persisting bradycardia and more pronounced lactacidaemia if the mother had completed a course of dexamethasone 8 h before (Jellyman *et al*., 2005).

Abnormal brain development. A course of betamethasone in ewes led to an acute drop in cerebral blood flow with a probable increase in anaerobic glucose metabolism in their preterm fetuses (McCallum *et al*., 2008). IUGR fetuses appear to be at special risk. A betamethasone course engendered oxidative damage in the hippocampus and other brain regions in IUGR (by umbilical artery ligation) sheep compared with their non-ligated twins (Miller *et al*., 2007). The glucocorticoid receptor is expressed in the hippocampus, and AG may cause hippocampal neuronal death (Gulino *et al*., 2009); disturbed development of the fetal hippocampus has also been linked to maternal stress (Glover *et al*., 2010). Primates exposed to prenatal dexamethasone showed impaired skilled motor reaching (Hauser *et al*., 2008).

Exaggerated postnatal stress response. Adult primates exposed to prenatal glucocorticoids show an upregulated cortisol response to stress (de Vries *et al*., 2007). This may lead to cortisol "allostasis" (*i.e*., a small but chronic damage inflicted by cortisol surges to various biological processes).

"Programming" of the metabolic syndrome. An extensive literature in various animal models including primates, indicates that prenatal exposure to glucocorticoids predisposes to adult obesity, hyperlipidaemia, liver steatosis, glucose intolerance, and hypertension (de Vries *et al*., 2007). Epigenetic mechanisms, *e.g*. through methylation of DNA, are thought to be responsible for these changes.

Outstanding clinical issues

One size may not fit all. As would be expected, some pharmacokinetic differences according to the body-mass-index of the mother have been

demonstrated, with slightly faster betamethasone clearance with higher body weight (Della Torre *et al*., 2010). Future studies may evaluate the benefits of a dosage adjusted for body weight or body-mass-index category.

Betamethasone or dexamethasone? The two AG regimes are generally presented as perfect alternatives. However, some randomised trials observed differences in maternal or neonatal outcome (Elimian *et al*., 2007; Roberts & Dalziel, 2010) which need to be scrutinised further.

Less effective after 7 days? AG are thought to be most effective when given <7 days before the actual birth (Roberts & Dalziel, 2010). However, this conclusion is plagued by a number of methodological and statistical issues, *e.g*. analysis according to a variable unknown at the time of randomisation may lead to spurious results; the trials generally did not perform interaction testing (Gates & Brocklehurst, 2007).

The diabetes connection. While preclinical data would support a beneficial effect of dexamethasone on fetal lung development in diabetic pregnancies (Rotenberg & Gewolb, 1993), no randomised clinical trials are available. Theoretically, the increase in fetal glycaemia might partly counteract the effect of AG. Antenatal betamethasone appear to increase oxidative stress parameters in fetuses of mothers with pregestational diabetes (Verhaeghe *et al*., 2011). AG increase the risk of gestational diabetes in pregnancies complicated by pre-eclampsia (RR = 2.7, CI 1.1-6.5; Amorim *et al*., 1999) or threatened preterm delivery if combined with β-adrenergic agonists (Fisher *et al*. 1997). AG typically worsen glycaemic control in diabetic gravidas, even with anticipatory adjustments in insulin dose in women who were on insulin previously; insulin may need to be commenced in gravidas with gestational diabetes treated with a diet.

IUGR. No randomised clinical trials are available. A Dutch case-control study (88 pregnancies) showed a comparable neonatal outcome with or without AG in preterm fetuses with IUGR and abnormal Doppler parameters (van Stralen *et al*., 2009). A transient return of end-diastolic blood flow in the umbilical artery following antenatal betamethasone, which occurs in two-thirds of IUGR fetuses, appears to predict a better neonatal outcome (Robertson *et al*., 2009).

Judicious clinical use of AG

While the neonatal benefits of AG have been shown in large randomised trials (Roberts & Dalziel, 2010), the current "evidence-based" use is over-the-top and needs to evolve into a strategy that takes account of both potential benefits and harms, as with any medication. Specifically, the maternal and fetal condition must be taken into the balance.

We urgently need more data on the benefit-risk balance of AG in fetuses with IUGR (van Stralen *et al*. 2009). The same is true for fetuses with equivocal wellbeing (non-reactive heart rate tracing): the transient deterioration in the heart rate pattern may lead to a diagnosis of fetal distress (Lunshof *et al*., 2005) and prompt unnecessary early delivery. IUGR fetuses appear to be more sensitive to the protein-catabolic actions of AG (Verhaeghe *et al*., 2007), and their brain may be more vulnerable to AG (Miller *et al*., 2007). Until further data become available, AG should be used in IUGR pregnancies on an individualised base.

In diabetic pregnancies, the best strategy is very frequent monitoring (both by the patient and the caregivers) and optimisation of glycaemic control, which substantially reduces the risk of adverse pregnancy outcome including pre-eclampsia (Holmes *et al*., 2011), polyhydramnios, and spontaneous and induced preterm delivery (Lepercq *et al*., 2004). Given the absence of randomised trials and the possible adverse metabolic effects for mother and fetus, AG should be administered in as few diabetic pregnancies as possible.

Randomised trials do not support the use of AG in pregnancies at 34-36 weeks to reduce the risk of transient tachypnoea, although there is a benefit for neonatal jaundice (Roberts & Dalziel, 2010, Porto *et al*., 2011). Repeat administration of AG should be avoided as much as possible, given the inhibitory effect on fetal growth (Wapner *et al*., 2006; Murphy *et al*., 2008) and the concerns about cerebral palsy (Wapner *et al*., 2007) and attention-deficit disorder (Crowther *et al*., 2007). Even a rescue course (*i.e*., an booster of AG before delivery) may not be beneficial (Peltoniemi *et al*., 2007).

Above all, we need better prediction models for preterm birth in gravidas presenting with threatened preterm labor without ruptured membranes. The current prediction is based on three pillars: a history of preterm delivery, cervical length by ultrasound, and the fetal fibronectin test. Although this is certainly an improvement on a purely clinical prediction, the positive predictive value of a short cervix or a positive fibronectin test for delivery within 7 days remains disappointingly low (Iams *et al*., 1994). For example, in case of threatened preterm labour and a positive fibronectin test at 31 weeks, 17 fetuses need to be treated with AG to prevent 1 case of neonatal respiratory distress syndrome associated with preterm birth within 7-10 days of testing; without the test, the number of fetuses needed to treat rises to 109 (Honest *et al*., 2002). Clearly, too many fetuses

exposed to AG ultimately are born at the time of sufficient endogeneous cortisol, *i.e.* at or after 35 weeks of gestational age.

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