Antenatal glucocorticoid therapy: a caveat to the applause

Pre-term delivery creates a series of untimely challenges for the newborn, with the lungs, in particular, poorly prepared for independent existence ex utero. In many mammals, rising glucocorticoid levels in the fetal circulation just before birth act as a physiological stimulus to the development of immature systems, inducing critical events such as pulmonary surfactant production. A number of clinical trials have examined the use of high doses of synthetic glucocorticoids in threatened pre-term labour to prevent or ameliorate its consequences. A recent review of such evidence by the Cochrane Library reports 18 trials involving over 3700 babies [1]. The overview suggests a clear, significant and very substantial reduction in mortality (odds ratio 0.60) and morbidity (odds ratio 0.53) from neonatal respiratory distress syndrome and intraventricular haemorrhage in pre-term infants born to women given large doses of dexamethasone or betamethasone in the days before delivery. This authoritative review, as others, provides no suggestions of adverse consequences of perinatal glucocorticoid treatment in the short or medium term of subsequent childhood. So high-dose glucocorticoids sound an ideal approach for an obstetrician faced with a threatened preterm labour. But glucocorticoids have a long and well-rehearsed list of serious adverse effects in other circumstances, so is there any caveat in obstetric use?

When glucocorticoids were first exploited therapeutically more than 40 years ago, these ‘magic bullets’ were administered with considerable enthusiasm, including during pregnancy. Early results showed that the offspring of women treated with glucocorticoids when pregnant had reduced birth weight, and similar fetal growth-retarding effects were observed in experimental animals, including non-human primates (reviewed in [2]). A plethora of recent epidemiological studies in many distinct human populations have linked low birth weight and other markers of restrained growth in early life with a substantially increased risk of hypertension, type II diabetes and other cardiovascular risk factors in adult life [3]. Given the growth-retarding effects of glucocorticoids on the human fetus, their key role in determining the trajectory of organ maturation and their direct hypertensive and hyperglycaemic effects in vivo, some investigators began to wonder whether glucocorticoids might be responsible for these epidemiological links. These groups showed, in rats and sheep, that even very transient glucocorticoid exposure during specific ‘windows’ of fetal life could permanently programme or ‘hardwire’ tissue responses, leading to persistent elevations of blood pressure and blood glucose levels throughout adult life. But do such effects occur in humans? In an important addition to the story, Doyle and colleagues [4] now report that antenatal glucocorticoid treatment for 48 h of babies born prematurely is associated with significantly higher systolic and diastolic blood pressure in adolescence. These data provide the first clear evidence for such long-term effects of glucocorticoids in humans. So should we provide an additional health warning as well as ongoing cardiovascular and metabolic checks to survivors of pre-term glucocorticoid treatment?

Before advocating any change to clinical practice, the limitations of the study of Doyle et al. [4] need to be assessed. First of all, as the authors remark, the selection of fetuses to be given pre-term glucocorticoids was non-random. Some took part via a clinical trial, but others were allocated on the basis of the preference of the attending obstetrician. There is no information to illuminate the selection criteria used here, and caution needs to be exercised, as these may have been the ‘sicker’ pregnancies, although this contention is not supported by any differences in birth weight or gestational age between the glucocorticoid-exposed and control groups. Another concern is the number of exclusions from the original population; these subjects declined to take part in blood pressure measurements, but were these individuals similar in all respects to those reported? Well probably, but we are not told about levels of persisting disability here that might have skewed both their willingness to take part in the study and also the outcome. Exclusion of data from subjects taking part in the study but who suffered from cerebral palsy confined the changes to elevated systolic blood pressure in those treated antenatally with steroids.

A crucial point is whether this population is applicable to the majority of pregnancies treated with antenatal glucocorticoids, which are often used both to stimulate fetal organ maturation and to help to prevent premature delivery. The population was chosen on the basis of very premature birth (around 29 weeks). The babies were therefore tiny, with almost half below 1 kg. Whether effects in such extreme prematurity can be extrapolated to more common problems later in the third trimester is unclear. Indeed, in rats, sensitivity to dexamethasone programming of offspring glucose–insulin homeostasis are confined to the final third of gestation [5]. Greater prematurity may not equate with greater sensitivity to steroid programming. Clearly the long-term effects of
antenatal glucocorticoids in the last 10 weeks of gestation need to be determined in humans. A key point will be to dissect persisting cardiovascular and metabolic effects in babies exposed to antenatal glucocorticoids who were then carried to term compared with term controls. Another concern here is that we may be looking at a ‘survivor effect’ in these very premature infants. Blood pressure levels ‘track’ from infancy. Perhaps higher blood pressure in the presence of glucocorticoids promotes survival, whereas in the absence of glucocorticoids a different cardiovascular configuration is more advantageous. Such issues are difficult to dissect in this population, but are critical to address.

The lack of any effect of birthweight on later blood pressure is at first glance surprising. Perhaps this work [4] is a description of the dissociation of fetal growth and the programming of hypertension by glucocorticoids. However, the babies were very premature, but not particularly small-for-dates, which perhaps abrogates an association largely described for small, but term, deliveries. Blood pressure measurements in adolescence may be problematic, as the substantial differences in growth rate and timing of puberty complicate interpretation. Indeed, pubertal development may be affected by antenatal events [6]. The data provided in the paper [4] to support matched pubertal staging are not wholly reassuring, given the rather crude clinical measures employed. For how many boys were testicular volumes available? How precisely were these assessed? What was the exact timing of menarche in the girls? Even small differences in these parameters may substantially affect blood pressure levels in adolescence. Moreover, the relationship between birth weight and blood pressure is not readily observed in adolescence, perhaps for reasons of the disparate growth rates. The glucocorticoid-exposed group were taller and heavier at age 14 years, although this did not wholly account for the differences in blood pressure. Furthermore, considerable debate surrounds the issue of postnatal catch-up growth as a factor in the link between prenatal growth restriction and later cardiovascular disease, and greater numbers of subjects will be required in order to convincingly dissect out these important factors. Thus it will be important to determine whether the glucocorticoid-exposed population of Doyle et al. [4] show increasing blood pressure differences compared with both premature untreated and term controls as they enter adult life.

Clearly, antenatal glucocorticoids have very substantial immediate benefits in threatened pre-term labour. However, the study by Doyle et al. [4] suggests that there may be adverse long-term cardiovascular consequences. Whether other after-effects indicated by animal studies, including type II diabetes/insulin resistance, occur in humans needs to be investigated. Perhaps the key message is that we need better prospective controlled trials here.

Meanwhile, where antenatal glucocorticoids are used, their dose, as in all other situations, should be minimized; some steroid is good, but more is not necessarily better.

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REFERENCES

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