
COMMENTARY

Repeated Antenatal Glucocorticoid Exposure and the Developing Brain

Commentary on the article by Modi *et al.* on page 581

OLAF DAMMANN AND STEPHEN G. MATTHEWS

From Neuroepidemiology Unit, Department of Neurology, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, U.S.A. [O.D.] and Departments of Physiology and Obstetrics and Gynecology, Faculty of Medicine, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, Ontario, M5S 1A8, Canada [S.G.M.]

Ever since the landmark discovery by Liggins that maternal glucocorticoid (GC) treatment accelerates lung maturation in fetal sheep (1), a number of studies have demonstrated the beneficial effects of antenatal GC therapy for preterm infants. On the other hand, any potentially harmful effects are of crucial importance for the long-term development of these children.

Recent audits have identified the growing practice of prescribing multiple courses of glucocorticoids, if the risk of preterm delivery persists. Indeed, an Australian survey identified 97% of obstetricians prescribing antenatal glucocorticoids while 85% prescribed repeated courses (2). Similar results were recently reported for a survey of British obstetricians, where some centers may prescribe up to 11 repeat courses (3). Although a single course of glucocorticoid treatment is highly effective in preventing pulmonary complications, there is no conclusive evidence as to whether repeated GC therapy provides any further benefit. Moreover, there is growing evidence from animal studies that repeat GC exposure can have life-long effects on behavior and endocrine function (4).

Brain damage in the neonate has traditionally been divided into distinct patterns according to gestational age at birth. More recently, however, "preterm-type" damage has been identified among infants born near or at term, mainly in studies employing magnetic resonance imaging (MRI) (5, 6). This observation leads to the question of whether antenatal interventions (such as repeated glucocorticoid therapy) usually restricted to preterm infants can have any beneficial neurologic effects among infants of mothers with threatening preterm delivery, who eventually carry their baby until term.

Many observational studies have yielded a reduced risk of brain damage and subsequent neurodevelopmental disability among preterm infants after a single complete course of antenatal GCs (7). Some colleagues have raised considerable concern, since the efficacy of repeated dose therapy is not sup-

ported by the same kind of evidence (8). On the other hand, we do not have conclusive evidence that repeated doses are always harmful.

One additional piece of evidence that multiple doses might modify the trajectory of human brain development is published in this issue of Pediatric Research (9). Among 10 term or near term infants exposed to multiple courses of antenatal GCs, three measures of brain growth were reduced when compared with six nonexposed term infants. This result was statistically significant for reduced complexity of cortical folding and for brain surface area, but not for brain volume. Of note, 2 of the 10 GC-exposed infants had discrete lesions, that are not usually considered predictors of long-term disability (one child had a caudate cyst, another had multiple small white matter abnormalities identified as hemorrhages). Nine of the 10 exposed, and 2 of the 6 nonexposed infants had a diffusely abnormal white matter signal, interpreted as an increased water content. Indeed, most abnormalities seen among the exposed may serve as indicators of reduced (or slowed) brain maturation, but are not clearly associated with an increased risk of later neurodevelopmental disability.

Diffuse white matter damage characteristics such as ventriculomegaly and delayed myelination, have been implicated in the etiology of cerebral palsy (10). Neither was identified following repeated GC treatment in the present study. With respect to the lack of effect on myelination, Modi *et al.* offer the explanation that there is very little new myelination within the immature brain between 25 and 35 wk gestation (9). On the other hand, some investigators have concluded that a large number of myelinating sites are active during the third trimester (11).

When considering the impact of synthetic GCs (such as those administered to pregnant women identified at risk of preterm labor), it is important to note that endogenous GCs (cortisol in humans) are essential for normal brain development. Cortisol exerts a wide spectrum of effects in most regions of the developing brain. These include sub-cellular reorganization, alteration of neuron-neuron and neuron-glial in-

O. Dammann receives support from United Cerebral Palsy Research and Educational Foundation (EH-003-98). S.G. Matthews receives support from the Canadian Institutes of Health Research and the Natural Sciences and Engineering Council of Canada.

teraction, and modification of neurogenesis and programmed cell death (apoptosis) [for review see ref. (4)]. Animal studies have shown that sustained elevation or depletion of endogenous GCs in the fetal brain can significantly modify these processes, and can permanently modify the structure and function of the brain (12). The report by Modi and colleagues certainly indicates that structural modification may also occur in the brains of human fetuses exposed to synthetic GCs in late gestation. If this is the case, important questions that remain are: (1) Is there recovery of structure to the “normal state” after birth?, and (2) are there long-term functional consequences of these changes? To date, animal studies would suggest the answer to the first question is “at least partial” and to the second is “yes.”

Although the study of Modi *et al.* raises an important and current clinical issue, it deserves comment because it has a number of methodological limitations that need to be considered to put these results into perspective. First, this is a very small study (10 compared with 6 infants). An appropriate power calculation would almost certainly have led to a much larger study and, in turn, to more robust results. A second limitation is that the six unexposed infants were almost 1 month older at imaging (median 39.5 wk) than the 10 exposed infants (median 36 wk). Although the authors adjusted for postmenstrual age in analyses of covariance when considering the *quantified* morphometric brain measures, no such adjustment is possible when looking at MRI signal *quality*, for example, the reduced echo from the white matter seen in almost all GC-exposed but only two of the six non GC-exposed neonates. Moreover, control for gestational age at birth was apparently attempted by posthoc adjustment, not by a matching process as mentioned in the abstract (but not specified elsewhere in the manuscript). Third, whenever two groups of individuals are defined by the presence or absence of a medical intervention in a nonrandomized fashion, and are then compared with regard to a specific outcome, the indication for the intervention might be a strong confounder of any observed association between the intervention and the outcome. In the present scenario, this concept of *confounding by indication* translates into an increased risk of brain (growth) abnormality among infants exposed to factors that have led to the repeat GC treatment. Indeed, 9 of the 10 exposed mothers were treated with GC in clinical situations, which might, in and of themselves, be markers of an increased risk for cerebral palsy (*i.e.* multiplicity, premature rupture of membranes, poor obstetric history, antenatal bleeds). Finally, those infants who were

exposed to multiple GC treatments and went on until term were not only exposed to GC for a long time, but also to all other potentially harmful adversities including those previously mentioned that led to the initiation of GC treatment. We do not know at what gestational age the first dose was administered in the 10 exposed pregnancies, nor do we know how the MRI-based brain morphometrics compare with infants exposed to only one complete course of GC.

While the limitations of this type of small nonrandomized study might be of secondary importance to some individuals, others might consider these kinds of detail at least as equally important as the undoubtedly meticulous and sophisticated use of MRI techniques, brain morphology quantification, and the cautious interpretation of results offered by Modi and coworkers. We agree that it would be immensely difficult, expensive, and probably infeasible to perform the same kind of study in a large number of infants. While these potential sources of bias limit the inferences that can be drawn from this study, they do not reduce the potential importance of this work as a hypothesis generating study. However, multivariable risk analyses, not restricted to comparisons of means, are crucially needed as a solid information base before any further conclusions are drawn.

REFERENCES

1. Liggins GC 1969 Premature delivery of foetal lambs infused with glucocorticoids. *J Endocrinol* 45:515–523
2. Quinlivan JA, Evans SF, Dunlop SA, Beazley LD, Newnham JP 1998 Use of corticosteroids by Australian obstetricians—a survey of clinical practice. *Aust N Z J Obstet Gynaecol* 38:1–7
3. Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G 1999 Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. *Br J Obstet Gynaecol* 106:977–979
4. Matthews SG 2000 Antenatal glucocorticoids and programming of the developing CNS. *Pediatr Res* 47:291–300
5. Truwit CL, Barkovich AJ, Koch TK, Ferriero DM 1992 Cerebral palsy: MR findings in 40 patients. *AJNR Am J Neuroradiol* 13:67–78
6. Okumura A, Hayakawa F, Kato T, Kuno K, Watanabe K 1997 MRI findings in patients with spastic cerebral palsy. I: Correlation with gestational age at birth. *Dev Med Child Neurol* 39:363–368
7. O’Shea TM, Doyle LW 2001 Perinatal glucocorticoid therapy and neurodevelopmental outcome: an epidemiologic perspective. *Semin Neonatol* (in press)aq
8. Whitelaw A, Thoresen M 2000 Antenatal steroids and the developing brain. *Arch Dis Child Fetal Neonatal Ed* 83:F154–157
9. Modi N, Lewis H, Al-Naqeeb N, Ajayi-Obe M, Doré CJ, Rutherford M 2001 The effects of repeated antenatal glucocorticoid therapy on the developing brain. *Pediatr Res* 50:581–585
10. Leviton A, Gilles F 1996 Ventriculomegaly, delayed myelination, white matter hypoplasia, and “periventricular” leukomalacia: how are they related? *Pediatr Neurol* 15:127–136
11. Gilles FH, Leviton A, Dooling EC 1983 The developing human brain - growth and epidemiologic neuropathology. John Wright PSG Inc, Boston, p 139
12. Gould E 1994 The effects of adrenal steroids and excitatory input on neuronal birth and survival. *Ann N Y Acad Sci* 743:73–93