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## Giving steroids before elective caesarean section

*Neonatal respiratory morbidity is halved, but they may be harmful in the long term**Papers pp 662, 665*

In recent years the caesarean section rate in developed countries has been rising. This may be because improved techniques to control haemorrhage, infection, and thromboembolism have increased the safety of the procedure. As a result obstetricians and pregnant women have a reduced threshold for choosing it. However, although maternal risks have decreased, the effects on the baby of surgical delivery before the due date continue to be debated.

In this issue (p 662), Stutchfield et al confirm previous reports that elective caesarean section before 40 weeks' gestation increases neonatal admissions to the special care unit for respiratory distress (mainly for transient tachypnoea of the newborn).<sup>1,2</sup> In the control group of the randomised controlled trial, 11.4% were admitted at 37 weeks, 6.2% at 38 weeks, and 1.5% at 39 weeks. If women were given two intramuscular injections of 12 mg of betamethasone in the 48 hours before delivery the rates of admission were 5.2% at 37 weeks, 2.8% at 38 weeks, and 0.6% at 39 weeks. Although none of the babies in the control group died, admission will have increased parental anxiety and the cost to the NHS and may have long term sequelae. Giving mothers betamethasone before elective caesarean section halved neonatal respiratory morbidity, so should we give steroids to all mothers before delivery?

We need to know what the potential harms for the fetus are. Lawson has summarised the growing number of reports of adverse long term effects associated with antenatal steroids.<sup>3</sup> Animal studies show that maternal corticosteroid administration delays myelination in the fetal brain (which in humans normally continues up to the age of 2 years) and reduces the growth of all fetal brain areas, particularly the hippocampus.<sup>4</sup> There may be long term effects on the setting of the hypothalamo-pituitary axis and glucose homeostasis.<sup>5</sup> In preterm infants, antenatal corticosteroids have been associated with higher systolic and diastolic blood pressures in adolescence, possibly leading to clinical hypertension.<sup>6</sup> Other studies suggest that repeated courses of antenatal steroids reduce neonatal head circumference and birth weight.<sup>7,8</sup> Multivariate analyses of the behaviour of children in the Western Australian preterm infant follow-up study have shown that increasing the number of antenatal exposures to glucocorticoids is associated with reduced birth weight and an increase in behavioural disorders at age 3.<sup>5</sup>

In 2000, the National Institutes for Health reported that the current benefit and risk data are insufficient to support routine use of repeat or rescue courses of

antenatal corticosteroids in clinical practice.<sup>9</sup> Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat courses. Until data establish a favourable ratio of benefit to risk, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.<sup>9</sup> This conclusion is supported by the American College of Obstetricians and Gynecologists and a Cochrane review.<sup>10,11</sup>

Currently, the evidence for harmful effects is strongest for repeated courses of steroids. The effect of a single course on cognitive function, however, is more reassuring, as shown by Dalziel et al in this issue (p 665).<sup>12</sup> However, in their companion paper in the *Lancet* they report small but significant increases in insulin resistance which "could signify a raised risk of diabetes and cardiovascular disease as this cohort ages."<sup>11</sup> We should not forget that more than 2 million children were born with abnormalities of the genital tract before it was realised that these were caused by diethylstilbestrol given to their mothers as an (ineffective) treatment for threatened miscarriage,<sup>13</sup> and more than 10 000 babies were born with phocomelia before we realised that this was caused by the use of thalidomide in pregnancy.<sup>14</sup>

The data presented by Stutchfield et al show that delaying non-urgent elective caesarean section until 39 weeks is much more effective in avoiding neonatal admission than giving steroids.<sup>1</sup> For the 15% or so of such women who will go into labour between 37 and 39 weeks, the inconvenience of having their caesarean "out of hours" is likely to be less than that of having their baby admitted to special care. Most will only be in early labour, avoiding the complications of an acute intrapartum emergency.

A single course of steroids reduces neonatal mortality in babies born before 34 weeks and this perhaps justifies the small risk of long term side effects. However, no such substantial benefit has been shown after this gestation. Delaying delivery until 39 weeks, unless necessary, would seem a more prudent option than giving steroids whose long term safety, even as a single course, remains questionable.

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## Safer prescribing for children

*Will be boosted by European and US laws and the new British national formulary for children*

Paediatric prescribing can be precise, beneficial, and safe. It can also be confusing, based on little or no evidence of effectiveness, and can put children at risk. The nature of marketing authorisations (formerly product licences) for drugs merely enhances the paradox. They were designed as a means of obtaining approval for use by an appropriate regulatory body, usually a government agency; so the decision to apply for authorisation is influenced more by commercial than clinical considerations.<sup>1</sup> One result is that unlicensed and “off label” prescribing is common. Paediatricians, general practitioners, and others are torn between providing treatment which their experience and reason have deemed suitable and denying it because of the lack of research data underpinning indications, dosages, or formulations.

A study in five European hospitals showed that 39% of drugs prescribed for children were off label and a further 7% were unlicensed.<sup>2</sup> Similar studies in general practice of prescriptions for children found that 11% were off label or unlicensed in the United Kingdom, 33% in France, and 29% in the Netherlands.<sup>3-5</sup> Furthermore, neonatologists have little choice but to use drugs in unauthorised ways because their patients are rarely entered into trials of new preparations: 80% of infants in an Australian neonatal intensive care unit received an off label or unlicensed preparation.<sup>6</sup> Such prescribing is a problem not just for doctors: patients in a paediatric isolation ward in Germany who were treated with unlicensed or off label drugs had a significantly increased risk of adverse drug reactions.<sup>7</sup>

Complacency about the lack of evidence based information on medicines for children is unacceptable. But several initiatives—three which should encourage high quality research and one which should provide authoritative information on prescribing—should go a long way to solving this problem.

The NHS health technology assessment programme is to commission a portfolio of research projects on medicines for children. Proposals should reach [www.ncchta.org](http://www.ncchta.org) by 1 pm on 19 October 2005.

The European Commission has responded to professional and public concerns by proposing a directive on medicinal products for paediatric use.<sup>8</sup> It includes

establishing an expert committee to assess and approve all protocols for paediatric drug trials. This committee would consider whether studies are likely to show therapeutic benefit and would be expected to turn down those it thought would unnecessarily duplicate other work, while not delaying authorisation of medicines for other ages. In addition the European Medicines Agency has issued a draft guideline on pharmacovigilance among children.<sup>9</sup>

The proposed European directive on medicinal products for children has much in common with the Pediatric Research Equity Act passed by the US Senate in July 2003. This empowers the Food and Drug Administration (FDA) to require manufacturers to test medicines for safety and effectiveness in children and to establish protocols for paediatric dosing and administration. The FDA can waive such requirements when a drug is unlikely to be used in children and can defer decisions on paediatric prescribing when a drug needs urgent authorisation for adult use.<sup>10</sup>

This week sees the publication of the *BNF for Children*, which aims to offer sound up to date information on paediatric prescribing, much of which goes beyond marketing authorisations.<sup>11</sup> Its provenance is the *British National Formulary* (BNF), which has provided authoritative and regularly updated prescribing advice for the past 50 years, and *Medicines for Children*, a popular and much used publication of the Royal College of Paediatrics and Child Health.

The *BNF for Children* has been validated against emerging evidence, guidelines on best practice, and advice from a network of clinical experts. The UK Departments of Health will distribute it to all prescribers in England, Wales, and Scotland and to a limited number in Northern Ireland. An online version for England is almost ready.

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Competing interests: HM is an employee of the BMJ Publishing Group and an external relations adviser to the Royal College of Paediatrics and Child Health, which are among the publishers of the *BNF for Children*, but he has received no remuneration related to BNFC.

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