

Antenatal steroids and fluid balance in very low birthweight infants

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Arch Dis Child Fetal Neonatal Ed 2005;90:F509–F513. doi: 10.1136/adc.2005.071688

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Accepted 2 May 2005
Published online first 5 May 2005

Objectives: To determine if insensible water loss (IWL) differed between infants exposed or not exposed antenatally to corticosteroids and to explore possible mechanisms for the early postnatal diuresis associated with antenatal steroid exposure.

Design: Retrospective analysis of prospectively collected data.

Setting: Level three neonatal intensive care unit.

Patients: Ninety six infants, median gestational age 27.5 weeks (range 23–33).

Main outcome measures: Comparison of the IWL, urine output and osmolality, fluid input, electrolyte imbalance, respiratory illness severity (as assessed by surfactant requirement, maximum peak inspiratory pressure, and inspired oxygen concentration), and cardiovascular status (as assessed by inotrope requirement) between infants with antenatal corticosteroid exposure and gestational age matched controls.

Results: The infants exposed to antenatal steroids differed significantly from the controls in having both a lower IWL ($p = 0.0135$) and a higher urine output ($p = 0.0036$) on day 1, and fewer developed hyponatraemia ($p = 0.027$) on day 2. Fewer of those exposed to antenatal steroids required inotropes ($p = 0.06$), but their respiratory status was similar to that of the controls.

Conclusions: Infants exposed to antenatal corticosteroids have a lower IWL. The results suggest that greater skin maturation, but also better perfusion rather than less severe respiratory status, explains the early diuresis in infants exposed to antenatal steroids.

Fluid and electrolyte problems are very common in very prematurely born infants, partly because of their high insensible water loss (IWL) and partly because of high infusion rates of intravenous fluids which may be given in an attempt to compensate for the expected losses. Treatments that reduce IWL are therefore highly desirable. It has been suggested that corticosteroids administered antenatally may result in enhancement of fetal epithelial cell maturation and improvement in skin barrier function¹ as, in one study,¹ a higher early infant urine output after antenatal corticosteroid administration was associated with a lower IWL. In another study,² however, no significant differences were seen in transepidermal water loss according to antenatal steroid status. It is clearly important to determine whether antenatal steroid exposure does reduce IWL, as this would inform decisions on appropriate fluid prescription. Thus our aim was to determine whether IWL differed significantly between infants with or without antenatal steroid exposure. Antenatal steroid administration potentially has many other effects on infants including improving their respiratory³ and cardiovascular status,⁴ which could affect urine output. Thus an additional aim was to explore possible mechanisms for the early postnatal diuresis associated with antenatal steroid exposure¹ by comparing fluid and electrolyte balance, inotrope requirement, and severity of respiratory illness in prematurely born infants exposed or not to antenatal steroids.

METHODS

A retrospective analysis was undertaken of prospectively collected data from very low birthweight infants born before 34 weeks gestation who had been entered in a randomised trial examining the effect of perinatal fluid input on the development of chronic lung disease.⁵ The study was approved by the research ethics committee of the King's

Healthcare NHS Trust. The infants had been randomised to receive one of two crystalloid fluid regimens regardless of their antenatal steroid exposure, but for the purposes of this paper they were then stratified according to steroid exposure status (see below). Fluid regimen A was 70 ml/kg on day 1, 90 ml/kg on day 2, 110 ml/kg on day 3, 120 ml/kg on day 4, 140 ml/kg on day 5, and 150 ml/kg on days 6 and 7. Infants on fluid regimen B, compared with those on regimen A, were to be prescribed about 20% less maintenance fluid over the first week. Fluid input on either fluid regimen, however, was only increased if the infant had lost weight and there were no signs of fluid overload, such as hyponatraemia (serum sodium <135 mmol/l). An extra 30 ml/kg/day maintenance fluids was given while the infant received phototherapy. Phototherapy was started if the infant's bilirubin exceeded the phototherapy level for gestational age using standard charts. Colloid infusions were not routinely prescribed, but 5% albumin was administered to infants who were hypotensive but had no signs of heart failure, and fresh frozen plasma was given to infants with coagulation abnormalities. All fluid input (crystalloid and colloid) was recorded hourly and then totalled for the 24 hour period. Urine was collected on open nappies or, for extremely low birthweight babies, on cotton wool balls placed on the nappy. As soon as the infant voided, the nappy or cotton wool ball was weighed to determine the amount of urine passed. If an infant was oliguric and the bladder palpable, this was manually expressed. The urine output was then totalled for each 24 hour period. Infants were weighed at least daily using bedscales. From the daily fluid intake and output and weight, the IWL was estimated using the formula: $IWL = \text{total fluid intake} - \text{fluid output} + \text{weight loss in grams}$.

Abbreviations: FiO_2 , fractional inspired oxygen concentration; GFR, glomerular filtrate rate; IWL, insensible water loss

Table 1 Fluid balance in infants who were and were not exposed to antenatal steroids

	Antenatal steroids	Controls	p Value
Gestational age (weeks)	27.5 (23–33)	27.5 (23–33)	>0.99
Birth weight (g)	971 (570–1500)	892 (600–1498)	0.97
Caesarean section	25 (52)	20 (42)	0.41
Female	25 (52)	27 (46)	0.84
IWL (g)			
Day 1	32 (0–126)	51 (0–138)	0.0135
Day 2	19 (0–171)	41 (0–147)	0.436
Fluid input (ml/kg)			
Day 1	77 (38–191)	76 (46–128)	0.78
Day 2	89 (39–146)	86 (35–143)	0.56
Urine output (ml/kg)			
Day 1	38 (4–105)	22 (1–117)	0.0036
Day 2	89 (26–204)	80 (0–148)	0.264
Urine osmolality (mOsm/l)			
Day 1	191 (103–1443)	235 (104–501)	0.115
Day 2	221 (104–501)	234 (76–484)	0.88
Urine sodium (mmol/l)			
Day 1	48 (9–139)	56 (16–199)	0.081
Day 2	63 (13–158)	64 (11–146)	0.87
Weight change by day 2 (% of birth weight)	−1.05 (−10.6 to 20.4)	+1.18 (−8.9 to 17.8)	0.066

The fluid input reflects all fluid input—that is, both crystalloid and colloid.
Data are median (range) or number (%).

All infants followed the unit's routine policy with regard to monitoring—that is, their urine osmolality was measured from the first urine passed each morning. Electrolytes, creatinine, and bilirubin were assessed daily, but more frequently if abnormal. Deviations from this policy occasionally occurred if an infant was stable and receiving more than half their nutrition enterally. No sodium supplements were given in the first 24 hours after birth, although the patency of indwelling arterial lines was maintained by an infusion of heparinised 0.45% saline. Subsequently the amount of sodium supplementation was altered to keep the serum sodium concentration between 135 and 145 mmol/L.⁶ Blood pressure was measured hourly, usually by intra-arterial monitoring. Hypotension (a mean blood pressure less than the infant's gestational age) was treated initially with up to two boluses of a colloid or crystalloid solution, and, if that failed to improve the blood pressure, a dopamine infusion was started. Inotropes were used as first choice for blood pressure support if there was evidence of myocardial ischaemia.

The infants were nursed in closed incubators with 75–80% humidification, except for the first few hours after birth when indwelling arterial and central lines were being placed. They were ventilated using humidified gases via oral shouldered endotracheal tubes, which we have previously shown to have minimal or no leak.⁷ Infants were started on enteral feeding (0.5 ml/h) as soon as their clinical condition permitted (the volume of enteral feeding was included in the crystalloid volume received). If the infant was intolerant of enteral feeds, parenteral feeding was prescribed from day four.

The nurses recorded each infant's ventilatory settings and inspired oxygen requirement on an hourly basis. Arterial blood gases were checked at least four hourly from samples obtained from catheters sited for clinical purposes. Ventilatory settings and the fractional inspired oxygen concentration (F_{iO_2}) were adjusted to ensure the blood gases were kept in a pre-determined range (pH 7.25–7.40, Pa_{O_2} 7–10 kPa, $Paco_2$ 5–7 kPa). From the nursing charts, the infant's maximum peak inspiratory pressure and F_{iO_2} in the first 48 hours of birth were noted. Exogenous surfactant (Survanta) was administered to all infants with respiratory distress syndrome within two hours of birth if they were fully ventilated and had an inspired oxygen concentration of more than 30%. A second dose was given 12 hours later if the

infant was still fully ventilator dependent with a supplementary oxygen requirement. Infants were described as having a patent ductus arteriosus if the diagnosis had been confirmed by echocardiography and they had required treatment. All infants underwent serial cranial ultrasound examination at least in the first week after birth and were described as having an intracerebral haemorrhage if there was bleeding into the ventricles or brain substance.

Infants from the "fluid trial"⁵ whose mothers had received antenatal corticosteroid therapy within seven days of delivery were identified. The decision to administer antenatal steroids was by the obstetric staff on clinical grounds. The policy of the maternity unit was to administer corticosteroids (a complete course consisted of two doses of 12 mg dexamethasone 12 hours apart) to all mothers in whom delivery was expected before 34 weeks gestation, unless the mother was septicaemic or delivery was imminent. An attempt was then made to match each subject by gestational age to an infant from the fluid trial whose mother had received no steroids antenatally (controls).

Statistical analysis

The data were tested using the Shapiro Wilk W and D'Agostino Skewness test and found to be non-normally distributed. Differences therefore between the two groups, in particular with regard to their IWL, urine output, severity of respiratory illness (as indicated by their maximum peak inspiratory pressure, and F_{iO_2} , and surfactant requirement), and cardiovascular status (as reflected by inotrope requirement), were assessed for statistical significance using the Wilcoxon rank sum test or χ^2 test as appropriate.

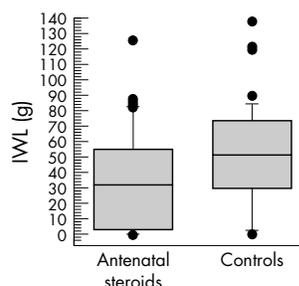


Figure 1 A box and whisker plot of the insensible water loss (IWL) data on day 1 according to antenatal steroid exposure.

Table 2 Metabolic disturbances according to antenatal steroid exposure

	Antenatal steroids	Controls	p Value
Day 1			
Hyponatraemia	6 (16)	7 (18)	>0.99
Hypertnatraemia	2 (5)	5 (13)	0.432
Hypoglycaemia	10 (21)	14 (30)	0.478
Phototherapy	1 (2)	8 (17)	0.0305
Day 2			
Hyponatraemia	2 (4)	9 (20)	0.027
Hypertnatraemia	14 (30)	10 (20)	0.477
Hypoglycaemia	13 (30)	12 (26)	0.815
Phototherapy	9 (20)	16 (34)	0.160

Data are number (%).

RESULTS

It was possible to match 48 infants whose mothers had received corticosteroids antenatally with 48 infants whose mothers had received no antenatal steroids. Twenty eight of the mothers had received a single complete course, nine had received more than two complete courses, and 11 a single dose of dexamethasone.

Infants whose mothers had received antenatal steroids had on day 1 a lower IWL ($p = 0.0135$; table 1, fig 1) and also a higher urine output ($p = 0.0036$). Fewer of the antenatal steroid group on day 1 required treatment with phototherapy ($p = 0.0305$; table 2) or inotrope support ($p = 0.06$; table 3) and on day 2 developed hyponatraemia ($p = 0.027$). There were, however, no significant differences between the two groups with regard to their fluid input (table 1) or the severity of their respiratory illness (table 3).

DISCUSSION

We have shown that prematurely born infants who had been exposed to antenatal steroids have a lower IWL. This is in keeping with the findings of Omar *et al.*,¹ who reported lower IWL in each of the first four days after birth in 16 extremely low birthweight infants exposed to antenatal corticosteroids. Jain *et al.*,² however, found no influence of either sex or antenatal steroids on transepidermal water loss from the abdominal skin of prematurely born infants. Their results are surprising given the effects of antenatal steroids in animal models.^{1–10} Female rat pups have been noted to have a more mature epithelial barrier than male pups of the same gestational age; on day 20 female rat pups had transepidermal water loss rates 40% less than that of male pups.¹⁰ The explanation for the sex differences in transepidermal water loss is that oestrogen accelerates, whereas testosterone

retards, epidermal barrier maturation. Daily antenatal steroid administration in rats has been shown to accelerate the maturation rate of the stratum corneum and diminish transepidermal water loss.⁸ In addition, prematurely born rats exposed to antenatal steroids had accelerated epidermal/peridermal maturation, resulting in less dehydrated skin.⁹ Jain *et al.*² compared infants exposed to antenatal steroids between 1997 and 1998 to historical controls born a decade earlier in 1985 to 1986. During that 10 year period, there have been many changes in neonatal care—for example, routine administration of exogenous surfactant; such changes may have biased their comparison between the two groups.² In contrast, our groups were recruited contemporaneously and, although they must have differed with regard to the predictability of their premature delivery, they were individually matched for gestational age and were similar with respect to birth weight, mode of delivery, and routine aspects of neonatal care. In these two similar groups, we showed differences in IWL related to antenatal steroid exposure, which may be due to steroid induced maturation of the skin epithelial barrier.^{1–9}

We confirmed that antenatal steroid administration is associated with a greater early urine output.¹ This association may be explained by a specific effect of corticosteroids on renal function. Chronic treatment of methylprednisolone has been shown to increase the glomerular filtrate rate (GFR) of rats,¹¹ and fetal lambs injected with betamethasone had a higher GFR than controls.¹¹ In addition, antenatal steroids have been shown in both animal and human studies to affect renal cell differentiation, with an increase in renal adenylate cyclase activity and tubular function.¹² Other studies, however, have not shown an effect of antenatal corticosteroids on either tubular function¹³ or GFR.¹³ Tubular reabsorption of β_2 microglobulin was not affected by prenatal glucocorticoid administration, and GFR (as estimated by the gentamicin half life) did not differ between infants exposed or not to one or more doses of betamethasone antenatally.¹³

The infants exposed antenatally to steroids had similar postnatal weight changes by day 2 (table 1). Thus, although they had a higher urine output on day 1, this is likely to have been balanced by their significantly lower IWL. Indeed, their significantly lower requirement for phototherapy would suggest that they were not more dehydrated, and indeed on days 1 and 2 the proportion of infants with hypertnatraemia did not differ significantly between the two groups. Hyponatraemia, however, was more common in the controls, suggesting that fluid balance was more appropriate in the infants exposed to antenatal steroids. It is possible that the higher incidence of hyponatraemia in the controls, given that they had a higher IWL and some had experienced weight

Table 3 Cardiovascular and respiratory status, morbidity, and mortality

	Antenatal steroids	Controls	p Value
Inotrope support			
Day 1	13 (27)	23 (48)	0.06
Day 2	15 (33)	24 (51)	0.093
Surfactant treatment	29 (60)	35 (73)	0.279
Max PIP (cm H ₂ O)	18 (14–38)	20 (12–42)	0.412
Max FiO ₂	54 (21–100)	64 (21–100)	0.148
PDA	9 (19)	16 (33)	0.163
ICH	5 (10)	9 (19)	0.368
Oxygen dependency at:			
28 days	25 (64)	22 (59)	0.814
36 weeks PCA	9 (24)	12 (33)	0.442
Mortality	12 (25)	14 (29)	0.818

Data are number (%) or median (range).

PIP, Peak inspiratory pressure; FiO₂, fractional inspired oxygen; PDA, patent ductus arteriosus; ICH, intracerebral haemorrhage; PCA, postconceptional age.

What is already known on this topic

- Fluid and electrolyte imbalance are very common in prematurely born infants, and this is partly due their high insensible water loss (IWL)
- Evidence on whether infants exposed antenatally to corticosteroids have a lower IWL is conflicting; they do, however, have an early postnatal diuresis, but whether this is explained by greater skin maturation and or other mechanisms remains uncertain

loss, may be explained by greater urine wasting of sodium. Overall, however, there was a small weight gain in the controls and thus the hyponatraemia may reflect fluid overload.

The group exposed antenatally to steroids were less likely to require inotrope support than the control group. This is in keeping with the finding that the mean arterial pressure was significantly higher in lambs treated antenatally with betamethasone.¹⁴ The exact mechanism for the blood pressure increases with antenatal glucocorticoid treatment are not clear. In lambs exposed antenatally to betamethasone, however, their cardiac output was unchanged, suggesting that their blood pressure increases may be related to increases in peripheral vascular resistance. The lower inotrope requirement of our infants exposed antenatally to corticosteroid may mean they had better renal perfusion and hence higher urine output. It is also possible that the higher urine output resulted from lower concentrations of arginine vasopressin reflecting better cardiovascular status. Postnatally, angiotensin II and arginine vasopressin concentrations have been shown to be significantly lower in betamethasone treated animals by about three hours after birth,¹⁵ and this was associated with an increase in urine output and sodium excretion. The lower arginine vasopressin concentrations were attributed to an improved cardiovascular status rather than steroid induced suppression of arginine vasopressin secretion.

Improvement in respiratory status is associated with a postnatal diuresis,^{16, 17} although the temporal relation of the two events is controversial.^{16, 17} Thus a possible explanation that we considered for the higher urine output of the antenatal steroid groups was that they may have milder respiratory disease, given the known effects of antenatal steroids. Antenatal steroid administration can improve respiratory function by earlier clearance of fetal lung fluid.¹⁸ Glucocorticoids have been shown to upregulate Na,K-ATPase mRNA expression in the immature mouse lung.¹⁸ Na,K-ATPase provides the energy for the active transport of sodium across the pulmonary epithelium and hence fetal lung fluid resorption. We, however, found no significant differences in the proportions of the two groups who required surfactant, nor in their maximum inspired oxygen or peak pressure requirement. We also did not find any significant differences in morbidity or mortality between our two groups, but it is possible that the numbers studied were too small to demonstrate an effect. Nevertheless, our results do not suggest that differences in respiratory status explain the higher urine output seen in the antenatal steroid group.

There are weaknesses to our study. The initial study was not designed to determine the effect of antenatal steroids on fluid balance and the infants were not randomised to receive antenatal steroids. The policy of the obstetricians was to administer corticosteroids to all mothers in whom delivery was expected before 34 weeks gestation, unless the mother

What this study adds

- This study shows that very prematurely born infants exposed antenatally to corticosteroids have lower IWL than gestational age matched controls
- The results suggest that greater skin maturation and better perfusion, rather than less severe respiratory status, explain the early diuresis in infants exposed to antenatal steroids

was septicemic or delivery was imminent. Thus there are likely to be differences in the antenatal pathologies of the mothers of the two groups, with a greater incidence of such problems as premature rupture of the membranes and pre-eclampsia in the antenatal steroid group. We are, however, not aware that such pregnancy complications affect IWL in infants. Clearly, the best method of assessing the impact of antenatal steroids on fluid balance of very low birthweight infants would be to undertake a randomised trial, but, given the known benefits of antenatal steroids, such a trial would be unethical. We have therefore compared the results from infants exposed to antenatal steroids with controls matched for gestational age who were cared for contemporaneously, and thus our results are not biased by the infants being exposed to different management eras. A strength is that all the data collection was undertaken prospectively and was very detailed, allowing us to examine the effect of antenatal steroid exposure not only on fluid balance, but also blood pressure and respiratory status. Although most of the infants had been exposed to at least one complete course of antenatal steroids, a minority had only received one dose of dexamethasone. This may have lessened any effect of antenatal corticosteroid exposure, yet we still saw significant differences between our two groups.

We have shown that, compared with gestational age matched controls, prematurely born infants exposed antenatally to steroids had a lower IWL on day 1. They also had a higher urine output, in association with a lower requirement for inotrope support, but no significant differences in their respiratory support. We therefore conclude that greater skin maturation and better renal perfusion explain the early diuresis noted in infants exposed to antenatal corticosteroids.

ACKNOWLEDGEMENTS

GD was supported by a Children Nationwide Medical Research Fund/Nestle Research Fellowship, and VK by a project grant from the South East Thames NHS Research & Development Directorate. We thank Mrs Deirdre Gibbons for secretarial assistance.

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Competing interests: none declared

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