

**Physiological effects of ROP (Retinopathy of Prematurity) examination: A randomised controlled trial comparing a NIDCAP-based (Newborn Individualised Developmental Care and Assessment Programme) model and conventional care.**

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**Background:** ROP examination is a necessary but stressful procedure in neonates. It has known adverse physiological effects. For example, significant changes in oxygen saturation and heart rate following examination of the eyes have been reported<sup>1</sup>. NIDCAP is a highly skilled method of neonatal care. It may have some benefit in reducing response to stress.

**Objectives:** To objectively look at the trend in physiological effects of ROP examinations, comparing two types of care; a NIDCAP-based approach and a conventional method. Also, to look at characteristics of neonates (such as those on CPAP and/or less than 1500g) who may potentially benefit from the intervention.

**Methods:** Infants eligible for ROP screenings were randomised from two centres (London and Lund) into the intervention (NIDCAP) group or control (conventional) group at the first examination. Subsequent ROP examinations were alternated with either NIDCAP-based care or conventional care. Physiological data on oxygen saturation, pulse rate and percentage of activity were continuously recorded using a NELLCOR pulse oxymetry monitor. The recordings were blindly evaluated using Malincrodt software before and during the examinations, including the periods of 1, 2, 3 and 4 hours following the procedures. Ethical approval was granted from both centres.

**Results:** Physiological recordings suitable for analysis were obtained from 68 examinations. (London: n=32, Lund: n=36; intervention: n=38, control: n=30). At the start of the study, there were no significant differences seen in all the physiological data between the control and intervention groups;  $p > 0.05$ . In London, there was a significant reduction in the number of desaturations/min at 1 hour in the intervention group (-0.07) compared to control (0.03);  $p=0.008$ . Multivariate analysis showed that babies receiving CPAP in both centres had lower maximum pulse rate (MPR) in the intervention group than the control group following the examinations at 2 hours (173 vs 189;  $p=0.01$ ), 3 hours (173 vs 188;  $p=0.04$ ) and 4 hours (175 vs 188;  $p=0.01$ ). Mean pulse rate was also significantly less ( $p < 0.05$ ) in the intervention group than the control at 1, 2, 3 and 4 hours following ROP screening. In both centres, babies in the intervention group had significantly less percentage of activity at 1 hour after the procedure (40% vs 51%;  $p=0.005$ ). In London, babies <1500 g in the intervention group were also significantly less tachycardic at 3 and 4 hours (MPR: 170 vs 190;  $p=0.02$ , 174 vs 191;  $p < 0.001$ ).

**Discussion:** The study demonstrated that infants who received NIDCAP-based care had significantly less adverse physiological effects of ROP examinations. These effects were more evident in babies who were less than 1500g or requiring CPAP. The benefits may be more pronounced in London due to a greater difference in care between the two groups in the study, as NIDCAP is more widely practiced in Lund.

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<sup>1</sup> Laws, David et al. British J of Ophthalmology 1996 May; 80(5):425-428.

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## Neurological outcome of premature infants following a controlled-trial of skin-to-skin contact

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**Background:** Preterm infants are at risk of neurodevelopmental impairment due to brain injury. The Neonatal Intensive Care Unit (NICU) environment may compound these problems. Developmental care is a broad category of interventions designed to minimise the stress of the NICU environment. One such intervention is mother-infant skin-to-skin contact (SSC). We have previously reported a controlled trial of SSC in preterm infants admitted to two NICUs and found no significant difference in maternal or infant outcomes (1). However the presence of brain injury, as indicated by abnormal brain imaging, was not taken into account in the analysis.

**Objective:** To investigate the neurological outcomes of preterm infants entered into a controlled trial of SSC, taking into account evidence of brain injury as shown by cranial ultrasound scan (CUS) data from the neonatal period and/or brain magnetic resonance imaging (MRI) obtained after 12 months corrected age.

**Methods:** Seventy-eight infants born below 32 weeks gestation were recruited within the first week after birth and assigned to a control group receiving standard care, or an intervention group in which mothers were encouraged to provide a session of SSC once daily for 4 weeks. Infants were assessed at 12 months postmenstrual age using the revised Griffiths' Developmental Scale to give a developmental quotient (DQ) and the Hammersmith Infant Neurological examination to derive an optimality score (OS). The results of the CUS from the neonatal period and the MRI scans at 12 month assessment were analysed (74 CUS and 30 MRI scans) blind to group allocation. A composite imaging score (normal, mildly abnormal, severely abnormal) was calculated for each infant. Approval was obtained from the institutes' Research Ethics Committee.

**Results:** The average total number of minutes of SSC in the intervention group was 507.36. Analysis of baseline characteristics confirmed no significant differences between infants in the two arms of the study. Seven children died and 13 were lost to follow up. Severely abnormal imaging was present in 5 infants (1 control, 4 SSC). Overall DQ, and personal-social, hearing-language, eye-hand co-ordination and performance, but not motor, sub-quotients were higher in the intervention group but these differences were not significant. There was evidence of a significant interaction between group and imaging abnormality ( $p=0.019$ ). Multivariate analysis having allowed for imaging abnormality showed overall DQ to be significantly higher in the intervention group (mean difference 13.2, 95% CI 3.1 to 23.4;  $p=0.01$ ). There was no difference in neurological status as measured using the OS.

**Discussion:** Skin-to-skin contact is associated with improved overall DQ in preterm infants when evidence of brain injury is taken into account. These findings support the use and continue evaluation of SSC for improving neurological outcomes in preterm infants.

# Preterm infants on inotropes have different cerebral oxygen metabolism measured by near infrared spectroscopy

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**Background:** Preterm infants are often prescribed inotropes to maintain mean arterial blood pressure (MAP). The effect of inotropes on cerebral oxygen metabolism remains unknown. Spatially resolved spectroscopy (SRS) measures the mean cerebral oxygen saturation (SmcO<sub>2</sub>) at the cotside.<sup>1</sup> SmcO<sub>2</sub> is dependent on both cerebral oxygen delivery and consumption.

**Aim:** Using SRS, we studied normotensive infants (NT) and infants who were on inotropes (INO, dopamine) for hypotension. We aim to compare the relationship between SmcO<sub>2</sub> and cerebral oxygen delivery (CDO<sub>2</sub>) in these infants.

**Method:** The study was approved by the Joint UCL/UCLH Committees on the Ethics of Human Research, and parental consent was obtained prior to study. Fourteen infants in the NT group and 10 infants in the INO group, born at median (range) gestational age of 25 (23-32) weeks, were studied at median (range) postnatal age of 18 (4-103) hours. Four infants in the NT group and 3 infants in the INO group developed intraventricular haemorrhage. Using a NIRO-300 spectrometer (Hamamatsu Photonics, K.K., Japan), stable baseline SmcO<sub>2</sub> was averaged over the 5 minutes immediately prior to cerebral blood flow (CBF) measurements. CBF was measured using the oxygen bolus method.<sup>2</sup> The averaged value of 5 CBF readings was obtained to compute CDO<sub>2</sub> (CDO<sub>2</sub> = CBF x cerebral arterial oxygen content). Between 1 and 3 sets of replicate measurements of SmcO<sub>2</sub> and CDO<sub>2</sub> were obtained over 1 to 3 hours to derive the mean value for each infant.

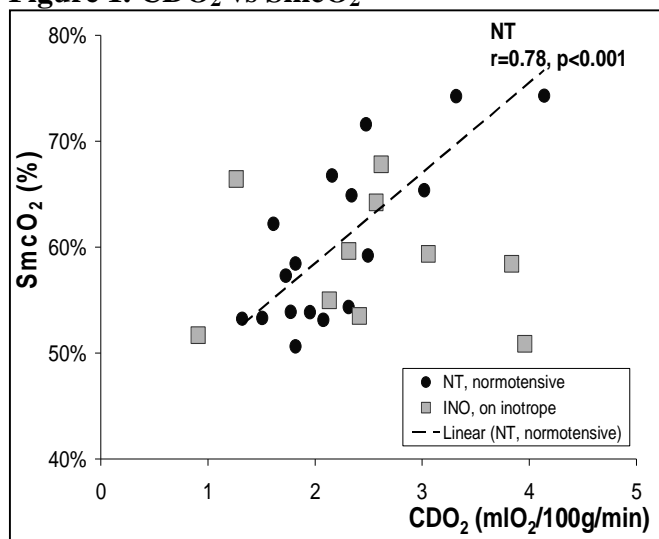
**Results:** Median (IQR) SmcO<sub>2</sub> was 58.4 (53.7-65.1)% and CDO<sub>2</sub> was 2.3 (1.8-2.6)ml O<sub>2</sub>/100g/min. There was no significant difference in SmcO<sub>2</sub> and CDO<sub>2</sub> between the NT and INO groups. In NT infants, CDO<sub>2</sub> positively correlated with SmcO<sub>2</sub> (r=0.78, p<0.001) (fig.1), suggesting coupling of cerebral perfusion and tissue oxygenation. In contrast, no correlation existed between CDO<sub>2</sub> and SmcO<sub>2</sub> in the INO infants.

**Conclusion:** Infants on inotropes have uncoupling of cerebral perfusion and tissue oxygenation. The underlying aetiology of our findings remains to be clarified, but may relate to initial clinical condition leading to hypotension to a direct effect of inotropes on the cerebral circulation. Whilst effective in raising systemic blood pressure, inotropes might not improve cerebral oxygenation.

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Figure 1. CDO<sub>2</sub> vs SmcO<sub>2</sub>



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# Impact of the ductus arteriosus on systemic perfusion in the first 48 hours of postnatal life in preterm infants

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**Background:** Patency of the ductus arteriosus is physiological in the first 48 hours of postnatal life in term and preterm infants. Although pulmonary and systemic pressures may remain relatively balanced at this time high volume ductal shunt (as assessed by reversal of diastolic descending aortic blood flow) has been seen as early as 7 hours postnatal age in some sick preterm infants<sup>1</sup>.

**Aims:** To examine whether significant volume of ductal shunting is common in the first 48 hours, and to assess whether systemic perfusion as assessed by superior vena cava (SVC) blood flow is compromised by ductal shunting in the first 48 hours of postnatal life in preterm infants.

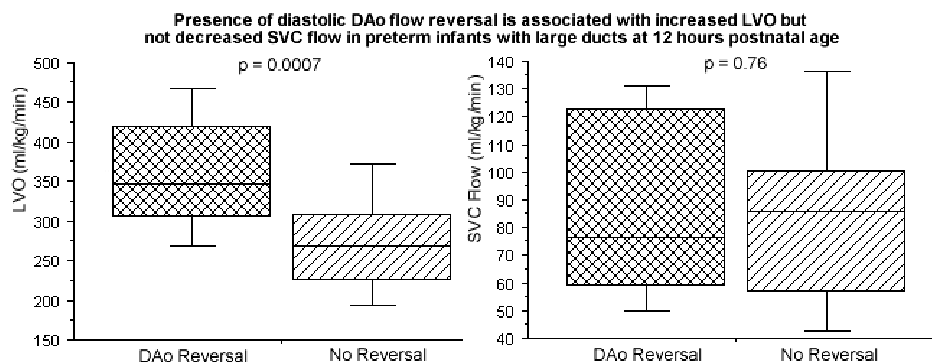
**Methods:** Infants <31 weeks gestation were examined by echocardiography at 5, 12, 24 and 48 hours postnatal age. Duct diameter and left ventricular output (LVO) were assessed by standard methods. SVC flow was assessed as described previously<sup>2</sup>. Pattern of diastolic descending aortic (DAo) flow was assessed from a low subcostal sagittal view. The relationship between SVC flow and ductal size was examined using univariate regression analysis, with correction for potential confounding factors by multiple regression. Volumes of flow were compared between infants with and without diastolic DAo flow reversal using a Mann-Whitney test. The local regional ethics committee approved the study and informed parental consent was obtained in all cases.

**Results:** Eighty infants were studied, with median (range) birth weight 1060 (510-1900) grams and gestation 28 (24-30) weeks. Of infants with patent ducts, pure systemic to pulmonary shunting was seen in 66%, 85%, 89% and 95% of cases at 5, 12, 24 and 48 hours postnatal age respectively.

At 5 hours ductal size was not associated with volume of SVC flow on univariate analysis. At 12 hours increased duct diameter was associated with decreased volume of SVC flow on univariate analysis ( $R^2=0.095$ ,  $p=0.006$ ). This association remained significant when correcting for gestation, birth weight, antenatal steroid use and severity of respiratory disease on multivariate analysis ( $p=0.004$ ), but not when correcting for  $pCO_2$  ( $p=0.24$ ). Infants with duct diameter greater than the median and reversal of diastolic DAo flow had increased LVO (346 vs 268 ml/kg/min,  $p=0.0007$ ), but not decreased SVC flow ( $p=0.76$ ) when compared to infants with duct diameter greater than median but no DAo reversal (Figure). Similar results were at 24 and 48 hours.

**Conclusion:** Even in postnatal life ductal shunting is predominantly systemic

pulmonary. Increased volume of ductal shunt may not be independently associated with decreased upper body perfusion in the first 48 hours in preterm infants. In general, as volume of ductal shunt increases, left ventricular output increases, maintaining upper body perfusion.



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## Cardiac MRI at 3.0 Tesla in Preterm Infants

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**Background:** Evidence is emerging that cardiac function seems to be an important determinant of outcome in preterm infants. Low superior vena cava flow is common in the first hours after birth and has been associated with subsequent periventricular or intraventricular haemorrhage<sup>1</sup>. However cardiac function in the preterm population is poorly understood. Commonly used bedside tests such as blood pressure and capillary refill time have a very low specificity and sensitivity at detecting low blood flow in preterm infants<sup>2</sup>. Echocardiography is invaluable to investigate cardiac morphology but relatively imprecise as a measure of function in individuals. Cardiac magnetic resonance imaging (CMRI) is the method of choice for assessment of cardiac function in adults, but has not been used previously in the preterm population. CMRI in adults is usually done at 1.5 T, however we hypothesised that in preterm infants it would be possible to take advantage of higher field strengths.

**Aims:** To assess the feasibility of undertaking CMRI in preterm infants and to develop novel approaches to acquire images at 3.0 T.

**Methods:** All studies were carried out following written parental consent and with approval of Hammersmith Hospital Research Ethics Committee. Eight preterm babies underwent cardiac MRI. We operated the scanner in its normal mode that complies with all relevant safety guidelines. We carried out monitoring in initial examinations to verify that subjects showed no sign of stress, such as elevated temperature during or after the examinations. Gestational age was median 29 weeks (range 26 –33+5 weeks). Median birthweight was 1370g (808 – 2200g). The median corrected gestational age at time of MRI was 35 weeks (32 – 40 weeks). Two of the infants had known patent ductus confirmed on echocardiogram and were oxygen dependent. Infants were fed and allowed to fall into natural sleep. Each scan took approximately 45 minutes. Babies were monitored throughout the scan by a trained neonatologist.

*Image Acquisition:* All scans were carried out on a Philips 3T Intera system. T1 weighted anatomical sequence was performed followed by a series of balanced fast field echo sequences to assess function

*Data Analysis:* Left ventricular volume was measured by area-length calculations. The following left ventricular parameters were then estimated: ventricular ejection fraction (ml), ventricular end-diastolic and end-systolic volumes (ml) ventricular stroke volume (ml) and cardiac output (l/min).

*Intra- and inter- observer variability:* Two investigators estimated each parameter ten times for a single patient studied and the coefficient of variation (cv) was calculated for each investigator. Comparing estimates for single measurement assessed inter-observer variability

**Results:** Imaging was successful in 7/8 infants, and these images were sufficient to allow detailed assessment of cardiac function. Median ejection fraction was 74.6% [69.3-76]; stroke volume 2.9mls [1.5-10.3]; cardiac output 0.4L/min [0.2-1.6]; end diastolic volume 3.8mls [1.2-11]; end systolic volume 0.3mls [0.3-3.2]. Two dimensional real time CMRI movies provided precise visualisation of cardiac function. Interobserver variability ranged from 2-9% and intra observer variability 1-6% for each parameter measured.

**Conclusion:** This preliminary study demonstrates that CMRI can provide detailed assessment of cardiac function in preterm infants, and this can be achieved at 3.0 T. Infants with PDA showed strikingly increased left ventricular output, achieved by increase in end diastolic volume with unchanged ejection fraction

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## Use of polyethylene bags for temperature management during pre-transport stabilisation.

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### Introduction

The importance of thermal management in preterm infants is well recognised. The use of plastic bags during initial resuscitation and stabilisation has been demonstrated to improve admission temperatures in infants less than 28 weeks gestation<sup>1</sup>, and the subsequent clinical course of infants less than 26 weeks gestation<sup>2</sup>. Thermal management during inter-hospital transport of such infants remains challenging.

### Aim

To evaluate the use of polyethylene bags in aiding optimal thermal management during pre-transport stabilisation.

### Design

For a six-month period from October 2004 to March 2005, infants of < 30 weeks gestation and <10 days of age were placed in plastic bags by the transport team at the earliest safe opportunity after its arrival at the referring hospital. This was prior to any non-urgent intervention. Infants remained in the bags until transferred to the receiving unit. Anterior abdominal wall temperature was continually monitored and recorded every 15 minutes and immediately following completion of each phase of the transfer, namely stabilisation (time between team's arrival & infant being placed into transport incubator), after transfer into the transport incubator and on arrival at the receiving unit. The study group were compared with all similar transfers carried out by the team over the preceding 10 months. Trans-Warmer Mattresses were used as standard within the maximally pre-warmed transport incubator in both groups.

### Results

The two groups were not similar. Infants in the study group were significantly smaller and more premature compared to the historical controls. One infant in the control group died during stabilisation.

The temperatures of the two groups upon the transport team's arrival at the referring hospital did not differ significantly. Significantly more infants placed in plastic bags had temperatures in the normal range immediately following stabilisation. The time taken for stabilisation did not differ significantly. There was no difference in the number of babies with normal temperatures on arrival at the receiving unit.

	Before use of plastic bags (n=22)	After use of plastic bags (n=29)	p value
Mean (Range) Completed weeks of gestation	27 (23-29)	25 (22-29)	0.005
Mean (Range) Postnatal age days	2.0 (1-10)	2.4 (1-7)	0.649
Mean (Range) Birth weight kg	1.02 (0.54-1.50)	0.817 (0.43-1.43)	0.014

	Before Polyethylene bags		After Polyethylene bags		p value
	Infants with temp. <36.4°C	Infants with temp. >36.4°C	Infants with temp. <36.4°C	Infants with temp. >36.4°C	
Pre stabilisation	9	12	10	19	0.57
Post stabilisation	7	14	2	27	0.02
Transport incubator	7	14	3	26	0.07
Receiving hospital	3	18	2	27	0.63

### Conclusion

Achievement and maintenance of skin temperatures to >36.4°C is significantly improved during the initial phases of the transport process when preterm infants are placed in plastic bags at the beginning of pre transport stabilisation.

### References

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## Neonatal Formula Feeding in Sheep Alters Regional Adipose Tissue Deposition as a Young Adult.

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### Introduction:

Obesity is becoming the major health burden facing westernised societies. Excess adipose tissue mass, specifically 'centripetal' i.e. around the abdomen, increases the risk of a range of adverse health outcomes. Adult total adiposity is influenced by the prenatal diet, but preliminary data in animal models suggest regional adiposity is not. However in sheep, at least, there appears a defined window of time in which regional adipose tissue deposition is organised and thereafter remains unchanged. This largely occurs during the lactation period. In this study formula-feeding vs. natural rearing of lambs was used as a model to test the hypothesis that altered nutrition over this time would influence regional adipose tissue in the young adult at one year of age.

### Methods:

Singleton offspring from 16 twin-bearing ewes were randomly allocated to be reared with the ewe as a singleton (Control, n=8) or be separated from the ewe and solely receive formula (Formula-Fed, n=8) from birth to weaning (10-12 weeks). The quantity of formula allocated *ad libitum* (1-1.5 L/d Lamlac) was based upon current recommendations to maintain neonatal growth rates similar to ewe-reared offspring. After weaning all individuals were maintained together in an enclosed environment designed to promote increased growth rates and fat deposition to one year of age. Individuals were regularly weighed and blood samples taken during the fed and fasted state for determination of metabolic variables and at the end of experiments were humanely euthanased with electrocortical stunning and exsanguination. All animal protocols and procedures were ethically approved locally and performed under the UK Animals (Scientific Procedures) Act, 1986.

### Results:

Growth rate up to one year of age was greater in formula-fed relative to ewe-reared offspring with the result that these offspring were heavier at this time (maximum growth rate,  $418 \pm 26$  vs.  $350 \pm 14$  g/d  $P=0.002$ ; weight at 1yr,  $97 \pm 2$  vs.  $87 \pm 2$  kg  $P=0.03$ ; days to  $\frac{1}{2}$ max weight  $133 \pm 4.7$  vs.  $124 \pm 4$  days  $P=NS$ , respectively). Total visceral adipose was similar between groups ( $7242 \pm 349$  vs.  $7791 \pm 429$  g for control and formula-fed, respectively) but the regional deposition was different (e.g. % total deposited in omental and perirenal regions was  $58 \pm 3$  and  $36 \pm 3$  % respectively in Controls, but  $48 \pm 2$  and  $47 \pm 2$  % in formula-fed). Concentrations of circulating metabolites were unaltered in the fasted state (e.g. non-esterified fatty acids,  $0.35 \pm 0.17$  vs.  $0.27 \pm 0.10$  mmol/L; triglycerides  $0.21 \pm 0.05$  vs.  $0.25 \pm 0.06$  mmol/L, glucose  $4.31 \pm 0.16$  vs.  $4.21 \pm 0.19$  mmol/L in formula-fed and control sheep, respectively) but plasma homocysteine was elevated ( $18.8 \pm 1.7$  vs.  $12.2 \pm 0.4$   $\mu$ M).

### Conclusions:

In sheep, infant formula-feeding has no major effect on resting, fasted metabolic state but specifically results in an increase in plasma homocysteine concentration. Plasma homocysteine concentrations greater than  $15$   $\mu$ M in humans predict increased risk of CVD. There was also a specific redistribution (10% shift) of internal adipose depots away from omental towards perirenal sites. The metabolic consequences of this shift are unclear but such an effect has not been seen in sheep to date, to our knowledge, following many diverse nutritional paradigms.

## Role of thyroid hormones in the deposition of hepatic glycogen in fetal sheep near term

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**Introduction:** Glycogen content in the fetal liver increases towards term in preparation for glucose homeostasis after birth. Hepatic glycogen deposition is induced by the prepartum rise in circulating cortisol concentrations in the fetus. The prepartum cortisol surge also stimulates the production of triiodothyronine ( $T_3$ ) from thyroxine ( $T_4$ ), and causes an increase in plasma  $T_3$  near term. However, the effect of thyroid hormones on glycogen content in the fetal liver is unknown. Therefore, this study investigated hepatic glycogen content in sheep fetuses after experimental manipulation of thyroid hormone concentration by  $T_3$  infusion and fetal thyroidectomy (TX).

**Methods:** All surgical and experimental procedures were carried out in accordance with UK Home Office legislation. Under general anaesthesia (1.5% halothane in  $O_2$ - $N_2O$ ), thyroid glands were removed from 13 fetuses at 105-110 days of gestation (term  $145 \pm 2$  days), and catheters were implanted into the femoral artery and vein of a further 15 fetuses at 115-120 days. These and 10 untreated fetuses were divided into six experimental groups:

- 1) infused with saline i.v. for 5 days ( $n=5$ ) or untreated ( $n=2$ ), and tissue collection at 130 days
- 2) infused with cortisol i.v. for 5 days, and tissue collection at 130 days ( $n=5$ ,  $2-3 \text{ mg kg}^{-1} \text{ day}^{-1}$ )
- 3) infused with  $T_3$  i.v. for 5 days, and tissue collection at 130 days ( $n=5$ ,  $8-12 \text{ } \mu\text{g kg}^{-1} \text{ day}^{-1}$ )
- 4) TX and tissue collection at 130 days ( $n=7$ )
- 5) TX and tissue collection at 144 days ( $n=6$ )
- 6) untreated and tissue collection at 144 days ( $n=8$ )

On the day of tissue collection, all ewes and fetuses were administered a lethal dose of sodium pentobarbitone. Umbilical arterial blood and liver samples were obtained at delivery by Caesarean section. Plasma cortisol and thyroid hormone concentrations were measured by radioimmunoassay, and hepatic glycogen content was determined by amyloglucosidase assay. Data were analysed by one-way and two-way ANOVA, and unpaired t-test ( $p < 0.05$ ).

**Results:** On the fifth day of infusion, plasma  $T_3$  concentrations were significantly higher in the fetuses infused with  $T_3$  ( $0.93 \pm 0.23 \text{ ng ml}^{-1}$ ) and cortisol ( $0.67 \pm 0.07 \text{ ng ml}^{-1}$ ), compared with those infused with saline ( $0.23 \pm 0.02 \text{ ng ml}^{-1}$ ). Plasma  $T_3$  concentrations increased with gestational age to  $0.58 \pm 0.05 \text{ ng ml}^{-1}$  in the intact fetuses, but were reduced to  $0.13 \pm 0.02 \text{ ng ml}^{-1}$  in the TX fetuses.

In immature fetuses infused with  $T_3$ , hepatic glycogen content was increased above that seen in the saline-infused fetuses ( $45.6 \pm 5.4$  versus  $28.0 \pm 4.3 \text{ mg g}^{-1}$ ), but not to the level seen in fetuses infused with cortisol ( $102.9 \pm 13.2 \text{ mg g}^{-1}$ ).

At 130 days of gestation, hepatic glycogen in the TX fetuses ( $48.3 \pm 5.7 \text{ mg g}^{-1}$ ) was significantly greater than in the intact fetuses ( $28.0 \pm 4.3 \text{ mg g}^{-1}$ ). However, the normal increment in hepatic glycogen content seen between 130 and 144 days of gestation was abolished when the prepartum rise in  $T_3$ , but not cortisol, was prevented by fetal TX. At 144 days, hepatic glycogen in TX fetuses ( $55.7 \pm 4.0 \text{ mg g}^{-1}$ ) was significantly lower than in the intact fetuses ( $108.8 \pm 6.6 \text{ mg g}^{-1}$ ).

**Conclusions:** Therefore, thyroid hormones have an important role in stimulating glycogen deposition in the fetal liver near term, and may mediate, in part, the maturational effect of cortisol.

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## **The influence of size at birth on lipid storage and peroxisome proliferator activated receptor $\gamma$ (PPAR $\gamma$ ) expression in adipose tissue (AT).**

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Epidemiology has shown that infants of low birth weight show poor neonatal growth and increased susceptibility to adult diseases such as diabetes and obesity in later life. PPAR $\gamma$  is a transcription factor involved in the regulation of adipose tissue development and lipid metabolism and is implicated in type 2 diabetes. Pigs provide an ideal model to examine the influence of size at birth due to the natural variance in piglet weight within a litter, impairment of glucose tolerance and increased body fat has been observed in low birth weight offspring in adulthood (3, 4). This study examined whether birth weight influences the expression of PPAR $\gamma$  and the extent of lipid storage during early life in the pig.

Piglets from 11 litters were ranked according to body weight at birth and 3 animals from each were assigned to small (SFD n=11), normal (NFD n=11) or large for dates (LFD n=11) groups. Piglets were euthanased with an overdose of barbiturate (100 mg kg<sup>-1</sup> pentobarbital sodium: Euthatal) on days 7 (n=15) and 14 (n=18) to obtain AT. Adipose tissue triacylglyceride (TAG) content was measured using a commercial kit following extraction by the Folch method. PPAR $\gamma$  expression in AT was measured using RT-PCR as described previously (1). GLM analysis was carried out to investigate statistical differences; results are presented as means  $\pm$  standard errors.

TAG content of adipose tissue was not found to be significantly affected by birth weight (e.g. day 7; SFD, 141.2 $\pm$ 87.5; NFD, 266.6 $\pm$ 43.2; LFD, 237.8 $\pm$ 59.3 mg.dL<sup>-1</sup> although TAG content more than doubled over the second week of life in the SFD piglets, compared to an increase of only 10-20% in the NFD and LFD group (SFD day 7; 141.2 $\pm$ 87.5; SFD day 14; 368.9 $\pm$ 12.7 mg.dL<sup>-1</sup> (P=0.06)). PPAR $\gamma$  mRNA abundance was similar between NFD and SFD piglets, but was significantly lower in LFD compared to NFD piglets on day 14 (NFD; 161.1 $\pm$ 15.0; LFD 121.1 $\pm$ 6.7 (P<0.05) arbitrary units).

Enhanced TAG storage during early development in SFD piglets suggests that these piglets are laying down increased lipid reserves. It is possible that these increased reserves will lead to impaired glucose tolerance and obesity in later life. PPAR $\gamma$  mRNA expression in these piglets was unaltered, suggesting impaired ability to regulate an influx of lipid. In view of the potentially deleterious long term consequences of accelerated growth in the smaller infants; this may be one factor putting these individuals at increased risk of later metabolic disease.

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## Leptin – its role in adaptation at birth and later health and disease

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Leptin is a 16 kDa hormone secreted primarily from white adipose tissue that in the adult has a major role in regulating appetite. Since the discovery of leptin in 1994 it has been found to have a number of functions relating to the regulation of energy homeostasis and reproduction. In this regard leptin may mediate a number of potentially adverse adaptations to excess fat deposition therefore impacting on both cardiovascular and kidney function, outcomes that may be programmed in utero (1). With regard to the role of leptin in fetal and neonatal development this appears to vary greatly between species and is related in part to maturity at birth. In addition, leptin can have opposite effects in the fetus compared with the newborn. For example, leptin promotes the appearance of the brown adipose tissue specific mitochondrial uncoupling protein (UCP)1 in the ovine fetus (2) but has the reverse effect after birth (3). In the newborn, leptin can also influence mitochondrial protein abundance within the lung where it promotes the loss of UCP2 and enhances cortisol sensitivity at the same time as accelerating the post-partum decrease in plasma cortisol (4). The abundance of leptin in fetal adipose tissue is further determined by the amount of food consumed by the mother at different stages of pregnancy. To this extent reducing maternal food intake coincident with the period of rapid placental growth can result in greater fetal fat deposition at birth plus raised leptin expression, although the magnitude of this adaptation is dependent on the level of maternal food intake in late gestation (5). With regard to the longer term consequences of maternal and fetal dietary manipulation then the offspring can show raised blood pressure and enhanced adipocyte leptin secretory capacity as adults (6) even when raised under a standard nutritional environment. Our current research is now addressing the extent to which such outcomes may be amplified by exposure to reduced physical activity plus excess food consumption after birth. This indicates the rapidity with which obesity can be induced in the juvenile period and accompanied by adverse effects on cardiovascular physiology which are potentially mediated by leptin.

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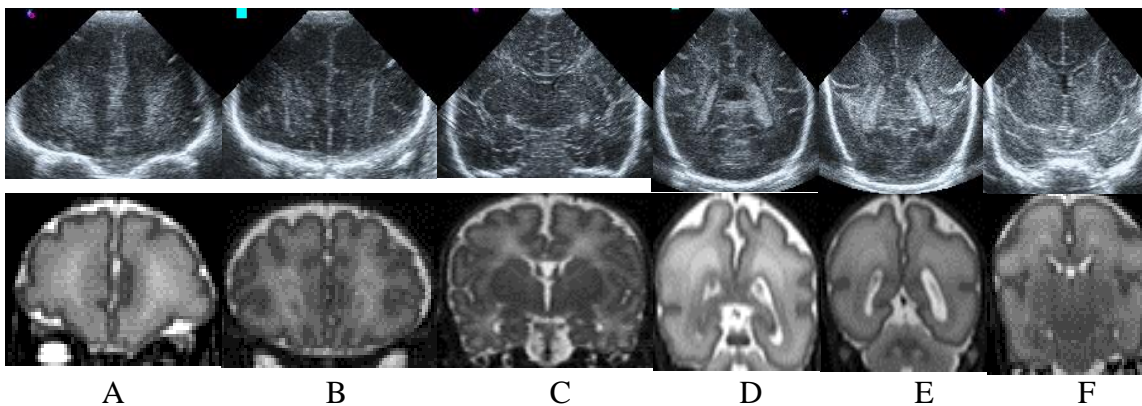
## Frequently encountered cranial ultrasound (cUS) features in the preterm infants' brain: correlation between cUS and MRI

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**Background.** Neonatal cUS is a reliable tool for detecting major lesions (1). CUS is not considered as good as MRI for lesion definition and more subtle abnormality and not all echogenicity on cUS correlates with later pathology. In preterm infants, areas of bilateral, symmetrical echogenicity are frequently encountered in frontal white matter (WM) and margins of lateral ventricles (LV). Based on studies on normal brain development (2-4), it can be hypothesized that these features represent maturational processes.

**Objective.** To determine whether the frequently seen bilateral and symmetrical features on neonatal cUS reflect maturational processes

**Patients and Methods.** Preterm infants (GA<35 wks) who had a cUS and MRI examination on the same day were eligible. Ethical approval for brain MRI was given and parental consent obtained. A Siemens Antares US scanner and 3 Tesla MRI system were used. CUS and T<sub>2</sub>-weighted MRI scans were reviewed for: frontal echogenic blush (A), echogenic lines around/below LV (B), echogenicity running superolaterally from anterior horn of LV (C), echogenic lines running parallel to LV (D), temporo-occipital echogenic blush (E), and echolucent tract emanating from the corpus callosum (F). We also tried to distinguish on cUS: basal ganglia (BG) structures, the internal capsule (IC), myelination, and the subplate.



**Results.** Twenty-six preterm infants (mean GA 29.9 weeks) were studied. Sensitivity of cUS for maturational features on MRI was 100% for features A, B and F, 93% for feature C, and 90% for feature D. No MRI-correlate was found for feature E. The features were best seen on early cUS as compared to scans nearer to term. BG structures were distinguishable on cUS, but the IC and subplate were not seen. The posterior brainstem was always very echolucent. This may reflect myelination but myelin in the IC was not identified on normal scans.

**Discussion.** There is a good correlation between cUS and MRI for the bilateral symmetrical echogenic areas in preterm infants. The features are mainly present on early preterm scans and correlate with maturational features on MRI. Care should be taken not to interpret these features as representing pathology.

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## Perinatal outcome of pregnancies in women with type 1 and 2 diabetes in England, Wales and Northern Ireland 2002/2003.

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**Background/Aim:** In 1989 the St Vincent declaration set a 5 year aim to achieve outcomes in diabetic pregnancies that were similar to those in non-diabetic pregnancies (1). In the mid 1990s, poor outcomes were reported in a number of regional UK studies. This prompted CEMACH to start a national enquiry programme to: a) provide information on perinatal mortality, congenital anomalies and other adverse neonatal outcomes for diabetic pregnancies in England, Wales and Northern Ireland; and b) assess clinical standards of care in women and babies from preconception to the postnatal period. We report on main outcomes.

**Methods:** *Design:* Descriptive population based study. *Population:* Pregnancies in women with pre-gestational diabetes (type 1 and 2) delivering or booking from 1<sup>st</sup> March 2002 to 28<sup>th</sup> February 2003. *Data collection:* By health professionals in 231 maternity units using a structured questionnaire. CEMACH attained Section 60 approval for its programme of work in December 2003.

**Results:** There were 3808 pregnancies to women with diabetes reported to CEMACH (1 in 260 births in E, W and NI): 2767 (73%) type 1 diabetes and 1041 (27%) type 2 diabetes. Maternal-age adjusted mortality rates showed a significant increase in stillbirth, perinatal and neonatal mortality rates compared to the general population (see table). There was no apparent difference in mortality between type 1 and 2 diabetes.

	Rate [95% CI] in women with type 1 & 2 diabetes n= 2536*	National rate† n = 620841	Rate Ratio [95% CI]
Stillbirth	26.8 [19.8-33.8]	5.7	4.7 [3.7-6.0]
Perinatal death	31.8 [24.2-39.4]	8.5	3.8 [3.0-4.7]
Neonatal death	9.3 [5.2-13.3]	3.6	2.6 [1.7-3.9]

\* Births occurring in one calendar year † Source: CEMACH data

The prevalence of major congenital anomalies was 41.8 per 1000 births compared to 21 per 1000 (prevalence ratio = 1.9 [1.6-2.3] p<0.001), using maternal age-specific data for 2002-03 from the European surveillance of congenital anomalies registry (EUROCAT). The difference between observed and expected prevalence of anomalies related to a particular increase seen in: a) neural tube defects, n=12, (prevalence ratio = 3.4 [1.5-7.4] p<0.001); and b) congenital heart disease, n=60, (prevalence ratio = 3.3 [2.3-4.6] p<0.001).

A total of 1296/3536 babies (36.7%) delivered prematurely (compared to 7.3% (p<0.001) in the general population: Office for National Statistics, 2002). Birth weight distribution of singleton babies showed a 2 fold increase in macrosomic babies (21% ≥ 4000g versus 11% (p<0.001) in the general population: NHS maternity statistics England 2002). There was no significant difference in birth weight distribution between type 1 and 2 diabetes (p=0.3). Shoulder dystocia incidence in singleton vaginal births of these diabetic pregnancies was 7.9% and Erb's palsy incidence was 4.5/1000 (compared with 0.42/1000 in UK: British Paediatric Surveillance Unit 1999). Overall admission to a neonatal unit was 56% including 32.6% of term babies admitted to a neonatal unit for special care. These findings were found in association with a poor preparation for pregnancy: 35% of mothers received preconception counselling, 37% had a preconception glycaemic control measurement and 39% took folic acid supplements before conception.

**Conclusion:** In the UK in 2002, babies of mothers with diabetes were at increased risk of poor outcome both in term of mortality and morbidity compared to those from normal pregnancies. Babies of women with type 1 and 2 diabetes had similar apparent risks of a poor outcome.

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## Measuring the severity of illness in babies: how do CRIB, CRIB II, SNAPPE II and Blood Lactate compare?

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**Background:** Illness severity scores estimate the probability of hospital mortality for ill neonates. Elevated blood lactate (BL) concentrations too have been shown to relate to poor outcomes in neonates but have not been directly compared with illness severity scores.

**Aim:** To compare the performance of the neonatal illness severity scores (CRIB, CRIB II and SNAPPE-II) and BL for prediction of mortality among very low birth weight infants.

**Methods:** Babies of <32 weeks' gestation and/or birth weight <1500 g admitted to the neonatal unit between 1999 and 2003 were included in the analysis. Babies with inevitably lethal malformations, those given comfort care only, early (<2 h of age) neonatal deaths, and those in whom BL levels were not available for the first 6 hours of life were excluded. The outcome of interest was in-hospital mortality. The discriminatory ability of the scores and BL was assessed by calculating the area under the receiver operating characteristic curves (AUC). Hosmer-Lemeshow (HL) test was used to measure the goodness of fit of the models. The study was approved by the Shropshire local research ethics committee.

**Results:** Of the 312 eligible infants, BL was measured during the first 6 hours in 269 (86.2%). Their mean (SD) gestation and birth weight were 29 (2.5) weeks, and 1205 (373) g, respectively. 98% were inborn, 77% had received antenatal steroids, 47% were born by caesarean section, and 59% required ventilation for a median (IQR) duration of 3 (1-9) days. There were 41 (15.2%) in-hospital deaths.

The lowest BL concentrations during first 6 hours were significantly higher among non-survivors than survivors (median (IQR) – 4.8 (2.7-9.1) vs 1.8 (0.99-3) mmol/l,  $p<0.0001$ ). Higher BL during first 6 hours was associated with increasing mortality [lowest BL<2.5 mmol/l (n=155) – mortality 4.5%, BL 2.5-4.9 mmol/l (n=64) - 22%, BL 5 -9.9 mmol/l (n=33) - 33%, and BL  $\geq$ 10 mmol/l (n=17) – 53%]. Compared to survivors, non-survivors had significantly higher median (IQR) illness severity scores [9 (7-12) vs 1 (1-3) for CRIB, 12 (9-16) vs 5 (3-8) for CRIB II, and 56 (32-63) vs 8 (0-23.5) for SNAPPE II;  $p<0.0001$  for all]. The illness severity scores showed significantly greater discrimination for mortality than the lowest 6-h BL concentrations [AUC (SE): CRIB - 0.92 (0.023), CRIB II - 0.91 (0.022), SNAPPE II - 0.89 (0.026) vs BL - 0.78 (0.041),  $p=0.003$ ]. Indeed, the Draper grid of gestation and birth weight was similar to the illness severity scores [AUC (SE) 0.86 (0.036),  $p=0.12$ ]. All the scores and BL showed good calibration (HL: CRIB -  $p=0.37$ , CRIB II - 0.60, SNAPPE II - 0.65, and BL - 0.39).

**Conclusions:** Elevated BL during early hours after birth is associated with increased in-hospital mortality. However, CRIB, CRIB II and SNAPPE II discriminate better between survivors and non-survivors than the BL levels. Indeed, gestation and birth weight appear to be as reliable measures of mortality risk in very low birth weight infants as the scores of illness severity.

## Assessment of infant lung function at follow up

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**Background:** The efficacy of respiratory interventions in the neonatal period given with the hope of improving respiratory outcome can be quantitatively determined by assessment of respiratory function in infancy. Unfortunately, only a few randomised trials have incorporated such assessments, as respiratory function measurements at follow up have been restricted to specialist centres, because of the expertise required to perform and interpret them. A new generation of infant plethysmographs have been produced which could make infant respiratory measurements more routinely available. One of these (Jaeger master screen baby body plethysmograph, Viasys Ltd), however, has been demonstrated to record lower lung volumes than previously published values (1) or results obtained from a helium gas dilution technique (2).

**Objectives:** To compare the results obtained from a new generation plethysmograph (Jaeger) and an older research plethysmograph (Hammersmith), both in vivo and in vitro and assess if any differences found in lung volume ( $FRC_{pleth}$ ) were explained by different sensitivities to the adiabatic effect.

**Methods:** In vivo, 11 children were measured (median postnatal age 13 (range 5-15) months) were assessed. In vitro, the systems were assessed using a variable volume lung model containing 0, 32g or 72g (completely filling the chambers of the lung model) of copper wire to minimise adiabatic effects.

**In vivo results:** The airway resistance ( $R_{aw}$ ) measured by the Jaeger plethysmograph (median 3.98 (range 1.05 - 6.74) kPa/l/s) results were higher than that measured by the Hammersmith plethysmograph (2.36 (1.46-5.19) kPa/l/s) ( $p < 0.001$ ). In addition the within patient variability was higher with the Jaeger (median coefficient of variability 17.2 %) than with the Hammersmith plethysmograph (9.9 %) ( $p < 0.001$ ).

**In vitro results:** The volumes measured (expressed as a percentage of the actual volume) were 60-64 %, 70-75 % and 87-89% for the Jaeger, and 73-78 %, 97-99% and 100-103% for the older plethysmograph ( $p < 0.001$ ) with 0, 32 and 72g of copper wire respectively. The Jaeger plethysmograph was more sensitive to the adiabatic effect ( $p < 0.001$ ).

**Conclusion:** The Jaeger plethysmograph under records FRC in vivo and in vitro, this is at least partially explained by a greater sensitivity to the adiabatic effect, it also has a wider variability in  $R_{aw}$  measurements. These results emphasise the need to comprehensively validate all new lung function assessment systems before introducing them into clinical practice.

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## Exploring subplate evolution of the fetal cortex using magnetic resonance imaging

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**Objective:** To investigate the potential of using fetal MRI to document, *in vivo*, the evolution of the subplate, a transient layer of the developing cortex which until now has been restricted to *in vitro* exploration (1)

**Method:** Ethical approval for these studies was obtained from the Hammersmith Hospital Ethics Committee. Investigation centred on two-dimensional measurements of intraparenchymal laminar diameters, in ten regions of interest, using clinical T<sub>2</sub>-weighted MRI images from twenty-six single foetus pregnancies ranging from 20 to 35 weeks gestational age. Bi-parietal diameter, ventricular diameter and germinal matrix were also assessed. The coefficient of variability for all measurements was between 0.14 and 1.87%.

**Results:** At 20 weeks gestation the subplate is visible globally as a thick band of characteristic high intensity, subjacent to the developing cortical plate. A distinctive pattern of development follows, diameter peaking around 29 weeks, before becoming increasingly isodense to neighbouring layers, restricted to gyral crests and finally MRI invisible. Regional variation in the timing of these events was evident. Cortical plate diameter appeared constant throughout.

**Discussion:** The developmental course observed correlates with that established using *in vitro* investigation. In common with other aspects of brain development subplate maturation occurs earlier in primary cortical areas, with association cortex lagging behind.

**Conclusion:** Fetal MRI can indeed be used to qualitatively and quantitatively analyse subplate development, providing a potential means of assessing cortical developmental disturbances antenatally. Comparison of subplate evolution in the normal fetus with the postnatal evolution in the preterm infant may allow insights into the neurocognitive impairments in children born preterm.

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## **Patterns of brain injury seen in neonates presenting with a postnatal collapse.**

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**Purpose of study:** There is little information regarding aetiology and outcome in apparently well newborns found collapsed in the early postnatal period. We present our perinatal data, brain imaging findings and outcome in term neonates, who collapse within hours of birth in whom no infective or metabolic cause is found.

**Subjects/methods:** Term infants considered well at birth who have an acute postnatal collapse (< 60 hours) that required extensive resuscitation were included in this study. Images were all done as part of clinical investigation with parental permission and ethical approval from the Hammersmith Hospital Ethics Committee for the MR studies. Cases were selected from all term inborn infants with these symptoms (5) and regional referral (5) in the last 12 years.

**Data collected:** Family and pregnancy histories. Labour onset and progress, evidence of fetal distress, analgesia, acute events, type of delivery. Infant gestational age (GA), sex, birth weight (BW), head circumference (HC), Apgar score, cord pH; time of collapse, relation to feeding, pH post resuscitation, cerebral function monitor /EEG findings, results of septic, metabolic and post mortem findings; neurodevelopmental follow-up. All but one infant had a brain MRI within 14 days from delivery.

**Results:** Ten infants fulfilled the entry criteria; all were Caucasian, 6 male, one twin; mean maternal age was 31.7 years (27-38); 8 were primipara; one had a hemiplegia from age 16; 5 infants were born by spontaneous vaginal delivery (1 breech, 1 OP, 2 water births), 4 with forceps and 1 by emergency section. One had meconium stained liquor. Mean Apgar scores were 7 (3-9) and 9 (8-10) at 1 and 5 minutes. Cord pH was 7.18-7.21 (n=3). Three infants only required 5 inflation breaths after delivery. Mean GA was 38 weeks (36-41); mean BW 3.04kg (1.9-4.0); mean HC 34.7cm (32-37.7). Mean age of collapse was 8.5 hours (10 min–55 hrs). All infants needed extensive resuscitation and seven developed seizures within 12 hours of their collapse. Mean pH and BE post-collapse were 6.83 (6.4-7.2) and -21.7g/dL (11.3-29.6). No infant had X-ray signs of aspiration or a blood glucose < 2.5mmol/L. None had evidence of an antenatally established insult, a metabolic disorder or sepsis. Seven infants had severely abnormal basal ganglia and thalami typical of acute severe hypoxia-ischaemia with acute brain stem injury; five of these also had injury to white matter and four to the cortex. They all had severe encephalopathy, a severely abnormal CFM/EEG and all died. When available, post-mortem data confirmed the pattern of injury. Three infants had neuroimaging without persisting abnormalities; all had symptoms of persistent pulmonary hypertension (PPHN) and normal background CFM. All had normal neurodevelopmental outcomes (1-6 years).

**Discussion:** In this study infants who collapse postnatally divide into two groups: (1) those with severe acute damage to the central grey matter/brainstem consistent with severe hypoxia-ischaemia; only one of these infants had a normal delivery, all but one collapsed in their mother's arms in relation to breast-feeding and all died. (2) those with normal imaging and background CFM who have a PPHN-like illness (two were water births); their collapse seemed unrelated to feeding; they had a normal outcome. There were no antenatal problems identified in either group and no clear evidence of intrapartum asphyxia. Why this pattern of damage occurs remains unexplained.

1 Badawi N, et al. BMJ 1998; 1549-53

2 Cowan F et al. Lancet 2003; 361: 736-42.

## Postnatal systemic corticosteroids – where to now?

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**Background:** Systemic postnatal corticosteroid therapy in ventilator-dependent infants has short-term benefits. However, controversy exists about its effects on long-term survival free of neurosensory impairments and disabilities.

**Aim:** To review available data on the long-term effects of systemic postnatal corticosteroid treatment in very preterm infants.

**Methods:** Randomised controlled trials (RCTs) of postnatal corticosteroid therapy for prevention or treatment of CLD in preterm infants reporting rates of both mortality and long-term neurological outcomes were reviewed and their data synthesised. Including the DART study, there were twenty-one studies with data on 1791 randomised infants which met eligibility criteria. In addition to usual meta-analyses for overall and subgroups effects, the relationship between the corticosteroid effect on the combined outcome, death or cerebral palsy, and the risk of CLD in control groups was analysed by weighted meta-regression.

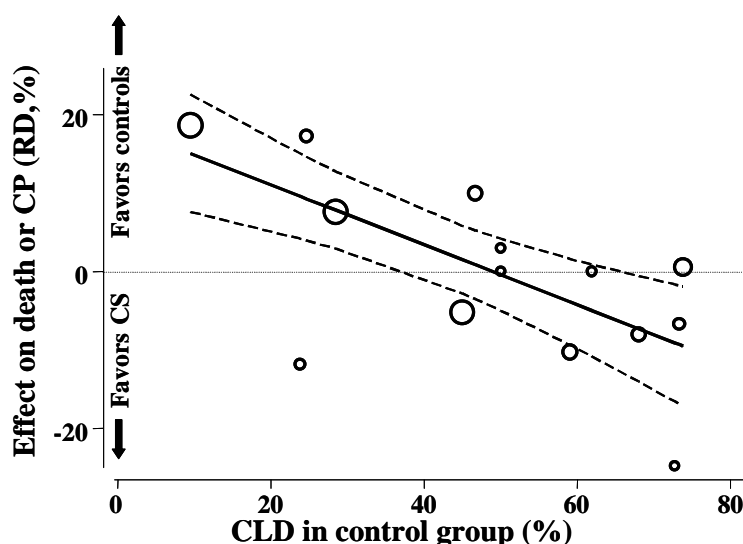
**Results:** Among all infants randomised a significantly higher rate of cerebral palsy after corticosteroid treatment (typical risk difference [RD] 0.04, 95% CI 0.01, 0.07;  $P=0.005$ ) was partly offset by a non-significant reduction in mortality (typical RD  $-0.02$ , 95% CI  $-0.06$ , 0.02;  $P=0.33$ ). Consequently there was no significant effect of corticosteroid treatment on the combined rate of mortality or cerebral palsy (typical RD 0.02, 95% CI  $-0.02$ , 0.07;  $P=0.28$ ). Adverse effects of steroids on cerebral palsy were mostly limited to studies where treatment started in the first week of life. On meta-regression there was a significant negative relationship between the treatment effect on death or cerebral palsy and the risk of CLD in control groups ( $P=0.002$ ) (Figure 1). Addition of the DART study data did not change this relationship.

**Figure 1.** Risk difference (RD, %) for death or cerebral palsy (CP) among all participants, vs. rate of chronic lung disease (CLD, %) in the control group. The area of each circle is proportional to the individual study's weight.

Regression line and its 95% confidence intervals (CI) are shown.

Regression equation:  $Y = 18.7 - 0.38X$ ;  $P = 0.002$ .

CS = corticosteroids



Based on the 95% CI, with risks of CLD below 35% corticosteroid treatment significantly increased the chance of death or cerebral palsy, whereas with risks of CLD exceeding 65% it reduced this chance.

**Conclusions:** Long-term adverse effects of postnatal corticosteroids may be limited to treatment started early in the first week, when the level of risk for CLD is low.