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PROTECTING THE PREMATURE BRAIN: CURRENT EVIDENCE BASED STRATEGIES FOR MINIMISING PERINATAL BRAIN INJURY IN PRETERM INFANTS

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ABSTRACT
Improving neurodevelopmental outcome for preterm infants is an important challenge for neonatal medicine. The disruption of normal brain growth and neurological development is a significant consequence of preterm birth and can result in physical and cognitive impairments. Whilst advances in neonatal medicine have led to progressively better survival rates for preterm infants, there has only been a modest improvement in the proportion of surviving infants without neurological impairment, and no change in the proportion with severe disability. The overall number of children with neurodisability due to prematurity is increasing. Trials investigating novel therapies are underway and many have promising early results, however, in the interim, current treatments and management strategies that have proven benefit for neurodevelopment or reduction in neonatal brain injury, are often underutilised. We collate the evidence for the efficacy of such interventions, recommended by guidelines or supported by large meta-analysis or randomised control trials. We address controversies that have hindered uptake and problems with translating research into practice. We then look to the future of preterm neuroprotective care.

INTRODUCTION
Survival rates for preterm babies are increasing, however severe neurological impairment remains a significant consequence of preterm birth. Research continues into potential treatments for reducing both the risk of initial brain injury and subsequent neurodevelopmental problems; however, in the interim, these can be reduced by optimising currently approved and recommended practices.

Methods
Medline, Web of Science, the Cochrane database, national and international guidelines were searched for meta-analyses and randomised control trials (RCTs) of interventions affecting neurodevelopment and/or intraventricular haemorrhage (IVH) in preterm infants. We reviewed compliance using the National Neonatal Audit Programme (NNAP) – an audit of nearly all UK neonatal units and the UK Vermont Oxford Network database (VON), which covers 25% of UK very low birth weight deliveries.

ANTENATAL INTERVENTIONS
Neural development and brain growth are fundamentally affected by the in utero environment. Reducing antenatal risk, including rates of preterm labour is important, but beyond the scope of this review. Following onset of preterm labour, neuroprotective interventions can be implemented.

Antenatal Transfer for Anticipated Preterm Delivery
Mortality for extremely preterm infants (22-26 weeks) is reduced in centres offering the highest level of intensive care (tertiary centres), compared to less specialist centres (Odds Ratio (OR) 0.73 (95% confidence interval (95%CI) 0.59-0.9)), supporting the recommendation that care is centralised. Transport of these infants during the first 48 hours is however associated with increased rates of severe IVH, and babies born in tertiary centres have significantly better morbidity-free survival than infants transferred there after birth (OR 1.92 (95%CI 1.02-3.6)). Despite guidance, only 56% of births in England at 22-26 weeks occurred in tertiary centres in 2006. Whilst the difference in morbidity is likely multifactorial, the findings emphasise the
importance of coordinated neonatal and obstetric network strategies for safe antenatal centralisation.

**Antenatal Steroids**

Antenatal steroid therapy is one of the most important advances in perinatal care and has played a significant role in improving survival rates.\(^{11}\) The delay in translating research on the benefits of antenatal steroids into clinical practice was a main driver for the establishment of the Cochrane Collaboration\(^{12}\), and consequently antenatal steroids are recommended for all women with threatened preterm delivery before 34 weeks gestation.\(^{13}\) Despite this, only 54% of mothers in low and middle income countries are offered them\(^{14}\) while 85% of eligible deliveries received one or more doses of antenatal steroid in the UK.\(^{15}\) Notably only 67% of liveborn infants at 23 weeks were treated, and 25% of units had rates of 25% or lower.\(^{16}\)

Incidence of IVH and white matter damage are reduced following antenatal steroids\(^{11}\)\(^{17}\)(Table 1). This is secondary to vasoconstriction of cerebral vessels and anti-inflammatory effects, as well as increased cardiovascular stability related to reduced respiratory compromise.\(^{18}\)
Table 1: Impact on rates of adverse neurodevelopmental outcome for specified interventions

(IVH = Intraventricular Haemorrhage; CP = Cerebral Palsy; PVL = Periventricular Leukomalacia; RR = Relative Risk; AOR = Adjusted Odds Ratio)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome Affected</th>
<th>Risk Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal Steroids</td>
<td>IVH (all grades)</td>
<td>RR 0.54 [0.43-0.69]\textsuperscript{11}</td>
</tr>
<tr>
<td></td>
<td>Developmental Delay (3 years)</td>
<td>RR 0.49 [0.24-1.00]\textsuperscript{11}</td>
</tr>
<tr>
<td></td>
<td>CP (all severities 2-6 years)</td>
<td>RR 0.60 [0.34-1.03]\textsuperscript{11}</td>
</tr>
<tr>
<td>Magnesium Sulphate in Labour</td>
<td>CP (all severities 12-24 months)</td>
<td>RR 0.68 [0.54-0.87]\textsuperscript{19}</td>
</tr>
<tr>
<td></td>
<td>CP (severe and moderate 12-24 months)</td>
<td>RR 0.64 [0.44-0.92]\textsuperscript{19}</td>
</tr>
<tr>
<td></td>
<td>Gross Motor Dysfunction (18-24 months)</td>
<td>RR 0.61 [0.44-0.85]\textsuperscript{19}</td>
</tr>
<tr>
<td>Delayed Cord Clamping</td>
<td>IVH (all grades)</td>
<td>RR 0.59 [0.41-0.85]\textsuperscript{20}</td>
</tr>
<tr>
<td></td>
<td>Gross Motor Dysfunction (18-22 months)</td>
<td>OR 0.32 [0.10-0.90]\textsuperscript{21}</td>
</tr>
<tr>
<td>Caffeine</td>
<td>CP (all severities 12-22 months)</td>
<td>AOR 0.58 [0.39-0.87]\textsuperscript{22}</td>
</tr>
<tr>
<td></td>
<td>Cognitive Delay (18-22 months)</td>
<td>AOR 0.81 [0.66-0.99]\textsuperscript{22}</td>
</tr>
<tr>
<td>Prophylactic Indomethacin</td>
<td>IVH (Grades 3 and 4)</td>
<td>RR 0.66 [0.53-0.82]\textsuperscript{23}</td>
</tr>
<tr>
<td></td>
<td>Ventriculomegaly, PVL or other white matter echo-abnormalities</td>
<td>RR 0.80 [0.65-0.97]\textsuperscript{23}</td>
</tr>
<tr>
<td>Volume Ventilation</td>
<td>PVL and IVH (Grade 3 and 4)</td>
<td>RR 0.48 [0.28-0.84]\textsuperscript{24}</td>
</tr>
</tbody>
</table>

Meta-analysis shows lower rates of developmental delay and CP, and higher cognitive ability in children who received antenatal steroids compared to those who did not.\textsuperscript{11} Outcome was improved after a single course, even if preterm delivery was arrested.\textsuperscript{25} Evidence demonstrates benefits to the neonate with minimal risks to the mother, following delivery within seven days of a single complete course of corticosteroids.\textsuperscript{11} This includes cases where tocolysis has been used to delay delivery for treatment, even in the presence of chorioamnionitis.\textsuperscript{26}

A RCT is currently comparing outcomes following betamethasone verses dexmethasone\textsuperscript{27} since both are used with differing evidence as to which is safest and best.\textsuperscript{28, 29, 30} Likewise, the evidence for repeating treatment if delivery has not occurred within seven days is mixed. Meta-analysis revealed that infants exposed to multiple steroid courses have lower risk of early respiratory morbidity, but tend to have reduced birth weight and head circumference.\textsuperscript{31} Current guidance advises against multiple courses, although a single additional rescue course may be appropriate when the first was before 26 weeks gestation.\textsuperscript{28}
Magnesium Sulphate (MgSO₄)
MgSO₄, a drug widely used in obstetrics,³² was recognised as a potential neuroprotectant when data revealed a reduced incidence of IVH in babies whose mothers had received it.³³ Subsequently a decrease in the incidence of CP was presented³⁴ and animal models and clinical trials have since corroborated these findings.¹⁹ MgSO₄ acts as a non-competitive inhibitor at NMDA channels, blocking excess glutamate release, reducing excitotoxicity, and consequently oligodendroglial progenitor cell death,³⁵ as well as modulating the effects of pro-inflammatory cytokines which are known to correlate with neurological outcome.³⁶ In addition, due to MgSO₄’s vasoactive properties, further benefit may result from stabilisation of blood pressure³⁷ and cerebral arterial perfusion.³⁸

The overall risk of CP, the risk of severe and moderate CP and the incidence of gross motor dysfunction¹⁹ (Table 1) is reduced following antenatal MgSO₄. To date, no neurodevelopmental advantage has been seen in later childhood³⁹ ⁴⁰, however individual studies are underpowered to show this. As with many interventions, the lack of proven benefit to composite outcome in older children should not negate the positive early effects.⁴¹

MgSO₄ for neuroprotection prior delivery at <30 weeks is recommended internationally⁴²-⁴⁴ with consideration in deliveries <34 weeks also advocated in some regions.¹³ Uptake has however been sub-optimal. Only 38% of eligible UK infants <30 weeks registered on VON received antenatal MgSO₄ in the UK in 2014 and in 25% of units the rate was less than 16.8%.¹⁶ From a very recent NNAP report⁴⁵ estimated uptake is similar (36%), although data reporting was incomplete. Concerns about hypotonia and respiratory depression at birth, consequent to MgSO₄’s blockade of calcium into cells, are commonplace, but have not been demonstrated in large cohort studies or in the meta-analysis.⁴⁶ ⁴⁷ Furthermore, since MgSO₄ has anti-inflammatory effects, there have been concerns that it may increase sepsis. Although significant neuroprotective effects were not identified in the setting of chorioamnionitis⁴⁸, there is no evidence that infection risks are increased.¹⁵ The potential benefits of MgSO₄ for preterm deliveries 30-34 weeks are being studied, to provide clearer evidence at these higher gestations.⁴⁹

The MagNET trial⁵⁰ reported an increase in fetal death in mothers following MgSO₄ versus the control group. This concerning difference was only significant when MgSO₄ was used at high doses, and was not seen in meta-analysis.¹⁹ Cumulative high doses of MgSO₄ (>50g) are associated with IVH and increased mortality⁵¹⁵² making clear guidance on dosing crucial. Developing this is impeded by the variability in evidence.¹⁹ ³⁵ ⁵³ Differing dosing schedules, trial inclusion criteria and mixed intent (obstetric vs. fetal neuroprotective) complicate interpretation.⁵³ A blinded RCT is underway with a view to obtaining more conclusive evidence⁵⁴ since previous investigation found a lack of data comparing different regimens.⁵³ Currently 4g loading dose over 20-30minutes followed by an infusion of 1g/hour until birth or for a maximum of 24hours is endorsed in the UK.¹³ ⁵⁵

Management of Preterm Prelabour Rupture of Membranes (PPROM) to Reduce Chorioamnionitis and Early Onset Infection (EOS)
Chorioamnionitis and infections within the first 72 hours of life (EOS) contribute to adverse neurodevelopmental outcome⁵⁶ ⁵⁷ (Table 2). Cerebral hypoperfusion, capillary thrombosis and increased permeability of the blood brain barrier - allowing direct
passage of microbial products and proinflammatory cytokines into the cerebral tissue, have been suggested to cause fetal brain injury. Several key biomarkers have been identified as targets for future treatments to promote normal neurological development in the presence of antenatal infection, however prevention of chorioamnionitis following PPROM is currently the mainstay of recommendations. Prophylactic antibiotics and consideration of immediate delivery after 34 weeks are advocated in the UK, however both are controversial.

Table 2: Impact of acute morbidities on adverse neurodevelopmental outcome (CP = cerebral palsy; NEC = necrotising enterocolitis; EOS = early onset sepsis; LOS = late onset sepsis; OR = odds ratio; AOR = adjusted odds ratio).

<table>
<thead>
<tr>
<th>Acute Morbidity</th>
<th>Neurodevelopmental Outcome</th>
<th>Risk Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>CP (all types- 5 years)</td>
<td>EOS- OR 1.7 (0.84-3.45)</td>
</tr>
<tr>
<td></td>
<td>LOS – OR 1.71 (1.14-2.56)</td>
<td>EOS +LOS OR 2.33 (1.02 – 5.33)</td>
</tr>
<tr>
<td>NEC</td>
<td>Neurological impairment (18-22months)</td>
<td>AOR 1.7 (1.2, 2.4)</td>
</tr>
<tr>
<td></td>
<td>Diparetic CP (after surgical NEC + bacteraemia -24 months)</td>
<td>OR 8.4 (1.9 -39)</td>
</tr>
</tbody>
</table>

Antibiotics following PPROM (without chorioamnionitis) leads to prolongation of pregnancy, reduction in neonatal infection (Relative Risk (RR) 0.67, 95%CI 0.52-0.85) and fewer abnormal cranial ultrasound scans (RR 0.81, 95%CI 0.68 to 0.98). At school age however, there was no difference in functional, behavioural or attainment outcomes but increased levels of functional impairment were seen in children of mothers who had received erythromycin following spontaneous onset of preterm labour with intact membranes making correct diagnosis essential.

Timing of delivery following PPROM, without evidence of infection or fetal compromise, is also complex. Delayed delivery increases the risk of chorioamnionitis, however this needs to be balanced against the risks of preterm birth. Meta-analysis concluded that there was insufficient evidence to advocate either, in part since protocols were not comparable to current best practice. Recent RCTs have reported no difference in the incidence of neonatal sepsis, morbidity or mortality but increases in preterm complications were seen making recommendation for immediate delivery contentious.

POSTNATAL INTERVENTIONS
Following delivery, physiological instability and systemic inflammation predispose the preterm brain to IVH and white matter damage. Careful consideration and minimisation of these can protect the premature brain.

Deferred Cord Clamping (DCC)
DCC in preterm infants leads to reduction in mortality and multisystem morbidity including all grades of IVH. Recent studies have shown improved motor function at 18-22months (Table 1) whereas previously, no difference in developmental outcome had been recognised. Several mechanisms for the positive
effects are hypothesised\textsuperscript{72} including increased blood volume and oxygenation, prevention of iron deficiency anaemia, and the transfer of stem and progenitor cells with extensive proliferative capacity which may contribute to repairing tissues and promoting immunocompetence.\textsuperscript{21} Although DCC is recommended when the infant is born in good condition without the need for resuscitation,\textsuperscript{13} immediate clamping often predominates.\textsuperscript{42}

Hesitancy arises from the lack of consensus on optimal timing for DCC and theorised risks such as potential volume overload, polycythaemia, jaundice, and interruption of collection of blood for cord blood banking.\textsuperscript{20} 42 74 Concerns about delayed resuscitation, thermal care and technical difficulties are being addressed through the development and trialing of new equipment to allow transition to be assisted closer to the mother with the cord intact.\textsuperscript{75} 76 Studies have shown DCC to be feasible, safe and to have significant benefit to preterm infants, with no detriment from the risks above.\textsuperscript{20} 77

**Caffeine for Apnoea of Prematurity**

Recurrent apnoeas, are common in preterm infants, and are potentially harmful.\textsuperscript{78} In RCT, treatment with caffeine in the first 10 days decreased the incidence of CP and cognitive impairment at 18–21 months in low birth-weight at risk infants.\textsuperscript{22} This effect was only partially explained by the reduction in bronchopulmonary dysplasia, a co-morbidity that is independently associated with adverse neurodevelopmental outcome.\textsuperscript{52} 79 Caffeine has been shown to be safer than other methylxanthines and is recommended as a treatment for preterm infants.\textsuperscript{78}

Opinion varies as to when to start caffeine. It is hypothesised that starting caffeine early, prior to the period of greatest vulnerability to white matter injury, may be beneficial\textsuperscript{80}, however, the only significant benefit seen from this has been the incidence of a persistent ductus arteriosus (PDA).\textsuperscript{81} Subsequent studies have shown a reduction in death, bronchopulmonary dysplasia and PDA for infants given caffeine in the first three days of life compared to those who received it later \textsuperscript{82} 83 and a RCT is currently recruiting to investigate prophylactic versus therapeutic caffeine further.\textsuperscript{84}

Notably, the neuroprotective effect of caffeine was not significant at five years due to reduced statistical power.\textsuperscript{85} Increased incidence of cerebellar haemorrhage on MRI has been reported following high dose caffeine.\textsuperscript{80} However, there is extensive evidence that caffeine is safe at standard doses, and has lasting multi-system benefits for preterm infants.\textsuperscript{78}

**Indomethacin Prophylaxis for PDA**

Closure of the ductus arteriosus is delayed in up to 80% of infants born at <25 weeks\textsuperscript{86} and as many as 70% <28 weeks.\textsuperscript{86} PDA can be associated with IVH and abnormalities of cerebral perfusion as well as cardiac and pulmonary complications.\textsuperscript{86} Optimal management is a topic of great debate - whilst overall prevalence is high, one third resolve without intervention and not all of those that persist become clinically significant.\textsuperscript{87} 88 Trials investigating early versus late treatment of infants with known PDA (targeted treatment) have not shown any difference in mortality or cranial ultrasound abnormalities, leading authors to hypothesise that detriment occurs before the PDA becomes clinically significant.\textsuperscript{89} Additionally, targeting treatment depends
on access to echocardiographic expertise, which is not universal. Both the timing of intervention, and the need to treat at all are contested.\textsuperscript{88}

Indomethacin prophylaxis significantly reduces the incidence of severe IVH and led to a borderline significant reduction in ventriculomegaly, periventricular leukomalacia (PVL) or other white matter echo-abnormalities\textsuperscript{23} (Table 1). There was no difference in mortality, necrotising enterocolitis (NEC) or other complications.\textsuperscript{23} Fewer infants required surgical ligation following prophylaxis,\textsuperscript{23} hence were not exposed to the risks of cardiac surgery, which include detriment to neurodevelopment.\textsuperscript{90} In addition to closing, and therefore reducing the haemodynamic consequences of, the PDA, it is postulated that indomethacin may have a direct effect on the brain. It reduces prostaglandin synthesis and the cerebral vascular hyperemic response as well as promoting the maturation of the basement membrane and basal lamina making the brain less vulnerable to hypoxic, hypercapnic and hypertensive insults.\textsuperscript{91} Prophylaxis based on risk criteria has shown the effect of prophylactic indomethacin is more significant in infants at higher risk of IVH.\textsuperscript{92 93}

Practice is varied, with limited uptake despite convincing neonatal results.\textsuperscript{97} Indomethacin can be difficult to source, with supply limiting both clinical use and research and\textsuperscript{89} no difference in developmental outcome at 18-36 months was seen in meta-analysis.\textsuperscript{23} There are concerns this may be due to detriment caused to infants without a PDA, or those in whom it would close spontaneously.\textsuperscript{94 89}

There is however no evidence of harm, and a significant reduction in cognitive disability at 4–5 years\textsuperscript{95} and better language development in boys at 8 years\textsuperscript{96} have since been reported following prophylactic indomethacin. The harms of potentially unnecessary intervention in some need to be balanced against the benefit for others, yet the current cumulative evidence is that prophylactic indomethacin is safe and pertains to short-term neonatal advantages which are linked with improved neurodevelopmental outcome.\textsuperscript{23}

**Volume Targeted Ventilation to Prevent Hypocarbia**

Although antenatal steroids and surfactant have significantly reduced rates of mechanical ventilation, 69% of VON-registered UK infants <1500g were ventilated in 2014.\textsuperscript{16} This can lead to hypocarbia, causing changes in cerebral blood flow and perfusion pressure, predisposing to PVL.\textsuperscript{24} Meta-analysis revealed a statistically significant reduction in hypocarbia in patients receiving volume-targeted ventilation compared to pressure-limited ventilation.\textsuperscript{24} This translated into a reduction in the combined outcome of PVL or grade 3–4 IVH\textsuperscript{24} (Table 1). Although current data is underpowered to determine impact on long-term neurodevelopment, these short term benefits in reducing detectable brain injury, the mechanistic validity and the lack of demonstrable harm, provide a strong basis for using volume-targeted ventilation modes, when mechanical ventilation is required.\textsuperscript{24}

Risk is theoretically reduced further through end tidal or transcutaneous capnography, through earlier detection and therefore earlier correction of hypocarbia, however there is currently insufficient evidence to recommend or refute this.\textsuperscript{98 99}

**Preventing Causative Morbidities**
Late onset sepsis (LOS), NEC and poor nutritional status are associated with adverse neurodevelopmental outcomes for preterm infants (Table 2). A detailed exploration of the relative importance of different strategies to reduce their incidence is complex and beyond the scope of this review since there are no consensus recommendations and trials are ongoing, however some key interventions are briefly highlighted.

**Late Onset Sepsis**
Approximately 21–36% of very low birth weight preterm infants have LOS. Neurodevelopmental impairment is increased following clinical infection as well as culture positive sepsis and meningitis when compared to infants without suspected sepsis and the risk is increased further in infants who have experienced both EOS and LOS as a ‘double hit’.

Standardised care ‘bundles’ for central lines - setting and enforcing standards for insertion, maintenance and timely removal, decrease infections by up to 67%. Implementation of such a bundle resulted in improved cognitive outcome at 2 years in one report. Antimicrobial stewardship, limited postnatal steroid use, early enteral feeding with breast milk and meticulous hand hygiene are important and cost-effective strategies for reducing the burden of LOS. Preliminary data also suggests bovine lactoferrin supplementation alone and in combination with probiotics may reduce LOS with a large study now recruiting. Immune replacement therapy is being investigated, and prophylactic fluconazole in at risk populations has been shown to reduce invasive candidiasis.

**Necrotising Enterocolitis**
NEC is associated with structural brain injury and poor neurodevelopmental outcome (Table 2). NEC requiring surgery is associated with worse outcomes than NEC treated with antibiotics and withholding feeds, and the duration of NEC is proportional to neurodisability. It may be that the systemic inflammatory response associated with NEC results directly in brain injury, however, the causality is unproven and NEC could be a surrogate marker of other predisposing factors such as abdominal surgery, sepsis, organ immaturity or susceptibility to infection. Detailed discussion of strategies to reduce NEC rates, which may provide neuroprotective benefit, is beyond the scope of this review, but use of probiotics, lactoferrin, promotion of breast milk, avoidance of bovine-origin products and preventing infection are all likely to be beneficial.

**Emerging Strategies**
Melatonin, erythropoietin and stem cell therapies have all shown neuroprotective potential in early studies and research is ongoing into these, and other interventions. First week protein and energy intake are associated with 18 month developmental outcomes, and meta-analysis has shown that increasing early enteral nutrition may reduce neurodevelopmental impairment. Preterm infants fed with predominantly breast milk had higher deep nuclear grey matter volume at term corrected age, improved developmental scores at 18 months as well as higher IQ and academic achievement at 7 years, although this has not been seen in all studies. Research is ongoing into optimal nutritional regimens, however it is hypothesised the benefits of early nutrition and breast milk, including fortification, outweigh the risks.
Interventions to ameliorate neurological sequelae following an initial brain injury are also being researched. An RCT comparing drainage, irrigation and fibrinolytic therapy with conventional management after severe IVH with posthaemorrhagic ventricular dilatation, reported a reduction in the incidence of death, severe cognitive and physical disability at two years in the intervention group.\textsuperscript{125} School age follow-up results will be published shortly. Developmental intervention in infants at risk of disability may also improve outcomes, however, due to the heterogeneity of trials, more research is required to determining what type of intervention is most beneficial.\textsuperscript{126}

**SUMMARY AND CONCLUSIONS**
We present a review of interventions that are known to reduce the incidence of preterm brain injury and/or improve neurodevelopmental outcome. Although recommended, translation of this- like much other- research into practice is far from complete. Whilst research is ongoing in to new therapies and the relative importance and interplay of current strategies, broader awareness of available measures and their effective application may lead to improvement in neurodevelopmental outcome for the current cohort of premature infants.
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